CORRESPONDENCE

CORRECTION OF GRANULOCYTOPENIA IN FELTY’S SYNDROME BY GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR. SIMULTANEOUS INDUCTION OF INTERLEUKIN-6 RELEASE AND FLARE-UP OF THE ARTHRITIS

To the Editor:

Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been cloned recently and produced as a recombinant protein. In vivo studies demonstrated that GM-CSF can be used effectively to treat chemotherapy-induced leukopenia. However, not all patients respond to GM-CSF. Patients known to have cyclic neutropenia and large granular lymphocytosis (LGL) demonstrated only a monocytosis and eosinophilia, whereas no effect was noted on the granulocyte count. In view of the unpredictable response in agranulocytosis, we treated a patient with Felty’s syndrome with GM-CSF to study the efficacy in this disorder.

In 1968, seropositive rheumatoid arthritis (RA) was diagnosed in a 47-year-old woman. In the following years she was treated with chloroquine and 20 mg prednisolone daily. Neutropenia (<2,000/mm³) was noted in 1977, and Felty’s syndrome was diagnosed in view of the triad of RA, granulocytopenia, and splenomegaly (2 cm below the costal margin). In 1988, re-evaluation was performed as a result of a recent infection. The peripheral blood values were: Hb 10 g/dL, platelets 200,000/mm³, leukocytes 4,000/mm³ with 4% basophils, 0.3% eosinophils, 1% band forms, 1% neutrophils, 89% lymphocytes, and 1% monocytes.

Bone marrow investigation showed a normal cellularity with a normal myeloid/erythroid ratio of 1.9:1. The differential count demonstrated a maturation defect: 2% myeloblasts, 12% promyelocytes, 22% metamyelocytes, and 5% polymorphonuclear leukocytes. Cytogenetic studies did not show chromosomal abnormalities and LGL could be excluded by surface-marker analysis. On the basis of the persisting agranulocytosis, treatment with GM-CSF was started after informed consent.

Recombinant CHO-cell GM-CSF (Sandoz Ltd and Schering-Plough Corp, Basel, Switzerland; specific activity 8 x 10⁶ U/mg protein, free of endotoxin) was given subcutaneously, 4 µg/kg/d, twice daily, during 14 days. Maintenance therapy with prednisolone 6 mg daily was continued. Neutrophils and eosinophils increased dramatically from the sixth day of treatment to a peak level at the fourteenth day (Fig 1B). The differential leukocyte count at day 14 showed 1% basophils, 34% eosinophils, 7% band forms, 49% neutrophils, 4% lymphocytes, and 4% monocytes. After discontinuation of therapy all levels returned to the pretreatment values. Bone marrow

Fig 1. Temperature, leukocytes, and acute-phase proteins during GM-CSF therapy in a patient with Felty’s syndrome. (A) Body temperature. (B) Peripheral blood leukocyte counts: Mature neutrophils and band forms together (○--○), eosinophils (■--■), lymphocytes (□--□), and monocytes (■--■). (C) Serum levels of IL-6 (△--△), C-reactive protein (□--□), and serum amyloid A (○--○). Control baseline values: IL-6 bioassay <2 U/mL, CRP-ELISA <2.1 mg/L, and SAA-ELISA <2.7 mg/L. Therapy with GM-CSF, prednisolone, and acetaminophen are indicated in the horizontal bars.

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investigation at day 14 of treatment showed an increased cellularity with a myeloid/erythroid ratio of 3.7:1. However, the differential count demonstrated a persistent maturation defect: 2% myeloblasts, 15% promyelocytes, 24% meta- and myelocytes, and 11% polymorphonuclear neutrophils. In vitro cultures of bone marrow cells at day 0 and 13 demonstrated normal numbers of erythroid progenitor cells (64, 66 BFU-E/10^8 MNC), while scarce numbers of myeloid colonies were observed, 25 and 2 CFU-GM/10^8 MNC respectively.

However, within 1 day after start of GM-CSF administration, a flare-up of the arthritis of all affected joints was noted and associated with nausea and fever (39°C, Fig 1A). Repeated cultures of blood and urine were sterile. Joint pain and stiffness gradually increased during the 14 days. These symptoms were associated with an acute-phase response, reflected by high levels of C-reactive protein (CRP) and serum amyloid A (SAA), and preceded by highly elevated interleukin-6 (IL-6) levels in the circulation. As depicted in Fig 1C, the IL-6 level increased from 25 to 150 U/mL within 1 day after start of GM-CSF therapy and peaked at the second day (225 U/mL). CRP and SAA both showed a comparable pattern, with a lag time of 1 day. During the second week of treatment, IL-6, SAA, and CRP remained increased but at a lower level. In contrast to IL-6, the tumor necrosis factor α (TNFα) level demonstrated only a moderate increase during GM-CSF treatment: 39, 57, 61, 47, and 23 ng/L at days 0, 1, 2, 12, and 23, respectively (Medgenix, Brussels, Belgium; baseline values <5 ng/L). After discontinuation of GM-CSF therapy, IL-6 normalized within 2 days while CRP and SAA levels gradually declined to normal values. In addition, the clinical symptoms disappeared gradually after cessation of therapy.

This study demonstrates that GM-CSF can correct the granulocytopenia in Felty's syndrome. However, the observed bone marrow dysfunction was not abrogated by this growth factor. The maturation arrest at the metamyelocyte level persisted during GM-CSF administration and cessation of therapy resulted in the reappearance of the granulocytopenia. Furthermore it appeared that GM-CSF could trigger cells to release cytokines. In vitro studies have demonstrated that GM-CSF can induce the secretion of M-CSF, TNFα, and IL-1 from different cell types. In addition, GM-CSF is an important HLA-DR inducing factor of RA synovial cells. This study extends these observations and demonstrates that GM-CSF can induce the release of IL-6 in vivo. RA synovial cells might be responsible for the release of IL-6 by GM-CSF since these cells are the major source of circulating IL-6 in RA patients and in view of the clinical symptomatology of the described patient during GM-CSF treatment.

Finally, in vitro studies with human hepatocytes have demonstrated that different cytokines can induce the release of acute-phase proteins like CRP and SAA. Particularly, IL-6 appears to be a potent inducer of the acute-phase response. View in the time-course of IL-6 in the circulation and the pattern of the acute-phase response in this patient, it is most likely that IL-6 has induced the increase of CRP and SAA levels.

In summary, these data demonstrate that GM-CSF can correct granulocytopenia in Felty's syndrome and may be of use in patients with life-threatening infections. However, the monitoring of the acute-phase response during such an infection may be difficult to evaluate because of the release of IL-6 in the circulation.

To the Editor:

In the recent review on this subject (Blood 73:2051, 1989), Drs Champlin and Gale state that the value of central nervous system (CNS) prophylaxis in adults is controversial and that the likelihood of meningeal leukemia is "considerably lower" than in children, although they finally conclude that it should be given.

ACUTE LYMPHOBLASTIC LEUKEMIA: CENTRAL NERVOUS SYSTEM PROPHYLAXIS IN ADULTS

REFERENCES

Correction of granulocytopenia in Felty’s syndrome by granulocyte-macrophage colony-stimulating factor. Simultaneous induction of interleukin-6 release and flare-up of the arthritis

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