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Is G-CSF safe and useful in the treatment of infectious diseases in the non-neutropenic host?

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The relationship between leukopenia and the occurrence and outcome of infectious diseases has been known for decades. The production of myeloid cells in the bone marrow and their subsequent release into the circulation is regulated by growth factors, such as granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage CSF (Gm-CSF), macrophage CSF (m-CSF) and interleukin 3 (IL-3). Human G-CSF was cloned in 1986. It is an 18-kDa glycoprotein, encoded on chromosome 17, which differs from the location of several other growth factors, such as GM-CSF and IL-3, which are located on chromosome 5. G-CSF is secreted by monocytes/macrophages, but other cells, such as fibroblasts, vascular endothelial cells, and mesothelial cells, are also capable of producing G-CSF. G-CSF increased peripheral neutrophil counts by stimulating proliferation and shortening bone marrow transit time, thus reducing the neutrophil storage pool. The exact mechanisms of G-CSF production is not known, but there is evidence that there is an inverse relationship between G-CSF levels and neutrophil counts. Inactivation of the G-CSF gene by homologous recombination (G-CSF “knock-out” mice) causes chronic neutropenia, and treatment of these mice with *Listeria monocytogenes* resulted in more severe infections with increased mortality and absence of the development of neutrophilia [1]. Thus, G-CSF may be important not only for maintaining a sufficient number of circulating neutrophils but also for the induction of neutrophilia in infection. Besides its effect on neutrophil counts,

G-CSF can change the functional properties of neutrophils. It enhances phagocytosis and survival of neutrophils by delaying apoptosis and primes neutrophils for an oxidative burst. Furthermore, it alters the expression of several adhesion molecules on the neutrophilic membrane. A single dose of G-CSF increases the expression on neutrophils of CD64, which is low on resting neutrophils, thereby increasing neutrophil-mediated antibody-dependent cellular cytotoxicity. Additionally, G-CSF can increase the expression of CD11b/CD18, CD14, and CD66b (formerly CD67). CD11b/CD18 is essential for the adhesion of neutrophils to endothelial cells and serves as a receptor for opsonized bacteria. Neutrophilic CD14 is important for the priming of neutrophils by endotoxin. Finally, G-CSF downregulates L-selectin, which may have important implications for rolling the neutrophils along the vascular endothelium, which is the first step in adhesion. Hence, G-CSF changes the biological activity on neutrophils in many ways, and these effects may enhance the host's defense to invading microorganisms. Indeed, in patients with chemotherapy-induced neutropenia, administration of G-CSF reduced the severity and duration of the neutropenia and resulted in fewer infections and febrile episodes.

On the other hand, neutrophils may cause tissue destruction in sepsis and ischemia/reperfusion injury and have been implicated in the pathogenesis of the adult respiratory distress syndrome. Hence, the question arises whether G-CSF treatment on infections in the non-neutropenic host would do any good or be harmful. In several non-neutropenic animal models of sepsis, pretreatment with G-CSF reduced endotoxin-induced mortality and organ failure [2–4]. In small clinical studies, G-CSF appeared to have beneficial effects in patients suffering from pneumonia with severe sepsis, or with burn injuries or following major trauma [5–8]. Recent data indicate that the effects of G-CSF on the inflammatory host response are more complex than simply boosting the number of primed circulating neutrophils. It was shown by Hartung et al. [9] that, following in vivo administration of G-CSF to hu-

mans, ex vivo stimulation of whole blood resulted in a reduction of tumor necrosis factor alpha generation and an increase in the production of anti-inflammatory cytokines. However, in a study of human endotoxemia, administration of G-CSF 12 h prior to endotoxin challenge upregulated both the pro- and anti-inflammatory responses [10]. These seemingly contradictory results can be explained in part by differences in the effects of G-CSF when administered at various time points relative to endotoxin administration. In a recent study, we demonstrated that when G-CSF was administered 2 h prior to induction of endotoxemia in humans both the pro- and anti-inflammatory cytokine responses were enhanced, whereas when administered 24 h prior to endotoxin challenge, G-CSF reduced pro-inflammatory cytokine release though the anti-inflammatory responses were similar or increased [11]. In this study, de-

spite an increase in the release of pro-inflammatory cytokines, G-CSF prevented endotoxin-induced granulocyte accumulation in the lungs, most likely due to shedding of L-selectin from the neutrophilic membrane. It should be possible to find out whether G-CSF is beneficial or harmful in sepsis in the non-neutropenic host from well-designed clinical studies. The study reported by Gross-Weege et al. in this issue of *Intensive Care Medicine* indicates that G-CSF treatment of patients with systemic inflammatory response syndrome (SIRS) and sepsis, though increasing the circulating leukocyte count, was well tolerated and did not cause pulmonary injury. Hence, G-CSF treatment of patients with sepsis and SIRS does not seem to cause neutrophil-related tissue damage. The question whether G-CSF is beneficial in non-neutropenic infectious disease can now be answered initiating larger, controlled clinical studies.

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