CONCISE REPORT

Failure of Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor Therapy in Aplastic Anemia Patients With Very Severe Neutropenia

By Catherine Nissen, André Tichelli, Alois Gratwohl, Bruno Speck, Alison Milne, E.C. Gordon-Smith, and Jürg Schaedelin

Four patients with very severe aplastic anemia refractory to antilymphocyte globulin were administered recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF). One patient with minimal residual myelopoiesis responded transiently to two separate courses of GM-CSF at 4 and 8 µg/kg/d administered intravenously and another course at 4 µg/kg/d administered subcutaneously. Septicemia and bilateral pneumonia that had been resistant to conventional therapy resolved. Three patients with no evidence of residual myelopoiesis did not respond to GM-CSF. In one patient, the dose was increased to 32 µg/kg/d with no effect on hematopoiesis. Immediate side effects were minimal at GM-CSF doses up to 16 µg/kg/d. GM-CSF may, however, have been involved in the pathophysiology of thrombosis of the inferior vena cava in the patient administered 32 µg/kg/d. We conclude that GM-CSF does not induce hematopoiesis in long-standing, severe, treatment-resistant aplastic anemia with complete myelopoietic failure. However, in patients with minimal residual myelopoiesis, GM-CSF could be a promising adjuvant therapy for severe infection.

© 1988 by Grune & Stratton, Inc.

HUMAN RECOMBINANT hematopoietic growth factors have become available for clinical use. Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been shown to increase granulocyte counts in neutropenia associated with acquired immunodeficiency syndrome and with myelodysplastic syndromes. Positive effects on recovery of bone marrow function after autologous bone marrow transplantation have been reported. Some positive effects of GM-CSF have been observed in aplastic anemia. We present the results of GM-CSF administered to four patients with very severe, treatment-resistant aplastic anemia.

PATIENTS

Four patients with severe aplastic anemia who did not have a histocompatible donor for bone marrow transplantation and had failed to respond to treatment with antilymphocyte globulin (ALG) were administered GM-CSF (Table 1). All patients had received conventional treatment, including antibiotics, antifungal drugs, and granulocyte transfusions before GM-CSF administration. They had no reticulocytes and were dependent on red cell and platelet transfusions throughout the observation period.

Patient 1. A 38-year-old man developed severe aplastic anemia after non-A, non-B hepatitis in February 1987 (Fig 1A). He was admitted for ALG treatment March 16th, but his hematopoietic function did not improve, and he developed severe disseminated infection with Klebsiella and Aspergillus. When bilateral pneumonia progressed, he was given a first course of GM-CSF (4 µg/kg/d × 14, 24-hour continuous infusion) in an attempt to raise his neutrophil count. During and after GM-CSF treatment, his neutrophil count rose, his clinical condition improved, and his lungs cleared. He was splenectomized May 27th. Since his leukocyte count remained low, he was given a second course of GM-CSF (8 µg/kg/d × 14, 24-hour continuous infusion). The numbers of neutrophils and monocytes increased, and eosinophils appeared in the circulation. At this time, there was active myelopoiesis in the marrow but no erythropoiesis and thrombopoiesis. He was discharged in good clinical condition without antibiotic treatment. When his total leukocyte and neutrophil counts again decreased, he was administered a third course of GM-CSF (4 µg/kg/d subcutaneously in two daily doses) as an outpatient. A transient rise of leukocyte and neutrophil counts was observed. In an attempt to improve hematopoietic function, a second course of ALG was administered. The patient died unexpectedly of cerebral hemorrhage October 10th without signs of infection despite a platelet count of 53 × 10^9/L.

Patient 2. A 9-year-old girl was diagnosed as having severe idiopathic aplastic anemia in May 1987 (Fig 1B). After a first course of ALG, she developed disseminated aspergillosis. She had no circulating granulocytes when she was given a first course of GM-CSF (4 µg/kg/d × 14, 24-hour continuous infusion). A minimal increase in neutrophil and monocyte numbers occurred, and her clinical condition transiently improved. However, further fungal dissemination necessitated lobectomy of the right upper lung and unilateral nephrectomy. Despite splenectomy and three further courses of GM-CSF with increasing doses up to 32 µg/kg/d × 14, her neutrophil counts never substantially increased. Her bone marrow remained severely aplastic throughout the observation period. Active treatment was discontinued, and the girl died January 18, 1988.

Patient 3. A 30-year-old woman developed severe aplastic anemia in March 1987 after 6 months treatment of rheumatoid arthritis with salazopyrin (Fig 1C). On admission for ALG treatment, septicemia with Klebsiella, Staphylococcus epidermidis, and Candida albicans was documented. Her condition did not improve after ALG, and infection disseminated. After a first course of GM-CSF (8 µg/kg/d × 14, 24-hour continuous infusion) the neutrophil count showed a minimal increase, and septic skin lesions cleared. A second course of GM-CSF (16 µg/kg/d intravenously [IV]) was started at the end of July when the patient had no circulating neutrophils. The patient remained critically ill, and GM-CSF treatment was discontinued after two days at the patients request. She died on August 4th.

Patient 4. A girl of 7 was diagnosed as having idiopathic severe aplastic anemia in February 1987 (Fig 1D). She failed to respond to two courses of ALG administered in February and in July and

© 1988 by Grune & Stratton, Inc.

Blood, Vol 72, No 6 (December), 1988: pp 2045-2047

From Preclinical and Clinical Research, Sandoz, Ltd, Basel; the Departments of Research and Internal Medicine, University Hospital Basel, Switzerland; and the Department of Hematology, St George's University Hospital, London.

Submitted April 12, 1988; accepted July 19, 1988.

Address reprint requests to Catherine Nissen, MD, Department of Internal Medicine, University Hospital Basel, Kantonsspital, CH-4031 Basel, Switzerland.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

© 1988 by Grune & Stratton, Inc.

0006-4971/88/7206-0163$3.00/0

Blood, Vol 72, No 6 (December), 1988: pp 2045-2047

2045
developed septicemia and pneumonia with *Streptococcus pyogenes*. There were no circulating granulocytes, and the bone marrow was severely aplastic. A first course of GM-CSF (16 μg/kg/d x 14, 24-hour continuous infusion) did not affect the neutrophil counts. A second course of GM-CSF at the same dose was begun on August 28th but discontinued because of progressive deterioration of the patient, who died on September 12th.

SIDE EFFECTS OF GM-CSF

GM-CSF was well tolerated at doses up to 16 μg/kg/d. Possible side effects such as fever and a rash were difficult to ascribe to either GM-CSF or to infection and its conventional treatment. However, two patients had serious complications that may or may not have been due to GM-CSF. Patient 1 developed skin eruptions resembling exanthema exsudativum multiforme while receiving low-dose subcutaneous GM-CSF treatment. The cause of his fatal cerebral hemorrhage remains unexplained. During treatment with higher doses of GM-CSF, patient 2 complained of muscle pain. Shortly after termination of a high dose course (32 μg/kg/d) she developed unexplained thrombosis of the inferior vena cava.

---

**Table 1. Patient Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Etiology of Aplastic Anemia</th>
<th>Months From Diagnosis to GM-CSF Treatment</th>
<th>White Blood Counts Before GM-CSF (per μL)</th>
<th>Maximum Increase of Leukocyte Counts After GM-CSF (per μL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>38</td>
<td>Non-A/non-B hepatitis</td>
<td>2</td>
<td>0.32 0.03 0</td>
<td>0.57 0.18 0.09</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>9</td>
<td>Idiopathic</td>
<td>3</td>
<td>1.80 0.01 0</td>
<td>0.10 0.03 0</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>30</td>
<td>Salazopyrin for rheumatoid arthritis</td>
<td>4</td>
<td>0.50 0 0</td>
<td>0.12 0 0</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>7</td>
<td>Antimalaria drugs</td>
<td>5</td>
<td>0.20 0 0</td>
<td>0 0 0</td>
</tr>
</tbody>
</table>

---

**Fig 1.** Treatment schedule with GM-CSF and peripheral white blood counts in four patients with severe aplastic anemia.
GM-CSF IN VERY SEVERE APLASTIC ANEMIA

DISCUSSION

Four patients with very severe aplastic anemia refractory to ALG were given GM-CSF. Only one responded with a substantial increase of circulating neutrophils, which allowed clearance of infection. This patient was treated early after ALG therapy and had minimal residual myelopoiesis when GM-CSF treatment was initiated. In the other three patients GM-CSF had a minimal or no effect on neutrophil counts and did not influence the fatal course of infection. Two of them were administered GM-CSF after a long period of very severe neutropenia complicated by chronic infection. Although the number of patients described is small, the results of this study in four compassionate-need cases clearly indicate that GM-CSF is not able to reestablish myelopoiesis in critically ill patients with long-standing complete aplasia after ALG treatment. However, when administered at an earlier stage to patients who have minimal residual myelopoiesis, GM-CSF is a promising adjuvant to conventional treatment of infection.

In patients with aplastic anemia of mild to moderate severity, GM-CSF may yield better results than in this nonrepresentative group with particularly severe disease. Effects of GM-CSF were transient in all instances, which indicated that GM-CSF does not alter the disease course of aplastic anemia after ALG therapy. However, it is conceivable that clearance of infection may facilitate the ongoing autologous bone marrow reconstitution originally attempted with ALG treatment.

GM-CSF treatment can be potentially dangerous. In two of the patients described, interactions of GM-CSF with the vessel wall and/or the clotting system may have contributed to bleeding and thrombosis, possibly by activating macrophages to release unphysiologic amounts of cytokines. These complications were associated with long-term or high-dose GM-CSF. Therefore, we suggest that GM-CSF treatment should be limited to the minimal effective dose and duration in aplastic anemia patients previously treated with ALG, particularly since a higher dose was not effective when an intermediate dose of 16 µg/kg/d had failed.

Since severe neutropenia is a poor prognostic factor in aplastic anemia patients treated with either immunosuppression or bone marrow transplantation, attempts to increase circulating neutrophil counts with hematopoietic lymphokines seem warranted, even in the view of potential side effects.

In conclusion, this limited experience calls attention to the fact that GM-CSF is probably ineffective in patients with long-standing end-stage aplastic anemia. Its potential benefit when administered earlier in the disease course cannot be judged before extended clinical experience from ongoing trials is available.

REFERENCES

Failure of recombinant human granulocyte-macrophage colony-stimulating factor therapy in aplastic anemia patients with very severe neutropenia

C Nissen, A Tichelli, A Gratwohl, B Speck, A Milne, EC Gordon-Smith and J Schaedelin