Healing of Chronic Leg Ulcers in the Hemoglobinopathies With Perilesional Injections of Granulocyte-Macrophage Colony-Stimulating Factor

To the Editor:

Chronic leg ulcers in patients with inherited hemoglobin disorders are a cause of pain, repulsive appearance, disability, absence from or inability to work, and are a considerable cost. Conventional treatment is often disappointing. Their cause is complex. In most instances, they start as superficial abrasions resulting from minor trauma, scratches, local friction, or insect bites. Then, they expand rapidly because of the associated inadequate oxygen delivery, local edema resulting from venous insufficiency and possibly heart failure, local infections, and inappropriate medical procedures. Other factors that have been implicated include the decreased red blood cell deformability and the adherence of young reticulocytes to the vascular endothelium, which may cause obstruction of the blood flow and severe cutaneous ischemia. Fetal hemoglobin (HbF) may also interfere both by inhibiting the sickling process and through its high oxygen affinity. Chronic leg ulcers do not heal easily. Avoidance of trauma and venous congestion along with meticulous cleanliness and good care of minor abrasions are a prerequisite for preventing further expansion. Other measures that have been proposed to date include increasing the total hemoglobin with blood transfusions, improving the blood flow with pentoxifylline, preventing local thrombosis with antithrombin III, supporting the healing of the ulceration with peptide matrix, improving local oxygenation by flushing the area with oxygen, and preventing HbS polymerization through the increase of HbF with hydroxyurea, recombinant human erythropoietin (r-huEPO), or arginine butyrate (reviewed by Eckman1).

In this letter, we report the beneficial effects obtained with local injections of granulocyte-macrophage colony-stimulating factor (GM-CSF; Mielogen-Molgramostin; Schering-Plough) in one patient with sickle cell disease and three patients with thalassemia whose chronic leg ulcers could not heal despite the large variety of treatments applied over the past years, including the topical impregnation with this factor, as suggested by Pieters et al2 a few years ago. Topical injections of GM-CSF have been successfully applied for the healing of chronic leg ulcers of other etiologies.3,4 Before starting, the procedure was explained to the patients and was fully accepted. The GM-CSF solution (300 µg) was injected in small portions (usually 4 to 8) through a 26-gauge needle within the margins of the ulcers, twice per week over 2 months. In some instances, a small quantity of the solution was gently applied over the open wound. Standard care was not neglected. On the occasion, the levels of interleukin-6 (IL-6), IL-1, tumor necrosis factor (TNF), IL-8, and transforming growth factor β (TGFβ), 24 hours before and 24 hours after the administration of GM-CSF, were also determined using an enzyme-linked immunosorbent assay (ELISA) technique.

Patient no. 1 was a 28-year-old man with compound Hb S/β-thalassemia (CD39) who had a chronic painful ulcer in the right ankle (3.5 × 2.5 cm) over the last 2 years. The patient had received hydroxyurea since 1995. His total Hb values varied between 8.0 and 9.0 g/dL; 33% of it was HbF. Patient no. 2 was a 49-year-old woman with thalassemia major (IVS1-nt110/CD39) and a deep ulcer in her left ankle (2.0 × 1.5 × 1.2 cm) over the last 25 years. She was on regular transfusions, maintaining a pretransfusion Hb level of 8.0 g/dL. Patient no. 3 was a 32-year-old woman with thalassemia major (IVS1-nt110/CD39). She had never complied with regular treatment and received sporadic blood transfusions, keeping a pretransfusion Hb level of approximately 6.0 g/dL. This woman had two large ulcers in her right leg (7.0 × 6.5 and 5.0 × 4.5 cm) and one ulcer in the ankle area of the left (3.0 × 3.0 cm). Patient no. 4 was a 38-year-old woman with thalassemia intermedia (IVS1-nt1/nt 1570) who had a painful ulcer in her right leg for the past 20 years (1.5 × 0.5 cm). Her usual total Hb varied around 8 g/dL; 8.0% of it was HbF.

Fig 1. The deep chronic leg ulcer in patient no. 2 (A) before and (B) at the end of therapy.
In conclusion, subcutaneous perilesional injections of GM-CSF may play an important role in the healing of chronic ulcers in patients with hemoglobinopathies, especially when these have persisted over several years despite intensive treatment, as in the case of the patients of this report. Treatment is relatively well-tolerated and the associated side effects (pain and fever) respond easily to mild analgesics. The activity of GM-CSF is pleiotropic. It includes local attraction of neutrophils, hence improving the clearance of bacteria and debris, promotion of neovascularization, enhancement of keratinization, and acceleration of the formation of new tissue.

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REFERENCES

TT Virus: A Mother-to-Child Transmitted Rather Than Bloodborne Virus

To the Editor:

An unenveloped single-stranded DNA virus, TT virus (TTV), was initially identified as a transfusion-transmissible agent reported to be associated with non-A-G hepatitis by Nishizawa et al. At present, transfusion of blood and blood products is supposed to be a major route of TTV transmission.

In the recent report, Okamoto et al developed the TTV detection polymerase chain reaction (PCR) system by exchanging the primers from RD037,038,052 to NG059,061,063, and showed that 12% of healthy blood donors were positive for TTV in Japan. Whereas several investigators have used their own original primers sets located in a more homogeneous region of the TTV sequence, many investigators have used Okamoto et al’s primers in their study concerned with TTV.

More recently, Takahashi et al reported a newly developed PCR diagnostic system that is 10 to 100 times more sensitive than Okamoto et al’s method and detected TTV DNA in 92 (92%) of 100 individuals who visited their hospital for health screening. We used this method and measured TTV DNA in various samples as indicated in Table 1. Paired samples (upper half of Table 1) were obtained from mothers admitted to our hospital for delivery of infants this year. Serum samples of infants or children (bottom half of Table 1) were obtained from individuals during outpatient visits for minor transient diseases or health checks this year. Informed consent was obtained from all of the individuals.

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