G-CSF in Peg-IFN induced neutropenia in liver transplanted patients with HCV recurrence

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Abstract

AIM: To evaluate the efficacy of granulocyte colony stimulating factors (G-CSF) in liver transplanted patients with hepatitis C (HCV) recurrence and Pegylated-IFN α-2b induced neutropenia, and to evaluate the impact of G-CSF administration on virological response.

METHODS: Sixty-eight patients undergoing antiviral treatment for post-liver transplantation (OLT) HCV recurrence were enrolled. All patients developing neutropenia received G-CSF.

RESULTS: Twenty three (34%) received G-CSF. Mean neutrophil count at the onset of neutropenia was 700/mmc (range 400-750/mmc); after 1 mo of G-CSF it increased to 1210/mmc (range 300-5590/mmc) (P < 0.0001). Three patients did not respond to G-CSF. Treatment duration was similar in neutropenic and non-neutropenic patients. No differences in the rate of discontinuation, infections or virological response were observed between the two groups. G-CSF was protective for the onset of de novo autoimmune hepatitis (P < 0.003).

CONCLUSION: G-CSF administration is effective in the case of Peg-IFN induced neutropenia increasing neutrophil count, prolonging treatment and leading to sustained virological response (SVR) rates comparable to non-neutropenic patients. It prevents the occurrence of de novo autoimmune hepatitis.

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Key words: Granulocyte colony stimulating factors; Liver transplantation; Hepatitis C virus recurrence; Antiviral treatment

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INTRODUCTION

Both interferons (IFNs) and pegylated interferons (Peg-IFNs) may induce neutropenia[1-4]. This side effect may limit adherence to treatment which is one of the most important factors related to virological response[1,5-7].

In immunocompetent patients, neutropenia has not been associated with infections. However, in oncological immunodepressed patients neutropenia is associated with infections[8-10] and liver transplanted patients are immunosuppressed. In fact, liver transplanted patients have a high rate of infections reaching 56% within the first year post transplantation[11-13]. This ease at infections coupled to the baseline leukopenia induced by the immunosuppressive regimens challenging the management of these patients by the clinician.

There are no guidelines on the use of granulocyte colony stimulating factors (G-CSF) for the treatment of IFN induced neutropenia. Moreover, the impact of G-CSF administration during antiviral therapy for chronic hepatitis C has not been determined yet.

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Nevertheless, the use G-CSF is becoming a standard of care in this setting, especially in liver transplanted patients, and is recommended by several authors.[5,14-19]

A recent study by our group showed that G-CSF administration has a protective effect for the development of de novo autoimmune hepatitis during antiviral therapy in transplanted patients.[20]

This effect is not surprising as G-CSF has been shown to have several immunological properties: induces T-regulator (T-regs) mobilization and activity, both directly and through the expansion of tolerogenic myeloid precursor and type 2 dendritic cells mobilization; moreover it skews the cytokine profile, inducing tolerogenic dendritic cells and T-regs, which finally suppresses T cell activity[21-26].

The aims of the present study were to evaluate the efficacy of G-CSF use in liver transplanted patients with hepatitis C virus (HCV) recurrence and Peg-IFN α-2b induced neutropenia, and to evaluate the impact of G-CSF administration on virological response.

MATERIALS AND METHODS

Patients undergoing antiviral treatment for post orthotopic liver transplantation (OLT) HCV recurrence were consecutively enrolled in Bologna Liver Transplantation Centre between October 2001 and April 2005. All patients received Peg-IFN α-2b at the dose of 1.0 mcg/kg once weekly (Peg-Intron®, Schering-Plough, Italy), and Ribavirin (Rebetol®, Schering-Plough, Italy) at a dose of 8-10 mg/kg per day. Transplanted patients had to fulfil the following criteria for antiviral treatment: detectable HCV-RNA by PCR, elevated (> 1.0 ×) serum alanine aminotransferase (ALT) levels and histological features of HCV hepatitis on liver biopsy. Exclusion criteria were: evidence of decompensated liver disease, histological evidence of rejection and drug-related injury, HBsAg positivity, human immunodeficiency virus (HIV) positivity, moderate to severe anemia (Hb < 10 g/dL), neutropenia (neutrophil count < 1000/mm³), thrombocytopenia (PLT < 50000/mm³), impaired renal function (creatinine clearance < 50 mL/min), significant history of cardiovascular and psychiatric diseases, ongoing alcohol abuse and previous post-LT treatment with PEG-IFN.

Hematologic determinations were carried out using conventional tests at baseline and weekly for the first month, then monthly until the end of the study.

All patients developing neutropenia during antiviral treatment received Granulocyte Colony-Stimulating Factor (G-CSF) (Granulokine®, Roche, Italy). Below 750/mmcc neutrophils, G-CSF 300 μg/wk was administered and in case of non significant response the dose was increased to 600 μg/wk. When the neutrophil count did not increase satisfactorily, despite G-CSF administration, Peg-IFN dose was reduced. When neutrophils fell below 500/mmcc despite G-CSF administration, antiviral treatment was discontinued. G-CSF treatment was continued until restoration of neutrophil count to values comparable
to the patient’s baseline. None of the patients received azathioprine or mycophenolate mofetil.

All patients gave written informed consent according to the Ethical Committee Procedures of our Hospital for the administration of off label drugs.

Statistical analysis

Data were analyzed on an intention-to-treat-basis. Results are presented as median (range). Non parametric tests were used to compare variables between groups (Wilcoxon, χ² test). All P < 0.05 by the two-tailed test were considered significant. All data analyses were conducted using the MedCalc Package.

RESULTS

Sixty-eight patients (46 males and 22 females), median age 59 (22-68 years) were enrolled in the study (Table 1). Ten patients were cirrhotic at enrolment. Twenty three (34%) received G-CSF according to our study design. Table 2 shows the baseline characteristics of patients developing neutropenia or not and of all patients together. The only factor related to neutropenia development was pre-treatment neutrophil count, which was significantly lower in patients who later developed neutropenia and were treated with G-CSF. Median neutrophil count at the onset of neutropenia was 700/mmcc (range 400-750/mmcc) and after one month

| Table 1 Baseline characteristics of patients at enrolment |
|------------------|------------------|
| Sex (M/F)         | 46/22            |
| Age, median (range) | 59 (22-68)     |
| BMI, median (range)  | 24.2 (15.5-40.5) |
| Months since LT, median (range)  | 15.5 (1-151) |
| Previous acute cellular rejection n (%) | 13 (19) |
| Days since OLT, mean | 36 (24-90)    |
| Previous CMV infection n (%) | 14 (21) |
| Genotype n (%)       |                 |
| 1                  | 53 (76.5)       |
| 2                  | 6 (9)           |
| 3                  | 4 (6)           |
| 4                  | 5 (7)           |
| Viral load (MEq/mL, median (range)) | 10.6 (0.009-40) |
| ALT (IU/L, median (range)) | 136 (62-945) |
| Neutrophil count (× 10³/mmcc) mean ± SD | 3 ± 1.2 |
| Hemoglobin (g/dL) mean ± SD | 12.9 ± 1.5 |
| Cirrhosis n (%)       | 10 (15)         |
| Pre-LT antiviral treatment n (%) | 29 (45) |
| Post-LT antiviral treatment n (%) | 15 (22) |
| Induction immunosuppression n (%) |       |
| Monoclonal antibodies | 10 (14)       |
| Steroids            | 49 (72)         |
| Other               | 3 (4)           |
| NA                  | 6 (10)          |
| Maintenance immunosuppression n (%) |       |
| Cyclosporine         | 30 (44)         |
| Tacrolimus           | 22 (32)         |
| Cyclosporine + steroids | 6 (9)        |
| Tacrolimus + steroids | 9 (13)        |
| Other               | 1 (1.5)         |

LT: Liver transplantation; OLT: Orthotopic liver transplantation; CMV: Cytomegalovirus.
of G-CSF administration it increased to 1210/mm³ (range 300-5590/mm³) (P < 0.0001) (Figure 1). Mean G-CSF treatment duration was 4.9 ± 3.6 mo. Three patients did not respond to G-CSF administration after one month; two patients had an improved neutrophil count with an increased dose of G-CSF and a reduction of Peg-IFN dose and continued treatment until the end of the planned 48 wk period, the other discontinued treatment. No patient had to reduce their Peg-IFN dose in the non-neutropenic group. Table 3 shows Ribavirin (RBV) and Peg-IFN dose modification during treatment in both groups. At multivariate analysis, several factors were evaluated (age, sex, time from OLT, type of immunosuppression, presence of cirrhosis, basal neutrophil count) but none was associated with non response to G-CSF.

The mean treatment duration was similar in neutropenic and non-neutropenic patients regardless of G-CSF administration and genotype (Figure 2A).

Causes of premature discontinuation are shown in Table 4. No significant differences in the rate of discontinuation were observed between the two groups (neutropenic and non-neutropenic) (Figure 2B).

Two severe infections were observed in the G-CSF group (1 pneumonia and 1 urinary infection) and 5 in the non-neutropenic patients (3 pneumonias, 1 liver abscess and 1 cytomegalovirus) (P = No significance) (Figure 2C). Among neutropenic patients, the neutrophil counts were 700/mm³ and 900/mm³ respectively at the onset of infections. In non-neutropenic patients developing infections, the neutrophil count was > 1000/mm³ in all at the onset of neutropenia.

**Viral response**

Sustained virological response was 30% in the G-CSF group versus 35% in the non-neutropenic patients (P = NS) (Figure 2D).

**Autoimmune diseases**

In the G-CSF group no *de novo* hepatic autoimmune disease was observed, while 9 patients in the other group developed autoimmune hepatitis (P < 0.03) (Figure 3). This pathological entity has already been extensively described by our group[28] and therefore won’t be discussed in detail here. *De novo* autoimmune hepatitis diagnosis was performed in patients with an unexplained cause of graft dysfunction, after the exclusion of other known causes (infections, anastomoses complications, acute or chronic rejection) and the application of the International Autoimmune Hepatitis Group score[27]. This disease was related to severe patient and graft outcome; in fact two patients died and two had a graft failure with one patient re-enlisted for transplant. In our series no rejection episodes were observed.

The incidence of non hepatic autoimmune manifestations was similar in the two groups. One patient had autoimmune thyroiditis and another had systemic lupus erythematosus (SLE) responding to mean ± SD

Cirrhosis n (%) 10 (15)

Induction immunosuppression n (%) 4 (17) 6 (13) NS

Cyclosporine 10 (43) 20 (44) NS

Cyclosporine + steroids 1 (4) 5 (11) NS

Tacrolimus 8 (34) 14 (31) NS

Tacrolimus + steroids 3 (13) 6 (13) NS

Maintenance immunosuppression n (%) 1 (3) 5 (11) NS

NA 1 (3) NS

Table 4 Causes of premature discontinuation in the two groups

| Discontinuation cause     | G-CSF group n (%) | Non neutropenic group n (%) |
|---------------------------|-------------------|-------------------------------|
| Liver decompensation      | 3                 | 3                             |
| Severe asthenia           | 2                 | 1                             |
| Neutropenia               | 1                 | 1                             |
| Anemia                    | 1                 | 1                             |
| Toxic hepatitis           | 1                 | 1                             |
| Non response              | 1                 | 1                             |
| Liver abscess             | 1                 | 1                             |
| *De novo* AIH             | 9                 | 1                             |
| *De novo* HBV infection   | 1                 | 1                             |

AIE: Autoimmune hepatitis; HBV: Hepatitis B virus.

**Figure 1** Neutrophil count response after 1 mo of granulocyte colony stimulating factors administration.

![Graph showing neutrophil count response after 1 mo of G-CSF administration](https://www.wjgnet.com)

**Table 3 Peg-IFN and RBV dose reductions n (%)**

|                      | G-CSF | No G-CSF | P     |
|----------------------|-------|----------|-------|
| RBV reduction        | 6/26  | 17/37    | 0.4   |
| RBV withdrawal       | 4/17  | 3/6      | 0.2   |
| Peg-IFN + RBV reduction | 2/8 | 1/2      | 0.2   |

Peg-IFN: Pegylated interferons; RBV: Ribavirin.

**Table 2 Characteristics of patients developing neutropenia**

|                          | G-CSF | No G-CSF | P     |
|--------------------------|-------|----------|-------|
| Sex (M/F)                | 10/13 | Dec 33   | NS    |
| Age, median (range)      | 60 (41-68) | 58 (22-67) | NS    |
| Months since LT, median (range) | 15 (2-151) | 19 (1-148) | NS    |
| Genotype n (%)           | 1 (3) | 1 (4)    | NS    |
| 1                        | 1 (73) | 36 (80) | NS    |
| 2                        | 2 (8.6) | 4 (8.8) | NS    |
| 3                        | 2 (8.6) | 2 (4.4) | NS    |
| 4                        | 2 (8.6) | 3 (6.6) | NS    |
| Neutrophil count (<10³/mm³) | 2.23 ± 0.96 | 3.14 ± 1.22 | 0.0021 |

G-CSF: Granulocyte colony stimulating factors.
steroid treatment\textsuperscript{28} in the G-CSF group, while among non-neutropenic patients, one had autoimmune gastritis.

**DISCUSSION**

Our data shows that G-CSF administration is effective in resolving neutropenia in transplanted patients treated with Peg-IFN α-2b for HCV recurrence. The improvement or the resolution of neutropenia allowed us to prolong treatment duration to a time which is comparable to that of non-neutropenic patients and presumably contributed to patients reaching an SVR rate which was comparable in the two groups. G-CSF administration did not affect the rate of infections or the occurrence of non hepatic autoimmune diseases, while it was a protective factor for the development of de novo autoimmune hepatitis. The only predictive factor related to the development of neutropenia during antiviral treatment was pre-treatment neutrophil count.

Clinical experience, mainly from studies in immunocompetent patients, suggests that maintenance of optimal dosages of Peg-IFN and RBV results in higher rates of SVR. Previous studies on liver transplanted patients have shown that, overall, a SVR between 30\% and 45\% is achievable\textsuperscript{29-33}. Therefore, in our opinion, adjunctive treatments allowing the maintenance of optimal dosages of Peg-IFN and RBV during treatment are advisable. In our series the rate of SVR was not significantly different among patients treated and not treated with G-CSF. The lack of a statistically significant difference could be affected by the small number of patients, but the rate of SVR in neutropenic patients treated with G-CSF is comparable to what is reported in literature. Moreover, although not statistically significant, a larger proportion of patients had to reduce or suspend RBV in the G-CSF group, and this factor might have contributed to the smaller SVR rate in this group.

There are currently no guidelines on the use of G-CSF in IFN induced neutropenia. Therefore, no established common approach to its use is defined in both the immunocompetent and the transplanted patient. In this context we arbitrarily defined cut off values to begin G-CSF administration. In consideration of the immune depression of our patients we chose a high cut off level of 750 neutrophils/mmc for initiation of treatment in
order to prevent infections. We are aware that previous studies in immunocompetent patients did not show a correlation between the absolute number of neutrophils and infections\cite{32,36,37}, but in immunodepressed oncological patients this correlation exists\cite{38-40}; this induced us to choose a safer cut off value. Unfortunately ours was not a randomised study, because in our opinion it would be not ethical not to treat a severe neutropenia in a transplanted immunosuppressed patient. Nevertheless, in our study infections seemed to be independent of neutrophil count. Anyway, our study shows that G-CSF use in transplanted patients is safe and effective.

With regard to autoimmune diseases, our study suggests that G-CSF protected from de novo autoimmune hepatitis but not from other systemic autoimmune manifestations. This is not surprising, as G-CSF has been reported to have different effects in different autoimmune diseases\cite{48-50}. This probably depends on the immune pathogenetic mechanisms underlying the different diseases. However, the apparently induced non hepatic autoimmune manifestations did not significantly impact on patients outcome while de novo hepatitis was severe and related to high patient and graft loss, suggesting that the onset of non hepatic autoimmune manifestations does not contraindicate G-CSF use in this population.

In conclusion, our study supports G-CSF administration in transplanted patients with HCV recurrence developing Peg-IFN induced neutropenia because it is effective in increasing the neutrophil count. G-CSF administration prolongs treatment duration in neutropenic patients leading to SVR rates which are comparable to that of non-neutropenic patients. A pre-emptive treatment with G-CSF could be advisable in patients with very low pre-treatment neutrophil counts. G-CSF seems to have a protective role against the occurrence of de novo autoimmune hepatitis, a recently defined pathogenetic entity related to a severe outcome. Prospective randomized studies are needed in order to evaluate the protective effect of prophylactic G-CSF administration to prevent this form of autoimmune hepatitis.

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