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A short course of granulocyte–colony-stimulating factor to accelerate wound repair in patients undergoing surgery for sacrococcygeal pilonidal cyst: proof of concept

CARLO MARIA FRONTICELLI BALDELLI[1], MARCO RUELLA[2,3], STEFANO SCUDERI[1], MANUELA MONNI[1], ROBERTO PASSERA[4], PAOLA OMEDÈ[5] & CORRADO TARELLA[2,3]

[1]*VI Division of General Surgery, AOU San Giovanni Battista, University of Torino, Italy,* [2]*Division of Hematology and Cell Therapy, AO Ordine Mauriziano, University of Torino, Italy,* [3]*Molecular Biotechnology Center (M.B.C.), University of Torino, Italy,* [4]*Division of Nuclear Medicine, and* [5]*Division of Hematology, AOU San Giovanni Battista, University of Torino, Italy*

Abstract

Background aims. Stem cells, namely easily accessible bone marrow-derived cells (BMC), are reportedly capable of tissue repair in different damaged organs and might favor wound healing. The present study was undertaken to evaluate the feasibility and safety of BMC mobilization induced by granulocyte–colony-stimulating factor (G-CSF) in patients undergoing surgery for sacrococcygeal pilonidal cysts (SPC). To evaluate the possible clinical benefit of G-CSF in reducing the time to complete resolution, a comparison with a control group receiving surgery without G-CSF was performed. *Methods*. Eight patients with complex SPC were included in this prospective trial. Patients were treated with G-CSF (5 μg/kg b.i.d.) for 3 consecutive days; standard surgical exeresis of the pilonidal cyst was scheduled on day 2 of mobilization. Mobilization was assessed in terms of circulating $CD34^+$ cells and granulocyte–macrophage colony-forming unit (CFU-GM) progenitors. *Results*. Mobilization of $CD34^+$ cells and CFU-GM occurred in all patients, along with a marked increase in white blood cells (median peak value 28 435/μL, day 3). G-CSF was well tolerated and no adverse events occurred. All patients received the planned surgical treatment without any complications. Interestingly, the G-CSF group patients had a median time to resolution (117 days, range 110–130) significantly shorter than control patients (145 days, range 118–168) ($P = 0.034$). *Conclusions*. G-CSF administration, along with BMC mobilization, is feasible and well tolerated in patients undergoing surgery for SPC; clinical results compare favorably with those observed in controls not receiving G-CSF; the results suggest the potential use of G-CSF as an additional treatment to accelerate wound healing in patients undergoing surgery.

Key Words: *bone marrow-derived stem cells, granulocyte–colony-stimulating factor, mobilization, sacrococcygeal pilonidal cyst, surgery, wound repair*

Introduction

Wound healing is a complex process that involves different cell populations, the extracellular matrix, growth factors and cytokines. The whole process of wound healing involves many phases: coagulation, hemostasis, inflammation, proliferation and wound remodeling with scar tissue formation (1). Various studies have shown that cytokines and chemokines may favor the regeneration of damaged tissues, hence promoting wound healing. Chemokines induce the recruitment of different cell types to the wound site, thereby contributing to healing. Via activation of specific receptors, mediators initiate intracellular downstream mechanisms, both cell migration and proliferation, and the clearance of cell debris. Platelets, macrophages, neutrophils, fibroblasts and keratinocytes release growth factors initiating a downstream mechanism to promote important processes in wound healing (2,3). In particular the infiltration of leukocytes in the injury site is important for antimicrobial functions, extracellular matrix degradation and stimulation of angiogenesis through the production of transforming growth factor (TGF)-β and Vascular endothelial growth factor (VEGF) (4). Indeed, previous studies have shown that a reduced leukocyte wound infiltration is associated with delayed tissue repair (5,6). Moreover, the action of stem cells, in particular the easily accessible bone marrow (BM)-derived cells (BMC), may be involved in tissue regeneration by transdifferentiation into a variety of

Correspondence: **Corrado Tarella**, MD, SCDU Ematologia e Terapie Cellulari, AO Ordine Mauriziano, Umberto I, University of Torino, L. go Turati 62, 10128, Torino, Italy. E-mail: corrado.tarella@unito.it

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adult cell types, including epithelial and endothelial cells. Indeed, BMC have an established role in neovascularization of ischemic tissues (7,8). Lastly, cytokines including granulocyte–colony-stimulating factor (G-CSF) might stimulate the local activation of mesenchymal stromal cells (MSC) (9–11).

Sacrococcygeal pilonidal cyst (SPC) seems to be a disease particularly suitable for exploiting the regenerating potential of cytokines and/or BMC. SPC is a disease occurring in adolescents and young adults (12,13) and it is currently considered to be an acquired disease caused by the penetration of loose hairs and cellular debris into the skin. This generates a subcutaneous cavitation that may remain without communication with the external surface of the skin, often asymptomatic for months to years. However, abscess formation and fistulas can develop causing pain, swelling, burning, purulent drainage and extreme discomfort to the patient. SPC can acquire the features of a chronic disease with recurrences, significant pain and multiple micro-abscesses that eventually migrate deeper into the subcutaneous tissue (complex SPC) (14–19).

The most direct treatment of SPC is surgery, particularly for patients presenting with an abscess. Complete surgical excision and drainage with healing by primary intention is the most common procedure. For patients with complicated and recurrent SPC, the standard approach is not satisfactory because surgical excision could be extensive, leading to the formation of a deep cavity. This wound is intentionally left open and free to heal by second intention, following the laying open technique (20–22). The wide excision performed for a complex pilonidal cyst requires approximately 6 weeks to heal by secondary intention, with some cases requiring up to 13 weeks or more (23–25). After granulation healing, complete cutaneous regeneration with scar formation is reached after 5–6 months, with some patients requiring up to 12 months before scar formation, with prolonged discomfort and a marked decrease in quality of life (26,27). After surgery, wound healing is a challenging clinical problem and efforts have been made regarding new therapeutic approaches for reducing the time to wound healing. The development of additional treatments for SPC is viewed with increasing interest, with the aim to reduce the time required for both wound granulation healing and cutaneous regeneration. Thus complex SPC requiring wide surgical excision is an ideal setting for verify the potential benefit of BMC and/or cytokines in stimulating tissue regeneration and wound healing.

A non-invasive and effective approach to obtaining large quantities of BMC in the peripheral blood, and possibly in the lesion site, is mobilization by cytokines. G-CSF is a member of a family of secreted glycoproteins that act on both neutrophils and granulocyte precursors in the BM to promote their differentiation, proliferation and maturation. Moreover, G-CSF induces the mobilization of neutrophils from the BM pool into the peripheral blood circulation, and controls neutrophil dynamics in the blood (28). G-CSF is used routinely in hematologic malignancies for BMC transplantation purposes and has potent mobilization capacity in healthy subjects (29,30). G-CSF-induced BMC mobilization has been employed recently in non-hematologic diseases with the aim of stimulating the regeneration of injured and damaged tissues. The procedure proved to be feasible and safe overall, as reported in various clinical settings, including patients with end-stage liver disease, amyotrophic lateral sclerosis and infected diabetic foot ulcers (31–34). G-CSF has also been used in combination with surgery in high-risk colorectal cancer to improve recovery (35) and to prevent immune-inflammatory dysfunction associated with major surgery (36). The safety, feasibility and efficacy of autologous stem cells given for non-hematologic tissue regeneration have been reported in various series, including patients with Crohn's fistulas (37,38). Recent work by Yuan *et al.* (39) demonstrated accelerated surgical wound healing using a hemostatic gauze scaffold loaded with nanoparticles containing sustained-release G-CSF. Moreover, Simsek *et al.* (40) have demonstrated the effectiveness of the controlled slow-release granulocyte–monocyte colony-stimulating factor (GM-CSF) system in burn wound healing. In rats, local stromal-derived factor (SDF)-1 and/or systemic G-CSF can effectively increase BMC homing to sites of traumatic injury in an additive way and improve wound healing (41).

Based on these observations, a single-center, open-label, pilot study was performed to evaluate the safety and feasibility of G-CSF-induced BMC mobilization in order to accelerate wound healing in patients with complex and recurrent SPC treated with the classical surgical approach.

Methods

The trial was designed as a single-center, open-label, case-control pilot study (EudraCT number 2005-004590-24) consisting of 3 days of treatment with G-CSF with surgery for complex SPC on day 2. The aims of the study were to define both the feasibility and safety of the procedure and to evaluate possible clinical improvement, with particular interest regarding the time required for complete cutaneous epithelization. The study group was compared with a matched control group for evaluating the overall outcome and the time to complete wound healing.