Treatment of chronic hepatitis C in patients with human immunodeficiency virus (HIV) with weekly peginterferon alpha-2b plus ribavirin : a multi-centred Belgian study

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Abstract

Background and study aims : **In Belgium, 10-15% of patients infected with the human immunodeficiency virus (HIV) are co-infected with hepatitis C virus (HCV). Because of increased incidence of antiretroviral drug-related hepatotoxicity and more rapid clinical evolution towards end-stage liver disease, treatment of chronic hepatitis C becomes a priority. We report the results of a multi-centred Belgian study evaluating efficacy and safety of peginterferon alpha-2b plus ribavirin in HIV-HCV co-infected patients without AIDS and without decompensated liver disease.**

Patients and methods : **Forty-one patients, all genotypes, were screened to participate. Eventually 37 received treatment with peginterferon alpha-2b (1.5 µg/kg/week) plus daily weight-based ribavirin for 52 weeks. About one third of the patients were genotypes 1, 2/3, and genotype 4, most of the latter being of Central African origin. About 56% of the patients had severe fibrosis (Metavir score ≥ F3).**

Results : **Sustained viral response (SVR) at 24 weeks of follow-up was observed in 10/37 (27%) of patients. SVR was higher in genotype 2/3 compared to genotype 1/4 (46.7% versus 13.6% ; p = 0.06) and in low (F0-F1) versus high (F2-F4) grade fibrosis (p = 0.06). Treatment was withdrawn for side effects in 11/37 patients (30%). One Child A cirrhosis patient at the start of therapy died 7 months after treatment withdrawal as a result of severe haemolytic anaemia.**

Conclusions : **It can be concluded that weight-based peginterferon alpha-2b plus ribavirin can be successful in selected HIV-HCV co-infected patients. Caution should be applied in patients with advanced liver disease.** (Acta gastroenterol. belg., **2009**, 72, **389-393**).

1. Introduction

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection are major health problems, worldwide. Although both viruses are transmitted with high efficacy via direct blood-to-blood contact, HCV is less easily transmitted via the sexual route than HIV. The prevalence of HCV co-infection in different geographical regions is closely related to the prevalence of blood-borne (mainly intravenous drug abuse) HIV infection. Within Europe, high rates of HCV co-infection are observed in the Eastern European countries such as Belarus or Ukraine, where intravenous drug abuse is the main route of HIV transmission, HCV co-infection rates being as high as 70%. Conversely, in Central to Western European countries such as Belgium, where the main mode of transmission is via sexual intercourse, HCV co-infection rates are much lower, between 10-15% (1). Before the advent of highly active antiretroviral therapy (HAART), treatment of HIV-HCV co-infected patients was directed primarily towards managing HIV-related opportunistic infections with little, if any, attempts to treat the HCV infection. With the dramatic reduction of most opportunistic infections in the HIV-infected patients and the resultant rise in longevity, increasing numbers of these patients are undergoing assessment and treatment of HCV infection (2). Further, the increased incidence of antiretroviral drug-related hepatotoxicity and the more rapid clinical evolution towards end-stage liver disease has made treatment of chronic hepatitis C a priority in these patients (3). Treatment regimens using interferon alpha (or combination therapy with interferon alpha + ribavirin) have had lower sustained viral response rates in co-infected patients than in HCV mono-infected patients (2). The current standard care for chronic infection with HCV in individuals without other infections is pegylated interferon + ribavirin (4). Several recent trials have found varying rates of sustained viral response to this combination in HIV-HCV co-infected patients ; the responses ranging from 27 to 55% (5-14) and generally lagging behind those in HCV mono-infected patients. Further, safety issues have been raised in several of these studies (15). We present here the results of our multi-centred study evaluating the efficacy and safety of peginterferon alpha-2b + ribavirin in HIV-HCV co-infected patients in Belgium.

2. Patients and methods

2.1. *Patients*

To be eligible for the study, patients had to be aged 18 years or older, to be infected with both HIV and HCV,

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to have elevated alanine aminotransferase levels documented on two or more occasions within the previous 6 months, findings on liver biopsy within the previous 12 months that were consistent with chronic hepatitis C infection, and compensated liver disease. The diagnosis of HIV infection was made by positive antibody detection by ELISA (Enzygnost Anti-HIV ½ Plus, Dade Behring), further confirmed by INNO-LIA HIVI-II Score, Innogenetics, Gent, Belgium. Quantification of HIV-RNA was performed using COBAS AMPLICOR HIV-1 MONITOR test, v1.5 Ultrasensitive, Roche Diagnostics (with a detection limit of 50 copies/mL). HCV infection was confirmed by detection of HCV RNA using polymerase chain reaction (PCR) assay. For inclusion in the study, no severe HIV-related immunodepression could be present (meaning a CD4 cell count above $> 200 \times 10^6$/L and/or no history of opportunistic infection within 6 months prior to enrolment). Patients were not eligible if they had neutropenia ($< 1.5 \times 10^9$/L), thrombocytopenia ($< 90 \times 10^9$/L), anaemia (< 11.0 g/dL haemoglobin), serum creatinine elevated beyond the laboratory's upper limit of normal (ULN), HBsAg positivity, evidence of decompensated liver disease (total bilirubin level > ULN, except for non-hepatitis related factors such as Gilberts disease ; prothrombin time prolonged > 3 s ; albumin < 3.5 g/dL ; history or presence of ascites fluid ; bleeding varices ; or hepatic encephalopathy), severe psychiatric disorders especially depression, active seizure disorder requiring medication, significant cardiovascular or chronic pulmonary disease, poorly controlled diabetes mellitus, auto-immune disorders, haemophilia or haemoglobinopathies, evidence of active or suspected malignancy or other clinically significant coexisting medical conditions. Patients were excluded in case of alcohol intake > 80 g/d, active illicit drug use (injection or inhalation) or methadone substitution within 2 years prior to enrolment into the present study. Women of child bearing potential were not recruited if they were unwilling to use effective contraception. Also excluded were potential participants who had received interferon alpha or ribavirin previously.

2.2. *Study design*

The study was conducted in 9 Belgian reference centres in an open, non-controlled, prospective trial. The protocol was approved by the ethics committees of the participating centres. All patients gave their written informed consent to participation. The study followed the Helsinki Declaration and Good Clinical Practice guidelines. Eligible patients were treated with subcutaneous injections of 1.5 µg/kg bodyweight peginterferon alpha-2b (PegIntron®, Schering-Plough, Kenilworth, NJ, USA) once a week, plus daily ribavirin (800 mg for patients weighing < 65 kg, 1000 mg if weighing 65-85 kg, 1200 mg if weighing > 85 kg) for 52 weeks, independent of viral genotype. The treatment period was followed by a 24-week observation period. Pre-treatment biopsy specimens were centrally scored according to the Metavir system (16). The activity scores were from 0 (none) to 3 for severe necro-inflammatory activity, and the fibrosis scores were from 0 (none) to 4 (cirrhosis). HIV infection was treated, when indicated, according to the international guidelines available at the moment of study inclusion. Concomitant medication, including antidepressants, were allowed to relieve side effects, at discretion of the investigators.

2.3. *Assessment of efficacy*

Serum HCV RNA was measured using a qualitative PCR assay (Cobas Amplicor HCV test, version 2.0, Roche Diagnostics ; limit of detection 50 IU/mL) at the time of screening, at weeks 24 and 52, and at week 24 of follow-up. HCV RNA was quantified by PCR (Cobas Amplicor HCV Monitor Test, version 2.0, limit of detection 600 IU/mL) at baseline.

The primary efficacy end point was a sustained virologic response (SVR), defined as a serum HCV RNA level below the assay's detection limit (< 50 IU/mL) at 24 weeks of follow-up. Patients who had not had HCV RNA measurement conducted at 24 weeks of follow-up were considered to have had treatment failure. Viral genotyping was performed by line probe assay (INNO-LiPA, Innogenetics, Zwijndrecht, Belgium) at baseline on entry into the study.

2.4. *Assessment of safety*

Safety of treatment was assessed by physical examination, laboratory tests and spontaneous reports of clinical adverse events by the patients. The consultation visits were at weeks 2, 4, 8, 12 and at 6-week intervals thereafter during the treatment period of up to 52 weeks. Follow-up visits were for a further 6, 12 and 24 weeks following the cessation of treatment. Adverse events were graded according to the World Health Organization (WHO) scale as mild (grade 1), moderate (grade 2), severe (grade 3) and life-threatening (grade 4). CD4 cell counts and HIV-RNA loads were determined at screening, at baseline, and at weeks 12, 24, 36 and 52, as well as at weeks 12 and 24 of follow-up.

The study protocol allowed dose reductions (by half in the case of peginterferon alpha-2b and by 200 mg per day but reduction to no lower than 600 mg per day in the case of ribavirin) when required for the clinical management of significant adverse events, or in the case of laboratory analysis abnormalities. If the adverse event was resolved or improved, a return to the initial dosing level was permitted at the discretion of the investigator.

Treatment was discontinued if the following had occurred : virologic non-response at week 24 of treatment, grade 4 adverse events, interruption of therapy for more than 2 weeks due to patient non-compliance with treatment and/or due to adverse events, CD4 cell count decrease to $< 200 \times 10^6$/L, rise in HIV RNA load by > log 0.5 above baseline at any time during treatment despite

modification of the antiretroviral regime. Treatment was discontinued at the request of the patient or if in the opinion of the attending physician the patient was not benefiting from the treatment or the treatment was detrimental to the patient's best interest. In case of premature withdrawal from the study for whatever reason, the patients were encouraged to return for follow-up appointments at 6, 12 and 24 weeks after treatment discontinuation and at the predefined week 52 and 24 weeks of follow-up. HIV therapy could be modified during the study period at discretion of the HIV physician, in function of possible side effect or suspected drug interactions.

2.5. *Data presentation and statistical evaluation*

The analyses were calculated on an intention-to-treat basis (all patients who received at least one dose of the study medication were included in the analyses of efficacy and safety). Continuous variables were expressed as median and range.

In this study, the responses are end-of treatment and sustained virologic response. All responses were analyzed as dichotomous variables.

The relationship between response (dichotomous variable) and a qualitative variable was explored by means of the Fisher's exact test. Spearman correlation coefficients between quantitative variables were computed.

The Student *t*-test and Kruskal-Wallis test were used for comparing quantitative variables between 2 groups.

All p values < 0.05 were considered statistically significant.

3. Results

3.1. *Characteristics of the patients*

Between September 2001 and December 2003, 41 patients were screened for the study. Four patients did not commence treatment either because they chose not to participate (n = 2) or did not attend the scheduled appointment for treatment (n = 1) or because of a serious medical event occurring between screening and the first treatment (n = 1). These patients were excluded from analysis. The baseline characteristics of the patients are presented in Table 1. Of note, two thirds of the study participants were receiving an antiretroviral treatment at inclusion and almost all of them had an undetectable HIV viral load (< 50 copies/mL). Most HIV treatments consisted of the combination of one non-nucleoside reverse transcriptase inhibitor (NNRTI) with 2 nucleoside reverse transcriptase inhibitor (NRTI).

Table 1. — **Baseline characteristics of the included patients (n = 37)**

Characteristic	N
Age; years, median (range)	34 (17-60)
Gender	N (%)
Male	24 (65)
Female	13 (35)
Bodyweight; kg, median (range)	70 (51-125)
Body mass index; kg/m^2 median (range),	24 (20-45)
Ethnicity, N	
Caucasian	29
Black	7
Asian	1
HCV genotype,	N (%)
1	11 (29.7)
2	1 (2.7)
3	13 (35.1)
Co-infection 2 and 3	1 (2.7)
4	11 (29.7)
HCV RNA (n = 34),	N (%)
High (≥ 850,000 IU/mL)	18 (53)
Low (< 850,000 IU/mL)	16 (47)
Mode of HCV infection	N
Intravenous drug abuse	15
Transfusion	7
Other or unknown	15
Liver fibrosis (Metavir score) (n = 34)	N (%)
F0	1 (2.9)
F1	5 (14.7)
F2	9 (26.5)
F3	17 (50.0)
F4	2 (5.8)
CD4 cell count; × 10^6/L, median (range)	481 (222-1169)
HIV RNA (n = 34)	N (%)
< 50 copies/mL	22 (65)
> 50 copies/mL	12 (35)
Antiretroviral treatment	N (%)
No	13 (35)
Yes	24 (65)
3 NRTI	5
2 NRTI + 1 NNRTI	13
2 NRTI + 1 PI	6

NRTI denotes nucleoside reverse transcriptase inhibitor; NNRTI non-nucleoside reverse transcriptase inhibitor; PI protease inhibitor.

3.2. *Virologic response*

End of treatment virologic response at 52 weeks was obtained in 14/37 patients (38%).

SVR at 24 weeks follow-up was observed in 10/37 patients (27%), 7 of whom had genotype 2 and/or 3, while 3 had genotype 1 and none had genotype 4. SVR for the patients with genotype 1 was 3/11 (27%), 7/15 (47%) for genotypes 2 and/or 3, and 0/11 (0%) for genotype 4.

Three patients were virologic relapsers, all of whom were genotype 4. In 1 patient with genotype 4 HCV RNA was not determined at week 24 of follow-up and was, therefore, considered as treatment failure.

Prior to applying Fisher's exact test, the HCV genotype was grouped in 2 categories for genotype (Genotype 1 or 4 ; Genotype 2 or 3), fibrosis score (low fibrosis : F0-F1 ; high fibrosis : F2-F4), and HCV viral load (low : < 850,000 IU/mL ; high : ≥ 850,000 IU/mL).

No significant difference with respect to end-of-treatment response was detected between the two HCV genotype groups (p = 0.49). The proportion of patients showing an end-of-treatment response was nevertheless numerically lower in the HCV genotype 1 or 4 group (31.8%) than in the HCV genotype 2 or 3 group (46.7%).

A borderline significant difference with respect to SVR was detected between the two HCV genotype groups (p = 0.06). The proportion of patients with a sustained virologic response was lower in the HCV

genotype 1 or 4 group (13.6%) than in the HCV genotype 2 or 3 group (46.7%).

There was a trend that patients with low fibrosis (F0-F1) have higher SVR rate versus patients with high fibrosis (≥ F2) (n/n 6/33, 18% versus n/n 27/33, 82% ; p = 0.06). There was no significant difference in SVR between high or low HCV-RNA load (p = 0.62).

For the HIV viral load, an indicator was derived using a cut-off value of 50 copies/mL. No significant difference with respect to SVR was detected between the two groups with respect to HIV viral load indicator at screening (p = 0.6870).

Nine patients were transferred out of the study as per protocol because of virologic non-response at week 24.

Nine of 10 patients with SVR received at least 80% of the prescribed dose of peginterferon plus ribavirin for at least 80% of treatment period. Only 1 patient who prematurely withdrew from treatment eventually had a SVR.

3.3. *Safety*

Treatment withdrawal due to side effects related to the study drugs was noted in 11 patients. One of these patients eventually died from broncho-pulmonary aspergillosis 7 months after treatment withdrawal. His case was reported elsewhere (17). Three patients had treatment interruption due to severe depression, 2 for severe haemolytic anaemia necessitating transfusion, 2 for drop in CD4 count to $< 200 \times 10^6$/L, 1 for pancreatitis and hyperglycaemia. Four other patients were treated with antidepressants, two of them had a SVR. Four additional patients stopped prematurely due to adverse events not related to the treatment.

Specific clinical side effects were flu-like symptoms (in 73%), symptoms suggestive of psychiatric disturbance (62%), anorexia (35%), cutaneous side-effects (29%), myalgia (27%), headache (22%), hair loss (11%), vertigo (11%). Anaemia was noted in 19%.

4. Discussion

The regimen used in this open, non-controlled, prospective, Belgian trial achieved a SVR rate of 27% in HIV/HCV co-infected patients. SVR was 47% for the genotype 2/3 patients, 27% in genotype 1, and 0% in genotype 4 patients. These values are similar to those from the recently published RIBAVIC study (7) where an overall SVR of 27% was noted and with significantly better results in genotype 2/3. We, as well, noted a better SVR in genotype 2/3 patients compared to genotype 1 and 4 ; albeit the difference was not statistically significant and was probably due to low numbers of patients. There was a trend for better SVR in patients with a low (F0-F1) compared to high fibrosis score (≥ F2).

The variability in the reported response rates to peginterferon and ribavirin in HIV/HCV co-infected patients may be explained, at least in part, by observable differences between the studies (ribavirin dosing, patient demographic characteristics, HCV genotype distribution, histological severity) and non-observable differences due to various forms of bias or measurement error (18). In our patient group, 56% had bridging fibrosis or cirrhosis (Table 1) compared to 39% in the RIBAVIC study (7) and 15% in the APRICOT study (6).

Of particular note was the relatively high proportion of genotype 4 patients in our population (30%) which is much higher proportion than HCV mono-infected patients in Belgium (19). The majority were Sub-Saharan black patients from Central Africa. None of these patients achieved SVR. Conversely, relatively favourable SVR rates are reported in HCV genotype 4 mono-infected patients from the Middle East while SVR was also reported to be significantly lower in black African patients (20,21). Whether this is due to ethnicity or other factors such as HCV genotype 4 sub-types is not clear.

We had decided, when designing the protocol, to use bodyweight-based doses of peginterferon alpha-2b and ribavirin, and to treat all patients for one year, independent of genotype. Studies have indicated that the use of bodyweight-based ribavirin in the treatment of co-infected patients is not associated with an increased risk of adverse effects, and may be associated with improved viral response (14,22). Because the efficacy of shorter treatment duration has not been adequately assessed in HIV-infected patients, the recommended duration of treatment is now 48 weeks for co-infected patients, including those with HCV genotype 2 and 3 (23).

As in the RIBAVIC study, a high dropout rate because of side effects was found. One patient eventually died from invasive pulmonary aspergillosis 7 months after early discontinuation of treatment at 12 weeks due to the development of severe Coombs positive haemolytic anaemia. This patient had a compensated cirrhosis at start of treatment and the case has been reported previously (17).

Several limitations of our study should be kept in mind. First, the study was non-controlled and the number of patients was limited. Furthermore, early viral response was not determined since the concept had not, as-yet, been established when the study was initiated, only the 24 week stopping rule was applied. Also, at the time of the study, some patients were treated with a combination of 3 NRTI, an antiretroviral regimen which is not recommended any more because of lower efficacy on HIV control. In addition, the numerous drug interactions and detrimental combinations between HIV and HCV therapies were not yet fully assessed. Some patients received zidovudine- or stavudine-containing regimens, which are now strongly discouraged concomitantly with anti-HCV drugs (23) and which might have been partly responsible of the high rate of side effects and dropouts.

We can, however, conclude from our results that the current standard treatment with bodyweight-based peginterferon alpha-2b and ribavirin for HCV mono-

infected patients can be applied in selected HIV-HCV co-infected patients despite the SVR rates being lower than in HCV mono-infected patients. The high dropout rate due to side effects should be taken into account, especially when treating patients with advanced liver disease. The relatively poor outcome, however, calls for new therapeutic approaches in this setting.

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