Prolonged treatment with granulocyte colony-stimulating factor in a patient with Felty’s syndrome and chronic renal failure from secondary amyloidosis

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Introduction

Felty’s syndrome is defined by the triad of rheumatoid arthritis, splenomegaly, and neutropenia, which can predispose a patient to the development of infections that are fundamentally cutaneous, and also infections of the respiratory tract.

In the majority of these patients the bone marrow shows an arrest in the maturation of the granulocytes. The pathogenesis is not well known. Several different mechanisms have been implicated, such as hypersplenism, maturation defects of myelopoiesis, autoimmune mechanisms, and a reduction in the production of stimulating factors for the granulocyte colonies.

Thus, granulocyte macrophage stimulating factor (GM-CSF) [1] and granulocyte colony-stimulating factor (G-CSF) [2–19] have been successfully used in the treatment of neutropenia and infectious complications associated with Felty’s syndrome.

Case report

Our patient was a 55-year-old male, in whom seropositive rheumatoid arthritis had been diagnosed in 1988. He had a 30-year history of chronic arthritis, for which he had received treatment with non-steroidal anti-inflammatory agents, gold sodium thiomalate, and D-penicillamine.

In March 1993, proteinuria was detected following the administration of D-penicillamine, which persisted after its withdrawal, becoming nephrotic and being accompanied by a slight deterioration in renal function. A renal biopsy was performed, revealing amyloid material (AA).

Treatment was started with methotrexate and chlorambucil successively. On 15 July 1994 coinciding with the administration of chlorambucil, the patient was admitted with fever, pancytopenia, and impaired renal function. Analysis on admission was: Hct, 23%; Hb, 7.5 g/dl; leukocytes, 1.1 × 10^9/l (neutrophils, 0.85 × 10^9/l), platelets, 84 × 10^9/l; serum creatinine, 291 µmol/l; total protein, 42 g/l; albumin, 16 g/l; urinary protein, 17 g/24 h; blood cultures, E. coli. Chlorambucil treatment was stopped and followed by a course of antibiotics which met with a good response. The analysis on leaving the hospital was: Hct, 24.8%; Hb, 8.7 g/dl; leukocytes, 4.1 × 10^9/l (neutrophils, 2.17 × 10^9/l); platelets, 92 × 10^9/l; serum creatinine, 318 µmol/l.

On the 18 February 1995 the patient was admitted with pneumonia (Haemophilus influenzae) and impaired renal function that required a programme of periodic haemodialysis.

On the 27 July 1995 the patient was admitted suffering from severe neutropenia (leukocytes 1.8 × 10^9/l, neutrophils 0.12 × 10^9/l) and splenomegaly, being diagnosed as Felty’s syndrome.

Bone marrow specimen showed an increase in immature forms such as promyelocytes and myelocytes, and a decrease in mature neutrophils, suggesting an arrest in neutrophil maturation.

Treatment with G-CSF was started at a dose of 300 µg/sc/day (5 µg/kg) with early response, showing an increase in both the leukocyte (7.8 × 10^9/l) and neutrophil (4.8 × 10^9/l) counts. G-CSF treatment was stopped after 5 days.

An episode of severe neutropenia (leukocytes 2.0 × 10^9/l and neutrophils 0.40 × 10^9/l) without further complications occurred on the 16 August 1995. G-CSF treatment at the same dosage was reinitiated. The appearance after 7 days of leukocytosis (16.9 × 10^9/l) with neutrophilia (neutrophils 13.4 × 10^9/l) required that the intervals between administration be increased to 3 days a week (subcutaneous, post-dialysis). Treatment was halted 44 days later due to leukocytosis (13.4 × 10^9/l) with neutrophilia (10.8 × 10^9/l).

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On the 18 October 1995, pneumonia coincided with a new episode of leukopenia $2.4 \times 10^9/l$ (neutrophils $0.52 \times 10^9/l$), for which antibiotics and G-CSF treatment $300 \mu g/sc/3$ days a week were given. The patient responded well, although to a lesser extent than that seen previously. This course of treatment was maintained during 84 days and then reduced to different doses, depending on the neutrophil count, until 239 days of continuous treatment had been completed (Figure 1).

The only complication observed during all cycles of the treatment with G-CSF was a decrease in the number of platelets, which each time spontaneously resolved itself after a period of 2 weeks, even during the third cycle of treatment (Figure 1).

Six months after treatment had ceased the patient remained on a programme of periodic haemodialysis without the appearance of any new complications, and with the neutrophil count within a normal range.

**Discussion**

G-CSF has been used in patients with Felty’s syndrome for the treatment of neutropenia and infectious complications [2–14] or in association with prednisone [15], cyclophosphamide [16,17], methotrexate [18] or prednisolone [19].

There are no general guidelines for treatment with G-CSF in patients with Felty’s syndrome, particularly with respect to the dosage quantities, the duration, and characteristic of the response. In most cases, however, there is a recovery in the neutrophil count. All cases reported have used subcutaneous administration, with the exception of Bhalla et al. [8] and Fraser et al. [15], who administered preliminary doses intravenously. Pixley [16] has described a case in which the patient did not respond to the administration of C-GSF alone. Pretreatment with bolus cyclophosphamide permitted the growth factor to relieve this impairment of late myeloid maturation and resulted in a brisk, albeit short, burst of neutrophilia. In others the response improved by the coadministration of methotrexate [18] and prednisolone [19].

We describe the first case of a patient with Felty’s syndrome and CRF caused by secondary amyloidosis undergoing a programme of periodic haemodialysis, and who received various cycles of G-CSF treatment at different dosages over an extended period of time.

The first two cycles of treatment lasted 5 and 44 days respectively and were started after the appearance of severe neutropenia in the analytical controls. The third cycle was started following the reappearance of neutropenia accompanying pneumonia. During the last cycle, a new episode of asymptomatic neutropenia coincided with a reduction in the dosage of G-CSF to $300 \mu g/ week$.

The good response and the absence of serious complications led us to slowly reduce the doses of G-CSF until the completion of 239 days of treatment. In all cycles the treatment produced at a very early stage a rapid recovery in the neutrophil count and a resolution of the infectious processes.

![Fig. 1](image_url) Neutrophil, leukocyte, and platelet response to recombinant granulocyte colony-stimulating factor in a patient with Felty’s syndrome.
During the whole period of treatment we found no complications other than a decrease in platelet count, with spontaneous resolution despite the continuation of treatment, as also described by Wandt et al. [6]. The discovery that G-CSF exerts influence on mature platelets would confirm the presence of functional receptors in these cells [20].

Other complications described in relation to the administration of G-CSF are exanthema [5], transient bone pains [15], exacerbation of the arthralgias [4,12], flare-up of arthritis [9,17] thrombocytopenia and anaemia [7,18], leukocytoclastic vasculitis [13], and leukocytoclastic vasculitis complicated by acute renal failure [14].

There are few patients, such as in our case, that have undergone continuous treatment over long periods of time: Graham and Coodley, 18 months [12]; Choi et al. 14 months [17]; Wandt et al., 375 days [6]; Fraser et al., 150 days [15]; Yasuda et al., 137 days [9]; Marfeuille et al., 63 days [11]. In all cases the dosages administered were no greater than 10 μg/kg/day and modified according to the patients response and tolerance to treatment.

Only Fohlman et al. [10] maintained treatment at a low and constant dosage of 150 μg (2 μg/kg/day/s.c.) over 40 days and without the appearance of secondary effects in a patient with Felty’s syndrome and infected lower limbs.

Since its first use by Hazemberg et al. [1], GM-CSF has been successfully used in the treatment of complications associated with Felty’s syndrome with accompanying secondary effects such as flare-up of arthritis and eosinophilia.

Kaiser et al. [3] treated one of their patients with GM-CSF over an initial period of 13 days and then, 15 months later, with G-CSF over 9 days. In both instances the patient responded well to treatment, with a resolution of the infectious complications and neutropenia. The patient did, however, suffer from fever and eosinophilia as side-effects of the GM-CSF treatment.

Given the good response, rapid recovery of neutrophil count, and minimal side-effects experienced by our patient, we conclude that G-CSF is useful in the treatment of neutropenia and infectious complications that occur in patients with Felty’s syndrome. We believe that after leukocyte levels have been restored, there is no cause for continued treatment with G-CSF, especially taking into account its high cost.

References

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