EXTENDED REPORT

Peg-IFNα/ribavirin/protease inhibitor combination in hepatitis C virus associated mixed cryoglobulinemia vasculitis: results at week 24

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ABSTRACT

Background The standard-of-care treatment of patients with hepatitis C virus (HCV)-mixed cryoglobulinemia (MC) vasculitis includes pegylated interferon α (PegIFN-α) plus ribavirin and/or rituximab. About 30–40% of patients are non-responders or relapsers to such combination.

Objective To analyse the safety and efficacy of Peg-IFNα/ribavirin/protease inhibitor combination in HCV-MC vasculitis.

Patients and methods Open-label, prospective, cohort study including 23 patients with HCV-MC vasculitis. Peg-IFNα/ribavirin was associated to telaprevir (375 mg three times daily, for 12 weeks, (n=15)) or boceprevir (800 mg three times daily, for 44 weeks, (n=8)) for 48 weeks.

Results The median age was 59 (52.5–66) years, with 48.8% women. Thirteen patients (56.5%) were complete clinical responders, and 10 (43.5%) were partial responders at week 24. The virological response (ie, HCV RNA negativation) was of 69.6% at week 24 (p=0.005). The cryoglobulin level decreased from 0.44 to 0.06 g/l (p=0.0006) and the C4 level increased from 0.09 to 0.15 g/l (p=0.045). Grades 3 and 4 adverse events (mainly anaemia, neutropenia and thrombocytopenia) were observed in 10 cases (43.5%). Twenty patients (87%) received erythropoietin, 9 (39.1%) had red cell transfusion, and 2 (8.7%) had granulocyte stimulating agents. Virological relapse (n=2) and depression (n=1).

Conclusions Peg-IFNα/ribavirin/protease inhibitor combination seems highly effective in HCV-MC. Such therapeutic regimen should be administered cautiously considering the high rate of side effects.

INTRODUCTION

Mixed cryoglobulinemia (MC) is a systemic vasculitis that mainly affects the small and, less frequently, medium-sized vessels.1 MC reflects the expansion of B cells producing a pathogenic IgM with rheumatoid factor (RF) activity.2 MC leads to clinical manifestations ranging from the so-called MC syndrome (purpura, arthralgia and asthenia) to more serious lesions with neurologic and renal involvement.3 With the discovery of hepatitis C virus (HCV) as the etiologic agent for most cases of MC, new opportunities and problems for crafting therapy of HCV MC have emerged. A new and major concern was the potential adverse effects that immunosuppressive therapy with glucocorticoids and cytotoxic drugs could have on an underlying chronic viral infection. Alternatively, the discovery of HCV provided the opportunity to control HCV-MC with antiviral therapy based on the belief that the underlying infection was driving immune complex formation and resultant vasculitis.4

Treatment of HCV-MC remains difficult and may target either the viral trigger (HCV) or the downstream B cell arm of autoimmunity.5–10 Two recent prospective randomised controlled trials have examined the safety and efficacy of rituximab for the treatment of patients with HCV-associated cryoglobulinemic vasculitis, in whom prior antiviral therapy failed to induce disease remission.6 9 These studies have demonstrated the superiority of rituximab monotherapy as compared with conventional therapy with corticosteroids, azathioprine, cyclophosphamide, methotrexate, or plasmapheresis. Rituximab was a well tolerated and effective treatment in 71.4–83% of patients with HCV-associated cryoglobulinemic vasculitis.6 9

Inducing a sustained virologic and clinical response (CR) and minimising the use of immunosuppressive drugs are the main goals in the treatment of patients with HCV-MC vasculitis.11 Antiviral therapy has been shown to reverse bone marrow monoclonal B cell expansion in patients with HCV-MC.12 Patients treated with pegylated interferon α (Peg-IFN-α)/ribavirin achieved sustained clinical and virological responses in up to 60% of cases.10 Although this approach affords a satisfactory response rate, additional therapy may be needed in MC patients with severe organ involvement and/or without virologic response.10

Orally, bioavailable inhibitor of the non-structural 3/4A HCV protease (ie, telaprevir and boceprevir) substantially enhanced rates of virological response when it was combined with Peg-IFNα/ribavirin in HCV-infected patients. Data are lacking regarding the efficacy of triple antiviral therapy (ie, Peg-IFNα/ribavirin/protease inhibitor combination) in HCV-MC patients. In the present study, we aimed to report the results at week 24 of the triple antiviral therapy in HCV-MC patients.
PATIENTS AND METHODS

Patients

This is an open-label, prospective, single-centre, cohort study including 23 unselected patients with HCV-associated MC vasculitis seen in the department of internal medicine (Hôpital La Pitié-Salpêtrière, Paris, France) between 2011 and 2012. They had a serum cryoglobulin >0.05 g/l on at least two occasions associated with purpuric or cutaneous ulcers, arthralgias, peripheral neuropathy, renal involvement and cardiac involvement. At baseline, five out 23 patients had no detectable cryoglobulin but cryoglobulin were positive earlier according to inclusion criteria. All patients were positive for HCV RNA. Inclusion criteria for the study were as follows: (1) chronic active HCV infection; (2) signs of MC vasculitis. The clinical evaluation included age, gender, recent weight loss, neurologic involvement (peripheral and/or central nervous system), cutaneous involvement (Raynaud’s phenomenon, purpura, distal ulcers), arthralgia, myalgia, sicca syndrome, gastrointestinal tract involvement, renal involvement (proteinuria, haematuria and glomerular filtration rate (GFR)), and clinical signs of hepatic involvement. The diagnosis of non-Hodgkin’s lymphoma was based on WHO criteria. The study was performed according to the Helsinki declaration. All patients gave informed consent.

Study design

A detailed description of the study design is provided in figure 1. All patients received antiviral therapy with Peg-IFNα2a (180 µg/week, n=15) or (2b, 1.5 µg/kg/week, n=8), subcutaneously plus ribavirin (600–1200 mg/day orally) for 48 weeks. Treatment with telaprevir consisted of oral administration at a dose of 750 mg three times daily for 12 weeks and boceprevir consisted of oral administration at a dose of 800 mg three times daily for 44 weeks. Treatment with telaprevir consisted of oral administration at a dose of 800 mg three times daily for 44 weeks. All patients received Peg-IFNα2a plus ribavirin during the 4-week lead-in period (figure 1) including in the Telaprevir group in order to evaluate the safety profile of PEG-IFNα2a/ribavirin (RBV) before the introduction of protease inhibitors. The study treatment was discontinued for all patients with a detectable HCV RNA at week 16. Four patients received the combination of rituximab at 375 mg/m² (on days +1, +8, +15 and + 22) plus Peg-IFNα2a/ribavirin/protease inhibitor combination because of severe neuropathy (n=2) or kidney involvement (n=2). Concomitant immunosuppressants included rituximab given 1 month before triple antiviral therapy in four patients, and four patients out the 23 received prednisone at a dose of 5 mg/day throughout the study.

Previous immunosuppressive therapy (ie, more than 6 months before entering the current study) included rituximab (n=13) of whom one received combination with fludarabine and cyclophosphamide and corticosteroids (n=4).

Immunologic and virologic markers

Laboratory evaluation included a complete haemogram, serum chemistry profile, RF, IgM level, C4 fraction of complement and cryoglobulin. Cryoglobulins were measured as previously described. Cryoglobulins were classified according to the method described by Brouet et al as either type II MC, which includes a monoclonal component, or type III MC, defined by the association of polyclonal immunoglobulins. GFR was determined as previously described by Cockcroft et al. A 24 h urine collection was also performed in order to quantify daily protein excretion. Kidney involvement was defined as the presence of at least two of the following parameters (ie, an increase creatinine, increase in daily proteinuria and/or haematuria).

Serum HCV RNA was measured by a reverse-transcription PCR (RT-PCR) assay (Abbott, real-time HCV) with a threshold of detection of 1.1 log10 IU/ml. HCV genotyping was performed using a second-generation line probe assay (LiPA; Innogenetics, Brussels, Belgium). Liver biopsy specimens were evaluated according to the previously validated Metavir scoring system.

Treatment efficacy

The response to treatment was analysed by comparing clinical, immunologic and virologic parameters at the initial evaluation, at weeks 4, 8, 12, 16 and 24. CR was defined by analysing the progression of the following main clinical signs: skin involvement (absence of purpura and/or leg ulcer), peripheral neuropathy (clinical and/or electrophysiologic improvement on two successive examinations), renal involvement (normalisation of serum creatinine level and disappearance of proteinuria and/or haematuria), and the absence of arthralgia.

A CR of MC vasculitis was defined by an improvement in all baseline clinical manifestations. A PR was defined by an improvement of at least half the baseline clinical manifestations. All other patients were classified as (NR). A complete virologic response was defined by the absence of detectable serum HCV RNA; the remaining patients were classified as virologic NRs. A complete immunologic response was defined by the absence of serum cryoglobulin, and a partial immunologic response by a >50% decrease in the baseline cryoglobulin level. Clinical relapse was defined as the reappearance of clinical signs of vasculitis, virologic relapse as the reappearance of detectable HCV RNA and immunologic relapse as the reappearance of serum cryoglobulin.

Statistical analysis

Data are expressed as the median, IQR for quantitative data and counts and percent for categorical data. Categorical variables were compared using Fisher’s exact or χ² tests, and continuous variables using the t test or Mann–Whitney U test when appropriate. Comparisons between baseline and end of follow-up values were tested using MacNemar’s test or Wilcoxon’s paired test. All tests were two-sided at a 0.05 significance level. Analyses were performed using R.2.9.2 statistical package (R Development Core Team, R: A Language and Environment for Statistical Computing, 2009, Vienna, Austria, http://www.R-project.org).
RESULTS

Characteristics of the HCV-MC patients

Patient characteristics are detailed in tables 1 and 2. Twenty-three HCV-MC patients, with a median age of 59 years (IQR, 52.5–66 years) were included. The main clinical features of MC included purpura (69.6%), polyneuropathy (52.2%), arthralgia (39.1%) and kidney involvement (26.1%). Among the 12 patients with polyneuropathy, five had sensory polyneuritis, four had sensory motor multinervitis and three had sensory motor polyneuritis. MC was present in all cases, with a median cryoglobulin level of 0.44 g/l (0.2–0.84). Twenty (87%) patients had a type II cryoglobulin with monoclonal IgMk in all cases except one (IgMλ). Median C4 serum level was of 0.09 g/l (0.06–0.13). HCV genotype was of type 1 in 22 patients.

Table 1  Baseline characteristics of the 23 HCV-associated MC patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All n=23</th>
<th>Boceprevir n=8</th>
<th>Telaprevir n=15</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Age</td>
<td>59 (52.5; 66)</td>
<td>59 (56.7; 68)</td>
<td>58 (51.5; 65.5)</td>
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<tr>
<td>Male gender (n,%)</td>
<td>12 (52.2)</td>
<td>4 (50)</td>
<td>8 (53.3)</td>
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<tr>
<td>HCV infection</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>HCV genotype:</td>
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<td></td>
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<td>1</td>
</tr>
<tr>
<td>1b</td>
<td>13 (56.5)</td>
<td>5 (62.5)</td>
<td>8 (53.3)</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>9 (39.1)</td>
<td>3 (37.5)</td>
<td>6 (40)</td>
<td></td>
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<td>4</td>
<td>1 (4.3)</td>
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<td>1 (6.7)</td>
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<tr>
<td>Metavir liver fibrosis score:</td>
<td></td>
<td></td>
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<td>0.51</td>
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<td>Stage 1</td>
<td>2 (8.7)</td>
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<td>2 (13.3)</td>
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<tr>
<td>Stage 2</td>
<td>10 (43.5)</td>
<td>3 (37.5)</td>
<td>7 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>4 (17.4)</td>
<td>1 (12.5)</td>
<td>3 (20)</td>
<td></td>
</tr>
<tr>
<td>Stage 4</td>
<td>7 (30.4)</td>
<td>4 (50)</td>
<td>3 (20)</td>
<td></td>
</tr>
<tr>
<td>Median baseline HCV RNA (log10 IU/ml)</td>
<td>6.2 (5.325; 6.53)</td>
<td>6.29 (5.292; 6.635)</td>
<td>6.07 (5.325; 6.485)</td>
<td>0.42</td>
</tr>
<tr>
<td>Median ALT level (IU/l)</td>
<td>52 (29; 70.5)</td>
<td>45 (28; 70.75)</td>
<td>53 (29.5; 68)</td>
<td>1</td>
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<tr>
<td>Haematologic variables</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Median haemoglobin count (g/dl)</td>
<td>13 (12.3; 14.65)</td>
<td>12.75 (12.6; 12.92)</td>
<td>13.6 (12.25; 14.75)</td>
<td>0.42</td>
</tr>
<tr>
<td>Median neutrophil count (×10^3 mm^-3)</td>
<td>3.03 (2.145; 4.18)</td>
<td>2.145 (1.775; 2.35)</td>
<td>3.74 (3.065; 4.68)</td>
<td>0.004</td>
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<tr>
<td>Median platelet count (×10^3 mm^-3)</td>
<td>159 (110; 197)</td>
<td>104.5 (91; 222.2)</td>
<td>159 (124.5; 191)</td>
<td>0.48</td>
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<td>Previous response to antiviral therapy (PegIFNα/ribavirin)*</td>
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<td></td>
<td>0.16</td>
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<tr>
<td>Naive</td>
<td>4 (17.4)</td>
<td>1 (12.5)</td>
<td>3 (20)</td>
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<td>No response</td>
<td>8 (34.8)</td>
<td>2 (25)</td>
<td>6 (40)</td>
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<tr>
<td>Partial response</td>
<td>5 (21.7)</td>
<td>4 (50)</td>
<td>1 (6.7)</td>
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<td>Relapse</td>
<td>6 (26.1)</td>
<td>1 (12.5)</td>
<td>5 (33.3)</td>
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<tr>
<td>MC related</td>
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<td>Type of cryoglobulinaemia:</td>
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<td>0.53</td>
</tr>
<tr>
<td>Type II</td>
<td>20 (87)</td>
<td>8 (100)</td>
<td>13 (86.7)</td>
<td></td>
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<td>Type III</td>
<td>3 (13)</td>
<td>0</td>
<td>2 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Median serum cryoglobulin level (g/l)</td>
<td>0.443 (0.2; 0.845)</td>
<td>0.22 (0.1975; 0.719)</td>
<td>0.59 (0.305; 0.915)</td>
<td>0.32</td>
</tr>
<tr>
<td>Median serum C4 level (g/l)</td>
<td>0.09 (0.06; 0.13)</td>
<td>0.14 (0.1175; 0.24)</td>
<td>0.08 (0.06; 0.1)</td>
<td>0.013</td>
</tr>
<tr>
<td>Median serum rheumatoid factor levels (IU/ml)</td>
<td>60.5 (13; 145)</td>
<td>43 (13; 115)</td>
<td>61 (19; 165.5)</td>
<td>0.6</td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Purpura</td>
<td>16 (69.6)</td>
<td>6 (45)</td>
<td>10 (66.7)</td>
<td>1</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>12 (52.2)</td>
<td>5 (62.5)</td>
<td>7 (46.7)</td>
<td>0.67</td>
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<tr>
<td>Arthralgia</td>
<td>9 (39.1)</td>
<td>1 (12.5)</td>
<td>8 (53.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Kidney involvement</td>
<td>6 (26.1)</td>
<td>1 (12.5)</td>
<td>5 (33.3)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Except where indicated otherwise values are median (IQR) and n (%).

*No response was defined as a reduction of less than 2log10 in HCV RNA; partial response was defined as undetectable HCV RNA at the end of a previous course of therapy with HCV RNA positivity thereafter.

ALT, alanine aminotransferase; HCV, hepatitis C virus; MC, mixed cryoglobulinemia.
Fourteen patients (60.9%) had elevated serum alanine aminotransferase (ALT) levels, and the median ALT concentration was 52 IU/l (29–70.5). The median HCV RNA level was 6.2 log10 IU/ml (5.3–6.5). Eleven patients (47.8%) had severe liver fibrosis (ie, a stage 3 and 4 Metavir fibrosis score), and seven had child A cirrhosis. The median (IQR) haemoglobin, neutrophil count were 112 (81–217) g/l and 7 (3–18) × 10^3, respectively. Four patients (17.4%) were antiviral treatment naïve, 13 (56.5%) were partial responders or NRs and 6 (26.1%) were virological relapers. No significant differences were observed regarding baseline characteristics in the two treatment regimens (ie, boceprevir versus telaprevir) except for a higher median neutrophil count and lower median C4 complement levels between the two treatment regimens (ie, boceprevir versus telaprevir).

### Treatment efficacy

The main treatment-related data are summarised in tables 1–3 and figure 2. Thirteen patients (56.5%) were complete clinical responders, and 10 (43.5%) were partial responders at week 24. CR was achieved in 11 patients (47.8%) at week 12. Purpura improved in 15/16 (93.7%) (p=0.003), arthralgia in 8/9 (88.8%) (p=0.045), kidney involvement in 5/6 (83.3%) (p=0.24) and polynephropathy in 5/12 (41.6%) (p=0.7). GFR increased from 42.3 (25.5–77.8) to 63.4 (35.9–155) ml/min at week 24, and daily proteinuria decreased from 0.55 (0.4–7.6) to 0.2 (0–0.3) g (see online supplemental figure 1). Haematuria was present in 5/6 (83.3%) at baseline, and disappeared in all cases at week 24. Median Birmingham Vasculitis Activity Score (BVAS) decreased from 9 (3–18) to 0 (0–6) (p<0.0001). Clearance of cryoglobulin was observed in 22.2% at week 24. The cryoglobulin level decreased from 0.44 to 0.06 g/l at week 24 (p=0.0006). The C4 serum level increased from 0.09 to 0.15 g/l at week 24 (p=0.045) (figure 2).

The virological response (ie, HCV RNA undetectable) was of 69.6% at week 24 (p=0.003). Triple antiviral therapy induced a significant decrease in the HCV viral load from 6.2 to 1.1 log10 IU/ml at week 24 (p=0.0006). Sixteen patients (69.5%) had early virological response at week 8. The ALT level normalised in 9 out of 14 (64.3%) patients (p=0.44). The kinetics of virological response to triple antiviral therapy (table 3) showed 8.7, 69.6, 73.9, 73.9 and 69.6% of undetectable HCV RNA at week 4, 8, 12, 16 and 24, respectively.

No significant difference was found in terms of CR rate between the two treatment regimens (ie, boceprevir vs telaprevir). Purpura improved in 100% vs 90%, neuropahty improved in 40% vs 42.8%, arthralgia improved in 100% and 87.5%, and kidney involvement improved in 100% and 80% with boceprevir and telaprevir, respectively. HCV RNA negativity at week 24 was observed in 62.5% vs 73.3% with boceprevir and telaprevir, respectively. Among the four patients who received the combination of rituximab at 375 mg/m² (on days +1, +8, +15 and +22) plus Peg-IFNa/ribavirin/protease inhibitor combination two were complete clinical responders and two were partial responders.

### Tolerance of treatment

Table 4 summarises the tolerance profile of the triple antiviral therapy. The main side effects of antiviral therapy included fatigue.
(87%), neutropenia (78.3%), anaemia (73.9%), thrombocytopenia (65.2%), infection (47.8%), pruritus (39.1%), depression (21.7%), and nausea (21.7%). The proportion of side effects with triple antiviral therapy was higher than that observed in our previous series of HCV-MC patients treated with Peg-IFNα/ribavirin alone where the main side effects included fatigue (45.4%), anaemia (36.3%), neutropenia (20%), thrombocytopenia (18.2%), depression (14.5%) and pruritus (7.3%).

Grade 3 and 4 adverse events (mainly anaemia, neutropenia and thrombocytopenia) were observed in 10 cases (43.5%). Twenty patients (87%) received erythropoietin, 9 (39.1%) had red cell transfusion and 2 (8.7%) had granulocyte-stimulating agent. There was a trend towards higher proportion of pruritus (46.6% vs 25%) and anaemia (86.6% vs 57.1%), although not statistically significant, with telaprevir compared with boceprevir. Antiviral therapy discontinuation was required in eight (34.7%) patients because of virological non-response (n=5), virological relapse (n=2) and depression (n=1).

**DISCUSSION**

Orally, bioavailable inhibitor of the non-structural 3/4A HCV protease, substantially enhanced rates of virological response when it was combined with Peg-IFNα/ribavirin in HCV patients. Data are lacking regarding the efficacy of triple antiviral therapy in HCV-MC patients. Here we first report that triple antiviral therapy (ie, Peg-IFNα/ribavirin/protease inhibitor combination) significantly improved the rates of virological and CRs in patients with HCV-MC vasculitis. The complete CR rate at week 24 was of 56.5% and HCV RNA was undetectable in 69.5% of cases. This was higher than that observed in our previous series of HCV-MC patients treated with Peg-IFNα/ribavirin alone where 43.6% were complete clinical responders and 60% had undetectable HCV RNA at week 24.8

The early virological response rate of 69.5% at week 8 is likely to be clinically meaningful. As compared with Peg-IFNα plus ribavirin (used alone until week 4), the association of the protease inhibitor allowed the negativation of HCV RNA in
42 out of 21 (66.6%) patients at week 8. Inducing a sustained virologic and CR, and minimizing the use of immunosuppressive drugs are the main goals in the treatment of patients with HCV-MC vasculitis. We have previously shown that early virological reponse was the main predictive factor of complete remission of the MC vasculitis. Immunosuppressive drugs may be useful initially for the control of life-threatening organ involvement while awaiting the generally slow response to antiviral treatments.

Nephropathy is considered as a major cause of morbidity and mortality in MC vasculitis. We previously reported that HCV-MC patients with a GFR lower than 70 ml/min were 5.6 times less likely to be complete clinical responders to Peg-IFNα plus ribavirin. A striking conclusion drawn by this study is the high efficacy of Peg-IFNα/ribavirin/ protease inhibitor combination on kidney involvement. All six patients achieved significant improvement of kidney involvement, although two out of six received the combination of rituximab.

The safety profile of triple antiviral therapy was consistent with previous studies in HCV-infected patients. However, the addition of a protease inhibitor in HCV-MC patients was associated with increased rates of anaemia, fatigue and infections as compared with Peg-IFNα plus ribavirin alone. Grades 3 and 4 adverse events (mainly anaemia, neutropenia and thrombocytopenia) were observed in 43.5% of patients. The use of erythropoetin was needed in 87% of patients, and 40% required red cell transfusions. However, only one patient experienced treatment discontinuation due to severe depression.

The two therapeutic regimens (ie, telaprevir and boceprevir) were comparable in terms of clinical and virological parameters at baseline. No significant difference was observed regarding the clinical and virological response between groups. The safety profile was similar except for a trend towards higher rate of anaemia with the telaprevir association. In agreement with previous reports, toxic skin eruption was observed in 25% of patients treated with telaprevir. The two NS3/4A protease inhibitors, telaprevir and boceprevir, were approved in Europe and in the USA in 2011 in combination with Peg-IFNα and ribavirin for the treatment of chronic hepatitis C related to HCV genotype 1, in both treatment naïve and treatment-experienced patients. Sustained virological response rates in the ranges of 66–75% and 59–66% have been achieved in these two patient populations, respectively, with treatment duration of 24–48 weeks. In our study, one patient with HCV genotype 4 was included because of severe and refractory MC. He achieved a partial CR despite virological failure.

Immunosuppressive agents are typically reserved for HCV-MC patients with severe disease manifestations, such as membranoproliferative glomerulonephritis, severe neuropathy and life-threatening complication. Rituximab is usually used for the control of severe vasculitis lesions while awaiting the generally slow response to antiviral treatments. Rituximab may also represent an alternative therapeutic option in patients’ refractory or intolerant to antiviral therapy. Based on the limitations of each therapy (ie, antiviral and rituximab), and the 20–30% of MC patients who continue to have active disease while receiving anti-CD20 monoclonal antibody or antiviral therapy, the combination of rituximab with Peg-IFNα/ribavirin/protease inhibitor appears logical in HCV-MC patients with severe disease manifestations. In the present study, four patients received the combination of rituximab plus Peg-IFNα/ribavirin/protease inhibitor combination with clinical improvement in all cases, of whom two were complete clinical responders.

In conclusion, Peg-IFNα/ribavirin/protease inhibitor combination seems highly effective in HCV-MC vasculitis. Such therapeutic regimen should be administered cautiously considering the high rates of side effects. Long-term follow-up is warranted to further analyse the safety and efficacy of the Peg-IFNα/ribavirin/protease inhibitor combination in HCV-MC. The sustained virological response can be assessed definitively at week 72.


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