Antiviral therapy in hemodialyzed HCV patients: efficacy, tolerance and treatment strategy

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Antiviral therapy in hemodialyzed HCV patients: efficacy, tolerance and treatment strategy

Short title: Antiviral therapy in dialyzed HCV patients

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Abbreviations: ALT, Alanine aminotransferase; ESRD, End-stage renal disease; HCV, Hepatitis C virus; Peg-IFN, Pegylated interferon; RVR, Rapid virological response; EVR, Early virological response; SVR, Sustained virological response

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List of how each author was involved with the manuscript:

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Philippe Mathurin: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; study supervision

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SUMMARY

Background: In end-stage renal disease (ESRD) patients, HCV eradication improves patient and graft survival. **Aim:** Determine optimal use of erythropoietin and ribavirin, compare ribavirin concentrations with those of HCV patients having normal renal function and evaluate SVR in a prospective observatory of ESRD candidates for renal transplantation. **Methods:** Thirty-two naïve patients were treated with Peg-IFN- α 2a and ribavirin. Two different schedules of ribavirin and EPO administration were used: starting ribavirin at 600 mg per week and adapting EPO when hemoglobin fell below 10 g/dL (*adaptive strategy*), or starting ribavirin at 1,000 mg per week while increasing EPO from the start of treatment (*preventive strategy*). **Results:** Patients treated with the adaptive strategy had lower median hemoglobin levels (9.6 vs. 10.9 g/dL, $p=0.02$) and more frequently median Hb levels below 10 g/dL (58 vs. 5%, $p=0.0007$) despite lower median ribavirin doses (105 vs. 142 mg/day, $p<0.0001$) than patients treated with the preventive strategy. There was a trend for more frequent transfusion in patients treated with the adaptive strategy than in patients treated with preventive strategy (50 vs. 20 %, $p=0.08$). Compared to patients with normal renal function, ESRD patients had lower ribavirin concentrations during the first month (0.81 vs. 1.7 mg/l, $p=0.007$) and similar concentrations thereafter. SVR was reached in 50%. **Conclusions:** Peg-IFN and an adapted schedule of ribavirin are effective in ESRD patients. Increasing EPO from the start of treatment provides better hematological tolerance. The optimal dosage of ribavirin remains unsettled in light of the frequency of side-effects.

Keywords: Hepatitis C; end-stage renal disease; hemodialysis; antiviral therapy; sustained virological response; tolerance, treatment strategy

INTRODUCTION

In patients with end-stage renal disease (ESRD), chronic hepatitis C virus (HCV) infection leads to enhanced morbidity and mortality, either before ^{1, 2} or after ^{3, 4} renal transplantation. This increased mortality is related to excessive liver-related death when compared to patients without HCV infection ^{1, 4}. Moreover, patients undergoing renal transplantation may have an increased risk of HCV-mediated allograft nephropathy and diabetes mellitus ⁵⁻⁸. Therefore, viral eradication may improve the outcome of HCV patients after renal transplantation.

Combination therapy with pegylated interferon (Peg-IFN) and ribavirin is the standard therapy for chronic HCV infection. This regimen is usually contraindicated in renal transplant recipients because of an increased risk of graft rejection ^{9, 10}. In hemodialyzed patients, only markedly reduced doses of ribavirin may be used ¹¹. However, the exact dose of ribavirin is unknown and there is a high risk of drug-related toxicity, mainly hemolytic anemia, due to the increase in ribavirin exposure ^{12, 13}. This explains why most studies in ESRD patients tested ribavirin-free treatment schedules ^{14, 15}, with approximately one-third of patients achieving a sustained virological response (SVR) regardless of genotype ^{16, 17}. When considering the impact of ribavirin on the SVR rate in HCV patients with normal renal function, it is speculated that adding this molecule to the therapeutic regimen of ESRD-infected patients might increase the probability of viral eradication. Regimens of Peg-IFN with low doses of ribavirin have been tested in a prospective study ¹⁸ and in small series of hemodialyzed patients ¹⁹⁻²¹. Those studies yielded promising rates of SVR with acceptable hematological tolerance. Nevertheless, additional data are required to define the optimal schedule of treatment combining high efficacy and a good safety profile. In addition, comparison between ribavirin concentrations in ESRD patients and in patients with normal renal function treated with conventional doses of ribavirin may be helpful.

Erythropoietin (EPO) is the gold standard therapy for ESRD patients with anemia, and leads to a drastic reduction in the red cell transfusion requirement²². In the specific setting of HCV patients without renal failure, the use of recombinant erythropoietin for anemia during combination therapy enables maintenance of higher ribavirin doses^{23, 24}. Currently, for HCV patients with ESRD, no guidelines exist for treating antiviral therapy-associated anemia.

We began a prospective follow-up observatory in ESRD patients who were candidates for renal transplant, and treated them with Peg-IFN- α 2a and an individual schedule of ribavirin. In the present study, we only considered naïve patients treated with Peg-IFN- α 2a and an adapted schedule of ribavirin. Our aims were: a) to define optimal use of EPO and adequate doses of ribavirin tailored by the hemoglobin level; b) to compare ribavirin concentrations in ESRD patients and HCV patients with normal renal function treated with conventional doses of ribavirin; and c) to evaluate SVR rates.

PATIENTS AND METHODS

Patients

Prospective follow-up of ESRD candidates for renal transplant treated with Peg-IFN and an individual schedule of ribavirin was started. Antiviral therapy was not begun in cases of decompensated liver disease and if any of the following hematological criteria were present: 1/ hemoglobin (Hb) <8.5 g/dL; 2/ white blood cells <2,000/mm³ (neutrophil count <1,000/mm³); 3/ platelet count <80,000/mm³.

Treatment strategy

Prospective follow-up was first initiated at Lille Hospital and was approved by the Ethical Committee of Lille Hospital (CP number 06/38). Patients were treated with a combination of Peg-IFN- α 2a (PEGASYS[®]; Roche, Hertfordshire, UK) 135-180 μ g once a week and an adapted schedule of ribavirin (COPEGUS[®]; Roche, Hertfordshire, UK). In the present study, only naïve patients were considered.

All patients were treated with intravenous recombinant human EPO (Neorecormon[®], Roche, Epoetin-alfa, Eprex[®], Janssen Cilag S.p.A, Turnhout, Belgium or darbepoietin α , Aranesp[®], Amgen, Neuilly sur Seine, France). To use the same units for EPO dosage, we multiplied the dose of darbepoietin- α in μ g by 200 to obtain the equivalence in terms of units of Eprex or Neorecormon as previously done²⁵.

Two different schedules of administration of ribavirin and EPO were used. In a first step, ribavirin was started at 600 mg per week (200 mg thrice weekly). EPO was used according to hemoglobin levels, with a stepwise increase only when Hb fell below 10 g/dl (*adaptive strategy of EPO administration*). As analysis of the results of the first patients revealed that blood transfusions were frequent, we modified the schedule of treatment thereafter. Ribavirin was started at 1000 mg per week (200 mg 5 times a week), while EPO

was increased from the start of the treatment according to Hb levels before the start of treatment and then adapted to Hb levels during treatment with a stepwise increase so as to reach 11 g/dl (*preventive strategy of EPO administration*).

After preliminary presentation of our experiment, 3 other centers (Hôpital Erasme, Brussels, CHU Nice and CHU Caen) decided to treat their HCV patient candidates for renal transplantation using the second treatment strategy. All data were prospectively collected and sent to the Lille center.

A stepwise reduction in the Peg-IFN- α 2a dose was allowed so as to manage adverse events or laboratory abnormalities. A stepwise reduction in ribavirin doses was planned when Hb fell to 8.5 g/dl despite an increase in EPO to a maximum dose of 90,000 I.U./week. A stepwise reduction in EPO doses was planned when Hb levels increased to above 12 g/dl.

At the Lille and Nice Hospitals, ribavirin concentrations were measured monthly up until the 6th month, and at 9 and at 12 months of treatment in patients treated with the second strategy.

Patients were assigned to receive treatment for 48 weeks if they were infected with HCV-1 or -4, while a 24-week treatment duration was used in HCV-2 or -3 patients. Those showing a slow virological response were evaluated for 6-month prolonged therapy. Antiviral therapy was discontinued in HCV-1 or -4 patients with detectable HCV RNA 6 months after the start of treatment.

Virological tests

Anti-HCV antibodies were determined using a chemiluminescence immunoassay (Architect[®] anti-HCV assay; Abbott Diagnostics, Abbott Park, IL, USA). HCV genotyping was performed using a direct sequencing assay, Trugene[®] HCV 5'NC Genotyping Kit (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). Levels of serum HCV RNA were

quantified by real-time PCR (Cobas[®] AmpliPrep/Cobas TaqMan[®] HCV Test, Roche Diagnostic Systems, Basel, Switzerland). The range of linear quantification was from 43 to 69 millions IU/mL. The lower limit of detection was 15 IU/ml. SVR was defined as undetectable HCV RNA 6 months after the end of antiviral therapy.

Statistical analysis

Ribavirin doses were assessed monthly. EPO doses were measured prior to the beginning of treatment, as well as monthly during treatment and during the three months following treatment. Viral load was determined before beginning treatment, and during treatment: at one month; at three months; at six months; and at the end of treatment. It was also evaluated 6 months after stopping treatment. Hb levels were monitored every week during the first month, and then every month thereafter both during and after treatment.

Data were expressed as percentage or median (95% CI). Analyses were conducted using variance analysis, the chi-square test, two-sided Fisher exact test, Mann–Whitney test, Wilcoxon test and two-sample Student's t-test when appropriate. All statistical testing was two-tailed at the 5% level. All statistical analyses were performed using NCSS 2005 software (NCSS, Kaysville, UT, USA). The analyzed endpoints were: A/ safety profile, including detailed evolution of Hb levels and EPO doses during treatment; B/ evolution of ribavirin dosage and concentrations; and C/ rates of SVR.

RESULTS

Characteristics of patients

Starting in January 1, 2004, 32 hemodialyzed naïve HCV patients who were candidates for renal transplant were prospectively followed up (table 1). All patients were treated with Peg-IFN- α 2a (median doses of 180 μ g once a week, 95% CI: 135-180). Twelve patients were treated with the first strategy in which ribavirin was started at 600 mg per week (corresponding to an average of 86 mg/day, 95% CI: 57-86, adaptive strategy) and 20 with the second strategy in which ribavirin was started at 1000 mg per week (corresponding to an average of 142 mg/day, 95% CI: 142-142, preventive strategy) (see methods).

A/ Safety profile

A1/ Evolution of hemoglobin levels during treatment and need for transfusion according to adaptive versus preventive strategy

The median decrease in Hb levels between the start of treatment and the third month was 2.6 g/dL (95% CI: 1.6-3.6). No patient had an Hb level higher than 16 g/dL. When compared to patients treated with preventive strategy, those treated with adaptive strategy had lower median Hb levels from the start to the end of antiviral therapy (9.6 vs. 10.9 g/dL, $p=0.02$), and more frequently median Hb levels below 10 g/dL (58 vs. 5%, $p=0.0007$). There was a trend for more frequent transfusion in patients treated with adaptive strategy than in patients treated with preventive strategy (50 vs. 20 %, $p=0.08$) (table 2). The starting dose of Peg-IFN- α 2a did not influence hematological tolerance.

A2/ Side effects

Six patients discontinued treatment prematurely due to serious side effects, without significant differences between adaptive and preventive strategies (table 2). There were no differences in the frequency of side effects regarding the starting dose of Peg-IFN- α 2a. Two patients treated with preventive strategy died during antiviral therapy. Those 2 deaths did not

appear to be directly related to antiviral treatment. The first patient, 39-years-old, died of cerebral hemorrhage after 4 months of treatment. He had cirrhosis and chronically suffered from hypertension. He was receiving 80 µg/week of Aranesp. His highest Hb level under treatment was 10.6 g/dL. The last Hb level was 8.3 g/dl and the last platelet count 92,000/mm³. The second patient died after 6 months of treatment. He was 73-years-old. He developed extradural hematoma after an accidental fall; he was receiving Eprex 80,000 U/week. His highest Hb level under treatment was 11.7 g/dL. The last Hb level was 8.8 g/dl and the last platelet count 44,000/mm³. For the latter patient, we cannot exclude the possibility that treatment-induced thrombopenia aggravated the course of extradural hematoma.

A3/ Evolution of EPO doses during treatment

Overall, the median dose of EPO was increased by 141% (95% CI: 75%-250%, $p<0.0001$) when compared to doses before starting antiviral therapy. Median total dose of EPO was similar in patients treated with adaptive or preventive strategy (12,833 vs. 20,250 IU/mL, respectively, $p=0.1$). Conversely, there was a difference in the timing of the EPO increase: EPO doses increased within the first month in 17 vs. 60% ($p=0.02$) of patients treated with adaptive and preventive strategies, respectively (figure 1).

B/ Ribavirin doses and concentrations

When compared to patients given preventive treatment, patients who were given the adaptive strategy had lower median ribavirin doses during treatment: 105 vs. 142 mg/day ($p<0.0001$). These differences were sustained until the end of antiviral therapy.

Ribavirin concentrations were measured in 11 patients using preventive strategy and in 34 patients with normal renal function treated at with subcutaneous Peg-IFN and standard doses of ribavirin (800-1,200 mg per day according to genotype and body weight). Hemodialyzed patients had lower ribavirin concentrations than patients with normal renal

function during the first month of treatment, at 2 weeks (0.49 vs. 1.3 mg/l, $p=0.002$) and at 1 month (0.81 vs. 1.7 mg/l, $p=0.004$). There were no significant differences thereafter.

C/ Virological results

All patients reached the 6 months follow-up period. Sixteen patients (50%) attained a SVR (40% for HCV-1, 4 patients; 86% for HCV-2, 3 patients, $p=0.02$) (table 3). There was no difference in SVR rates between patients treated with the adaptive or preventive strategy (58 vs. 45%, NS) neither in those infected with genotype 1 (44 vs. 40%, NS) nor in those infected with genotype 2 or 3 (100 vs. 75%, NS). Ribavirin and EPO dosages were no different between responders and non-responders (data not shown). However, ribavirin concentration at one month was higher in responders than in non-responders (2.96 vs. 0.76 mg/dL, $p=0.04$). Other predictive factors in SVR were baseline HCV RNA, fibrosis stage and undetectable HCV RNA at 1 month and at 3 months (data not shown).

DISCUSSION

In ESRD candidates for renal transplantation, viral eradication is an attractive option when considering the deleterious effect of HCV infection on patient and graft survival¹⁻⁴. However, this group of patients is usually considered difficult to treat because of the high risk of drug-related toxicity, mainly hemolytic anemia, due to the increase in ribavirin exposure^{12, 13}. The present study reporting only results on naïve patients observed that pegylated bitherapy induced a SVR of 40% in HCV-1 and 4 patients and 86% in HCV-2 and 3 patients. In addition, it provides data on the safety profile of antiviral therapy and suggests a means of using EPO, or so-called preventive strategy, which permits maintaining the ribavirin dose without inducing significant anemia. However, since there were no differences between patients treated with the two strategies in terms of SVR, median EPO doses or treatment discontinuation rates, we cannot firmly conclude that preventive strategy is more effective than adaptive strategy. Finally, since they were sequentially administered, comparison of the two therapeutic strategies was suboptimal.

Despite the use of higher ribavirin doses, preventive strategy involving increased EPO from the start of antiviral therapy led to better hematological tolerance than adaptive strategy which involves increasing EPO on demand. This preventive strategy integrates the pharmacokinetics of EPO, as it requires approximately 3 weeks before EPO induces an increase in Hb levels²⁶. However, it must be pointed out that intensive monitoring, as was done in this study, is mandatory so as to minimize the risk related to EPO-induced polycythemia. With this close follow-up of Hb levels, no patient had Hb levels equal to or higher than 16 g/dl under treatment in the present study.

At first glance, the 2 deaths observed (6% of the overall population) might be considered to preclude evaluation of pegylated bitherapy in ESRD patients under dialysis. However, several studies in untreated hemodialyzed HCV patients showed an approximate 5-

10% and 15-20% death rate at 1 and 4 years, respectively ^{1, 27}. This poor prognosis is no doubt related to the fact that these patients frequently have rapid progression of arteriosclerosis and suffered from multiple co-morbidities such as hypertension and diabetes mellitus, in addition to those related to HCV infection. The 2 patients who died in the present study suffered from such co-morbidities: one patient had cirrhosis and the other was 73-years-old. Although we cannot formally exclude the possibility that these drugs were partly responsible for the 2 deaths, this seems unlikely, since the last measurements of Hb levels were 8.3 and 8.8 g/dL in these 2 cases, and we did not observe any significant increase in blood pressure, psychiatric disorders or infection. Nevertheless, patients must be carefully selected when antiviral treatment is considered. As this study only included candidates for renal transplantation, our recommendations for treating ESRD patients only apply to this highly select group of patients.

This study also confirms that combination therapy with Peg-IFN and an adapted schedule of ribavirin is effective in ESRD patients. These results seem more positive than those reported when Peg-IFN is used alone ²⁸⁻³¹, and are similar to or even more favorable than those reported in other small series of patients treated with Peg-IFN and ribavirin ¹⁹⁻²¹; they are also close to those observed in HCV patients with normal renal function ³²⁻³⁴. However, they differ from results of another recent study reporting a high rate of SVR (97%) ¹⁸. As a complement to other studies, our report provides data which enable narrowing the range of adequate ribavirin doses in hemodialyzed patients, leading to sufficient exposure. In previous studies ^{18-21, 35-37}, hemodialyzed patients were not treated with ribavirin doses higher than 400 mg per day. The observed 1-month delay before reaching steady-state ribavirin concentrations suggests that 1000 mg per week is not yet optimal, and provides additional evidence that 1400 mg per week may be better adapted. This seems important when considering the impact of early ribavirin exposure on SVR rates in HCV-1 patients with

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normal renal function³⁸. Regarding Peg-IFN- α 2a, 135 μ g/week is currently considered the standard dose in ERSD patients.

In conclusion, candidates for renal transplantation, when treated with Peg-IFN and adapted doses of ribavirin, attained a SVR in nearly the same proportions as patients with normal renal function. However, they require a specific strategy for EPO use and close monitoring of clinical and biological parameters. The optimal daily dose of ribavirin is still unsettled.

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Tables Legends

Table 1: Baseline demographic and clinical characteristics of the study population according to the strategy used

* Data expressed as median (95% CI)

** According to the METAVIR scoring system

Table 2: Hematological tolerance, side-effects and treatment discontinuation

* Discontinuation of treatment due to severe asthenia in one case and to sepsis in the other

** Discontinuation of treatment due to severe asthenia in three cases and to febrile neutropenia in the fourth case

Table 3: Virological results according to genotype

Abbreviations: RVR, rapid virological response; EVR, early virological response; SVR, sustained virological response; VR, virological response

* $p = 0.008$ between genotype 1-4 patients and genotype 2-3 patients

** $p = 0.03$ between genotype 1-4 patients and genotype 2-3 patients

Figures legends

Figure 1: Evolution of EPO doses during treatment

EPO doses (U/week)

Full line: adaptive strategy for EPO administration

Dotted line: preventive strategy for EPO administration

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Table 1: Baseline demographic and clinical characteristics of the study population according to the strategy used

	Adaptive strategy (n=12)	Preventive strategy (n=20)	<i>p</i> value
Sex ratio (men/women)	4/8	15/20	0.02
Genotype 1 / 2 / 3 /4	9 /1 /2 /0	10 /2 /2 /6	0.2
Age (years) *	46 (36-55)	52 (49-55)	0.2
Body mass index (kg/m ²) *	20.6 (18.4-25.4)	24.0 (20.9-26.0)	0.06
Viral load (IU/ml) *	1,900,000 (228,204-4,940,000)	274,500 (123,000-1,104,445)	0.1
Duration of hemodialysis (years) *	18.1 (1.1-27.2)	1.8 (1.0-8.9)	0.08
Duration of infection (years) *	25.6 (15.9-30.4)	21.1 (19.9-23.2)	0.3
ALT (ULN) *	0.75 (0.40-1.05)	0.70 (0.50-0.95)	0.9
Fibrosis stage ^{\$} *	1 (0-2)	1 (1-2)	0.4
Fibrosis ≥ 3 ** (n, %)	1 (8%)	4 (20%)	0.4

* Data expressed as median (95% CI)

** According to the METAVIR scoring system

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Anti-viral therapy in dialyzed HCV patients

Table 2: Hematological tolerance, side-effects and treatment discontinuation

	Adaptive strategy for EPO administration (n=12)	Preventive strategy for EPO administration (n=20)	<i>p</i> Value
Hematological tolerance			
Median Hb levels at the start of the treatment (g/dL, 95% CI)	12.1 (10.5-13.1)	12.6 (11.9-13.6)	0.13
Median Hb levels under treatment (g/dL, 95% CI)	9.6 (9.3-11.0)	10.9 (10.6-11.4)	0.02
Median Hb levels under treatment <10 g/dL – no. (%)	7 (58%)	1 (5%)	0.0007
Median nadir Hb levels (g/dL, 95% CI)	7.7 (6.5-8.9)	9.0 (8.4-9.5)	0.006
Patients transfused - no. (%)	6 (50%)	4 (20%)	0.08
Severe side effects - no. (%)	6 (50%)	8 (40%)	0.6
Severe asthenia - no. (%)	2 (17%)	5 (25%)	
Infection – no. (%)	1 (8%)	1 (5%)	
Depression – no. (%)	1 (8%)	0 (0%)	
Death - no. (%)	0 (0%)	2 (10%)	
Other side effect – no. (%)	2 (17%)	0 (0%)	
Discontinuation of treatment due to side effects - no. (%)	2 (17%) *	4 (20%) **	0.8

* Discontinuation of treatment due to severe asthenia in one case and to sepsis in the other
** Discontinuation of treatment due to severe asthenia in three cases and to febrile neutropenia in the fourth case

Anti-viral therapy in dialyzed HCV patients

Table 3: Virological results according to genotype

	RVR	EVR	Undetectable HCV RNA at month 3	End-of- treatment VR	Relapse	SVR
Overall population - no. (%)	9/31 (29)	27/32 (84)	18/32 (56)	25/32 (78)	9/25 (36)	16/32 (50)
Patients with genotype 1-4 - no. (%)	6/25 (24)	20/25 (80)	11/25 (44)*	18/25 (72)	8/18 (44)	10/25 (40)**
Patients with genotype 2-3 - no. (%)	3/6 (50)	7/7 (100)	7/7 (100)*	7/7 (100)	1/7 (14)	6/7 (86)**

Abbreviations: RVR, rapid virological response; EVR, early virological response; SVR, sustained virological response; VR, virological response

* p =0.008 between genotype 1-4 patients and genotype 2-3 patients

** p =0.03 between genotype 1-4 patients and genotype 2-3 patients

Figure 1