Treatment of Chronic Hepatitis C in Special Populations

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INTRODUCTION

We will focus on the antiviral treatment of HCV infection in special populations, namely patients with hematological diseases, psychiatric disorders or kidney diseases (hemodialyzed patients and kidney recipients). In these patients, the prevalence of HCV infection is high (10 to 90%), mainly related to blood transfusions (before 1990) or clotting factor transfusions before 1986 and to the solvent-detergent procedure of viral inactivation (genotype 1b), as well as nosocomial transmission with frequent mixed infections. In hemophiliacs [1, 2] or hemodialysis patients [3], the natural history of HCV infection is similar to that of the general population, while it is accelerated in alcoholic patients [4] and kidney recipients [3,5] with increased viral replication and a higher frequency of cirrhosis. Early treatment is logical and cost effective by decreasing the prevalence of cirrhosis and hepatocellular carcinoma before irreparable severe liver lesions have occurred and before highly complex populations of HCV genomes have been generated.

TREATMENT OF CHRONIC HEPATITIS C IN PATIENTS WITH HEMATOLOGICAL DISEASES

Hemophiliac patients

Hemophilia does not modify the recommended therapeutic strategies because there are risks of liver-related mortality, whatever the HIV status [1]. The tolerance and efficacy of interferon alone and combination therapy with ribavirin are similar to that in the general population [6, 7], even with HIV co-infection [8] and a risk of lactic acidosis associated with the use of nucleoside analogue reverse transcriptase inhibitor (NRTI). To date there is no experience of combination therapy with pegylated interferon and ribavirin, but this should be the first line treatment. Even if there are limited data about the risk of developing anti-FVIII antibodies in hemophiliac patients treated with interferon [9], monitoring of these patients should be recommended.

Thalassemic patients

In thalassemic patients, a sustained virologial response is obtained in 40 to 57% of cases with interferon monotherapy with no more side-effects than in other populations [10-16]. There is limited data about interferon and ribavirin but efficacy seems to be comparable to that observed in the general population [16]. Ribavirin therapy may be difficult to manage because of pre-existing anemia but treatment is relatively well tolerated with enhancement of blood transfusions. Finally, iron overload may limit the efficacy of treatment [17].

As in the general population, pegylated interferon-alpha in association with low and increasing doses of ribavirin should be recommended in thalassemic patients. The place of associated erythropoietin therapy in these patients needs be discussed.

TREATMENT OF CHRONIC HEPATITIS C IN PATIENTS WITH PSYCHIATRIC DISEASES

Psychiatric diseases, such as depression, are more frequently found in HCV-infected patients than in the general population [18]; this seems to be related both to chronic disease and to fear of the future [19] as well as to past medical history because some HCV-infected patients are alcoholic or ex-intravenous drug abusers, which may be associated

with psychiatric disorders [20, 21] such as schizophrenia [22]. Treatment with pegylated interferon and ribavirin is associated with mental side-effects in 20 to 40% of cases [23]. Results of therapy in this population are limited and contradictory [24-25] and a psychiatric evaluation, clear explanations to the patient and his family and close follow-up are recommended before treating patients with severe liver disease. The use of preventive or therapeutic antidepressant medication also helps decrease or control side-effects [25-31].

In a recent study including patients with psychiatric disorders, ex-intravenous drug users using methadone or who had stopped drug abuse for at least 3 months and a control group, the mental side-effects were neither more frequent nor more severe in the psychiatric population than in the control group and compliance to treatment was comparable [32]. No increase in underlying psychiatric disease was noted.

In summary, antiviral treatment in psychiatric patients, including psychotic patients may be proposed but should include multidisciplinary management, with a psychiatric evaluation before treatment and close follow-up as well as possible preventive antidepressant therapy.

TREATMENT OF CHRONIC HEPATITIS C IN PATIENTS WITH EXCESSIVE ALCOHOL CONSUMPTION

Chronic alcohol consumption increases HCV viremia [4, 33, 34]. No data are available about compliance to antiviral therapy in heavy drinkers, but it may be decreased as was found in the HIV-infected patients studied in highly active anti-retroviral therapy (HAART) [35]. Little is known about the effects of alcohol on the safety of anti-HCV treatment, but one study has suggested that interferon may trigger alcoholic hepatitis [36]. The efficacy of interferon therapy is decreased in heavy drinkers [37-39]. Patients should therefore be asked to reduce or stop alcohol during the 3 to 6 months preceding anti-HCV combination treatment of pegylated interferon and ribavirin to improve treatment efficacy and safety.

TREATMENT OF CHRONIC HEPATITIS C IN PATIENTS WITH RENAL DISEASES

HCV infection is frequent in patients with end-stage renal failure who receive chronic hemodialysis with a prevalence varying from 10 to 65% according to the geographical area [40]. The prevalence is significantly associated with the duration of dialysis and the number of transfused blood products [41]. It has dramatically declined with hemovigilance [42, 43] even if, despite the high efficiency of blood screening and erythropoietin therapy, there is a continued yearly incidence of HCV contamination of 1.4% [43] suggesting nosocomial transmission. HCV contamination may result in cirrhosis in 10% of dialysis patients. Immunosuppressive regimens for the prevention of allograft rejection results in: (1.) increased HCV viral replication [44]; (2.) frequent histopathological deterioration with a 25% prevalence of biopsy-proven extensive fibrosis or cirrhosis within a mean 5 years after transplantation) [45]; (3.) rare fibrosing cholestatic hepatitis [46]. Liver disease results in a significant decrease in survival [47].

In dialysis patients, liver biopsy (or biochemical markers) should be performed to assess the histopathological impact: most patients will have mild liver disease which does not require antiviral treatment compared to those with significant liver disease (fibrosis score ≥2). In dialysis patients, ribavirin is contraindicated for pharmacokinetic reasons (accumulation of ribavirin metabolites in erythrocytes); a ribavirin/interferon-alpha combination should not be used due to the risk of deep and long-lasting hemolytic anemia in dialysis patients with a poor secretion of erythropoietin [48].

Thus, standard interferon-alpha therapy appears to be the only alternative in dialysis patients: it is feasible with a standard schedule, 3MU subcutaneously three times a week after hemodialysis. In dialysis patients, the biochemical and virological efficacy (summarized in Table 1) is, at least as good as in the general population with a 20 to 90% rate of viral eradication depending on the dose and duration of treatment [49-55] and on virological factors. Moreover, histological improvement is common, even without virological efficacy [50]. Tolerance is poorer than in non-hemodialyzed patients since treatment discontinuation is necessary in 20 to 40% of cases with a high incidence of cardiovascular side-effects, anemia, erythropoietin resistance and general symptoms (weight loss) [55]. It should be noted that persistent detectable viremia

2 months after the beginning of treatment suggests that there will be no lasting viral eradication [55]. Nevertheless, treatment could be continued if the therapeutic aim is improvement of the disease in hemodialysed patients with severe liver disease (palliative treatment to reduce fibrosis in the absence of virological efficacy (Figure 1).

Authors	**N**	**Mos**	**ALT N (%)**	**PCR (%)**	**Relapse (%)**	**SVR** (%)**
Koenig et al.	23	5	50	65	33	43
[49]	14*					
Pol et al.	19	6	85	53	62	20
[50]	1*					
Casanovas et al.	10	12	90	10	0	20
[54]						
Izopet et al.	23	6	85	92	54	42
[51]	3*	12		90	0	90
Degos et al.	37	12	70	66	NT	19***
[55]	21*					

Table 1: Treatment of chronic hepatitis C by interferon-alpha in hemodialysis patients.
* number of treatment discontinuation or reduction.
**SVR=sustained virological response (negative PCR at least 6 months after discontinuation).
*** 38% of patients who received a 12-month course (n=12).

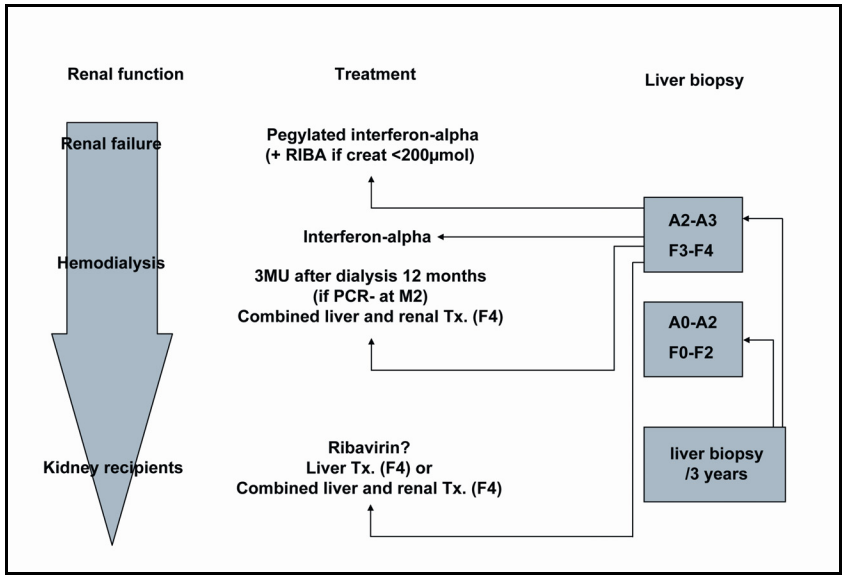

Figure 1: Therapeutic options in HCV-infected patients with renal disorders. Antiviral therapies should be proposed to patients with active and/or fibrotic liver lesions while patients with low fibrotic activity will not be treated and will receive regular liver biopsies (every 3 years) for early detection of histopathological deterioration. Patients with cirrhosis may benefit from liver transplantation or combined renal and liver transplantation depending on renal function.

The greater efficacy and poorer tolerance could be due to the significantly greater pharmacokinetic area under the curve of interferon-alpha showing an increased half life (10 hours vs. 6 hours) and to the upper concentration because of the decrease in renal clearance in dialysis patients [56]. Because of the specific pharmacokinetics of interferon in dialysis patients the use of pegylated interferon is unclear and is under evaluation [57].

In acute hepatitis C, which may occur in dialysis patients at a yearly incidence of 2.6% [58], interferon may be less effective than in the general population [59]: viral clearance is obtained in 26% and 51% of hemodialyzed patients treated by 3MU and 6-10MU for 3 months (compared to spontaneous clearance in 5.6%) [60].

In essential mixed cryoglobulinemia associated with HCV infection, interferon-alpha may improve urinary protein excretion, renal failure and hematuria but recurrence of the nephrotic syndrome is common after treatment discontinuation [61, 62]. The real benefit of higher doses or durations of interferon-alpha or of a combination with ribavirin (in the absence of renal failure) is anecdotal considering the high rate of relapse after treatment discontinuation and should be confirmed in large series.

Finally, interferon-alpha is not recommended in kidney allograft recipients since it is not effective and associated with an unacceptably high rate of allograft rejection (15 and 29%) [63, 64]. Interferon-alpha-related nephrotoxicity has also been reported in the absence of graft rejection with glomerular nephropathy or acute interstitial nephritis. Among the 42 reported kidney recipients who were treated with interferon-alpha therapy for HCV infection, 47.6% had acute renal failure after a mean 3.6 months of therapy (range 11 days to 9 months) and 65.0% resumed dialysis; in contrast, only 5.9% had a long-term virological response. This is also why the treatment of HCV in kidney recipients must be discussed before the renal transplantation even if anecdotal encouraging results of combination therapy have been reported in kidney recipients.

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