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Long-Term Effects of G-CSF Therapy in Cyclic Neutropenia

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CORRESPONDENCE



Long-Term Effects of G-CSF Therapy in Cyclic Neutropenia

TO THE EDITOR: Cyclic neutropenia is a rare hematologic disease that is characterized by regular oscillations in blood neutrophil counts from normal levels (absolute neutrophil count [ANC], $>1.5 \times 10^9$ per liter) to severe neutropenia (ANC, $<0.2 \times 10^9$ per liter), usually with a cycle length of about 21 days.¹ When patients with this disorder have neutropenia, they often have fever and mouth ulcers and are at risk for severe infections. Cyclic neutropenia is usually an autosomal dominant disorder caused by mutations in the gene encoding neutrophil elastase (*ELANE*).²

We first reported the use of granulocyte colony-stimulating factor (G-CSF) in patients with cyclic neutropenia 28 years ago.³ Shortly thereafter, a randomized clinical trial showed that G-CSF prevented infections in such patients.⁴ Subsequently, we followed these patients and 350 others, including 191 affected patients in 37 families, through the Severe Chronic Neutropenia International Registry (SCNIR), which records treatments, serious infections, hospitalizations, cancers, and deaths.⁵ We defined severe infection as hospitalization for infection requiring antibiotics (e.g., febrile neutropenia, pneumonia, bacteremia, and peritonitis).

The six patients in our original study are now between the ages of 38 and 94 years. Five of the

six have *ELANE* mutations. The eldest, who does not have an *ELANE* mutation, had spontaneous improvement and stopped G-CSF. The other five patients have maintained good health while receiving G-CSF injections at least three times per week for nearly 30 years. One patient has decreased bone density, and idiopathic thrombocytopenic purpura developed in another; otherwise there have been no clinically significant complications. In aggregate, the six patients have received more than 6.6 g of G-CSF over approximately 150 patient-years of observation.

Figure 1A summarizes data for 356 patients with cyclic neutropenia. Among the 239 patients who have been prospectively followed through the SCNIR (including the 6 patients from our original study), there was a consistent history of recurrent fevers, mouth ulcers, and infections before the initiation of G-CSF.³ In this group, there have been 18 episodes of severe infection (3 of which were fatal in patients who did not have substantial coexisting illness) among the patients who were not receiving G-CSF and 2 episodes among those who were receiving G-CSF (including 1 patient who also had chronic renal failure). Kaplan–Meier analysis suggests that G-CSF prevents severe infections in patients with cyclic neutropenia ($P=0.02$) (Fig. 1B). An analysis of the whole population of 356 patients, which included records from family histories, showed 36 episodes of sepsis in untreated patients, as compared with 2 in patients who were receiving G-CSF.

Adverse events have generally not limited G-CSF treatment of cyclic neutropenia. Bone pain, the most common adverse effect, usually abates with repeated injections. One patient who had never initiated treatment with G-CSF received a diagnosis of chronic myeloid leukemia that required hematopoietic stem-cell transplantation. One G-CSF-treated patient who was receiving long-

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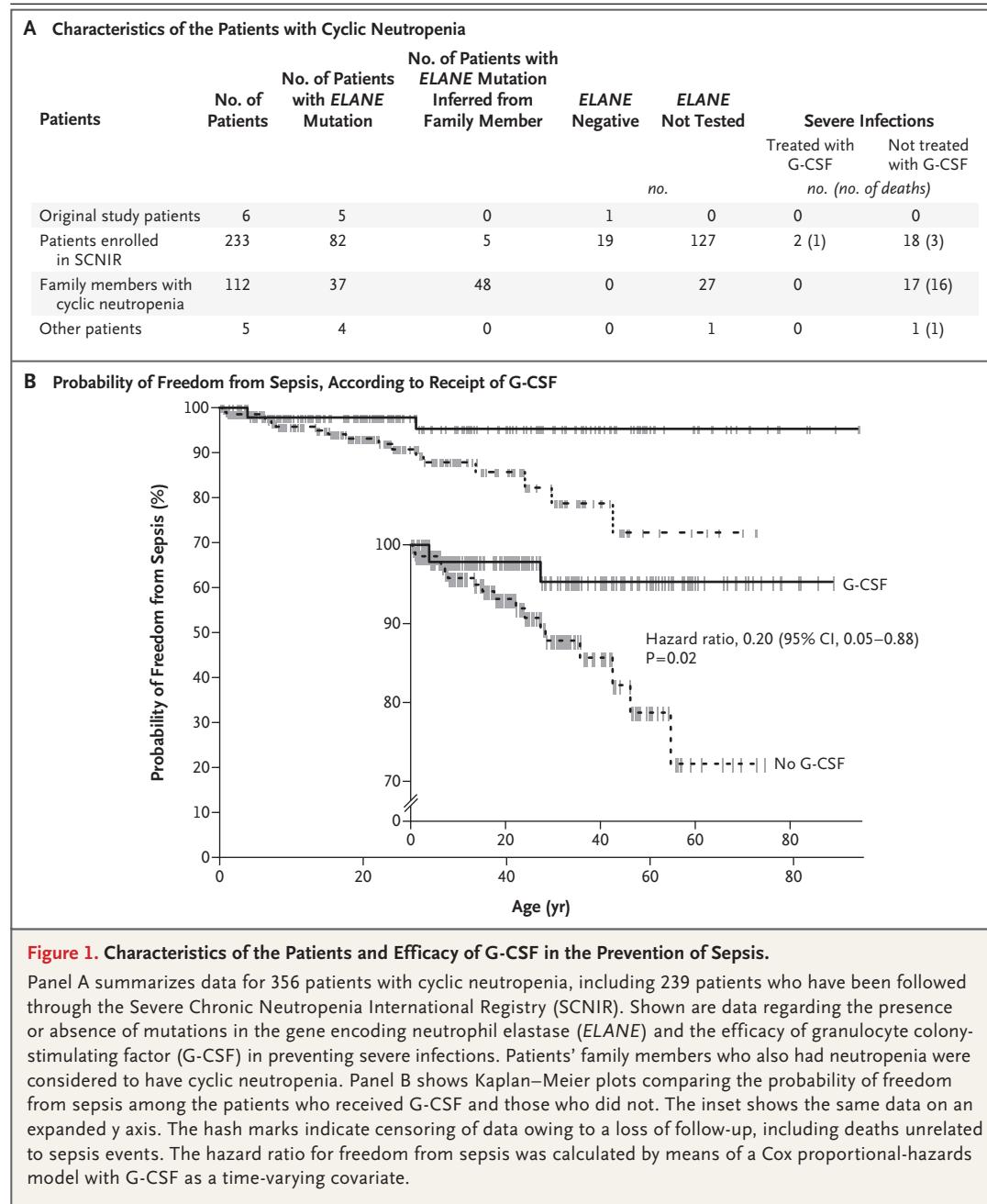


Figure 1. Characteristics of the Patients and Efficacy of G-CSF in the Prevention of Sepsis.

Panel A summarizes data for 356 patients with cyclic neutropenia, including 239 patients who have been followed through the Severe Chronic Neutropenia International Registry (SCNIR). Shown are data regarding the presence or absence of mutations in the gene encoding neutrophil elastase (*ELANE*) and the efficacy of granulocyte colony-stimulating factor (G-CSF) in preventing severe infections. Patients' family members who also had neutropenia were considered to have cyclic neutropenia. Panel B shows Kaplan-Meier plots comparing the probability of freedom from sepsis among the patients who received G-CSF and those who did not. The inset shows the same data on an expanded y axis. The hash marks indicate censoring of data owing to a loss of follow-up, including deaths unrelated to sepsis events. The hazard ratio for freedom from sepsis was calculated by means of a Cox proportional-hazards model with G-CSF as a time-varying covariate.

term chronic immunosuppressive therapy for Henoch-Schönlein purpura underwent hematopoietic stem-cell transplantation for acute myeloid leukemia (AML). Another patient underwent transplantation as a primary treatment for cyclic neutropenia. None of these patients survived.

Since our original report, we have recorded nearly 3000 patient-years of treatment with G-CSF without other hematologic complications or cases of AML in treated patients and no AML in any known family members. On the basis of these

long-term observations, we believe that G-CSF is a remarkably safe and effective treatment to prevent infections and improve the quality of life in patients with cyclic neutropenia.

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Tiotropium in Early-Stage COPD

TO THE EDITOR: Zhou and colleagues (Sept. 7 issue)¹ found that, in China, tiotropium was more effective than placebo in improving lung function and reducing the frequency of acute exacerbations of chronic obstructive pulmonary disease (COPD) among patients with disease of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 (mild) or 2 (moderate) severity. However, in China, patients with mild or moderate COPD rarely present to health care providers with respiratory symptoms and, in our experience, seldom receive medications. Therefore, the key issues are whether there is a need to introduce community-based screening to identify early-stage disease and whether an intervention in this group with medication (as compared with targeted smoking-cessation advice, for example) would prove cost-effective. Do the authors recommend the introduction of widespread lung-function screening in China, and if so, how would they select the population for screening?

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1. Zhou Y, Zhong N, Li X, et al. Tiotropium in early-stage chronic obstructive pulmonary disease. *N Engl J Med* 2017;377:923-35.

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TO THE EDITOR: Declines in the forced expiratory volume in 1 second (FEV₁) after bronchodilator use are thought to reflect long-term progressive deterioration in airway structures. However, Zhou et al. found no change at all between tiotropium and placebo over months 6 to 24 (Fig. 2A of the article, available at NEJM.org). The decline slopes were exactly parallel, with differences between the tiotropium group and the placebo group of 109 ml at month 6 and 110 ml at month 24. The FEV₁ in each group declined 60 ml over a period of 18 months of observation.

I do not think that there is some special benefit from tiotropium before month 6, because 29% of the patients in the placebo group (110 patients) and 16% of those in the tiotropium group (63 patients) withdrew before 6 months (Fig. 2C of the article). Missing data, not decline, is the likely explanation for the difference in the FEV₁ in the early months of the trial. A definitive long-term study has shown that tiotropium has