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

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

Héctor Orozco, MD; Jorge Arch, MD, PhD; Heriberto Medina-Franco, MD; Juan P. Pantoja, MD; Quintín H. González, MD; Mario Vilatoba, MD; Carlos Hinojosa, MD; Florencia Vargas-Vorackova, MD, PhD; José Sifuentes-Osornio, MD

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.

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 labora-
tory measurements were carried out without knowledge of the group to which the patient was allocated. The protocol was re-
viewed 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 char-
acterized by septic involvement of 2 or more abdominal quad-
rants at the time of surgical intervention and with positive peri-
toneal cultures, were included. Exclusion criteria were terminal
renal, hepatic, or lung failure;15 positive pregnancy test; cur-
cent treatment with an immunosuppressive drug17; tuberculosis;
or leukemia.

INTERVENTION

Standard intravenous antibiotic therapy consisting of ceftriax-
one sodium (1 g twice daily), amikacin sulfate (15 mg/kg per
day), and metronidazole (300 mg 3 times daily) was started at
the time of diagnosis. In patients allergic to β-lactams, ofloxa-
cin (400 mg twice daily) was administered together with met-
ronidazole. According to the random allocation schedule, mol-
gramostim (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 treat-
ment was suspended after a minimum of 5 days of administra-
tion, when clinical improvement, normal temperature for at least
2 days, and normal white blood cell (WBC) count were ob-
erved. Antibiotic treatment was modified according to the an-
timicrobial susceptibility of the microorganisms isolated.

MEASUREMENTS

Clinical data, WBC count, abdominal cultures, and Acute Physi-
ology and Chronic Health Evaluation II scores were obtained on
admission.15,16 Clinical evaluations and WBC count were per-
formed 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 du-
ration of in-hospital stay related to the episode of abdominal sep-
sis and/or complications; and emergence of infectious and non-
fungal complications, mortality, and adverse reactions to drugs.
For the calculation of direct medical costs, and for international
comparability, the costs per hospital day, for specific antibiotics, and
for molgramostim were derived from the study by Price at al.19

STATISTICS

Continuous variables were summarized in terms of mean ± SD
or mean (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.

RESULTS

Sixty-one patients were included in the trial during a 19-
month recruitment period. Two patients from group 1 and

### Table 1. Patients’ Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 28)</th>
<th>Group 2 (n = 30)</th>
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</thead>
<tbody>
<tr>
<td>Sex, 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>
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<td>WBC count/mL, mean ± SD</td>
<td>13.5 ± 5.8</td>
<td>14.5 ± 9.1</td>
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<td>Neutrophils, mean ± SD, %</td>
<td>82.6 ± 8.3</td>
<td>80.1 ± 11.5</td>
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<td>Intraoperative diagnosis, No. (%)</td>
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<td>Acute appendicitis</td>
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<td>Small-bowel perforation†</td>
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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.

1 from group 2 were excluded because they refused therapy after randomization. Baseline demographic character-
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diagnosis were statistically comparable in both groups

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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 non-traumatic 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, keratinocyte proliferation, and fibroblast modulation, contributing in this way to the healing process.

In 1994, in a rat model of cecal ligation and puncture treated with 20 µg of recombinant murine GM-CSF, Toda et al failed to show improvement in 48-hour survival but observed some inhibition of early leukocyte sequestration in the peritoneal cavity. Later, Gennari et al found a 75% survival rate in a mouse model of cecal ligation and puncture plus transfusion and burn treated with recombinant murine GM-CSF, 100 ng/d for 6 days. This survival was significantly superior to the 30% observed in the placebo-treated animals (P <.001) and was attributed to improvement in gut barrier function and better ability to kill bacteria. Austin et al conducted a trial in a mouse model of trauma, administering GM-CSF or isotonic sodium chloride solution intraperitoneally for 5 days before performance of cecal ligation and puncture. The group receiving GM-CSF had a better survival rate (40% vs 5%; P <.05), as well as better macrophage function, less nitric oxide, and reduced bacterial growth indexes. Clinical trials with GM-CSF have been conducted in neutropenic and pediatric patients with sepsis. Bilgin et al compared a 7-day administration of GM-CSF, 5 µg/kg per day, vs placebo in a randomized trial of 60 neonates with neutropenia and clinical signs of sepsis. Good tolerance of GM-CSF, no adverse reactions, a statistically significant increase in neutrophil count on day 7, and improved survival (10% vs 30%) were observed, suggesting that GM-CSF is effective in neonatal sepsis with neutropenia.

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 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 (range), d</td>
<td>2 (1-5)</td>
<td>4 (2-8)</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Time with antibiotic therapy, median (range), d</td>
<td>9 (1-12)</td>
<td>13 (5-21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hospital stay, median (range), 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>
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</table>

Abbreviation: CT, computed tomography.
Results of our study are consistent with those reported by others. 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.

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, 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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cias Medicas y Nutricion Salvador Zubiran, Vasco de Quiroga 15, Mexico City, 14000, Mexico (JSO@quetzal
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REFERENCES


