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Randomized Prospective Controlled Trial of Recombinant Granulocyte Colony-Stimulating Factor as Adjunctive Therapy for Limb-Threatening Diabetic Foot Infection

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Adult diabetic patients admitted to our Diabetes Center from September 1996 to January 1998 for severe, limb-threatening foot infection were consecutively enrolled in a prospective, randomized, controlled clinical study aimed at assessing the safety and efficacy of recombinant human granulocyte colony-stimulating factor (G-CSF) (lenograstim) as an adjunctive therapy for the standard treatment of diabetic foot infection. Forty patients, all of whom displayed evidence of osteomyelitis and long-standing ulcer infection, were randomized 1:1 to receive either conventional treatment (i.e., antimicrobial therapy plus local treatment) or conventional therapy plus 263 μg of G-CSF subcutaneously daily for 21 days. The empiric antibiotic treatment (a combination of ciprofloxacin plus clindamycin) was further adjusted, when necessary, according to the results of cultures and sensitivity testing. Microbiologic assessment of foot ulcers was performed by both deep-tissue biopsy and swab cultures, performed at enrollment and on days 7 and 21 thereafter. Patients were monitored for 6 months; the major endpoints (i.e., cure, improvement, failure, and amputation) were blindly assessed at weeks 3 and 9. At enrollment, both patient groups were comparable in terms of both demographic and clinical data. None of the G-CSF-treated patients experienced either local or systemic adverse effects. At the 3- and 9-week assessments, no significant differences between the two groups could be observed concerning the number of patients either cured or improved, the number of patients displaying therapeutic failure, or the species and number of microorganisms previously yielded from cultures at day 7 and day 21. Conversely, among this small series of patients the cumulative number of amputations observed after 9 weeks of treatment appeared to be lower in the G-CSF arm; in fact, only three patients (15%) in this group had required amputation, whereas nine patients (45%) in the other group had required amputation ($P = 0.038$). In conclusion, the administration of G-CSF for 3 weeks as an adjunctive therapy for limb-threatening diabetic foot infection was associated with a lower rate of amputation within 9 weeks after the commencement of standard treatment. Further clinical studies aimed at precisely defining the role of this approach to this serious complication of diabetes mellitus appear to be justified.

Foot and lower-limb infections are major causes of morbidity and mortality in diabetic patients. Besides being responsible for about 20% of all hospitalizations related to diabetes (2), these lesions have consistently been ascertained to be significant risk factors for nontraumatic lower-extremity amputation (10), 45 to 60% of which have been estimated to occur in diabetic patients (5). The effects of peripheral neuropathy, peripheral vascular disease, and infection often combine to predispose an individual to ulcer formation and its serious complications.

The incidence and severity of infections occurring in diabetic patients are also enhanced by the dysfunction of the antibacterial defense system associated with diabetes mellitus; in particular, defects in neutrophil function can be observed, and deficiencies in leukocyte adherence, chemotaxis, phagocytosis, superoxide production, and intracellular killing have been described (15, 16, 21).

Granulocyte colony-stimulating factor (G-CSF) is a glycoprotein that specifically regulates survival, proliferation, and differentiation of neutrophilic granulocyte precursors and stimulates the function of mature neutrophils (20). This endogenous hemopoietic factor is able to actively stimulate the function of both normal and defective neutrophils (19) both in vitro and in vivo (13). G-CSF is widely used as an adjunctive treatment to chemotherapy in patients with oncologic neutropenia, as well as in patients with myelosuppression following bone marrow transplantation and several other conditions (e.g., severe chronic neutropenia, acute leukemia, aplastic anemia, and myelodysplastic syndromes) (23). In nonneutropenic subjects, G-CSF administration determinates neutrophilia and affects the functional activity of mature polymorphonuclear leukocytes. Studies on the administration of G-CSF before experimental infection of nonneutropenic animals have repeatedly shown significant benefits after administration of G-CSF either alone or in combination with antibiotics (7, 8, 17), supporting the hypothesis that G-CSF could have a favorable impact on the treatment of serious bacterial and fungal infections in nonneutropenic patients (8, 14, 17). In this setting the rationale for using G-CSF in combination with antibiotics is based on studies showing that the stimulation of neutrophil production can

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enhance the inflammatory response and lead to a better outcome of infection (17). In a prospective, randomized, controlled clinical study with nonneutropenic diabetic patients with foot infection, Gough et al. (11) have reported a better clinical outcome in patients treated with G-CSF.

The burden of amputation is high in diabetic patients with limb-threatening foot infection. In this light, we performed a controlled clinical study principally aimed at evaluating the efficacy and safety of systemic G-CSF in the clinical setting described above.

(A preliminary report of this study has been presented previously [F. de Lalla, G. Pellizzer, M. Strazzabosco, Z. Martini, G. DuJardin, L. Lora, P. Fabris, P. Benedetti, and G. Erle, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. MN-31, 1998].)

MATERIALS AND METHODS

From September 1996 to January 1998, adult diabetic patients of both sexes admitted to the Diabetes Center of our hospital for severe, limb-threatening foot infection were consecutively enrolled in a prospective, randomized, controlled clinical study to test the safety and efficacy of G-CSF as an adjunctive agent for the standard treatment of foot infection. Exclusion criteria were as follows: treatment with antibiotics for any proven or suspected infection during the 2 weeks preceding patient recruitment; superficial, non-limb-threatening infection; patient's refusal of consent; immediate risk of major above-ankle amputation for critical leg ischemia (ankle systolic blood pressure less than 50 mm Hg or ankle /brachial blood pressure index less than 0.5) (11); any critical condition with immediate risk of death; renal impairment (serum creatinine level, >1.6 mg/dl); history of allergic reactions to either ciprofloxacin or clindamycin; or any contraindication to G-CSF administration (e.g., myelodysplasia or myeloid leukemia).

At enrollment, the baseline evaluation included the following: demographic data, duration of diabetes, Wagner classification of the ulcer (22), staging for osteomyelitis according to Cierny et al. (6), ankle/brachial blood-pressure index, and vibration perception threshold determination for the classification of either vasculopathy or neuropathy. Foot infection was classified as either limb threatening or life threatening by taking into account both the clinical characteristics of the ulcer(s) and the extension and severity of infection (4). Accordingly, severe limb-threatening infection was defined by the presence of full-thickness ulcer, more than 2 cm of cellulitis with or without lymphangitis, bone or joint involvement, and systemic toxicity.

Diagnosis of osteomyelitis relied mainly on detection of exposed bone or positive probe on bone testing (12); plain radiography and scintigraphy (with technetium-99m- and indium-111-labeled leukocytes) were performed when bone palpation was impossible and when better evaluation of the extent of bone involvement was required.

Since one of the most crucial shortcomings of studies of diabetic foot infection is the comparability of cases, in order to obtain a reliable comparison of the extent and severity of infection, information on the following features was collected at enrollment: local infection signs, pus discharge, crepitation, sinus, cellulitis >2 or <2 cm, ischemia, number of ulcers, necrosis, fasciitis, abscess, infection of soft tissues extending far beyond the site of ulcer, lymphangitis, distant sites of infection, polymicrobial infection, isolation of gram-positive or gram-negative organisms and anaerobes, fever, leukocyte count >10,000 or <3,000/mm^3, blood culture, and probe to bone.

Patients were randomized (1:1) to receive either conventional treatment alone (local treatment plus systemic antibiotic therapy) or the same treatment plus glycosylated recombinant human G-CSF (rHuG-CSF; lenograstim). Confidential informed consent for G-CSF administration was obtained.

Local treatment consisted of careful debridement of soft tissues and bone at enrollment and, thereafter, of daily inspection, cleaning with sterile water, disinfection with povidone iodine, surgical removal of necrotic tissues whenever required, and occlusive dressing of foot lesions. The local treatment provided to the study patients was the same provided to any other patient attending our institution with a similar foot condition. Empiric antibiotic therapy was based on the combination of ciprofloxacin and clindamycin, according to the consensus standard (4). Intravenous therapy (ciprofloxacin at 400 mg twice daily plus clindamycin at 900 mg three times daily) was administered in the case of more serious infection (e.g., when either febrile disease, extended cellulitis with lymphangitis, incomplete debridement of necrotic tissues, or extensive bone involvement had been observed), and the therapy was then switched to the oral route when appropriate. Oral regimen (ciprofloxacin at 750 mg twice daily plus clindamycin at 300 mg four times daily) was considered appropriate for less critical patients (4, 9). Adjustments to treatment were performed, when indicated, on the basis of microbiologic cultures and sensitivity testing. G-CSF was administered subcutaneously at a dosage of 263 μg daily for 21 days to the patients randomized to receive conventional plus adjunctive therapy. In the course of treatment, G-CSF was temporarily reduced to 175 μg if the neutrophil count was observed to exceed 35,000 cells/mm^3, while it was discontinued if the neutrophil count was over 50,000 cells/mm^3 and further readministered only when the count fell to less than 35,000 mm^3. A 3-week duration of G-CSF treatment was considered to be required for a real improvement of limb-threatening, chronically infected lesions, the main features of which were necrosis and osteomyelitis.

All patients required insulin administration by means of either continuous intravenous infusion or a multiple-dose regimen.

Clinical and serum biochemical parameters (creatinine, aspartate aminotransferase level, alanine aminotransferase level, erythrocyte sedimentation rate, C-reactive protein level) were assessed weekly for the first 21 days and every 2 weeks for 6 weeks thereafter. Blood glucose levels were monitored daily; the blood cell count was also determined daily for the first week and on alternate days for 2 weeks thereafter.

Because of the potential bias linked to the adjunctive therapy, foot lesions were clinically monitored and evaluated by the same investigator, who was not informed about the study randomization. The "blind" clinician was the plastic surgeon; his only task was to fill out a form weekly; the following main characteristics of the lesion were listed and scored on the form: degree of debridement, conditions of the granulation tissue, state of the margins of the ulcer, and width of the ulcer. At each clinical observation, a picture was taken to allow the comparison through both the picture and the filled-out form of the actual lesion with that of the previous week. The blinded clinician had no access to any medical record except the form and the pictures. At the end of treatment, the entire sequence of pictures was reevaluated with the listed and scored clinical data for the final evaluation.

Microbiologic assessment of ulcers was performed at enrollment and at days 7 and 21 thereafter. Following surgical debridement, scrubbing, and cleansing with sterile gauze soaked in sterile saline, a superficial swab specimen and a deep-tissue biopsy specimen were collected simultaneously from the deep base of the ulcer; samples were inserted into a transport tube containing solid medium suitable for both aerobic and anaerobic microorganisms (Venturi Transystem, Pbi, Copan, Italy) and delivered to the laboratory for immediate processing (within 15 min after collection). Disk diffusion sensitivity testing was performed with clinical isolates according to the guidelines of the British Society for Antimicrobial Chemotherapy (3).

Patients were monitored over 6 months, namely, for the average healing time estimated for a limb-threatening foot infection (1). Nevertheless, because the purpose of the study was aimed at the acute-phase treatment, the major endpoints were assessed at weeks 3 and 9 as (i) cure, defined as complete closure of the ulcer without signs of underlying bone infection; (ii) improvement, defined as eradication of pathogens (swab or tissue culture negative) coupled with marked or complete reduction of cellulitis but incomplete closure of the ulcer or closure of the ulcer but persistent signs (local pain, erythema, and swelling) of active underlying bone infection; or (iii) failure, defined as the absence of any clinical improvement irrespective of cultures results. Amputation, defined as any excision of bone segment, was considered failure when its indication was due to persistent infection after 15 days of appropriate antibiotic therapy and local treatment.

An indication for amputation was assessed by the members of the orthopedic staff of our hospital; no one of them had been directly involved in this study or, as a consequence, had been blinded as to the treatment.

Statistical analysis was performed by a one-sample *t* test and by the Mann-Whitney U test for the comparison of continuous and categorical variables, respectively. All statistics were performed by using the Statistics package Statistica for Windows (version 5.0).

RESULTS

Forty eligible patients were recruited over 14 months, and all of them could be evaluated for both the efficacy and the safety of the therapeutic regimens studied. It is noteworthy that no withdrawal of study medication due to side effects was required and all patients strictly adhered to the protocol.

TABLE 1. General and baseline features of patients enrolled

Characteristic[a]	G-CSF group (n = 20)	Control group (n = 20)	P
No. of males/no. of females	16/4	14/6	
Mean age (yr [range])	56.6 ± 8.6 (42–74)	59.8 ± 9.6 (44–85)	0.27
Mean duration of diabetes (yr [range])	15.6 ± 8.6 (1–46)	18.5 ± 8.6 (12–30)	0.22
No. (%) of patients with:			
Wagner grade 3	13 (65)	14 (70)	0.12
Wagner grade 4	7 (35)	6 (30)	0.12
No. (%) of patients with the following type of lesion:			
Neuropathic	13 (65)	14 (70)	0.12
Ischemic	2 (10)	0	0.31
Mixed	5 (25)	6 (30)	
Mean ± SD ABI	0.96 ± 0.34	1.29 ± 0.50	0.04[b]
Mean ± SD VPT	35.8 ± 14.6	43.2 ± 0.47	0.19
No. of patients with WBC count >10,000/mm^3	1	5	0.08
Mean ± SD neutrophil count/mm^3	7,800 ± 3,500	8,300 ± 3,500	0.21
No. of patients with ESR >70 mm/h	11	13	0.52
No. of patients with positive blood cultures	0	2	0.15
No. (%) of patients with osteomyelitis	20 (100)	20 (100)	0.16
No. of patients with life-threatening infection	0	2	0.15

[a] ABI, ankle/brachial blood-pressure index; VPT, vibrator perception threshold; WBC, leukocyte; ESR, erythrocyte sedimentation rate.
[b] Not relevant, since all values were >0.8.

The baseline demographic and general characteristics of the patients in both study groups were comparable, as reported in Table 1. All patients had infections that fulfilled the definition of limb-threatening infection. Two patients receiving only standard treatment had life-threatening infections. At enrollment, the clinical features of foot lesions, as described above, also appeared to be comparable in the two patient groups (Table 2). Osteomyelitis, classified as 2Bsl to 4Bsl (6), was diagnosed in all patients recruited. Bone involvement could be detected in all patients: 10 toes, 6 metatarsal segments, 3 toe-metatarsal bone, and 1 malleolus in the treatment group and 11 toes, 6 metatarsal segments, and 3 toe-metatarsal bone, in the control group.

The probe was positive for all patients; an indium-labeled leukocyte scan coupled with a technetium-99m bone scan was performed for 15 patients (9 patients in the treatment group and 6 controls) for confirmation of the probe results. Six and four patients in the treatment and control groups, respectively, had visible bones at enrollment.

Visible infected wet gangrene could be recorded in eight cases patients (four patients in each arm), all involving toes. In no patient was vascular reconstruction necessary during the study period.

The microorganisms isolated from ulcers in the course of follow-up are reported in Table 3. At enrollment, 74 strains overall were isolated, 41 (55%) of which were from the G-CSF group and 33 (45%) were from control patients. For the G-CSF and control groups, gram-positive organisms were recovered from 25 and 24 patients, respectively, gram-negative organisms were recovered from 4 and 5 patients, respectively, and anaerobes were recovered from 12 and 4 patients, respectively. Polymicrobial infection was detected in 14 (70%) patients treated with G-CSF and 10 (50%) patients under standard treatment. At day 21 after therapy commencement, 11 isolates were recovered from the G-CSF group and 8 were recovered from the control patients. At this time no anaerobic strain could be isolated, and 15 of the 19 (79%) isolates were gram-positive isolates, being mainly represented by staphylococci (12 of 15 [80%]), most of which (11 of 12 [92%]) were

TABLE 2. Clinical characteristics of lesions at enrollment

Characteristic	G-CSF group (n = 20)	Control group (n = 20)	P
No. of ulcers/patient (mean ± SD)	1.4 ± 0.6	1.4 ± 1.0	0.93
No. (%) of patients with more than one ulcer	6 (30)	5 (25)	0.72
No. of isolates/patient (mean ± SD)	2.05 ± 1.2	2.30 ± 1.6	0.59
No. (%) of patients with polymicrobial infection	14 (70)	10 (50)	0.20
No. (%) of patients with cellulitis diameter >2 cm	10 (50)	15 (75)	0.10
No. (%) of patients with probing to bone positive	20 (100)	20 (100)	1.00
No. (%) of patients with an abscess	1 (5)	3 (15)	0.29
No. (%) of patients with ulcer diameter >2 cm	13 (65)	11 (55)	0.51

TABLE 3. Bacterial isolates at enrollment and after 3 weeks of treatment

Microorganism[a]	No. (%) of isolates			
	Enrollment		Wk 3	
	G-CSF group (n = 20)	Control group (n = 20)	G-CSF group (n = 20)	Control group (n = 20)
Gram-positive aerobes				
CNS-MS	1	5		
CNS-MR			5	3
SA-MS	8	8	1	
SA-MR	2	2	2	1
Corynebacterium spp.	2	2	2	1
Enterococcus spp.	7	3		
Streptococcus agalactiae	4	4		
Streptococcus pyogenes	2			
Gram-negative aerobes				
Pseudomonas aeruginosa			1	1
Escherichia coli	4	1		2
Proteus mirabilis		2		
Enterobacter aerogenes		1		
Klebsiella pneumoniae		1		
Anaerobes				
Bacteroides fragilis	5	2		
Fusobacterium spp.	2	1		
Peptostreptococcus spp.	4	1		
Prevotella bivia	1			
Total	41 (55)	33 (45)	11 (58)	8 (42)

[a] CNS-MS, methicillin-sensitive, coagulase negative staphylococci; CNS-MR, methicillin resistant, coagulase negative staphylococci; SA-MS, methicillin sensitive *Staphylococcus aureus*; SA-MR, methicillin resistant *Staphylococcus aureus*.

methicillin resistant. During the entire follow-up, no statistical differences were found between the two groups in terms of either species or the number of isolates per species.

The mean numbers of isolates per patient yielded in the course of follow-up were 0.95 and 1.05 at day 7 for the G-CSF treatment and standard treatment groups respectively, and 0.55 at day 21 for both groups, confirming that the microbiologic features of ulcer yields were comparable between the two groups even in terms of both global yield and organism type.

Following sensitivity testing, the conventional empiric antibiotic therapy had to be adjusted for 24 of 40 patients (60%), 12 in each arm. The median duration of antibiotic therapy was 62.5 days (range, 30 to 163 days; mean duration, 68.9 ± 29.2 days) in the G-CSF group and 60 days (range, 30 to 119 days; mean duration 58.7 ± 23.7 days) in the control group (P = 0.23). Oral therapy (ciprofloxacin combined with clindamycin) could be administered to 13 of 20 (65%) patients in the G-CSF group and to 11 of 20 (55%) patients under standard treatment; intravenous therapy had to be given to 7 of 20 (35%) patients treated with G-CSF and to 9 of 20 (45%) patients in the other study arm (P = 0.5).

Glucose metabolism could be satisfactorily controlled in all patients. All patients were regularly attending the outpatient diabetic clinic, and they showed satisfactory glycemic control at enrollment, as deduced from the glycate hemoglobin levels.

No side effects specifically due to rHuG-CSF were recorded. The dosage of rHuG-CSF had to be reduced in two patients because of an absolute neutrophil count higher than 35,000 cells/mm^3, but the neutrophil count exceeded 50,000 cells/mm^3 in none of the patients. The mean counts detected in the rHuG-CSF group and the standard treatment group were 25,200 ± 3,500 and 6,500 ± 4,400 cells/mm^3, respectively (P = 0.002).

No patient was cured during the first 3 weeks of treatment, although improvement was observed in 12 of 20 (60%) and 9 of 20 (45%) patients belonging to the G-CSF group and the standard treatment group, respectively (P was not significant). After 3 weeks of treatment, one amputation (5%) occurred in the G-CSF group and five (25%) had to be performed in the control group (P = 0.08). Failure rates, which included amputations, which were required due to the persistence of infection, were comparable in both groups, at weeks 3 and 9 (P was not significant) (Table 4). Nevertheless, considering only amputation, a significantly (P = 0.038) lower cumulative number of amputations was observed in the rHuG-CSF group after a 9-week follow-up, when three amputations had been necessary in the G-CSF group whereas nine were performed in the control group. The two major amputations had both been undergone by patients under standard treatment; one was performed at day 21 after study commencement and the other was performed at day 30 after study commencement. Two amputations of metatarsal bones were also performed: one in the standard treatment group (at day 25) and another in the G-CSF group (at day 45). In summary, eight toes had to be amputated, six of which belonged to patients under standard treatment and two of which belonged to patients given G-CSF as an adjunctive therapy.

Both patients with life-threatening infection at the time of randomization and belonging to the standard treatment group were classified as improved at week 9.

Patients were further evaluated 6 months after enrollment. Four patients (all in the G-CSF group) were lost to follow-up. Of the remaining patients from that arm of the study, 13 (81%) were cured or displayed stable conditions, while 3 (19%) either worsened or experienced an ulterior ulcer infection. The corresponding figures for the standard treatment groups were 15 of 20 (75%) and 5 of 20 (25%), respectively (P was not significant).

DISCUSSION

The present study with diabetic patients with severe limb-threatening infection has shown that an adjunctive treatment with G-CSF for 3 weeks was well tolerated but could not significantly affect the clinical and biological parameters of the healing process; indeed, pathogen eradication and resolution of cellulitis did not seem to be influenced by G-CSF administration. Even in the long-term follow-up (6 months) the out-

TABLE 4. Comparison of treatment outcomes in the two study groups at weeks 3 and 9 after therapy commencement

Outcome	Wk 3			Wk 9		
	No. (%) of patients		P	No. (%) of patients		P[a]
	G-CSF group (n = 20)	Control group (n = 20)		G-CSF group (n = 20)	Control group (n = 20)	
Cure	0	0		7 (35)	7 (35)	1.00
Improvement	12 (60)	9 (45)	0.34	8 (40)	4 (20)	0.17
Failure	8 (40)	11 (55)	0.34	5 (25)	9 (45)	0.19

[a] χ^2 test.

comes appeared to be equivalent for both study groups. However, we noted a lower incidence of cumulative amputation in G-CSF-treated patients by the first 9 weeks after enrollment, i.e., three amputations (15%) among G-CSF-treated patients versus 9 (45%) amputations among patients in the control group ($P = 0.038$). Since the major indication for amputation was persistence or worsening of infection, we can speculate that the lower rate of amputation in the G-CSF-treated group could be linked to a more effective response to the infection. There is a general agreement on the fact that a strong effort should always be attempted to prevent amputations (18), in light of both quality-of-life standards and social implications (e.g., need for rehabilitation, home care, and social service support).

However, in our study the difference is lost when amputations are classified as failures. Furthermore, we would emphasize that the orthopedic physicians who made the decision to perform amputatations for our patients were not blinded as to the treatment because they had not been involved in the study.

The use of G-CSF as adjuvant therapy for the treatment of foot infections in diabetic patients has previously been studied by Gough et al. (11) in a double-blind placebo-controlled study with 40 patients. They showed that G-CSF treatment was significantly associated with an improved clinical outcome of foot infection: the G-CSF–antibiotic combination was in fact observed to enhance the eradication of pathogens from the infected ulcers, to quicken the resolution of cellulitis, and to shorten the duration of both intravenous antimicrobial therapy and the duration of hospital stay with respect to control patients who had received the same antibiotic regimen alone. In addition, none of the patients among the G-CSF treatment group required surgery, but surgery was required for four patients in the control group (P was not significant).

Some crucial differences between that study and our study should, however, be highlighted. In the study of Gough et al. (11), most patients had ulcers of short duration, a few patients presented with limb-threatening infection, only 60% of the patients had evidence of osteomyelitis, and swab culture was the sole test used for microbiologic assessment. Furthermore, G-CSF (filgrastim) had been administered for 7 days, and all patients had received an intravenous combination of four antibiotics (ceftazidime, amoxicillin, flucloxacillin, and metronidazole) until resolution of both cellulitis and ulcer discharge. In contrast, only patients with limb-threatening infection were enrolled in our study; all of them had chronically infected ulcers and evidence of osteomyelitis; cultures of both deep-tissue biopsy specimens and swab specimens were done. Furthermore, rHuG-CSF was administered for 21 days and a two-antibiotic (ciprofloxacin and clindamycin) combination was initially (empirically) administered. Hence, these two studies do not appear to be fully comparable in terms of either the clinical characteristics of the patients enrolled or the treatment protocol, as may be expected for randomized studies evaluating new therapeutic approaches and thereby performed with populations with different characteristics. Some differences in the results obtained by Gough et al. (11) and us might therefore be related to different patient features.

In addition, assessment of the severity and prognosis of diabetic foot infection may often be a hard task: diabetic foot is a multifactorial condition, and not all factors retain the same weight in determining the final outcome of therapy. However, even in light of these considerations, it seems confirmed that G-CSF may represent an interesting new therapeutic option for the treatment of diabetic foot infection.

Further prospective, randomized, clinical trials with larger numbers of patients could better define the role of G-CSF in this clinical setting.

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