Molgramostim (GM-CSF) Associated With Antibiotic Treatment in Nontraumatic Abdominal Sepsis

A Randomized, Double-blind, Placebo-Controlled Clinical Trial

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Hypothesis: The addition of molgramostim (recombinant human granulocyte-macrophage colony-stimulating factor) to antibiotic therapy for nontraumatic and generalized abdominal sepsis is effective and has a significant impact on length of hospitalization, direct medical costs, and mortality.

Design: Randomized, double-blind, placebo-controlled clinical trial.

Setting: Tertiary referral center.

Patients: Fifty-eight patients with abdominal sepsis.

Interventions: Patients were allocated to receive, in addition to ceftriaxone sodium, amikacin sulfate, and metronidazole, molgramostim in a daily dosage of 3 µg/kg for 4 days (group 1) or placebo (group 2). Antibiotics were administered for at least 5 days and discontinued after clinical improvement had occurred and white blood cell count had been normal for 48 hours.

Main Outcome Measures: Time to improvement, duration of antibiotic therapy, hospital stay, complications, mortality, and adverse reactions to drugs.

Results: Median time to improvement was 2 days in group 1 and 4 days in group 2 (P < .005). Median length of hospitalization was 9 and 13 days, respectively (P < .001), and median duration of antibiotic therapy was 9 and 13 days, respectively (P < .001). Numbers of infectious complications in the 2 groups were, respectively, 6 and 16 (P = .02); of residual abscesses, 3 and 5; and of deaths, 2 and 2. Costs per patient were $12,333 and $16,081 (US dollars), respectively.

Conclusion: Addition of molgramostim to antibiotic therapy reduces the rate of infectious complications, the length of hospitalization, and costs in patients with nontraumatic abdominal sepsis.

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Recent studies in animal models of peritonitis, as well as pilot trials in patients with sepsis, point out that GM-CSF, when used as adjuvant therapy, might reduce mortality, disability, and, potentially, health care costs. This randomized, double-blind, placebo-controlled clinical trial was conducted to assess the efficacy of one form of GM-CSF, molgramostim, added to standard antibiotic therapy in patients with generalized nontraumatic peritonitis.¹⁰⁻¹⁴

See Invited Critique at end of article

METHODS

DESIGN

Adult patients with generalized peritonitis were included in this randomized, double-blind, placebo-controlled trial. All underwent surgery and were given intravenous antibiotics. During surgery, they were randomly allocated to receive...
either molgramostim, 3 µg/kg per day for 4 days (group 1), or an identical-appearing placebo (group 2). Clinical and laboratory measurements were carried out without knowledge of the group to which the patient was allocated. The protocol was reviewed and approved by the institutional review board, and all patients gave written informed consent.

ELIGIBILITY CRITERIA
Patients aged 18 to 80 years, with generalized peritonitis characterized by septic involvement of 2 or more abdominal quadrants at the time of surgical intervention and with positive peritoneal cultures, were included. Exclusion criteria were terminal renal, hepatic, or lung failure; positive pregnancy test; current treatment with an immunosuppressive drug; tuberculosis; or leukemia.

INTERVENTION
Standard intravenous antibiotic therapy consisting of ceftriaxone sodium (1 g twice daily), amikacin sulfate (15 mg/kg per day), and metronidazole (500 mg 3 times daily) was started at the time of diagnosis. In patients allergic to β-lactams, ofloxacin (400 mg twice daily) was administered together with metronidazole. According to the random allocation schedule, molgramostim (3 µg/kg per day) or an identical-appearing placebo was administered subcutaneously during 4 days beginning in the operating room at the time of randomization. Antibiotic treatment was suspended after a minimum of 5 days of administration, when clinical improvement, normal temperature for at least 2 days, and normal white blood cell (WBC) count were observed. Antibiotic treatment was modified according to the antimicrobial susceptibility of the microorganisms isolated.

MEASUREMENTS
Clinical data, WBC count, abdominal cultures, and Acute Physiology and Chronic Health Evaluation II scores were obtained on admission.17,18 Clinical evaluations and WBC count were performed on a daily basis during hospital stay and every 2 weeks for up to 2 months after discharge. The following outcomes were recorded: time to improvement, defined as normalization of body temperature and bowel movements; time with antibiotic therapy, defined as duration of antibiotic treatment for abdominal sepsis and/or infectious complications; hospital stay, defined as the duration of in-hospital stay related to the episode of abdominal sepsis and/or complications; and emergence of infectious and noninfectious complications, mortality, and adverse reactions to drugs. For the calculation of direct medical costs, and for international validity, the costs per hospital day, for specific antibiotics, and for molgramostim were derived from the study by Price et al.19

STATISTICS
Continuous variables were summarized in terms of mean ± SD or median (interval). Nominal and discrete variables were summarized as absolute and relative frequencies. Analysis was performed on an intention-to-treat basis. The 2-tailed t test for independent samples was used to compare means, and the Mann-Whitney test was used to compare medians. The Fisher test was used to compare nominal and discrete variables. P < .05 was considered statistically significant.

RESULTS
Sixty-one patients were included in the trial during a 19-month recruitment period. Two patients from group 1 and 1 from group 2 were excluded because they refused therapy after randomization. Baseline demographic characteristics, Acute Physiology and Chronic Health Evaluation II score, results of laboratory tests, and intraoperative diagnosis were statistically comparable in both groups (Table 1). Microorganisms isolated from the peritoneal fluid of patients in groups 1 and 2 were as follows: Escherichia coli (16 and 17 patients, respectively), Enterococcus species (12 and 9 patients), Streptococcus species (2 and 5 patients), Klebsiella species (4 and 1 patient), Pseudomonas species (0 and 3 patients), Enterobacter species (0 and 2 patients), Staphylococcus (2 and 0 patients), Clostridium species (1 and 0 patients), Bacteroides species (0 and 1 patient), polymicrobial (9 and 10 patients), and Candida species (1 and 1 patients).

After 24 hours of treatment, WBC count showed a gradual increase in group 1. On day 2, mean WBC count was 17.8 × 10^3/µL in group 1 and 12.2 × 10^3/µL in group 2 (P < .001). On day 4, mean values were 20.1 × 10^3/µL and 10.0 × 10^3/µL, respectively (P < .001). The WBC values returned to normal in both groups at the second week after randomization and remained so up to 8 weeks of follow-up (Figure).

Median time to clinical recovery and improvement was 2 days in group 1 and 4 days in group 2 (P < .005). Median hospital stay was 9 and 13 days (P < .001), and median time with antibiotic therapy was 9 and 13 days (P < .001), respectively (Table 2). Because of 2 early deaths in group 1, the minimum hospital stay and duration of antibiotic therapy were 1 day.

Six episodes of infectious complications developed in group 16 and in group 2 (P = .02). Three patients from group 1 had residual abscess (presence of a collection of fluid detected by ultrasound or computed tomographic scan with a positive culture); 2 required reoperation and 1 underwent percutaneous drainage. In group 2, 5 patients had residual abscess; 4 required reoperation and 1 underwent percutaneous drainage. Wound infections were less common in group 1 (3 vs 9 cases), as was pneumonia (0 vs 2 cases).

Table 1. Patients’ Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 30)</th>
<th>Group 2 (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. M/F</td>
<td>13/17</td>
<td>16/15</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>43.2 ± 15.9</td>
<td>49.2 ± 16.5</td>
</tr>
<tr>
<td>APACHE II score, mean ± SD</td>
<td>7.3 ± 6.3</td>
<td>7.7 ± 6.4</td>
</tr>
<tr>
<td>WBC count/µL, mean ± SD</td>
<td>13.5 ± 5.8</td>
<td>14.5 ± 9.1</td>
</tr>
<tr>
<td>Neutrophils, mean ± SD, %</td>
<td>82.6 ± 8.3</td>
<td>80.1 ± 11.5</td>
</tr>
<tr>
<td>Intraoperative diagnosis, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute appendicitis</td>
<td>16 (57)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Small-bowel perforation*</td>
<td>2 (7)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Colonic perforation†</td>
<td>5 (18)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Gangrenous cholecystitis</td>
<td>3 (11)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Perforated peptic ulcer</td>
<td>0</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Other‡</td>
<td>2 (7)</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation II; WBC, white blood cell.

*Includes ischemic, Meckel diverticulum, and complicated obstruction.
†Includes diverticulitis and ulcerative colitis.
‡Includes unidentified perforation sites.
Five adverse reactions were observed in group 1, 3 possibly related to molgramostim administration (1 case of thrombocytopenia, 1 of generalized rash, and 1 of nausea) and 2 apparently not related (1 case of deep vein thrombosis and 1 of superficial phlebitis). In group 2, 7 adverse reactions were observed, specifically 1 case of liver and lung failure, 2 cases of pneumonia, 1 eventration, 1 allergy to β-lactams, 1 pulmonary embolism, and 1 episode of encephalopathy.

There were 2 deaths in group 1 and 2 in group 2. Deaths in group 1 occurred early (within 12 hours after surgery) and were due to sepsis and pulmonary embolism. Deaths in group 2 occurred 5 and 7 days after intervention and were due to multiple organ failure and sepsis.

Direct medical costs (in US dollars) in group 1 were $9963 for hospitalization, $1170 for antibiotics, and $1200 for molgramostim, giving a total of $12 333 per patient. In group 2, costs were $14 391 for hospitalization and $9963 for hospitalization, $1170 for antibiotics, and $1200 for molgramostim, giving a total of $12 333 per patient. This resulted in a savings of $3748 per patient treated with molgramostim.

**COMMENT**

Our data show that addition of molgramostim to the standard treatment of patients with abdominal sepsis of nontraumatic origin is safe and effective, reducing the rate of infectious complications, the duration of antibiotic therapy, and the length of hospital stay. To our knowledge, this is the first trial to evaluate and demonstrate the clinical usefulness of GM-CSF in abdominal sepsis in humans. It has been observed experimentally that GM-CSF has several effects in peritonitis, such as enhancement of hematopoiesis and immune reaction, and it may also play a role in the down-regulation of inflammatory mediators that are produced by bone marrow cells during abdominal sepsis. It is well known that GM-CSF enhances many of the granulocyte and monocyte-macrophage functions, such as the generation of superoxide anion in response to bacterial peptides, among many others. Also, it has been demonstrated that GM-CSF induces endothelial proliferation and migration, and stimulates in vitro neutrophil and monocyte phagocytosis,

In a randomized, placebo-controlled trial involving 40 patients with diabetic foot infections, Gough et al evaluated the effect of a different colony-stimulating factor, granulocyte colony-stimulating factor, as an adjuvant therapy. They found that this treatment induced statistically significant differences in terms of earlier eradication of pathogens from infected ulcers (P = .02), quicker resolution of soft tissue infections, shorter hospital stay, shorter duration of intravenous antibiotic treatment, and increased neutrophil production. In another study, in neutropenic patients with bacterial and fungal infections, treatment with antibiotics plus GM-CSF resulted in a significantly better response rate than antibiotics plus placebo.

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**Table 2. Clinical Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group 1 (n = 28)</th>
<th>Group 2 (n = 30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to improvement, median (d)</td>
<td>2 (1-5)</td>
<td>4 (2-8)</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Time with antibiotic therapy, median (d)</td>
<td>9 (1-12)</td>
<td>13 (5-21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hospital stay, median (d)</td>
<td>9 (1-12)</td>
<td>13 (5-21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Infectious complications, No. (%)</td>
<td>6 (21)</td>
<td>16 (53)</td>
<td>.02</td>
</tr>
<tr>
<td>Surgical wound infection</td>
<td>3</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Adverse events, No. (%)</td>
<td>5 (18)</td>
<td>7 (23)</td>
<td>.75</td>
</tr>
<tr>
<td>CT scan–guided drainage, No. (%)</td>
<td>1 (4)</td>
<td>1 (3)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Reoperations, No. (%)</td>
<td>2 (7)</td>
<td>4 (13)</td>
<td>.67</td>
</tr>
<tr>
<td>Deaths, No. (%)</td>
<td>2 (7)</td>
<td>2 (7)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

Abbreviation: CT, computed tomography.
Results of our study are consistent with those reported by others.\textsuperscript{25,27} Administration of GM-CSF together with antibiotics induces a progressive and significant rise in white blood cell count and neutrophils. The observed improvement in clinical outcomes in terms of lower number of infectious complications, shorter hospital stay, faster clinical improvement, and shorter duration of antibiotic therapy is also consistent with published evidence showing that colony-stimulating factors may be of great help in patients with infectious diseases associated with neutropenic and nonneutropenic conditions.\textsuperscript{28}

The microorganisms isolated in our patients were common pathogens involved in abdominal sepsis. The low isolation rate of anaerobes, however, deserves further comment. In our environment there is frequently a difficulty in the handling of abdominal cultures in that samples remain stored in adverse conditions for long periods of time, affecting the rate of isolation of anaerobes.

Adverse reactions during molgramostim administration were observed in 3 patients. One patient developed a rash that disappeared once molgramostim treatment was suspended, 1 developed thrombocytopenia, and 1 had nausea. This low incidence of adverse reactions agrees with the study by Dierdorf et al.,\textsuperscript{27} who observed 68 patients with neutropenic pneumonia of fungal or bacterial origin treated with GM-CSF, 5 µg/kg per day for 13 days. Adverse events were rash (1 patient), fever or chills (2 patients), malaise (1 patient), myalgia (2 patients), and increased myeloblast count (1 patient). Good tolerability was observed in 89%, and no aggravation of pulmonary inflammation or sepsis occurred.

With regard to costs, addition of molgramostim to standard antibiotic therapy resulted in substantial savings (23%) in direct medical costs. The savings are mainly produced by the significant reduction in length of hospital stay and time with antibiotic therapy.

In conclusion, our data support the addition of molgramostim to standard antibiotic treatment of patients with abdominal sepsis of nontraumatic origin. Because of its efficacy and safety, adjuvant therapy with molgramostim may be of great benefit for this group of severely ill patients, by reducing the number of infectious complications, accelerating clinical improvement, and shortening the duration of antibiotic therapy. Additional benefits of molgramostim are shorter hospital stay and lower direct medical costs. Further studies to confirm these results would be desirable.

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REFERENCES