PARTICULARITES DE L'INFECTION VHC ET DE LA THERAPEUTIQUE ANTI-VHC CHEZ LES PATIENTS CO-INFECTES VIH/VHC

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UNIVERSITE PARIS 6- PIERRE ET MARIE CURIE

Année 2007 **N°**

THESE

Pour l'obtention du

DOCTORAT EN SANTE PUBLIQUE : EPIDEMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMEDICALE

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Soutenue le 3 septembre 2007

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Je tiens à remercier

M. le Dr Fabrice CARRAT, qui m'a fait l'honneur de diriger cette thèse

Mme. la Pr. Geneviève CHENE et M. le Pr Yazdan YAZDANPANAH qui m'ont fait l'honneur d'accepter d'être rapporteur de cette thèse

Mme la Pr Christine ROUZIOUX et M. le Pr Jean François DELFRAISSY qui m'ont fait l'honneur d'être examinateur de cette thèse

M. le Pr. Alain-Jacques VALLERON, qui m'a fait l'honneur d'être Président de cette thèse

Je tiens aussi beaucoup à remercier toutes les personnes sans qui ces travaux n'auraient pas vu le jour

Christian PERRONNE, pour la confiance qu'il m'a accordée en m'associant à l'essai RIBAVIC

Fabrice CARRAT, pour ses qualités humaines et scientifiques et pour son soutien et encouragement constant. Notre rencontre se fit à l'occasion de l'élaboration de l'essai RIBAVIC. Elle fût une étape déterminante dans ma vie professionnelle car elle permit de découvrir à la clinicienne que je suis, l'autre versant de la recherche clinique. Il m'a laissé libre de mener mes travaux à ma guise, tout en étant présent et pertinent aux moments où j'en avais besoin. Je tiens plus que tout, à exprimer ma profonde reconnaissance.

Alain-Jacques VALLERON qui m'a accueilli dans son unité et qui encouragea et soutint l'aventure RIBAVIC

Isabelle GODEREL, Chafia BENRENDJEM, Nadia BENRENDJEM, Juliette DEHAYES de l'unité INSERM U707, sans qui ces travaux n'auraient pu aboutir

L'Agence Nationale de Recherche sur le SIDA et les Hépatites, promoteur de l'essai RIBAVIC et de la cohorte RIBAVIC

Le SIDACTION, qui a soutenu pendant deux années mon travail de thèse

I- INTRODUCTION

Avec l'introduction des inhibiteurs de protéase en 1996, l'espérance de vie des patients infectés par le VIH augmenta du fait d'une diminution importante de la morbidité et de la mortalité secondaires aux infections opportunistes. Par ailleurs, l'infection par le VHC touchait environ 25% des patients VIH+, dont plus de 70% des patients toxicomanes et hémophiles coinfectés par le VIH et par le VHC. Les complications liées au VHC risquaient donc de devenir un facteur majeur de morbidité et de mortalité. C'est dans ce contexte qu'en 1998, le traitement de la co-infection VHC rarement discuté avant l'ère des inhibiteurs de protéase, compte tenu d'une réponse médiocre à la monothérapie par IFNα et d'un pronostic de vie lié au VIH estimé en moyenne à 10 ans, fût reconsidéré. Il fût dès lors décider de mettre en place un essai thérapeutique évaluant la réponse au traitement anti-VHC dans cette population. C'est ainsi que débuta en 2000, sous l'égide de l'ANRS, l'essai RIBAVIC HC02, essai randomisé et multicentrique comparant l'association de la ribavirine 800 mg/j à l'Interféron 3 MUI x3/semaine ou au PEG-α-2b Interféron 1,5 µg/kg/semaine pendant 48 semaines. Cet essai qui inclus plus de 400 patients permit d'évaluer non seulement la réponse thérapeutique mais également différents aspects de la tolérance thérapeutique et notamment la mise en évidence d'effets secondaires graves liés à une aggravation de la toxicité de certains antirétroviraux anti-VIH lors de l'association avec la ribavirine. Les travaux réalisés à partir des données de cet essai permirent de définir de nouvelles recommandations thérapeutiques dans la prise en charge de la co-infection VIH-VHC mais également d'analyser certains paramètres de l'histoire naturelle du VHC. En 2001, à la lumière des caractéristiques

des patients inclus dans l'essai Ribavic, (une immunodépression peu profonde avec des CD4 moyens à 522/mm3 et un stade A de la classification CDC dans 55% des cas et près de 40% des patients ayant un score F3 ou F4), il nous apparût que pour près de 40% des patients, le pronostic vital à court et moyen terme risquait d'être lié à l'évolution de l'hépatite chronique C, plutôt qu'à l'infection par le VIH. C'est dans ce contexte que nous décidâmes de créer une cohorte des patients inclus dans l'essai RIBAVIC afin d'évaluer chez ces patients l'éventuel bénéfice clinique d'un traitement par bithérapie anti-VHC en fonction de la réponse virologique et/ou biochimique et/ou histologique et d'identifier aussi les risques de progression vers la cirrhose et/ou de développement d'un hépatocarcinome. La cohorte RIBAVIC EP10 débuta en 2001.

Buts et cheminement du travail

L'histoire naturelle ainsi que la prise en charge thérapeutique diffèrent chez les patients co-infectés VIH/VHC comparées aux patients mono-infectés par le VHC. Nous allons décrire ces différents aspects en portant une attention plus particulière à l'apport contributifs de nos travaux :

- une charge virale VHC plus élevée
- une évolution plus fréquente et plus rapide vers un stade de fibrose avancé
- une hépatotoxicité des antirétroviraux majorée par la co-infection VHC
- une réponse thérapeutique au traitement anti-VHC plus faible (inférieure à 40%)
- un risque de non réponse au traitement anti-VHC (absence de diminution > 2 log à S12) et un risque de rechute (à l'arrêt de traitement à S48) plus élevés

- des effets secondaires liés au traitement anti-VHC plus fréquents avec notamment, un risque majoré de toxicité mitochondriale, de décompensation hépatique, d'anémie, d'infection bactérienne et d'amaigrissement.

II- EPIDEMIOLOGIE DE LA CO-INFECTION VIH/VHC

En France, la co-infection VIH/VHC touchait 24,3% des patients VIH+ en 2004. Toutes les études réalisées dans les pays ayant accès aux traitement anti-rétroviraux montrent une augmentation de la morbidité et la mortalité liée à l'hépatite chronique C. Dans certaines populations, l'hépatite C est devenue la première cause de mortalité non-VIH [1]. Dans l'étude EUROSIDA ayant inclus 4043 patients suivis dans différentes cohortes européennes, l'incidence des décès liés au VHC est passée de 8,6% en 1996 à 11,9% en 2000 ($p<0,001$). En France, parmi les 822 décès signalés par 185 hôpitaux en 2000, 29% des patients décédés étaient co-infectés par le VHC, 8% par le VHB, et 4% par à la fois le VHC et le VHB [2]. Les décès étaient le plus souvent de cause hépatique (31% des cas) ou secondaire à l'infection par le VIH (29%) parmi les patients co-infectés VIH/VHC. Près de la moitié des patients décédés de cause hépatique avaient des CD4 supérieurs à 200/mm^3. Dans une autre étude française portant sur une cohorte de 25 178 patients VIH+, parmi les 265 décès observés, 129 (48.7%) étaient secondaires à l'infection par le VIH, 38 (14.3%) à une insuffisance hépato-cellulaire (95% des patients étant co-infectés par le VHC), et 98 (36.7%) à des causes différentes [3]. Les décès de cause hépatique (14.3%) étaient significativement plus fréquents en 2001 comparés à 1995 (1.5%; $P < 0.01$) et à 1997 (6.6%; $P < 0.01$). Dans cet intervalle, la prévalence du carcinome hépatocellulaire comme cause de décès avait augmenté significativement (1995, 4.7%; 1997, 11%; 2001, 25%; $P < 0.05$). Dans une étude portant sur une cohorte de 6945 patients aux Etats-Unis suivis entre 1996 et 2004, les décès de cause hépatique étaient les seuls, bien que non significativement à augmenter en nombre absolu au cours du temps : 0,009 personnes/années en 1996 à 0,16

personnes/années en 2004 (p=0,1) [4]. Cependant, une étude espagnole récente rapporte un déclin de la morbi- mortalité secondaire au VHC depuis 2002. Une analyse rétrospective entre janvier 1996 et décembre 2004, a analysé l'ensemble des cas d'admissions hospitalières (2527 admissions chez 2008 patients VIH+). L'admission était secondaire à une insuffisance hépato-cellulaire dans 345 cas (14%), avec une augmentation significative entre 1996 et 2002 [9.1% (30/329) versus 26% (78/294)], respectivement. Mais depuis 2002, un déclin est observé . En 2004, seulement 11% (29/253) des admissions étaient secondaires à une insuffisance hépato-cellulaire. De même la mortalité hépatique était passée de 9% (5/54) en 1996, à 59% (10/17) en 2001 et à 20% (3/15) en 2004. L'hépatite chronique C était responsable des admissions et/ou des décès dans 73.5% des cas. Après ajustement sur l'âge, le taux des CD4 et la consommation d'alcool, la diminution de l'incidence des décès secondaires à insuffisance hépato-cellulaire dans les années 2003-2004 est confirmée (OR 0.1 ; $IC_{95\%}$ 0.02-0.6 ; p=0.01) [5]. Cette diminution de la morbi- mortalité hépatique pourrait s'expliquer par une prise en charge plus précoce de l'infection par le VHC et à une diminution de l'utilisation de traitements hépatotoxiques, notamment des INTI ayant une toxicité mitochondriale élevée comme l'association stavudine-didanosine.

Pourquoi l'infection par le VHC est-elle plus sévère dans cette population ?

III- INFLUENCE DE L'INFECTION VHC SUR L'INFECTION PAR LE VIH

Avant l'ère des traitements antirétroviraux hautement actifs, les études réalisées ne montraient aucune influence de la coinfection VHC sur la progression clinique et virologique du VIH. Depuis l'ère des traitements antirétroviraux hautement actifs, les

études sur une éventuelle influence délétère de la coinfection VHC sur la progression clinique et virologique du VIH sont contradictoires. Une étude faite sur 3111 patients débutant un traitement antirétroviral suivis dans la cohorte suisse montrait que l'infection par le VHC était un facteur indépendant de progression vers le SIDA et de mortalité (HR 1.7 $IC_{95\%}$ 1.26-2.30). Ce résultat ne s'expliquait pas par un recours moins important au traitement antirétroviral ou à une moindre tolérance de celui-ci. En revanche, la restauration immunitaire sous traitement antirétroviral était moins importante (HR pour une augmentation d'au moins 50 CD4 : 0.79 - $IC_{95\%}$ 0.72-0.87). En revanche, dans une cohorte américaine de 1955 patients, le risque de développer un SIDA (HR 1.03- $IC_{95\%}$ 0.86-1.23) ou de décès (HR, 1.05; $IC_{95\%}$, 0.85 -1.30) ne différait pas entre les patients co-infectés VIH-VHC [231 évènements SIDA (26.4%) et 153 décès (17.5%)] et les patients mono-infectés par le VIH, [264 évènements SIDA (24.4%) et 168 décès (15.5%)]. L'augmentation des CD4 ne différait également pas dans les deux groupes [6]. Dans la cohorte EUROSIDA (5957 patients, 1960 (33%) VIH/VHC+ et 3997 (67%) monoinfectés par le VIH). aucune association entre une augmentation de l'incidence des évènements SIDA ou de décès n'était observé entre les patients co-infectés VIH/VHC et les patients mono-infectés par le VIH (adjusted incidence rate ratio [IRR], 0.97 [IC_{95}, 0.81-1.16]). Parmi les 2260 patients débutant un traitement antirétroviral, la réponse immunologique ou virologique ne différait pas entre les 2 groupes [7].

IV- INFLUENCE DE L'INFECTION VIH SUR L'INFECTION PAR LE VHC

IV- 1- L'infection par le VIH augmente la charge virale VHC

Chez les patients co-infectés, la charge virale plasmatique VHC est 1.5 à 2 fois plus élevée comparée aux patients mono-infectés par le VHC. Avant l'ère des traitements antirétroviraux hautement actifs, la charge virale VHC était inversement corrélée au degré d'immunodépression. [8, 9]. Toutefois, l'immunodepression n'est pas le seul facteur en cause car chez les patients atteints d'hépatite C au moment de la contamination par le VIH, une augmentation significative de la virémie VHC a été rapportée dès la séroconversion VIH [10]. Paradoxalement, la restauration immunitaire sous traitement antirétroviral incluant un inhibiteur de protéase (IP) ne s'accompagne pas d'une baisse de la charge virale VHC mais d'une augmentation modérée (moins de 0,6 log) mais significative de celle-ci, qui n'est pas corrélée à une augmentation des transaminases [11-13]. Il n'existe pas d'explication claire à l'augmentation de la charge virale VHC sous traitement anti-rétroviral. Dans certaines études, l'augmentation de l'ARN VHC était plus importante chez les patients débutant leur traitement antirétroviral à un stade plus avancé d'immunodépression. Ainsi dans une étude comparant la cinétique virale VHC selon le stade immunitaire à l'initiation du traitement antirétroviral, elle était de 0,43 $\log_{10}$ UI/ml et de 0,59 $\log_{10}$ UI/ml respectivement à 16 et 48 semaines de traitement en cas de CD4 < 350/mm3 et de seulement 0,26 $\log_{10}$ UI/ml et 0,1 $\log_{10}$ UI/ml en cas de CD4 > 350/mm3 [11]. Dans d'autres études, l'augmentation de la charge virale VHC différait selon l'IP (nelfinavir ou lopinavir) [14] ou selon la charge virale VIH avant traitement [15].

IV-2- Charge virale VHC élevée : Rôle des IP ?

Une charge virale VHC élevée est un facteur de risque d'échec du traitement anti-VHC. Mieux comprendre les facteurs liés à une charge virale VHC peut donc permettre une meilleure optimisation du timing des traitements anti-VIH et anti-VHC chez les patients co-infectés VIH/VHC.

Nous avons analysé les facteurs de risque liés à une charge virale VHC élevée parmi les 379 patients inclus dans l'essai RIBAVIC chez qui les données à fois de la charge virale VHC et du score histologique hépatique étaient disponibles.

Les facteurs retenus pour l'analyse étaient l'âge, le sexe, le score METAVIR moyen pour l'inflammation et la fibrose, la cirrhose, la durée de l'infection par le VHC, le génotype VHC, la durée de l'infection par le VIH, le taux des lymphocytes CD4, le traitement antirétroviral, la durée du traitement antirétroviral, une charge virale VIH < 400 copies/ml, l'utilisation des inhibiteurs non nucléosidiques de la reverse transcriptase (INNTI) et des IP. Une régression linéaire multiple a été utilisée pour étudier la corrélation entre ces facteurs et la charge virale VHC.

312 patients (82.3%) recevaient un traitement antirétroviral pendant une durée moyenne de 4.37 (3.3) années. La moyenne des CD4 à l'inclusion étaient 528/mm^3 (± 244) et 65.7% des patients avaient une charge VIH < 400 copies/ml. L'analyse par régression linéaire multiple identifiait deux facteurs indépendants associés à une charge virale VHC élevée: le génotype VHC 1 ou 4 (β+ 0.32±0.1; p=0.0022) et les IP (β+0.28±0.12; p=0.0247). En revanche, le traitement antirétroviral en soit était indépendamment associé à une charge virale VHC plus basse (β -0.31±0.12; p=0.0128). La charge virale VHC était en moyenne de 6.07 ± 0.71 $\log_{10}$ UI/ml chez les 67 patients ne recevant pas de traitement antirétroviral versus 5.83 ± 0.74 $\log_{10}$

UI/ml (p=0.0089) chez les 312 patients traités par antirétroviraux ; elle était de 5.96 ± 0.63 log_{10} UI/ml chez les 148 patients traités par IP versus 5.71 ± 0.8 log_{10} UI/ml (p=0.0144) chez les 164 patients ne recevant pas de traitement antirétroviral incluant un IP.

Notre étude qui a porté sur un grand nombre de patients avec une durée de traitement antirétroviral prolongée (4,3±3,3 ans) confirme les résultats des études longitudinales ayant un suivi supérieur à un an, montrant une augmentation de la charge virale VHC chez les patients recevant un traitement antirétroviral incluant un IP. En revanche, le traitement antirétroviral en soit était associé à une charge virale VHC plus basse. La charge virale VHC était significativement différente chez les patients traités par trois INTI seuls (n=28), par un traitement antirétroviral incluant un INNTI (n=99) et par un traitement antirétroviral incluant un IP (n=148) : 5,7 ±0,68 log_{10} UI/ml versus 5,68 ± 0,86 log_{10} UI/ml versus 5,96 ± 0,62 log_{10} UI/ml (p=0.042), respectivement. La nature transversale de l'étude ne permet pas de conclure à un lien de causalité. Les mécanismes impliqués dans l'impact négatif des IP sur la charge virale VHC sont inconnus. Le nadir des CD4 inférieur à 350/mm^3 (282 ± 195//mm^3) dans le groupe de patients traités par antirétroviraux. Aucune association entre le nadir des CD4 et la charge virale VHC n'était observée. A notre connaissance, il n'existe pas d'étude ayant évalué la cinétique virale VHC sous traitement antirétroviral n'incluant pas des IP. La charge virale VHC plus basse observée chez les patients traités par antirétroviraux n'incluant pas des IP comparée à celle observée aux patients non traités pour le VIH ou à celle des patients sous antirétroviraux incluant des IP suggère que la cinétique virale VHC peut différer selon le régime thérapeutique. Il semble donc intéressant de réaliser des études longitudinales comparant la cinétique virale VHC selon différents traitements anti-

rétroviraux afin de mieux comprendre l'augmentation paradoxale de la charge virale VHC observée au cours des traitements incluant les IP. Par ailleurs, notre étude confirme que l'infection par le VIH en soit est associée à une charge virale VHC élevée, avant même l'installation d'une immunodépression sévère. La charge virale VHC était en moyenne de 6.07 ± 0.71 $\log_{10}$ UI/ml chez les 67 patients ne recevant pas de traitement antirétroviral alors que leur moyenne de CD4 était élevée (522 ± 205/mm^3).

QAD 200984

Research Letter

AIDS 2007, **21**:000–000

High hepatitis C virus viral load in HIV/hepatitis C virus-co-infected patients: a different influence of protease inhibitor and non-protease inhibitor-based HAART?

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We examined the possible relationships between hepatitis C virus (HCV) viral load and host factors, viral factors, and anti-HIV therapy in 379 HIV/HCV-co-infected patients. Multiple linear regression analysis identified two independent factors associated with higher HCV viral load, HCV genotype 1 or 4 infection and protease inhibitor-based antiretroviral therapy. Antiretroviral therapy in general was independently associated with lower HCV viral load. This suggests that HCV viral load kinetics could differ according to the choice of HAART regimen.

The efficacy of pegylated interferon and ribavirin combination is lower in HIV/hepatitis C virus (HCV)-co-infected patients than in HCV-mono-infected patients, ranging between 27 and 40% [1,2]. A high HCV viral load is an important predictive factor of this poor outcome and partly explains this disparity in virological response rates [1,2]. A better knowledge of the factors associated with high HCV viral load in HIV/HCV-co-infected patients might help to optimize the timing and choice of antiviral therapies. Here we analysed the possible relationships between HCV viral load and host factors, viral factors, and anti-HIV treatment in a large population of HIV/HCV-co-infected patients.

This study involved HIV/HCV-co-infected patients who were enrolled in the ANRS HC02 Ribavic trial. The results of the Ribavic trial have been reported in detail elsewhere [1].

Statistical analyses of baseline risk factors are based on data for the 379 patients for whom both HCV viral load and METAVIR scores were available. The baseline variables chosen for statistical analysis were age, sex, mean METAVIR scores for hepatic necroinflammation and fibrosis, cirrhosis, duration of HCV infection, HCV genotype, duration of HIV infection, previous AIDS diagnosis, HIV viral load below 400 copies/ml, CD4 cell count, antiretroviral therapy, mean duration of antiretroviral therapy, and the use of non-nucleoside reverse transcriptase inhibitors (NNRTI) or protease inhibitors (PI). Because of the strong correlation between the use of antiretroviral therapy and the use of nucleoside reverse transcriptase inhibitors (NRTI; all but one of the patients receiving antiretroviral therapy received NRTI), the use of NRTI was not introduced in the model. Linear regression analysis was used to examine the correlation between log levels of baseline HCV viral load and all other variables. The Mann–Whitney test was used to compare differences in HCV viral load. Significance was assumed at the 5% level.

The demographic and biological characteristics of the 379 patients included in this analysis are shown in Table 1. Multiple linear regression analysis identified two independent factors associated with higher HCV viral load: HCV genotype 1 or 4 infection ($\beta = +0.33$, SE 0.106; $P = 0.0022$) and PI-based antiretroviral therapy ($\beta = +0.37$, SE 0.014; $P = 0.0097$). In contrast, antiretroviral therapy in general was independently associated with a lower HCV viral load ($\beta = -0.54$, SE 0.20; $P = 0.008$). The variability of HCV viral load explained by the model was $r^2 = 0.16$. The mean HCV-RNA level was $5.99 \pm 0.64 \log_{10}$ IU/ml in patients with genotype 1 or 4 infection and $5.69 \pm 0.83 \log_{10}$ IU/ml in those with genotype 2, 3 or 5 infection ($P = 0.0022$). The mean HCV-RNA level was $6.07 \pm 0.71 \log_{10}$ IU/ml in the 67 patients not receiving antiretroviral therapy and $5.83 \pm 0.74 \log_{10}$ IU/ml ($P = 0.0089$) in the 312 patients receiving antiretroviral therapy ($5.96 \pm 0.63 \log_{10}$ IU/ml in the 148 patients treated with PI-containing regimens and $5.71 \pm 0.8 \log_{10}$ IU/ml in the 164 patients treated with other regimens; $P = 0.0144$). The results were similar when we included in the model the variable 'antiretroviral therapy-naive patients' ($n = 48$) instead of 'ongoing antiretroviral therapy' with a higher HCV-RNA level (mean $6.17 \pm 0.7 \log_{10}$ IU/ml) in antiretroviral therapy-naive patients ($\beta = +0.32$, SE 0.14; $P = 0.0255$).

There was no correlation between the HCV-RNA level and age, sex, the mean METAVIR scores for hepatic necroinflammation and fibrosis, cirrhosis, the duration of HCV or HIV infection, AIDS, HIV viral load below 400 copies/ml, the CD4 cell count, the mean duration of antiretroviral therapy, or the use of NNRTI-containing regimens.

As a low CD4 cell count nadir has previously been linked to a higher HCV viral load during HAART, we performed the same analysis in the subgroup of patients receiving antiretroviral therapy ($n = 312$), and added

Table 1. Demographic, biological and histological characteristics of the 379 HIV/hepatitis C virus-co-infected patients.

Variable	Value
Age, mean years (SD)	39.7 (5.4)
Men, no. (%)	278 (73.3)
HCV infection	
Intravenous drug use, no. (%)	298 (78.6)
Duration of HCV infection in years, mean (SD)	15.2 (6.2)
Metavir fibrosis score, mean (SD)	2.33 (1.01)
Metavir inflammation score, mean (SD)	1.75 (0.69)
Cirrhosis (F4), no. (%)	61 (16.3)
HCV genotypes 1 or 4, no. (%)	230 (60.6)
HCV genotypes 2, 3 or 5, no. (%)	149 (39.3)
Serum HCV RNA[a] ($\log_{10}$ IU/ml), mean (SD)	5.92 (0.11)
HIV infection	
Duration of HIV infection in years, mean (SD)	10.5 (4.3)
AIDS, no. (%)	62 (16.3)
CD4 cell count (/μl), mean (SD)	528 (244)
Plasma HIV-1 RNA < 400 copies/ml, no. (%)	249 (65.7)
Mean (SD) $\log_{10}$	3.24 (0.97)
No ART, no. (%)[b]	67 (17.7)
Duration of ART in years, mean (SD)[b]	4.37 (3.3)
Component drugs in antiretroviral regimens[b]	
PI, no. (%)	148 (39.0)
NNRTI, no. (%)	99 (26.1)
NRTI, no. (%)	313 (82.5)

ART, Antiretroviral therapy; HCV, hepatitis C virus; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
[a]Quantified by using the Versant HCV-RNA v3.0 method, range of quantification 2.79–6.89 $\log_{10}$ IU/ml (Bayer Diagnostics, Eragny, France).
[b]Zero in patients not receiving ART.

the nadir CD4 cell count to the model. The mean nadir CD4 cell count was 282 ± 195 cells/μl. Two independent factors were associated with a higher HCV viral load in this subgroup, namely HCV genotype 1 or 4 infection ($\beta = +0.307$, SE 0.141; $P = 0.0317$), and PI-based antiretroviral therapy ($\beta = +0.303$, SE 0.142; $P = 0.0358$); the nadir CD4 cell count did not influence the HCV viral load.

Although the HCV viral load is 1.5 to 2 times higher in HIV/HCV-co-infected patients than in HCV-mono-infected patients [3], the factors responsible for this difference are controversial. A negative correlation between the CD4 cell count and HCV viral load was observed before the HAART era [3,4]. HAART initiation was associated with a paradoxical increase in the HCV viral load in several studies [5,6]. As HAART improves immune function, the mechanisms of the HCV-RNA increase remain unclear.

Our study involved a large number of patients who had been on antiretroviral therapy for a mean of 4.3 ± 3.3 years. Our results are in line with the findings of longitudinal studies with more than one year follow-up, showing a link between PI-based antiretroviral therapy and an increase in HCV viral load, but in contrast, we found a negative relationship between the HCV viral load and antiretroviral therapy in general [5,6]. In our study, HCV viral load was high (mean 6.07 ± 0.71 $\log_{10}$ IU/ml) in the subgroup of patients not receiving antiretroviral therapy, despite high CD4 cell counts (mean 522 ± 205 cells/μl), and was higher than in patients receiving antiretroviral therapy (5.83 ± 0.74 $\log_{10}$ IU/ml). Among antiretroviral-treated patients, the mean HCV viral load was significantly different in the 28 patients receiving triple-NRTI regimens than in the 99 patients receiving NNRTI-based HAART and the 148 patients receiving PI-based HAART (respectively 5.7 ± 0.68, 5.68 ± 0.86 and 5.96 ± 0.62 $\log_{10}$ IU/ml; $P = 0.042$). In this subgroup of patients, PI-based HAART ($\beta = +0.303$; $P = 0.0358$) remained independently associated with a higher HCV viral load.

There are two mutually compatible explanations for these observations: the indications for PI-based antiretroviral therapy are linked with HCV viral load; and PI-based antiretroviral therapy itself leads to an increase in the HCV viral load. Our cross-sectional design does not formally permit a choice between these two explanations. The mechanisms involved in the negative impact of PI-based antiretroviral therapy on the HCV viral load remained unknown. The only significant differences between PI-treated and PI-untreated patients were a greater age (40.5 ± 5.1 versus 39.0 ± 5.6 years; $P = 0.024$) and a lower nadir CD4 cell count (216 ± 145 versus 317 ± 193 cells/μl; $P < 0.0001$) in PI-treated patients. These factors were considered in the linear regression analysis, and cannot therefore explain the effect of PI after adjustment. Some studies have shown that subjects with baseline CD4 cell counts of less than 350 or less than 100 cells/μl are most likely to have an increased HCV viral load during PI-based HAART [5,6]. Although the mean nadir CD4 cell count was lower than 350 cells/μl (282 ± 195 cells/μl) in our study, we found no association between the HCV viral load and the nadir CD4 cell count or the Centers for Disease Control and Prevention class of HIV infection in patients receiving antiretroviral therapy. An alternative explanation could be a drug-specific impact on the HCV viral load. Contrary to our study, all previous studies showing an increase in the HCV viral load during HAART involved only PI-based regimens. One study showed a drug-specific differential response with longer HCV-RNA flare-ups in patients receiving nelfinavir-based HAART than in patients receiving lopinavir-based HAART [5]. Our study also suggests that HCV viral load kinetics could differ according to the HAART-containing regimen.

In agreement with previous studies, we found that the HCV viral load was higher in patients with HCV genotypes 1 or 4 than in patients with genotypes 2, 3 or 5 [7]. In contrast to reports in HCV-mono-infected patients but in keeping with those in HIV/HCV-co-infected patients, we found no association between the HCV viral load and the degree of liver activity or fibrosis and cirrhosis [8,9].

Finally, the comparison of the different HCV viral load assays showed clearly a high correlation between them but also a significant difference in viral titres [10]. This difference could be of importance as in clinical practice, a single-value cutoff (800 000 IU/ml) is often used to define the difference between low and high virus titres. As we did not use a dichotomous variable defined as above or below a cutoff, but rather a continuous variable, similar results would be expected if other quantitative HCV assays were used in this analysis.

In conclusion, these findings may have implications for anti-HCV therapy, as higher HCV-RNA levels are associated with poorer responses. Longitudinal studies are needed to determine why antiretroviral therapy without PI is associated with a lower HCV viral load than both PI-based antiretroviral therapy and no antiretroviral therapy.

Acknowledgements

The authors would like to thank David Young for editing the manuscript.

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Sponsorship: Agence Nationale de Recherche sur le SIDA and SIDACTION.

Received: 10 February 2007; revised: 11 April 2007; accepted: 18 April 2007.

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IV-3- L'infection par le VIH augmente le risque d'évolution vers la cirrhose et l'hépatocarcinome et raccourcit le délai d'évolution vers la cirrhose

Alors que le délai moyen d'évolution vers la cirrhose est de 30 ans chez les patients mono-infectés par le VHC, il est estimé à 15 ans chez les patients co-infectés [5, 6, 7]. Dix à 15 ans après la contamination VHC, 15% à 25% des patients co-infectés VIH-VHC versus 2,6% à 6,5% des patients mono-infectés VHC risquent de développer une cirrhose [8, 16, 17].

Dans une étude prospective portant sur 233 hémophiles VHC+ avant l'ère des traitements antirétroviraux hautement actifs, une insuffisance hépatocellulaire était survenue chez 9% des patients coinfectés par le VIH (vs 0% chez les patients VIH-, p=0,034) dans les 10 à 20 ans suivant la contamination par le VHC [18]. L'incidence (cumulée) de l'insuffisance hépatocellulaire était de 17±4%, 10 ans après la contamination VIH. Dans une autre étude portant sur 4865 hémophiles VHC+, toujours avant l'ère des traitements antirétroviraux hautement actifs, le risque cumulé de mortalité liée à une insuffisance hépatocellulaire ou à un hépatocarcinome était de 1,4% à tout âge, de 0,1%, 2,2% et 14,3% respectivement pour les patients infectés avant 25 ans, 25-44 ans et 45 ans et plus. Chez les patients coinfectés par le VIH, ce risque s'élevait à 6,5% à tout âge, à 3,8%, 17,1% et à 18,7% respectivement pour les mêmes tranches d'âge [19]. Le risque de morbidité et de mortalité lié au VHC survenait 10 ans après la contamination.

Enfin, l'hépatocarcinome dont l'incidence est multipliée par plus de 5 en cas de co-infection VIH, survient à un âge plus jeune et après une durée plus courte de l'infection par le VHC [3, 20]. Ainsi dans une étude cas-contrôle, l'âge moyen et la

durée de l'infection par le VHC des patients co-infectés était respectivement de 42 et 18 ans versus 69 et 28 ans dans le groupe mono-infecté par le VHC [21].

Enfin,une méta-analyse portant sur l'ensemble des études ayant analysé l'influence du VIH sur l'évolution de l'hépatite chronique C retrouve un risque de développer une cirrhose multiplié par 2 (IC_{95} ; 1,4-3,07) et de décompensatoin hépatique multiplié par 6,14 (IC_{95} 2,86- 13,2) [22].

IV-4- Facteurs de risque d'aggravation de la fibrose

De nombreuses études ont cherché à identifier les déterminants de la progression de la fibrose chez les patients co-infectés. Il est maintenant clairement démontré que cette évolution n'est pas linéaire et qu'une cirrhose peut apparaître en quelques mois [23, 24]. Cette évolution vers la cirrhose peut-être très rapide et les déterminants de cette évolution péjorative ne sont pas bien connus et donc non maîtrisés [23]. Ainsi dans une étude réalisée chez 174 patients ayant eu deux biopsies hépatiques (délai médian entre les deux biopsies 2,9 ans), une progression de 2 points du score Ishak de fibrose était observée dans 24 % cas. Parmi les patients ayant une fibrose minime (F0-F1) à leur première biopsie, 22% avaient une progression de 2 points. Aucun facteur de risque n'était identifié, notamment quant au traitement antirétroviral (oui/non) mais 82% des patients étaient traités, sa durée et sa nature (traitement par didanosine), au nadir des CD4 en dehors d'un taux d'ALAT plus élevé [25].

Distribution du score de fibrose à la première et seconde biopsies hépatiques

Biopsie hépatique	F0	F1	F2	F3-F4	F5-F6
1ère	49%	29%	10%	12%	----
2nd	39%	29%	18%	10%	4%

Avant l'ère des HAART, 3 facteurs étaient identifiés : un taux de CD4 < 200/mm^3, l'âge et la consommation d'alcool [26]. Depuis l'ère des HAART, le rôle protecteur ou délétère du traitement anti-rétroviral est débattu. Certaines études ont démontré un bénéfice du traitement anti-rétroviral incluant notamment des IP [27, 28]. Dans une étude française ayant inclut 116 patients, le délai avant la mise sous traitement antirétroviral était significativement plus prolongé chez les patients ayant un score Metavir F3F4 comparé aux patients avec un score de fibrose plus bas (16 versus 13 ans, p=0.01) [28]. Dans une autre étude portant sur 285 patients [81% de patients hémophiles; 1er groupe (n= 93) traités par HAART après 1995; 2nd groupe traités par INTI après 1992 (n= 55); et 3ème groupe non traités pour le VIH (n=137)] suivis régulièrement entre 1990-2002, la mortalité hépatique était respectivement de 0.45, 0.69, et 1.70 pour 100 personnes-années. Le traitement par HAART (OR 0.106 - $IC_{95\%}$ 0.020-0.564]), le traitement antiretroviral (OR 0.283 $IC_{95\%}$ 0.103-0.780), le taux des lymphocytes CD4 (OR 0.746 $IC_{95\%}$ 0.641-0.868] par 50 CD4/mm^3) et l'âge (OR 1.065 $IC_{95\%}$1.027-1.105 par année) étaient des facteurs indépendants de survie [29]. En revanche, dans une étude portant sur 914 patients co-infectés VIH-VHC de la cohorte EUROSIDA avec des ALT élevées et ayant eu une biopsie hépatique entre 1992 et 2002, le traitement antirétroviral n'était pas associé à un score de fibrose

plus ou moins sévère [30]. Le score METAVIR était F0, F1, F2, F3 et F4 dans respectivement dans 10%, 33%, 22%, 22%, et 13% des cas. Les facteurs de risque associés à un score METAVIR F3 ou F4 en analyse multivariée étaient un âge >35 ans [OR, 2.95; IC_{95}, 2.08-4.18], la consommation d'alcool >50 g/jour [OR, 1.61; IC_{95}, 1.1-2.35], et un taux des CD4+ <500 /mm^3 [OR, 1.43; IC_{95}, 1.03-1.98]. L'absence de contrôle de la réplication virale VIH a également été associée à une progression plus rapide de la fibrose. Dans une étude portant sur 656 patients, la progression de la fibrose était comparable chez les patients mono-infectés par le VHC (n=382) et les patients co-infectés VIH/VHC traités avec une charge virale VIH< 400 copies/ml (51.2% des patients) (0.136 vs. 0.128 Ishak unité de fibrose/an, P=0.29). En revanche, la progression de la fibrose était plus rapide chez les patients ayant une charge virale VIH > 400 copies/ml (0.151) comparé aux patients mono-infectés VHC (0.128, p=0.015) et aux patients co-infectés VIH/VHC avec une charge virale VIH indétectable (0.122, p=0.013). La charge virale VIH, le score de l'inflammation hépatique et l'âge étaient corrélés à la progression de la fibrose [31].

IV-5- Hépatotoxicité du traitement antirétroviral

L'incidence de l'hépatotoxicité des traitements antirétroviraux est en moyenne de 10 à 15% [9]. Elle est de grade 3-4 dans 5 à 10% des cas. Elle augmente avec la durée de traitement et en cas de co-infection VHC ou VHB. Elle est plus élevée en cas de trithérapie incluant un inhibiteur de protéase (IP) et/ou INNTI comparée aux bithérapies INTI [32]. Ainsi dans la cohorte Aquitaine, l'incidence moyenne de cytolyse hépatique grave était de 3% à 6 mois, 4,8% à 1 an et 12,7% à 2 ans en cas

de bithérapie de INTI (n=1249) et de 5,5% à 6 mois, 8% à 1 an et 13,2% à 2 ans en cas de trithérapie incluant un IP (n=748). Le délai médian de survenue d'une cytolyse hépatique grave était de 252 jours en cas de bithérapie de INTI et de 164 jours en cas de trithérapie incluant un IP. En analyse multivariée, les facteurs de risque indépendants de cytolyse hépatique étaient un antécédent de cytolyse hépatique et la coinfection VHB et/ou VHC (risque multiplié par plus de 3). Le risque de cytolyse hépatique était indépendant de l'IP et /ou des INTI, de la charge virale VIH et des lymphocytes CD4. Chez les patients ayant des ALAT initiales normales, les seuls facteurs de risque indépendants étaient la coinfection VHB et/ou VHC [32].

IV-5-a-Mécanismes de l'hépatotoxicité du traitement antirétroviral

Les mécanismes de l'hépatoxicité observés sous traitement antiretroviral sont partiellement connus et probablement multifactoriels. Le rôle de la restauration immunitaire sous traitement antirétroviral hautement actif est très probable dans les cas de cytolyse hépatique accompagnant une séroconversion VHC. Ainsi, dans une cohorte australienne de 133 patients répondeurs à un traitement antiviral incluant un IP, 3 patients (2%) ont présenté une cytolyse hépatique symptomatique (ALAT > 5 N). Ces 3 patients avaient une coinfection VIH-VHC mais chez 2 patients, la séroconversion VHC est survenue après la restauration immunitaire, alors que l'ARN-VHC était présent sur l'analyse rétrospective des sérums avant l'initiation du traitement antiviral [33]. La restauration immunitaire peut être également très rarement à l'origine d'une négativation de l'ARN-VHC qui est alors associée à une augmentation des lymphocytes CD8 et à une cytolyse hépatique [34]. En revanche, le rôle de la restauration immunitaire dans les autres cas de cytolyse hépatique et/ou

d'aggravation histologique reste débattu [13]. Une corrélation entre le niveau d'augmentation des lymphocytes CD4 et le risque de cytolyse hépatique n'a pas été observée [13]. En revanche, des paramètres immunitaires autres que l'augmentation des lymphocytes CD4, en particulier les réponses immunitaires spécifiques du VHC pourraient être impliqués. Ainsi une augmentation des lymphocytes CD8 et des marqueurs de la réponse immunitaire spécifique anti-VHC, comme le CD26 soluble, marqueur de l'activité immunitaire T dans les processus inflammatoires hépatiques et l'augmentation des IgG anti-core du VHC a été observée chez les patients développant une cytolyse hépatique sous traitement antirétroviral hautement actif [35].

Tous les antirétroviraux ont potentiellement une toxicité hépatique mais la contribution de chacun est souvent difficile à déterminer. Les INTI induisent une toxicité mitochondriale en inhibant l'ADN polymérase γ, enzyme responsable de la réplication de l'ADN mitochondrial. La déplétion de l'ADN mitochondrial hépatique peut se manifester par une stéatose microvesiculaire, une acidose lactique et dans certains cas par une insuffisance hépato-cellulaire [36]. Le gradient in vitro de la toxicité mitochondriale des INTI déterminé par évaluation de la déplétion de l'ADN mitochondrial est le suivant : zalcitabine > didanosine > stavudine > zidovudine > lamivudine = abacavir [37]. Le rôle de la didanosine a été mis en évidence comme facteur de risque de décompensation hépatique ou d'aggravation histologique au cours du traitement anti-VHC (cf ci dessous). Il vient également d'être mis en évidence comme facteur de risque d'évolution cirrhotique chez des patients mono-infectés VIH [38]. Ainsi dans une étude ayant répertorié dans une cohorte de 3200 patients VIH+, tous les cas de cirrhose cryptogénétique (absence de co-infection VHB ou VHC, de consommation d'alcool...) ont été analysés. Dix patients avaient un

score de fibrose F3-F4 et 9 patients ont développé une insuffisance hépato-cellulaire (ascite, thrombose porte, hémorragie digestive et encéphalopathie). Dans cette étude cas-témoins, l'exposition prolongée à la didanosine était le seul facteur de risque identifié [38].

Les mécanismes de l'hépatotoxicité des IP, en dehors de celle secondaire à des concentrations plasmatiques élevées, ne sont pas connus [9]. Un rôle bénéfique des IP comparé aux bithérapies d'INTI, sur le score inflammatoire et de fibrose a été suggéré [27]. Ces résultats n'ont pas été confirmés dans d'autres essais et pourraient s'expliquer par un biais de sélection [39].

Deux mécanismes sont impliqués dans l'hépatotoxicité des INNTI : 1- une réaction d'hypersensibilité qui se manifeste le plus souvent plusieurs jours à plusieurs semaines après le début du traitement et qui touche également d'autres organes comme la peau et; 2- une toxicité intrinsèque directe limitée au foie et dont l'incidence augmente avec la durée du traitement et en cas de co-infection VHB ou VHC [40]. L'hépatotoxicité à court terme de la névirapine peut être sévère avec des cas d'hépatite fulminante. La toxicité à long terme de la névirapine et de l'efavirenz sont comparables [41]. Dans une étude transversale comparant chez 152 patients l'impact des IP versus des INNTI sur la fibrose, un traitement antirétroviral à base de névirapine était associé à un score de fibrose supérieur à 3 (OR, 2.56; 95% CI, 1.02-6.58). Le risque de progression de la fibrose > 0.2 unités/année était plus élevé sous névirapine (AOR, 3.82; 95% CI, 1.9-7.6) et était diminué sous IP (AOR, 0.39; 95% CI, 0.2-0.8) [42]. Il est à noter que dans ces études le rôle des INTI associés n'est pas analysé et que la névirapine était très souvent donnée en association avec la combinaison stavudine-didanosine.

En cas de cirrhose, les concentrations sériques des INNTI augmentent alors que celles des IP ne semblent pas modifiées. Ainsi, dans une étude portant sur 268 patients co-infectés VIH/VHC indemnes de cirrhose décompensée (35 patients traités par névirapine, 46 par éfavirenz, 56 par lopinavir, 58 par atazanavir et 73 par atazanavir boosté), les concentrations médianes plasmatiques de l'efavirenz et de la névirapine étaient chez les patients porteurs d'une cirrhose comparée aux patients indemnes de cirrhose de 3.4 vs. 1.9 micro g/mL (p<.01) et de 6.6 vs. 5.8 micro g/mL (p=0.33) respectivement [43]. Une concentration supérieure au seuil de toxicité de l'efavirenz (>4 micro g/mL) était plus fréquente en cas de cirrhose (31% vs. 3%; P<.001). Pour la névirapine, la même tendance se dégageait : 50% des patients porteurs d'une cirrhose avaient une concentration >8 micro g/mL versus 27% chez les autres patients (P=.27). En revanche, les concentrations des IP ne différaient selon la présence ou non d'une cirrhose

IV-6- Rôle de la stéatose hépatique

Chez les patients mono-infectés par le VHC, la stéatose hépatique est associée à des facteurs liés à l'hôte (obésité, diabète, hyperlipidémie et consommation d'alcool), à des facteurs viraux comme le génotype 3 et à la fibrose [44-48]. Sa prévalence varie entre 30% et 70% selon les études [44, 46, 49]. Chez les patients monoinfectés par le VIH, la stéatose hépatique peut être une complication du traitement antirétroviral, notamment des INTI et des IP [50-52]. La prévalence et la sévérité de la stéatose et les possibles interactions entre la stéatose et les facteurs liés à l'hôte, aux virus VIH et VHC et au traitement antirétroviral ont été analysés dans l'essai

RIBAVIC [53]. L'influence des différentes variables cliniques et biologiques a été évaluée en analyse univariée et multivariée chez 395 patients. La stéatose était présente chez 241 patients (61%); 149 (38%) patients avaient une stéatose grade 1 (<30%), 64 (16%) une stéatose grade 2 (30%-70%) et 28 (7%) une stéatose grade 3 (> 70% hépatocytes). En analyse multivariée, cinq facteurs de risque indépendants étaient associés à la stéatose : le génotype 3 (OR 2.59 95% CI 1.68- 3.97) (p< 0.0001), le score METAVIR de fibrose (OR 1.39 95% CI 1.10- 1.75) (p= 0.0053), le body mass index (OR 1.16 95% CI 1.09- 1.25) (p= 0.0013), la charge virale VHC (OR 1.59 95% CI 1.19- 2.11) (p=0.0012) et la ferritine (OR 1.13 95% CI 1.06- 1.21) (p< 0.0003). Le génotype 3 étant un facteur de risque de stéatose, une analyse stratifiée sur le génotype 1 et 3 a été réalisée. Les facteurs de risque indépendants associés à la stéatose étaient le BMI (OR 1.17 95% CI 1.03- 1.32; p=0.015) et la charge virale (OR 2.81 95% CI 1.73- 4.57; p< 0.0001) chez les patients infectés par le génotype 3, et le score METAVIR de fibrose (OR 1.92 95% CI 1.31- 2.81; p=0.0009), le BMI (OR 1.15 95% CI 1.03- 1.29; p = 0.015) et la ferritine (OR 1.15 95% CI 1.06- 1.26; p = 0.0011) chez les patients infectés par le génotype 1. Dans cette étude, la prévalence de la stéatose était similaire à celle observée dans la population mono-infectée VHC et les facteurs de risque identifiés ne différaient pas de ceux décrits chez les patients mono-infectés par le VHC. Elle était associée au génotype 3 et était corrélée à la charge virale VHC chez ces patients. Chez les patients infectés par le génotype 1, la stéatose était associée à une fibrose sévère. Le BMI était un facteur de risque, tout génotype confondu. Les caractéristiques liées à l'infection par le VIH, notamment le traitement antirétroviral ne semblaient pas influencer la stéatose. Nos résultats sont en accord avec d'autres études n'ayant pas retrouvé d'association entre la stéatose et le traitement antirétroviral [54, 55]. Seule une étude a mis en évidence une

association entre le risque de stéatose et un traitement par stavudine [56]. Bien que 42% des nos patients étaient traités par stavudine pendant une durée moyenne de 5,5 ± 2,7 ans, aucun lien entre la stéatose et un traitement par un INTI particulier n'était retrouvé dans notre étude. Ainsi, l'étude des facteurs de risque de la stéatose hépatique chez les patients co-infectés VIH/VHC n'a pas permis d'identifier de facteurs propres à la co-infection pouvant contribuer à expliquer l'évolution plus fréquente et plus sévère vers la fibrose.

Hepatic steatosis in HIV–HCV coinfected patients: analysis of risk factors

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Objective: To evaluate the prevalence and severity of steatosis and possible interactions between steatosis, host factors, viral factors, and treatment for HIV infection in HIV–hepatitis C virus (HCV) coinfected patients.

Methods: Steatosis was assessed among 395 HIV–HCV coinfected patients who were enrolled in the ANRS trial HC02 Ribavic and for whom histological data were available. Steatosis was graded as follows: 0 (none); 1 (< 30% hepatocytes containing fat); 2 (30–70%); 3 (> 70%).

Results: Steatosis was present in 241 patients (61%), of whom 149 (38%) had grade 1, 64 (16%) grade 2 and 28 (7%) grade 3. In multivariate analysis, the following five independent risk factors were associated with steatosis: HCV genotype 3 [odds ratio (OR), 3.02; 95% confidence interval (CI), 1.91–4.79; $P < 0.0001$], the mean METAVIR fibrosis score (OR, 1.43; 95% CI, 1.11–1.84; $P = 0.0053$), the body mass index (BMI; OR, 1.13; 95% CI, 1.05–1.21; $P = 0.0013$), HCV viral load (OR. 1.65; 95% CI, 1.22–2.23; $P = 0.0012$) and ferritin (OR, 1.13; 95% CI, 1.06–1.21; $P < 0.0003$). As HCV genotype 3 was a risk factor for steatosis, further exploratory analyses were stratified according to the HCV genotype (1 and 3). Factors independently associated with steatosis were BMI and HCV viral load in patients with HCV genotype 3 infection and the mean METAVIR fibrosis score, the BMI and ferritin in patients with HCV genotype 1 infection.

Conclusion: Steatosis is particularly frequent in HIV–HCV coinfected patients, who appear to have the same risk factors for steatosis as HCV monoinfected patients. None of the characteristics of HIV infection, including antiretroviral therapy, was independently associated with steatosis.

AIDS 2006, **20**:525–531

Keywords: genotype 3, fibrosis, HCV viral load, body mass index, antiretroviral therapy

Introduction

Hepatic steatosis, i.e., the accumulation of lipids (mainly triglycerides) in the hepatocyte cytoplasm, is a frequent histological finding during chronic hepatitis C virus (HCV) infection [1–3]. The prevalence in HCV monoinfected patients is between 30 and 70% [1–4]. Steatosis is associated with host factors (overweight, diabetes, hyperlipidaemia and excess alcohol intake), viral factors such as HCV genotype 3 and fibrosis [2,4–6]. In

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Received: 28 July 2005; revised: 14 November 2005; accepted: 6 December 2005.

ISSN 0269-9370 © 2006 Lippincott Williams & Wilkins

HIV monoinfected patients, hepatic steatosis is a recognized complication of nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) therapy [7–9]. Consequently, there may be significant interplay among factors influencing steatosis in HIV–HCV coinfected patients. As steatosis accelerates fibrosis, we examined the prevalence and severity of steatosis, and the possible interactions among steatosis, host factors, viral factors, and HIV treatment in a large population of HIV–HCV coinfected patients.

Methods

This study involved 395 HIV–HCV coinfected patients who were enrolled in the ANRS trial HC02 Ribavic and for whom histological data were available. The results of this trial have been reported in detail elsewhere [10]. Briefly, 412 HIV–HCV coinfected patients who had never received interferon or ribavirin were randomly assigned to receive either weekly subcutaneous injections of 1.5 μg/kg peginterferon alfa-2b (ViraferonPeg®, Schering-Plough, Kenilworth, New Jersey, USA) plus daily ribavirin (Rebetol®, Schering-Plough) (800 mg), or thrice-weekly subcutaneous injections of 3 MU of interferon alfa-2b plus daily ribavirin (Rebetol®, Schering-Plough) (800 mg) for 48 weeks. Patients were eligible for the trial if they had detectable serum HCV RNA, interpretable results of liver biopsy performed within the previous 18 months and showing at least mild activity or fibrosis, a CD4 cell count $> 200/\mu m$, stable HIV RNA load ($< 1 \log_{10}$ variation in the previous 3 months) at randomization, and stable or no antiretroviral treatment during the previous 3 months. The main ineligibility criteria were active narcotic consumption and/or self-reported daily alcohol intake exceeding 40 g (women) or 50 g (men) within 3 months before entry to the study; decompensated cirrhosis; and positive HBs antigenaemia.

Biochemical and haematological tests were done in local laboratories. HCV RNA tests, viral genotyping and pathological evaluation of biopsy specimens were performed in central laboratories.

HCV RNA was detected with a PCR assay (Amplicor 2.0 HCV Monitor; Roche Diagnostics Systems, Basel, Switzerland) with a detection limit of 50 IU (100 copies)/ml. HCV RNA levels were measured with a branched-chain DNA assay (bDNA3.0; Bayer Diagnostics, Tarrytown, New York, USA) with a detection limit of 615 IU (3200 copies)/ml. HCV genotyping was performed by sequence analysis of the 5′ untranslated region.

Two experienced pathologists blinded to the clinical and laboratory findings assessed all biopsies on standard stained sections. The mean delay between liver biopsy and entry to the study was 7.15 ± 7.08 months. Steatosis was graded as follows: 0 (none); 1 (< 30% hepatocytes containing fat); 2 (30–70%); 3 (> 70%). Hepatic necroinflammation and fibrosis were graded with the METAVIR scoring system (scores ranging from 0 to 3 for necroinflammatory activity, and 0 to 4 for fibrosis) [11].

The following data were collected at enrolment: age, sex, birth place (France, North Africa, Sub-Saharan Africa, Asia, other), body mass index (BMI), antiretroviral drugs, duration of HIV and HCV infection (defined as the date of first transfusion or the date of first intravenous drug use), the METAVIR scores, biochemical test results, liver enzyme activities, transferrin saturation, serum ferritin, fasting blood glucose, CD4 lymphocyte counts, plasma HIV RNA load and plasma HCV RNA load. Diabetes and lipodystrophy were collected in the history of the patients reported by the physician at inclusion.

The Cochran–Armitage test for trends was used to identify links between steatosis and qualitative variables, and Spearman's rank correlation test was used to test for associations with quantitative variables. Other comparisons used the Chi-squared test for qualitative variables and the Mann–Whitney test for quantitative variables. A proportional-odds cumulative logistic regression model was constructed with steatosis as the response variable, in three ordered levels. Explanatory variables with $P < 0.20$ in univariate analysis were included in the multivariate models and selected by using a stepwise procedure. All statistical tests were two-sided, with a type I error of 5%.

Results

The mean size of liver biopsy was 18.1 mm (± 8.1). Steatosis was present in 241 (61%) of the 395 HIV–HCV coinfected patients, of whom 149 (38%) had grade 1, 64 (16%) grade 2, and 28 (7%) grade 3. In view of the relatively small number of patients with grade 2 and 3 steatosis, these patients' data were pooled for statistical analysis.

Most patients were male (73.4%), white (75.7%) and the mean age was 39.7 (± 5.4) years. Intravenous drug use was the risk factor for HCV transmission in 80% of cases. The mean BMI was 22.3 ± 2.9 kg/m^2. Five patients were obese (BMI > 30 kg/m^2). The distribution of HCV genotypes was as follows: genotype 1, 190 cases (48.1%); genotype 2, 12 cases (3%); genotype 3, 138 cases (34.9%); genotype 4, 51 cases (12.9%). In total, 297 patients (75%) were receiving antiretroviral therapy at the time of liver biopsy.

Factors associated with grade of steatosis

Demographic and laboratory data are summarized in Table 1 and Table 2 according to grade of steatosis. In univariate analysis, patients with grade 1 or grade 2/3 steatosis were significantly older (39.8 ± 5.4 and

Table 1. Demographic characteristics and laboratory and histological findings of 395 HIV–HCV coinfected patients according to grade of steatosis.

	0	1	2/3	P^a
n	154	149	92	
Age [mean years (SD)]	39.0 (5.3)	39.8 (5.4)	40.6 (5.7)	0.03
Men [n (%)]	109 (71)	112 (75)	69 (75)	0.42
Birth place France [n (%)]	111 (72.1)	115 (77.2)	73 (79.3)	0.17
Body mass index	21.6 (2.8)	22.3 (2.8)	23.5 (3.1)	< 0.0001
Diabetes	3 (2)	4 (2.7)	5 (5.4)	0.14
HIV infection				
Duration of HIV infection in years [mean (SD)]	11.0 (4.7)	10.5 (4.2)	9.8 (4.1)	0.007
AIDS [n (%)]	34 (22)	18 (12)	14 (15)	0.09
Lipodystrophy syndrome [n (%)]	19 (12)	24 (16)	19 (21)	0.08
CD4 cell count (/μl) [mean (SD)]	516 (233)	501 (209)	529 (253)	0.63
Plasma HIV1 RNA				
< 400 copies /ml [n (%)]	102 (66)	93 (62)	66 (72)	0.49
[mean (SD)] $\log_{10}$	3.8 (0.8)	3.7 (0.7)	3.5 (0.6)	0.17
No antiretroviral therapy [n (%)]	48 (31)	35 (23)	15 (16)	0.008
Duration of antiretroviral therapy in years [mean (SD)][a]	3.9 (3.5)	4.3 (3.4)	4.2 (3.3)	0.49
Component drugs in antiretroviral regimens[b]				
PI [n (%)]	48 (31)	46 (31)	38 (41)	0.14
NNRTI [n (%)]	44 (29)	36 (24)	18 (20)	0.11
NRTI [n (%)]	105 (68)	111 (75)	75 (82)	0.0206
HCV infection				
Duration of HCV infection in years [mean (SD)]	15.3 (6.1)	15.3 (6.5)	15.9 (6.3)	0.63
Risk group for HCV infection				
Intravenous drug use [n (%)]	122 (79)	119 (80)	75 (82)	0.67
Fibrosis score [mean (SD)]	1.8 (0.8)	2.2 (0.8)	2.1 (0.9)	0.004
Inflammation score [mean (SD)]	1.3 (0.5)	1.4 (0.5)	1.4 (0.5)	0.17
Many septa (F3), cirrhosis (F4) [n (%)]	31 (20)	50 (34)	28 (30)	0.04
HCV genotype 3 [n (%)][c]	35 (23)	57 (38)	46 (51)	< 0.0001
Serum HCV RNA ($\log_{10}$ IU/ml) [mean (SD)]	5.8 (0.8)	5.8 (0.7)	6.1 (0.6)	0.006
ALT (X normal upper limit) [mean (SD)]	1.9 (1.6)	2.6 (2.2)	2.2 (1.4)	0.0024
AST (X normal upper limit) [mean (SD)]	1.7 (1.2)	2.4 (1.7)	2.0 (1.2)	0.0002
GGT (X normal upper limit) [mean (SD)]	2.7 (3.0)	3.1 (2.6)	3.1 (3.2)	0.15
Alk Ph (X normal upper limit) [mean (SD)]	0.7 (0.3)	0.8 (0.4)	0.8 (0.4)	0.79
Transferrin saturation (%) [mean (SD)]	37.5 (20.6)	35.8 (16.7)	34.0 (16.2)	0.51
Ferritin (mg/l) [mean (SD)]	207 (210)	314 (317)	436 (711)	0.0001
Blood fasting glucose	5.07 (0.83)	5.08 (1.04)	5.54 (2.82)	0.15

[a]Cochran–Armitage test for trend for qualitative variables or Spearman's rank correlation test for quantitative variables.
[b]Equal to zero in 98 (25%) patients not receiving antiretroviral therapy before or at the time of liver biopsy.
[c]Genotype was unavailable for two patients.PI, Protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; HCV, hepatitis C virus; ALT, alanine aminotransferase, AST, aspartate aminotransferase; GGT, gammaglutamyl transferase, Alk Ph, alkaline phosphatase.

40.6 ± 5.7 years, respectively) than patients with no steatosis (39.0 ± 5.3 years; $P = 0.03$). A highly significant positive correlation ($P < 0.0001$) was found between the BMI and the grade of steatosis. The mean BMI ($\pm$ SD) of patients with no steatosis was 21 ± 2.8 kg/m^2, compared to 22.3 ± 2.8 kg/m^2 and 23.5 ± 3.1 kg/m^2, respectively, in patients with grade 1 and grade 2/3 steatosis. Only 12 patients had diabetes, and the possible impact of this factor on steatosis could not therefore be evaluated. Four diabetic patients had grade 1 steatosis and five had grade 2/3 steatosis. No correlation was found between steatosis and sex or ethnicity.

Table 2. Factors associated with steatosis in multivariate logistic regression analysis.

	Odds ratio	95% CI	*P*
HCV genotype 3	3.02	1.91–4.79	< 0.0001
Body mass index (per unit increase)	1.13	1.05–1.21	0.0013
Mean METAVIR fibrosis score	1.43	1.11–1.84	0.0053
HCV viral load (per $\log_{10}$ increase)	1.65	1.22–2.23	0.0012
Ferritin (per 100 mg/l increase	1.13	1.06–1.21	0.0003

CI, Confidence interval.

The mean duration of HIV infection was significantly shorter (9.8 ± 4.1 years) among patients with grade 2/3 steatosis than in patients with grade 1 steatosis (10.5 ± 4.2 years) and patients without steatosis (11.0 ± 4.7 years) ($P = 0.007$). In total, 297 patients (75%) were receiving antiretroviral therapy before or at the time of liver biopsy. Patients with steatosis grade 2/3 were more likely to be receiving antiretroviral therapy than were patients with grade 1 steatosis (84% versus 77%) and patients without steatosis (69%) ($P = 0.008$). NRTI-based treatment was more frequent among patients with steatosis grade 2/3 than among patients with grade 1 or grade 0 steatosis (82%, 75% and 68%, respectively; $P = 0.02$). No

particular NRTI was associated with steatosis. No correlation was observed between steatosis and AIDS status, the CD4 cell count, HIV viral load, or PI or non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimens. Lipodystrophy was present in 15.7% overall, i.e., 21% in patients with grade 2/3 steatosis, 15% in patients with grade 1 steatosis, and 11% in patients with no steatosis ($P = 0.08$).

Steatosis was more prevalent in patients with genotype 3 infection than in patients infected by other genotypes (genotype 3, 74.6%; genotype 1, 51.6%, genotype 2, 41.6%; genotype 4, 64.7%) and was also significantly more severe in patients with genotype 3 infection ($P < 0.001$). Higher HCV viral load was also correlated with the severity of steatosis ($r = 0.14$; $P < 0.006$).

The severity of steatosis was significantly associated with the severity of fibrosis (r, 0.14; $P = 0.004$): the mean METAVIR fibrosis score was 2.1 ± 0.9, 2.2 ± 0.8 and 1.8 ± 0.8, in patients with grade 2/3 steatosis, patients with grade 1 steatosis, and patients without steatosis, respectively. Severe liver fibrosis (METAVIR score F3 or F4) was also more frequent in patients with grade 2/3 steatosis and patients with grade 1 steatosis (30% and 34%, respectively) than in patients without steatosis (20%; $P = 0.04$). The grade of steatosis correlated with serum levels of alanine aminotransferase (r, 0.15; $P = 0.0024$), aspartate aminotransferase (r, 0.18; $P = 0.0002$) and ferritin (r, 0.2; $P = 0.0001$). In particular, patients with steatosis grade 2/3 had higher ferritin levels (436 ± 711 mg/l) than patients with grade 1 steatosis (314 ± 317 mg/l) and patients without steatosis (207 ± 210 mg/l) while transferrin saturation was not associated with steatosis. No correlation was observed between steatosis and the duration of HCV infection, the risk group for HCV infection, the METAVIR necroinflammation score, the serum level of gamma glutamyl transferase, alkaline phosphatase or the fasting blood glucose.

Multivariate analysis identified five independent risk factors associated with steatosis, namely HCV genotype 3 ($P < 0.0001$), the mean METAVIR fibrosis score ($P = 0.0053$), the BMI ($P = 0.0013$), HCV viral load ($P = 0.0012$) and ferritin ($P < 0.0003$). As HCV genotype 3 was a risk factor for steatosis, further exploratory analyses were stratified according to the HCV genotype (1 and 3). In patients with HCV genotype 3 infection, BMI [odds ratio (OR), 1.17; 95% confidence interval (CI), 1.03–1.32; $P = 0.015$] and HCV viral load (OR, 2.81; 95% CI, 1.73–4.57; $P < 0.0001$; Fig. 1) were independently associated with steatosis. In patients with HCV genotype 1 infection, the mean METAVIR fibrosis score (OR, 1.92; 95% CI, 1.31–2.81; $P = 0.0009$), BMI (OR, 1.15; 95% CI, 1.03–1.29; $P = 0.015$) and ferritin (OR, 1.15; 95% CI, 1.06–1.26; $P = 0.0011$) were independently associated with steatosis.

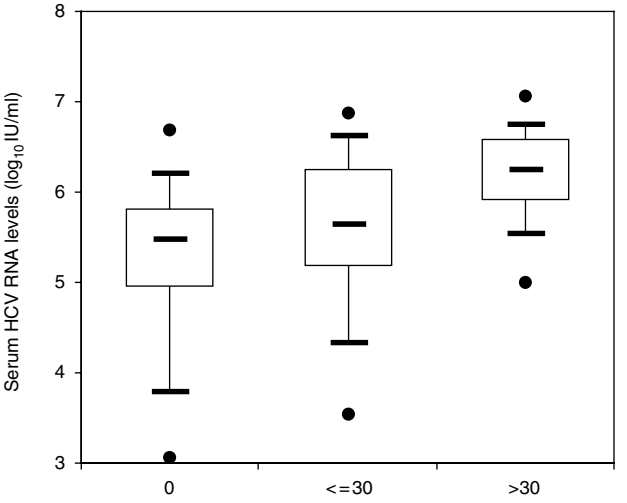

Fig. 1. Correlation between serum HCV RNA levels and steatosis grade in patients infected by HCV genotype 3. Grade of steatosis: 0 (none) to grade 1 (< 30% hepatocytes containing fat) and grade 2 and 3 (> 30% hepatocytes containing fat).

Discussion

To our knowledge, this is the largest study of steatosis in HIV infected patients with chronic hepatitis C. Steatosis was present in 241 (61%) of cases, a prevalence similar to that observed in HCV monoinfected patients (30–70%) [2,4,12,13].

In multivariate analysis, steatosis was associated with BMI, HCV genotype 3, HCV viral load, METAVIR fibrosis score and ferritin levels. The correlation between BMI and steatosis was not dependent on the HCV genotype in our dually infected patients, in agreement with another study in HIV–HCV coinfected patients [14], whereas this association is usually found only with genotype 1 in HCV monoinfected patients [2,5,15]. BMI also correlated with the duration of HIV infection (r, -0.18; $P = 0.0004$), explaining the counter intuitive and artefactual relationship between the duration of HIV infection and steatosis in univariate analysis. Steatosis usually occurs in patients with a BMI > 25 kg/m^2 and can be improved by weight loss [2,3,16]. In our study, the mean BMI of patients with grade 2 or 3 steatosis was higher than that of patients with grade 1 steatosis and patients without steatosis, but remained below the World Health Organization thresholds for overweight and obesity (≥ 25 and > 30 kg/m^2, respectively). In HCV monoinfected patients, visceral obesity rather than total fat mass seems to play an important role in the development of steatosis [2]. We did not measure visceral fat in our patients, but it is noteworthy that most were receiving antiretroviral therapy, which can cause lipodystrophy [17]. However, lipodystrophy did not correlate with

steatosis, but this may due to the low prevalence of lipodystrophy in our population.

Hepatic steatosis is a well established complication of some NRTI and PI treatment [7–9]. However, we found a correlation between steatosis and both antiretroviral therapy in general and NRTI-based treatment (but not PI-based treatment), but only in univariate analysis. In multivariate analysis, due to adjustment on the fibrosis score, antiretroviral therapy was not independently associated with steatosis ($P = 0.11$). The proportion of METAVIR scores F3 or F4 was 17% in patients not receiving antiretroviral therapy versus 31% in those receiving the antiretroviral therapy before or at the time of liver biopsy ($P = 0.009$). There are two not-mutually exclusive explanations for these observations: the reasons underlying antiretroviral therapy are also linked with fibrosis and steatosis; and the antiretroviral therapy is involved in a causal manner to a higher degree of fibrosis and steatosis. Although our cross-sectional design does not formally permit us to choose between these two explanations, we believe that the first explanation is more likely as the duration of antiretroviral therapy in treated patients (n = 297) was not associated with steatosis or fibrosis ($P = 0.16$ and $P = 0.27$, respectively), excluding a dose–response relationship and arguing against causality. Finally, our results are in line with those of others studies which failed to demonstrate a link between antiretroviral therapy and steatosis [14,18]. In contrast, Sulkowski *et al.* found that steatosis was associated with stavudine use [19]. Although 42% of patients of our study were treated with stavudine during a mean time of 5.5 ± 2.7 years, no particular NRTI was associated with steatosis.

As in HCV monoinfected patients, the prevalence of steatosis differed significantly according to the HCV genotype, i.e., patients with genotype 3 infection had a higher prevalence (74.6%) than patients infected by genotype 1 (41.6%). HCV viral load was also associated with the severity of steatosis. In HCV monoinfected patients, HCV viral load has only been linked to steatosis in patients infected by genotype 3 [2,6]. Our finding could be the result of the higher HCV viral loads observed in HIV–HCV coinfected patients and reinforce the link between the production of viral proteins, including the HCV capsid proteins and steatosis [20,21]. However, our multivariate analysis stratified according to the HCV genotype (1 and 3) also showed that steatosis correlated with HCV viral load in genotype 3 infected patients (OR, 2.85; 95% CI, 1.79–4.54; $P < 0.0001$) but not in genotype 1 infected patients. In HIV-seronegative patients infected by HCV genotype 3, steatosis frequently improves during successful anti-HCV therapy, suggesting a possible direct pro-steatotic role of this genotype [22]. We have previously shown, on the same patients, that steatosis significantly improves in patients infected by HCV genotype 3 who have a sustained virologic response to anti-HCV therapy (−13%, $P < 0.001$), but not in patients infected by HCV genotype 1 [10].

In HCV monoinfected patients, the onset and progression of steatosis are strong independent predictors of both the severity and the progression of fibrosis [2–5, 23–25]. In our study, the severity of steatosis was related to a higher hepatic fibrosis score, independently of the HCV genotype and of factors (e.g., age and CD4 cell count) that can influence the rate of HCV disease progression in HIV–HCV coinfected patients [14,26]. However, as in HCV monoinfected patients, in multivariate analysis stratified by genotype 1 and 3, steatosis was associated with fibrosis in genotype 1 infected patients (OR, 1.83; 95% CI, 1.29–2.60; $P = 0.0007$) but not in genotype 3 infected patients [4,6,15].

Increased ferritin levels in the presence of normal transferrin saturation have been reported in non-infected HIV patients with steatosis but usually did not reflect iron overload [27–29]. However, recent reports found that hyperferritinemia is an independent risk factor for faster liver progression in HCV monoinfected patients [25,28]. We showed too a correlation between steatosis and increased ferritin levels (OR, 1.13; 95% CI, 1.06–1.21; $P < 0.0003$) but in multivariate analysis stratified by genotype 1 and 3, this correlation persists only in genotype 1 infected patients (OR, 1.15; 95% CI, 1.06–1.26; $P = 0.0011$), suggesting a role for hyperferritinemia in fibrosis progression.

As the liver biopsies in this study were all performed to determine whether anti-HCV therapy was indicated, our findings may not be representative of the general HIV–HCV coinfected population. In HIV-seronegative populations, a synergistic interaction between steatosis and even low alcohol consumption is a major determinant of liver fibrosis severity [30]. Indeed, alcohol is believed to impair mitochondrial β-oxidation of fatty acids by causing oxidative damage to mitochondrial enzymes [31]. This risk factor was not evaluable as all our patients were requested to limit their daily alcohol consumption during the 3 months preceding enrolment. Additionally, several studies have shown that the frequency of steatosis varies significantly with ethnicity [32,33]. No such correlation was found in our study but this may be due to the fact that most of our patients were native of France. Our findings contrast with those of a study in HIV–HCV coinfected patients in which age was found to be the only independent factor associated with steatosis, whereas male sex, age, BMI, genotype 3a and histological fibrosis correlated to steatosis in HCV monoinfected patients [18]. In this study, the distribution of HCV genotypes was genotype 1 (80% versus 48% in our study) and genotype 3 (11% versus 35% in our study) and 33% of patients had no fibrosis (versus 0% in our study). Patients were also older (47 ± 7 versus 39.7 ± 5.4 years). These differences together with the number of patients

(92 versus 395 in our study) may explain the different findings.

Finally, it is noteworthy that steatosis quantification was performed on routinely stained biopsies. The staining allows an accurate estimation of macrovacuolar steatosis, the most common histopathological feature of HCV-induced steatosis, but might underestimate microvesicular steatosis, a histological pattern of steatosis often related to mitochondrial toxicity. Such assessment is only possible on frozen sections with special staining which were not available in this study.

In conclusion, this large study showed a high prevalence of steatosis in HIV–HCV coinfected patients. The same risk factors for steatosis were identified in these patients as in HCV monoinfected patients. Steatosis was associated with HCV genotype 3 and correlated with HCV viral load. In patients with genotype 1 infection steatosis was associated with more severe fibrosis but not with HCV viral load. The BMI was also an independent risk factor for steatosis in patients with both genotype 1 and genotype 3 infection. In contrast, steatosis was not related to characteristics of HIV infection, including antiretroviral therapy.

Acknowledgments

We thank David Young for editing the manuscript.

Supported by the Agence Nationale de Recherche sur le SIDA and SIDACTION.

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V- INSULINO-RESISTANCE ET CO-INFECTION VIH/VHC

Les patients co-infectés VIH/VHC semblent être à haut risque de développer une insulinorésistance voire un diabète. En effet, d'une part, les traitement antirétroviraux comme les INTI et les IP induisent une insulinorésistance. D'autre part, l'infection par le VHC constitue un facteur de risque d'insulinorésistance et de diabète [57].

L'incidence et les facteurs de risque de développer une insulinorésistance (HOMA Test > 3.8- glycémie à jeun x insulinémie à jeun/22.5) ont été étudiés dans une cohorte de 137 patients VIH+, naïfs de traitement antirétroviral, et traités pendant 48 semaines avec le même traitement antirétroviral [58]. Quinze patients avaient un HOMA test >3.8 à S48, soit une incidence de 13%. Les facteurs de risque indépendants de survenue d'une insulinorésistance étaient un traitement par indinavir (beta-coefficient 5.45, $IC_{95\%}$ 1.30-22.8; P=0.02), et une sérologie VHC positive (beta-coefficient 5.22, $IC_{95\%}$ 1.34-20.33; P=0.01).

Les patients infectés par le VHC ont une incidence du diabète plus élevée que les patients atteints d'une hépatopathie chronique non VHC. Ainsi dans une étude transversale portant sur 9841 patients, les patients VHC+ âgés de plus de 40 ans avaient un risque de diabète de type II multiplié par 3 comparé aux patients non infectés par le VHC alors qu'aucune différence n'était observé avec les patients ayant une infection chronique par le VHB [59]. Dans une cohorte prospective de 1084 patients non diabétiques à l'inclusion, 548 ont développé un diabète de type II au cours d'un suivi de plus 9 ans. La prévalence de l'infection par le VHC était de 0.8%. Dans le groupe de patients à haut risque de développer un diabète (âge et BMI élevés), ceux infectés par le VHC avaient un risque multiplié par 11 (RH, 11.58; $IC_{95\%}$ 1.39-96.6) de développer un diabète [60]. Le traitement anti-VHC

améliore la tolérance au glucose ou diminue la survenue d'une intolérance au glucose ou d'un diabète chez les patients ayant une réponse virologique soutenue [57, 61]. Ainsi dans une étude ayant inclus 525 patients VHC+ et traités par Peg-interféron et ribavirine, l'incidence d'une intolérance au glucose ou d'un diabète était multipliée par deux chez les non répondeurs comparée aux patients ayant une réponse virologique soutenue, même après ajustement sur l'âge, les antécédents familiaux de diabète et le sexe masculin [57]. Par ailleurs, il a été montré dans des modèles transgéniques que la protéine core du VHC est capable d'induire une insulino-résistance, une stéatose et un diabète de type 2. L'insulinorésistance augmente la lipolyse adipocytaire qui est à l'origine d'une augmentation du taux circulant des acides gras libres qui à son tour s'accompagne d'une augmentation de la masse grasse hépatique et d'une stéatose pouvant se compliquer de cirrhose voire de carcinome hépatocellulaire [57]. Ainsi l'insulinorésistance serait un facteur aggravant la progression de la fibrose. Dans une étude transversale portant sur 79 patients co-infectés VIH/VHC, l'insulinorésistance n'était pas associée à une progression de la fibrose [62]. En revanche. dans la cohorte Hepavih (130 patients co-infectésVIH/VHC), un Homa Test > 4 était retrouvé dans 26.9% des cas. Les patients ayant une insulinorésistance avaient un BMI plus élevé (p=0.0002) comparé aux autres patients et avaient un risque de fibrose sévère (étudié par le Fibroscan) multiplié par 4.2 ($IC_{95\%}$ 1.4-12.7, p=0.01) [63].

VI- METHODES D'EVALUATION DE LA FIBROSE

Plusieurs scores biochimiques associant des paramètres directs ou indirects de la fibrose ont été étudiés chez les patients co-infectés VIH/VHC. La validité de ces tests

a été évaluée dans l'essai RIBAVIC. Le Fibrotest, les scores APRI, Forns, Hepascore, SHASTA, le Fibromètre et Fib-4 ont été testés chez 272 patients inclus dans RIBAVIC et pour lesquels le bilan biologique de ces tests a pu être réalisé secondairement. Il est à noter que compte tenu des critères d'inclusion, aucun patient n'avait un score F0. La taille de la biopsie hépatique était en moyenne de 18.6 mm. Le score Metavir de fibrose était F1 dans 68 (25%) des cas, F2 dans 109 (40%) des cas, F3 dans 67 (25%) des cas et F4 dans 28 (10%) des cas. La performance diagnostique pour la détection d'une fibrose significative (score METAVIR ≥ F2) appréciée par l'aire sous la courbe Roc était de 0.64 pour le fibrotest (haptoglobine, bilirubine, Gamma GT, alpha 2 macroglobuline, Apo1, âge et sexe), de 0.69 pour l'Hepascore (bilirubine, Gamma GT, alpha 2 macroglobuline, acide hyaluronique, âge et sexe) et de 0.70 pour le fibromètre (plaquettes, temps de prothrombine, ASAT, alpha2-macroglobulin, acide hyaluronique, urée et âge). La performance diagnostique pour la détection d'un score METAVIR F3F4 était de 0.72, 0.76 et 0.78, respectivement. Les scores Fib-4 (âge, AST, ALT, plaquettes), APRI (ASAT /LSN= multiple de la limite de supérieure à la normale) x 100 plaquettes (10^9/l) et Forns (âge, plaquettes, Gamma GT, cholestérol) n'étaient pas applicables dans 37%, 53% et 61%, respectivement. Leur aire sous la courbe Roc pour la détection d'une fibrose significative (score METAVIR ≥ F2) était de 0.65, 0.65 et 0.59 respectivement. Le coefficient de corrélation de Spearman était de 0.484 pour le fibromètre, de 0.456 pour l'hépascore et de 0.372 pour le fibrotest. Le fibromètre avait un index de corrélation significativement supérieur aux autres scores ($p<0.05$) exceptés pour l'hepascore et le fibrotest. Le score des tests correspondait au score histologique (moins de 2 points de différence pour le score de fibrose) dans 71%

pour le fibromètre, 68% pour l'Hepascore, 62% pour le fibrotest, 43% pour le Fib-4, 33% pour le score Apri .et 22% pour le score Forns.

En conclusion, 3 scores, fibromètre, hépascore et fibrotest, étaient applicables chez l'ensemble des patients et avaient la meilleure corrélation avec le score histologique. Néanmoins, les performances de ces scores demeurent inférieures à celles observées chez les patients mono-infectés VHC (0.64-0.7 versus 0.82-0.91 pour la détection d'une fibrose significative (score METAVIR ≥ F2). Ces résultats peuvent s'expliquer d'une part par les caractéristiques de l'étude (absence de patients ayant un score F0 et 25% de patients avec un score F1) et d'autre part, par de nombreux facteurs de confusion liée à la co-infection VIH/VHC (thrombopénie secondaire au VIH et au VHC, augmentation des Gamma GT, médicamenteuse, alcoolique ou secondaire au VHC…, de la bilirubinémie liée au traitement antirétroviral…, de la cholestérolémie secondaire au traitement antirétroviral).

Le Fibroscan (l'élastométrie ultrasonore impulsionnelle) est une technique non invasive qui permet de mesurer quantitativement la dureté du foie qui est corrélée au degré de fibrose. Dans une étude réalisée sur 72 patients co-infectés VIH/VHC, l'aire sous la courbe Roc était de 0.72 pour la détection d'un score de fibrose ≥ 2 et de 0.97 pour un score F4 [64].

VII- REPONSE AU TRAITEMENT ANTI-VHC

L'association Peg-interféron et ribavirine est actuellement le traitement optimal de l'hépatite C chronique. Chez les patients mono-infectés par le VHC, elle permet d'obtenir une réponse virologique soutenue dans plus de 50 % des cas en cas de génotype 1 et dans plus de 80% des cas en cas de génotypes 2 ou 3 [65, 66]. Trois

grands essais ont évalué la réponse au traitement anti-VHC chez les patients co-infectés VIH-VHC, l'essai RIBAVIC HC02, l'essai APRICOT et l'essai ACTG A5071 [67-69]. Tous ont montré des résultats plus décevants de l'association Peg-interféron et ribavirine chez ces patients (au plus 40%), et ce indépendamment du niveau d'immunodépression (tableau 1) :

Tableau 1 : Principaux résultats de 3 grands essais évaluant l'association Peg-interferon chez les patients co-infectés VIH-VHC

	Ribavic- ANRS HC02	Apricot	ACTG 5071
Nombre de patients	412	868	133
Traitements de l'essai	PegIFNa2b+RBV Vs IFN a2b 3 MUIx3/semaine+RBV	PegIFN a2a+RBV vs Peginterferon a2a+placebo vs IFN a2a 3 MUIx3/semaine+RVB	PegIFN a2b+RBV vs IFNa2b 3 MUIx3/semaine+RBV
Doses d'IFN	1.5 μg/kg/semaine	180 μg/semaine	1 μg/kg/semaine
Posologie de la ribavirine	800 mg/j	800 mg/j	Dose progressive de 600 mg/j à 1000 mg/j
Cirrhose %	39 (Metavir F3 ou F4)	10	14
Plus de 80% de la durée prévue de traitement	57	61	88*
Réponse virale prolongée			
PegIFN+	27	40	27

ribavirine			
IFN+ribavirine	20	12	12

*arrêt du traitement défini par le protocole à S24 en cas d'échec virologique et/ou histologique

Nous détaillerons plus en détail les résultats de l'essai RIBAVIC (ANRS HC 02) : essai randomisé et multicentrique ayant comparé l'association de la ribavirine 800 mg/j à l'Interféron 3 MUI x3/semaine (n = 210) ou au PegIFN-□-2b 1,5 µg/kg/semaine (n = 206) pendant 48 semaines et ayant inclus 416 patients entre avril 2000 et janvier 2002. Les principaux critères d'inclusion étaient : un ARN-VHC positif, des lymphocytes CD4 > 200/mm^3, un ARN- VIH stable depuis plus de 3 mois, l'absence de cirrhose décompensée et une absence de modification du traitement antirétroviral dans les 3 mois précédent la pré-inclusion. Les patients étaient comparables dans les deux groupes avec un âge moyen de 39,5 ans, une infection par le VIH évoluant depuis 10,6 ans, un stade C du CDC dans 15 % des cas, des CD4 moyens à 510/mm^3, une charge virale VIH < 400 copies/ml dans 65 % des cas et un traitement antirétroviral dans 80 % des cas. Le score METAVIR moyen était de 1,8 pour l'inflammation et de 2,3 pour la fibrose ; 38 % des patients étaient au stade F3 ou F4. Le génotype VHC était 1 et/ou 4 dans 65 % des cas. Les résultats à S72 (n=383) montrent en intention de traiter, une réponse virale prolongée dans 27% des cas dans le bras PegIFN versus 20% dans le bras IFN (p =0.047) tous génotypes confondus et de 17 % versus 6 % (p=0.006) en cas de génotype 1 et/ou 4. Les résultats étaient comparables en cas de génotype 2 ou 3 (44% versus 43 %). Les facteurs prédictifs d'une réponse virale prolongée étaient : - le génotype 2, 3 ou 5 (RR 3,77- IC_{95} 2,69-4,93 ; p< 0.001), un âge < 40 ans, l'absence de traitement par

inhibiteurs de protéase et des transaminases > 3 fois la normale à l'inclusion. Le taux des lymphocytes CD4 à l'inclusion, la durée de l'infection par le VIH, l'ARN VHC quantitatif, le score de fibrose, la dose de ribavirine rapportée au poids n'étaient pas des facteurs prédictifs de réponse. L'analyse des facteurs prédictifs de réponse virale prolongée stratifiée sur le génotype VHC montrait que chez les patients infectés par le génotype 1 ou 4, le traitement par pegIFN (RR 2,43- IC_{95} 1,12- 3,79 ; p=0.03) et une charge virale VHC < 5,7 log10 UI/ml (RR 2,07 IC_{95} 1,04- 3,74 ; p= 0.04) étaient indépendamment associés à une réponse virologique soutenue. Chez les patients infectés par le génotype 2, 3 ou 5, l'absence de traitement par inhibiteurs de protéase (RR 1,8 IC_{95} 1,17-2,42, p=0,01), un âge inférieur à 40 ans (RR 1,60 IC_{95} 1,08-2,10, p=0,02) et des transaminsases > 3 fois la normale à l'inclusion (RR 1,57 IC_{95} 1,07-2,02, p=0,03) étaient indépendamment associés à une réponse virologique soutenue.

Dans l'essai Apricot (868 patients inclus), les facteurs prédictifs d'une réponse virale prolongée étaient le génotype VHC non 1 (OR 3,37 ; IC_{95} 1,96- 5,80 ; p<0.001) et une charge virale VHC à l'inclusion inférieure ou égale à 800 000 UI/ml (OR 3,56 ; IC_{95} 2,00- 6,36 ; p<0.001) [68]. Dans l'essai ACTG A5071 (133 patients inclus), les facteurs prédictifs d'une réponse virale prolongée étaient : le traitement par pegIFN, un génotype non 1, une charge virale VIH détectable à l'inclusion et l'absence d'antécédent de toxicomanie [69].

Pegylated Interferon Alfa-2b vs Standard Interferon Alfa-2b, Plus Ribavirin, for Chronic Hepatitis C in HIV-Infected Patients

A Randomized Controlled Trial

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Context Treatment of chronic hepatitis C virus (HCV) infection in human immunodeficiency virus (HIV)–infected patients is a growing concern. Most data on the virologic efficacy and safety of the combination of peginterferon alfa-2b and ribavirin in coinfected patients come from uncontrolled studies.

Objective To study the safety and efficacy of peginterferon alfa-2b plus ribavirin vs standard interferon alfa-2b plus ribavirin in HIV-HCV coinfected patients.

Design and Settings A multicenter, randomized, parallel-group, open-label trial. Patients were enrolled from February 2000 to February 2002 and followed up for 72 weeks.

Patients Four hundred twelve HIV-HCV coinfected patients with detectable serum HCV-RNA, abnormal liver histology, a CD4 cell count of at least 200×10^6/L, and stable plasma HIV-RNA.

Intervention Treatment with ribavirin 400 mg twice a day, orally, plus either peginterferon alfa-2b (1.5 μg/kg subcutaneous injection once a week) or standard interferon alfa-2b (3 million units of subcutaneous injection 3 times a week) for 48 weeks.

Main Outcome Measures Sustained virologic response, defined by undetectable serum HCV-RNA at week 72.

Results More patients had sustained virologic responses in the peginterferon group than in the standard interferon group (27% vs 20%, $P=.047$). This difference between the treatments was found in patients with HCV genotype 1 or 4 infection (17% for peginterferon vs 6% for standard interferon, $P=.006$) but was not found in patients with HCV genotype 2, 3, or 5 (44% for peginterferon vs 43% for standard interferon, $P=.88$). Together, a decline in HCV-RNA of less than 2 $\log_{10}$ from baseline and detectable serum HCV-RNA at week 12 predicted 99% of treatment failures. Histologic activity diminished and fibrosis stabilized in virologic responders. The 2 regimens showed similar tolerability although dose modifications for clinical and biological events were more frequent with peginterferon. Eleven cases of pancreatitis or symptomatic hyperlactatemia were observed, all in patients receiving didanosine-containing antiretroviral regimens.

Conclusion In combination with ribavirin, treatment with peginterferon alfa-2b is more effective than standard interferon alfa-2b for HCV infection in HIV-infected patients.

JAMA. 2004;292:2839-2848 www.jama.com

ABOUT ONE THIRD OF HUMAN IMmunodeficiency virus (HIV)–infected patients in Europe and the United States are also infected by hepatitis C virus (HCV) while 5% to 10% of HCV-infected patients are also infected by HIV.[1,2] Human immunodeficiency virus coinfection accelerates the progression of HCV infection, which is now a leading cause of morbidity and mortality among HIV-infected individuals.[3-7]

The treatment of chronic HCV infection was transformed in the 1990s by the advent of the interferon-ribavirin combination and was further improved with the use of pegylated interferon (peginterferon), in which a polyethylene glycol molecule is added to standard interferon, yielding a longer

For editorial comment see p 2909.

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half-life and more favorable pharmacokinetics.[8,9] Two forms of peginterferon (alfa-2a and alfa-2b) have been approved for use with or without ribavirin. In combination with ribavirin, both peginterferons provide sustained virologic responses in 54% to 63% of HIV-seronegative HCV-infected patients (7% to 12% higher than with standard interferon-ribavirin).[10-12]

In vitro antagonism between ribavirin and some antiretrovirals (especially zidovudine and stavudine) delayed the use of ribavirin in HIV-coinfected patients, but a recent randomized trial of the stavudine-ribavirin combination showed no negative impact on antiretroviral efficacy.[13]

Recently, 2 randomized controlled studies showed the efficacy and safety of peginterferon alfa-2a plus ribavirin in HIV-HCV coinfected patients.[14,15] The few available data on the virologic efficacy and tolerability of peginterferon alfa-2b plus ribavirin in HIV-HCV coinfected patients come mainly from small uncontrolled or single-center trials.[16-19] The aim of our prospective randomized study of initial treatment of chronic HCV in HIV-infected patients was to compare the efficacy of a 48-week course of ribavirin combined with either standard interferon alfa-2b or peginterferon alfa-2b.

METHODS

Patient Selection

Adults who had never received interferon and who had the following characteristics were eligible for the study: second-generation enzyme-linked immunosorbent assay positivity for anti-HCV antibodies and polymerase chain reaction–based assay positivity for HCV-RNA in serum; interpretable results of liver biopsy performed within the previous 18 months, showing at least mild activity or fibrosis; anti-HIV antibody positivity and a stable plasma HIV-1 RNA level (variation of less than 1 $\log_{10}$ copies $\times 10^6$/L during the 3 months before randomization); stable antiretroviral treatment during the preceding 3 months (or no antiretroviral treatment); and a CD4 cell count higher than 200×10^6/L. Patients were not eligible if they had neutropenia ($<1.5 \times 10^9$/L neutrophils); thrombocytopenia ($<100 \times 10^3$/μL platelets); anemia (<11.0 g/dL hemoglobin); a serum creatinine level higher than 1.70 mg/dL (150 μmol/L); circulating hepatitis B surface antigen positivity; decompensated cirrhosis (defined as biopsy-proved cirrhosis with serum albumin below the lower limit of normal: a prothrombin level <60%; a total bilirubin level higher than the upper limit of normal; or a history of ascites, hepatic encephalopathy or esophageal varices); biliary, tumoral, or vascular liver disease; psychiatric disorders (history of major depression, suicide attempts, suicidal ideation, or other severe psychiatric disorders; psychosis); a history of seizures; cardiovascular disease; poorly controlled diabetes mellitus; or autoimmune disorders; or if they had actively injected illicit drugs 3 months before enrollment or reported daily alcohol intake greater than 40 g (women) or 50 g (men). Women were not eligible if they were unwilling to use effective contraception.

Study Design and Treatment Regimens

This randomized, phase 3, open-label, parallel-group study was conducted in 71 French centers. The study was approved by the ethics committee of Saint-Germain en Laye hospital and by the sponsor's institutional review board (Agence Nationale de Recherches sur le SIDA [ANRS]). All the patients gave their written informed consent. The study was designed by the Groupe d'Etude et de Recherche en Médecine Interne et Maladies Infectieuses sur le Virus de l'Hépatite C (GERMIVIC) joint study group, which comprised experts in internal medicine, infectious diseases, and hepatology. Data analysis was performed by the sponsor and the authors, both of whom were independent of the drug manufacturers. The study followed the Helsinki Declaration and Good Clinical Practices.

Patients were randomly assigned to receive subcutaneous injections of 1.5 μg/kg peginterferon alfa-2b (Peg Intron, Schering-Plough, Kenilworth, NJ) once a week or subcutaneous injections of 3 million units of interferon alfa-2b (Intron A, Schering-Plough) 3 times a week for 48 weeks. All patients also received 400 mg of ribavirin twice a day (Rebetol, Schering-Plough), orally. Randomization was managed by the central data center (INSERM U444, Paris, France). Randomization was balanced within centers, with blocking within strata. The randomization code was developed using a computerized random number generator to select random permuted block sizes of 2, 4, 6, and 8. The randomization list was concealed from the medical monitor (located in the data center), who assigned participants to the treatment groups after reviewing the eligibility criteria. Allocated treatments were communicated to the investigator during the week preceding the visit at which the first treatment prescription was planned.

The patients were evaluated after 2 and 4 weeks of treatment, every 4 weeks thereafter during treatment, and 4, 12, and 24 weeks after treatment was completed. Patients were followed up until week 72 to assess sustained responses.

Biochemical and hematologic tests were performed in local laboratories. Hepatitis C virus–RNA tests, viral genotyping, and histological evaluation of biopsy specimens were performed in central laboratories. Liver biopsy was performed at the end of follow-up.

Assessment and End Points. Hepatitis C virus–RNA was detected with a polymerase chain reaction assay (Amplicor 2.0 HCV Monitor, Roche Diagnostics Systems, Basel, Switzerland) with a detection limit of 50 IU (100 copies) $\times 10^3$/L. Hepatitis C virus–RNA levels were measured with a branched-chain DNA assay (bDNA3.0, Bayer Diagnostics, Tarrytown, NY) with a detection limit of 615 IU (3200 copies) $\times 10^3$/L. Hepatitis C virus genotyping was performed by sequence analysis of the 5′ untranslated region. The pri-

mary end point for efficacy was a sustained virologic response, defined as undetectable serum HCV-RNA at week 72. The secondary end point was histological improvement. Virologic and histologic end points were evaluated by individuals blinded to the treatment assignments. Pretreatment biopsy specimens were examined locally before randomization and were then coded and evaluated in parallel with those obtained at week 72, by 2 experienced pathologists (A.B. and C.D.). Hepatic inflammation and fibrosis were graded with the Metavir scoring system[20] (scores ranging from 0 [none] to 3 for severe necroinflammatory activity, and 0 [none] to 4 for cirrhosis) and Ishak's classification[21] (scores ranging from 0 [none] to 12 for severe inflammation, and 0 [none] to 6 for cirrhosis). Histological improvement in disease activity or fibrosis was defined as a decrease of 1 point or more between the relevant pretreatment and posttreatment Metavir and Ishak subscores.[22] Histological aggravation was defined as a score increase of 1 point or more.

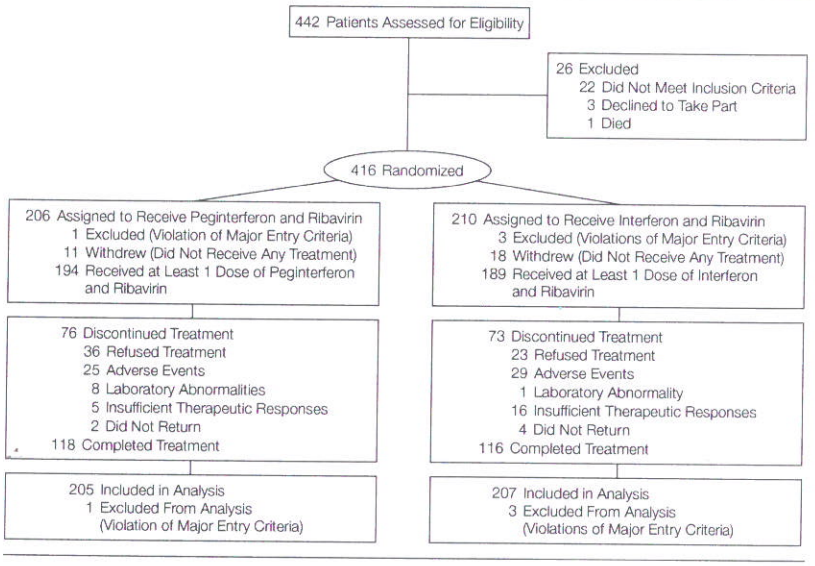
Special attention was paid to the possible effect of treatment on HIV infection (CD4 cell count, HIV viral load). Adverse events were graded 1 (mild) to 4 (life-threatening), using the ANRS grading system.[23] Stepwise reductions in the peginterferon alfa-2b dose to 1 and 0.5 µg/kg per week, and reductions in the interferon alfa-2b dose to 1.5 million units 3 times a week or the ribavirin dose to 600 mg/d, were allowed to manage adverse events or laboratory abnormalities that had reached predefined thresholds. Patients who discontinued therapy prematurely because of adverse effects were encouraged to remain in the study.

Statistical Analysis

The study was designed to have a power of 80% to detect a 15% difference (chosen for its clinical relevance) between the rates of sustained virologic response (from 20% vs 35% to 40% vs 55%) at a 5% level of significance (2-tailed test). Intention-to-treat analysis was used as the primary analysis for all measures of efficacy. Patients violating major eligibility criteria were excluded from the analyses. Patients who missed the final examination (week 72) were included as nonresponders. Histological responses were only analyzed in patients who underwent both a pretreatment and a posttreatment biopsy. Patients who received at least 1 dose of study medication were included in the safety analysis.

The Cochran-Mantel-Haenszel test (or Fisher exact test) was used to compare categorical variables, with stratification by center for comparisons between treatment groups and stratification by center and treatment group for other categorical variables. The Wilcoxon rank-sum test was used to compare quantitative variables between the groups. Logistic regression analyses were used to explore the influence of treatment and pretreatment characteristics on the response. Characteristics with P values below 0.20 in univariate analysis were included in multivariate models based on a backward elimination procedure. Adjusted odds ratios were transformed into approximated risk ratios (RRs) to correct for overestimation due to common events.[24] The Mac-Nemar χ^2 test or the Wilcoxon signed-rank test was used to compare pretreatment and posttreatment characteristics. All statistical tests were 2-tailed; $P<.05$ was considered statistically significant. We used SAS, version 8.2 (SAS Institute Inc, Cary, NC).

Figure 1. Patient Flow Diagram



RESULTS

Characteristics of the Patients

Patients were enrolled from February 2000 to February 2002. The trial ended in October 2003. A total of 442 patients were screened for eligibility, of whom 416 met the entry criteria and were randomly assigned to a treatment group (FIGURE 1). Four patients were excluded after randomization: 3 patients tested HCV-RNA–negative in the central laboratory, and one patient had previously received interferon alfa. Twenty-nine patients withdrew before receiving the study treatment because they refused or did not come for treatment or because a serious medical event occurred between randomization and the first treatment visit. During the follow-up period 4 patients in the peginterferon group and 1 patient in the standard interferon group withdrew. The pretreatment characteristics of the patients were similar in the 2 groups (TABLE 1).

Virologic Responses

A sustained virologic response (main end point) was obtained in 56 patients (27%) in the peginterferon group and 41 patients (20%) in the standard interferon group ($P=.047$). End-of-treatment virologic responses (at 48 weeks) were obtained in 72 (35%) and 44 (21%) of patients, respectively ($P=.001$). Undetectable serum HCV-RNA was obtained in 30 patients (15%) in the peginterferon group and 15 pa-

Table 1. Baseline Characteristics of the Patients*

Characteristics	Peginterferon Alfa-2b Plus Ribavirin (n = 205)	Interferon Alfa-2b Plus Ribavirin (n = 207)	P Value†
Age, mean (SD), y	39.5 (5.5)	39.7 (5.4)	.70
Sex, No. (%)			
Men	158 (77)	146 (71)	.33
Women	47 (23)	61 (29)	
Body weight, mean (SD), kg	67.4 (11.5)	65.9 (11.1)	.21
Birth place, No. (%)			
France	150 (73)	158 (76)	.65
Mediterranean countries	42 (20)	35 (17)	
Other	13 (6)	14 (7)	
HIV infection			
Estimated duration of infection, median (range), y	11.4 (0.5-18.0)	11.7 (0.5-18.5)	.80
CDC disease stage, No. (%)			
A	109 (53)	107 (52)	.81
B	59 (29)	68 (33)	
C	37 (18)	32 (15)	
CD4 cell count, median (range), $\times 10^6$/L	477 (137-1310)	486 (158-1259)	.32
HIV-RNA, No. (%), copies/mL			
<400	143 (70)	130 (63)	.07
≥400	62 (30)	77 (37)	
HIV-RNA, $\log_{10}$, median (range), copies/mL	3.6 (2.7-4.9)	3.6 (2.7-5.9)	.56
Antiretroviral treatment, No. (%)			
None	34 (17)	38 (18)	.59
NRTI	169 (82)	169 (82)	.82
NNRTI	69 (34)	63 (30)	.48
Protease inhibitor	75 (37)	86 (42)	.99
HCV infection			
Estimated duration of infection, median (range), y	16 (2-30)	17 (3-33)	.17
Mode of infection, No. (%)			
Injecting drug use	165 (80)	162 (79)	.39
Transfusion	12 (6)	18 (9)	
Other or unknown	28 (14)	27 (13)	
Serum alanine aminotransferase, mean (SD), × ULN	2.2 (1.9)	2.2 (1.7)	.56
Sustained alanine aminotransferase below the ULN, No. (%)‡	31 (16)	34 (18)	.49
HCV-RNA, median (range), IU × 10^6/L§	937 (0.615-20 859)	842 (1.1-12 141)	.85
HCV genotype, No. (%)‖			
1	99 (48)	99 (48)	.95
2 or 3	78 (38)	77 (38)	
4	26 (13)	28 (14)	
Other¶	2 (1)	1 (0)	
Liver histology, No. (%)#			
Metavir activity, mean (SD), score	1.7 (0.7)	1.8 (0.7)	.56
Metavir fibrosis, mean (SD), score	2.3 (1.0)	2.3 (1.0)	
Bridging fibrosis or cirrhosis, No. (%)	80 (39)	80 (39)	.93

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; ULN, upper limit of normal.
*Not all percentages sum to 100 because of rounding.
†Cochran-Mantel Haenszel χ^2 test, with stratification for the center.
‡Normal alanine aminotransferase values (below the ULN) at preinclusion and treatment initiation. Unavailable for patients who withdrew before treatment initiation.
§Hepatitis C virus–RNA values were unavailable for 33 patients (12 in the peginterferon group, 21 in the standard interferon group). The main reason was withdrawal from the study before treatment initiation.
‖The genotype was unavailable for 2 patients (both in the standard interferon group) who withdrew before treatment initiation.
¶A patient in each group had both genotype 1 and 4 infection.
#Four hundred eight patients (204 in the peginterferon group, 204 in the standard interferon group) had a pretreatment liver biopsy.

tients (7%) in the standard interferon group ($P=.04$) at week 4, 67 (33%) and 51 (25%) at week 12 ($P=.09$), and 83 (40%) and 57 (28%) at week 24 ($P=.004$).

A total of the 67 (99%) of the 68 patients in the peginterferon group and all 91 (100%) of patients in the standard interferon group who had detectable serum HCV-RNA and a viral load decline of less than 2 $\log_{10}$ IU × 10^3/L from baseline at week 12 failed to achieve a sustained virologic response at week 72 ($P=.43$, Fisher exact test).

Twenty-one patients (17%) with HCV genotype 1 or 4 infection who received peginterferon alfa-2b plus ribavirin had a sustained virologic response compared with 8 patients (6%) who received interferon-alfa2b plus ribavirin ($P=.006$, FIGURE 2). Among patients with HCV genotype 2, 3, or 5 infection, the rates of sustained virologic response were not different between the 2 treatment groups (35 [44%] vs 33 [43%], respectively, $P=.88$). Among patients who took at least 80% of the planned total dose, sustained virologic responses were achieved in 44 (40%) of 111 patients in the peginterferon group and 33 (29%) of 115 patients in the standard interferon group ($P=.30$).

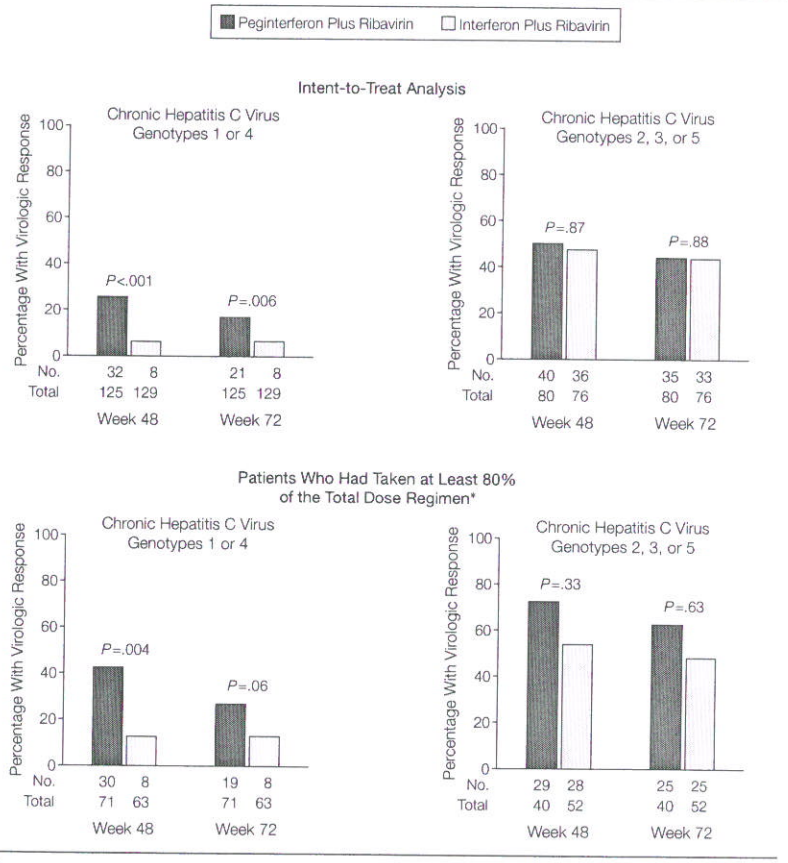
Independent Factors Associated With Sustained Virologic Response

TABLE 2 shows the variables that were included in the multiple logistic regression models on the basis of univariate analysis. Preliminary analysis showed that the sustained virologic response rates were influenced by the HCV genotype. A first multiple logistic regression model confirmed this result and showed that HCV genotypes 2, 3, or 5 were the main predictors of response (adjusted risk ratio [RR], 3.77; 95% confidence interval [CI], 2.69-4.93; $P<.001$). Other predictors were no protease inhibitor treatment, age 40 years or younger, and baseline alanine aminotransferase greater than 3 upper limits of normal. Because preliminary findings also indicated that the treatment effect differed according to the HCV genotype, further exploratory analyses were stratified according to the genotype. In patients with HCV genotype 1 or 4 infection, peginterferon treatment (RR, 2.43; 95% CI, 1.12 to 3.79; $P=.03$) and HCV viral load ≤5.7 $\log_{10}$ IU x 10^3/L (RR, 2.07; 95% CI, 1.04 to 3.74; $P=.04$) were independently associated with a sustained virologic response. In patients with HCV genotypes 2, 3, or 5, the absence of protease inhibitor treatment (RR, 1.80; 95% CI, 1.17-2.42; $P=.01$), age 40 years or younger (RR, 1.60; 95% CI, 1.08-2.10; $P=.02$), and baseline alanine aminotransferase more than 3 times the upper limits of normal (RR, 1.57; 95% CI, 1.07-2.02; $P=.03$) were independently associated with a sustained virologic response. Liver histology, the per kilogram body weight ribavirin dose, and the CD4 cell count were not independently associated with a sustained virologic response.

Histological Responses

Paired pretreatment and posttreatment histological results were available for 205 patients (50%, TABLE 3). The reasons for missing posttreatment results were refusal of biopsy in 153 cases (74%), failure to return in 46 cases (22%), and clotting disorders in 8 cases (4%). The only significant difference in baseline characteristics between patients with and without posttreatment biopsy was a higher mean (SD) Metavir fibrosis score in patients with available posttreatment results (2.4 [1.0] vs 2.2 [1.0]), $P=.03$).

Figure 2. End-of-Treatment Virologic Responses (Week 48) and Sustained Virologic Responses (Week 72)



*This represents all patients who took at least 80% of the planned total dose by hepatitic C virus genotype.

For disease activity, the Metavir score change was –0.19 in the peginterferon group and 0.01 in the standard interferon group ($P=.02$); and the mean changes in the Ishak grade were –0.57 and –0.26 ($P=.24$), respectively. The decline in both subscores was significant among sustained virologic responders while the subscores were stable among nonresponders. Changes in fibrosis did not differ between the 2 groups, but fibrosis worsened in patients who did not have a sustained virologic response. Steatosis improved significantly in patients infected by HCV genotype 3 who had a sustained virologic response (–13%, $P<.001$).

Safety

Similar proportions of patients in the 2 groups withdrew from the study because of clinical adverse events or laboratory abnormalities (TABLE 4). The doses of the study treatments were modified in 31 (16%) of patients in the peginterferon group and 13 (7%) of patients in the standard interferon group because of clinical adverse events ($P=.004$), and in 38 (20%) and 13 (7%) of patients respectively because of laboratory abnormalities ($P=.004$).

The incidence of most clinical adverse events was similar between the 2 treatment groups. The following parameters were not significantly different by week 12 in the peginterferon vs standard interferon groups: hemoglobinemia (–18 and –14 g/L, respectively, $P=.01$, at week 12), platelets (–34.3 vs –21.3 $\times 10^3$/μL, $P=.004$), neutrophils (–1.10 vs –0.70 $\times 10^9$/L, $P=.009$), lymphocytes (–0.66 vs –0.54 $\times 10^9$/L, $P=.06$), and CD4 cells (–121 vs –110 $\times 10^6$/L, $P=.21$). These parameters generally remained stable after week 12, then returned to near baseline values shortly after treatment cessation. When viral loads less than 400 copies/mL were attributed a value of 2.6 $\log_{10}$, mean (SD) HIV viral load ($\log_{10}$ copies/mL) was 2.96 (0.66) at baseline and 3.12 (0.86) at the end of treatment in the peginterferon group ($P<.001$), 3.04 (0.73) and 3.09 (0.78) respectively, in the standard interferon group ($P=.12$).

Seven deaths occurred among randomized patients: there were 5 deaths in the peginterferon group (2 from liver failure, 1 from metastatic neuroendocrine carcinoma, 1 from metastatic vulvar cancer—the patient who tested negative for HCV infection in the central laboratory—and 1 from accidental nitrate propyl overdose before the first dose of study treatment), and 2 deaths in the standard interferon group (1 from liver failure and 1 from liver cancer). One of the deaths from liver failure was considered possibly related to peginterferon-ribavirin therapy. This patient had fibrosis (F2) on a biopsy performed 9 months before the first dose of study treatment, was at Centers of Disease Control and Prevention stage A, and received didanosine, stavudine, and abacavir. He discontinued the study treatment after 8 weeks because of severe thrombocytopenia. He was hospitalized at week 12 with symptoms of decompensated cirrhosis and ascites infection. Liver biopsy showed significant cirrhosis (F4). Death occurred at week 32 from sepsis and liver failure. The proportion of patients reporting serious adverse events was generally similar among the groups. Symptomatic mitochondrial toxicity (symptomatic hyperlactatemia, lactic acidosis, or acute pancreatitis) occurred

Table 2. Virologic Responses According to Baseline Variables

Variable	No./Total (%) of Patients: Peginterferon Alfa-2b Plus Ribavirin	Interferon Alfa-2b Plus Ribavirin	Total	*P* Value*
Age, y				
>40	18/82 (22)	15/92 (16)	33/174 (19)	.13
≤40	38/123 (31)	26/115 (23)	64/238 (27)	
Sex				
Men	41/158 (26)	25/146 (17)	66/304 (22)	.15
Women	15/47 (32)	16/61 (26)	31/108 (29)	
HIV infection				
CD4 cell count, $\times 10^6$/L				
<500	23/108 (21)	22/117 (19)	45/225 (20)	.20
>500	33/97 (33)	19/90 (21)	52/187 (28)	
HIV-RNA, copies/mL				
<400	37/143 (26)	20/130 (15)	57/273 (21)	.18
≥400	19/62 (30)	21/77 (27)	40/139 (29)	
Protease inhibitor therapy				
Yes	13/75 (17)	14/86 (16)	27/161 (17)	.05
No	43/130 (33)	27/121 (22)	70/251 (28)	
HCV infection				
HCV genotype†				
1 or 4	21/125 (17)	8/129 (6)	29/254 (11)	<.001
2, 3, or 5	35/80 (44)	33/76 (43)	68/156 (44)	
HCV viral load, $\log_{10}$ IU $\times 10^3$/L‡				
>5.7	31/122 (25)	21/120 (18)	52/242 (21)	.03
≤5.7	24/71 (34)	19/66 (29)	43/137 (31)	
Alanine aminotransferase, × ULN				
≤3	40/161 (25)	24/158 (15)	64/319 (20)	.001
>3	16/44 (36)	17/49 (35)	33/93 (35)	
Cirrhosis§				
Yes	10/36 (28)	1/29 (3)	11/65 (17)	.09
No	46/168 (27)	40/175 (23)	86/343 (25)	

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; ULN, upper limit of normal.
*Cochran-Mantel Haenszel χ^2 test, with stratification for the center and treatment.
†The genotype was missing for 2 patients, both in the standard interferon group, who withdrew before treatment initiation.
‡HCV-RNA values were missing for 33 patients (12 in the peginterferon group, 21 in the standard interferon group).
§408 patients (204 in the peginterferon group, 204 in the standard interferon group) had a pretreatment liver biopsy.

in 11 patients, 9 patients receiving peginterferon and 2 patients receiving standard interferon. All these patients were receiving didanosine.

COMMENT

In this population of HIV-infected patients with chronic HCV, peginterferon alfa-2b plus ribavirin yielded more sustained virologic responses than standard interferon alfa-2b plus ribavirin. Efficacy and tolerability in the peginterferon group were in keeping with the results of 3 uncontrolled trials, in which the sustained virologic response rates to peginterferon alfa-2b plus ribavirin were 28% to 31%.[16-18] However, the absolute difference between the 2 groups (7%) was smaller than initially expected (15%); and was also smaller than in recent trials comparing peginterferon alfa-2a with standard interferon alfa-2a[14,15] and in a small single-center trial comparing peginterferon alfa-2b with standard interferon alfa-2b.[19] A high frequency of severe HIV- and/or HCV-related disease (62% of serious adverse events were unrelated to the study treatments, and 40% of our patients had bridging fibrosis or cirrhosis) and a high baseline prevalence of characteristics associated with poorer adherence to treatment (injection drug use, 79%; psychiatric disorders, 21%)[25] may have contributed to the smaller than expected difference between the 2 treatment groups in our study. However, the fact that we did not exclude such patients may make our results relevant to the general population of patients living with HIV and HCV coinfection in the United States and Europe.[26,27]

The benefit of peginterferon alfa-2b relative to standard interferon alfa-2b was most apparent in patients with genotype 1 or 4 infection. No significant differences were found between the treatment groups in patients with genotype 2 or 3 infection. Similar findings have been reported for HIV-seronegative and HIV-seropositive patients in studies comparing either peginterferon alfa-2b[11,19] or peginterferon alfa-2a[12] plus ribavirin with standard interferon plus ribavirin.

The HCV genotype was the predominant predictor of a sustained virologic efficacy, consistent with most previous studies of both HIV-seropositive[16,18] and HIV-seronegative patients.[10,11,28,29] A young age, a lower HCV-RNA level, or a higher pretreatment alanine amino transferase level are also reported to be predictive of sustained virologic responses.[14-16,18,29,30] The higher virologic failure rates that we observed among patients treated with protease inhibitors may be related to drug hepatotoxicity,[31] increased HCV replication,[32] restoration of anti–HCV immune responses[33] or cytochrome P450–mediated drug interactions.[34] Liver histology and the CD4 cell count were not independent predictors of the virologic response in our study, contrary to some previous reports[16,18] but in line with recently published clinical trials.[14,15]

The effect of treatment on histologic activity was similar to that observed in the HIV-seronegative population.[11] Interestingly, the progression of fibrosis was slowed when a virologic response was achieved.

Overall, tolerability was similar in the peginterferon and standard interferon groups. However, serious adverse events were far more frequent (35%) than what has been reported among HIV-seronegative patients (10%-15%). The incidence of opportunistic infections did not appear to be affected by anti-HCV therapy. Mitochondrial toxicity was particularly frequent in patients receiving didanosine, as previously reported,[16,18,35,36] possibly owing to increased intracellular concentrations of active triphosphorylated didanosine metabolites. As a result, a warning was added to the didanosine product information in September 2002, stating that ribavirin should be used cautiously in patients also receiving didanosine.[37] It is noteworthy that the

Table 3. Histologic Responses in Patients With Paired Pretreatment and Posttreatment Biopsy Samples by Treatment and Sustained Virologic Responses

Characteristic	Peginterferon Alfa-2b Plus Ribavirin (n = 100)		Interferon Alfa-2b Plus Ribavirin (n = 105)	
	Patients With SVR (n = 35)	Patients Without SVR (n = 65)	Patients With SVR (n = 25)	Patients Without SVR (n = 80)
Activity				
Metavir score, mean (SD), change	−0.3 (0.5)	−0.1 (0.6)	−0.3 (0.6)	0.1 (0.5)
P value	<.001*	.13	.07	.10
Ishak grade, mean (SD), change	−1.2 (1.5)	−0.2 (1.5)	−1.0 (1.4)	0.0 (1.4)
P value	<.001	.21	.002	.84
Condition, No. (%)				
Improving	11 (31)	11 (17)	9 (36)	7 (9)
Worsening	0	0	0	0
Fibrosis				
Metavir score, mean (SD), change	0.0 (0.6)	0.2 (0.7)	0.0 (0.7)	0.3 (0.9)
P value	>.99	.08	>.99	.002
Ishak stage, mean (SD), change	0.0 (0.9)	0.3 (1.4)	−0.1 (1.0)	0.6 (1.2)
P value	>.99	.09	.63	<.001
Condition, No. (%)				
Improving	4 (11)	10 (15)	5 (20)	11 (14)
Worsening	3 (9)	12 (18)	2 (12)	27 (34)
Steatosis				
HCV genotype 3, mean (SD), change	−13.2 (24.2)	7.5 (17.0)	−12 (32.8)	4.8 (31.1)
P value	.001	.23	.06	.25
Other genotypes, mean (SD), change	0.6 (24.8)	−2.4 (24.7)	11.7 (11.3)	−2.8 (26.4)
P value	.94	.91	.13	.63

Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.
*Wilcoxon signed-rank test.

patient who died from liver failure that was possibly related to the treatment had cirrhosis at the time of death and received didanosine; both these factors were recently reported as independent risk factors for hepatic decompensation.[38]

In combination with ribavirin, peginterferon alfa-2b is more effective than standard interferon alfa-2b for initial treatment of HCV infection with genotypes 1 and 4 in HIV-infected patients. Treatment can be discontinued after 3 months if a satisfactory virologic response is not obtained at this time. Coadministration of ribavirin with didanosine should be avoided. However, the poor outcome of HIV-coinfected patients and particularly that of patients with HCV genotype 1 infections calls for new therapeutic approaches in this setting.

Table 4. Incidence of Treatment Discontinuation, Dose Modifications, and Adverse Events*

Variable	No. (%) of Patients: Peginterferon Alfa-2b Plus Ribavirin (n = 194)	No. (%) of Patients: Interferon Alfa-2b Plus Ribavirin (n = 189)	*P* Value†
Treatment discontinuation			
All reasons	76 (39)	73 (39)	.20
Clinical adverse events or laboratory abnormalities	33 (17)	30 (16)	.70

Dose Modifications	Peginterferon	Ribavirin	Interferon	Ribavirin	Peginterferon vs Interferon	Ribavirin vs Ribavirin
All reasons	64 (33)	44 (23)	39 (21)	29 (15)	.04	0.19
Clinical adverse events	26 (13)	17 (9)	11 (6)	8 (4)	.01	0.053
Laboratory abnormalities	28 (14)	22 (11)	7 (4)	10 (5)	.003	0.09
Anemia	1 (1)	19 (10)	1 (1)	8 (4)	.94	0.13
Neutropenia	14 (7)	1 (1)	3 (2)	1 (1)	.04	0.81
Thrombocytopenia	9 (5)	0 (0)	1 (1)	0 (0)	.09	
≥1 Adverse event (clinical adverse event or laboratory abnormalities), grade						
1, Mild	169 (82)		147 (78)		.38	
2, Moderate	176 (91)		168 (89)		.76	
3, Severe	125 (64)		107 (57)		.09	
4, Life-threatening	62 (32)		65 (34)		.83	
Specific treatment-related clinical adverse event‡						
Influenzalike symptoms§	172 (89)		151 (80)		.10	
Depression	46 (24)		55 (29)		.35	
Weight loss	46 (24)		30 (16)		.03	
Injection-site reaction	44 (21)		5 (3)		.001	
Reduced appetite	38 (20)		31 (16)		.59	
Irritability	32 (16)		40 (21)		.27	
Bronchitis or cough	26 (13)		34 (18)		.22	
Insomnia	19 (10)		31 (17)		.02	
HIV-related clinical adverse events						
Increased lipodystrophy	37 (19)		40 (21)		.65	
Oral candidiasis	30 (15)		24 (13)		.39	
≥1 Serious adverse event	68 (35)		67 (35)		.81	
≥1 Treatment-related serious adverse events	30 (15)		23 (12)		.21	
Specific serious adverse events‖						
Psychiatric disorders	8 (4)		7 (4)		>.99	
Liver failure	4 (2)		5 (2)		.75	
Pneumonia or sepsis	6 (3)		13 (7)		.10	
Symptomatic mitochondrial toxicity	9 (5)		2 (1)		.06	
Liver enzyme activities >10 ULN	16 (8)		17 (9)		.86	
Neutropenia $<5 \times 10^9$/L	10 (5)		3 (2)		.09	

*Values are for patients who received at least 1 dose of study medication.
†Cochran-Mantel Haenszel χ^2 test, with stratification for the center, unless otherwise specified.
‡As judged by the investigator. Only events that occurred in at least 15% of patients in either treatment group are shown in this table. Participants could have more than 1 adverse event.
§Any report of fatigue, fever, rigor, myalgia, or headache.
‖Adverse events that occurred in at least 4 patients in at least 1 treatment group are shown. Patients could have more than 1 adverse event. Serious adverse events were defined as fatal or life-threatening events and those that required or prolonged hospitalization, resulted in persistent or clinically significant disability or in offspring, or required intervention to prevent 1 of the specific adverse events listed. Fisher exact test was used for comparisons between groups.

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Financial Disclosures: Dr Carrat has received research grants, served as a consultant for, or has received travel expenses from Roche, GlaxoSmithKline, Chiron, Schering-Plough, and Aventis; Dr Bani-Sadr has received travel expenses from Bristol-Myers Squibb and Gilead; Dr Pol has served as a consultant for Roche, Schering-Plough, and Gilead; Dr Lunel-Fabiani has received travel expenses from Schering-Plough, Roche, and Ortho-Clinical Diagnostics; Dr Morand has received research grants from or has served as a consultant for GlaxoSmithKline and Bristol-Myers Squibb; Dr Pialoux has received research grants from or served as a consultant for Aventis, Roche, GlaxoSmithKline, Bristol-Myers Squibb; Dr Piroth has received research grants from, served as a consultant for, or has received travel expenses from Roche and Boehringer-Ingelheim; Dr Salmon-Céron has served as a consultant for and received travel expenses from Roche, Bristol-Myers Squibb, GlaxoSmithKline, and Gilead; Dr Pialoux has received a grant from Aventis; Dr Degott has served as a consultant for Roche and Schering-Plough; and Dr Cacoub has served as a consultant for or has received travel expenses from Sanofi Synthelabo, Servier, Schering-Plough, and Chiesi.

Author Contributions: Dr Perronne had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Statistical analysis: Carrat.

Obtained funding: Salmon-Ceron, Cacoub.

Administrative, technical, or material support: Carrat, Bani-Sadr, Lunel-Fabiani, Benzekri, Degott, Cacoub.

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Funding/Support: The study was supported by a grant from the Agence Nationale de Recherches sur le SIDA, a publicly funded agency involved in clinical research on HIV and HCV. The drugs were provided by Schering-Plough.

Role of the Sponsor: Agence Nationale de Recherches sur le SIDA staff participated in the design and conduct of the study, and in data collection and analysis. However the agency had no role in data interpretation or in the preparation, review, or approval of the manuscript. Schering-Plough had no role in the study design or conduct, data collection, analysis or interpretation, or the preparation, review, or approval of the manuscript.

Acknowledgment: We thank David Young for his critical review of the manuscript, and we thank the patients who participated in the study.

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VII-1- Réponse virologique à S4 et S12, autres facteurs prédictifs indépendants d'une réponse virologique soutenue

Compte tenu du taux de réponse virale prolongée (au plus 40%) inférieur à celui observé chez les sujets mono-infectés VHC (60%) avec l'association IFN-pegylé et ribavirine et d'un pourcentage d'arrêts pour effets secondaires plus élevé, il est fondamental de pouvoir identifier dès les premiers mois du traitement anti-VHC, les patients susceptibles d'avoir une réponse virale prolongée pour limiter la survenue des effets secondaires et le coût du traitement. La valeur prédictive de la cinétique virale précoce de l'ARN-VHC sous traitement a déjà été démontrée chez les patients mono-infectés VHC. Ainsi, la négativation de l'ARN VHC dès S4 est le meilleur marqueur prédictif d'une réponse virologique soutenue [70-72] et l'absence de réduction supérieure à 2 log de l'ARN-VHC à S12 est prédictive de l'absence de réponse virologique dans plus de 95% des cas [73-75]. Ces résultats sont confirmés chez les patients co-infectés. Les essais Ribavic et Apricot ont évalué les valeurs prédictives de la réponse virologique, définie par un ARN VHC indétectable et/ou une diminution > 2 log de l'ARN VHC : analyse à S2, S4 et S12 chez 323 patients dans l'essai Ribavic (Tableau 2) et à S4, S12 et S24 chez 289 patients dans l'essai Apricot (Tableau 3). Dans l'essai RIBAVIC, la valeur prédictive négative de l'absence de réponse virologique (diminution < 2 log de l'ARN- VHC) était de 94% à S4 et de 99% à S12 [76]. Dans l'essai Apricot, elle était plus intéressante à S12 comparé à S4 (98% versus 88%). Dans l'essai ACTG A5071, les résultats précédents étaient confirmés : 100% de valeur prédictive négative en cas d'absence de réponse virologique à S12 [69].

Dans l'essai Ribavic, l'indétectabilité de l'ARN VHC dès S4 avait une valeur prédictive positive élevée à 97%. En revanche, à la fois dans l'essai Ribavic et Apricot, la valeur prédictive positive de la réponse virologique (ARN VHC indetectable et/ou une diminution > 2 log) à S12 n'était que de 60% et 56% respectivement. Ainsi, plus de 40% des patients ayant une réponse virologique à S12 présentaient une rechute. L'essai Ribavic a également montré que la décroissance de l'ARN VHC était significativement plus lente chez les patients rechuteurs comparés aux patients répondeurs long terme à S2 (2.2 ± 1.06 versus 1.14 ± 0.64 log UI/ml ; $p < 0.0001$), à S4 (3.07±1.16 versus 2.03±1.14 log UI/ml ; $p<0.001$) et à S12 (4.03 ± 0.94 versus 3.49 ± 0.92 ; $p=0.02$), suggérant que chez les patients rechuteurs, une prolongation du traitement au delà de 48 semaines pourrait permettre d'obtenir une réponse virale prolongée.

En conclusion, les résultats observés chez les patients co-infectés VIH-VHC sont comparables à ceux observés chez les patients mono-infectés par le VHC :

- l'absence de réponse virologique à S12 sous bithérapie interferon-pegylé et ribavirine est prédictive d'un échec virologique dans plus de 95% des cas.
- la négativité de l'ARN VHC dès S4 constitue la meilleure valeur prédictive d'une réponse virologique long terme.
- une décroissance lente de l'ARN VHC est associée à un pourcentage élevé de rechutes (plus de 40%). Chez ces patients, une prolongation du traitement au delà de 48 semaines, notamment en cas génotype (1 ou 4) pourrait permettre une diminution du risque de rechute. En effet, une étude réalisée chez des patients mono-infectés par le VHC, a évalué l'intérêt d'une prolongation de la bithérapie peginterferon-alfa2a (180 microg/semaine) plus ribavirine (800 mg/jour) de 48 à 72 semaines chez les patients ayant une virémie VHC détectable à S4. Alors que la

réponse virale en fin de traitement était comparable dans le groupe 48 semaines (n=165) et le groupe 72 semaines (n=161), le taux de réponse virale prolongée était significativement plus élevé chez les patients traités 72 semaines (45% versus 32% ; p=0.01). Chez les patients infectés par le génotype 1, la réponse virale prolongée était de 28% dans le bras 48 semaines (n = 149) et de 44% dans le bras 72 semaines (n = 142)- (p = .003) [77].

Tableau 2 : Valeurs prédictive positive et négative de la réponse virologique observée sous traitement dans l'essai Ribavic

	Valeur prédictive positive à S2, S4, S12 (%)			Valeur prédictive négative à S2, S4, S12 (%)		
	S2	S4	S12	S2	S4	S12
ARN VHC < 50 UI/ml	90	97	81	75	81	95
Diminution > 2 log UI/ml de l'ARN VHC	73	59	51	86	94	99
ARN VHC < 50 UI/ml ou Diminution > 2 log UI/ml de l'ARN VHC	72	68	60	86	94	99

Tableau 3 : Valeur prédictive positive et négative de la réponse virologique observée sous traitement dans l'essai Apricot

Patients (N)	ARN VHC < 50 UI/ml ou diminution > 2 log de l'ARN VHC (%) à S4, S12 et S24	Réponse virale prolongée à S72 (%)	Valeur prédictive positive à S4, S12 et S24 (%)	Valeur prédictive négative à S4, S12 et S24 (%)
Tout genotype (289)	52; 71; 75	40	66; 56; 53	88; 98; 99
Genotype 1 (176)	40; 63; 68	29	58; 45; 43	90; 98; 100
Genotype 2,3 (95)	80 ; 88; 89	62	74; 70; 69	84; 100; 100

VII-2- Non réponse au Traitement anti-VHC – Facteurs de risque et rôle de l'abacavir ?

Les essais RIBAVIC et APRICOT ont également montré que le pourcentage de patients présentant une diminution inférieure à 2 log à S12 après un traitement par peginterferon plus ribavirine était plus élevé (29 à 33%) comparé aux patients monoinfectés VHC (14%) [66, 78]. Chez ces patients, la poursuite du traitement pendant une durée supplémentaire de 36 semaines ne permet pas d'obtenir une

réponse virologique soutenue dans plus de 95% des cas et l'arrêt du traitement est donc recommandé. Comme nous l'avons vu ci-dessus, différents facteurs prédictifs de la réponse virologique soutenue ont déjà été identifiés mais ceux ci comparent les patients en succès thérapeutique aux patients rechuteurs et aux patients n'ayant pas négativé leur charge virale VHC. Or, les patients rechuteurs ont une décroissance lente de leur charge virale VHC et une prolongation du traitement au delà de 48 semaines peut permettre l'obtention d'une réponse virologique soutenue [77]. En revanche, chez les patients non répondeurs, la décroissance de la charge virale VHC dans les 3 premiers mois est de l'ordre d'1 log et reste stable en cas de poursuite du traitement anti-VHC [79, 80]. Comprendre les facteurs associés à une non réponse au traitement sont fondamentaux pour mieux appréhender les mécanismes associés à une résistance au traitement anti-VHC. Nous avons donc étudié les facteurs de risque associés à l'absence de réponse virologique (moins de 2 log de réduction de la charge virale VHC) chez les patients traités par l'association peginterferon plus ribavirine et ayant eu une observance supérieure à 80% dans l'essai RIBAVIC [81].

Parmi les 154 patients ayant pris au moins 80% de la dose prescrite de l'association peginterferon plus ribavirine pendant les12 premières semaines, 57 (37%) patients n'ont pas présenté une réponse virologique: 10.3 % des patients infectés par le génotype 2 ou 3 et 53.1% des patients infectés par le génotype 1 ou 4. En analyse multivariée, la charge virale VHC (OR, 2.11; IC_{95}, 1.11-4.0, p=0.022), le genotype 1 ou 4 (OR, 12.13; IC_{95}, 4.27-34.47, p<0.0001), un traitement antirétroviral incluant l'abacavir (OR, 4.92; IC_{95}, 1.50-16.06, p=0.0083) et le taux de bilirubine à l'inclusion (OR, 4.52; IC_{95}, 1.53-13.36, p=0.0064) étaient significativement associés au risque de non réponse. En revanche, les facteurs suivants n'étaient pas associés à un risque d'échec virologique précoce : l'âge, le sexe, la durée moyenne de l'infection

par le VIH ou le VHC, le stade SIDA, le taux des CD4, une charge virale VIH < 400 copies/ml, le traitement antirétroviral, la durée moyenne du traitement antirétroviral, la dose moyenne quotidienne de ribavirine, le score moyen de fibrose et d'inflammation selon la classification METAVIR, la présence de stéatose et le taux des ASAT, ALAT, GGT, Phosphatases Alcalines et le taux de prothrombine.

L'association observée entre l'absence de réponse virologique et un traitement par abacavir est inattendue et évocatrice d'une interaction médicamenteuse. Il a été montré un risque d'échec virologique majeur avec des trithérapies de INTI associant des analogues puriniques de le reverse transcriptase comme le tenofovir ou la didanosine avec l'abacavir sans que l'on ait pu démontrer un antagonisme entre ces antiviraux [82, 83]. La ribavirine est également un analogue de la purine qui est antagoniste de certains INTI par inhibition de la 5'-monphosphate dehydrogenase. In vitro, l'antagonisme avec l'abacavir est faible comparé avec la zidovudine ou la stavudine mais il existe aucune donnée sur un éventuel antagonisme des INTI vis à vis de la ribavirine [84]. Suite à la présentation de ce travail, une équipe espagnole a évalué l'impact de l'abacavir sur la réponse au traitement par peg-interféron et ribavirine et retrouve des résultats comparables aux nôtres. Sur un total de 426 patients traités par cette association, les facteurs indépendants associés à l'absence de réponse virologique soutenue étaient : une charge virale VHC élevée à la baseline (OR, 1.92; IC_{95}, 1.33-2.78, p<0.001), le génotype VHC 1 ou 4 (OR, 4.76; IC_{95}, 2.78-8.33, p<0.001) et un traitement antirétroviral incluant l'abacavir (OR, 2.04; IC_{95}, 1.08-3.85, p=0.03). L'abacavir est également retrouvé comme facteur de risque d'échec virologique précoce (diminution < 2 log de l'ARN VHC à S12) et de rechute. En revanche, l'abacavir n'est plus retrouvé comme facteur de risque d'échec au traitement anti-VHC si l'analyse porte sur le sous groupe de patients ayant une

concentration plasmatique élevée de ribavirine à S4 (> 2 μg/ml à S4), suggérant l'existence d'une inhibition compétitive entre la ribavirine et l'abacavir.

Could Tenofovir Modify the Model End-Stage Liver Disease (MELD) Score in Patients With End-Stage Liver Disease Eligible for Liver Transplantation?

To the Editor:

We carefully read the letter by Buchacz et al[1] published in the December 15, 2006 issue of this journal. Although the letter did not show clear evidence of renal impairment in patients with advanced HIV diseases treated with tenofovir, we outline some considerations about the importance of the selection of antiretroviral drugs in patients who are candidates for liver transplantation.

Tenofovir is currently one of the most frequently prescribed drugs worldwide as a part of combination antiretroviral therapy and has been shown to be highly effective in the treatment of HIV-infected patients.[2] Although it is generally well tolerated, several different kinds of kidney toxicity have been described with tenofovir, including Fanconi syndrome, diabetes insipidus, and acute renal failure.[3,4] Proximal tubular damage (proximal tubular bicarbonate wasting), low-grade proteinuria, hypokalemia, and hypophosphatemia have been described.

HIV coinfection accelerates the course of hepatitis viruses (hepatitis C virus [HCV] and hepatitis B virus [HBV]), inducing liver damage. The progression of liver fibrosis is faster in HIV-HBV-HCV–coinfected patients, reducing the survival of patients with end-stage liver disease (ESLD), which has become the leading cause of death among coinfected subjects.[5]

HIV-infected patients are considered as candidates for orthotopic liver transplantation (OLT). They have shown a survival rate comparable to that observed in monoinfected patients.[6]

In coinfected patients, the model end-stage liver disease (MELD) score is considered the best scoring system. The system has been designed to improve the organ allocation system in liver transplantation to ensure that available organs are directed to transplant candidates based on the severity of their liver disease rather than on the length of time they have been on the waiting list. The parameters considered for the calculation of the MELD score are serum creatinine, total bilirubin, and international normalized ratio (INR).

Because the availability of liver organs is limited and OLT in HIV is particularly complex and expensive, the correct allocation of livers becomes fundamental. Any factor that could influence renal function, and thus serum creatinine, should modify the MELD score and change the organ allocation. The use of tenofovir in patients with ESLD and eligible for OLT may be a cause of increased serum creatinine and a subsequent MELD score modification. Therefore, tenofovir should be used cautiously in this category of patients, and when its use is mandatory, careful monitoring of renal function is needed.

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Early Virologic Failure in HIV-Coinfected Hepatitis C Patients Treated With the Peginterferon-Ribavirin Combination

Does Abacavir Play a Role?

To the Editor:

HIV coinfection increases the percentage of patients who show hepatitis C virus (HCV) RNA declines of <2 logs at 12 weeks of peginterferon (pegIFN) and ribavirin combination therapy to 29% to 33%.[1,2] We wanted to identify baseline host-related or virus-related factors that might predict early virologic failure of pegIFN α-2b plus ribavirin therapy in patients coinfected with HIV and HCV.

The results of the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) HC02-Ribavic Study have been reported elsewhere.[1] In brief, 206 of 416 HIV/HCV-coinfected patients who had never received interferon or ribavirin were randomly assigned to receive weekly subcutaneous injections of 1.5 μg/kg of pegIFN α-2b (ViraferonPeg; Schering-Plough, Kenilworth, NJ) plus 800 mg/d of ribavirin for 48 weeks, and 210 patients were randomly assigned to receive thrice-weekly subcutaneous injections of 3 megaunits of interferon α-2b plus 800 mg/d of ribavirin for 48 weeks. Only patients treated with pegIFN α-2b plus ribavirin and who had taken at least 80% of the total prescribed dose regimen were analyzed here. Early virologic responses were defined by undetectable serum HCV RNA in a qualitative polymerase chain reaction (PCR) assay (Amplicor 2.0 HCV Monitor, detection limit of 50 IU/mL; Roche Diagnostics Systems,

Pleasanton, CA) or a decrease of more than 2 $\log_{10}$ in serum HCV RNA in a quantitative PCR assay (bDNA3.0, detection limit of 615 IU/mL; Bayer Diagnostics, Tarrytown, NY) at week 12. We used the χ^2 test or Fisher exact test to analyze qualitative variables and the Mann-Whitney test to analyze quantitative variables. Logistic regression models were used to test possible associations between nonresponse (outcome variable) and pretreatment characteristics (input variables). Characteristics with $P < 0.10$ in univariate analysis were included in multivariate models based on a backward elimination procedure. All statistical tests were 2-sided, with a type I error of 5%.

A total of 194 patients received at least 1 dose of pegIFN α-2b plus ribavirin, and 154 of these patients received at least 80% of their study medication during the first 12 weeks of treatment. Fifty-seven patients (37%) did not have an early HCV virologic response; their mean decline in HCV viral load during the first 12 weeks of treatment was 0.6 ± 0.6 $\log_{10}$ IU/mL. We analyzed the clinical and virologic data to identify baseline factors that were predictive of early HCV virologic failure. Univariate analysis identified higher HCV viral load, genotype 1 or 4 infection, abacavir-based antiretroviral therapy, and elevated gamma-glutamyl transferase (GGT) and bilirubin levels (Table 1). In multivariate analysis, elevated baseline HCV viral load, HCV genotype 1 or 4 infection, abacavir-based antiretroviral therapy, and an elevated baseline bilirubin level remained significantly associated with the risk of early HCV virologic failure (see Table 1).

Because HCV genotype 1 or 4 infection was the most influential risk factor for early virologic failure, we repeated the analyses in the subgroup of patients infected by these genotypes. In multivariate analysis, abacavir-based antiretroviral therapy (odds ratio [OR] = 4.15, 95% confidence interval [CI]: 1.14 to 15.13; $P = 0.031$) and an elevated baseline bilirubin level (OR = 5.2, 95% CI: 1.34 to 20.36; $P = 0.017$) remained significantly associated with the risk of early virologic failure.

Several patient-related and virus-related factors have been shown to influence the response to optimal interferon-ribavirin combination therapy for HCV infection.[1–4] Most studies compared patients with sustained virologic responses and those with virologic relapse or no response. Nonresponders differ from patients who relapse, in whom HCV RNA becomes undetectable during treatment but then reappears on treatment withdrawal. In nonresponder HCV-monoinfected patients, the average drop in HCV viral load at week 12 is 1 $\log_{10}$, with no subsequent decline during continued treatment.[3] Our study confirms that a high baseline HCV viral load and HCV genotype 1 or 4 infection are the most important baseline predictors of early virologic failure.

The link found here between the risk of early nonresponse to anti-HCV therapy and abacavir exposure was unexpected and points to a possible role of drug interaction. In multivariate analysis, concomitant treatment with abacavir and pegIFN-ribavirin was associated with an adjusted 4.9-fold increase in the risk of nonresponse to anti-HCV therapy. The only significant differences between abacavir-treated and abacavir-untreated patients were a longer duration of antiretroviral therapy and a higher baseline GGT level in abacavir-treated patients. These factors were considered in multivariate analysis, and therefore cannot explain the effect of abacavir after adjustment. Poor HIV virologic responses were recently reported with triple–nucleoside reverse transcriptase inhibitor (NRTI) regimens consisting of tenofovir plus another purine NRTI (abacavir or didanosine), but there was no evidence of plasma pharmacokinetic or intracellular phosphorylation interactions.[5–7]

Ribavirin is a purine ribonucleoside analogue used to treat hepatitis. In HIV/HCV-coinfected patients treated for both infections, ribavirin can affect intracellular NRTI levels by inhibiting inosine 5′-monophosphate dehydrogenase. In vitro, the level antagonism on HIV is lower when ribavirin is combined with abacavir rather than with stavudine or zidovudine.[8] The potential loss of ribavirin efficacy on HCV during concomitant use of these NRTIs has not previously been reported, however.

The only host factor predictive of early HCV virologic failure in our study was an elevated serum bilirubin level at baseline. The pathophysiology of bilirubin elevation in this setting is not known, although a correlation between serum bilirubin and hepatic fibrosis is well established. Other factors known to have a negative influence on anti-HCV therapeutic outcome, such as older age, higher body mass index, advanced fibrosis or cirrhosis, liver steatosis, and the daily dose of ribavirin (12.2 mg/kg on average in our study), were not associated with early virologic failure in our study.[3,4] Only 5 patients were from sub-Saharan Africa, and the possible impact of ethnicity on the virologic response could not therefore be evaluated.

If confirmed, the negative interaction observed here between ribavirin and

TABLE 1. Factors Associated With Lack of Early Virologic Response (EVR) to HCV Therapy at Week 12: Univariate and Multivariate Logistic Regression Analysis

	Patients With EVR	Patients With No EVR	Univariate Analysis Crude OR [95% CI]	*P*	Multivariate Analysis Adjusted OR [95% CI]	*P*
Serum HCV RNA (log10 IU/mL), mean (SD)	5.74 (0.8)	6.08 (0.58)	2.12 [1.23 to 3.67]	0.007	2.11 [1.11 to 4.00]	0.0224
HCV genotype 2 or 3, n (%)	52 (53.6)	6 (10.3)	1.00			
HCV genotype 1 or 4, n (%)	45 (46.4)	51 (89.5)	9.82 [3.86 to 25.03]	< 0.001	12.13 [4.27 to 34.47]	< 0.0001
Stavudine-based antiretroviral therapy, n (%)	48 (49.5)	20 (35.1)	0.55 [0.28 to 1.08]	0.084		
Abacavir-based antiretroviral therapy, n (%)	8 (8.3)	14 (24.5)	3.62 [1.41 to 9.29]	0.007	4.92 [1.50 to 16.06]	0.0083
GGT (× normal upper limit), mean (SD)	2.42 (2.33)	3.81 (3.15)	1.21 [1.06 to 1.39]	0.005		
Bilirubin (× normal upper limit), mean (SD)	0.64 (0.35)	0.80 (0.50)	2.52 [1.12 to 5.65]	0.025	4.52 [1.53 to 13.36]	0.0064

abacavir on the response to anti-HCV therapy has to be taken into account in clinical practice.

ACKNOWLEDGMENTS

This study received financial support from ANRS Essai HC 02 and SIDACTION. Results are to be presented at the 14th Conference on Retroviruses and Opportunistic Infections (CROI 2007), Los Angeles, CA, February 25–28, 2007.

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Expanded Services for the Prevention of Mother-to-Child HIV Transmission

Field Acceptability of a Pilot Program in Lusaka, Zambia

To the Editor:

At the start of 2007, an estimated 2.3 million children in sub-Saharan Africa were infected with HIV, most of whom had acquired the virus around the time of birth.[1] As services in the region move toward more complicated and efficacious drug regimens for prevention of mother-to-child transmission of HIV (PMTCT),[2] acceptability is a critical component to overall program effectiveness. Several studies have observed poor follow-up among patients concerned about stigma or disclosure of their HIV status.[3,4] The risk of viral drug resistance after use of drugs such as nevirapine (NVP) may only add to a patient's reluctance to adhere to specific PMTCT drug regimens.

We evaluated a pilot program designed specifically to link PMTCT services, provided routinely as part of antenatal care, to long-term HIV care and treatment in Lusaka, Zambia. Kanyama Health Center is among the largest of the Lusaka District's 24 primary care centers and the site of robust government programs for PMTCT[5] and antiretroviral therapy (ART).[6] To link PMTCT to HIV care and treatment, we implemented specific referral procedures. This began with a scripted talk on the benefits of long-term HIV care and the importance of $CD4^+$ cell count screening. All women were encouraged to enroll into long-term HIV care and treatment. Women interested in enrollment that day were escorted by community health workers to the on-site HIV care and treatment facility and seen immediately.

Given the heavy clinic burden, we used dedicated staff members, 2 nurses and 1 clinical officer, to expedite the enrollment of pregnant women into long-term HIV care. Initial evaluation consisted of a medical history, physical examination (including World Health Organization [WHO] staging), and $CD4^+$ cell count screening. A follow-up appointment was made for 2 to 3 weeks later to review laboratory results and determine the need for ART. ART eligibility was based on Zambian National Guidelines:[7] $CD4^+$ count <200 cells/mm^3 (regardless of WHO stage), WHO stage 4 (regardless of $CD4^+$ cell count), and WHO stage 3 with $CD4^+$ count <350 cells/mm^3.

Pregnant women who did not qualify for ART were offered 1 of 3 drug regimens for PMTCT: single-dose NVP, short-course zidovudine (ZDV), or a combination of the two (ZDV + NVP). Patients actively participated in decision making. As part of a standardized counseling script, advantages of each regimen were reviewed: higher efficacy (ZDV + NVP), discreetness (NVP alone), and minimal risk for HIV resistance (ZDV alone). Illustrations and patient materials were used to help convey important points. Data were collected from March 1, 2005, the launch of the pilot program, to October 15, 2005, when a new initiative to link ART and PMTCT services was introduced in the health center. This analysis was deemed exempt from human subjects review by the Institutional Review Boards of the University of Zambia and the University of Alabama at Birmingham.

Over the course of the pilot program, 680 pregnant women were newly diagnosed with HIV and 433 (64%) were referred from antenatal care by district

VII-3- Rechute à l'arrêt du traitement

Le taux de rechute des patients co-infectés VIH-VHC est également plus élevé : 17,8% dans l'essai RIBAVIC et 22% dans l'essai APRICOT chez les patients ayant une réponse virologique à S48 ; 14.7% et 22,2% des patients traités par l'association peginterféron plus ribavirine dans l'essai APRICOT et dans l'essai RIBAVIC respectivement. Dans un essai portant sur 256 patients co-infectés VIH-VHC traités par peginterferon plus ribavirine et ayant un ARN VHC indétectable à S48, 62 patients (24%) présentaient une rechute : 33% en cas de génotype 1; 18% en cas de génotype 2 ou 3 et 21% en cas de génotype 4 [85]. Trois facteurs de risque indépendants de rechute étaient retrouvés : une charge virale VHC ≥ 500 000 UI/ml à la baseline [RR, 4,81 – IC $_{95\%}$ 1.52-15.22 ; p=0.008], l'absence de réponse virologique rapide (ARN VHC < 50 UI/ml à la semaine 4) [RR, 2.94 – IC $_{95\%}$ 1.22-7.09 ; p=0.02] et un traitement antirétroviral concomitant [RR, 2.71 – IC $_{95\%}$ 1.03-7.13 ; p=0.04]. Le rôle délétère d'un traitement antirétroviral concomitant apparaît également dans cette étude et démontre à nouveau la nécessité d'étudier un éventuel impact négatif des INTI sur l'activité de la ribavirine.

VIII- TOLERANCE DU TRAITEMENT ANTI-VHC

La tolérance et l'adhérence au traitement sont plus difficiles chez les patients co-infectés ; le taux d'arrêt des traitements est plus élevé (25 % et 39 % dans le bras peginterferon plus ribavirine dans l'essai APRICOT et de l'essai RIBAVIC, respectivement) comparé à celui observé chez les patients mono-infectés par le VHC

(moins de 15% dans les grands essais de la littérature). Dans l'essai RIBAVIC, 16 % des patients ont présenté des effets indésirables graves ou des anomalies biologiques grade 3 ou 4. Les effets secondaires du traitement sont comparables à ceux observés chez les patients mono-infectés par le VHC : troubles psychiatriques… mais, certaines complications comme l'anémie, les complications infectieuses, l'amaigrissement sont plus fréquentes et d'autres, comme celles liées à la toxicité mitochondriale sont quasiment jamais décrites chez les patients mono-infectés par le VHC.

VIII-1-Majoration du risque de toxicité mitochondriale au cours du traitement anti-VHC

Le traitement anti-VHC augmente le risque de toxicité mitochondriale secondaire au traitement antirétroviral. En effet, 1- la ribavirine est un analogue nucléosidique de la guanosine et potentialise la toxicité mitochondriale de certains analogues nucléosidiques ; 2- l'IFN a également une toxicité mitochondriale [86].

Deux types d'effets secondaires rarement observés chez les patients mono-infectés VHC ont été observés chez les patients co-infectés : des pathologies secondaires à une toxicité mitochondriale et des décompensations hépatiques. L'analyse des cas observés dans l'essai RIBAVIC a été publiée respectivement dans J AIDS et Clinical Infectious Diseases [87, 88].

Dans l'essai RIBAVIC, 11 patients ont présenté une toxicité mitochondriale symptomatique: une pancréatite aiguë dans 5 cas et une hyperlactatémie symptomatique dans 6 cas. L'incidence était de 47.5 patients/années. En analyse multivariée, la didanosine multipliait par 46 le risque de toxicité mitochondriale

symptomatique (IC_{95} : 7.4-infini). L'incidence augmentait à 200.2 patients/années chez les patients traités par didanosine. L'association didanosine et ribavirine est synergique in vitro : augmentation de la phosphorylation de la didanosine par inhibition de l'inosine monophosphate déhydrogénase et multiplication par plus de 80 de l'activité in vitro de la didanosine [89-91]. L'augmentation des concentrations de la didanosine est probablement à l'origine d'une majoration de sa toxicité. L'association didanosine/ ribavirine n'est donc plus recommandée depuis 2002 .

Alors que chez les patients monoinfectés par le VHC porteurs d'une cirrhose non décompensée, le risque de décompensation hépatique est de l'ordre de 2 à 4% par an et est rarement observé au cours du traitement anti-VHC, une incidence élevée de décompensation hépatique a été notée dans les essais APRICOT et RIBAVIC.

Mauss S et al, ont rapporté 14 cas de décompensation hépatique parmi les 859 patients inclus dans l'essai Apricot [92]. Les 14 patients avaient une cirrhose ; l'incidence de la décompensation hépatique dans le sous groupe de patients avec une cirrhose était de 10,4% (14/134).

Dans l'analyse univariée ayant comparé les 13 patients (les 13/14 ayant présenté une décompensation hépatique dans les 24 premières semaines du traitement anti-VHC) aux 120 patients avec cirrhose, l'augmentation de la bilirubine et des phosphatases alcalines, la diminution de l'albuminémie, des plaquettes et de l'hémoglobine, tous marqueurs connus d'une cirrhose avancée, étaient associées au risque de décompensation hépatique. Un traitement par la didanosine était également associé à ce risque (OR 4,06 - $p< 0.03$). En analyse multivariée, ces mêmes facteurs de risque étaient retrouvés.

Des résultats comparables ont été retrouvés dans l'essai RIBAVIC. Parmi les 383 patients ayant reçu au moins une dose de traitement, 7 ont présenté une

décompensation hépatique spontanée. L'incidence de la décompensation hépatique chez les patients cirrhotiques était comparable à celle observée dans l'essai APRICOT, 8.3 % (5/60) et 10.4% (14/134), respectivement. En analyse multivariée, trois facteurs de risque étaient identifiés : la didanosine (OR, 8,8 ; IC 95%, 1,2-102,3, p< 0.02), la cirrhose (OR, 8,8 ; IC 95%, 1,2-104.2, p< 0.02) et une bilirubine élevée (OR, 7,9 ; IC 95%, 1,08-93,3, p< 0.03). Il est intéressant de noter que parmi ces 7 patients, 1- l'évolution de la fibrose était particulièrement rapide dans 2 cas (score Métavir A2 F2, 9 et 10 mois avant le traitement anti-VHC); 2- une patiente décédait dans un tableau d'insuffisance hépatique en dépit d'une réponse virologique VHC soutenue. La toxicité mitochondriale de la didanosine, majorée par la ribavirine, est ainsi également en cause dans le risque d'aggravation hépatique chez les patients co-infectés VIH-VHC

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Risk Factors for Symptomatic Mitochondrial Toxicity in HIV/Hepatitis C Virus–Coinfected Patients During Interferon Plus Ribavirin–Based Therapy

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Objective: To evaluate the incidence, clinical features, and risk factors for symptomatic mitochondrial toxicity in HIV/hepatitis C virus (HCV)–coinfected patients receiving anti-HCV therapy.

Methods: All cases of symptomatic mitochondrial toxicity reported in 416 patients participating in an open, randomized trial of peg-interferon α-2b plus ribavirin vs. interferon α-2b plus ribavirin for 48 weeks were reviewed. Associations with antiretroviral treatments and with clinical and laboratory findings were sought by univariate and multivariate analysis.

Results: Eleven of the 383 patients who received at least 1 dose of anti-HCV treatment developed symptomatic mitochondrial toxicity (symptomatic hyperlactatemia and pancreatitis in 6 and 5 patients, respectively). All cases occurred in patients being treated for HIV infection, and the incidence of symptomatic mitochondrial toxicity was 47.5 per 1000 patient-years. In multivariate analysis, symptomatic mitochondrial toxicity was significantly associated with didanosine-containing antiretroviral regimens (odds ratio 46; 95% CI, 7.4 to infinity; $P < 0.001$), but not with stavudine or with nucleoside reverse transcriptase inhibitor regimens not containing didanosine. The incidence of symptomatic mitochondrial toxicity was 200.2 per 1000 patient-years in patients receiving didanosine. Demographic characteristics were not associated with symptomatic mitochondrial toxicity.

Conclusions: Coadministration of ribavirin with didanosine should be avoided. If unavoidable, patients should be monitored closely for mitochondrial toxicity. Didanosine should be suspended if clinical signs or symptoms of mitochondrial toxicity occur.

Key Words: HIV/hepatitis C virus coinfection, hyperlactatemia, lactic acidosis, pancreatitis, didanosine and ribavirin

(*J Acquir Immune Defic Syndr* 2005;40:47–52)

Combination therapy with peg-interferon (pegIFN) and ribavirin is currently the standard of care for patients with hepatitis C virus (HCV) infection.[1–3] Although IFN-α impairs mitochondrial DNA transcription and ribavirin is a guanosine nucleoside analogue, symptomatic mitochondrial toxicity has not previously been described in HCV-monoinfected patients receiving this combination.[1,2,4] In contrast, several recent reports show that the use of the ribavirin–interferon combination for chronic hepatitis C in HIV-seropositive patients receiving highly active antiretroviral therapy can cause mitochondrial toxicity.[5,6] The aims of this study were to study the incidence of symptomatic mitochondrial toxicity in HIV/HCV-coinfected patients participating in a large trial comparing pegIFN α-2b plus daily ribavirin with thrice-weekly of 3 million units of IFN α-2b plus daily ribavirin; to describe the laboratory and clinical outcomes associated with symptomatic mitochondrial toxicity; and to identify associated risk factors.

METHODS

The results of the Agence Nationale de Recherche sur le SIDA HC02 Ribavic trial have been reported elsewhere.[3] In brief, 416 HIV/HCV-coinfected patients who had never received IFN or ribavirin were randomly assigned to receive either weekly subcutaneous injections of 1.5 μg/kg pegIFN α-2b (ViraferonPeg, Schering-Plough, Kenilworth, NJ) plus daily ribavirin (Rebetol, Schering-Plough) (800 mg) (n = 206), or thrice-weekly subcutaneous injections of 3 MU of IFN α-2b plus daily ribavirin (Rebetol, Schering-Plough) (800 mg) (n = 210) for 48 weeks. Patients were eligible if they had detectable

Received for publication February 14, 2005; accepted June 8, 2005.
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serum HCV RNA, liver biopsy results showing at least mild activity or fibrosis, a CD4 cell count above 200/mm^3, and stable HIV RNA load (<1-log variation in the previous 3 months) at randomization, and stable or no antiretroviral treatment during the previous 3 months. The main ineligibility criteria were active narcotic consumption or self-reported daily alcohol intake exceeding 40 g (women) or 50 g (men) within 3 months before entry to the study, decompensated cirrhosis, and hepatitis B surface antigen antigenemia.

For this study, we reviewed all recorded cases of symptomatic mitochondrial toxicity, defined as symptomatic hyperlactatemia or pancreatitis. Symptomatic hyperlactatemia was defined as a lactate elevation (venous lactate >2 mM) with clinical signs. Pancreatitis was diagnosed on the basis of typical clinical findings (eg, abdominal pain in a patient with no other causes of abdominal pain) with supporting biochemical signs or amylase or lipase activity more than 3 times the upper limit of normal.

The following data were collected at inclusion and every 4 weeks during follow-up: age, sex, body mass index, antiretroviral drugs received, anti-HCV treatment received, duration of HIV and HCV treatment, Metavir score at inclusion, symptoms and signs, biochemical test results, liver enzyme activities, CD4 lymphocyte counts, plasma HIV RNA load, and plasma HCV RNA load. Lipase, amylase, and lactate were assayed at the request of the treating physician. Serum bicarbonate and lactate were assayed in venous blood.

The χ^2 test or the Fisher exact test was used to analyze qualitative variables and the Mann-Whitney *U* test was used for quantitative variables. A logistic regression model was used to test possible associations between symptomatic mitochondrial toxicity (independent variable) and antiretroviral regimens (dependent variables). An exact method was used to calculate odds ratios and 95% CIs.[7] Incidence rates of mitochondrial toxicity events were calculated by using the number of person-days of ribavirin therapy as denominator,

TABLE 1. Clinical Characteristics of 11 HIV-HCV-Coinfected Patients With Symptomatic Mitochondrial Toxicity During Anti-HCV Treatment

Patient	Age/Sex	HCV Transmission Group	Antiretroviral Therapy, Daily Dose, and Duration (mo)	Metavir Score
Patients with symptomatic hyperlactatemia				
1	55/M	Unknown	ddI, 400 mg/d (22), d4T, 80 mg/d (22)	A1F3
2	39/F	IV drug use	ddI, 250 mg/d (34), d4T, 60 mg/d (34), NVP, 400 mg/d (34)	A2F2
3	35/F	IV drug use	ddI, 400 mg/d (36), d4T, 80 mg/d (36)	A2F3
4	42/M	IV drug use	ddI, 400 mg/d (56), d4T 80 mg/d (56), NVP, 400 mg/d (5)	A2F3
5	54/M	Transfusion	ddI, 250 mg/d (14), NFV 2500 mg/d (14), EFV 600 mg/d (25)	A1F3
6	47/F	IV drug use	ddI, 250 mg/d (25), 3TC, 300 mg/d (25), EFV, 600 mg/d (25)	A1F4
Patients with pancreatitis				
7	42/M	IV drug use	ddI, 500 mg/d (3) 3TC, 300 mg/d (3) NFV, 2500 mg/d (3)	A1F2
8	30/M	Transfusion	ddI, 400 mg/d (24), d4T, 60 mg/d (29), 3TC 300 mg/d (29)	A2F4
9	42/M	Unknown	ddI, 400 mg/d (11), d4T, 80 mg/d (11), EFV, 600 mg/d (11)	A2F1
10	44/F	Transfusion	ddI, 250 mg (14), d4T, 60 mg/d (40), ABC 600 mg/d (14)	A1F1
11	40/F	IV drug use	ddI, 200 mg/d (24), d4T, 60 mg/d (24), RTV, 200 mg/d (12), SQV, 800 mg/d (12)	A1F2

Patient	Anti-HCV Treatment, Duration (wk) at the Diagnosis	Symptoms	HIV/HCV Treatment Interruption (yes/no) and Outcome
Patients with symptomatic hyperlactatemia			
1	PegIFN–ribavirin (20)	Asthenia, nausea, vomiting, weight loss (15 kg), myalgia, dyspnea	Yes/yes/resolution
2	PegIFN–ribavirin (44)	Lipoatrophy, asthenia, weight loss (4 kg)	Switch to AZT, 3TC, NVP/yes/resolution
3	IFN–ribavirin (28)	Lipoatrophy, weight loss (10 kg), asthenia	Yes/ribavirin at W28 and peg-IFN at W36/resolution
4	PegIFN–ribavirin (20)	Asthenia, weight loss (6 kg), neuropathy	d4T at W20/no/stable
5	PegIFN–ribavirin (20)	Asthenia, weight loss (10 kg)	Yes/yes/resolution
6	PegIFN–ribavirin (8)	Asthenia, nausea	Yes/no/death at W64 (hepatic decompensation)
Patients with pancreatitis			
7	IFN–ribavirin (48)	Weight loss (6 kg), abdominal pain, vomiting	Yes/yes/resolution
8	PegIFN–ribavirin (44)	Abdominal pain, asthenia, fever	Yes/yes/resolution
9	PegIFN–ribavirin (28)	Abdominal pain	Yes/yes/resolution
10	PegIFN–ribavirin (15)	Acute abdominal pain	No/ddI/resolution
11	PegIFN–ribavirin (16)	Asthenia, nausea, vomiting, anorexia	Yes/ddI/resolution

Inflammation stage: A0, no histologic activity; A1, mild activity; A2, moderate activity; and A3, severe activity.
Fibrosis stage: F0, no fibrosis; F1, portal fibrosis; F2, septal fibrosis; F3, numerous septa without cirrhosis; F4, cirrhosis.
ABC, abacavir; AZT, zidovudine; EFV, efavirenz; IV, intravenous; NFV, nelfinavir; NVP, nevirapine; RTV, ritonavir; SQV, saquinavir.

and the number of events as numerator, in patients who took at least 1 dose of anti-HCV treatment. All statistical tests were 2-sided, with a type I error of 5%.

RESULTS

Symptomatic mitochondrial toxicity occurred in 11 of the 383 patients who received at least 1 dose of study medication (symptomatic hyperlactatemia and pancreatitis in 6 and 5 patients, respectively). The clinical and biologic characteristics of these 11 patients are summarized in Tables 1 and 2, respectively. The mean baseline CD4 cell count was 426 cells/mm^3 ($\pm$176), and plasma HIV RNA load ranged from less than 200 copies/mL (5 patients) to 33,200 copies/mL. Severe liver fibrosis (Metavir score F3 or F4) was present in 55% of the 11 patients. All the patients were receiving antiretroviral treatment. The regimens included didanosine (ddI) in every case, stavudine (d4T) in 8 cases, lamivudine (3TC) in 3 cases, abacavir in 1 case, protease inhibitors (PI) in 3 cases, and nonnucleoside reverse transcriptase inhibitors (NNRTIs) in 5 cases. The most common dual-NRTI regimen was ddI plus d4T (8 patients). The mean duration of ddI therapy at the diagnosis of symptomatic mitochondrial toxicity was 23.9 months ($\pm$14.4). ddI was used at the recommended doses, namely 400 mg (tablets) or 500 mg (powder) daily for patients weighing more than 60 kg and 250 mg daily (tablets) for patients under this weight.

Nine of the 11 patients were in the pegIFN–ribavirin arm. The mean interval between the outset of anti-HCV treatment and the diagnosis of symptomatic mitochondrial toxicity was 26.5 weeks ($\pm$13.4).

The clinical manifestations of symptomatic hyperlactatemia were general weakness (5 patients), weight loss (5 patients; $\geq$6 kg in 4 cases), nausea (2 patients), severe rapid-onset lipoatrophy (2 patients), dyspnea (1 patient), and peripheral neuropathy (1 patient). No intercurrent acute health disorders were diagnosed. Five patients had hyperlactatemia (>3 mM; $\geq$5 mM in 2 cases). Two patients (lactate level unknown in 1) had evidence of metabolic acidosis (bicarbonate levels 15 and 16 mM). In patients with pancreatitis, the main symptoms of pancreatitis were abdominal pain (4 patients) with or without nausea/vomiting (2 patients). The median serum lipase elevation was 10 times the upper limit of normal (range, 3.53–10 IU/L). A large increase in gamma-glutamyl transferase (GGT) levels was observed in 6 of the 11 patients (median elevation from 4.95 [2–7.4] to 14.35 [6–30] the upper limit of normal). By contrast, alanine aminotransferase (ALT) and alkaline phosphatase (alk Ph) levels were not significantly different from baseline values.

All but 1 of the patients (the patient with neuropathy) made a full recovery. However, one patient (patient 6) died 15 months later from liver failure, despite a sustained HCV virologic response.

Factors Associated With Symptomatic Mitochondrial Toxicity

Univariate analysis showed no association with age, gender, the body mass index, HCV transmission group, AIDS status, CD4 cell count, HIV viral load, mean duration of antiretroviral treatment, mean duration of HIV or HCV infection, ALT, GGT, or alk Ph levels, HCV viral load and HCV genotype, mean Metavir inflammation and fibrosis scores, or the HCV treatment arm (pegIFN plus ribavirin or standard IFN plus ribavirin) (Table 3).

The possible role of antiretroviral agents was analyzed by both single NRTI, NNRTI, and PI used at the initiation of anti-HCV treatment. Univariate analysis showed no

TABLE 2. Biologic Characteristics of 11 HIV/HCV-Coinfected Patients Who Developed Symptomatic Hyperlactatemia (n = 6) or Pancreatitis (n = 5) During Anti-HCV Treatment

Patients With Symptomatic Hyperlactatemia	ALT at Baseline/at the Event*	Alk Ph at Baseline/at the Event*	GGT at Base line/at the Event*	Lactates (mM) at the Event	Bicarbonates (mM) at the Event
1	1.2/3	1/3.9	2/30	7.4	26
2	1/2.6	1/1.1	2.3/6	3.8	ND
3	10.4/1.4	1/1.4	5.1/15.1	3.9	24
4	2/1	1/ND	3.2/3.4	7.3	ND
5	1/1	1/ND	2.6/1.5	ND	16
6	1/1.9	1/1.9	7.4/19.6	4.3	15
Patients With Pancreatitis	**ALT at Baseline/at the Event***	**Alk Ph at Baseline/at the Event***	**GGT at Base line/at the Event***	**Amylasemia at the Event***	**Lipasemia at the Event***
1	1.2/2.1	1/1.25	4.8/10.7	4	10
2	2.4/1.2	1.1/1	6.7/13.6	1	3.7
3	1.4/1	1/1	1.2/2.6	2.9	9.3
4	1.5/1	1/1	1/1	1.4	6.3
5	2.7/1.5	1/1	7/4.5	1.8	3.53

*Expressed as times the upper limit of normal.
ND, not done.

association with PI- or NNRTI-containing regimens. Among the NRTIs, only ddI was significantly associated with an increased risk of symptomatic mitochondrial toxicity. To study the impact of specific NRTI combinations, 4 groups of NRTI regimens were determined a priori. Two contained ddI (with or without d4T), 1 contained d4T but not ddI, and 1 contained neither ddI nor d4T. Eighty-three patients received regimens that included ddI, either with d4T (n = 52) or without d4T (n = 31). Symptomatic mitochondrial toxicity occurred in 8 (15.4%) of the 52 patients treated with ddI and d4T and in 3 (9.6%) of the 31 patients treated with ddI without d4T. No cases occurred among the 122 patients receiving d4T without ddI or in the 112 patients receiving an NRTI regimen containing neither d4T nor ddI. Multivariate analysis showed

TABLE 3. Characteristics of the Patients at Baseline

	Patients Without Symptomatic Mitochondrial Toxicity	Patients With Symptomatic Mitochondrial Toxicity	*P* Value
Total patients, n	372	11	
Age in years, mean (SD)	39.6 (5.3)	41.6 (8.1)	0.27
Men, n (%)	276 (74)	6 (55)	0.17
Body mass index, mean (SD)	22.3 (3.0)	22.3 (2.8)	0.71
Duration of HIV infection in years, mean (SD)	10.5 (4.4)	11.3 (4.6)	0.55
AIDS, n (%)	62 (17)	1 (9)	0.92
CD4 cell count (mm^3), mean (SD)	518 (229)	426 (176)	0.25
Plasma HIV-1 RNA			
Patients with <400 copies/mL, n (%)	245 (66)	7 (64)	1.0
Mean (SD) $\log_{10}$	3.7 (0.7)	3.5 (0.7)	0.52
Duration of HCV infection in years, mean (SD)	16.5 (5.1)	14.8 (4.8)	0.28
Risk group for HCV infection, n (%)			
Intravenous drug use	296 (80)	6 (55)	0.06
Transfusion	25 (7)	3 (27)	
Other	51 (14)	2 (18)	
Histology			
Inflammation score, mean (SD)	1.77 (0.69)	1.45 (0.52)	0.13
Fibrosis score, mean (SD)	2.32 (1.01)	2.55 (1.04)	0.45
Many septa (F3), cirrhosis (F4), n (%)	145 (39)	6 (55)	0.36
HCV genotype, n (%)			0.52
Genotype type 1	178 (48)	4 (36)	
Genotype types 2 or 3	148 (40)	4 (36)	
Genotype type 4	46 (12)	3 (27)	
ALT (normal upper limit), mean (SD)	2.2 (1.8)	2.33 (3.0)	0.45
GGT (normal upper limit), mean (SD)	2.8 (2.8)	3.7 (2.8)	0.26
Alk Ph (normal upper limit), mean (SD)	0.77 (0.34)	0.78 (0.23)	0.39
Serum HCV RNA, IU/mL, mean (SD) $\log_{10}$	5.87 (0.75)	5.93 (0.68)	1
Treatment assigned PegIFN α-2b, n (%)	185 (50)	9 (82)	0.06
Ongoing antiretroviral treatment	306 (82)	11 (100)	0.22
Duration of antiretroviral treatment in years, mean (SD)	5.3 (2.9)	6.0 (2.2)	0.23
Number of antiretroviral drugs*			
2	37 (12)	3 (27)	
≥3	268 (88)	8 (73)	0.5
Component drug of antiretroviral regimens			
Protease inhibitor, n (%)	151 (49)	2 (18)	0.06
NNRTI, n (%)	116 (38)	5 (45)	0.75
NRTI, n (%)	303 (99)	11 (100)	1
d4T	165 (54)	8 (73)	0.36
Zidovudine	104 (34)	0	0.02
3TC	223 (73)	3 (27)	0.0025
ddI	72 (23)	11 (100)	0.001
Abacavir	36 (12)	1 (9)	1

*A total of 317 patients were receiving antiretroviral therapy; 1 patient received only 1 antiretroviral drug.
The body mass index is weight in kilograms divided by height in meters squared.

that ddI, with or without d4T, was associated with symptomatic mitochondrial toxicity (OR 46, 95% CI, 7.4 to infinity; $P < 0.001$) compared with regimens with neither ddI nor d4T. The risk of symptomatic mitochondrial toxicity was not increased in patients treated with d4T without ddI (OR 1.8; 95% CI, 0.4–11.3). Likewise, triple-NRTI regimens without ddI were not associated with symptomatic mitochondrial toxicity. The risk of symptomatic mitochondrial toxicity associated with ddI was similar whether patients were receiving 1 or 2 other NRTIs.

DISCUSSION

The incidence of symptomatic hyperlactatemia in adults receiving at least 1 NRTI has been estimated in 2 prospective studies to be 8 to 20.9 per 1000 patient-years.[8,9] In our study, as in HCV-monoinfected patients treated with the IFN–ribavirin combination, we observed no cases of symptomatic mitochondrial toxicity in patients receiving anti-HCV treatment without concurrent antiretroviral therapy. Conversely, the incidence of symptomatic mitochondrial toxicity in patients receiving both anti-HCV and anti-HIV therapy was higher (47.5 per 1000 patient-years, based on 278 patient-years of ribavirin therapy) than that reported in patients receiving anti-HIV treatment alone, suggesting that an interaction between the 2 treatments increases the risk of symptomatic mitochondrial toxicity.

We found that concomitant ddI therapy in patients receiving both IFN (standard or pegylated) and ribavirin was associated with an adjusted 46-fold increase in the risk of symptomatic mitochondrial toxicity compared with patients receiving antiretroviral regimens that did not contain ddI. The incidence of symptomatic mitochondrial toxicity was 200.2 per 1000 patient-years (based on 55 patient-years of ddI and ribavirin therapy), pointing to synergism between ddI with ribavirin. Indeed, although the lack of a no-ribavirin arm theoretically undermines the conclusion that these events are related to ribavirin rather than interferon, in vitro studies had shown that ribavirin enhances both the efficacy and the toxicity of ddI.[10–13] Furthermore, all previously reported HIV/HCV-coinfected patients who developed symptomatic mitochondrial toxicity while receiving IFN (standard or pegylated) combined with ribavirin, in addition to anti-HIV therapy, were also receiving ddI.[5,6,14–16]

In our study the incidence of symptomatic mitochondrial toxicity was not significantly different between patients who were taking both ddI and d4T and those taking ddI alone or combined with NRTIs other than d4T. No cases were observed among patients treated with d4T without ddI, or with a triple-NRTI combination without ddI. This is consistent with the results of an in vitro study showing that mitochondrial DNA depletion in hepatocytic cells due to the ddI–d4T combination was not more severe than with ddI alone.[17] Our results are also in keeping with those of a large cross-sectional study, in which ddI-containing regimens doubled the relative risk of hyperlactatemia, whereas the risk was similar with d4T and zidovudine; the incidence in the 2 groups depended on whether the latter drugs were combined with ddI or 3TC.[18]

Mitochondrial toxicity can produce a broad spectrum of clinical disorders, but initial symptoms (nausea, vomiting, and abdominal pain or, in cases with more insidious onset, fatigue and weight loss) are generally nonspecific.[8,19] In our patients, the clinical manifestations usually consisted of weight loss, weakness, nausea, and abdominal pain and were therefore indistinguishable from common adverse effects of IFN–ribavirin combination therapy.[1,2] Serum lactate and lipase should therefore be assayed in patients presenting with these manifestations or with more acute symptoms. Attention must also be paid to gradually increasing GGT levels, as this is not a common effect of HCV infection. As in previously reported cases of symptomatic mitochondrial dysfunction, we noted a gradual significant increase in GGT levels (mean 14.35, range 6–30 upper limit of normal (ULN) in 6 of our patients.[5,15] The pancreatic toxicity of ddI is dose related: its frequency is 1% to 7% with currently recommended doses, and most cases occur within the first 6 months of therapy.[20–22] In our study the observed incidence of pancreatitis in ddI-treated patients was 6%; it might have been higher, however, as amylase and lipase were not routinely assayed during the trial. The median duration of ddI therapy at the diagnosis of pancreatitis was 14 months (range, 3–24 months), suggesting that the addition of ribavirin increased the risk (median duration of HCV treatment: 26 weeks; range, 15–48 weeks).

CONCLUSION

In this study, no cases of symptomatic mitochondrial toxicity occurred in anti-HCV–treated patients who were not also taking antiretroviral therapy or whose antiretroviral regimen did not contain ddI. Conversely, concomitant treatment with ddI and the IFN–ribavirin combination resulted in a 46-fold increase in the relative risk of symptomatic mitochondrial toxicity. These results, together with other published data, suggest that coadministration of ribavirin and ddI should be avoided; if unavoidable, patients should be monitored closely for signs of mitochondrial toxicity.

ACKNOWLEDGMENT

The authors thank David Young for editing the manuscript.

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Spontaneous Hepatic Decompensation in Patients Coinfected with HIV and Hepatitis C Virus during Interferon-Ribavirin Combination Treatment

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Spontaneous hepatic decompensation was observed in 7 of 383 patients coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) who were receiving treatment with interferon and ribavirin. Multivariate analysis identified the following risk factors: didanosine use (odds ratio [OR], 8.8; 95% confidence interval [CI], 1.2–102.3; $P < .02$), cirrhosis, (OR, 8.8; 95% CI, 1.2–104.2; $P < .02$), and elevated total bilirubin level (OR, 7.9; 95% CI, 1.08–93.3; $P < .03$). Didanosine should thus not be given to patients with cirrhosis, particularly when treatments for HCV and HIV infections have to be administered concomitantly.

The introduction of HAART in the mid-1990s led to a substantial decrease in both morbidity and mortality associated with opportunistic diseases. With the resulting increase in life expectancy, diseases associated with hepatitis C virus (HCV) infection have become more frequent in the HIV-infected population, with several studies reporting that they are the leading cause of non-AIDS–related deaths among coinfected patients [1, 2]. Combination therapy with peginterferon and ribavirin is currently the standard of care for patients with HCV infection [3, 4], but this treatment is associated with a high prevalence of intolerable adverse effects among HIV-HCV–coinfected patients [4, 6]. We observed a disturbing rate of spontaneous hepatic decompensation among HIV-HCV–coinfected patients enrolled in a randomized, controlled trial comparing peginterferon alfa-2b plus ribavirin with conventional IFN alfa-2b plus ribavirin [4]. The aim of the present study was to analyze the biological and clinical features of, the outcome of, and possible risk factors for spontaneous hepatic decompensation in such patients.

Methods. The results of the ANRS HC02 RIBAVIC study have been reported elsewhere [4]. In brief, of 416 HIV-HCV–coinfected patients who had never received IFN or ribavirin, 206 were randomly assigned to receive either weekly subcutaneous injections of 1.5 μg/kg of peginterferon alfa-2b (ViraferonPeg; Schering-Plough) plus 800 mg/day of ribavirin for 48 weeks, and 210 were randomly assigned to receive thrice-weekly subcutaneous injections of 3 MU of IFN alfa-2b plus 800 mg/day of ribavirin for 48 weeks. Patients were eligible for study enrollment if they had detectable levels of HCV RNA in serum, underwent liver biopsy that showed at least mild hepatic inflammation or fibrosis, had a CD4 cell count of >200 cells/mm^3, had a stable HIV RNA load (defined as a variation of <1 log copies/mL during the previous 3 months) at randomization, and had received stable or no antiretroviral treatment during the previous 3 months. The main ineligibility criteria were active narcotic use and/or a self-reported daily alcohol intake of >40 g (for women) and >50 g (for men) within 3 months before entry to the study, presence of decompensated cirrhosis, and presence of hepatitis B virus surface antibody antigenemia.

Hepatic inflammation and fibrosis stage, classified by use of the Metavir scoring system [5], were assessed by means of liver biopsy performed ⩽18 months preceding inclusion in the study. Hepatic inflammation (reflecting the severity of necroinflammatory lesions) was scored on a 4-point scale, as follows: 0, no histologic activity; 1, mild activity; 2, moderate activity; and 3, severe activity. Liver fibrosis (reflecting the stage of fibrosis) was scored on a 5-point scale, as follows: 0, no fibrosis; 1, fibrosis without septa; 2, portal fibrosis with few septa; 3, portal fibrosis with many septa; and 4, cirrhosis.

A total of 383 patients who received at least 1 dose of study medication were included in this analysis. We reviewed all of the following events corresponding to hepatic decompensation: ascites, jaundice (serum bilirubin level, >51 mmol/L), hepatic encephalopathy, and bleeding from esophageal varices. Only cases of spontaneous hepatic decompensation were analyzed. Nine patients had hepatic decompensation, which was spontaneous in 7, related to hepatocellular carcinoma in 1, and related to staphylococcal septicemia in 1. The sex of each patient was recorded, and data on the following characteristics were obtained at the

Received 9 June 2005; accepted 2 August 2005; electronically published 11 November 2005.

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Clinical Infectious Diseases 2005; 41:1806–9

1058-4838/2005/4112-0020$15.00

Table 1. Clinical characteristics of 7 patients coinfected with HIV and hepatitis C virus (HCV) who developed spontaneous hepatic decompensation during treatment for HCV infection.

Patient	Age, sex	CDC	Antiretroviral therapy	Metavir score, by condition		Duration of treatment for HCV infection, weeks	Time to decompensation after start of treatment for HCV infection, weeks	Received interrupted treatment, by infection treated		Outcome
				Hepatic inflammation[a]	Fibrosis[b]			HIV	HCV	
1	39, F	B	Stavudine, lamivudine, nelfinavir	1	4	Peginterferon-ribavirin, 32	24	Yes	Yes	Death at month 33
2	49, M	A	Didanosine, stavudine, abacavir	2	2	Peginterferon-ribavirin, 8	12	No	Yes	Death at week 30
3	35, F	B	Didanosine, stavudine, nelfinavir	1	2	IFN-ribavirin, 1	1	Yes	No	Resolution
4	47, F	C	Didanosine, lamivudine, efavirenz	2	4	Peginterferon-ribavirin, 48	60	Yes	No	Death at week 64
5	36, M	B	Didanosine, nevirapine, nelfinavir	2	4	IFN-ribavirin, 32	20	Yes	Yes	Death at week 37
6	44, M	C	Zidovudine, lamivudine, nelfinavir	1	4	IFN-ribavirin, 48	20	No	No	Death at month 28
7	37, M	A	Didanosine, stavudine, ritonavir, saquinavir	2	4	IFN-ribavirin, 13	13	Yes	Yes	Resolution

[a] Scores reflect the severity of necroinflammatory lesions, as follows: 0, no histologic activity; 1, mild activity; 2, moderate activity; and 3, severe activity.
[b] Scores reflect the stage of fibrosis, as follows: 0, no fibrosis; 1, portal fibrosis; 2, septal fibrosis; 3, numerous septa without cirrhosis; and 4, cirrhosis.

Table 2. Factors associated with spontaneous liver decompensation, according to results of univariate logistic regression analysis.

Factor	Patients with spontaneous hepatic decompensation (n = 7)	Patients without spontaneous hepatic decompensation (n = 376)	P
Metavir fibrosis score[a]	3.4 ± 0.1	2.3 ± 1	.008
Bilirubin level, times the upper limit of normal	1.33 ± 0.5	0.71 ± 0.4	.001
Alkaline phosphatase level, times the upper limit of normal	1.09 ± 0.5	0.76 ± 0.33	.05
Platelet level, platelets/mm^3	102,571 ± 41,564	194,306 ± 67,240	<.001
Prothrombin time, % of normal time	76 ± 18.5	91 ± 10.9	.009
Duration of antiretroviral treatment, years	7 ± 2.9	4.3 ± 3.3	.03
Received didanosine, proportion (%) of patients	5/7 (71.4)	77/310 (24.8)	<.006
Duration of didanosine treatment, years	3.15 ± 1.0	2.2 ± 1.6	.07

NOTE. Data are mean values ± SD, unless otherwise indicated.

[a] Fibrosis stage was classified as follows: 0, no fibrosis; 1, portal fibrosis; 2, septal fibrosis; 3, numerous septa without cirrhosis; and 4, cirrhosis.

time of screening and every 4 weeks during the follow-up period: age, duration of HIV infection, duration of HCV infection (defined as the date of either the first blood transfusion or initial injection narcotic use), receipt of antiretroviral drugs, receipt of treatment for HCV infection, Metavir score, symptoms, results of biochemical assays, liver enzyme activities, CD4 lymphocyte count, plasma HIV RNA load, and HCV RNA load.

The χ^2 test or Fisher's exact test were used to analyze qualitative variables, and the Mann-Whitney U test was used for analysis of quantitative variables. A logistic regression model was used to test possible associations between spontaneous hepatic decompensation (input variable) and pretreatment characteristics (outcome variables). Characteristics with P values of <.20 in univariate analysis were included in multivariate models by use of a backwards elimination procedure. An exact method was used to calculate ORs and 95% CIs [7]. All statistical tests were 2-sided, with a type I error of 5%.

Results. Spontaneous hepatic decompensation occurred in 7 of 383 patients who received at least 1 dose of study medication. The clinical and biological characteristics of these 7 patients are summarized in table 1. The mean Metavir scores at baseline for hepatic inflammation and fibrosis were 1.7 ± 0.7 and 3.4 ± 0.1, respectively. Five patients had compensated cirrhosis.

Three patients were in the peginterferon alfa-2b–ribavirin arm. The time between the start of HCV therapy and decompensation was ⩽24 weeks for 6 patients and 60 weeks for 1 patient. In the 2 patients with a fibrosis score of 2, based on findings of pretreatment liver biopsy (performed 9 and 10 months before the outset of treatment for HCV infection for patients 2 and 3, respectively), a second liver biopsy performed during hepatic decompensation showed a Metavir score of 2 (for hepatic inflammation) and 4 (for fibrosis) in both cases. Patients were infected with HCV genotype 1 in 5 cases and with HCV genotype 3 and 4 in 1 case each. There was no increase in the HCV RNA load before hepatic decompensation. The HCV RNA load decreased to a level less than the detection limit (50 IU/mL) in patient 4 one month after the onset of treatment for HCV infection, and it remained undetectable throughout the follow-up period.

All patients were receiving antiretroviral treatment at the onset of hepatic decompensation. The mean baseline CD4 cell count was 403 ± 243 cells/mm^3, and all but 1 patient had a plasma HIV load <200 copies/mL. The antiretroviral regimen included didanosine for 5 patients, stavudine for 4, lamivudine for 3, abacavir for 1, nelfinavir for 4, efavirenz for 1, and ritonavir-saquinavir for 1. The mean duration of antiretroviral therapy was 7 ± 2.9 years. The mean duration of didanosine therapy at the onset of hepatic decompensation was 3.15 ± 1 years.

Five of 7 patients died as a result of hepatic decompensation. Patient 4 had an undetectable HCV load (<50 IU/mL). This patient had developed symptomatic hyperlactatemia after 1 month of treatment for HCV infection. Hepatic decompensation resolved in the 2 surviving patients; treatment for HCV infection was stopped for 1 patient, and treatment for HIV infection was stopped for both patients.

Univariate analysis showed that spontaneous hepatic decompensation was significantly associated with a higher Metavir score for fibrosis, higher total bilirubin and alkaline phosphatase levels, lower platelet counts, lower prothrombin levels, a longer history of antiretroviral treatment, didanosine exposure, and a longer duration of didanosine exposure (table 2). The following factors were not associated with spontaneous hepatic

Table 3. Factors associated with spontaneous liver decompensation, according to results of multivariate logistic regression analysis.

Factor	OR (95% CI)	P
Didanosine	8.8 (1.2–102.3)	.02
Metavir fibrosis score of 4[a]	8.8 (1.2–104.2)	.02
Bilirubin level below the normal range	7.9 (1.08–93.3)	.03

[a] Fibrosis stage was classified as follows: 0, no fibrosis; 1, portal fibrosis; 2, septal fibrosis; 3, numerous septa without cirrhosis; and 4, cirrhosis.

decompensation: age, sex, body mass index, AIDS status, HIV load, CD4 cell count, mean duration of HCV or HIV infection, HCV load, HCV genotype, mean Metavir score for hepatic inflammation, hemoglobin and alanine aminotransferase levels, leukocyte count, HCV treatment arm, or use of protease inhibitors, nonnucleoside reverse-transcriptase inhibitors, or nucleoside reverse-transcriptase inhibitors (NRTIs) other than didanosine. In multivariate analysis, didanosine (OR, 8.8; 95% CI, 1.2–102.3; $P < .02$), cirrhosis (defined as a Metavir score for fibrosis of 4; OR, 8.8; 95% CI, 1.2–104.2; $P < .02$), and a bilirubin level greater than the upper limit of normal (OR, 7.9; 95% CI, 1.08–93.3, $P < .03$) remained significantly associated with spontaneous hepatic decompensation (table 3).

Discussion. Host risk factors for spontaneous hepatic decompensation are markers for cirrhosis—namely, high Metavir scores for fibrosis, elevated total bilirubin and alkaline phosphatase levels, and low platelet counts and prothrombin levels. The link we observed between the risk of spontaneous hepatic decompensation and the duration of antiretroviral treatment, previous didanosine exposure, and the duration of didanosine exposure suggests a role of drug toxicity. Multivariate analysis revealed that concomitant treatment with didanosine and IFN alfa-2b–ribavirin or peginterferon alfa-2b–ribavirin was associated with an adjusted 8.8-fold increase in the risk of spontaneous hepatic decompensation. The role of drug toxicity is also supported by the rapidly progressing fibrosis to cirrhosis observed in 2 patients (the Metavir fibrosis score was 2 less than 10 months before the onset of treatment for HCV infection), together with the death due to liver failure at week 60 of a patient with an HCV virological response who had developed symptomatic hyperlactatemia at week 4 of treatment for HCV infection. In addition, didanosine was also identified as a risk factor for hepatic decompensation in another large trial comparing peginterferon (with or without ribavirin) and IFN-ribavirin in HIV-HCV–coinfected patients [8]. The rate of decompensation among patients with cirrhosis was similar in the study by Mauss et al. [8] (10.4% [14 of 134 patients]) and our study (8.3% [5 of 60 patients]).

Liver toxicity is a complication of antiretroviral therapy, and it is even more frequent among patients who also have chronic hepatitis C [9–11]. NRTIs induce mitochondrial toxicity by inhibiting mitochondrial γ polymerase [12]. Furthermore, ribavirin is known to enhance didanosine phosphorylation, and most reported cases of symptomatic mitochondrial toxicity in HIV-HCV–coinfected patients receiving IFN-α–ribavirin or peginterferon alfa–ribavirin concomitantly with therapy for HIV infection have involved didanosine [13–17].

Because HIV-infected patients with hepatitis C require treatment for HCV infection, clinicians should be aware of the potential overlapping toxicity of treatments for HCV-HIV coinfection. If treatment for the 2 infections must be administered concomitantly, didanosine should be avoided, particularly for patients with advanced liver fibrosis. This could enhance the safety of treatments for HIV-HCV coinfection, notably by helping to avoid hepatic decompensation.

Acknowledgments

Financial support. ANRS, Essai HC02, and SIDACTION.
Potential conflicts of interest. All authors: no conflicts.

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VIII-2- Incidence et facteurs de risque d'infection bactérienne

La neutropénie est un effet secondaire observé avec une fréquence allant jusqu'à 50% dans certaines études menées chez les patients co-infectés VIH/VHC [93, 94]. Elle est plus sévère sous peg-IFN comparé à l'IFN standard [93]. Chez les patients mono-infectés par le VHC, les infections bactériennes sont rares [93]. La faible incidence de ce risque n'a pas d'explication claire : est-elle liée aux recommandations de diminution de la posologie de l'interféron en cas de neutropénie, à l'utilisation des facteurs de croissance ou au fait que la baisse des polynucléaires neutrophiles n'est pas associée à un risque infectieux plus élevé. Dans l'essai RIBAVIC, l'incidence des infections bactériennes était plus élevée (54 pour 1000 patients-années) que chez les patients mono-infectés VHC (24 pour 1000 patients/années) [95]. Dix sept patients ont présenté des infections bactériennes. Seul un patient avait une neutropénie à l'inclusion (770/mm^3). Il développa une sinusite à S12 en dépit de la correction de la neutropénie sous facteurs de croissance. Parmi les 54 patients (14%) ayant présenté une neutropénie < 750/mm^3 en cours de traitement, seulement 2 patients ont présenté une infection bactérienne. En analyse multivariée, trois facteurs étaient associés au risque d'infection bactérienne : la durée moyenne de l'infection par le VHC (hazards ratio (HR), 1.2; $IC_{95\%}$, 1.07 to 1.35, p = 0.0015), le taux de prothrombine à l'inclusion (HR, 0.95; $IC_{95\%}$, 0.91 to 0.98, p = 0.003) et le taux d'hémoglobine à l'inclusion (HR, 0.71; $IC_{95\%}$, 0.52 to 0.96, p = 0.027). Ces trois facteurs sont donc associés à l'infection par le VHC, la baisse hémoglobine pouvant être secondaire à la fois liée à l'infection par le VHC et par le VIH. Chez les patients mono-infectés par le VHC, la fibrose est associée à une majoration du risque d'infection bactérienne [96]. Dans notre étude, il

semble donc que le risque d'infection bactérienne soit associé au score de fibrose d'autant que la thrombopénie était également un facteur de risque significatif en analyse univariée. En effet, la durée de l'infection par le VHC est associée à un score de fibrose élevé chez les patients co-infectés VIH/VHC [30]. Par ailleurs, une hémoglobine et un taux de prothrombine bas sont tous deux des marqueurs d'un score de fibrose élevé. En revanche, comme c'est le cas chez les patients mono-infectés par le VHC, le taux des globules blancs ou des neutrophiles à l'inclusion ne constituaient pas un facteur de risque [93, 97, 98]. Ce résultat est en accord également avec une étude faite chez les patients co-infectés [99]. Par ailleurs, alors que le Peg-interféron est associé à un risque plus élevé de neutropénie, il ne constituait pas un facteur de risque d'infection bactérienne en cours de traitement [93].

Risk factors for bacterial infections in HIV/HCV-coinfected patients treated with interferon plus ribavirin

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Key words: HIV/HCV coinfection, bacterial infection, HCV therapy, HCV viral load

Total number of words: 1729

Financial support: ANRS, Essai HC 02, SIDACTION

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Abstract

Bacterial infections occurred in 17 of 383 HIV/HCV-coinfected patients receiving interferon plus ribavirin. Three factors were identified by multivariate analysis: mean duration of HCV infection (hazards ratio (HR), 1.2; 95% CI, 1.07 to 1.35, p = 0.0015), baseline prothrombin level (HR, 0.95; 95% CI, 0.91 to 0.98, p = 0.003), and baseline hemoglobin level (HR, 0.71; 95% CI, 0.52 to 0.96, p = 0.027). Markers of advanced liver fibrosis and not neutropenia were predictors of increased susceptibility to bacterial infections.

Combination therapy with pegylated interferon (peg-IFN) and ribavirin is currently the standard of care for patients with HCV infection [67-69]. A common adverse effect of interferon alfa therapy is neutropenia due to bone marrow suppression [93, 94]. Peginterferon causes more severe neutropenia than standard interferon [93]. Bacterial infections are infrequent in HCV-monoinfected patients, but their incidence in HIV-coinfected patients is unknown [93]. The objective of this study was to determine the incidence and risk factors for bacterial infections among HIV/HCV-coinfected patients enrolled in a randomized controlled trial comparing pegylated interferon alfa-2b plus ribavirin with conventional interferon alfa-2b plus ribavirin (the ANRS HC02 RIBAVIC study)[67].

Methods

The results of the ANRS HC02 RIBAVIC study have been reported elsewhere [67]. In brief, 206 of 416 HIV/HCV-coinfected patients who had never received interferon or ribavirin were randomly assigned to receive weekly subcutaneous injections of 1.5 µg/kg peginterferon alfa-2b (ViraferonPeg®, Schering-Plough) plus 800 mg/day ribavirin for 48 weeks, and 210 patients were randomly assigned to receive thrice-weekly subcutaneous injections of 3 MU of interferon alfa-2b plus ribavirin 800 mg/day for 48 weeks. Patients were eligible if they had detectable serum HCV RNA, liver biopsy results showing at least mild activity or fibrosis, a CD4 cell count above 200/mm^3 and stable HIV RNA load (less than 1 log variation in the previous 3 months) at randomization, and stable or no antiretroviral treatment during the previous 3 months. The main ineligibility criteria were active narcotic consumption and/or a self-reported daily alcohol intake exceeding 40 g (women) or 50 g (men) within 3 months before entry to the study; decompensated cirrhosis; HBs antigenemia; leukopenia (< 3000 cells/mm^3); and neutropenia (< 1500 cells/mm^3).

Liver inflammation and fibrosis, classified with the METAVIR scoring system, were assessed by means of liver biopsy done less than 18 months before inclusion. Disease activity (reflecting the intensity of necroinflammatory lesions) was scored as follows: A0, no histologic activity; A1, mild activity; A2, moderate activity; and A3, severe activity. Liver fibrosis was scored on a 5-point scale, as follows: 0, no fibrosis; 1, fibrosis without septa; 2, portal fibrosis with few septa; 3, portal fibrosis with many septa; and 4, cirrhosis [100].

Three hundred eighty-three patients who received at least one dose of study medication were included in this analysis. We reviewed all events corresponding to bacterial infections that occurred during or less than two weeks after stopping treatment for HCV infection. Episodes of infection were recorded if they were confirmed (positive culture or radiography) or suspected, and if they required oral or parenteral antibiotic therapy. The investigators were advised to reduce the peginterferon alfa 2b dose from 1.5 µg/kg to 1.0 or 0.5 µg/kg per week if the neutrophil count fell below 900 or 750/mm^3, respectively, and to reduce the interferon alfa 2b dose from 3.0 to 1.5 million units three times per week if the neutrophil count fell below 750/mm^3.

The following data were collected at enrolment and, where relevant, every four weeks during follow-up: age, sex, duration of HIV infection, duration of HCV infection (defined as the date of the first transfusion or the date of initial intravenous narcotic use), antiretroviral drugs received, anti-HCV treatment received, the Metavir score, symptoms, biochemical assay values, the CD4 lymphocyte count, plasma HIV viral load, and HCV viral load.

The primary endpoint was the time to onset of bacterial infections during treatment for HCV infection. Data were censored at the time of the last anti-HCV treatment intake or at the time of death or loss to follow-up, whichever occurred first. Univariate Cox proportional-hazards models were used to identify factors associated with the primary endpoint. As the number of events was few in relation to the number of included independent variables, factors with P

values below 0.05 in univariate analysis (Wald Chi-square test) and confirmed also by bootsrap analysis were included in a multivariate Cox proportional-hazards model based on a backwards elimination procedure. This last model was also evaluated by boostrap analysis. Quantitative factors identified in multivariate analysis were dichotomized around the median. All statistical tests were two-sided, with a type I error of 5%.

Results

Eighteen bacterial infections occurred in 17 of the 383 patients who received at least one dose of study medication. There were two cases of pyelonephritis and one case of prostatitis due to *Escherichia coli*, one case of diarrhea due to *Klebsiella oxytoca*, two cases of septicemia (1 due to *Salmonella enterica* and one to *Staphycoccus aureus*), one case of *Streptococcus pneumoniae* meningitis, eight lower respiratory tract infections (two in the same patient), one case of sinusitis and two cases of cellulitis.

Fifteen patients (88.2%) were men, and the mean age was 39.9 (±5.4) years. Intravenous drug use was the risk factor for HCV infection in 88.2% of cases. Four patients had compensated cirrhosis and 14 were receiving antiretroviral therapy (mean duration (±SD) 5.5 ± 4.5 years). Two patients received cotrimoxazole prophylaxis. At baseline, the mean (± SD) CD4 lymphocyte count was 425 (±205) cells/mm^3 and plasma HIV RNA load was < 400 copies/ml in 8 patients. Twelve patients were in the interferon alfa 2b-ribavirin arm. The median time between the beginning of HCV therapy and the onset of bacterial infection was 20 weeks (range, 2-40). All the patients recovered on intravenous antibacterial therapy. Four patients permanently stopped taking HCV therapy.

Only one patient who developed an infection had neutropenia at baseline (770/mm^3). He developed sinusitis at week 12, despite the correction of neutropenia by granulocyte colony-

stimulating factor therapy started at week 4. During the course of HCV therapy, 54/383 patients (14%) developed neutropenia <750/mm^3, but only two presented bacterial infections.

Table 1 lists factors with P values of <0.05 in univariate analysis. Patients who developed infections had a significantly longer history of HCV infection (19.7 ± 5.8 years versus 16.2 ± 4.9 years; p = 0.0046) than other patients. The other baseline variables significantly associated with the risk of bacterial infection were a lower hemoglobin level, a lower leukocyte count, a lower neutrophil count, a lower platelet count and a lower prothrombin level.

The following baseline factors were not significantly associated with the risk of bacterial infection: age, sex, body mass index, HCV transmission group, mean METAVIR scores for hepatic necroinflammation and fibrosis, cirrhosis, HCV genotype, HCV treatment arm, duration of HIV infection, prior AIDS diagnosis, HIV viral load, CD4 cell count, antiretroviral therapy, mean duration of antiretroviral therapy, use of nucleoside reverse transcriptase inhibitors, protease inhibitors or non nucleoside reverse transcriptase inhibitors, lymphocyte count, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, alkaline phosphatase and bilirubin.

In multivariate analysis, the mean duration of HCV infection (HR, 1.2; 95% CI, 1.07 to 1.35, p =0.0015), the baseline hemoglobin level (HR, 0.71; 95% CI, 0.52 to 0.96, p = 0.027), the baseline prothrombin level (HR, 0.95 95% CI, 0.91 to 0.98, p = 0.003) remained significantly associated with the risk of bacterial infection.

Discussion

We found a 54 per 1000 patient-years incidence rate of bacterial infections during anti-HCV treatment. Independent risk factors for bacterial infections in our patients, whose HIV infection was well controlled, were a longer history of HCV infection, lower baseline

hemoglobin and prothrombin levels. Thus, two of the three risk factors identified here were only HCV-related. It is noteworthy that the duration of HCV infection correlates with the severity of fibrosis in HIV/HCV-coinfected patients and that advanced liver fibrosis is associated with increased risk of bacterial infection [22, 27, 30, 67, 96]. Although cirrhosis was not more frequent in patients who had bacterial infections (4/16 patients, 25%), low hemoglobin and prothrombin levels are established markers of advanced liver fibrosis. Another marker of liver fibrosis, a low platelet count, was also associated with the risk of bacterial infection, but only in univariate analysis. Furthermore, in HCV mono-infected patients, low reticulocyte count was identified as the only baseline measure that predicted subsequent infection [94].

Neutropenia is not a risk factor for bacterial infection in HCV-monoinfected patients treated with interferon alfa plus ribavirin [93, 97, 98]. Although interferon dose reductions for neutropenia were significantly more frequent in the peginterferon arm of our study (7% versus 2%; p=0.04), as previously observed elsewhere, the type of interferon (pegylated versus standard) was not a risk factor [67-69]. In our study, only 2 patients among the 54 (3.7%) who developed neutropenia during the course of HCV therapy presented bacterial infection. Our results are in keeping with those of Cooper CL, et al which observed that neutrophil nadir did not predict infection risk or rate. Interferon-induced neutropenia does not therefore appear to increase the risk of bacterial infections [99].

In conclusion, factors independently associated with the risk of bacterial infection during interferon-ribavirin combination therapy in HIV/HCV-coinfected patients are related to the duration of HCV infection and to markers of liver fibrosis, but in contrast, not to neutropenia or characteristics of HIV infection, including CD4 cell count

Acknowledgments: We thank David Young for editing the manuscript.

Table 1 Characteristics of the Patients at Baseline

	Patients without bacterial infection	Patients with bacterial infection
Total patients, n	366	17
Age [mean years (SD)]	39.6 (5.4)	39.9 (5.4)
Duration of HIV infection in years [mean (SD)]	10.4 (4.4)	12.5 (3.6)
AIDS, [No. (%)]	58 (15.8)	5 (29.4)
CD4 cell count – (/mm^3) [mean (SD)]	534 (247)	425 (205)
Patients with <400 copies /ml, [No. (%)]	244 (66.6)	8 (47.1)
Duration of HCV infection in years [mean (SD)]	16.2 (4.9)	19.7 (5.8)
Serum HCV RNA (IU/ml), [mean (SD)] log_{10}	5.82 (0.74)	6.13 (0.69)
Treatment assigned- Interferon a-2b, [No. (%)]	177 (48.3)	12 (70.6)
Hemoglobin g/dl [mean (SD)]	14.5 (1.4)	13.8 (1.59)
Leucocyte count (/mm^3) [mean (SD)]	6148 (2112)	5070 (1776)
Neutrophil count (/mm^3) [mean (SD)]	3220 (1637)	2451 (1117)
Platelet count (/mm^3) [mean (SD)]	194 (68)	159 (58)
Prothrombin time (% of normal)[mean (SD)]	91.9 (10.9)	84.2 (13.3)
Alk Ph (normal upper limit) [mean (SD)]	0.76 (0.34)	0.91 (0.31)
Bilirubin (normal upper limit) [mean (SD)]	0.71 (0.4)	0.94 (0.7)

Table 2. Univariate and multivariate analysis of baseline factors associated with the risk of bacterial infection (only factors with $p< 0.05$ are shown for the univariate analysis)

	Univariate		Multivariate	
Baseline factor	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Higher duration of HCV infection (years)**	1.153 (1.045-1.273)	0.0046	1.153 (	0.0047
Higher hemoglobin (g/dl)	0.685 (0.495-0.946)	0.022	0.72(0.52 - 0.96)	0.0046
Lower leukocyte count (/mm^3)	1.0 (0.99-1.00)	0.031		
Lower neutrophil count (/mm^3)	1.0 (0.99-1.00)	0.044		
Higher platelet count (/mm^3) [mean (SD)]	0.99 (0.983- 0.999)	0.036		
Higher prothrombin time (% of normal)	0.948 (0.916-0.982)	0.003	0.95 (0.91 - 0.98)	0.017

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VIII-3- Incidence et facteurs de risque d'anémie

L'anémie constitue une des complications les plus fréquentes du traitement anti-VHC. Elle est secondaire à la fois à une hémolyse due à la ribavirine et à une myélosuppression due à l'IFN [101]. Dans l'essai RIBAVIC, en raison de l'antagonisme décrit in vitro entre la ribavirine et la zidovudine et la stavudine, et d'une hémoglobine plus basse chez les patients co-infectés VIH-VHC, la posologie retenue pour la ribavirine fût de 800 mg/jour [102, 103]. Depuis, il est montré qu'une posologie de ribavirine plus élevée (1000-1200 mg/j voire plus) et/ou une posologie de ribavirine par kg de poids supérieure à 10.6 mg/kg sont associées à une meilleure réponse virologique chez les patients infectés par un génotype non 2 non 3 [65, 104]. Dans l'essai RIBAVIC, la posologie moyenne de ribavirine était de 12.3 ±2,1 mg/kg. Chez les patients mono-infectés VHC, le risque d'anémie sévère définie par une hémoglobine inférieure à 10 g/dl est d'environ 8 à 9% en cas de traitement par pegIFN et ribavirine.[65, 66] Dans l'essai RIBAVIC, en dépit d'une posologie de ribavrine à 800 mg/j, 15,9% (61/383) des patients ont présenté une anémie sévère (Hb < 10 g/dl.) ; 20,1% des patients traités par l'association peginterferon plus ribavirine. L'anémie survenait dans un délai médian de 4 semaines (extrêmes ; 2-48 semaines) et avant S12 dans 68,8% des cas. En analyse multivariée, le risque de développer une anémie était significativement associé à la prise de zidovudine (OR, 3.27 $IC_{95\%}$, 1.64 - 6.54, p = 0.0008) et au traitement par peginterferon (OR, 2.35; $IC_{95\%}$, 1.16 - 4.57, p = 0.0179). En revanche, une hémoglobine élevée à l'inclusion (OR, 0.35 $IC_{95\%}$, 0.26 to 0.49, p< 0.0001) ou un traitement antirétroviral incluant des

IP (OR, 0.51 $IC_{95\%}$, 0.30 to 0.86, p = 0.0114) étaient associés à une diminution du risque d'anémie.

D'autres études ont montré également le rôle de la zidovudine dans le risque de survenue d'une anémie [105-107]. La zidovudine a une activité myélosuppressive, probablement par inhibition de la synthèse de l'ARN messager de la globine [108]. Par ailleurs, contrairement aux autres INTI comme l'abacavir, la lamivudine et la stavudine, elle est associée à une augmentation des concentrations de la ribavirine [107]. Cette étude a montré également un effet protecteur des IP vis à vis du risque d'anémie. Plusieurs études ont montré qu'un traitement antirétroviral hautement actif était associé à une correction de l'anémie (secondaire à l'infection par le VIH), probablement en partie du fait de l'efficacité immuno-virologique [109, 110]. Les IP semblent avoir, outre leur activité anti-VIH, d'autres fonctions cellulaires. Ainsi, il a été montré que le ritonavir diminuait l'apoptose des cellules progénitrices de l'hématopoièse et stimulait la croissance de ceux-ci in vitro [111]. Ces activités pourraient expliquer pourquoi les inhibiteurs de protéase et non, les INNTI ont un effet protecteur vis à vis du risque d'anémie.

Chez les patients mono-infectés par le VHC, d'autres facteurs de risque comme l'âge ou la clairance de la créatinine ont été décrits [112]. Dans notre étude, la clairance de la créatinine était associée au risque d'anémie seulement en analyse univariée, alors que l'âge, le sexe et la créatininémie ne l'étaient pas suggérant que le principal facteur de risque de baisse de l'hémoglobine est le poids et donc la dose de ribavirine rapportée au poids (significatif en univariée).

En conclusion, il est désormais recommandé, dans la mesure du possible, d'interrompre la zidovudine avant de débuter un traitement anti-VHC chez les patients co-infectés.

 doi:10.1111/j.1365-2893.2007.00846.x

Risk factors for anaemia in human immunodeficiency virus/hepatitis C virus-coinfected patients treated with interferon plus ribavirin

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Received July 2006; accepted for publication October 2006

SUMMARY. The most frequent and the most troublesome adverse effect of interferon plus ribavirin-based therapy is anaemia. The aim of this analysis was to determine the incidence and risk factors of anaemia (Hb < 10 g/dL) in human immunodeficiency virus/hepatitis C virus (HCV)-coinfected patients receiving anti-HCV therapy. We reviewed all cases of anaemia occurring among 416 patients participating in a randomized, controlled 48-week trial comparing peginterferon (peg-IFN) alpha 2b plus ribavirin with interferon alpha-2b plus ribavirin. Univariate and multivariate analyses were used to identify links with antiretroviral treatments, HCV therapy and clinical and laboratory findings. Sixty-one (15.9%) of the 383 patients who received at least one dose of anti-HCV treatment developed anaemia. In multivariate analysis the risk of anaemia was significantly associated with zidovudine (OR, 3.27 95% CI, 1.64–6.54, $P = 0.0008$) and peg-IFN (OR, 2.35; 95% CI, 1.16–4.57, $P = 0.0179$). The risk of anaemia was lower in patients with higher baseline haemoglobin levels (OR, 0.35 95% CI, 0.26–0.49, $P < 0.0001$) and in patients receiving protease inhibitor-based antiretroviral therapy (OR, 0.51 95% CI, 0.30–0.86, $P = 0.0114$). Zidovudine discontinuation could help to avoid anaemia associated with anti-HCV therapy.

Keywords: anaemia, human immunodeficiency virus/hepatitis C virus coinfection, peginterferon, protease inhibitor, ribavirin, zidovudine.

INTRODUCTION

Combination therapy with peginterferon (peg-IFN) and ribavirin is currently the standard of care for patients with hepatitis C virus (HCV) infection [1,2]. The most frequent and the most troublesome adverse effect of this combination is anaemia, due to both haemolysis induced by ribavirin and to bone marrow suppression by interferon [3]. As full adherence to HCV therapy is crucial for virological success, we attempted to identify risk factors for anaemia in human immunodeficiency virus (HIV)/HCV-coinfected patients participating in a large randomized-controlled trial comparing pegylated interferon alpha-2b plus ribavirin with conventional interferon alpha-2b plus ribavirin (the ANRS HC02 RIBAVIC study) [1].

Abbreviations: BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; peg-IFN, peginterferon.

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METHODS

The results of the ANRS HC02 RIBAVIC study have been reported in detail elsewhere [1]. In brief, 206 of 416 HIV/HCV-coinfected patients who had never received interferon or ribavirin were randomly assigned to receive weekly subcutaneous injections of 1.5 μg/kg peg-IFN alpha-2b (ViraferonPeg®, Schering-Plough, Kenilworth, ND, USA) plus ribavirin 800 mg/day, while the remaining 210 patients received thrice-weekly subcutaneous injections of 3 MU of interferon alpha-2b plus ribavirin 800 mg/day, for 48 weeks. Patients were eligible if they had detectable serum HCV RNA, liver biopsy results showing at least mild activity or fibrosis, a CD4 cell count above 200/mm^3, stable HIV RNA load (<1 log variation in the previous 3 months), and stable antiretroviral treatment (or no antiretroviral

treatment) during the previous 3 months. The main ineligibility criteria were active narcotic consumption and/or self-reported daily alcohol intake exceeding 40 g (women) or 50 g (men) within 3 months before entry to the study; decompensated cirrhosis, HBs antigenaemia and anaemia (<10 g/dL).

Liver inflammation and fibrosis, classified with the METAVIR scoring system, were assessed by means of liver biopsy <18 months before enrolment. Disease activity (reflecting the intensity of necroinflammatory lesions) was scored as follows: A0, no histologic activity; A1, mild activity; A2, moderate activity and A3, severe activity. Liver fibrosis was scored on a 5-point scale, as follows: 0, no fibrosis; 1, fibrosis without septa; 2, portal fibrosis with few septa; 3, portal fibrosis with many septa and 4, cirrhosis.

Three hundred and eighty-three patients who received at least one dose of study medication were included in this analysis. We focused on cases of anaemia (<10 g/dL) occurring during HCV treatment. The dose of ribavirin was lowered to 600 mg daily when the haemoglobin level fell below 10 g/dL, while both anti-HCV combinations were discontinued if the haemoglobin level fell below 8.5 g/dL. The full dose of ribavirin was resumed when the haemoglobin level rose to at least 10 g/dL. Two anaemic patients received erythropoietin after their haemoglobin level fell below 10 g/dL.

The following data were collected at enrolment and, where relevant, every 4 weeks during follow-up: age, sex, body mass index (BMI), duration of HIV infection, HIV disease stage (Centers for Disease Control and Prevention classification), duration of HCV infection (date of first transfusion or narcotic injection), antiretroviral drugs received, anti-HCV treatment received, Metavir score, symptoms, blood biochemistry, CD4 lymphocyte count, and plasma HIV and HCV viral loads.

The chi-squared test or Fisher's exact test was used for qualitative variables and the Mann–Whitney test for quantitative variables. A logistic regression model was used to identify associations between anaemia (outcome variable) and pretreatment characteristics (input variables). Characteristics with *P*-values below 0.20 in univariate analysis were included in multivariate models based on a backward elimination procedure. All statistical tests were two-sided, with a type I error of 5%.

RESULTS

At least one dose of study medication was received by 383 patients. Three-quarters of the patients were men, and the mean age was 39.7 ± 5.4 years. Intravenous narcotic use was the risk factor for HCV infection in 79% of cases. Three hundred and seventeen patients (83%) were receiving antiretroviral therapy at enrolment. At baseline, the mean haemoglobin level was 14.5 ± 1.4 g/dL. Men had a higher mean haemoglobin concentration than women (14.8 ± 1.3 *vs* 13.6 ± 1.2 g/dL). Anaemia occurred in 61 patients (15.9%), after <12 weeks of treatment in 42 cases (68.8%). The median time between the outset of anti-HCV therapy and the onset of anaemia was 4 weeks (range, 2–48 weeks). The mean duration of anti-HCV treatment was slightly but not significantly shorter in patients who developed anaemia than in the other patients (247 ± 116 *vs* 268 ± 104 days; $P = 0.067$). The rates of sustained virological responses were not significantly different between the groups (19.6% ($n = 12/61$) *vs* 26.4% ($n = 85/322$); $P = 0.33$). The incidence of ribavirin discontinuation for all causes was similar in the two groups [$n = 29/61$ (47.5%) *vs* $n = 119/322$ (36.9%); $P = 0.15$], but the incidence of anaemia-related ribavirin discontinuation was higher in the first group (five patients and one patient; $P < 0.0001$).

Univariate analysis showed that anaemia was significantly associated with the following baseline variables: a lower BMI, a higher daily ribavirin dose (per kg body weight), a lower haemoglobin level, lower leucocyte and neutrophil counts, lower alanine aminotransferase levels and lower creatinine clearance, as estimated with the Cockcroft–Gault formula (CrCL) (Table 1). Anaemia was more likely to occur in the peg-IFN alpha-2b arm than in the interferon alpha-2b arm (63.9% *vs* 48.1%; $P = 0.0258$).

The possible role of nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PIs) used at the outset of anti-HCV treatment was also examined. Among the NRTIs, only zidovudine was significantly associated with an increased risk of anaemia ($P < 0.0001$). No association was observed with NNRTI-containing regimens. Patients who were taking a PI-containing regimen were less likely to develop anaemia (27.8% *vs* 42.5%, $P = 0.0334$).

The following factors were not associated with the risk of anaemia: age, sex, mean duration of HIV and HCV infection, AIDS status, baseline CD4 cell count, HIV viral load below 400 copies/mL, ongoing antiretroviral therapy, the mean duration of previous antiretroviral treatment, the HCV transmission group, the mean METAVIR scores for necroinflammation and fibrosis, cirrhosis, HCV viral load and the HCV genotype, lymphocyte and platelet counts, the AST level, serum GGT and alkaline phosphatase levels, the prothrombin time, and the serum creatinine concentration.

In multivariate analysis, zidovudine (OR, 3.27 95% CI, 1.64–6.54, $P = 0.0008$) and peg-IFN (OR, 2.35; 95% CI, 1.16–4.57, $P = 0.0179$) remained significantly associated with a higher risk of anaemia. In contrast, a higher baseline haemoglobin level (OR, 0.35 95% CI, 0.26–0.49, $P < 0.0001$) and PI-based antiretroviral therapy had a protective effect (OR, 0.51 95% CI, 0.30–0.86, $P = 0.0114$) (Table 2).

These factors were also independently associated with a decrease by 25% of the baseline haemoglobin level which was observed in 92 (24%) patients on treatment. Multivariate odds-ratios were 3.72 (95% CI, 1.99–6.96,

Table 1 Baseline factors associated with anaemia in univariate logistic regression analysis

	Patients without anaemia	Patients with anaemia	*P*-value
Total number of patients	322	61	
Age [mean years (SD)]	39.4 (5.3)	41.0 (5.6)	0.0663
Women [no. (%)]	79 (24.5)	22 (36.1)	0.0803
Body mass index [mean (SD)]	22.4 (2.9)	21.3 (2.88)	0.0018
Duration of HIV infection in years [mean (SD)]	1.06 (4.3)	10.0 (4.7)	0.47
AIDS [no. (%)]	51 (15.8)	12 (19.7)	0.45
CD4 cell count – (/mm3) [mean (SD)]	538 (250)	478 (218)	0.10
Patients with <400 HIV copies/mL [no. (%)]	215 (66.7)	37 (60.6)	0.37
Ongoing antiretroviral treatment	266 (83.1)	49 (83.3)	0.58
Duration of antiretroviral treatment in years [mean (SD)]*	4.5 (3.2)	3.9 (3.2)	0.33
Components of antiretroviral regimens*			
Protease inhibitor [no. (%)]	137 (42.5)	17 (27.8)	0.0334
Non-nucleoside reverse transcriptase inhibitor [no. (%)]	97 (30.1)	20 (32.8)	0.76
Nucleoside reverse transcriptase inhibitor [no. (%)]	266 (82.6)	49 (80.3)	0.71
Stavudine [no. (%)]	161 (50.0)	13 (21.3)	<0.0001
Zidovudine [no. (%)]	76 (23.6)	33 (54.1)	<0.0001
Lamivudine [no. (%)]	192 (59.6)	39 (63.9)	0.57
Didanosine [no. (%)]	70 (21.7)	12 (19.6)	0.86
Abacavir [no. (%)]	36 (11.2)	6 (9.8)	1.0
Duration of HCV infection in years [mean (SD)]	16.4 (5.0)	16.3 (5.1)	0.9
Risk group for HCV infection			
Intravenous drug use [no. (%)]	251 (77.8)	51 (86.6)	0.39
Inflammation score [mean (SD)]	1.77 (0.67)	1.68 (0.74)	0.42
Fibrosis score [mean (SD)]	2.30 (1.0)	2.42 (1.05)	0.45
Cirrhosis (F4) [no. (%)]	48 (15.1)	12 (19.6)	0.34
Ribavirin daily dose per kilogram of body weight (mg/kg) [mean (SD)]	12.25 (2.18)	12.82 (1.89)	0.0251
Treatment assigned-peginterferon a-2b [no. (%)]	155 (48.1)	39 (63.9)	0.0258
Genotype type 1 or 4 (*vs* 2 or 3) [no. (%)]	193 (59.9)	39 (63.9)	0.66
Serum HCV RNA (IU/mL) [mean (SD)] $\log_{10}$	5.87 (0.7)	5.9 (0.7)	0.7101
Haemoglobin level g/dL [mean (SD)]†	14.7 (1.3)	13.1 (1.4)	<0.0001
Leukocyte count (/mm^3) [mean (SD)]	6223 (2113)	5444 (1970)	0.0094
Neutrophil count (/mm^3) [mean (SD)]	3275 (1660)	2702 (1320)	0.013
Lymphocyte count (/mm^3) [mean (SD)]	2203 (827)	2061 (846)	0.16
Platelet count (/mm^3) [mean (SD)]	192 (64)	195 (86)	0.63
ALT (times upper limit of normal) [mean (SD)]	2.3 (1.9)	1.6 (1.3)	0.0005
AST (times upper limit of normal) [mean (SD)]	2.04 (1.4)	1.7 (1.2)	0.1212
GGT (times upper limit of normal) [mean (SD)]	2.8 (2.8)	2.7 (2.7)	0.7779
Alk Ph (times upper limit of normal) [mean (SD)]	0.76 (0.33)	0.77 (0.39)	0.9413
Bilirubin (times upper limit of normal) [mean (SD)]	0.72 (0.44)	0.68 (0.41)	0.5597
Prothrombin time (% of normal)[mean (SD)]	92 (10)	89 (13)	0.11
Serum creatinine (μmol/L)	74.4 (15.4)	76.3 (20.3)	0.98
CrCl (mL/min) [mean (SD)]	114.3 (43.8)	102.3 (28.5)	0.0101

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; Alk Ph, alkaline phosphatase; CrCl, creatinine clearance (Cockcroft–Gault formula).

*Zero in patients not receiving antiretroviral therapy (317 patients were receiving antiretroviral therapy; one patient was receiving only one antiretroviral drug).

†In the group of patients with anaemia, three had a baseline haemoglobin level between 10 and 11 g/dL.

$P < 0.0001$) for zidovudine, 1.98 (95% CI, 1.13–3.45, $P = 0.016$) for peg-IFN and 0.67 (95% CI, 0.045–1.01, $P = 0.058$) for PI-based antiretroviral therapy.

The Kaplan–Meier for anaemia-free survival relative to antiretroviral therapy (with or without zidovudine, with or without PIs) are shown in Fig. 1. Changes in the mean

Table 2 Factors associated with anaemia in multivariate logistic regression analysis

	Odds ratio	95% CI	*P*-value
Baseline haemoglobin level	0.36	0.26–0.49	<0.0001
Zidovudine use	3.27	1.64–6.54	0.0008
Protease inhibitor-based antiretroviral therapy	0.51	0.30–0.86	0.0114
Peginterferon therapy	2.35	1.16–4.57	0.0179

haemoglobin level during HCV therapy in patients treated with zidovudine-based antiretroviral therapy and in patients treated without zidovudine-based antiretroviral therapy are shown in Fig. 2.

DISCUSSION

Among HIV-seronegative HCV-infected patients, the haemoglobin level falls below <10 g/dL in 8–9% of cases during peg-IFN–ribavirin combination therapy [4,5]. In this study of 383 HIV/HCV-coinfected patients, despite the use of a

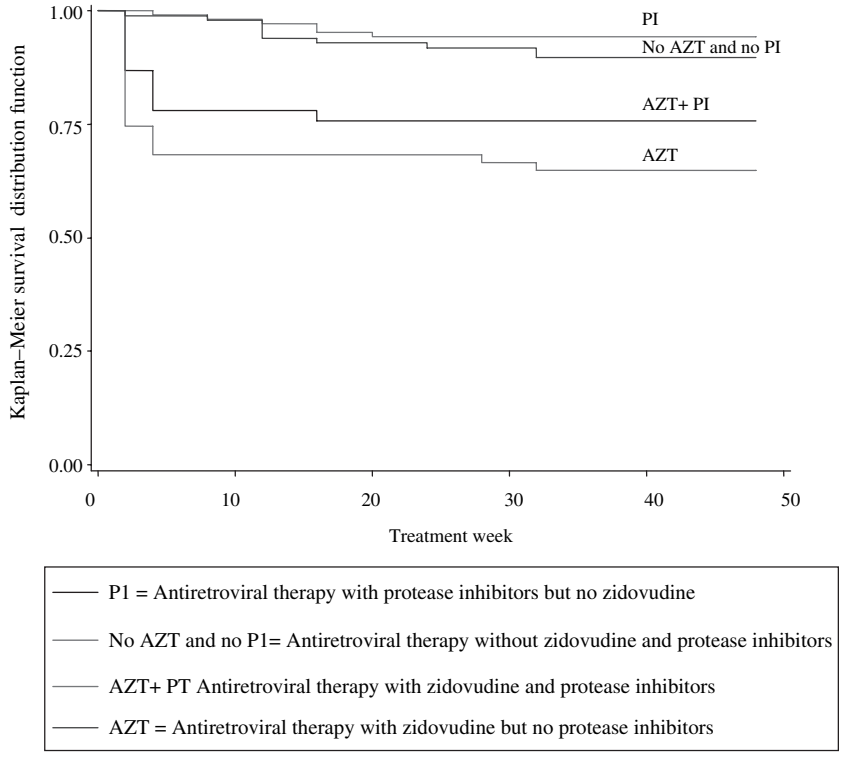

Fig. 1 Kaplan–Meier estimates of anaemia-free survival relative to antiretroviral therapy during hepatitis C virus therapy Log-rank test: $P < 0.001$.

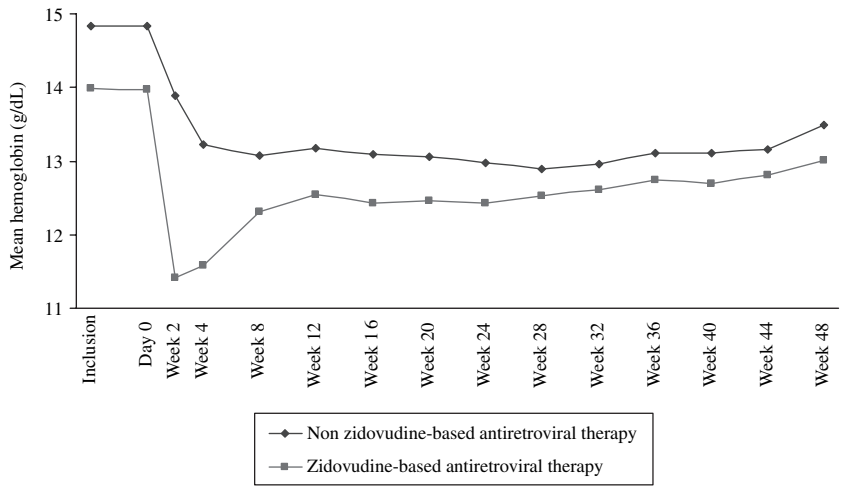

Fig. 2 Changes in the mean haemoglobin level during hepatitis C virus therapy in patients treated with zidovudine-based antiretroviral therapy and in patients treated without zidovudine-based antiretroviral therapy.

lower ribavirin starting dose (800 mg/day), 15.9% of patients developed anaemia, defined as a haemoglobin concentration below 10 g/dL. A lower baseline haemoglobin level, zidovudine therapy and peg-IFN therapy were associated with a significantly increased risk of anaemia. In contrast, PI-based antiretroviral therapy roughly halved the risk.

As ribavirin interfere with thymidine analogues such as zidovudine and stavudine, and can aggravate didanosine toxicity, a low ribavirin starting dose (800 mg/day) was used in this trial [6]. However, the mean dose was above 10.6 mg/kg (12.3 ± 2.1 mg/kg), which is the dose associated with sustained virologic responses among HIV-seronegative HCV-infected patients receiving peg-IFN alpha-2b and ribavirin [4].

Concomitant treatment with zidovudine was associated with an adjusted 3.3-fold higher risk of anaemia among patients receiving the interferon–ribavirin combination, confirming the results of previous studies [7–9]. Zidovudine affects haematopoietic lineages and reduces globin mRNA synthesis [10]. Zidovudine, contrary to abacavir, lamivudine and stavudine, also increases ribavirin plasma levels [7]. In HCV-monoinfected patients and in HIV/HCV-coinfected patients, the daily ribavirin dose, expressed per kilogram of body weight, is the main determinant of ribavirin plasma levels [7]. In HIV/HCV-coinfected patients treated with peg-IFN plus ribavirin, higher ribavirin plasma levels are independently associated with a fall in the haemoglobin level [7]. We also found a correlation between the daily ribavirin dose per kilogram of body weight and the risk of anaemia, but only in univariate analysis. Nevertheless, our results suggest that zidovudine and ribavirin have synergistic haematologic toxicity. Interestingly, all three patients who stopped taking zidovudine after developing anaemia in our study were able to resume ribavirin therapy at the initial dose. Patients taking stavudine-based antiretroviral therapy were significantly less likely to develop anaemia, confirming the higher risk of haematologic disorders with zidovudine-based regimens compared with stavudine-based regimens [11].

In this study, PI-based therapy, but not NNRTI-based therapy, had a preventive effect on anaemia. The introduction of highly active antiretroviral therapy based on PI or NNRTI is associated with a correction of pre-existing anaemia [12,13]. The mechanisms underlying these positive effects are unclear but may involve antiretroviral efficacy. PIs, in addition to their effects on HIV replication, appear to affect various cellular functions. In particular, ritonavir has been associated with decreased apoptosis of haematopoietic progenitors and also directly stimulates progenitor cell growth *in vitro* [14].

Although peg-IFN enhances the suppression of haematopoiesis in all three lineages relative to standard interferon, the mean decrease in the haemoglobin level, and the risk of anaemia (<10 g/dL), is similar with the two interferons in HCV-monoinfected patients [4,5,15]. In contrast, we found that peg-IFN-2b was associated with an adjusted 2.3-fold higher risk of anaemia relative to standard interferon. However, treatment discontinuations and dose adjustments for anaemia were similarly frequent in patients receiving peg-IFN and standard interferon [1].

Lower baseline creatinine clearance and older age have been identified as risk factors for anaemia in HCV-monoinfected patients treated with standard interferon plus ribavirin [16]. In our study, lower baseline creatinine clearance, estimated with the Cockcroft–Gault formula, which includes age, sex, body weight and the serum creatinine level, was also associated with anaemia but only in univariate analysis. Anaemia was not associated with age, sex or the serum creatinine level in univariate analysis, suggesting that the most important determinant of anaemia is body weight and, thus, the daily ribavirin dose per kg.

In conclusion, clinicians should be aware of the potential interference between treatments for HCV and HIV infection regarding the haemoglobin level. The haemoglobin level should be closely monitored, particularly during the first 3 months of HCV therapy, the period during which 68.8% of the cases of anaemia observed in our study occurred. Anaemia did not negatively impact on the anti-HCV treatment outcome in our study. However, higher doses of ribavirin given in combination with pegylated interferon have been linked to higher rates of viral eradication in several studies [17,18]. If anti-HCV and anti-HIV treatments must be administered concomitantly, then zidovudine discontinuation prior to HCV therapy, particularly when alternative antiretroviral options are available could help to avoid anaemia and thereby permit the use of higher ribavirin doses.

ACKNOWLEDGEMENTS

We thank David Young for editing the manuscript. This study was financially supported by ANRS, Essai HC 02, SIDACTION.

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VIII-4-Amaigrissement au cours du traitement anti-VHC : incidence et facteurs de risque

L'amaigrissement est un effet secondaire fréquent du traitement anti-VHC. Une perte de poids est observée dans plus de 20% des cas chez les patients mono-infectés par le VHC traités par peg-interferon (peg-IFN) et ribavirine [93]. Néanmoins, l'amplitude de cette perte de poids n'a jamais été décrite. Chez les patients co-infectés VIH-VHC, l'incidence de la perte de poids est plus fréquente. Dans une étude ayant comparé la perte de poids au cours du traitement anti-VHC entre les patients co-infectés VIH-VHC et ceux mono-infectés VHC, une perte de poids (>/=5% du poids initial) était observée respectivement dans 76% versus 39% [113].

Dans l'essai RIBAVIC, 122 patients (28%) ont présenté une perte de poids supérieure à 10% de leur poids à l'inclusion. En analyse multivariée, l'âge > 40 ans (HR, 1.59, 95% CI 1.09 - 2.31, p = 0.016), un BMI > 22 (HR, 1.72 95% CI, 1.16 - 2.55, p=0.0069), un traitement par peginterferon alfa-2b (HR, 1.82; 95% CI, 1.24 - 2.69, p =0.0022) et le sexe féminin (HR, 1.60 95% CI, 1.05 to 2.43, p=0.027) étaient significativement associés au risque de survenue d'un amaigrissement sévère. En revanche, les patients traités par INNTI avaient un risque moindre de développer un amaigrissement sévère (HR, 0.62 95% CI, 0.39 to 0.96, p=0.034).

Le délai moyen entre le début du traitement anti-VHC et une perte de poids supérieure à 10% était de 26.4 ± 11.3 semaines. La perte de poids maximale était de 10,8% et survenait à la semaine 44 du traitement. L'amaigrissement s'accompagnait d'une baisse de l'albuminémie qui passait de 41.7 ± 4.6 g/l à la baseline à 40.5 ± 5.2 g/l à la semaine 48. Cette baisse était significativement supérieure à celle observée chez les patients ne présentant pas un amaigrissement majeur (40.5 ± 5.2 g/l versus

41.7 ± 4.7 g/l ; p = 0.0331). Six mois après l'arrêt du traitement, le poids augmentait mais restait toujours inférieur au poids initial (64.5 ± 12.4 kg versus 68.6 ± 12.6 kg)

Severe weight loss in HIV/HCV-coinfected patients treated with interferon plus ribavirin: incidence and risk factors- article soumis le 16 mai 2007

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Key words: HIV/HCV coinfection, weight loss, peginterferon, non nucleoside reverse transcriptase inhibitor

Total number of words: 2053

Financial support: ANRS, Essai HC 02, SIDACTION

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Abstract:

Objective: Weight loss is reported by more than 20% of HCV-monoinfected patients treated with the peginterferon (peg-IFN) and ribavirin combination. The aim of this study was to determine the incidence and risk factors of severe weight loss (≥10%) in HIV/HCV-coinfected patients participating in a randomized, controlled 48-week trial comparing peginterferon alfa 2b plus ribavirin with interferon alfa-2b plus ribavirin. Methods: Univariate and multivariate analyses were used to identify links with antiretroviral treatments, anti-HCV therapy, and clinical and laboratory findings.

Results: One hundred twenty-two (28%) of 383 patients who received at least one dose of anti-HCV treatment subsequently had severe weight loss. In multivariate analysis, age > 40 years (HR, 1.59, 95% CI 1.09 to 2.31, p = 0.016), BMI > 22 (HR, 1.72 95% CI, 1.16 to 2.55, p=0.0069), peginterferon alfa-2b (HR, 1.82; 95% CI, 1.24 to 2.69, p =0.0022) and female sex (HR, 1.60 95% CI, 1.05 to 2.43, p=0.027) were associated with severe weight loss. In contrast, patients taking NNRTI-containing antiretroviral regimens were less likely to lose weight (HR, 0.62 95% CI, 0.39 to 0.96, p=0.034).

Conclusion: These findings show that severe weight loss is a frequent side effect of anti-HCV therapy in HIV/HCV-coinfected patients. The underlying mechanisms remain to be identified, and the possible benefits of early nutritional intervention should be studied.

The pathogenesis of weight loss in HIV/HCV-coinfected patients is multifactorial. Both HIV infection and chronic HCV infection induce a hypermetabolic/hypercatabolic state associated with weight loss [114, 115]. Antiretroviral therapy can lead to lipoatrophy and weight loss, and weight loss is reported by more than 20% of HCV-monoinfected patients treated with the peginterferon (peg-IFN) and ribavirin combination [93]. The degree and possible determinants of weight loss during anti-HCV therapy in HIV/HCV-coinfected patients are poorly documented.

The aim of this study was to determine the incidence and risk factors of severe weight loss ($\geq$10%) in HIV/HCV-coinfected patients participating in a large randomized controlled trial comparing pegylated interferon alfa-2b plus ribavirin with conventional interferon alfa-2b plus ribavirin for 48 weeks (the ANRS HC02 RIBAVIC study)[67].

Methods

The results of the ANRS HC02 RIBAVIC study have been reported in detail elsewhere [67]. Only the 383 patients who received at least one dose of study medication (weekly subcutaneous injections of 1.5 µg/kg peginterferon alfa-2b (ViraferonPeg®, Schering-Plough) plus ribavirin 800 mg/day; or thrice-weekly subcutaneous injections of 3 MU of interferon alfa-2b plus ribavirin 800 mg/day, for 48 weeks) were included in this study.

Patients were eligible if they had never received interferon or ribavirin, had detectable serum HCV RNA, liver biopsy results showing at least mild activity or fibrosis, a CD4 cell count above 200/mm^3, stable HIV RNA load (less than 1 log variation in the previous three months), and stable antiretroviral treatment (or no antiretroviral treatment) during the previous three months. The main ineligibility criteria were active narcotic consumption and/or

self-reported daily alcohol intake exceeding 40 g (women) or 50 g (men) within 3 months before entry to the study; decompensated cirrhosis, and HBs antigenemia.

Liver inflammation and fibrosis, classified using the METAVIR scoring system, was assessed by means of liver biopsy performed within 18 months before inclusion. Disease activity (reflecting the intensity of necroinflammatory lesions) was scored as follows: A0, no histologic activity; A1, mild activity; A2, moderate activity; and A3, severe activity. Liver fibrosis was scored on a 5-point scale, as follows: 0, no fibrosis; 1, fibrosis without septa; 2, portal fibrosis with few septa; 3, portal fibrosis with many septa; and 4, cirrhosis.

The following data were collected at inclusion, every four weeks during follow-up, and 4, 12, and 24 weeks after completion of anti-HCV treatment: age, sex, weight, BMI, duration of HIV infection, Centers for Disease Control and Prevention stage of HIV infection, duration of HCV infection (defined as the date of the first transfusion or first intravenous narcotic use), antiretroviral drugs received, anti-HCV treatment received, the Metavir score, biochemical assay values, the CD4 lymphocyte count, plasma HIV viral load, and HCV viral load. Serum albumin was measured every 12 weeks.

The primary endpoint was the time to weight loss > 10% during treatment for HCV infection. Data were censored at the time of the last anti-HCV treatment intake or at the time of death or loss to follow-up, whichever occurred first. Univariate Cox proportional-hazards models were used to identify factors associated with the primary endpoint. Factors with P values below 0.2 in univariate analysis (Wald Chi-square test) were included in a multivariate Cox proportional-hazards model based on a backwards elimination procedure. Quantitative factors identified in multivariate analysis were dichotomized around the median. All statistical tests were two-sided, with a type I error of 5%.

Results

Baseline clinical and biological characteristics of the patients are summarized in Table 1. Three-quarters of the patients were men, and mean age was 39.7 ± 5.4 years. Intravenous narcotic use was the risk factor for HCV infection in 79% of cases. Three hundred seventeen patients (83%) were receiving antiretroviral therapy at enrolment. The mean baseline weight was 66.7 ± 11.3 kg. Severe weight loss ($\geq$ 10% versus baseline) occurred in 111 patients (28.9%). The mean time between the outset of anti-HCV therapy and the onset of severe weight loss was 26.4 ± 11.3 weeks. At this time the mean weight and mean BMI had fallen from 68.6 kg ± 12.6 and 23.1 ± 3.1 at baseline to 61.9 ±11.9 and 20.8 ± 2.9, respectively. The maximum weight loss was 10.8% of baseline weight and occurred at week 44. The serum albumin level fell gradually, from 41.7 ± 4.6 g/l at baseline to 40.5 ± 5.2 g/l at week 48, and was significantly lower at week 48 in patients who had severe weight loss than in other patients (40.5 ± 5.2 g/l versus 41.7 ± 4.7 g/l; p = 0.0331).

After completion of anti-HCV treatment, mean weight and BMI increased to 63.7 ± 11.9 kg and 21.4 ± 2.8, respectively, at 12 weeks, and to 64.5 ± 12.4 kg and 21.7 ± 2.9, respectively, at 24 weeks. The serum albumin level was similar in the two groups 24 weeks after treatment completion (41.5 ± 4.7 g/l in patients with severe weight loss and 42.01 ± 4.87 g/l in patients without severe weight loss).

Lipodystrophy occurred in 4 patients who had severe weight loss and in 3 other patients. Severe weight loss was one of the main clinical manifestations of symptomatic mitochondrial toxicity. Five out of 6 patients with symptomatic mitochondrial toxicity presented severe weight loss.

The mean duration of anti-HCV treatment was significantly longer in patients who had severe weight loss than in the other patients (305 ± 59 versus 251 ± 117 days; p=0.0021). The incidence rates of anti-HCV drug discontinuation for all reasons, and for severe weight loss,

were lower in patients who had severe weight loss than in the other patients [n= 33/61 (29.7%) versus n=111/272 (43%), p=0.015; and 3 patients versus 7 patients, respectively]. The frequency of anti-HCV dose adjustments was similar in the two groups (60.3% (n= 67/111) versus 68.3% (n=186/272); p=0.15). The rates of sustained viral response were also similar (25.2% (n=28/111) versus 25.3% (n=69/272)).

Univariate analysis showed that severe weight loss was significantly associated with age > 40 years (p=0.012) and a body mass index (BMI) > 22 (p=0.016) (Table 2). Weight loss was also more frequent in the peginterferon alfa-2b arm than in the interferon alfa-2b arm (p=0.01).

The possible role of nucleoside reverse transcriptase inhibitors (NRTI), non nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) used at the outset of anti-HCV treatment was also examined. No association was observed with NRTI- or PI-containing regimens. No particular NRTI or NRTI combination, and particularly the NRTI combination of stavudine plus didanosine, was associated with an increased risk of weight loss. Triple NRTI regimens were not associated with weight loss. In contrast, patients who were taking an NNRTI-containing regimen were less likely to lose weight (p=0.023).

The following factors were not associated with the risk of weight loss: baseline weight, serum albumin, mean duration of HIV and HCV infection, AIDS status, baseline CD4 cell count, HIV viral load below 400 copies/ml, ongoing antiretroviral therapy, the mean duration of previous antiretroviral treatment, the HCV transmission group, the mean METAVIR scores for necroinflammation and fibrosis, cirrhosis, HCV viral load, and the HCV genotype.

In multivariate analysis, age > 40 years (HR, 1.59, 95% CI 1.09 to 2.31, p = 0.016), a BMI > 22 (HR, 1.72 95% CI, 1.16 to 2.55, p=0.0069), peginterferon alfa-2b (HR, 1.82; 95% CI, 1.24 to 2.69, p =0.0022), and female sex (HR, 1.60 95% CI, 1.05 to 2.43, p=0.027) remained significantly associated with a higher risk of severe weight loss, while NNRTI-based

antiretroviral therapy was associated with a lower risk (HR, 0.62 95% CI, 0.39 to 0.96, p=0.034).

Discussion

The degree and time course of weight loss was not reported in large registration trials comparing pegylated interferon plus ribavirin with standard interferon plus ribavirin in HCV-monoinfected patients [65, 66]. Relative to these latter patients, HIV/HCV-coinfected patients seem to have a higher incidence of weight loss during peginterferon-ribavirin combination therapy. In one study, 76% of HIV/HCV-coinfected patients and 39% of HIV-seronegative HCV-infected patients lost at least 5% of their baseline weight [116]. In our study of 383 HIV/HCV-coinfected patients, 28% of participants lost at least 10% of their baseline weight during anti-HCV therapy. The mean time between the outset of anti-HCV therapy and the onset of severe weight loss ($\geq$10%) was 26.4 weeks. The degree of weight loss increased with the duration of anti-HCV treatment.

Bodyweight loss of as little as 5% is associated with increased morbidity and mortality in HIV-infected patients [117, 118]. In our study, weight loss was associated with a decline in the serum albumin concentration, which was significantly lower at week 48 than in patients who did not have severe weight loss (40.5 ± 5.2 g/l versus 41.7 ± 4.7 g/l; p = 0.0331). Furthermore, weight loss > 5% (mean 6%) persisted 24 weeks after the completion of anti-HCV therapy in the patients with severe weight loss.

The mechanism of weight loss during IFN treatment is unknown, but contributory factors may include inadequate food intake, cytokine imbalance, and adipocyte apoptosis [119, 120]. In HCV-monoinfected patients, no baseline characteristics such as age, gender, weight, ethnicity or histological stage have been linked to the risk of weight loss [119]. In contrast, in our

HIV/HCV-coinfected patients, older age, a higher baseline BMI and female gender were independent risk factors for severe weight loss. It is not known whether the weight loss observed during anti-HCV therapy primarily affects lean or fat mass. We only noted changes in overall weight, BMI, and the albumin level. A reduction in bodyweight or in the BMI owing to a loss of body cell mass is a sign of wasting, whereas bodyweight and BMI reductions due to loss of adipose tissue are not [118]. The type of weight loss depends on baseline fat mass [118, 121]: individuals in whom fat mass represents > 15% of bodyweight at baseline lose less lean mass than other individuals [118]. The links between severe weight loss and older age, higher baseline BMI, and female gender observed here suggest that fat accounted for the bulk of weight loss. Indeed, women, who generally have a higher proportion of fat than men, tend to lose more fat than lean mass, and the fat mass index increases gradually with age [118, 122-124].

The roles of the different potential causes of weight loss can be difficult to distinguish in HIV-HCV-coinfected patients receiving both antiretroviral therapy and anti-HCV therapy. One of the most important confounding factors is lipoatrophy due to the mitochondrial toxicity of some antiretroviral drugs. The initial symptoms of mitochondrial toxicity, such as weight loss, are generally indistinguishable from common side effects of interferon-ribavirin combination therapy [87]. In our study, lipodystrophy was rare (< 3.6%) regardless of weight loss, but severe weight loss was one of the main clinical manifestations of symptomatic mitochondrial toxicity in five patients with severe weight loss.

Thymidine analog NRTIs (stavudine and, to a lesser extent, zidovudine) are strongly associated with lipoatrophy. In this study, antiretroviral therapy, its duration, and its nature (NRTI or NRTI combinations such as stavudine plus didanosine, or triple NRTI versus dual NRTI regimens) were not associated with severe weight loss. In contrast, Lo Re et al. found

that regimens including more than two NRTIs were associated with an increased risk of weight loss [113].

In our study, NNRTI-based therapy, contrary to PI-based therapy, was associated with a lower risk of weight loss. The mechanisms underlying this effect are unclear. The only significant difference between NNRTI -treated and PI-treated patients was that the latter were slightly older (38.9 versus 40.5 years, p=0.02), and this difference was taken into account in multivariate analysis.

In HCV-monoinfected patients, weight loss is more frequent (+9%) among those treated with peginterferon than those treated with standard interferon [65, 93]. In keeping with this result, we found that peginterferon-2b was associated with an adjusted 1.8-fold-higher risk of severe weight loss relative to standard interferon.

In conclusion, weight loss is a frequent and potentially severe side effect of anti-HCV therapy in HIV/HCV-coinfected patients. In addition, it can persist for more than six months after the completion of anti-HCV therapy. Weight loss was not related to the characteristics of HIV infection, including antiretroviral therapy per se, but it was sometimes the main clinical manifestation of antiretroviral mitochondrial toxicity. Interestingly, concomitant NNRTI-based antiretroviral therapy was associated with a lower risk of weight loss. The mechanisms of this weight loss remain to be identified, and the possible benefits of early nutritional intervention should be studied.

Acknowledgments: We thank David Young for editing the manuscript.

Table 1. Characteristics of the Patients at Baseline

	Patients without weight loss < 10%	Patients with weight loss ≥ 10%
Total number of patients	272	111
Age [mean years (SD)]	39.2 (5.2)	40.9 (5.8)
Women [No. (%)]	67 (25)	34 (31)
Body mass index [mean (SD)]	21.9 (2.8)	23.1 (3.1)
Weight in kilograms [mean (SD)]	65.9 (10.7)	68.6 (12.6)
Serum albumin level (g/L)	42.3 (4.7)	41.7 (4.3)
HIV infection		
Duration of HIV infection in years [mean (SD)]	10.6 (4.4)	10.2 (4.3)
AIDS [No. (%)]	47 (17)	16 (14)
CD4 cell count (/mm^3) [mean (SD)]	531 (245)	522 (248)
Patients with <400 HIV genome copies/ml, [No. (%)]	178 (65)	74 (66)
Duration of HCV infection in years [mean (SD)]	16.4 (5.1)	16.5 (5.1)
Ongoing antiretroviral treatment	226 (83)	89 (80)
Duration of antiretroviral treatment in years [mean (SD)] *	4.49 (3.3)	4.14 (3.27)
Component drugs of		

antiretroviral regimens*		
Protease inhibitors [No. (%)]	105 (38)	49 (44)
Non-nucleoside reverse transcriptase inhibitors [No. (%)]	91 (33)	26 (23)
Nucleoside reverse transcriptase inhibitors [No. (%)]	225 (82)	90 (81)
Three nucleoside reverse transcriptase inhibitors	28 (12)	9 (10)
Stavudine	122 (45)	52 (47)
Zidovudine	78 (29)	31 (28)
Lamivudine	168 (62)	63 (57)
Didanosine	60 (22)	22 (20)
Abacavir	30 (11)	12 (11)
Stavudine plus Didanosine	35 (13)	16 (14)
HCV infection		
Risk group for HCV infection Intravenous drug use [No. (%)]	216 (79)	86 (77)
Metavir Inflammation score [mean (SD)]	1.77 (0.68)	1.72 (0.70)
Metavir Fibrosis score [mean (SD)]	2.32 (1.02)	2.34 (0.98)
Cirrhosis (F4), [No. (%)]	45 (16)	15 (13)
HCV Genotype type 1 or 4	158 (58)	74 (66)

(versus 2 or 3), [No. (%)]		
Serum HCV RNA (IU/ml), [mean (SD)] $\log_{10}$	5.85 (0.75)	5.92 (0.73)
Peginterferon a-2b, [No. (%)]	128 (47)	66 (59)

The body mass index is weight in kilograms divided by height in meters squared

*Zero in patients not receiving antiretroviral therapy (317 patients were receiving antiretroviral therapy; one patient was receiving only one antiretroviral drug)

Table 2: Univariate and multivariate Cox regression analyses: relative risks of weight loss ≥ 10% after the outset of anti-HCV therapy

	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% IC)	P value	Hazard Ratio (95% IC)	P value
Age > 40 years	1.61 (1.11-2.34)	0.012	1.59 (1.09-2.31)	0.016
BMI > 22	1.61 (1.09-2.36)	0.016	1.72 (1.16-2.55)	0.0069
Female sex	1.38 (0.92-2.06)	0.12	1.60 (1.05-2.43)	0.027
Peginterferon	1.64 (1.13-2.4)	0.01	1.82 (1.24-2.68)	0.0022
NNRTI-based antiretroviral therapy	0.60 (0.38-0.93)	0.023	0.61 (0.39-0.96)	0.034

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Notre étude montre que la perte de poids est sévère au cours du traitement anti-VHC chez les patients co-infectés VIH-VHC. En effet, une perte de poids de 10% mais aussi de 5% est associée à une augmentation de la morbidité et de la mortalité de l'infection par le VIH [117, 118].

Les mécanismes de l'amaigrissement au cours du traitement par IFN sont inconnus. Les facteurs suggérés sont une diminution des apports par perte d'appétit, une modification de la production des cytokines et une augmentation de l'apoptose des adipocytes [119, 120]. Le type d'amaigrissement, touchant préférentiellement la masse grasse ou la masse maigre, n'est également pas connu. Dans notre étude, les facteurs de risque retrouvés comme le sexe féminin, un âge plus élevé, un BMI plus élevé tendent à suggérer que la perte de poids touche plutôt la masse grasse.

Chez les patients mono-infectés par le VHC, l'âge, le sexe, le poids, l'ethnie et le score histologique ne sont pas associés à un risque plus élevé d'amaigrissement [119]. Chez les patients co-infectés VIH-VHC, la perte de poids peut être multifactorielle. Elle peut ainsi être secondaire au traitement anti-VHC mais aussi liée à une lipoatrophie secondaire au traitement antirétroviral [87]. En effet, l'amaigrissement est l'un des premiers signes cliniques de la lipoatrophie [87]. Dans notre étude, l'incidence de survenue de lipodystrophie chez l'ensemble des patients était faible (< 3.6%), mais un amaigrissement sévère était l'une des premières manifestations cliniques d'une toxicité mitochondriale symptomatique chez 5 des patients ayant présenté un amaigrissement sévère. Alors que les analogues thymidiniques de la reverse transcriptase comme la stavudine et dans une moindre mesure la zidovudine sont associés au risque de lipoatrophie, dans notre étude, le traitement antirétroviral en soi, la durée du traitement antirétroviral, les INTI n'étaient pas associés à un risque plus élevé d'amaigrissement sévère. En revanche, les

INNTI et non les IP étaient associés à un risque moindre. Il n'existe pas d'explication claire à ce dernier résultat. La seule différence significative entre les patients traités par INNTI et ceux traités par IP était un âge plus élevé chez les patients traités par IP (38.9 versus 40.5 ans, p=0.02). Ce facteur était inclus dans l'analyse multivariée et ne peut donc expliquer l'effet des INNTI après ajustement.

Notre étude confirme également un risque plus élevé d'amaigrissement sévère sous peginterferon comparé à l'interféron standard (9% de différence chez les patients mono-infectés par le VHC) [65, 93]

En conclusion, l'amaigrissement est sévère et fréquent au cours du traitement anti-VHC chez les patients co-infectés VIH-VHC et persiste en partie après l'arrêt du traitement. Il peut révéler une toxicité mitochondriale. Les mécanismes de cet amaigrissement mériteraient d'être étudiés et la prise en charge de cet effet secondaire mieux codifiée.

IX- IMPACT HISTOLOGIQUE DU TRAITEMENT ANTI-VHC

L'objectif majeur du traitement anti-VHC est l'amélioration histologique. Le taux de réponse prolongée à l'association peg-interferon plus ribavirine n'étant que de 28 à 40% chez les patients VIH/VHC, il est primordial d'évaluer l'impact histologique et notamment d'évaluer l'incidence et les facteurs de risque d'aggravation histologique au cours du traitement anti-VHC [67, 68]. Dans l'essai RIBAVIC, la diminution du score Metavir ou du score d'Ishak était significativement plus importante chez les patients ayant eu une réponse virologique. En revanche, le score de fibrose s'était aggravé chez les autres patients [67]. Dans l'essai Apricot, le bénéfice histologique

était également significativement associé à une réponse virologique prolongée : 69% des patients traités par l'association peginterferon et ribavirine et ayant une réponse virologique soutenue avaient une amélioration histologique. Un bénéfice histologique était également observé chez 32 à 43% des patients non répondeurs virologiquement [125].

Dans l'essai RIBAVIC, 205 patients parmi les 383 patients ayant reçu au moins une dose de traitement anti-VHC ont eu une biopsie à la fois avant traitement et après traitement. Les deux biopsies étaient interprétables pour chaque patient dans 198 cas. Un score Metavir de fibrose plus élevé était la seule différence significative observée entre les patients n'ayant eu que la seule biopsie pré-traitement et ceux ayant eu les deux biopsies (2.4±1.0 versus 2.2±1.0; p=0.03) respectivement mais le stade de Ishak était comparable (2.6 ± 1.2 versus 2.0 ± 4.0; p=0.88). Le taux de réponse virologique soutenue était plus élevé chez les patients ayant eu deux biopsies comparé aux autres (30.3% versus 16.7%; p=0.0024). La durée moyenne entre les deux biopsies était de 109 ± 33.7 semaines. Une aggravation histologique définie par une augmentation de 2 points du stade Ishak de fibrose pour les stades inférieurs à 5 et de 1 point pour le stade 5, était observée chez 34 patients (17.1%). Aucun des patients n'avait un stade 6 à l'inclusion. Treize patients avaient une aggravation de 3 points et 3 patients étaient passés d'un stade 5 à 6. Le score des lésions nécroinflammatoires restait stable chez les patients ayant une aggravation de score de fibrose (4.65 ± 1.6 en pré-thérapeutique et 4.62 ± 1.10 en post-thérapeutique) mais diminuait chez les autres patients (4.46 ± 1.31 en pré-thérapeutique et 3.97 ± 1.11 en post-thérapeutique).

En analyse univariée, les patients ayant une aggravation de score de fibrose recevaient plus souvent un traitement antiretroviral (97% versus 78%; p=0.041) et

avaient moins souvent une réponse virologique soutenue (5.9% versus 35.4%; p= 0.019). Aucune association n'était observée avec les INNTI- et les IP. Les INTIs globalement et parmi les INTIs, la didanosine et la stavudine étaient significativement associés à l'aggravation de la fibrose. L'association de INTI la plus fréquente était l'association stavudine- lamivudine dans 11 cas, zidovudine –lamivudine dans 8 cas et didanosine-stavudine dans 8 cas. Les facteurs suivants n'étaient pas associés à une aggravation de la fibrose : l'âge, le sexe, la durée moyenne de l'infection VIH ou VHC, le taux des CD4, la charge virale VIH la durée moyenne du traitement antirétroviral, le score histologique initial (fibrose ou inflammation), la présence de stéatose, la charge virale VHC, le génotype VHC, le bras de traitement VHC (interféron versus peginterféron) et la durée du traitement anti-VHC.

En raison de la forte association entre la variable traitement antirétroviral et les INTI (tous les patients traités recevaient des INTIs), la variable traitement antirétroviral n'a pas été introduite dans l'analyse multivariée. La didanosine (OR 3.30 95% CI 1.41-7.71; p= 0.00582) et l'absence de réponse virologique soutenue (OR 2.91 95% CI 1.19-7.08; p= 0.018) demeuraient significativement associées à l'aggravation de la fibrose.

Ainsi, en dépit d'une durée moyenne de traitement supérieure à 40 semaines, un nombre élevé de patients non répondeurs (32/138 (23.2%) ont présenté une aggravation du score de fibrose. Il ne semble donc pas que le traitement anti-VHC ait diminué le pourcentage de patients ayant une aggravation rapide du score de fibrose. En effet, deux études réalisées à l'ère des HAART ont montré qu'environ 25% des patients présentaient une aggravation rapide du score de fibrose dans un délai inférieur à 4 ans [126]. Cette étude montre à nouveau le rôle délétère de la didanosine et met en lumière le rôle de la toxicité mitochondriale dans l'aggravation

histologique. Dans les études faites chez les patients non traités pour le VHC, le rôle des IP ou des INNTI dans l'évolution de la fibrose a été étudié avec des réponses contradictoires quant à leur rôle bénéfique ou délétère mais le rôle des INTIs n'a jamais été étudié [28, 42]. La réplication VHC est associée à une déplétion de l'ADN mitochondrial dans les cellules mononuclées qui se corrige en cas de réponse virologique VHC prolongée chez les patients ne recevant pas de traitement antirétroviral [127]. En revanche, une aggravation de la déplétion de l'ADN mitochondrial est observée en cas de traitements concomitants anti-VHC et antirétroviral, suggérant un effet additif de la toxicité mitochondriale de la ribavirine et des traitements antirétroviraux [127]. Ainsi, l'aggravation de la fibrose pourrait être la résultat d'un effet synergique entre l'absence de correction de la déplétion de l'ADN mitochondrial chez les patients non répondeurs et une augmentation de la toxicité mitochondriale secondaire à l'association de la ribavirine et des INTIs. Ce résultat confirme ceux montrés précédemment : multiplication par 46 du risque de toxicité mitochondriale symptomatique et multiplication par 8.8 du risque de décompensation hépatique en cas d'association de la didanosine avec le traitement anti-VHC [87, 88]. Il est à noter qu'aucun des 7 patients ayant présenté une décompensation hépatique spontanée dans l'essai Ribavic n'a été inclus dans l'analyse ci dessus car aucun de ces patients n'avait eu une seconde biopsie hépatique.

Chez les patients mono-infectés par le VHC, la stéatose est un facteur prédictif de l'aggravation de la fibrose [128, 129]. Alors que la stéatose à l'inclusion était associée à un score de fibrose plus sévère dans l'essai RIBAVIC, elle ne constituait pas un facteur de risque d'aggravation de la fibrose. Ceci pourrait s'expliquer par le court délai entre les 2 biopsies. Le score inflammatoire a également été associé à la progression de la fibrose à la fois chez les patients mono-infectés par le VHC et les

patients co-infectés VIH/VHC, mais ne l'était pas dans notre étude [30, 31, 130]. Le taux de CD4 et ou l'absence de réplication virale VIH ont été associés à une progression de la fibrose [26, 30, 31, 131]. Dans notre étude, la plupart des patients avaient un bon contrôle immuno-virologique avec des CD4 supérieurs à 500/mm^3 en moyenne et une charge virale VIH inférieure à 400 copies/ml dans 68.2% des cas.

En conclusion, une aggravation sévère de la fibrose peut survenir dans un délai court et en dépit du traitement anti-VHC chez les patients co-infectés VIH-VHC. La toxicité mitochondriale des INTIs semble jouer un rôle majeur. Idéalement, il faudrait proposer le traitement anti-VHC avant le traitement anti-VIH. En cas de traitement concomitant, il serait souhaitable d'utiliser les INTIs ayant la plus faible toxicité mitochondriale.

Progression of fibrosis in HIV/HCV-co-infected patients treated with interferon plus ribavirin-based therapy: analysis of risk factors

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Running title: Fibrosis worsening in HIV/HCV-co-infected patients treated with interferon plus ribavirin

Key words: fibrosis worsening, fibrosis progression, ribavirin, didanosine, HIV/HCV-coinfection, HCV therapy

Financial support: Agence Nationale de Recherche sur le SIDA and SIDACTION

Total number of words: 2552

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Abstract

Objective: To determine the prevalence and determinants of fibrosis worsening in HIV/HCV-coinfected patients receiving anti-HCV therapy.

Methods: Among 383 HIV/HCV-coinfected patients who received at least one dose of anti-HCV treatment (weekly subcutaneous injections of 1.5 g/kg peginterferon alfa-2b plus daily ribavirin or thrice-weekly subcutaneous injections of 3 MU of interferon alfa-2b plus daily ribavirin for 48 weeks), paired pretreatment and post-treatment liver biopsy specimens were available and interpretable in 198 cases. Hepatic necro-inflammation and fibrosis were graded with Ishak's classification. Histological worsening of fibrosis was defined as a score increase of 2 points or more in patients with stage < 4 fibrosis, and as a score increase of 1 point in patients with stage 5 fibrosis.

Results: The mean interval between the two biopsies was 109 ± 34 weeks. Fibrosis worsened in 34 patients (17.1%). In univariate analysis, ongoing antiretroviral therapy, failure to achieve a sustained viral response, nucleoside reverse transcriptase inhibitor therapy (NRTI), didanosine therapy and stavudine therapy were significantly associated with fibrosis worsening. In multivariate analysis, didanosine (OR 3.30 95% CI 1.41-7.71; p= 0.00582) and failure to achieve a sustained viral response (OR 2.91 95% CI 1.19-7.08; p= 0.018) remained significantly associated with fibrosis worsening.

Conclusion: The mitochondrial toxicity of antiretrovirals such as didanosine seems to play a major role in fibrosis worsening during HCV therapy. Therefore, anti-HCV therapy should ideally be administered before antiretroviral treatment initiation. If anti-

HCV and anti-HIV treatments have to be administered concomitantly, then NRTIs with the lowest mitochondrial toxicity should be preferred.

Introduction

Compared to HCV monoinfection, concurrent infection by HIV and HCV results in more rapid progression toward cirrhosis and liver failure [132, 133]. This progression is not linear over time and may occur after only a few years [23]. In the pre-HAART era, a low CD4 cell count, and also a longer estimated duration of HCV infection, daily alcohol intake and a higher necro-inflammation score were associated with fibrosis progression [26, 131, 132]. The effect of HAART on liver fibrosis is controversial [28]. For unknown reasons, rapid fibrosis worsening is still described in some HIV-infected patients with high CD4 cell counts [126, 134, 135]. Anti-HCV treatment has been associated with improvement of fibrosis in patients who achieve a sustained viral response and also in non responders in HCV mono-infected patients [136, 137]. However, we observed a disturbingly high rate of fibrosis worsening among HIV/HCV-co-infected patients enrolled in a randomized controlled trial (the ANRS HC02 RIBAVIC study) comparing pegylated interferon alfa-2b plus ribavirin vith conventional interferon alfa-2b plus ribavirin. As the rate of sustained viral response to pegylated interferon (peg-IFN) and ribavirin is lower (less than 40%) among HIV/HCV-co-infected patients than among HCV-monoinfected patients, a better knowledge of the factors associated with fibrosis worsening during anti-HCV therapy is important to optimize the safety of this treatment. The aim of the present study was to identify biological and/or clinical features associated with worsening of fibrosis in HIV/HCV-co-infected patients treated for HCV infection.

Methods

This study involved 205 HIV/HCV-coinfected patients who were enrolled in the ANRS trial HC02 Ribavic and for whom both pre-treatment and post-treatment liver biopsies were available. The results of this trial have been reported in detail elsewhere [67]. Briefly, HIV/HCV-coinfected patients who had never received interferon or ribavirin were randomly assigned to receive either weekly subcutaneous injections of 1.5 g/kg peginterferon alfa-2b (ViraferonPeg®, Schering-Plough) plus daily ribavirin (Rebetol®, Schering-Plough) (800 mg), or thrice-weekly subcutaneous injections of 3 MU of interferon alfa-2b plus daily ribavirin (Rebetol®, Schering-Plough) (800 mg), for 48 weeks. Patients were eligible for the trial if they had detectable serum HCV RNA, liver biopsy performed within the previous 18 months and showing at least mild activity or fibrosis, a CD4 cell count above 200/mm^3, stable HIV RNA load (less than 1 log variation in the previous 3 months) at randomization, and stable or no antiretroviral treatment during the previous 3 months. The main ineligibility criteria were active narcotic consumption and/or self-reported daily alcohol intake exceeding 40 g (women) or 50 g (men) within 3 months before entry to the study; decompensated cirrhosis; and HBs antigenemia.

Biochemical and hematologic tests were done in local laboratories. HCV RNA assays, viral genotyping and pathological evaluation of liver biopsy specimens were performed in central laboratories.

HCV RNA was detected with a PCR assay (Amplicor 2.0 HCV Monitor; Roche Diagnostics Systems) with a detection limit of 50 IU per milliliter. HCV RNA levels were measured with a branched-chain DNA assay (bDNA3.0; Bayer Diagnostics) with a detection limit of 615 IU per milliliter. HCV genotyping was performed by sequence analysis of the 5’ untranslated region.

The following data were collected at enrollment: age, sex, body mass index (BMI), antiretroviral drugs, duration of HIV and HCV infection (defined as the date of first transfusion or the date of first intravenous drug use), Ishak scores, biochemical test results, liver enzyme activities, CD4 lymphocyte counts, plasma HIV RNA load and plasma HCV RNA load. The patients were also evaluated 24 weeks after treatment completion. A sustained viral response (SVR,- the primary endpoint for efficacy in the RIBAVIC trial) was defined by undetectable serum HCV RNA in a qualitative PCR-based assay (Amplicor 2.0 HCV Monitor; Roche Diagnostics Systems) 24-weeks after treatment completion (study week 72).

Pre-treatment biopsy specimens were evaluated with those obtained at week 72, by two experienced pathologists blinded to the clinical and laboratory findings. Hepatic necro-inflammation and fibrosis were evaluated with Ishak's classification in which activity ranges from 0 to 12, and fibrosis from stage 0 (none) to stage 6 [138]. Histological worsening of fibrosis was defined as a score increase of 2 points or more in patients with stage < 4 fibrosis and as a score increase of 1 point in patients with stage 5 fibrosis.

The Chi square test or Fisher's exact test was used to analyze qualitative variables, and the Mann Whitney test was used for quantitative variables. Logistic regression models were used to test possible associations between histological worsening of fibrosis (outcome variable) and pre-treatment characteristics (input variables). Characteristics with P values below 0.10 in univariate analysis were included in multivariate models based on a backward elimination procedure. All statistical tests were two-sided, with a type I error of 5%.

Results

A total of 383 patients received at least one dose of study medication -194 patients received peginterferon alfa-2b plus ribavirin and 189 received conventional interferon alfa-2b plus ribavirin-. Paired pretreatment and post-treatment liver biopsy specimens were available for 205 patients and were both interpretable in 198 cases. There was no significant difference in baseline characteristics between patients with and without post-treatment biopsy. The Ishak fibrosis stage was also similar (2.6 ± 1.2 versus 2.0 ± 4.0; p=0.88). The rate of sustained viral response was significantly higher in patients with paired biopsies than in the others patients (30.3% versus 16.7%; p= 0.0024).

The mean interval between the pretreatment liver biopsy and entry to the study was 40 ± 31 weeks. The second biopsy was obtained, on average, 30 ± 16 weeks after the end of treatment. The mean interval between the two biopsies was 109 ± 34 weeks. The mean size of the pretreatment and post-treatment liver biopsy was 17.6 mm (± 8.2) and 18.2 mm (± 8.6), respectively.

The clinical and biological characteristics of these 198 patients are summarized in Table 1. Most patients were male (70.7 %), and mean age was 39.9 ± 5.2 years. Intravenous drug use was the risk factor for HCV transmission in 80.3 % of cases. One hundred sixty-one patients (81.3%) were receiving antiretroviral therapy at enrolment. The mean Ishak scores for necro-inflammation and fibrosis were 4.5 ± 1.4 and 2.6 ± 1.2, respectively. Steatosis was present in 127 (64.1%) patients. One hundred six patients (53.5%) received conventional IFNa2b plus ribavirin and 92 patients (46.5%) received peginterferon alfa-2b plus ribavirin. The mean duration of anti-HCV therapy was 314 ± 60 days. Sixty patients (30.3%) had a sustained viral response.

Fibrosis worsening occurred in 34 patients (17.1%). Pretreatment and posttreatment histologic stages of fibrosis are summarized in Table 2. None of the patients had stage 6 fibrosis at baseline. Thirteen patients had a score increase of 3 points. The necroinflammatory grade remained stable in patients with fibrosis worsening (4.65 ± 1.6 pretreatment and 4.62 ± 1.10 post-treatment) but fell in the other patients (4.46 ± 1.31 and 3.97 ± 1.11 respectively).

In univariate analysis, patients with fibrosis worsening were more likely than the other patients to be receiving antiretroviral therapy (97% versus 78%; p=0.041) and less likely to have a HCV sustained viral response (5.9% versus 35.4%; p= 0.019)(Table 3). No association was observed between fibrosis worsening and the use of NNRTI- or PI- containing regimens at baseline. NRTIs and, among the NRTIs, didanosine and stavudine, were significantly associated with fibrosis worsening. The most frequent dual-NRTI combinations in patients with fibrosis worsening were stavudine-lamivudine (11 cases), zidovudine-lamivudine (8 cases) and didanosine-stavudine (8 cases).

The following factors were not associated with the risk of fibrosis worsening: age, sex, mean duration of HIV and HCV infection, AIDS status, baseline CD4 cell count, HIV viral load below 400 copies/ml, mean duration of antiretroviral treatment, HCV transmission group, mean ISHAK scores for necro-inflammation and fibrosis, steatosis and the mean percentage of steatosis, HCV viral load, HCV genotype, daily ribavirin dose (per kg of body weight), the anti-HCV treatment arm and the duration of anti-HCV therapy.

As all patients who received antiretroviral therapy received NRTIs, the use of antiretroviral therapy was not introduced in multivariate analysis. Didanosine (OR 3.30 95% CI 1.41-7.71; p= 0.00582) and failure to have a sustained viral response

(OR 2.91 95% CI 1.19-7.08; p= 0.018) remained significantly associated with fibrosis worsening (Table 3).

Discussion

To our knowledge, this is the first study to analyze risk factors for fibrosis worsening during anti-HCV therapy in HIV/HCV-coinfected patients. Fibrosis worsened within 2 years in 17.1% of patients (n=34) who started a 48 weeks course of interferon plus ribavirin. Thirteen (38.2%) of these 34 patients had at least a 3 Ishak grade increase in fibrosis. Fibrosis worsening was related both to failure to have a sustained viral response (OR 2.91 95% CI 1.19-7.08; p= 0.018) and to didanosine based-antiretroviral therapy (OR 3.30 95% CI 1.41-7.71; p= 0.00582). As the rate of sustained viral response was significantly higher in patients with paired biopsies than in patients without paired biopsies (30.3% versus 16.7%; p=0.0024), and as the baseline demographic, disease and histological characteristics were similar in the two groups, the rate of fibrosis worsening was probably not overestimated in the study population.

The histological response correlates with sustained viral response status in both HCV-monoinfected and HCV/HIV-coinfected patients [67, 125, 137, 139, 140]. Progression of fibrosis slowed by anti-HCV therapy in HCV-monoinfected patients, even when there is no sustained viral response and maintenance therapy with low dose peginterferon is currently under evaluation [137, 140]. In our study, even though anti-HCV therapy lasted more than 40 weeks on average, we noted no significant improvement in fibrosis in virologic non responders [67]. Furthermore, a high percentage of non responders (32/138, - 23.2%) had a worsening of their fibrosis.

Therefore, interferon-based therapy does not appear to prevent rapid progression of fibrosis in HCV/HIV-coinfected patients. Indeed, two HAART-era studies showed a similar rate of rapid fibrosis progression (around 25% if patients in less than 4 years) in HIV/HCV- coinfected patients not treated for HCV infection [126, 134]. Liver biopsy is the gold standard for evaluating liver fibrosis, despite the dual pitfalls of sampling error of biopsy and inter-observer variability between pathologists. These were not an issue in the present study as the mean length of the biopsy was more than 15 mm and biopsies were read by expert hepatologists.

Didanosine therapy was a major determinant of fibrosis worsening in this study. Studies of the impact of antiretroviral drugs on liver fibrosis have given conflicting results, but most focused on the PIs or NNRTIs and not on specific NRTIs [28, 42, 141]. In our study, didanosine and stavudine were both associated with fibrosis worsening in univariate analysis and didanosine remained independently associated with fibrosis worsening in multivariate analysis, whereas the durations of antiretroviral therapy, PI exposure and NNRTI exposure were not associated with fibrosis progression. The mitochondrial toxicity of NRTI is due to inhibition of mitochondrial polymerase and indirect damage of some liver functions [36, 51]. In-vitro, the mitochondrial toxicity of NRTI for the Hep G2 cell line has been graded, in descending order, as follows: zalcitabine, didanosine, stavudine [36]. In addition, ribavirin is known to enhance ddI phosphorylation, thereby potentiating both the efficacy and the toxicity of this drug.[90].

Our data point to the involvement of mitochondrial toxicity in the observed progression of fibrosis. HCV replication, which correlates with the extent of mt DNA depletion in peripheral blood mononuclear cells (PBMC) in HCV/HIV-co-infected patients may be reversed by successful anti-HCV therapy [125]. In contrast, a

significant depletion of PBMC mitochondrial content is observed when antiretroviral therapy is combined with anti-HCV therapy, supporting a potential additive effect on mitochondrial toxicity of ribavirin and antiretroviral drugs [125]. Therefore, fibrosis worsening during anti-HCV therapy could be due to a synergistic detrimental effect involving the lack of any reduction in mitochondrial depletion in non responders and an enhancement of mitochondrial damage by combined antiretroviral therapy and anti-HCV therapy. We previously found that concomitant treatment with ddI and interferon-2b or peg-interferon-2b plus ribavirin was associated with an adjusted 46-fold increase in the risk of symptomatic mitochondrial toxicity and an adjusted 8.8-fold increase in the risk of spontaneous hepatic decompensation [87, 88]. Of note, none of the seven patients who had spontaneous hepatic decompensation in the RIBAVIC trial were included in this analysis as no post-treatment biopsy was available. Prolonged didanosine exposure has also been implicated in cryptogenic liver disease leading to severe liver complications, particularly variceal bleeding and portal thrombosis in patients free of active hepatitis C and/or B infection and who have no other common causes of liver disease (alcohol, medications, etc...)[38].

One limitation of this study is that alcohol consumption was not assessed during the treatment and follow-up period. In HIV seronegative populations as in HIV-infected patients, heavy alcohol consumption is an independent predictor of rapid liver fibrosis progression [26]. In the current study, all the patients should have limited daily alcohol consumption during the three months preceding their enrolment, but changes in alcohol consumption may have influenced fibrosis progression.

In HCV-monoinfected patients, the onset and progression of steatosis are strong independent predictors of both the severity and the progression of fibrosis [128, 129]. We have previously shown, in patients included in the Ribavic trial, that the severity

of steatosis is related to a higher hepatic fibrosis score [53]. However, the presence of steatosis and the mean severity of steatosis at baseline were not associated with a higher risk of fibrosis worsening in our study. This could be explained by the relatively short interval between biopsies and by the high prevalence of steatosis. Necro-inflammatory activity has also been linked to fibrosis progression both in HCV-mono-infected patients and in HIV/HCV-coinfected patients [30, 31, 130]. In contrast, baseline necro-inflammatory grade did not differ between patients with fibrosis worsening and other patients in our study. However, it should be noted that the necro-inflammatory grade remained stable in patients with fibrosis worsening and improved in the others patients.

An independent association has been reported between hepatic fibrosis progression and CD4 cell depletion and/or absence of HIV suppression [26, 30, 31, 131]. A large proportion of our patients had immuno-virological control of HIV disease on antiretroviral treatment. The mean CD4 cell count was above 500/mm^3 and HIV viral load was below 400 copies/ml in two thirds of cases. We found no association between the CD4 cell count, the CDC class of HIV disease and a lack of HIV suppression in patients with fibrosis worsening.

In another large trial (APRICOT) comparing peginterferona2a (with or without ribavirin) with interferona2a plus ribavirin in HIV/HCV-coinfected patients, histological worsening (defined as an increase in the Ishak-modified histological activity index of 2 or more points) was seen in 20% of patients treated with interferon plus ribavirin and in 13% of those treated with pegylated interferon plus ribavirin; the data for fibrosis worsening have not yet been reported. Interestingly, fibrosis worsened in 10% of patients in whom HCV was eradicated, compared to 5% of patients in our study [125]

In conclusion, the ultimate benefit of anti-HCV therapy is an improvement in the histologic status of the liver. However, in HIV/HCV-co-infected patients, fibrosis worsening can occur rapidly despite HCV therapy and HCV cure. Mitochondrial toxicity, involving a synergistic deleterious interaction between medications for HCV and HIV infections, and particularly didanosine, seems to play a major role. Therefore, anti-HCV therapy for HIV/HCV-co-infected patients should ideally be administered before antiretroviral treatment initiation. If anti-HCV and anti-HIV treatments must be administered concomitantly, then the NRTIs with the lowest mitochondrial toxicity should be preferred.

Acknowledgments: We thank David Young for editing the manuscript.

Table 1. Baseline characteristics of patients with histological worsening of fibrosis and other patients

	Patients with no histological worsening of fibrosis	Patients with histological worsening of fibrosis
Total number of patients	164	34
Age [mean years (SD)]	39.9 (5.2)	39.5 (5.1)
Men [No. (%)]	117 (71.3)	23 (67.6)
Body mass index [mean (SD)]	22.6 (2.9)	22.3 (3.0)
Duration of HIV infection in years [mean (SD)]	10.3 (4.4)	9.9 (4.3)
AIDS [No. (%)]	25 (15.2)	9 (26.5)
CD4 cell count (/mm^3) [mean (SD)]	520 (239)	563 (245)
Patients with <400 HIV copies /ml [No. (%)]	111 (67.7)	24 (70.6)
Ongoing antiretroviral treatment	128 (78)	33 (97)
Duration of antiretroviral treatment in years [mean (SD)]*	4.2 (3.5)	4.5 (2.9)
Components of antiretroviral regimens*		
Protease inhibitor [No.	58 (45.4)	15 (44.1)

(%)]		
Non-nucleoside reverse transcriptase inhibitor [No. (%)]	51 (31.1)	14 (41.2)
Nucleoside reverse transcriptase inhibitor [No. (%)]	128 (78)	33 (97)
Stavudine [No. (%)]	67 (40.8)	20 (58.2)
Zidovudine [No. (%)]	46 (28.0)	8 (23.5)
Lamivudine [No. (%)]	97 (59.1)	22 (64.7)
Didanosine [No. (%)]	24 (14.6)	12 (35.3)
Abacavir [No. (%)]	19 (11.6)	3 (8.8)
Didanosine plus Stavudine	13 (7.9)	8 (23.5)
Duration of HCV infection in years [mean (SD)]	15.1 (5.8)	15.5 (7.3)
HCV infection through intravenous drug use [No. (%)]	129 (78.6)	30 (88.2)
Necroinflammation (grade) [mean (SD)]	4.45 (1.31)	4.65 (1.57)
Fibrosis (stage) [mean (SD)]	2.30 (1.0)	2.42 (1.05)

Steatosis [No. (%)]	104 (63.4)	23 (67.6)
Steatosis [mean (SD)]	18.8 (26.3)	23.1 (27.9)
Ribavirin daily dose per kilogram of body weight (mg/kg) [mean (SD)]	12.3 (2.2)	12.4 (2.2)
Treatment assigned-Peginterferon a-2b, [No. (%)]	86 (52.4)	12 (63.9)
Duration of anti-HCV therapy in days [mean (SD)]	315.3 (55.4)	307.7 (35.3)
Genotype type 1 or 4 (versus 2 or 3), [No. (%)]	96 (58.5)	25 (73.5)
Serum HCV RNA (IU/ml), [mean (SD)] log10	5.87 (0.72)	5.9 (0.4)
Sustained viral response	58 (35.4)	2 (5.9)

*Zero in patients not receiving antiretroviral therapy

Table 2. Pretreatment and post-treatment Ishak stage in patients with histological worsening of fibrosis

		Post-treatment Ishak stage			
		Stage 3	Stage 4	Stage 5	Stage 6
Pre-treatment Ishak stage	Stage 1	6	0	0	0
	Stage 2		3	6	3
	Stage 3			7	4
	Stage 4				2
	Stage 5				3

Table 3: : Factors associated with histological worsening of fibrosis. Univariate and multivariate logistic regression analysis

	Univariate analysis		Multivariate analysis	
	Odds Ratio (95% IC)	P value	Odds Ratio (95% IC)	P value
Ongoing antiretroviral treatment	4.66 (1.06-20.4)	0.041		
Nucleoside reverse transcriptase inhibitor	9.28 (1.09-2.36)	0.031		
Stavudine	2.07 (0.97-4.38)	0.01		
Didanosine	3.18 (1.39-7.27)	0.006	3.30 (1.41-7.71)	0.00582
No HCV sustained viral response	2.84 (1.18-6.85)	0.019	2.91 (1.19-7.08)	0.018

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X- BENEFICE CLINIQUE DU TRAITEMENT ANTI-VHC ?

L'objectif ultime du traitement anti-VHC est un bénéfice clinique avec diminution voire un arrêt de l'évolution vers la cirrhose, une diminution du risque de décompensation hépatique ou de survenue d'un hépatocarcinome. Chez les patients mono-infectés par le VHC, une diminution significative du risque d'hépatocarcinome hépatique est observée chez les patients traités. Une étude japonaise portant sur 90 patients porteurs d'une cirrhose non décompensée randomisés entre l'absence de traitement ou un traitement par β-interféron pendant 6 mois et suivis pendant en moyenne 8.7 ans a montré une incidence de l'hépatocarcinome significativement plus basse parmi les patients traités (27% versus 73%), indépendamment de la réponse virologique. Dans une autre étude portant sur 132 patients porteurs d'une cirrhose non décompensée et traités par l'association IFN 3 à 5 M UI x3/semaine plus ribavirine pendant 24 à 48 semaines puis suivis en moyenne pendant 37 mois, un hépatocarcinome était diagnostiqué dans 5 cas chez les patients avec une réponse virologique soutenue et 11 cas chez les autres (p=0.0178). En analyse multivariée, l'absence de réponse virologique soutenue (OR 3.521 ; p=0.036), le sexe masculin (OR 6.269, p=0.011) et un âge élevé (OR 3.076 ; p=0.049) étaient associés au risque de survenue d'un hépatocarcinome.

Parmi les 383 patients de l'essai RIBAVIC ayant reçu au moins une dose de traitement, 248 ont été inclus dans la cohorte RIBAVIC. Le suivi médian de ces patients est de 33 semaines après le dernier suivi de l'essai RIABVIC (S72). Les caractéristiques à l'inclusion des patients inclus dans la cohorte et ceux non inclus ne différent pas. En revanche, les patients inclus dans la cohorte avaient un taux de réponse virologique soutenue plus élevé (29%). Les facteurs de risque d'évolution

vers une insuffisance hépatique terminale (décompensation ascitique, hémorragie digestive, ictère avec bilirubinémie > 51 mmol/l, encéphalopathie hépatique, hépatocarcinome, transplantation hépatique et décès lié au VHC) ont été analysés dans cette population. Les variables étudiées étaient la durée de l'infection par le VHC, le génotype VHC, la charge virale VHC, la réponse au traitement anti-VHC, le taux de CD4, une charge virale VIH < 200 copies/ml, le traitement antirétroviral et la nature de celui-ci et la consommation d'alcool. Neuf patients (4%) ont présenté une insuffisance hépatique terminale, dans tous les cas chez les patients en échec virologique VHC et dans 8 cas chez des patients ayant un score METAVIR de fibrose F3 ou F4. Six patients sont décédés (3 d'une décompensation hépatique, 2 d'un hépatocarcinome et 1 d'une encéphalopathie hépatique). En analyse univariée, l'absence de réponse virologique VHC (p=0.051), un score fibrose F3-F4 (p< 0.001) et un taux de CD4 < 350/mm^3 (p=0.035) étaient associés au risque d'insuffisance hépatique terminale. En analyse multivariée, un score fibrose F3-F4 (p< 0.001) et un taux de CD4 < 350/mm^3 (p=0.022) demeuraient associés au risque d'insuffisance hépatique terminale. Il existait une tendance pour l'absence de réponse virologique soutenue (p=0.068). Nous sommes en voie de collecter l'ensemble des données des patients inclus dans RIBAVIC et une nouvelle analyse devrait être réalisée l'été 2007 avec un suivi plus prolongé. Ces résultats intermédiaires montrent une nette tendance pour un bénéfice clinique du traitement anti-VHC. Aucun des 25 patients ayant un score METAVIR F3F4 et ayant une réponse virologique soutenue n'a présenté d'insuffisance hépatique terminale. Cette étude confirme également un risque plus élevé de décompensation hépatique en cas de score de fibrose élevé chez les patients co-infectés (7.4% par an versus 3 à 4% par an chez les patients

mono-infectés par le VHC). Ces résultats ont été présentés en 2006 à la Conférence Internationale sur le SIDA (XVI International AIDS Conference, Toronto) [142].

XI- INDICATIONS DU TRAITEMENT ANTI-VHC

Chez les patients mono-infectés par le VHC, l'instauration d'un traitement anti-VHC est recommandée en cas de score METAVIR ≥ A2F1 ou ≥ A1F2. Chez les patients co-infectés VIH-VHC, un consensus se dégage pour ne pas restreindre les indications thérapeutiques. La progression de la fibrose n'étant pas linéaire et ses déterminants n'étant pas tous identifiés, différer la traitement chez les patients ayant une fibrose minime n'est pas souhaitable. Par ailleurs, le traitement anti-VHC doit être prescrit également avant, dans la mesure du possible, l'instauration du traitement anti-VIH. En effet, les patients co-infectés sont exposés aux: risques - d'hépatotoxicité sous bithérapie ou trithérapie antirétrovirale; - d'évolution vers la cirrhose sous traitement antirétroviral dans un délai parfois très court et dont les facteurs prédictifs ne sont pas connus, - d'augmentation de la charge virale VHC sous traitement antirétroviral ; - d'effets secondaires liés notamment aux interactions entre la ribavirine et les analogues nucléosidiques et finalement ; - d'une adhérence au traitement probablement plus difficile.

XII- CONCLUSION

En conclusion, l'essai RIBAVIC et la cohorte RIBAVIC nous ont apporté les enseignements suivants :

- la cinétique de la charge virale VHC peut différer selon la nature du traitement antirétroviral.
- la prévalence de la stéatose (61%) est similaire à celle observée dans la population mono-infectée VHC et les facteurs de risque identifiés ne différent pas de ceux décrits chez les patients mono-infectés par le VHC : génotype 3, charge virale VHC élevée, score METAVIR de fibrose, BMI et ferritine élevés. Les caractéristiques liées à l'infection par le VIH, notamment le traitement antirétroviral ne sembient pas influencer la stéatose
- le taux de non réponse virologique (diminution de la charge virale VHC inférieure à 2 log à S12) sous traitement par peginterferon plus ribavirine est plus élevé (33%) comparé aux patients monoinfectés VHC (14%) et trois facteurs de risque sont identifiés, le génotype 1 ou 4, une charge virale VHC élevée et un traitement antirétroviral incluant l'abacavir. Ce dernier résultat suggère une interaction entre l'abacavir et la ribavirine. Il faut souligner qu'il existe aucune donnée sur l'impact des INTIs sur l'activité de la ribavirine.
- la valeur prédictive positive élevée de 97% de l'indétectabilité de l'ARN VHC dès S4 associée à une réponse virologique soutenue
- une valeur prédictive positive moins élevée de S12 : 60% (ARN VHC indétectable et/ou une diminution > 2 log)
- une décroissance de la charge virale VHC significativement plus lente chez les patients rechuteurs comparée aux patients répondeurs long terme à S2 et à S4

- un risque d'anémie élevé au cours du traitement anti-VHC, majoré par la co-prescription de zidovudine et de ribavirine

- un risque d'amaigrissement sévère élevé au cours du traitement anti-VHC, pouvant être révélateur d'une toxicité mitochondriale

- un risque bactérien non lié au taux des polynucléaires neutrophiles mais à la fibrose hépatique

- une majoration du risque de toxicité mitochondriale secondaire à l'interaction entre la didanosine et la ribavirine

- le rôle de la toxicité mitochondriale de la didanosine dans l'aggravation de la fibrose au cours du traitement anti-VHC avec majoration du risque de décompensation hépatique

- le bénéfice histologique et clinique d'une réponse virologique soutenue.

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RESUME

HCV/HIV-coinfection : Natural history and therapeutic issues

With the introduction of highly active antiretroviral therapy in 1996, liver disease has emerged as an important cause of morbidity and mortality in HIV/HCV-coinfected patients. In 2000, RIBAVIC HC02 trial, a randomized controlled trial (the ANRS HC02 RIBAVIC study) comparing pegylated interferon alfa-2b plus ribavirin vith conventional interferon alfa-2b plus ribavirin was conducted. In order to describe the effect of interferon plus ribavirin-based therapies on the incidence of long-term clinical outcomes in HIV/HCV-coinfected patients, a prospective cohort study was performed from the patients included in the ANRS HC02 RIBAVIC trial in 2001. The RIBAVIC trial and the cohort contribute to show these results :

- HCV viral load kinetics could differ according to the choice of HAART regimen.
- the prevalence (61%) and risk factors for steatosis are similar to that observed in HCV-monoinfected patients. None of the characteristics of HIV infection, including antiretroviral therapy, is independently associated with steatosis.
- the rate of sustained virological response is lower in HIV/HCV-coinfected patients (27%) than in HCV-monoinfected patients
- the rate of non response (HCV RNA decline of less than 2 logs at 12 weeks of peginterferon and ribavirin combination therapy) is high, ranging from 29% to 33% (14% in HCV-monoinfected patients). The potential loss of ribavirin efficacy on HCV during concomitant use of NRTIs, such abacavir, is suspected.
- the best positive and negative predictive values of sustained virological response (SVR) were respectively obtained with an undetectable HCV RNA at W4 (97%) and with more than a 2 log10 decrease at W12 (99%). The HCV viral load decrease at

week 2 and week 4 was significantly slower in relapsing patients than in patients with sustained virological response.

- During anti-HCV therapy, 1- severe anemia occurred in 15.9% of patients and was significantly higher in patients receiving zidovudine-based HAART ; 2- severe weight loss (> 10% of baseline weight) is frequent (28%) and could be one of the first clinical sign of a mitochondrial toxicity; 3- markers of advanced liver fibrosis and not neutropenia are predictors of increased susceptibility to bacterial infections 4- concomitant treatment with didanosine and interferon-2b or peg-interferon-2b plus ribavirin is associated with an increase risk of symptomatic mitochondrial toxicity, hepatic decompensation and fibrosis worsening.

RESUME

En 1998, le traitement de la co-infection VHC rarement discuté avant l'ère des HAART, compte tenu d'une réponse médiocre à la monothérapie par IFNα et d'un pronostic de vie lié au VIH estimé en moyenne à 10 ans, fût reconsidéré. C'est ainsi que débuta en 2000, l'essai RIBAVIC HC02, essai randomisé et multicentrique comparant l'association de la ribavirine 800 mg/j à l'Interféron 3 MUI x3/semaine ou au PEG-α-2b Interféron 1,5 µg/kg/semaine pendant 48 semaines. Une cohorte des patients inclus dans l'essai RIBAVIC (cohorte RIBAVIC EP10) débuta en 2001 pour évaluer le devenir à long terme de ces patients.

L'essai RIBAVIC et la cohorte RIBAVIC ont apporté les enseignements suivants :

- la cinétique de la charge virale VHC peut différer selon la nature du traitement antirétroviral.
- la prévalence et les facteurs de risque de la stéatose sont similaires à ceux observés dans la population mono-infectée VHC
- le taux de réponse virologique soutenue est inférieur chez les patients co-infectés (27%) comparé aux patients mono-infectés VHC (50%)
- le taux de non réponse virologique (diminution de la charge virale VHC inférieure à 2 log à S12) sous traitement par pegIFN plus ribavirine est plus élevé (33%) comparé aux patients monoinfectés VHC (14%). L'interaction entre la ribavirine et l'abacavir pourrait être un facteur de risque.
- l'indétectabilité de l'ARN VHC dès S4 est prédictive de la réponse à long terme (valeur prédictive positive 97%) et la décroissance de la charge virale VHC est significativement plus lente chez les patients rechuteurs comparée aux patients répondeurs long terme à S2 et à S4
- Au cours du traitement anti-VHC :1- le risque d'anémie est élevé et majoré par la co-prescription de zidovudine et de ribavirine ; 2- l'amaigrissement est fréquent et sévère et peut être révélateur d'une toxicité mitochondriale ; 3- le risque bactérien n'est pas lié au taux des polynucléaires neutrophiles mais à la fibrose hépatique ; 4- le risque de toxicité mitochondriale, d'aggravation de la fibrose et de décompensation hépatique est majoré par l'interaction entre la didanosine et la ribavirine
- une réponse virologique soutenue est associée à un bénéfice histologique et clinique.

MOTS CLES : Co-infection VIH/VHC, Peg-interferon, ribavirine