Lenograstim in the treatment of severe neutropenia in patients treated with Peg-IFN and ribavirin: the experience of a single hepatology unit

Trattamento mediante lenograstim della neutropenia grave in corso di terapia con Peg-IFN e ribavirina: esperienza di una singola unità di epatologia

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INTRODUCTION

The standard treatment of chronic hepatitis C (ECA C) is pegylated interferon-alpha (Peg-IFN) combined with ribavirin [1]. One of the most frequent causes of suspension of therapy or reduction of the doses of Peg-IFN is haematotoxicity, which includes anaemia and/or neutropenia and/or thrombocytopenia [2]. The use of growth factors (G-CSF) in responder patients allows effective doses of Peg-IFN and RIBA to be kept stable [3]. Lenograstim is a G-CSF that permits the therapy with Peg-IFN to be continued in cases of haematotoxicity. This study evaluates the efficacy and timing of lenograstim administration in a group of patients with chronic HCV who developed neutropenia during antiviral treatment.

METHODS

From January 2005 to December 2007, a total of 80 patients with chronic HCV infection, genotype 1, were treated with Peg-IFN 2b combined with ribavirin. Liver biopsy with Menghini needle’s 18 G confirmed diagnosis in 69/80 (86%) patients. Eleven patients refused the liver biopsy and were treated without histology. All patients were treated with standard doses of 80 mcg s.c./week of Peg-IFN 2b and 1200 mg/die of ribavirin. We checked quantitative HCV-RNA at 12 and 48 weeks of treatment. Every two weeks, two days before administration of the weekly dose of Peg-IFN 2b all patients had blood count and liver enzyme tests. Patients with absolute neutrophil counts <900 cells/mmc started on lenograstim (263 µg) 24 hours before administration of Peg-IFNα 2b (Figure 1). Indication for administering lenograstim was early viral response (EVR), defined as a reduction in the viral load of 2 log₁₀ or undetectable serum HCV-RNA at 12 weeks of treatment. Every week before the

![Treatment protocol](Image)

Figure 1 - Protocol of treatment: every two weeks before the dose of Peg-IFNα 2b neutrophil counts were made. In the event of neutrophil counts <900 cells/mm³, 24 hours before the PEG-IFN dose lenograstim was administered. With neutrophil counts >900 cells/mm³ PEG-IFN was administered and the neutrophil count was appraised after a week.
next dose of Peg-IFN neutrophil counts were appraised. If the neutrophil count was <900 cells/mm³, prior to the PEG-IFN dose lenograstim was administered. In the event of neutrophil counts >900 cells/mm³ PEG-IFN was administered and neutrophil counts were taken after a week. Prior to administering lenograstim, all patients undersigned an informed consent. The study was approved by the ethical committee of our institution.

**RESULTS**

Liver biopsy showed ECA at moderate activity in 44/69 patients, ECA at severe activity in 18/69 patients and ECA+ cirrhosis in seven patients. 28/69 patients without EVR were considered non responders to treatment; 52/80 (65%) patients responded to therapy with EVR. Of the latter, 18/52 patients (35%) showed Sustained Viral Response (SVR). In 24/52 (46%) no side effects were recorded. However, 20/52 (38%) patients had several side effects other than neutropenia and 8/52 (15%) patients showed severe neutropenia (<900 cells/mm³) (Figure 2). Lenograstim was administered to these patients in single doses subcutaneously after verifying severe neutropenia. In one patient, administration of lenograstim once weekly throughout the therapy (48 weeks) was necessary; in two patients it was occasionally administered; in six patients, administration of lenograstim was necessary every two doses of PEG-IFN (once every two weeks) (Table 1). The neutrophil count, tested seven days after administering lenograstim,

**Table 1 - Lenograstim administration mode in the 8 patients with severe neutropenia in our series.**

<table>
<thead>
<tr>
<th>Weekly dose of lenograstim</th>
<th>Patients (No.)</th>
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</thead>
<tbody>
<tr>
<td>Lenograstim/week throughout the therapy</td>
<td>1</td>
</tr>
<tr>
<td>Lenograstim 1 vial every 2 weeks</td>
<td>6</td>
</tr>
<tr>
<td>Lenograstim 1 vial every 4 weeks</td>
<td>0</td>
</tr>
<tr>
<td>Extemporaneous occasional administration</td>
<td>2</td>
</tr>
<tr>
<td>Total patients</td>
<td>8</td>
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varied from $4.2 \times 10^3$ to $16.5 \times 10^3$ cells/mm$^3$ (average $6.7 \times 10^3$). All patients [8] treated with lenograstim completed their therapy with interferon and six of them (75%) showed SVR, defined as undetectable serum HCV-RNA at 6-12 months of follow-up post-treatment. Two patients had a relapse of viral load and liver enzymes at 2 and 6 months from the end of antiviral therapy respectively. There were observed no side effects that forced the suspension of lenograstim or association with any other therapy. All patients treated with lenograstim resolved their neutropenia and were able to complete the therapeutic cycle (48 weeks).

**DISCUSSION**

The treatment of ECA C is Peg-IFN combined with ribavirin. The response to therapy varies according to viral genotype: 42-52% genotype 1, 76-82% genotype 2 and 3 [1, 2]. More than 75% of patients treated requires dose reduction or interruption of therapy due to the emergence of side effects such as depressive syndrome and haematotoxicity with anaemia and/or neutropenia and/or thrombocytopenia [2]. Neutropenia is a common adverse effect during treatment [3]. Light or moderate neutropenia can improve on reducing the doses of Peg-IFN$\alpha$; this may be enough to complete the treatment, but can result in a higher rate of treatment failure (detectable serum HCV-RNA and increase in liver enzymes). When neutropenia is severe, treatment must be interrupted [1, 3, 5]. The reduction in doses of Peg-IFN$\alpha$, which was necessary in 4-19% of the patients in our study, resulted in an appreciable reduction in the number of patients with SVR. In 19-38% of the patients severe neutropenia forced termination of the therapy. The use of G-CSF in responder patients allows the neutrophil count to be maintained at acceptable levels and therefore to stabilise actual doses of PEG-IFN and RIBA [6]. In Italy, a regulation issued by the Italian Drug Agency (AIFA) limits the prescription of the G-CSF (CUF note 30). CUF note 30 establishes that the products based on G-CSF can be prescribed only to patients with early viral response to therapy with Peg-IFN in monotherapy or ribavirin combined. EVR is defined as a reduction in the viral load of 2 log$_{10}$ or undetectable serum HCV-RNA at the 12$^{th}$ week of therapy in comparison with baseline values. Lenograstim is a glycosylated form of a recombinant therapeutic agent which is chemically identical or similar to an endogenous human granulocyte colony-stimulating factor (rHu G-CSF). The recommended dose is 150 mcg (19.2 MIU) per mq/die, equivalent to 5 mcg (0.64 MIU) per kg a day. Although G-CSF is commonly used during therapy with PEG-INF to improve neutropenia, its optimal dose and administration timing have not been established. Our study sought to establish such parameters and to assess the impact of G-CSF on antiviral treatment and hence indirectly on its results. Our experience confirmed the elevated effectiveness of lenograstim. All patients with neutropenia maintained the full dose of PEG-INF and finished the therapeutic cycle which they would have had to interrupt, thereby depriving them of the opportunity to have an SVR to the treatment. G-CSF was generally administered in single doses of 263 g every two weeks, effective in more than 87% of cases; only in 1/8 patients did neutropenia return severely after each administration of PEG-INF, which required that the administration of lenograstim be regularly associated. However, also this patient completed the cycle of treatment.

*Key words:* growth factors, hepatitis C, neutropenia, pegylated interferon.

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**SUMMARY**

Lenograstim is a G-CSF that allows therapy with Peg-IFN$\alpha$ to be continued in cases of haematotoxicity. This study evaluates the efficacy of lenograstim administration in a group of eight patients with chronic HCV-related hepatitis who developed neutropenia during antiviral treatment. Patients with absolute neutrophil counts <900 cells/mm$^3$ and early viral response received lenograstim at the dosage of 263 $\mu$g 24 hours prior to administration of Peg-IFN$\alpha$ 2b. All patients receiving lenograstim completed the antiviral treatment (48 weeks) with standard doses of PEG-IFN$\alpha$, with six of the eight patients (75%) showing a sustained virological response.
Il lenograstim è un G-CSF potenzialmente utile allo scopo di continuare la terapia con Peg-IFNa nei casi di mielotossicità con neutropenia. Nel presente studio, in una serie di 8 pazienti con ECA HCV-correlata, che avevano sviluppato neutropenia in corso di trattamento antivirale, è stata valutata l’efficacia, e i possibili protocolli di somministrazione, del lenograstim nella neutropenia IFN-indotta.

Il trattamento di supporto con lenograstim è stato iniziato solo in caso di risposta virologica precoce e lenograstim alla dose di 263 g è stato somministrato 24 ore prima della dose di Peg-IFNa2b. Tutti i pazienti trattati con lenograstim sono riusciti a completare il ciclo di terapia con interferone (48 settimane) a dosaggio pieno di PEG-IFNa e 6/8 pazienti (75%) hanno presentato una risposta virologica sostenuta.

RIASSUNTO

REFERENCES