Human Granulocyte Colony-stimulating Factor May Improve Outcome Attributable to Neonatal Sepsis Complicated by Neutropenia

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ABSTRACT. Objectives. To determine whether adjunctive therapy with recombinant human granulocyte colony-stimulating factor (rhG-CSF) could reverse sepsis-associated neonatal neutropenia and improve neonatal survival compared with conventional therapy in a phase I/II-type trial.

Study Design. An intravenous infusion of rhG-CSF (10 μg/kg/d × 3 d) was administered to 14 septic neutropenic neonates. Neutrophilic responses and outcome of these neonates were compared with 11 concurrently treated, retrospectively selected, case-matched control septic patients identified by using a search of medical records coded for sepsis with neutropenia (24 hours).

Results. Seven neonates with early-onset sepsis with neutropenia at birth and seven neonates with late-onset sepsis plus neutropenia (all with necrotizing enterocolitis) were entered in the rhG-CSF treatment group. Results were compared with a conventional therapy control group (five early onset, six late onset). No significant differences existed in the birth weight, gestational age, use of antibiotic therapy, magnitude of respiratory support, severity of metabolic acidosis, use of vasopressors, or other supportive therapy between the two groups. In the rhG-CSF-treated group and in the conventionally treated control group, the absolute neutrophil count (ANC) (mean ± SEM) was 585 ± 138 and 438 ± 152, respectively. The ANC increased to more than baseline in the rhG-CSF-treated group by 10-fold versus 2-fold at 24 hours, 18-fold versus 4-fold at 48 hours, 24-fold versus 5-fold at 72 hours (significant by one-way analysis of variance in the rhG-CSF group only), and 29-fold versus 16-fold at 7 to 10 days when compared with the conventional therapy group. There were no nonresponders in the rhG-CSF group by 24 hours after the first dose of study drug. Monocyte cell counts also increased significantly in both groups by 7 days after entry into this protocol but remained within normal range for age. No clinically significant effect on lymphocytes, erythrocytes, or platelet counts was noted. Thirteen patients in the rhG-CSF-treated group (92%; 13 out of 14) and five in the conventionally treated group (55%; 5 out of 11) survived to 28 days after the onset of the signs of sepsis. No adverse effects were noted in the rhG-CSF-treated group.

Conclusions. rhG-CSF can increase the neutrophil count in critically ill septic neutropenic neonates. This finding suggests that rhG-CSF may be effective in a therapeutically useful time frame to treat septic neonates with neonatal neutropenia attributable to bone marrow suppression or neutrophil consumption. Future randomized trials are needed to validate the beneficial effects of rhG-CSF and to determine whether any significant side effects of therapy exist. Pediatrics 1997;100(1). URL: http://www.pediatrics.org/cgi/content/full/100/1/e6; neonatal sepsis, recombinant human granulocyte colony stimulating factor, bacteremia, cytokines, very low birth weight, neutropenia.

ABBREVIATIONS. rhG-CSF, recombinant human granulocyte colony-stimulating factor; NEC, necrotizing enterocolitis; ANC, absolute neutrophil count.

Sepsis continues to remain a major reason for an increased morbidity and mortality in neonates. Bacterial sepsis occurs in .1 to 1% of term newborns, and is up to 50 times more common in extremely low birth weight infants (neonates below 800 g at birth). Four percent of deaths in the first 3 days of postnatal life and 45% of deaths after 2 weeks are related to infections, with no change in this pattern for the past 15 years. Mortality from neonatal sepsis depends upon the virulence of the organism, the gestational age of the neonate, and the particular combination and severity of the patient's concomitant illnesses.

Neonatal sepsis is also commonly associated with neutropenia as a result of a shortened neutrophil half-life from 6.3 hours to less than 4 hours, a limited ability to augment production of the neutrophil proliferative pool, defective production of cytokines, and a rapid depletion of the infant's neutrophil storage pool during bacteremia. The resulting neutropenia serves as an ominous marker for an exaggerated additional risk of mortality attributable to sepsis which rises to as high as 90%. Although the immature immune system is limited in a variety of ways, quantitative deficiencies of the myeloid and phagocytic system in general, and immaturity of neutrophil function in particular, are thought to contribute significantly to the high morbidity and mortality from bacterial sepsis in this population. Furthermore, as nosocomial infections are the most common cause of late-onset mortality and because this patient group contributes up to 70% of all in-hospital patient days (University Medical Center at Stony Brook, 1995), better methods of reducing morbidity and mortality attributable to late-onset nosocomial infections (≥4 days) as well as early-onset infections (<1 day) are desirable.
rhG-CSF has been considered to enhance stochastic entry into the granulocytic pathway, increase rapid egress of immature neutrophils into the peripheral circulation,\textsuperscript{20,21} and also, improve the killing capacity of mature neutrophils.\textsuperscript{22} In addition, septic neonates show reduced expression of granulocyte colony-stimulating factor yet the myeloid lineage from premature infants expresses receptors for this cytokine at adult levels.\textsuperscript{23,24} Taken together, these observations suggest that rhG-CSF replacement therapy may be beneficial in this population.

Recently, several case reports argue that administration of rhG-CSF contributed significantly to improved outcome attributable to neonatal septicemia even without neutropenia.\textsuperscript{25-28} In addition, we and others have found that persistent preeclampsia-associated neutropenia (\(>3\) consecutive days) could be reversed with rhG-CSF in severely affected neonates suggesting that the immature neonate’s bone marrow had a substantial and unanticipated reserve capacity in these two clinical conditions.\textsuperscript{29,30} The objective of this study is to determine whether rhG-CSF might prove helpful in the treatment of neonatal sepsis-associated neutropenia in a therapeutically useful time frame. We examined the effects of rhG-CSF on the peripheral white cell responses and survival of fourteen neutropenic and septic neonates and compared this with eleven neutropenic and septic neonates concurrently treated using only conventional therapy.

MATERIALS AND METHODS

Patient Selection

The study was conducted in the Neonatal Intensive Care Unit of the University Hospital of the State University of New York at Stony Brook from August 1994 to August 1996. Neonates treated with rhG-CSF were selected as potential candidates for therapy if they were considered to be septic (ie, systemic signs of infection) and were neutropenic for \(\geq 24\) hours (see below). Patients were enrolled into this Phase I/II-type toxicity trial after obtaining written informed consent from a parent. The protocol was approved by our Institutional Research Board and is registered with the Food and Drug Administration (IND #5616). Concurrently treated and conventionally-treated control patients were identified retrospectively from a review of hospital records identified for neonatal sepsis with associated neutropenia for \(\geq 24\) hours using the same study entry criteria.

Definitions

Neutropenia was defined as a total neutrophil count less than 1500 cells/mm\(^3\) using a minor modification of the criteria of Manroe, et al.\textsuperscript{31} Neutropenia was identified in two separate peripheral blood samples taken \(>12\) hours apart and obtained within \(24\) hours of the onset of clinical symptoms. The absolute neutrophil count was determined by multiplying the total leucocyte count (corrected for nucleated red blood cells and obtained by a Coulter Counter, model #STKS, Coulter Technologies, Miami, FL) by the percentage of polymorphonuclear leucocytes and band forms identified manually in peripheral venous or arterial blood. Metamyelocytes and myelocytes were not included because they may not be functionally active as a phagocytic defense system and contribute minimally to the total count.\textsuperscript{32}

Sepsis was suspected when a newly symptomatic (respiratory distress, apnea, temperature instability, and other well-accepted clinical signs of sepsis)\textsuperscript{33} and neutropenic (\(\geq 24\) hours) neonate had both an unexplained metabolic acidosis (\(>5\) meq/L) and hypotension (below age-appropriate normative data).\textsuperscript{34} Culture-positive sepsis was diagnosed when a positive blood culture was obtained in association with any of these signs. Culture-negative sepsis was defined as neutropenia for 24 hours in association with metabolic acidosis and hypotension.

Necrotizing enterocolitis was diagnosed when neutropenia existed in association with both clinical (ileus, bloody stools, and bilious drainage) and radiographic (pneumatosis intestinalis) signs of the disorder.\textsuperscript{29} Patients were followed by serial radiography every 8 hours until their condition improved, stabilized, or they perforated.

Treatment Protocol

Both the study population and the control population were treated with appropriate conventional therapeutic interventions including antibiotics, oxygen and mechanical ventilatory support, intravenous fluids, vasopressor drugs (dopamine or dobutamine), and other standard interventions deemed necessary by the attending neonatologist responsible for the clinical treatment of the neonate independent of study drug usage. In addition, neonates in the study group received intravenous rhG-CSF (Filgrastim; Amgen, Thousand Oaks, CA) at a dose of 10 \(\mu\)g/kg/d in 5% dextrose (final concentration, 15 \(\mu\)g/mL) for 1 hour\textsuperscript{29,30} daily for a maximum of 3 days administered via microbore tubing (0.8 mL dead space to limit drug loss on tubing). During and up to 72 hours after the administration of rhG-CSF, continuous cardiorespiratory monitoring, as well as frequent fluid and electrolyte measurements, were performed. Daily monitoring of complete peripheral white blood cell counts and manual differential counts were performed until they remained within the normal range in all neonates for a period of up to 2 weeks as is the current hospital routine in patients with this severity of infectious illness.

Statistics

Statistical analysis was performed using a one way analysis of variance with repeated measures followed by the Dunnet’s multirange test for multiple comparisons between the baseline value cell count and counts from subsequent time points for both patient groups. A \(\chi^2\) test was used to determine significance of difference in proportional data. All nominal data are reported as mean \(\pm\) SEM (a \(P\) value <.05 was considered significant with a power \(>8\)).

RESULTS

Infectious Course

Fourteen neonates were entered in the rhG-CSF plus conventional treatment group and 11 concurrently-treated neonates received only conventional medical treatment. The demographic clinical characteristics of both groups (Table 1) showed no significant differences. Seven patients from the rhG-CSF group and five from the conventionally-treated group had early-onset sepsis (\(<1\) day postnatal age) and were clinically symptomatic and neutropenic from birth. Seven neonates from the rhG-CSF group and six from the conventionally-treated group had late-onset sepsis (onset \(>4\) days postnatal age) with a median age of onset of 14 days in both the conventional and rhG-CSF-treated groups. All patients with late-onset sepsis had a normal ANC from birth but subsequently became neutropenic (\(<1500\) cells/mm\(^3\) \(\times\) 24 h) after the diagnosis of necrotizing enterocolitis.

Three symptomatic infants from each of the two treatment groups with early-onset sepsis (rhG-CSF and conventional) were bacteremic with Group B \(\beta\)-hemolytic Streptococcus. In addition, one neonate from rhG-CSF group and two neonates from the conventional treatment group grew gram-negative bacteria from their blood. Culture-negative sepsis was diagnosed in three neutropenic infants in the rhG-CSF treatment group who also had an unexplained metabolic acidosis (\(>5\) meq/L), hypoten-
Tension in the rhG-CSF treatment group and 3 out of 6 patients had perforated their viscus (3 out of 7 patients before delivery. Antibiotics were given to the mother less than 4 hours of maternal chorioamnionitis in which antepartum cal history and histopathological evidence (placenta) potentiation (treated with pressors), and apnea (>24 hours postnatal age) all before rhG-CSF therapy. He went on to develop pulmonary hemorrhage again on day 10 postnatal age after a routine tracheal toileting

Clinical Hospital Course

All neonates tolerated rhG-CSF well and in each case no adverse reactions were identified with regard to cardiovascular performance, electrolyte balance, skin reaction, irritability or worsening of respiratory function. One 930-g patient in the early sepsis group received surfactant for hyaline membrane disease and developed a pulmonary hemorrhage on day 3 postnatal age. This patient’s hospital course had been complicated by neutropenia, metabolic acidosis, hypotension (treated with pressors), and apnea (<24 hours postnatal age) all before rhG-CSF therapy. He went on to develop pulmonary hemorrhage again on day 10 postnatal age after a routine tracheal toileting (suctioning) procedure. This adverse event was considered to be unrelated to use of study drug. Patients in both groups also received conventional neonatal intensive care unit treatment for severe sepsis which included antibiotics for 10 days or more, ventilatory support of respiration (13 out of 14 vs 11 out of 11, P = ns), and vasopressors (dopamine and/or dobutamine: 7 out of 14 vs 7 out of 11, P = ns; Table 1) in the conventional and rhG-CSF treatment groups, respectively. Hematocrits were routinely maintained at or around 40% by transfusions with packed red blood cells.

Mortality

Thirteen neonates in the rhG-CSF group and five in the conventionally-treated group were alive at 28 days after the onset of their presenting illness (P < .03, power .8) and 12 neonates in rhG-CSF group and 4 in conventionally-treated group survived to discharge. In the 11 conventionally-treated patients, 3 of 5 neonates with early-onset sepsis died within 24 hours of treatment with only antibiotics plus supportive therapy and one additional neonate died 48 hours after initiating conventional treatment. None of the rhG-CSF-CSF-treated neonates died in the early-onset sepsis group.

Late-onset mortalities included one neonate in the rhG-CSF group who had NEC with severe hypotension, renal failure, and extensive necrosis of the intestine before study drug administration. This patient died before the administration of the second dose of rhG-CSF. A second patient died after a diagnosis of NEC associated with extensive necrosis of the small intestine that required ileal resection and ileostomy. This patient died of morbidity derivative of the initial diagnosis of NEC 7 months later attributable to short-gut syndrome, severe bronchopulmonary dysplasia, and cor pulmonale after an acute episode of aspiration pneumonia.

In the conventional-treatment patients with late-onset sepsis two neonates died from NEC as well. One neonate had septic shock, grew Escherichia coli from a blood culture and died before surgery at 14 days postnatal age (2 days after the diagnosis of NEC). The second neonate with NEC died on the third postoperative day with hypotensive shock presumed to be attributable to overwhelming sepsis.

rhG-CSF Effects on Peripheral White Blood Cell Counts and Differential Counts

The absolute neutrophil count at the time of entry into this protocol in the rhG-CSF treatment group was 585 ± 138/μm³ (mean ± SEM) and 438 ± 152/μm³ (P = ns) in the conventionally-treated group (Table 2). The neutropenia in all patients was present from 24 hours or more to 120 hours before the institution of rhG-CSF therapy.

The ANC increased by 7-fold versus 2-fold at 24 hours after entry into the study protocol in the rhG-CSF- and conventional-treatment groups, respectively. Subsequently, the ANC was increased by 13- fold vs 4-fold at 48 hours, 21-fold vs 5-fold at 72 hours (P < .05 vs day 0 in the rhG-CSF group only), and 27-fold vs 16-fold at 7 to 10 days after entry (P <
In both groups, day 7 to 9 vs day 0) in rhG-CSF- and conventional-treatment groups, respectively (Table 2 and Fig 1). All but the one patient with an ANC of zero (who expired less than 24 hours after entry into the protocol), showed a statistically significant response to rhG-CSF that persisted at 72 hours and peaked between 7 to 10 days after the last dose of rhG-CSF was administered. In contrast, conventionally-treated patients had ANC’s that were consistently lower than the rhG-CSF group on all days after entry into this protocol and were only significantly increased at the 7- to 10-day point (Fig 1 and Table 2).

The absolute monocyte count increased significantly more than baseline values at 7 to 10 days after the onset of sepsis in both patient groups (P < .05; Table 2). In all cases, there were no significant differences between the two groups at any time point and the rise in the monocyte cell count remained within the published normal range for this cell type.36

We observed no statistical or clinically significant effects on the hematocrit in these patients as they were transfused to keep it greater than 40%. At entry, the hematocrits were 37 ± 2% and 36 ± 2% (x ± SEM) for the rhG-CSF and conventional groups, respectively. At day 7 to 10, the values were 38 ± 2% and 39 ± 2%, respectively (P = ns). The absolute cell counts were noted to increase with regard to lymphocytes in both groups with a peak effect on day 7 to 10 after entry into this study protocol (P < .05 for both groups versus baseline in rhG-CSF- and conventionally-treated groups, respectively). However, absolute lymphocyte counts remained within normal range and there was no significant difference between the two groups at any time point. Also there were no clinically or statistically significant differences in platelet counts throughout the time for ei-

<table>
<thead>
<tr>
<th>Type of Cells</th>
<th>GCSF-Treated Group (n = 14)</th>
<th>Conventionally Treated Group (n = 11)</th>
</tr>
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<tbody>
<tr>
<td>Day 0</td>
<td>Day 1 Day 2 Day 3 Day 7–10 Day 0 Day 1 Day 2 Day 3 Day 7–10</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>3378 ± 624 558 ± 84 287 ± 168 11 349 ± 99 11 98 ± 36 296 ± 103 5 657 ± 207 654 ± 207 5</td>
<td></td>
</tr>
</tbody>
</table>
| Monocytes     | 2676 ± 770 1542 ± 1529 264 ± 489 62 ± 41 1011 ± 1010 11 104 ± 95 203 ± 77 14 104 ± 102 12 1326  
| Polymorphonuclear neutrophils | 909 ± 158 2096 ± 450 1198 ± 149 2007 ± 89 679 ± 228 203 ± 89 |
| Bands         | 188 ± 1215 1831 ± 754 2246 ± 1034 2431 ± 616 7 3229 ± 1475 8 |
| Polymorphonuclear neutrophils | 3457 ± 909 2079 ± 2079 555 ± 2079 2721 ± 2721 23 100 ± 2630 16 72 1491 |
| Absolute neutrophil count | 585 ± 138 4431 ± 1281 7633 ± 1885 23 100 ± 2630 23 775 ± 13 052 16 72 1491 |
| White blood cell count total | 4790 ± 911 11 190 ± 2630 15 189 ± 2721 23 100 ± 16 467 16 72 1491 |
| *P < .05 vs cell count value at baseline upon entry into protocol tested by 1-way analysis of variance with repeated measures followed by Dunnet’s multirange test; mean ± SEM. | 1795 ± 379 174 ± 100 |

Fig 1. The timing of the changes in the ANC in the rhG-CSF-treated neonates occurs sooner and remains longer than in the conventionally-treated control neonates. rhG-CSF group (n = 14, ●); no rhG-CSF group (n = 11, □). Numbers adjacent to individual points indicate the remaining live patients at each time point.
ther group (eg, 199 ± 73 and 101 ± 19/mm³ at entry and 219 ± 55 and 172 ± 57/mm³ at day 7 to 10 for rhG-CSF and conventional groups, respectively), and no patients were transfused with platelets.

**DISCUSSION**

We identified two groups of septic and neutropenic neonates who presented either at birth (<1 day postnatal age) or after the fourth day of postnatal life with systemic symptoms of sepsis including hypotension and metabolic acidosis. In either the early- or late-onset groups, the absolute neutrophil count increased in 24 hours or less after intravenous administration of rhG-CSF well before changes observed in a similar population of retrospectively selected case-matched, conventionally-treated control patients. The increase in the white blood cells in the rhG-CSF-treatment group was statistically significantly higher at 24 hours than that of the conventionally-treated control group in which the increase only achieved significance at 7 to 10 days after entry. The neonatal response followed a predictable pattern of timing similar to observations made in adult patients with sepsis or pneumonia.²⁷,³⁸

We used a single daily dose of rhG-CSF (10 μg/kg/d × 3 daily intravenous infusions) to evaluate white cell counts and clinical responses. This dosing protocol was adapted from a report by Gillian, Cairo and their colleagues³⁹ which showed a rapid rise in the ANC of nonneutropenic neonates with presumed sepsis, at 10 μg/kg/d and an increase in the bone marrow neutrophil storage pool by 72 hours after treatment. In addition, Makhlouf et al³⁰ showed that neutrophil counts could rise within 6 hours of administration and others showed a dose-dependent increase in neutrophils that plateaued around this level³¹,³⁸ followed by a sustained elevation for up to 2 weeks in newborns.²⁷,³⁸ This sustained rise follows presumably, from the stochastic theory of entry of more progenitor cells into the myeloproliferative pathway.³⁰ We chose to discontinue the rhG-CSF therapy after three daily doses because the magnitude of the ANC response begins to plateau in adults after 4 days of treatment and we found that neonatal cell counts had entered into the normal range by then.

We also examined the effects of rhG-CSF on other peripheral cell types and found a statistically significant elevation in the absolute monocyte and lymphocyte counts but no significant change in platelet number or hematocrit. The failure to identify a change in the hematocrit is likely a result of our practice of administering booster-packed red-cell transfusions to all oxygen requiring ventilated patients to maintain their hematocrits at or approximately 40%.³⁰,⁴¹ Although, the changes in the absolute monocyte and lymphocyte counts were statistically significant at the 7- to 10-day point, they always remained within the range of published normal values.³⁶ No adverse effects could be attributed to these unintended study drug responses. A similar trend in all cell count results was evident in the conventionally-treated patients as well (Table 2 and Fig 1).

The 10% mortality in our rhG-CSF treatment group was lower than in the matched conventionally-treated control patients (55%, P < .03, power ≥ .8) or to mortality in septic and neutropenic patients described in previous reports in which it was nearly 90%.¹⁴ Based on animal literature and adult studies, this effect would be anticipated. In rodents, administration of rhG-CSF at the onset of the inoculum lowers mortality in experimental group B β-hemolytic streptococcus sepsis compared with antibiotics alone.⁴² Similarly, administration of rhG-CSF with antibiotics in a rabbit model of gram-negative sepsis and neutropenia improves survival compared with antibiotics alone.⁴³ Because a survival benefit is also detected in adult humans with severe sepsis and multiorgan failure,⁴⁰ it is plausible that the improved survival we observed in neonates may eventually prove valid in a larger blinded randomized sample of patients. This putative improvement in survival may arise from the ability of rhG-CSF to augment neutrophil chemotaxis, enhance phagocytosis, increase superoxide production, accelerate antibody dependent cellular cytotoxicity, increase neutrophil FcγRI and C3bi expression, and increase respiratory burst activity.²² Treating extremely low birth weight neonates with a cytokine that can rapidly (<24 hours) augment the cellular immune responses has extraordinary potential for benefit in a population of patients with a more than 30% underlying incidence of bacterial sepsis at baseline risk that carries up to a 50% mortality²⁵ or even more with neutropenia.²,⁴,⁵,¹₄,¹₅ Although a good reason for cautious optimism, current thinking suggests that reperfusion injury (after hypoxia or reduced blood flow or both) may involve a significant activation of macrophages and local invasion of peripheral blood neutrophils, that could be detrimental to recovery.³⁰,⁴⁴ Thus, it is conceivable that bronchopulmonary dysplasia, NEC, retinopathy of prematurity, or even intraventricular hemorrhage may be considerably worsened by adjunctive treatment with this drug.

In the current series of 14 neonates and in 24 additional patients we have studied (IND #5616), as well as in the published neonatal literature where 77 neonatal patients are reported, there is no evidence of any clinically significant adverse effects attributed to rhG-CSF therapy.⁵⁻⁹,²⁵⁻⁷,²⁹,³⁰,³⁹,⁴⁵ In only one neonatal report in which thrombocytopenia existed before rhG-CSF was given was there an associated decrease in the platelet count.²⁷ In adult patients treated with rhG-CSF and antibiotics for community acquired pneumonia, pulmonary complications were reduced.³⁷ Moreover, in transplanted organs (liver) where reperfusion injury would be expected to be exaggerated, a lower incidence of graft rejection and postoperative infections was identified when patients were treated with rhG-CSF.⁴⁶ Therefore, at present, there does not seem to be any clinically significant adverse effects recognized or attributable to rhG-CSF cytokine therapy in septic and neutropenic neonates regardless of their underlying risk for hypoxia or reperfusion injury. Nevertheless, a larger series of similarly treated patients would be necessary to identify any potential, or more subtle adverse effects.

In conclusion, based upon the high mortality reported in the medical literature and the results of this and other anecdotal reports,¹,³⁻⁵,¹₄ it seems reasonable to consider rhG-CSF therapy in septic neonates with persistent neutropenia (>24 hours) in an attempt to
improve their overall chances for survival. However, this therapy must still be viewed as experimental until a randomized, placebo-controlled, double-blinded trial can be coordinated to validate the putative beneficial effects on outcome in neonates. Two multicenter trials are already in progress in the United States (late-onset sepsis) and in Europe (early-onset sepsis) to define these issues further.

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