Eur J Med Res (2005) 10: 29-35

A Randomized, Placebo-Controlled Study of the Use of Filgrastim in non Neutropenic Patients with Nosocomial Pneumonia

P. Hartmann[1,2], J. Lammertink[2], G. Mansmann[2], K. Hübel[2], B. Salzberger[1], H. Stützer[3], A. Engert[2], G. Fätkenheuer[2]

[1]Department of Internal Medicine I University of Regensburg, Germany
[2]Department of Internal Medicine I, [3]Institute for Medical Statistics, Informatics, and Epidemiology University of Cologne, Germany

Abstract: Pneumonia remains the number one cause of death from infectious diseases in Western Europe and the United States despite the introduction of potent broad-spectrum antibiotics. Granulocyte colony-stimulating factor is considered to improve host defense during infection and may be an effective adjunctive in the treatment of severe infections. We examined the efficacy of granulocyte colony-stimulating factor (r-metHUG-CSF, filgrastim) with regard to clinical response in non-neutropenic ICU patients with nosocomial pneumonia in a prospective, randomized, placebo-controlled trial.

28 patients with newly diagnosed nosocomial pneumonia were randomly assigned to receive 300-480 μg filgrastim or placebo subcutaneously for up to seven days. Study endpoints were death within 15 days, duration of antibiotic therapy and occurrence of serious adverse events (SAE).

No significant differences were observed in respect of 15-day (filgrastim1/12 vs. placebo 2/16) or 30-day mortality (1/12 vs.4/16, p = 0.355), and length of antibiotic treatment (13.5 vs.11.5 days, p = 0.985). Sepsis developed in 1/12 patients in the filgrastim and 6/16 patients in the placebo group (p = 0.184). None of the patients developed ARDS or any other SAE related to the study medication.

Filgrastim is safe in non-neutropenic ICU patients with nosocomial pneumonia. A benefit of filgrastim with regard to clinical endpoints could not be observed, while there was a trend toward reduced sepsis rate.
Key words: granulocyte-colony stimulating factor, nosocomial pneumonia, intensive care, sepsis

Introduction

Pneumonia remains the number one cause of death from infectious diseases in Western Europe and the United States despite the introduction of potent broad-spectrum antibiotics, improved supportive care and the application of preventive measures. The mortality rate for nosocomial pneumonia varies from 20% to 50% [1-4] pointing to the limited benefit of antibiotic therapy as the sole treatment modality for this illness. Thus, additional therapeutic interventions have been investigated focusing on the stimulation of host defense. One target of interest is the neutrophil granulocyte as the first line defense in bacterial infections. Potent host defense against bacterial infections requires an adequate number of neutrophils with intact functional capacities such as phagocytosis, generation of oxygen metabolites and bacterial killing. An impairment of these functional capacities has been shown in intensive care patients suffering from severe bacterial infections [5-7].

Granulocyte colony- stimulating factor (G-CSF) stimulates proliferation and maturation of neutrophils in the bone marrow and subsequently increases the number of functional neutrophils in the circulation. Filgrastim, a non-glycosylated recombinant human G-CSF (r-metHuG-CSF) has been approved as a pharmaceutical agent for neutropenic patients after myelosuppressive chemotherapy, and for mobilization of stem cells in bone marrow donors. In neutropenic patients, G-CSF shortens neutropenia and it reduces the rate of infectious episodes, the use of intravenous antibiotics as well as the length of hospitalization [8-10]. Priming with G-CSF enhances chemotaxis, intracellular oxygen metabolism, phagocytosis, and bactericidal activity upon stimulation with appropriate agents such as gram-negative cell wall components [11-14].

G-CSF was found to be beneficial in the treatment of various infections in animal studies, most important it significantly reduced mortality of bacterial pneumonia [15-21]. The application of G-CSF in non-neutropenic patients was found to be safe in several clinical trials investigating different infectious conditions such as sepsis, community-acquired pneumonia (CAP), meningitis, and surgical patients [22-29].

Filgrastim in patients with CAP established a reduction of severe complications indicating that more severely ill patients might profit from treatment with filgrastim [27]. This hypothesis was substantiated in a small study of 18 patients with pneumonia and severe sepsis in which mortality was significantly reduced from 67%in the placebo to 17%in the filgrastim group [30]. In both studies, filgrastim was associated with a reduction of end organ failure, including the acute respiratory distress syndrome (ARDS), a complication of pneumonia mediated by activated neutrophils [31]. The concern that G-CSF might trigger ARDS in non-

neutropenic patients was confuted by a study assessing filgrastim in severe CAP, where no evidence of filgrastim-related lung injury could be detected [26].

We conducted a randomized, placebo-controlled, double-blind study in order to evaluate the safety and the efficacy of filgrastim in combination with standard antibiotics to reduce the rate of mortality in critically ill, non neutropenic patients with nosocomial pneumonia.

Patients and Methods

Study Design

The protocol was approved by the Institutional Ethics Committee of the University of Cologne. All patients or their relatives gave written informed consent before study entry. The primary endpoint was mortality within 15 days after diagnosis of nosocomial pneumonia and initiation of the study. Secondary endpoints were defined as duration of antibiotic therapy and occurrence of serious adverse events (SAE). Initial inclusion criteria were nosocomial pneumonia in ICU patients who were not treated by antibiotics ≥ 48 hrs before first application of the study medication, and age ≥ 18 years. Because of slow recruitment, an amendment of the protocol permitted antibiotic pretreatment for up to 120 hrs. Exclusion criteria were defined as: baseline white blood cell count (WBC) <2 x 10^9/l, HIV-infection, known hematological malignancy, myelosuppressive therapy, pregnancy, or preexisting intolerance against filgrastim. Patients were recruited from the surgical and medical ICU of the University of Cologne. Elegible patients assigned by central randomization either to receive r-metHuG-CSF (filgrastim, Amgen Inc., Thousand Oaks, CA, USA) or placebo (0.9% NaCl, Braun, Germany) for up to seven days. Filgrastim was administered by a single daily subcutaneous injection dose of 300 µg (< 75 kg body weight) or 480 µg (> 75 kg). If WBC exceeded 75 x 10^9/l, the ad-ministration of study medication was interrupted until the WBC declined to 25 x 10^9/l. Before initiation of antibiotic therapy, a complete microbial screening of all relevant sites, especially blood cultures, sputum, tracheal aspirate, and (if possible) bronchoalveolear lavage (BAL) was performed. Antimicrobial treatment followed standard recommendation for empirical therapy, but was immediately specified after the determination of the pathogen and its resistance profile [32]. Blood counts, electrolytes, renal and hepatic function, coagulation parameters, and CRP were evaluated daily during ICU stay, otherwise at least at d1, d3, d7, d10, and d15. At d1, d7 and d15 patients were evaluated using a modified APACHE II scoring system [33]: If leukocytes exceeded 14.9 x 10^9/l at d7 and d15,the pretreatment WBC was taken as the scoring value to rule out all attributable effect of the study medication. Because of the impossibility to apply the Glasgow Coma Score (GCS) in intubated, sedated patients the APACHE II score was calculated without GCS. Vital signs were continuously monitored and patients were thoroughly examined at least once daily in awareness of possible SAEs. Patients were followed until discharge from hospital or death.

Definitions

The diagnosis of nosocomial pneumonia required a new or progressive pulmonary infiltrate on chest x-ray 72 hours after admission or after 48 hours of mechanical ventilation respectively in addition to two of the following criteria: temperature > 38 °C, production of purulent sputum, cough, rales, dyspnea or drop in paO2, pleuritic chest pain, leukocytosis (> 10 x 10^9/l) or leukopenia (< 3.5 x 10^9/l, but > 2 x 10^9/l), and detection of a relevant pathogen in sputum, tracheal aspirate, blood culture or BAL [34]. The diagnosis of ventilator-associated pneumonia (VAP) was established only if pneumonia was neither present nor developing at the time of intubation, but clinically evident >48 hrs thereafter. According to the point of time of onset after the patient was admitted to the ICU, VAP was defined as early-onset pneumonia (48-96 hrs after admission) and late-onset pneumonia (> 96 hrs) respectively. Sepsis was defined according to the criteria of Bone et al.[35]. The duration of antibiotic treatment was calculated as the number of days on intravenous antibiotics for treatment of pneumonia or, even if diagnosis was not definitive at treatment initiation and symptom related empirical antibiotic treatment was applied. A serious adverse event (SAE) was defined as any symptom, disease, or change of laboratory values (except changes in WBC), occurring during the first 30 days on study, that was life threatening, required treatment and prolongation hospitalization, or was associated with death of the patient.

Statistical Analyses

Based on the results of a previously published study [30], it was presumed, that the 15-day mortality could be reduced from 60%in the placebo to 20% in the filgrastim group. This 40% reduction should be detected with a power of 80% on a 5%-significance level. According to these assumptions a number of 2 x 18 patients was calculated by power analysis (Solo, BMDP Statistical Software, Cork,Ireland).The study was planned as a pilot study with adaptive design in order to confirm the primary hypothesis after precision of the filgrastim effect [36]. Data analysis was performed using SPSS 11.0 (SPSS Inc., Chicago, Ill.). Summary statistics for data are displayed as mean and standard deviation (SD) or median with range. Confirmatory statistics for the primary outcome measure were based on contingency table analysis using Fisher's exact test statistic with alpha = 0.05. Categorical variables were analyzed using Fisher's exact test statistic respectively chi-sqare statistics. Length of ICU and hospital stay, duration of ventilation and antibiotic therapy were compared by U-Mann-Whitney-Wilcoxon test.

Results

Patients

As mortality and recruitment frequency of patients were much lower than anticipated, the study board – considering the fact of the impossibility to confirm the study hypothesis – decided to close the study after 26 months. A total of 29 patients had been enrolled at

Table 1. Patients demographic data and features of pneumonia

NO. (%), median (range) as appropriate		**Filgrastim**	**Placebo**
Total number of patients		12	16
Sex			
	female	10 (83)	11 (69)
	male	2 (17)	5 (31)
Age (yrs)			
	median	66	63
	range	(27-78)	(30-74)
ICU		17 (85)	11 (85)
	medical	5 (42)	4 (33)
	surgical	7 (58)	12 (67)
Underlying condition			
Cardio-vascular		8 (67)	7 (44)
Trauma		3 (25)	5 (31)
Malignancy		1 (8)	3 (19)
Other		0 (0)	1 (6)
APACHE II*			
	median	13.0	12.5
	range	(5-28)	(2-25)
VAP		7 (58)	8 (50)
early onset		1 (8)	1 (6)
late onset		6 (50)	7 (44)
prolonged ventilation > 5 days		10 (83)	11 (69)

*without Glasgow Coma Scale and white blood count

this point of time. Thirteen patients had been randomized to receive filgrastim and 16 patients were assigned to the placebo group. One patient who had received a total of four doses of filgrastim was excluded from outcome evaluation because of protocol violation, but data were included in the intent-to -treat analysis of SAE. The baseline characteristics of the two treatment groups with regard to age, gender, and underlying medical condition, including the modified APACHE II were very similar (Table 1).

Patients in the control group were treated with placebo for exact 7 days, whereas in the filgrastim group the median treatment period was 7 days (range 4-8) dependent on the rise of WBC. The time-course of WBC is illustrated in Figure 1. With a mean value of 48.7 x 10^9/l a maximum was reached on d6 in the filgrastim group. The highest leukocyte count achieved in a patient was 78.6 x 10^9/l. After stop of filgrastim WBCs decreased rapidly, but differences were still significant between both groups on d15 (filgrastim: 17.7 x 10^9/l, placebo: 11.3 x 10^9/l; p = 0.0066).

Before administration of G-CSF / Placebo baseline leukocyte count was obtained on d-1 and d0. A prompt and significant increase of leukocytes was observed in the filgrastim group indicating that the dosage applied had appreciable biological activity. Values are presented as mean and standard deviation. The maximum mean value reached in the filgrastim group

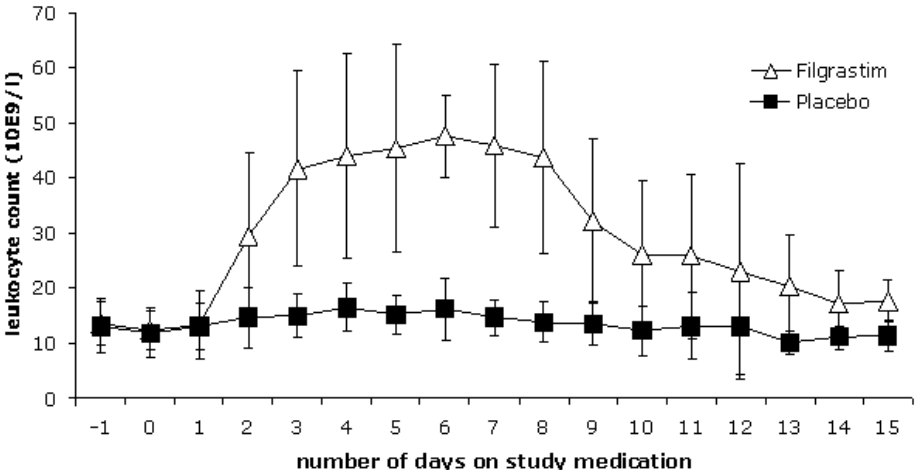

Fig. 1. Time-course of WBC.

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Culture Results

The results from the microbiological examination of blood, BAL, tracheal aspirate, and sputum are shown in Table 2. Overall 20 patients had one or more organisms cultured. The distribution of culture positive isolation sites as well as the number of isolated organisms was similar in both treatment groups. Gram-negative organisms were predominantly isolated (filgrastim: n = 7; placebo: n = 10) in comparison with gram-positive bacteria (filgrastim: n = 3; placebo: n = 2). Eight patients were culture negative (filgrastim: n = 3; placebo: n = 5). There was no clinical evidence of pneumonia due to *Legionella* and *Aspergillus* ssp. or respiratory syncytial virus (RSV).

Table 2. Culture results as obtained from different culture sites (blood, BAL, tracheal secretrion and sputum).

	Filgrastim	**Placebo**
Pathogen *		
Bacteroides ssp.	1	-
Enterobacter cloacae	2	2
Escherichia coli	1	1
Haemophilus influencae	1	1
Klebsiella ssp.	1	2
Morganella morganii	2	-
Proteus ssp.	1	1
Pseudomonas ssp.	2	3
Serratia marcescens	1	1
Coagulase-neg staphylococci	1	-
Staphylococcus aureus	2	2

*Patients may have had more than one organism cultured

Study Endpoints and Clinical Response

The analysis for the study endpoints and the clinical course of patients is given in Table 3. Three patients died within 15 days yielding an overall 15-day mortality of 11 %, thus no differences regarding survival could not be detected between both groups. The 30-day mortality for all patients was 18%. No additional death occurred in the filgrastim group within 30 days, whereas a total of 4 patients died in the placebo group (8% vs. 25%; p = 0.355). All four deaths in the placebo group occurred in the sequel of sepsis, however, three of these patients had underlying conditions bearing important risk factors for systemic infection in addition to nosocomial pneumonia (peritonitis following gastrointestinal perforation (2), empyema with ascending phlegmon of the lower limb). Overall seven patients developed sepsis during the first15 days of the study period (filgrastim: n = 1; placebo: n=6; p = 0.184). The in-hospital mortality rate was 25% in both groups with two additional deaths in the filgrastim group that were unrelated to the previous episode of pneumonia.

The use of filgrastim had no influence on the duration of intravenous antibiotic treatment for nosocomial pneumonia. First-line antibiotics were piperacillin-tazobactam (48%), 3rd or 4th generation cephalosporines (38%) either as single drug or in combination with gentamycin, fluoroquinolones (7%), and carbapenems (7%). Treatment was adapted according to culture results and clinical response.

Before study entry the duration of hospitalization obtained as days since admission (filgrastim: 6.0 placebo: 8.5) and days in the ICU (filgrastim: 5.5; placebo: 5.5) did not differ in the two treatment groups. The median time of hospitalization for all patients after

Table 3. Clinical course and outcome of study patients.

NO. (%), median (range), as appropriate	**Filgrastim** n = 12	**Placebo** n = 16	**p-value**
15-day mortality	1 (8.0)	2 (12.5)	0.999*
30-day-mortality	1	4 (25.0)	0.355*
Causes of death within 30 days			
Sepsis	-	4	
Cardiogenic shock	1	-	
Patients with sepsis	1 (8.0)	6 (37.5)	0.184*
Duration of antibiotic treatment (days)	13.5 (8-37)	11.5 (9-34)	0.985**
ICU stay (days)	21.5 (1-48)	15.0 (1-34)	0.163**
In-hospital stay (days)	35.5 (6-118)	19.0 (7-70)	0.377**
Length of ventilation (days)	5.0 (0-35)	2.5 (0-25)	0.174**

*Fisher´s exact p-value, **U-Mann-Whitney-Wilcoxon

study entry was 23 days and 16 days for the ICU stay. Filgrastim treated patients stayed a mean of six days longer in the ICU and were in total 17 days longer hospitalized than placebo treated patients, but this difference was mainly due to the long-term hospitalization of two patients.

In the 21 patients requiring mechanical ventilation there was no significant difference in the duration of ventilation between the two groups after study entry. The median duration of elevated temperature $\geq 38.0\,^{\circ}C$ was 3 days shorter in the Filgrastim group, however this was not statistically significant ($p = 0.639$).

Adverse Events

Treatment with filgrastim was well tolerated. Typical side effects, as bone pain and myalgia were not observed, however, they could hardly be obtained, as 85% of the filgrastim treated patients (76% of all patients) had been mechanical ventilated during the first days on study. None of the patients in the filgrastin group developed ARDS as defined by the American-European Consensus Conference Committee (29). In an intent-to-treat analysis of all randomized patients, no difference in regard to SAE was observed between both groups (Table 4). SAEs occurred in four filgrastim and five placebo treated patients with a total of 5 SAEs observed in the Filgrastim group and 8 SAEs in the placebo group. None of the SAEs was attributable to the application of filgrastim.

Table 4. Occurrence of serious adverse events (SAE) in all randomized study patients.

NO. (%)	**Filgrastim n=13**	**Placebo n=16**	**p-value**
No. of SAE	5	8	0.512*
Acute renal failure	1	-	
Hematothorax	1	-	
Gastrointestinal bleeding	1	-	
Intestinal infarction	-	1	
Perforation of gastric ulcer	-	1	
Stroke	-	1	
Death	2	4	
Attributable SAE	-	-	

* chi square p-value

Discussion

Nosocomial pneumonia is a frequent and often fatal complication in hospitalized patients, particularly in those who require mechanical ventilation for respiratory failure [37, 38]. New treatment strategies are needed to improve the outcome of patients who are severely ill with nosocomial or community-acquired pneumonia. This study was conducted to determine, whether filgrastim when added to antibiotic therapy and other standard management treatment strategies, would reduce the mortality in intensive care patients with nosocomial pneumonia.

15-day mortality, the primary efficacy endpoint, was not significantly different between the placebo and the filgrastim group. Furthermore no significant between-group differences were found for the secondary endpoints duration of antibiotic treatment and occurrence of SAEs. Also other efficacy indicators such as duration of mechanical ventilator support and time to death were not significantly different in both groups.

Our study was afflicted by some major critical points, which may have led to these negative results. The 30-day mortality (25%) was much lower than initially anticipated (60%) based on a previous report [30]. Recruited intensive care patients were not as severely ill as presumed, however, we cannot exclude an inclusion bias that possibly led to a reduced APACHE II score. As a direct consequence, the study hypothesis was impossible to confirm. Thus the study was closed after 26 months in acceptance of the subsequently lower power. However, a study by Meyanci and colleagues with a comparably small number cases found significantly better outcomes in patients with ventilator associated nososcomial pneumonia who were treated with G-CSF concomitantly to standard antibiotic treatment [39]. Stephens et al. obtained similar results favorable for G-CSF in patients with septic shock [40]. In contrast, the largest study published so far on the issue of G-CSF in critically ill patients, a multicenter, double-blind, placebo-controlled trial of the Pneumonia Study group, analyzing 699 patients with pneumonia and severe sepsis could not discriminate any significant between-group differences in respect of mortality or the clinical course of the patients [41]. Also a recently published systematic Cochrane review denies any evidence supporting the routine use of G-CSF in the treatment of pneumonia [42].

G-CSF is a natural component of host defense. Low serum G-CSF levels have been demonstrated to be associated with an adverse outcome regarding acute bacterial infections and sepsis [24, 43-45]. Application of G-CSF increases neutrophil numbers, enhances the neutrophils functional capacities and diminishes inflammatory markers as shown in animal studies and in humans [25, 46, 47]. Thus G-CSF should be the perfect candidate for biological immunotherapy in non-neutropenic patients with severe infections. A number of reasons are possible for the failure to detect any clinical benefit of adjunctive G-CSF treatment of severe infections. It recently has been demonstrated that preexisting endogenous G-CSF levels in critically ill patients are crucial for the beneficial effects of exogenously applied G-CSF on neutrophil counts and neutrophil functional capacities. G-CSF was less effective in patients with elevated endogenous G-CSF levels > 500 pg/ml [48]. Thus the therapeutic efficacy of G-CSF seems to be a matter of timing of its application in recognition of its local and systemic effects. While G-CSF acts inflammatory at the local side of infection by recruiting and optimizing the phagocytic capacities its systemic effect is both anti-inflammatory and immunosuppressive by inhibiting the production of inflammatory cytokines and expanding a T-helper cell

response. Preclinical and clinical studies substantiate the observation that timing may be the key to clinical efficacy. Beneficial results for the adjunctive use of G-SCF were most consistently observed, when G-CSF was administered as prophylaxis to patients at risk of infection or very early in the course of infectious diseases [27, 29, 49-51]. In our study as well as in other trials the administration of G-CSF may have been too late to alter the course of disease and outcome of these patients.

Another factor of influence on the efficacy of adjunctive treatment with G-CSF is the choice of antibiotic therapy. Filgrastim is known to increase the intracellular uptake of some antibiotics including ciprofloxacin [41]. In our study fluorochinolones were only applied in 7% of cases, thus a possible positive effect of adjunctive treatment with G-CSF for this particular subgroup could not be discriminated due to the small number of patients.

As in most other previous trials the application of filgrastim was safe in our study. None of the observed SAEs could be attributed to the use of filgrastim. We observed a prompt and significant increase of neutrophils in the filgrastim group indicating that the dosage applied had appreciable biological activity. In respect of the clinical course of patients there was only one noteworthy, even if not statistically significant, difference between the two treatment groups. All four deaths within 30 days in the placebo group occurred in the sequel of sepsis, while the only death in the filgrastim group was unrelated to infection. Overall sepsis developed in six placebo patients and only in one patient treated with filgrastim. Considering the small number of patients studied, this difference can neither clearly be attributed to the application of filgrastim, nor can it be excluded that filgrastim prevented the development of sepsis.

In conclusion, the application of filgrastim is safe and feasible in non-neutropenic, critically ill patients with nosocomial pneumonia. In this study adjunctive treatment with filgrastim did not reduce mortality in patients with nosocomial pneumonia, while there was a trend to a reduced sepsis rate in the filgrastim group. Our results are consistent with those of other studies with considerably higher statistical power. However, the consideration of the recently emerged knowledge about the delicate balance of endogenous G-CSF levels inducing local and systemic immunological effects is encouraging to design appropriate studies to investigate the optimal timing of exogenous G-CSF and its influence of the course of severe bacterial infections.

Acknowledgements: We are grateful to Jürgen Schölmerich for critical discussion of the manuscript.
This work was supported by AMGEN, Munich, Germany

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Received: November 10, 2004 / Accepted: December 15, 2004

Address for correspondence:
Pia Hartmann MD
Department of Internal Medicine I
Division of Infectious Diseases
D-93042 Regensburg, Germany
Tel: +49-941-944-7163
Fax: +49-941-5840542
e-mail: pia.hartmann@klinik.uni-regensburg.de