

ORIGINAL ARTICLE

Sargramostim for Active Crohn's Disease

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ABSTRACT

BACKGROUND

Sargramostim, granulocyte–macrophage colony-stimulating factor, a hematopoietic growth factor, stimulates cells of the intestinal innate immune system. Preliminary studies suggest sargramostim may have activity in Crohn's disease. To evaluate this novel therapeutic approach, we conducted a randomized, placebo-controlled trial.

METHODS

Using a 2:1 ratio, we randomly assigned 124 patients with moderate-to-severe active Crohn's disease to receive 6 μg of sargramostim per kilogram per day or placebo subcutaneously for 56 days. Antibiotics and aminosalicylates were allowed; immunosuppressants and glucocorticoids were prohibited. The primary end point was a clinical response, defined by a decrease from baseline of at least 70 points in the Crohn's Disease Activity Index (CDAI) at the end of treatment (day 57). Other end points included changes in disease severity and the health-related quality of life and adverse events.

RESULTS

There was no significant difference in the rate of the primary end point of a clinical response defined by a decrease of at least 70 points in the CDAI score on day 57 between the sargramostim and placebo groups (54 percent vs. 44 percent, $P=0.28$). However, significantly more patients in the sargramostim group than in the placebo group reached the secondary end points of a clinical response defined by a decrease from baseline of at least 100 points in the CDAI score on day 57 (48 percent vs. 26 percent, $P=0.01$) and of remission, defined by a CDAI score of 150 points or less on day 57 (40 percent vs. 19 percent, $P=0.01$). The rates of either type of clinical response and of remission were significantly higher in the sargramostim group than in the placebo group on day 29 of treatment and 30 days after treatment. The sargramostim group also had significant improvements in the quality of life. Mild-to-moderate injection-site reactions and bone pain were more common in the sargramostim group, and three patients in this group had serious adverse events possibly or probably related to treatment.

CONCLUSIONS

This study was negative for the primary end point, but findings for the secondary end points suggest that sargramostim therapy decreased disease severity and improved the quality of life in patients with active Crohn's disease.

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CROHN'S DISEASE IS A CHRONIC inflammatory disorder occurring throughout the gastrointestinal tract. Current treatment emphasizes the use of immunosuppressive agents. However, evolving understanding of the pathophysiology of Crohn's disease has indicated that alternative approaches, which avoid immunosuppression, may be useful. Specifically, Crohn's disease may result from defective functioning of intestinal innate immune defense, comprising intestinal epithelium and phagocytic cells of the lamina propria, including neutrophils and macrophages. Breakdown of this defensive barrier may permit persistent exposure of lamina propria cells to luminal microbes and microbial products, resulting in an aberrant, chronic inflammatory process mediated by T cells.¹⁻³ Thus, treatment directed at augmenting the intestinal innate immune defense rather than suppressing a secondary inflammatory response may be effective in Crohn's disease.

Granulocyte-macrophage colony-stimulating factor (GM-CSF), a myeloid growth factor, plays a pivotal role in the development and function of phagocytic cells. GM-CSF is also expressed by CD4+ T cells and Paneth cells of the intestinal epithelium. Furthermore, both myeloid and intestinal epithelial cells throughout the gastrointestinal tract express GM-CSF receptors.^{4,5} These findings suggest that GM-CSF may help maintain the function of the intestinal innate immune barrier and that exogenous GM-CSF may augment host defense and ameliorate inflammation associated with Crohn's disease.

Sargramostim (Leukine, Berlex) is a yeast-derived recombinant human GM-CSF, most commonly used for myeloid-cell recovery after chemotherapy. A pilot study of sargramostim without concomitant immunosuppressive therapy in 15 patients with moderate-to-severe active Crohn's disease demonstrated a high rate of clinical response and remission with limited adverse effects.⁶ We report the results of a randomized, placebo-controlled trial conducted to evaluate this unique approach in patients with moderate-to-severe active Crohn's disease.

METHODS

PATIENTS

Eligible patients were at least 18 years old with a confirmed diagnosis of moderate-to-severe active Crohn's disease, as defined by a score of 220 to 475 on the Crohn's Disease Activity Index (CDAI) (scores

can range from 0 to 600, with higher scores indicating more severe disease). Patients who had been taking stable doses of antibiotics or aminosalicylates for at least four weeks were eligible. Patients who had been taking azathioprine, mercaptopurine, methotrexate, or oral or rectal glucocorticoids within 4 weeks before the study began were not eligible, nor were those who had been receiving anti-tumor necrosis factor therapy within 12 weeks before the study began. Prior use of sargramostim or filgrastim was prohibited. Patients were excluded if they were pregnant or breast-feeding or had other serious medical conditions, an ostomy, symptoms of bowel obstruction or stricture, or detectable fecal ova, parasites, pathogenic bacteria, or *Clostridium difficile* toxin.

STUDY DESIGN

Patients were randomly assigned in a 2:1 ratio to receive sargramostim (6 µg per kilogram of body weight) or placebo subcutaneously daily for 56 days. The randomization (computer-generated by Almedica International) was stratified according to whether the patient had received prior second-line therapy for Crohn's disease. Permuted blocks of fixed size were generated for each stratum. Patients were required to complete all eligibility checks (checks of eligibility according to inclusion and exclusion criteria) before undergoing randomization. Efficacy and safety were evaluated every 2 weeks during treatment and 30 days after the end of treatment. After treatment, patients with a response were followed for up to six months for loss of clinical response. Study personnel were unaware of the patients' white-cell counts.

Participating institutions received approval from their institutional review boards. All patients gave written informed consent. The study was designed by the primary investigators in collaboration with the sponsor. Data were collected from individual sites by the sponsor, who held the data and conducted the initial statistical analyses. The academic authors had full access to the data and vouch for the veracity of the data and data analysis.

STUDY PROCEDURES AND MEASUREMENTS OF OUTCOME

Efficacy

Disease severity was measured by the CDAI.⁷ An exploratory analysis, not powered to assess statistical significance, was conducted in consenting patients at selected centers to assess mucosal response

with the use of the validated Crohn's Disease Endoscopic Index of Severity (CDEIS). Higher scores reflect increasing severity of mucosal disease.⁸ Numbers of draining fistulae before and after treatment were also assessed.

Quality of Life

The health-specific quality of life was measured by means of the Inflammatory Bowel Disease Questionnaire (IBDQ).⁹ Scores range from 32 to 224, with higher scores indicating a better quality of life.

Safety

All patients were evaluated for adverse events on the basis of their medical history, diary entries, and physical and clinical laboratory examinations. A reduction in the dose of sargramostim of 2 µg per kilogram per day was required in patients with an absolute neutrophil count of more than 40,000 per cubic millimeter. Serum samples obtained at baseline, day 29, day 57, and 30 days after treatment were screened for neutralizing antibodies against sargramostim by an enzyme-linked immunosorbent assay, followed by a GM-CSF-dependent bioassay.¹⁰

STATISTICAL ANALYSIS

The primary end point was a clinical response defined by a decrease from baseline of at least 70 points in the CDAI score at the end of treatment (day 57). Prospectively defined secondary end points included a clinical response defined by a decrease of at least 100 points in the CDAI score, remission (defined by a CDAI score of 150 or less), and an increase in the IBDQ score. Response and remission rates were also analyzed according to the use or nonuse of prior second-line therapy, smoking status, baseline C-reactive protein levels, and the presence or absence of serum antibody against *Saccharomyces cerevisiae*.¹¹

Using a two-sided Pearson chi-square test, we determined that 120 patients (80 in the sargramostim group and 40 in the placebo group) would need to be enrolled for the study to have a statistical power of 88 percent to detect an absolute difference between groups of 30 percent in the incidence of the primary end point, given a type I error rate of 0.05. Data were analyzed after the completion of the 30-day follow-up visit. No interim analyses were performed.

All analyses included all randomized patients who received at least one dose of study medication,

according to the treatment received. Statistical analyses described below were prospectively defined. Patients who prematurely discontinued treatment for any reason were considered to have had no response from that point onward. Missing continuous and categorical data were otherwise imputed by carrying the last observation forward. For time-to-event analyses, data on patients who did not reach the end point were censored at the time of the last follow-up visit. Efficacy data collected after the 30-day follow-up visit were evaluated without any type of imputation for missing data. Patients who withdrew during follow-up were considered to have had a loss of response from that time forward. Comparisons between the two treatment groups were adjusted for the stratification variable. All statistical tests were two-sided, and a P value of 0.05 was considered to indicate statistical significance. The Cochran-Mantel-Haenszel chi-square test was used to compare the two groups, stratified according to the use or nonuse of prior second-line therapy, on the basis of the proportion of patients who met criteria for a clinical response and remission. Changes in CDAI and IBDQ scores were analyzed by means of stratified rank tests, based on Van Elteren's test (a stratified version of the Wilcoxon rank-sum test).

RESULTS

BASELINE MEASURES

Between October 2001 and May 2003, 127 patients underwent randomization at 28 centers in the United States. Three patients withdrew consent before receiving treatment and were excluded from the analysis. Of 124 treated patients, 81 received sargramostim and 43 received placebo. One patient in the sargramostim group was enrolled in violation of the protocol: this patient had ongoing symptoms consistent with the presence of a small-bowel obstruction but was included in all analyses.

All demographic and disease characteristics, including prior use of medications for Crohn's disease, were similar in the two groups except for the median age and the duration of disease, which were younger and shorter, respectively, in the sargramostim group than in the placebo group (Table 1). Ninety percent of patients had previously received glucocorticoids, and 69 percent had received immunosuppressive agents.

Table 1. Demographic and Baseline Characteristics of the Patients.

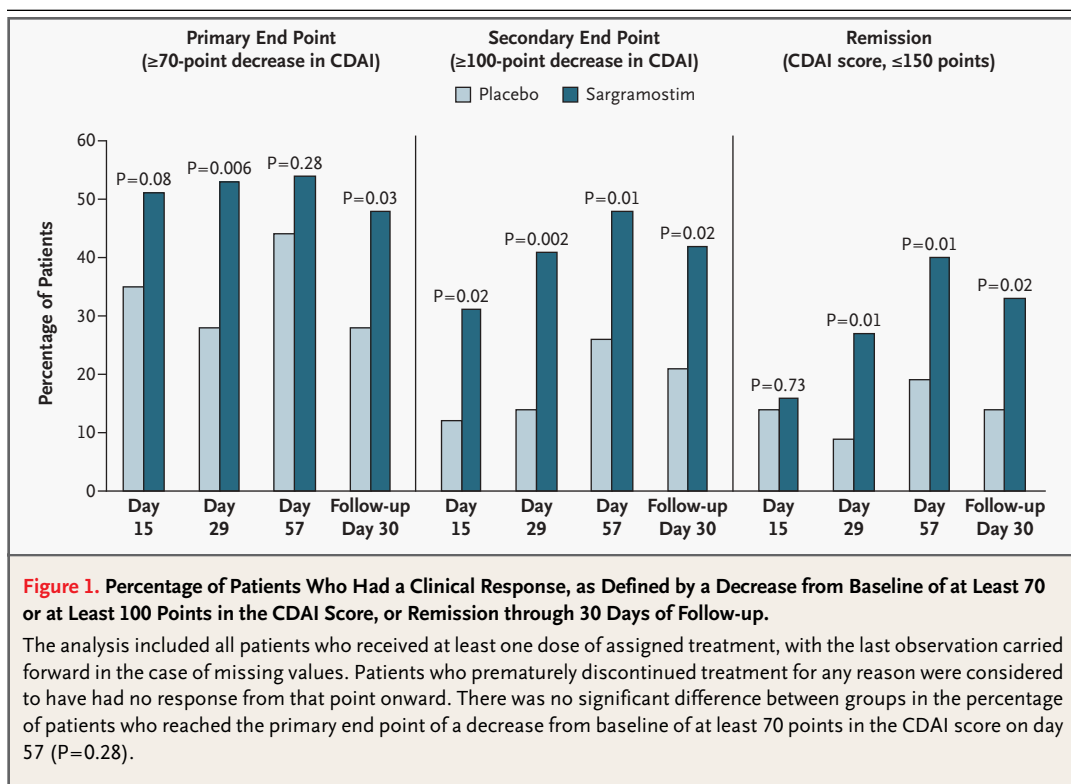
Characteristic	Placebo Group (N=43)	Sargramostim Group (N=81)
Sex — no. (%)		
Male	22 (51)	35 (43)
Female	21 (49)	46 (57)
Age — yr		
Median	41.0	36.0*
Range	21–74	20–72
Weight — kg		
Median	76.8	73.5
Range	46.4–121.1	43.3–146.8
Duration of disease — yr		
Median	9.9	7.7†
Range	0.7–38.7	0.4–28.9
CDAI score‡		
Median	300	300
Range	221–464	219–469
IBDQ score§		
Median	116	126
Range	62–186	54–177
Median C-reactive protein — mg/liter	9	10
Location of intestinal disease — no. (%)		
Small bowel only	9 (21)	15 (19)
Small bowel and colon	27 (63)	46 (57)
Colon only	7 (16)	20 (25)
Fistulizing disease	19 (44)	36 (44)
Tobacco use — no. (%)		
Prior	14 (33)	25 (31)
Current	14 (33)	14 (17)
None	15 (35)	42 (52)
Prior medications — no. (%)		
Unknown	4 (9)	2 (2)
Aminosalicylates	28 (65)	60 (74)
Antibiotics	32 (74)	59 (73)
Glucocorticoids	36 (84)	75 (93)
Immunosuppressants	30 (70)	56 (69)
Mercaptopurine	21 (49)	32 (40)
Azathioprine	15 (35)	30 (37)
Cyclosporine	4 (9)	1 (1)
Infliximab	26 (60)	38 (47)
Methotrexate	6 (14)	10 (12)
Other	2 (5)	3 (4)
Other	5 (12)	11 (14)
Concomitant use of antibiotics, aminosalicylates, or both — no. (%)	15 (35)	28 (35)

* P=0.02 for the comparison with the placebo group.

† P=0.05 for the comparison with the placebo group.

‡ CDAI scores can range from 0 to 600, with higher scores indicating more severe disease.

§ Scores for the IBDQ can range from 32 to 224, with higher scores indicating a better quality of life.



EFFICACY

Response and Remission

Treatment was discontinued prematurely in 7 patients in the placebo group, as compared with 21 patients in the sargramostim group (16 percent vs. 26 percent, P=0.26). A total of 37 patients in the placebo group (86 percent) and 57 patients in the sargramostim group (70 percent) met the criteria for end-of-treatment (day 57) evaluations.

The difference between groups in the prespecified primary outcome of a clinical response defined by a decrease from baseline of at least 70 points in the CDAI score was not significant on day 57 (54 percent in the sargramostim group, as compared with 44 percent in the placebo group; P=0.28). Although on the basis of the primary outcome, the trial should be considered negative, the rates of a prespecified secondary outcome, a clinical response defined by a decrease from baseline of at least 100 points in the CDAI score and remission on day 57, were significantly higher in the sargramostim group than in the placebo group (48 percent vs. 26 percent, P=0.01, and 40 percent vs. 19 percent, P=0.01, respectively) (Fig. 1). On day 29, as compared with the placebo group, the sargramostim group had significantly higher rates of response, as defined by a de-

crease of at least 70 points in the CDAI score (53 percent vs. 28 percent, P=0.006) or by a decrease of at least 100 points in the CDAI score (41 percent vs. 14 percent, P=0.002), and rates of remission (27 percent vs. 9 percent, P=0.01). The median CDAI score was significantly lower in the sargramostim group than the placebo group on day 29 (218 vs. 252, P=0.05) and day 57 (184 vs. 240, P=0.02) (Fig. 2). The median time to a response, as defined by a decrease of at least 70 points or at least 100 points in the CDAI score, was also significantly shorter in the sargramostim group than the placebo group (18 vs. 34 days, P=0.004, and 30 days vs. not reached, P=0.003, respectively), as was the time to remission (56 days vs. not reached, P=0.02).

Thirty days after treatment, 30 patients in the placebo group (70 percent) and 53 patients in the sargramostim group (65 percent) were evaluated. As compared with patients in the placebo group, patients in the sargramostim group had higher rates of response, as defined by a decrease of at least 70 points or at least 100 points in the CDAI score (48 percent vs. 28 percent, P=0.03, and 42 percent vs. 21 percent, P=0.02, respectively), as well as higher rates of remission (33 percent vs. 14 percent, P=0.02). The mean duration of follow-up after treat-

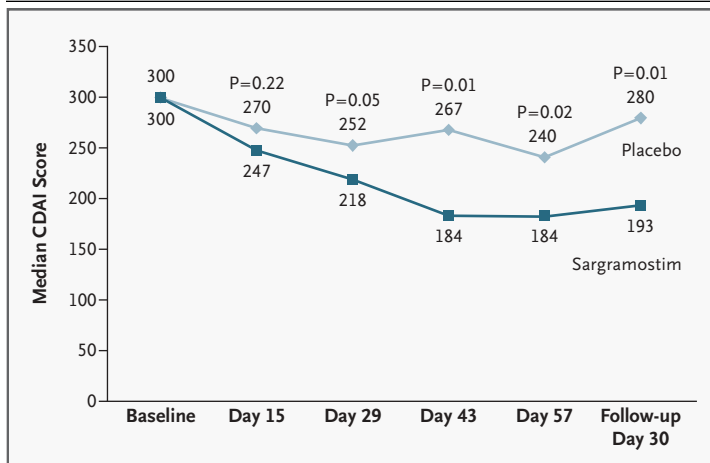


Figure 2. Median CDAI Scores over Time.

The analysis included all patients who received at least one dose of assigned treatment, with the last observation carried forward in the case of missing values. Patients who prematurely discontinued treatment for any reason were considered to have had no response from that point onward.

ment was 9.9 weeks among all patients with a response. The mean time to the loss of a clinical response was 9.7 weeks, and to the loss of remission 7.5 weeks.

Responses occurred in both stratification groups, although response and remission rates were higher among patients who had not received prior second-line therapy than among those who had. There were no significant differences in the rates of response and remission between patients who had normal baseline C-reactive protein levels and patients with elevated baseline levels. Sargramostim-treated patients who had ongoing tobacco use or seropositivity for antibodies against *S. cerevisiae* had response and remission rates that were similar to those of the overall group.

Mucosal Healing

Mucosal healing was evaluated with the use of the CDEIS in 10 patients in the placebo group and 19 patients in the sargramostim group. Median baseline scores were 5.9 (range, 0.1 to 18.8) in the placebo group and 4.3 (range, 0.0 to 18.8) in the sargramostim group ($P=0.16$). The median decrease in the CDEIS score within one week after the end of treatment was 1.7 in the sargramostim group and 0.8 in the placebo group ($P=0.28$). The median post-treatment scores were 5.6 (range, 0.9 to 16.3) and 1.5 (range, 0.0 to 7.3), respectively ($P=0.02$).

Fistulae

Draining fistulae were present at baseline in eight patients in the sargramostim group and five patients in the placebo group who completed treatment. At the end of treatment, draining fistulae were eliminated in four patients and decreased in one patient in the sargramostim group and were eliminated in two patients in the placebo group.

HEALTH-RELATED QUALITY OF LIFE

Improvements in the health-related quality of life were significantly greater in the sargramostim group than in the placebo group on day 29 (increase in the IBDQ score from baseline, 29 vs. 17 points; $P=0.02$), day 57 (increase, 28 vs. 16 points; $P=0.04$), and 30 days after treatment (increase, 17 vs. 7 points; $P=0.006$) (Table 2).

SAFETY AND TOLERABILITY

Discontinuations

Reasons for early discontinuation among patients in the sargramostim group included adverse events in 11, withdrawal of consent or lack of compliance in 6, worsening disease in 3, and physician's decision in 1. Reasons for early discontinuation among patients in the placebo group were adverse events in three, withdrawal of consent or lack of compliance in two, and worsening disease in two. Four of the patients in the sargramostim group who withdrew because of adverse events withdrew because of injection-site reactions or bone pain, three during the first week of treatment.

Adverse Events

There was no significant difference in the overall incidence of adverse events between the sargramostim group and the placebo group (98 percent vs. 93 percent, $P=0.22$) (Table 3). The majority of events were grade 1 or 2 in intensity, with three patients in the placebo group (7 percent) and six in the sargramostim group (7 percent) having a grade 3 or 4 adverse event. Two types of adverse events were reported more frequently in the sargramostim group than in the placebo group: injection-site reactions (90 percent vs. 12 percent, $P<0.001$) and bone pain (37 percent vs. 7 percent, $P<0.001$). One patient in the sargramostim group had the dose reduced to 4 μg per kilogram per day owing to fever, chills, and injection-site reactions beginning on day 6 and completed the study at this dose. The incidence of injection-site reactions declined after the second

week of treatment, and the majority of patients had five or fewer reactions. Bone pain was usually transient (median duration, seven days) and treated with acetaminophen.

Three patients in the sargramostim group had serious adverse events that were possibly or probably related to treatment. These included migraine three weeks after the discontinuation of sargramostim in a 29-year-old woman and an episode of anorexia, weakness, and lethargy in a 58-year-old man with poorly controlled hypertension and ischemic cardiac disease. The third patient was a 29-year-old woman who had transient right-sided weakness consistent with the occurrence of a possible demyelinating event after three weeks of treatment. During follow-up over the next four months, the patient's symptoms fully resolved with the exception of a small residual area of sensory deficit. No other diagnoses for her condition were identified. None of these events were associated with thromboembolic disease. One death occurred during the study, but it was determined to be unrelated to study medication. A 55-year-old woman with emphysema and atherosclerotic disease was enrolled in violation of the study protocol owing to ongoing symptoms of abdominal pain, nausea, and vomiting, consistent with the presence of a possible small-bowel obstruction or ischemia. She received sargramostim for 11 days and then was rehospitalized with persistent symptoms. Sargramostim was discontinued, and the patient underwent exploratory laparotomy; she died four days later. Autopsy revealed evidence of bowel infarction and no findings consistent with a diagnosis of Crohn's disease. Before surgery, her sargramostim-induced neutrophilia was resolving and her platelet counts were normal.

Laboratory Findings

White-cell, neutrophil, and eosinophil counts increased during sargramostim treatment. There were no dose reductions because of excessive neutrophil counts. Peak mean counts occurred on day 29 for white cells (24,400 per cubic millimeter; range, 9400 to 53,200) and eosinophils (6500 per cubic millimeter; range, 0 to 34,600) and on day 15 for neutrophils (14,800 per cubic millimeter; range, 5300 to 29,500). Elevated cell counts stabilized despite continued treatment with sargramostim. In all patients, blood counts returned to pretreatment levels after the discontinuation of sargramostim. There was no treatment-related thrombocytosis or

Time	Placebo Group	Sargramostim Group	P Value
	<i>median score (range)</i>		
Baseline	116 (62 to 186)	126 (54 to 177)	0.57
Day 29			
Overall	139 (79 to 200)	155 (60 to 207)	0.02
Change from baseline	17 (-37 to 78)	29 (-23 to 89)	0.02
Day 57			
Overall	138 (72 to 193)	156 (58 to 221)	0.03
Change from baseline	16 (-49 to 91)	28 (-42 to 103)	0.04
30-Day follow-up			
Overall	130 (63 to 193)	153 (62 to 221)	0.01
Change from baseline	7 (-48 to 80)	17 (-53 to 103)	0.006

* Scores for the IBDQ can range from 32 to 224, with higher scores indicating a better quality of life.

Adverse Event	Placebo Group (N=43)	Sargramostim Group (N=81)	P Value
	<i>no. of patients (%)</i>		
Any adverse event	40 (93)	79 (98)	0.22
Injection-site reaction	5 (12)	73 (90)	<0.001
Bone pain	3 (7)	30 (37)	<0.001
Headache	11 (26)	23 (28)	0.74
Asthenia	8 (19)	22 (27)	0.29
Pain	8 (19)	15 (19)	0.99
Upper respiratory tract infection	3 (7)	10 (12)	0.35
Dizziness	2 (5)	10 (12)	0.17
Abdominal pain	4 (9)	10 (12)	0.61
Back pain	5 (12)	8 (10)	0.76
Nausea	5 (12)	8 (10)	0.76
Hematoma at injection site	13 (30)	6 (7)	<0.001

clinically significant increases in other types of cells. No significant changes were observed in serum chemical values.

Antibody Formation

Only 1 of 78 patients in the sargramostim group who were tested had detectable neutralizing antibodies on day 57 (titer, 1:400) and 30 days after treatment (titer, 1:200). Sargramostim-induced neutrophilia disappeared in this patient with the devel-

opment of neutralizing antibodies. Absolute neutrophil counts returned to baseline values despite continued treatment. No drug-related adverse events were observed in association with antibody development.

DISCUSSION

We evaluated a new approach to therapy — using sargramostim to boost patients' immune system — on the basis of the hypothesis that Crohn's disease may result from an innate immune defect. The study was negative as designed, with no significant difference between groups in the rate of the primary end point of a clinical response defined by a decrease from baseline of at least 70 points in the CDAI score on day 57. However, there were positive secondary outcomes with regard to the end points of a decrease from baseline of at least 100 points in the CDAI score and remission on day 57 as well as a decrease of at least 70 points in the CDAI score at other times. Clinical responses were achieved without concomitant immunosuppressive therapy, were rapid and sustained, and were associated with significant improvements in disease-specific quality of life. Improvements were observed in mucosal healing in sargramostim-treated patients. These results suggest that a treatment designed to modulate intestinal innate immune defense may have a role in patients with Crohn's disease.

Injection-site reactions and bone pain were commonly associated with sargramostim therapy and led to the withdrawal of 4 of 81 patients. These events were usually transient and diminished with continued treatment. In at least two patients who had serious adverse events, prior medical conditions may have contributed substantially to the development of these events (e.g., baseline hypertension and a history of small-bowel obstruction and atherosclerotic disease). A third patient, who had transient right-sided weakness, may have had an underlying demyelinating condition, or sargramostim therapy may have brought on this condition. Patients with Crohn's disease are at increased risk for thrombosis and demyelinating disease.¹²⁻¹⁴ However, given these events, caution is warranted in the use of sargramostim therapy in patients with similar underlying conditions.

This study was undertaken to study the hypoth-

esis that Crohn's disease may result from impairments in innate immunity that contribute to defective intestinal barrier function. Recent observations provide support for this understanding of Crohn's disease. First, chronic enteritis that resembles Crohn's disease develops in animal models of impaired innate immunity or abnormalities of the mucosal barrier.¹⁵⁻¹⁷ Second, patients with genetically defined syndromes characterized by marked decreases in the number or function of neutrophils, such as glycogen storage disease type 1b, often have a Crohn's disease intestinal phenotype that responds to treatment with colony-stimulating factors.^{2,18,19} Third, specific genes have been linked to the development of Crohn's disease, including variants of *CARD15/NOD2*.^{20,21} *CARD15* activates nuclear factor- κ B in response to the detection of muramyl dipeptide, a component of the bacterial cell wall.^{22,23} In addition to being expressed in monocytes, macrophages, and dendritic cells, *CARD15* was recently shown to be present in intestinal epithelial cells, including Paneth cells.²⁴⁻²⁶ Disease-associated *CARD15* alleles impair normal cellular responsiveness to bacteria.²⁶ These data suggest that a deficiency in innate intestinal immune function may contribute to the development of Crohn's disease. GM-CSF enhances innate immune function.⁴ Furthermore, GM-CSF has been demonstrated to improve mucosal barrier function in the lung and gastrointestinal tract,^{27,28} and intestinal epithelial cells, including Paneth cells, express GM-CSF receptors and proliferate in response to GM-CSF in vitro.²⁹ The role of GM-CSF in the biology of Crohn's disease remains to be defined.

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APPENDIX

The members of the Sargramostim in Crohn's Disease Study Group are as follows: *Wake Research Associates, Raleigh, N.C.* — C. Barish; *Minor and James Medical, Seattle* — C. Bedard; *Presbyterian Medical Center, Philadelphia* — J. Deren; *University of Kentucky Medical Center, Lexington* — W.J.S. deVilliers; *Digestive Disorders Associates, Annapolis, Md.* — M. Epstein; *University of Louisville, Louisville, Ky.* — S. Galandiuk; *Gastroenterology Association of the East Bay Medical Group, Berkeley, Calif.* — S. Goldberg; *Winthrop University Hospital, Mineola, N.Y.* — J. Grendell; *University of North Carolina Hospitals, Chapel Hill* — K. Isaacs; *Gastrointestinal and Liver Specialist of Tidewater, Norfolk, Va.* — D. Johnson; *Long Island Clinical Research Associates, Great Neck, N.Y.* — S. Katz; *West Hills Gastroenterology Associates, Portland, Oreg.* — G. Koval; *Cleveland Clinic Foundation, Cleveland* — B. Lashner; *University of Washington Medical Center, Seattle* — S. Lee; *Albany Medical Center Hospital, Albany, N.Y.* — R. MacDermott; *Minnesota Gastroenterology, St. Paul* — R. McCabe, Jr.; *Oklahoma Foundation for Digestive Research, Oklahoma City* — P. Miner, Jr.; *McGuire Veterans Affairs Medical Center, Richmond, Va.* — W. Pandak, Jr.; *Columbia Gastroenterology Associates, Columbia, S.C.* — J. Popp, Jr.; *Nashville Medical Research Institute, Nashville* — R. Pruitt; *University of Pittsburgh Medical Center, Pittsburgh* — M. Regueiro; *Consultants for Clinical Research, Cincinnati* — M. Safdi; *Washington University Medical Center, St. Louis* — C. Stone; *Mount Sinai Medical Center, New York* — T. Ullman; *University of Florida and Veterans Affairs Medical Center, Gainesville* — J. Valentine; *Atlanta Gastroenterology Associates, Atlanta* — D. Wolf; *Gastroenterology Center of the MidSouth, Memphis, Tenn.* — Z. Younes; *Clinical Trials Management of Boca Raton, Boca Raton, Fla.* — A. Zwick.

REFERENCES

- Podolsky DK. Inflammatory bowel disease. *N Engl J Med* 2002;347:417-29.
- Korzenik JR, Dieckgraefe BK. Is Crohn's disease an immunodeficiency? A hypothesis suggesting possible early events in the pathogenesis of Crohn's disease. *Dig Dis Sci* 2000;45:1121-9.
- Wilk JN, Viney JL. GM-CSF treatment for Crohn's disease: a stimulating new therapy? *Curr Opin Investig Drugs* 2002;3:1291-6.
- Armitage JO. Emerging applications of recombinant human granulocyte-macrophage colony-stimulating factor. *Blood* 1998;92:4491-508.
- Fukuzawa H, Sawada M, Kayahara T, et al. Identification of GM-CSF in Paneth cells using single-cell RT-PCR. *Biochem Biophys Res Commun* 2003;312:897-902.
- Dieckgraefe BK, Korzenik JR. Treatment of active Crohn's disease with recombinant human granulocyte-macrophage colony-stimulating factor. *Lancet* 2002;360:1478-80.
- Best WR, Becktel JM, Singleton JW. Re-derived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI). *Gastroenterology* 1979;77:843-6.
- Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. *Gut* 1989;30:983-9.
- Irvine EJ, Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. *Gastroenterology* 1994;106:287-96.
- Kitamura T, Tojo A, Kuwaki T, et al. Identification and analysis of human erythropoietin receptors on a factor-dependent cell line, TF-1. *Blood* 1989;73:375-80.
- Peeters M, Joossens S, Vermeire S, Vlietinck R, Bossuyt X, Rutgeerts P. Diagnostic value of anti-Saccharomyces cerevisiae and antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease. *Am J Gastroenterol* 2001;96:730-4.
- Miehlsler W, Reinisch W, Valic E, et al. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? *Gut* 2004;53:542-8.
- Talbot RW, Heppell J, Dozois RR, Beart RW Jr. Vascular complications of inflammatory bowel disease. *Mayo Clin Proc* 1986;61:140-5.
- Kimura K, Hunter SE, Thollander MS, et al. Concurrence of inflammatory bowel disease and multiple sclerosis. *Mayo Clin Proc* 2000;75:802-6.
- Welte T, Zhang SS, Wang T, et al. STAT3 deletion during hematopoiesis causes Crohn's disease-like pathogenesis and lethality: a critical role of STAT3 in innate immunity. *Proc Natl Acad Sci U S A* 2003;100:1879-84.
- Hermiston ML, Gordon JI. Inflammatory bowel disease and adenomas in mice expressing a dominant negative N-cadherin. *Science* 1995;270:1203-7.
- Yamanaka R, Barlow C, Lekstrom-Himes J, et al. Impaired granulopoiesis, myelodysplasia, and early lethality in CCAAT/enhancer binding protein epsilon-deficient mice. *Proc Natl Acad Sci U S A* 1997;94:13187-92.
- Dieckgraefe BK, Korzenik JR, Husain A, Dieruf L. Association of glycogen storage disease 1b and Crohn disease: results of a North American survey. *Eur J Pediatr* 2002;161:Suppl 1:S88-S92.
- Couper R, Kapelushnik J, Griffiths AM. Neutrophil dysfunction in glycogen storage disease 1b: association with Crohn's-like colitis. *Gastroenterology* 1991;100:549-54.
- Ogura Y, Bonen DK, Inohara N, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature* 2001;411:603-6.
- Hugot JP, Chamaillard M, Zouali H, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature* 2001;411:599-603.
- Girardin SE, Boneca IG, Viala J, et al. Nod2 is a general sensor of peptidoglycan through muramyl dipeptide (MDP) detection. *J Biol Chem* 2003;278:8869-72.
- Inohara N, Ogura Y, Fontalba A, et al. Host recognition of bacterial muramyl dipeptide mediated through NOD2: implications for Crohn's disease. *J Biol Chem* 2003;278:5509-12.
- Ogura Y, Lala S, Xin W, et al. Expression of NOD2 in Paneth cells: a possible link to Crohn's colitis. *Gut* 2003;52:1591-7.
- Lala S, Ogura Y, Osborne C, et al. Crohn's disease and the NOD2 gene: a role for Paneth cells. *Gastroenterology* 2003;125:47-57.
- Hisamatsu T, Suzuki M, Reinecker HC, Nadeau WJ, McCormick BA, Podolsky DK. CARD15/NOD2 functions as an antibacterial factor in human intestinal epithelial cells. *Gastroenterology* 2003;124:993-1000.
- Pelaez A, Bechara RI, Joshi PC, Brown LA, Guidot DM. Granulocyte/macrophage colony-stimulating factor treatment improves alveolar epithelial barrier function in alcoholic rat lung. *Am J Physiol Lung Cell Mol Physiol* 2004;286:L106-L111.
- Unal AE, Cevikel MH, Ozgun H, Tunger A. Effect of granulocyte-macrophage colony stimulating factor on bacterial translocation after experimental obstructive jaundice. *Eur J Surg* 2001;167:366-70.
- Ramsay RG, Micallef SJ, Williams B, et al. Colony-stimulating factor-1 promotes clonogenic growth of normal murine colonic crypt epithelial cells in vitro. *J Interferon Cytokine Res* 2004;24:416-27.

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