

Filgrastim in Patients With Pneumonia and Severe Sepsis or Septic Shock*

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Study objectives: Evaluate the safety of filgrastim (recombinant methionyl human granulocyte colony-stimulating factor) administration, combined with standard therapy, in patients with pneumonia and either septic shock or severe sepsis who were receiving mechanical ventilation. **Design:** Multicenter, double-blind, randomized, placebo-controlled study.

Setting: ICU, multicenter.

Patients: Eighteen patients with pneumonia and hypotension, or in the absence of shock, two or more end-organ dysfunctions, were enrolled and treated. Baseline acute physiology and chronic health evaluation II scores and median age for the filgrastim (n = 12) and placebo (n = 6) groups were 25.0 and 49.5 years and 31.5 and 56.5 years, respectively.

Intervention: Filgrastim (300 µg) or placebo was administered IV daily for up to 5 days.

Measurements and results: Study end points included safety; biological response, including endogenous cytokine levels, endotoxin levels, and neutrophil counts; and mortality. Cytokine and endotoxin levels were highly variable in both groups. By day 29, 3 of 12 filgrastim-treated patients and 4 of 6 placebo-treated patients had died. There were no differences in types and occurrences of adverse events, including ARDS, or in outcome between the two groups. Three of four placebo-treated patients had persistent bacterial growth on bronchoscopy repeated after 48 h compared with 2 of 10 filgrastim-treated patients.

Conclusion: Filgrastim appeared to be well tolerated in this population of patients with pneumonia and severe sepsis or septic shock. Larger studies to determine the benefit of filgrastim in patients with pneumonia and sepsis or organ dysfunction are warranted. (CHEST 2001; 119:523–529)

Key words: acute physiology and chronic health evaluation II; clinical trial; filgrastim; pneumonia; sepsis; septic shock

Abbreviations: ANC = absolute neutrophil count; APACHE II = acute physiology and chronic health evaluation II; CAP = community-acquired pneumonia; CI = confidence interval; G-CSF = granulocyte colony-stimulating factor; IL = interleukin; IL-1ra = interleukin-1 receptor antagonist; r-metHuG-CSF = recombinant methionyl human G-CSF; TNF-α = tumor necrosis factor-α

Pneumonia continues to be a significant cause of both morbidity and mortality, particularly in the elderly, those with significant comorbid disease, or those who require mechanical ventilation. Despite causation by microorganisms that are typically sensi-

tive to available antibiotics, mortality rates for patients with severe pneumonia requiring ICU admission and mechanical ventilation remain 25 to 50%.¹ Although the pathogenesis of bacterial pneumonia is not fully understood and is probably multifactorial, alteration of lung host defenses and the virulence of the pathogen are recognized as important factors.

Neutrophils, an important component of the host defense response to infection, are among the first cells to respond to the mediators released by infected tissues. Concentrations of granulocyte colony-stimulating factor (G-CSF), one of the cytokines that acts on neutrophil proliferation, maturation, and function, have been demonstrated to increase significantly during bacterial sepsis and other bacterial infections, including bacterial pneumonia. This response suggests that G-CSF may have an important role in the regulation of the host defense response against invading pathogens.²

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Recombinant methionyl human G-CSF (r-metHuG-CSF, filgrastim) also has been shown to cause proliferation and differentiation of neutrophil precursors,³⁻⁵ enhance chemotaxis,⁶ and enhance superoxide production in response to chemoattractants.⁷ In animal models of pneumonia, administration of r-metHuG-CSF was associated both with reductions in viable bacteria counts and a significant improvement in survival.^{8,9}

Neutrophils also have been proposed to be an important factor in the pathogenesis of ARDS and may be involved in the development of the multiple-organ dysfunction syndrome.¹⁰ Enhancing neutrophil numbers and function may, therefore, potentially increase the risk of these adverse sequelae.

The current trial was conducted to determine the safety of filgrastim in immunocompetent patients with pneumonia and existing severe sepsis or septic shock, *ie*, patients at great risk for experiencing ARDS and multiple-organ dysfunction syndrome.

MATERIALS AND METHODS

This was a multicenter, double-blind, randomized, parallel-group, placebo-controlled, prospective study of filgrastim in patients with a diagnosis of either community- or hospital-acquired pneumonia with severe sepsis or septic shock.

Patients

The study was reviewed and approved by the appropriate institutional review boards. Patients or their legal designees gave written informed consent before any study procedure.

Men and women ≥ 18 years of age who were hospitalized in the ICU were eligible to be included if they had a diagnosis of pneumonia, made no earlier than 72 h before randomization; and a diagnosis of severe sepsis or septic shock, made no earlier than 24 h before randomization.¹¹ The diagnosis of pneumonia required the presence of fever (temperature $\geq 38^\circ\text{C}$) or hypothermia ($\leq 35.5^\circ\text{C}$), tachycardia (≥ 90 beats/min), a new or changing radiographic infiltrate, and need for mechanical ventilation. In addition, each patient required either a Gram's stain of a good-quality sputum or tracheal aspirate (< 10 epithelial cells and > 25 WBCs per low-power field), BAL, protected-specimen brush, or pleural fluid with a predominant morphology consistent with a respiratory pathogen or a positive culture of blood, pleural fluid, or bronchoscopy specimen above threshold (BAL $\geq 10^4$ cfu/mL or protected-specimen brush $\geq 10^3$ cfu/mL). Patients were considered to have community-acquired pneumonia (CAP) if the new radiographic infiltrate was present either at hospital admission or developed within 48 h of admission.

Patients were ineligible for the study if they had irreversible disease, other than sepsis, that was expected to have a rapidly fatal course; burns as the primary injury; cardiogenic shock as the primary acute condition; uncontrolled hemorrhage; myeloid malignancies; a bone marrow transplant within the past year; or a WBC count $< 1.0 \times 10^9/\text{L}$ or $> 40 \times 10^9/\text{L}$.

Antibiotics were chosen at the discretion of the treating physician, and other concomitant medications and transfusions of blood or blood products were administered as medically indicated.

Study Medication

Patients were randomized 2:1 to receive filgrastim or placebo. Filgrastim was provided in 2-mL vials containing 0.3 mg/mL for injection of 300 $\mu\text{g}/\text{d}$. Study drug was diluted in 5% dextrose in water with human serum albumin for administration by short IV infusion. Placebo, the vehicle for filgrastim, was prepared in 2-mL vials in the same manner. Study drug was given once daily for a maximum of 5 days. The first dose of study medication was given as soon as possible after randomization but no later than 24 h after diagnosis of severe sepsis or septic shock. Subsequent doses were given at 24-h intervals after the first dose and within 3 h after the WBC count was known.

Treatment with the study drug was discontinued in the event of a serious adverse event deemed possibly, probably, or definitely related to its administration; or a WBC count $> 75 \times 10^9/\text{L}$ at the 24-h nadir after drug administration.

Study End Points

Safety: Periodic clinical and laboratory determinations to assess safety and disease status were obtained from the start of study drug infusion, continuing through study day 8. Serious adverse events were assessed through day 29 or until hospital discharge or death, if earlier.

The incidence and resolution of new organ failure also were assessed as a safety end point. Organ failures present at study entry or developing within the first 8 days were considered new and potentially related to either sepsis or therapy. Resolution of these new organ failures was assessed through study day 29.

Biological Response: Biological response was defined as changes in peripheral blood neutrophil count and differential (through day 8) and levels of cytokines. Enzyme-linked immunosorbent assays for tumor necrosis factor- α (TNF- α ; Genzyme, Cambridge, MA), p55 soluble TNF- α receptor (Bender Medical Systems; now Biosource; Camarillo, CA), interleukin (IL)-1 β (Inctar; Stillwater, MN) and its receptor antagonist (IL-1ra; R & D Systems; Minneapolis, MN), IL-6 (Biosource; Camarillo, CA), IL-8 (R & D Systems), IL-10 (R & D Systems; Minneapolis, MN), G-CSF (R & D Systems), and endotoxin (Seikagaku Corp; Tokyo, Japan) were performed on serum and BAL fluid.

Blood was drawn for serum cytokine and endotoxin before dosing and at 6, 24, 48, and 72 h after the first dose of study drug, then frozen and stored with the baseline samples. BAL fluid for assay was obtained before dosing and repeated at 48 h after the first dose of study drug. All BAL specimens were obtained from the suspected site of pneumonia. In addition to the cytokine assays, a cell count, a differential cell count, and an albumin level were obtained on all BAL specimens.

Bronchoscopy with BAL sampling was obtained before study drug infusion in all patients if their primary physician considered the patient in stable enough condition to tolerate the procedure. Quantitative cultures were performed on all bronchoscopy specimens, even though the patients may have received up to 72 h of prior antibiotic therapy. A quantitative culture above a specific threshold was therefore not required for study entry. All BAL specimens were obtained after instillation of ≥ 120 mL of saline solution, and the first aliquot was discarded. Patients remaining intubated had BAL repeated at 48 h after receipt of the first dose of study drug. Repeat BAL specimens were obtained from the same anatomic area as baseline BALs.

Mortality: All causes of mortality observed on or before day 15 and day 29 were predefined study end points.

Statistical Methods

All patients receiving at least one dose of study drug were evaluated for safety. Differences between control and treated

groups in biological markers were assessed by rank sum test. Biological response was estimated by the greatest absolute change in blood or BAL markers from baseline and assessed for significance by paired *t* test. Median times to resolution of end-organ failures and to discharge from the ICU were estimated with life-table analyses. Point mortality estimates were compared using Cochran-Mantel-Haenszel statistics, adjusted for center.

RESULTS

Patients

Nineteen patients were enrolled in this study at three centers in the United States. One patient, initially assigned to the filgrastim group, was excluded from analyses because of death after randomization but before study drug infusion. Eighteen patients were evaluable for all safety and efficacy variables. A 2:1 randomization resulted in 12 patients receiving filgrastim (8 CAP) and 6 receiving placebo (3 CAP).

Sex ratios and median values (with range) for age, height, weight, vital signs, blood gas and ventilatory variables, and baseline acute physiology and chronic health evaluation (APACHE) II scores are shown in Table 1. Although all patients required mechanical ventilation at baseline, the median positive end-expiratory pressure was 12.5 cm H₂O for the placebo-treated group and 5.0 cm H₂O for the filgrastim-treated group (*p* = 0.016, rank sum test). Median baseline APACHE II scores were 31.5 for the placebo-treated group and 25.0 for the filgrastim-treated group. Although no difference between treatment groups was detected using a rank sum test (*p* = 0.630), the placebo group contained the two patients with the lowest APACHE II scores (< 15), as well as four patients with scores > 25, all of whom died while enrolled in the study.

Baseline bronchoscopy was performed in five of the seven patients with hospital-acquired pneumonia, and BALs demonstrated growth above threshold of Gram-negative organisms in four. The fifth had low-level growth of a Gram-negative organism. One patient also had positive blood cultures for *Pseudomonas aeruginosa*. Baseline bronchoscopy was performed in 10 of the 11 patients with CAP. Causative organisms for CAP were documented by one positive blood culture (*Streptococcus pneumoniae*) and one positive pleural fluid culture (β -hemolytic *Streptococcus*, *P aeruginosa*, and *Proteus*). The latter also had diagnostic growth of all organisms on BAL. One additional patient had diagnostic growth on BAL, and another had an anaerobe cultured from a protected-specimen brush specimen. Three other patients with CAP had growth of organisms (*Streptococcus* spp in two, *Klebsiella* sp and *Enterobacter* sp in the other) below diagnostic thresholds, and three

Table 1—Median Value and Range of Baseline Characteristics*

Variable	Placebo (N = 6)	Filgrastim (N = 12)
Women/men	2/4	4/8
Age, yr	56.5 (35–60)	49.5 (27–86)
APACHE II	31.5 (10–48)	25.0 (18–38)
Height, cm	180 (160–183)	166 (128–191)
Body weight, kg	79 (66–115)	67 (41–104)
Systolic BP, mm Hg†	114 (96–189)	117 (91–156)
Diastolic BP, mm Hg†	68 (30–82)	58 (34–83)
Respiratory rate, breaths/min	22 (8–35)	16 (10–30)
Oral temperature, °C	38 (34–39)	38 (36–40)
PaO ₂ , mm Hg	108 (63–189)	99 (38–177)
FIO ₂	0.70 (0.50–1.00)	0.60 (0.35–1.00)
PaO ₂ /FIO ₂ ratio	171 (79–272)	167 (76–295)
PEEP, cm H ₂ O	12.5 (12–16)	5.0 (0–10)
ANC, 10 ⁹ /mL	13.9 (11.1–17.1)	14.0 (3.3–26.0)
WBC, 10 ⁹ /mL	15.2 (12.8–19.2)	18.4 (4.5–26.8)
No. (%) patients with preexisting hypotension	4 (67%)	12 (100%)

*All patients required mechanical ventilation at study entry. PEEP = positive end-expiratory pressure; FIO₂ = fraction of inspired oxygen.

†Indicates on pressors as needed.

patients' cultures were sterile. The percentage of neutrophils on the BAL exceeded 50% for all three sterile specimens.

Study Medication

Two patients in the placebo-treated group and one in the filgrastim-treated group received fewer than five doses of study drug because of death, but no patient missed a dose of study drug. The mean exposure to study drug was 4.2 days for patients receiving placebo and 4.5 days for patients receiving filgrastim.

Safety

Overall five of six patients in the placebo-treated group had a total of 12 organ failures, one of which (ARDS) occurred after initial study drug infusion. In the filgrastim group, 12 patients had 16 end-organ failures, 3 of which (ARDS, 2; disseminated intravascular coagulation, 1) occurred after the initial dose of study drug. The mean time to resolution of all organ failures was > 29 days for the placebo-treated patients and 8 days for the filgrastim-treated patients. Resolution by day 29 was seen for 1 of the 12 events of end-organ failure in the placebo group and 12 of 16 events of end-organ failure in the filgrastim group. Of particular note, preexisting shock resolved during the study in 9 of 10 occurrences in filgrastim-treated patients but in none of the four occurrences in placebo-treated patients (Table 2).

In patients who did not have ARDS before randomization, one of three placebo-treated and two of seven filgrastim-treated patients experienced clinically defined ARDS after initiation of therapy. Mean BAL albumin levels before the first dose of study drug were 36 mg/dL (range, 3 to 91 mg/dL; 95% confidence interval [CI], -29 to 101) for the four placebo-treated patients and 91 mg/dL (range, 5 to 390 mg/dL; 95% CI, -12 to 195) for the nine filgrastim-treated patients in which initial bronchoscopy was performed (difference not significant, $p = 0.63$). By 48 h after the first dose of study drug, the mean BAL albumin levels increased to 94 mg/dL (range, 11 to 269 mg/dL; 95% CI, 196 to 284) in the placebo-treated group and decreased to 63 mg/dL (range, 1 to 243 mg/dL; 95% CI, -11 to 138) in the filgrastim-treated group (differences from baseline and between groups both not significant). Albumin levels in BAL 48 h after initiation of treatment increased to > 200 mg/dL in one of four placebo-treated and one of nine filgrastim-treated patients without elevated baseline values. Two patients in the filgrastim-treated group had baseline concentrations that exceeded 200 mg/dL. The initially elevated BAL albumin level decreased to a low level at 48 h in one while remaining persistently > 200 mg/dL in the other.

Complications from ARDS associated with subsequent infections (pneumonia or urinary tract infection) were the most commonly reported serious adverse event, involving three patients in both groups. The only event reported as possibly, probably, or definitely related to study drug was hyperbilirubinemia occurring in a filgrastim-treated patient. Patterns of abnormality in respiration, temperature, and BP measurements were similar between the two treatment groups.

Microbiological Response

Fourteen patients (4 placebo-treated, 10 filgrastim-treated) had bronchoscopy with BAL repeated 48 h after the first dose of study drug. Two of four placebo-treated patients had persistent growth of $> 10^3$ cfu/mL of the organism originally suspected of

causing pneumonia. In a third patient, *Serratia marcescens* was newly cultured at $> 10^4$ cfu/mL. In filgrastim-treated patients, 1 of 10 had persistent growth of $> 10^3$ cfu/mL of the original organism, and 1 patient had growth below threshold of a new organism. The remainder of the repeat BAL specimens had ≤ 10 cfu/mL of both the original and any new organisms.

Biological Response

No significant differences in the endogenous G-CSF concentrations at the time of randomization existed between placebo-treated and filgrastim-treated patients (Fig 1). Only two filgrastim-treated patients had undetectable G-CSF at baseline and both died. Markedly higher G-CSF values were detected in the filgrastim-treated patients 6 h after study drug infusion. The amounts of G-CSF measured in filgrastim-treated patients exceeded by several logarithms the highest documented, spontaneously occurring endogenous G-CSF amounts in both placebo-treated and in pretreatment filgrastim-treated patients. Trough levels before the subsequent doses of filgrastim were much lower and did not differ significantly from those of placebo-treated patients.

The biological activity of filgrastim was documented by a significant increase in circulating neutrophil counts (Fig 2). Differences in absolute neutrophil count (ANC) between placebo-treated and filgrastim-treated patients were significant ($p < 0.05$) from day 3 through day 7. The median peak ANC was $3.07 \times 10^9/L$ for filgrastim-treated and $1.42 \times 10^9/L$ for placebo-treated patients ($p < 0.05$). The median time to peak ANC was 6 days for filgrastim-treated and 1 day for placebo-treated patients ($p < 0.05$). The WBC count exceeded $75 \times 10^9/L$ on the day after the last dose of filgrastim in one patient.

An increase in the percent of neutrophils in BAL also occurred with filgrastim treatment. The mean percent of neutrophils increased from 75.5% (95%CI, 63.1 to 88.0) to 85.8% (95% CI, 75.5 to

Table 2—Resolution of End-Organ Failure*

Type of Organ Failure	Placebo (n = 6)				Filgrastim (n = 12)			
	At Randomization	By Day 8	Total	Resolution	At Randomization	By Day 8	Total	Resolution
Shock	4	0	4	0	10	0	10	9
ARDS	3	1	4	1	3	2	5	2
ARF	3	0	3	0	0	0	0	0
DIC	1	0	1	0	0	1	1	1

*ARF = acute renal failure; DIC = disseminated intravascular coagulation.

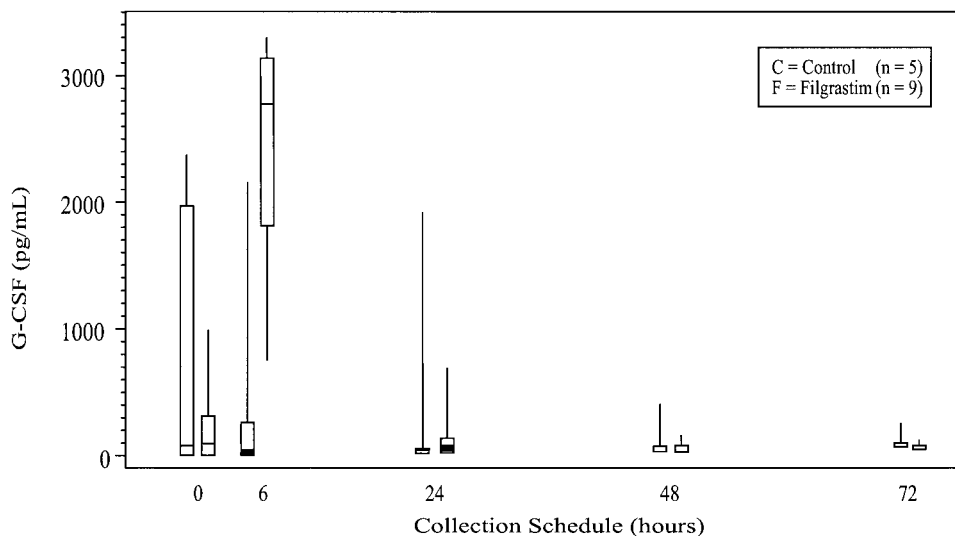


FIGURE 1. Median, quartile range, minimum, and maximum serum G-CSF concentrations. The 6-h measurement is after infusion of study drug, whereas the other measurements are before the next infusion.

96.1; $p < 0.05$). The mean percent BAL neutrophils decreased from 80.3% to 60.0% ($p = 0.13$) in the placebo-treated group.

Cytokine Response

No significant difference between placebo-treated or filgrastim-treated or between survivors and non-survivors was observed for any of the measured cytokines or endotoxin. Only the baseline IL-8 levels demonstrated a trend toward a difference between

the placebo (396.7 ± 386.4 pg/mL) and filgrastim-treated (85.3 ± 111.1 pg/mL; $p = 0.11$). IL-6 levels did not correlate with survival ($833.5 \pm 1,115$ pg/mL for survivors vs $1,517 \pm 2,529$ pg/mL for nonsurvivors, $p = 0.52$). Trends in serial cytokine levels also were not significantly associated with either treatment or mortality.

Serum TNF- α was detectable in eight patients (four placebo-treated and four filgrastim-treated; average, 49.8 ± 23.4 pg/mL). Five of these patients with detectable TNF- α at baseline died, including all four in the placebo group. Of the 15 patients who had BAL performed at baseline before study drug was administered, TNF- α was detected in six BAL samples (one placebo-treated patient and five filgrastim-treated patients; average, 131.7 ± 171.0 pg/mL). No significant ($> 1 \log_{10}$) gradient between BAL and serum TNF- α levels was found in any patient who underwent bronchoscopy.

In contrast, baseline IL-8 levels in BAL were detectable in all 15 patients: the BAL-to-serum gradient was > 100 in all but one patient. The mean baseline BAL IL-8 level was 25,485 pg/mL with a mean baseline serum level of 223 pg/mL. Although serial serum IL-8 values did not change more than $1 \log_{10}$, IL-8 levels increased by more than 1 logarithm on follow-up bronchoscopy in one of six placebo-treated and one of nine filgrastim-treated patients. These increases in BAL IL-8 levels were each associated with a significant increase in BAL albumin, the new appearance of measurable TNF- α in BAL fluid, and clinical ARDS.

The molar ratio of IL-1 α /IL-1 β exceeded $3 \log_{10}$ for all but two filgrastim-treated patients. The ratio

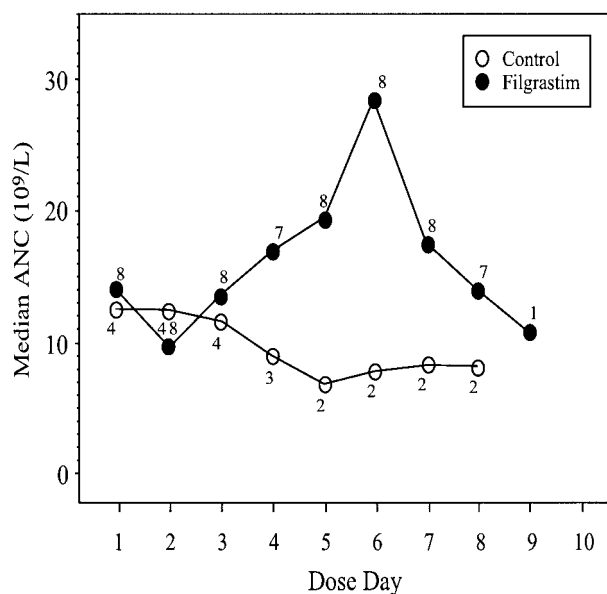


FIGURE 2. Circulating neutrophil response. Daily number of patients are above (filgrastim) or below (placebo) symbols.

remained $< 2 \log_{10}$ for one nonsurvivor, whereas the other patient, who survived, had an increased ratio of $> 3 \log_{10}$ by the 48-h measurement.

Endotoxin remained detectable throughout the 72-h testing period in those patients with measurable initial levels, including the filgrastim-treated patients. Serum endotoxin levels did not correlate with documented Gram-negative infections. The patient with bacteremic BAL-positive nosocomial *Pseudomonas pneumonia* had one of the lowest levels, whereas the patient with bacteremic, BAL-positive *S pneumoniae* CAP had one of the highest levels. The only patient with a level of > 20 pg/mL was in too unstable condition to undergo bronchoscopy.

Mortality

Six deaths were observed through day 15: 4 of the 6 patients (67%) in the placebo-treated group and 2 of the 12 patients (17%) in the filgrastim-treated group ($p = 0.042$ Cochran-Mantel-Haenszel). No patients died within the first 24 to 72 h of the study; all deaths occurred after ≥ 4 days of study. One additional death (a filgrastim-treated patient) was observed by day 29, which resulted in no significant difference in 29-day mortality ($p = 0.108$). Three of three placebo-treated patients with CAP died, whereas only one of eight filgrastim-treated patients with CAP died ($p = 0.024$). One of three and two of four placebo- and filgrastim-treated patients with hospital-acquired pneumonia died.

DISCUSSION

Results of this study suggest that filgrastim is safe when administered to patients with severe pneumonia complicated by severe sepsis or septic shock. Specifically, the incidence of ARDS with filgrastim treatment was identical to that of placebo, whether defined clinically or by serial BAL albumin values. Filgrastim treatment did not appear to delay or inhibit the resolution of ARDS by either clinical criteria or serial BAL albumin levels. Other organ failures also neither appeared to occur more frequently nor was resolution delayed with filgrastim treatment. Adverse events were also not increased in filgrastim-treated patients. Clearly, no trend in excess mortality was seen in the filgrastim group. All these positive safety outcomes were demonstrated despite a greater than twofold increase in peripheral leukocyte counts and an increased percent of BAL neutrophils.

Another randomized, placebo-controlled trial in patients with CAP showed that patients receiving filgrastim have a reduction in the incidence of disseminated intravascular coagulation and ARDS.¹²

However, that study was specifically designed to exclude patients at high risk of ARDS and other organ failures in contrast to the present study, which specifically included patients who either already had multiple-organ dysfunction syndrome or were at high risk because of septic shock. The higher severity of illness in the present study was documented by mean APACHE II scores of 31 and 25, compared with scores of 16 and 17 in the study by Nelson et al.¹² Extensive experience with patients with febrile neutropenia, although also a population with a relatively low risk of ARDS, has also shown very little risk of ARDS with the use of filgrastim.

The similar incidence of ARDS between filgrastim- and placebo-treated patients contrasts with animal studies, which suggested that enhanced neutrophil numbers and function may increase the risk of ARDS.¹³ The difference in the incidence of ARDS between the outcome of preclinical studies and clinical studies may be explained by the cytokine data. Our clinical data showed great heterogeneity of the cytokine response in both placebo-treated and filgrastim-treated patients. Proinflammatory cytokine levels (TNF- α , IL-1, IL-6, and IL-8) were generally low, with the exception of BAL IL-8 levels. Anti-inflammatory mediators (IL-10, soluble TNF- α receptor, and IL-1ra) were measurable in all patients at levels significantly higher than the corresponding proinflammatory mediator. Therefore, the cytokine milieu was very different from that induced in experimental models with the acute induction of a vigorous proinflammatory response with endotoxin or live bacteria infusion. In addition, filgrastim therapy was initiated after infection was already established rather than being given prophylactically.

Any potential benefit of filgrastim in severe pneumonia is most likely multifactorial. Although the numbers are small, filgrastim appeared to improve bacterial clearance, as documented by serial BAL quantitative cultures.¹⁴ In addition to enhancing neutrophil function,⁷ filgrastim also significantly increased the percent of neutrophils present in BAL fluid. Although control of the primary infection will clearly modulate cytokine levels, filgrastim also has a direct effect on TNF- α levels.¹⁵⁻¹⁷ Unfortunately, the range and duration of severe sepsis in the patients entered into this study resulted in extremely variable cytokine concentrations, and explanatory trends in cytokine levels could not be detected. Specifically, we could not document a decrease in serum TNF- α levels after filgrastim infusion.

In conclusion, this study suggests that filgrastim is well tolerated in the treatment of nonneutropenic patients with pneumonia and severe sepsis or septic shock. Although differences in baseline APACHE II score, IL-6 levels, or other factors may explain all or

part of the differences in outcome in this pilot study, the use of filgrastim as adjuvant therapy for severe pneumonia is worth exploring. Larger studies to determine its benefit in patients with pneumonia and sepsis or organ dysfunction are warranted.

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REFERENCES

- 1 Niederman MS, Bass JB Jr, Campbell GD, et al. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. *Am Rev Respir Dis* 1993; 148: 1418–1426
- 2 Cebon J, Layton JE, Maher D, et al. Endogenous hemopoietic growth factors in neutropenia and infection. *Br J Hematol* 1994; 86:265–274
- 3 Morstyn G, Campbell L, Souza LM, et al. Effect of granulocyte colony stimulating factor on neutropenia induced by cytotoxic chemotherapy. *Lancet* 1988; 1:667–672
- 4 Bronchud MH, Howell A, Crowther D, et al. The use of granulocyte colony-stimulating factor to increase the intensity of treatment with doxorubicin in patients with advanced breast and ovarian cancer. *Br J Cancer* 1989; 60:121–125
- 5 Lord BI, Bronchud MH, Owens S, et al. The kinetics of human granulopoiesis following treatment with granulocyte colony-stimulating factor *in vivo*. *Proc Natl Acad Sci USA* 1989; 86:9499–9503
- 6 Colgan SP, Gasper PW, Thrall MA, et al. Neutrophil function in normal and Chediak-Higashi syndrome cats following administration of recombinant canine granulocyte colony-stimulating factor. *Exp Hematol* 1992; 20:1229–1234
- 7 Weisbart RH, Golde DW. Physiology of granulocyte and macrophage colony-stimulating factors in host defense. *Hematol Oncol Clin North Am* 1989; 3:401–409
- 8 Hebert JC, O'Reilly M, Gamelli RL. Protective effect of recombinant human granulocyte colony-stimulating factor against pneumococcal infections in splenectomized mice. *Arch Surg* 1990; 125:1075–1078
- 9 Nelson S, Summer W, Bagby G, et al. Granulocyte colony-stimulating factor enhances pulmonary host defenses in normal and ethanol-treated rats. *J Infect Dis* 1991; 164:901–906
- 10 Repine JE, Beehler CJ. Neutrophils and adult respiratory distress syndrome: two interlocking perspectives in 1991. *Am Rev Respir Dis* 1991; 144:251–252
- 11 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20:864–874
- 12 Nelson S, Belknap SM, Carlson RW, et al. A randomized controlled trial of filgrastim as an adjunct to antibiotics for treatment of hospitalized patients with community-acquired pneumonia. *J Infect Dis* 1998; 178:1075–1080
- 13 Freeman BD, Correa R, Karzai W, et al. Controlled trials of rG-CSF and CD11b-directed MAb during hyperoxia and *E. coli* pneumonia in rats. *J Appl Physiol* 1996; 80:2066–2076
- 14 A'Court C, Garrard CS, Crook D, et al. Microbiological lung surveillance in mechanically ventilated patients, using non-directed bronchial lavage and quantitative culture. *Q J Med* 1993; 86:635–648
- 15 Charak BS, Brown EG, Mazumder A. Role of granulocyte colony-stimulating factor in preventing ceftazidime-induced myelosuppression *in vitro*. *Bone Marrow Transplant* 1995; 15:749–755
- 16 Kitabayashi A, Hirokawa M, Hatano Y, et al. Granulocyte colony-stimulating factor downregulates allogeneic immune responses by posttranscriptional inhibition of tumor necrosis factor-alpha production. *Blood* 1995; 86:2220–2227
- 17 Logan TF, Gooding W, Kirkwood JM, et al. Tumor necrosis factor administration is associated with increased endogenous production of M-CSF and G-CSF but not GM-CSF in human cancer patients. *Exp Hematol* 1996; 24:49–53