Recombinant Human Granulocyte-Macrophage Colony Stimulating Factor (sargramostim) as an Alternative Therapy for Fistulizing Crohn's Disease

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Background: Impaired neutrophil function has been proposed in the pathogenesis of Inflammatory Bowel Disease. Failure to control the response to bacteria and bacterial products triggers the inflammatory cascade. Genetic disorders of neutrophil dysfunction exhibit gastrointestinal manifestations similar to Crohn's disease. Treatments that enhance neutrophil and macrophage function with colony-stimulating factors have been successful in these conditions. Some studies using sargramostin in patients with Crohn's disease have suggested a beneficial effect in disease activity, including fistulizing disease. The goal of the study was to evaluate the safety and efficacy of sargramostin in patients with fistulizing Crohn's disease who had not responded to conventional therapy or had developed adverse reaction to infliximab requiring discontinuation of the drug.

Methods: Patients with fistulizing Crohn's disease who had failed conventional therapy were recruited. Sargramostin 6µg/kg subcutaneously daily for 8 weeks was prescribed. Follow-up included clinical evaluation, exam of the fistulas, laboratories, CDAI score, adverse events, compliance with therapy, quality of life assessment, and baseline and post-treatment abdomino-pelvic MRI.

Results: Three patients were enrolled. There were 4 perianal, 7 enterocutaneous and multiple enteroenteric fistulas. Two completed 8 weeks of treatment and 1 was discontinued at week 5 for a hypersensitivity reaction. Sargramostin was ineffective in all three.

Conclusions: The small number of patients and the severity of their disease do not allow any conclusions about the drug effectiveness. Placebo-controlled studies, perhaps with less complicated patients, are needed to define a role, if any, of this therapy in fistulizing Crohn's disease. [*P R Health Sci J 2010;1:60-65*]

Key words: Crohn's Disease, Fistulizing Crohn's Disease, Recombinant Human Granulocyte-Macrophage Colony Stimulating Factor

Crohn's Disease (CD) is an idiopathic chronic intestinal inflammation resulting from a sustained immune response in the gastrointestinal tract. Although detailed precipitating events are still unknown, it is thought that the disease process is multifactorial.1 The additive effect of genetic and environmental factors, loss of tolerance to intestinal bacterial flora, and immune dysfunction predispose to this sustained immune response (1).

Proinflammatory cytokines have been identified as key regulators of the disease process at the intestinal mucosa (2). There is increasing consensus that the mucosa of CD is dominated by CD4+ lymphocytes with T-cell Helper 1 (Th-1) phenotype characterized by the production of INF-γ, IL-2, TNF-α, and macrophage activation. Modern therapeutic agents for CD have focused on immunosuppresion of the inflammatory state induced by these cytokines (2). Infliximab is a chimeric monoclonal immunoglobulin antibody (IgG1) against tumor necrosis factor, a product of macrophages (3). It neutralizes biologic activity of TNF-α by inhibiting binding to its receptors. It is one of the first targeted therapies for patients who either suffer from moderate to severe inflammatory CD with an inadequate response to conventional therapy or present with fistulizing disease (4-5).

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The management of patients with fistulizing CD remains a major clinical challenge. Infliximab has greatly improved the treatment of fistulae, yet a significant group of patients fail to achieve complete cessation of fistulae drainage while others, after successful induction, lose response under maintenance treatment. The ACCENT II trial studied a group of responders to a loading infliximab dose of 5 mg/kg at weeks 0, 2, and 6, who were randomized at 14 weeks to receive infusions every 8 weeks. Of these, 64% did not achieve complete absence of draining fistulas, and 54% lost response to maintenance therapy at week 54 (6). Our experience using infliximab in Puerto Rican patients followed at the multidisciplinary Inflammatory Bowel Diseases (IBD) clinic has shown an overall complete response rate in 37% and a partial response rate in 46% of patients (7). Fistulizing disease was present in 25 cases: 40% achieved a complete response, and 45% a partial response. Five CD patients had ongoing deteriorating perianal fistulae despite conventional therapy, two of which required a diverting colostomy. One female patient with a rectovaginal fistula lost initial response during maintenance therapy with infliximab at 10 mg/kg given every eight weeks and two patients experienced adverse events during infliximab infusions. In addition, significant serious adverse events and toxicities of infliximab have been reported including opportunistic infections, acute infusion reactions, autoimmune disorders and the theoretical risk of cancer and lymphoma (6). This group of patients who fails conventional therapy along with those who have experienced adverse serious reactions to infliximab are left without an effective anti-fistulizing therapy, expectant of new alternative strategies for the treatment of CD.

In 2000, Korsenick and Dieckgrafe proposed a new hypothesis regarding the pathogenesis of CD (8-9). Their hypothesis assumed that an impaired neutrophil function deters the innate immune system's ability to control the commensal flora. Failure to control intestinal bacteria and bacterial products triggers an inflammatory cascade and causes an active adaptive immune response to be mounted. Genetic disorders of neutrophil dysfunction such as glycogen storage disease 1b and chronic granulomatous disease exhibit gastrointestinal manifestations similar to CD (10). Treatments directed to enhance neutrophil and macrophage function with colony-stimulating factors in these genetic syndromes have been successful (9-10). Also, results from open-label studies and one randomized, placebo-controlled study suggest that treatment of CD patients with sargramostim (Leukine®, Berlex, New Jersey), a yeast-derived recombinant human granulocyte-macrophage colony-stimulating factor, may attenuate severity of the disease, promote overall improvement and, in some cases, may induce disease remission (11-14). Korzenik et al reported elimination of draining fistulae in four patients receiving sargramostim (14). A similar response has been reported in a CD patient who achieved healing of a rectovaginal fistula as well as relief from the associated pain and tenderness (15). These findings support the hypothesis of Korsenik-Dieckgraefe and suggest a new therapeutic approach for the treatment of CD based on immune system stimulation.

In view of the preliminary data, we proposed a pilot study to evaluate the safety and efficacy of sargramostim in CD patients with fistulizing disease who had not responded to conventional therapy (antibiotics, oral glucocorticoids, infliximab, azathioprine, 6-mercaptopurine, methotrexate, or tacrolimus) or who had developed adverse events to infliximab requiring discontinuation of the drug.

Methods

Patients with fistulizing CD were identified at the University of Puerto Rico IBD clinics during regularly scheduled medical visits from May 2005 to June 2006. The study was approved by the University of Puerto Rico (UPR) Medical Sciences Campus Institutional Review Board (IRB). Medical record review was performed and patients were recruited as per inclusion and exclusion criteria. Male and female patients, age 21 or older who were able to consent and available for follow-up with the following criteria were included in the study: CD diagnosed by standard clinical, endoscopic, radiological, and histological criteria; and fistulizing disease (enteroenteric, enterovesical, rectovaginal, enterocutaneous, peristomal or perianal fistulae) present for at least three months prior to the beginning of the study with documented incomplete response to first line CD therapy and/or history of adverse events to infliximab therapy. Patients were allowed to continue any concomitant CD conventional therapy such as oral glucocorticoids, 6-mercaptopurine, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, tacrolimus, cyclosporine, oral and topical 5-ASA, or antibiotics at a stable dose for at least 12 weeks prior to the beginning and throughout the study. The last infliximab infusion or investigational drug must have been completed at least three months prior to receiving the first dose of the study drug. Female patients of childbearing potential had to have a negative pregnancy test within 2 weeks prior to receiving the first dose of sargramostim. A minimal or maximal CDAI score was not established as inclusion or exclusion criteria.

Exclusion criteria included patients with bowel disease other than fistulizing CD, gastrointestinal surgery within the 8 weeks prior to the first dose of the study drug, patients in need of gastrointestinal surgery for active GI bleeding, peritonitis, intestinal obstruction or intra-abdominal abscess. Patients with planned in-patient hospitalization during the 24 weeks of the study, presence or history of cancer of any type or definite gastrointestinal dysplasia within the last five years were excluded. Patients undergoing induction or maintenance therapy with anti-TNF therapies such as infliximab, natalizumab or etanercept were excluded. Allergy to yeast products, baseline serum creatinine level > 2.0 mg/dL, hemoglobin level < 8.0 gm/

dL, platelet count >800,000/mL, absolute neutrophil count of <1,000/uL or > 20,000/uL, liver enzymes (ALT, AST, ALP), or total bilirubin > 2X the upper limit of normal were grounds for exclusion. Prior use of sargramostim or filgastrim had to be completed at least three months prior to receiving the first dose of the study.

Sargramostim (Leukine®, Berlex, New Jersey) 6 μg/kg subcutaneously was prescribed daily for eight weeks. Physical examination was performed on every visit. A complete blood count was obtained in all patients prior to therapy and on weeks 2, 4, 6, 8, and 12. A comprehensive metabolic panel was performed at 0 and 8 weeks. Clinical evaluation including history and physical examination of the fistulizing disease was made and recorded on each visit. In addition, radiological interval changes were also evaluated via magnetic resonance imaging of the abdomen and pelvis for evaluation of fistulizing disease at the beginning of the study and on week 8. A Crohn's Disease Activity Index (CDAI) score (16) was also calculated in weeks 0, 4, 8, and 24. Clinical evaluations, blood sample collection, analysis, and dispensing of medications were completed at the GI Research Unit, University Hospital.

The efficacy of sargramostim was defined by a clinical response or reduction of 50% or more from baseline in the number of draining fistulae observed in two or more consecutive visits, significant radiologic changes as per magnetic resonance imaging or a decrease in CDAI scores by greater than 100 points at the end of treatment. A complete clinical response was described as remission of fistulizing disease by MRI, a CDAI < 150 at week 8, and maintenance of fistula closure for at least 4 weeks after treatment completion. The CDAI has a range from 0 to approximately 750: values below 100 are associated with inactive disease, 100 to 150 with mild inflammatory activity, 150 to approximately 210 with moderate disease, and values above 250 with severe disease activity. Disease relapse is defined by an increase in the CDAI of 100 points.

The health-specific quality of life was measured using the Spanish translation of the Rating Form for Inflammatory Bowel Disease Patients Concerns (RFIPC), and IBD questionnaire (IBDQ) (17-21) at weeks 0, 4, 8, 12, and 24. The RFIPC is a disease specific questionnaire that consists of 25 items or concerns which are graded on 100 mm visual analog scales (0 mm = 'not at all' and 100 mm = 'a great deal'). The RFIPC score is the mean of the 25 items with a higher score indicating a worse quality of life. The IBDQ score is the summation of 32 individual scores (bowel, systemic, social and emotional) and ranges from 32 to 224 with a higher score indicating a better quality of life.

Patients were evaluated for safety based on their medical history, physical and clinical laboratory evaluations. Medication interruption of up to two doses per week was allowed in the event of marked hematological abnormalities. Longer dose interruption was also allowed and determined depending on duration and severity of documented adverse effects as per the World Health Organization severity criteria (22). Compliance with therapy was determined by evaluation of a medication diary where the patient recorded the daily dose of sargramostim and time of administration. Up to two doses per week were allowed to be missed due to non-compliance. Early termination was to be performed at any time when the investigator deemed it necessary.

Results

Three patients were enrolled in the study between May 2005 and June 2006. All patients were male with a median age of 33 (range 32-40), CDAI of 129 (range 96-140), IBDQ of 80 (range 80-142) and RFIPC of 66 (range 84-72). Fistulizing disease included a total of 4 perianal, 7 enterocutaneous, and multiple enteroenteric fistulae. Two patients completed 8 weeks of sargramostin and a 16-week follow up period, and one patient was removed from the study at week 5. Detailed medical history and course of therapy for each patient are described below. Results of CD disease activity, health-specific quality of life, radiological and laboratory studies are summarized in Tables 1-3.

Patient 1

Patient 1 is a 32 year-old male patient with history of perianal fistulizing CD since 2003. The patient had received infliximab for four perianal fistulae but developed an anaphylactic reaction after three doses. Concomitant medications at the beginning of treatment included azathioprine, trimethoprim / sulfamethoxazole, mesalamine enemas, and acetaminophen / tramadol. The patient began sargramostim treatment on May 2005 at a calculated dose of 6 μg/kg (600 μg/day).

During the first week of treatment, the patient developed episodes of mild to moderate headaches following administration of the medication. At week 2, the patient suffered a sudden episode of bone pain in the left arm and lower extremities requiring emergency room evaluation and withholding of protocol medication for 2 days. His symptoms shortly subsided and sargramostim administration was continued. At week 4 visit, the patient complained of worsening episodes of headache, which had increased to moderate intensity requiring interruption of the medication. Sargramostim was subsequently adjusted to 4 μg/kg (400 μg/day) and restarted 6 days later. At week 5, the patient developed a generalized pruritic, erythematous, papular rash in the upper and lower extremities associated with mild shortness of breath. The possibility of a delayed hypersensitivity reaction to the study medication was entertained, and the patient was instructed to discontinue further medication administration.

At week four, the patient had no decrease in perianal fistulae output or closure, and increased CDAI score from 96 to 105 (p=NS). MRI of the pelvis at week 8 showed unchanged perianal fistulizing disease. Improvements in quality of life at week 4 were not observed (decrease of 15 points in the IBDQ score,

and 3 points increase in the RFPIC score). Following removal from the study, the patient pursued an alternative drug therapy for CD and did not complete the 16-week follow up period. In spite of the adverse symptoms in this patient, the laboratory profile revealed no signs of toxicity.

Table 1. Patient laboratory data

	WK 0	WK 2	WK 4	WK 6	WK 8	WK 12
Patient #1*						
WBC (cell/μL)	5500	22800	7000	7900	-	-
ANC (cell/μL)	3360	15048	3913	5506	-	-
HGB (g/dL)	15.1	14.6	15.1	14.4	-	-
HCT (%)	45.6	44.8	45.9	43.1	-	-
PLT (plts/μL)	189,000	187,000	252,000	265,000	-	-
Patient #2						
WBC (cell/μL)	9500	24500	46400	30800	44800	8700
ANC (cell/μL)	8008	19061	35728	22792	32704	7412
HGB (g/dL)	14	12.6	13.7	12.1	14	13.9
HCT (%)	42.6	38.6	40.8	37	43.8	43.2
PLT (plts/μL)	438,000	336,000	530,000	393,000	448,000	599,000
Patient #3						
WBC (cell/μL)	3500	22100	26400	7300	N/A	4000
ANC (cell/μL)	1911	15691	13200	3890	N/A	1988
HGB (g/dL)	11.5	12.9	12.5	13	N/A	12
HCT (%)	33.8	39.5	38.4	40.2	N/A	34.7
PLT (plts/μL)	394,000	296,000	301,000	312,000	N/A	328,000

*Results available up to week 6 due to early termination at week 5.
N/A= Not Available

Patient 2

Patient 2 is a 33 year-old male with CD presenting with three abdominal enterocutaneous fistulae since 2002. He received infliximab therapy for two years, which was discontinued due to minimal clinical improvement in 2004. The patient did not develop any adverse events to infliximab. At the beginning of the study, concomitant medications included azathioprine, amoxicillin / clavulanate, folic acid, ferrous sulfate and multivitamins. Patient began sargramostim treatment on June 2005 at a calculated dose of 6 μg/kg (360 μg/day).

Patient 2 completed 8 weeks of treatment with adequate medication compliance. During treatment, the patient only developed mild skin erythema at the injection site. No additional adverse events were reported during the study treatment period.

At the end of treatment, there was no decrease in fistulae output or closure. No radiological evidence of improvement in enterocutaneous fistulae was noted. The CDAI score increased from 128 to 173 in week 4, returning to baseline by week 24. Quality of life assessments showed no improvements during and following therapy. Complete blood counts and metabolic panels revealed no signs of toxicity from treatment.

Patient 3

Patient 3 is a 40 year-old male was history of fistulizing CD diagnosed on 1984. In 2005, therapy with infliximab was started for four enterocutaneous and multiple enteroenteric fistulae. After two years of therapy, infliximab was discontinued due to poor clinical response. No adverse events to infliximab were reported during this period. Medications in the beginning of the study included metronidazole, ciprofloxacin, prednisone, and acetaminophen / oxycodone. On October 2005, patient was enrolled in the study at a calculated sargramostim dose of 6 μg/kg (250 μg/day).

During the first weeks of treatment, the patient experienced episodes of chest wall discomfort following sargramostim administration. Discomfort was mild and improved with acetaminophen administration. Symptoms subsided after subsequent doses of sargramostim were administered. Dose adjustment was not necessary. He completed 8 weeks of treatment without any serious adverse event or relevant changes in laboratory results.

No improvement in fistulae output or closure was noted after 8 weeks of treatment. An MRI of the abdomen and pelvis showed worsening fistulizing disease at the end of treatment. The CDAI score decreased from 140 to 78 in weeks 8 and 24 while no significant interval changes were noted in the patient's quality of life during and following therapy.

Table 2. Disease activity index and quality of life values

	WK 0	WK 4	WK 8	WK 12	WK 24
Patient #1*					
CDAI**	95.4	105.0	-		-
IBDQ	80.0	65.0	-	-	-
RFPIC	83.8	86.2	-	-	-
Patient #2					
CDAI**	127.4	172.2	129.2		127.0
IBDQ	143.0	71.0	80.0	74.0	68.0
RFPIC	65.6	86.6	84.6	75.0	84.7
Patient #3					
CDAI**	139.2	86.6	77.8	78.0	
IBDQ	142.0	180.0	148.0	143.0	136.0
RFPIC	71.8	64.2	66.1	75.0	72.0

*Results available up to week 4 due to early termination at week 5.
**CDAI at week 12 not required as per study methodology.
CDAI = Cronh's Disease Activity Index
IBDQ = Inflammatory Bowel Disease Questionnaire
RFPIC = Rating Form of Inflammatory Bowel Disease Patient Concern

Table 3. Interval changes of clinical and abdominopelvic MRI findings

	WK 0	WK 8		
		Improved	Worsened	Unchanged
Patient #1*	Perianal fistulae			X
Patient #2	Enterocutaneous fistulae			X
Patient #3	Enteroenteric and enterocutaneous fistulae		X	

*Results at time of early termination (week 5)

Discussion

The management of CD remains a clinical challenge, particularly in patients refractory to conventional medical treatment. Reports of open-label studies and placebo-controlled studies have suggested overall improvement of active inflammatory CD in patients receiving sargramostim. Nevertheless, the effects of sargramostim in active fistulizing CD remain unknown.

In this pilot study, we evaluated the therapeutic effects and safety of sargramostim in three patients with active fistulizing CD that were either unresponsive or intolerant to conventional medical treatment. None of the patients showed clinical response in either fistula output or in closure rate. Radiological evaluations also failed to show interval improvement of their fistulizing manifestations. Furthermore, radiological findings in patient 3 worsened after treatment completion. CDAI scores were particularly low in our patients. Given our definitions, these patients were clinically in remission of their inflammatory manifestations as per their CDAI. Nevertheless, their fistulizing disease was evidently active by clinical and radiological evaluations. Calculated IBDQ and RFPIC showed minimal improvement in the quality of life of the patients after administration of sargramostim.

Clinical side effects noted in our study consisted of injection site erythema in patient 2, headaches and bone pain in patient 1 and musculoskeletal-type chest wall discomfort in patient 3. Only patient 1 required dose adjustment for these symptoms. Patient 1 developed a delayed hypersensitivity reaction after which medication administration was halted. This patient had also previously suffered a hypersensitivity reaction to infliximab. Hematological abnormalities included leukocytosis and neutrophilia, which were expected given the nature of the medication. There were no dose reductions due to excessive neutrophil count. No major hematological or metabolic panel abnormalities or serious adverse events were noted.

Sargramostim therapy was ineffective in our three patients with active fistulizing CD who had failed or were intolerant to conventional medical therapy. The number of patients enrolled was a major limitation in this study, therefore definite conclusions regarding efficacy and safety cannot be made. The complexity of the patient's clinical presentations was also a major limitation. By definition, these patients were therapeutically difficult and challenging given their failure to known conventional treatment strategies. Off-study clinical follow-up of these patients revealed minimal improvement of their disease after subsequent medical or surgical treatments. Patient 1 and 3 have had suboptimal improvement of their fistulizing disease after subsequent administration of adalimumab, a new approved medical alternative for active fistulizing CD. Patients 2 and 3 required surgical intervention after complications of perforating disease nearly one year after completion of this study. Conceptually, the severity and refractory nature of their disease could have precluded clinical response to sargramostim. For this reason, it is possible that in patients with less severe or recently developed fistulizing disease, sargramostim could be efficacious. Finally, no particular attention was given in this study to the patient's comfort regarding daily subcutaneous administration of the medication as opposed to interval intravenous or oral administration of other therapeutic modalities previously experienced by them.

While our study was conducted, Korzenick et al published a randomized, placebo-controlled study in 124 patients with moderate-to-severe active CD (14). This study mentions the elimination of draining fistulae in four out of eight patients after 56 days therapy of sargramostim (6 μg/kg, subcutaneous), and in two out of five patients in the placebo group. However, detailed baseline characteristics and follow up course of disease of the entire subgroup of patients with fistulizing CD (36 and 19 patients in the sargramostim and placebo groups, respectively) were not discussed separately nor any radiologic studies reported. As shown in our three patients, Korzenik et al did not observe a significant difference in CDAI score reduction between the sargramostim group and placebo groups by the end of treatment. Different from our criteria, patients on immunosuppressants or glucocorticoids were not enrolled in the study.

In conclusion, sargramostim therapy was ineffective in three CD patients with active enterocutaneous, enteroenteric, and perianal fistulae. No clinical or radiologic responses were observed after 56 days of therapy or during the 16 weeks follow up period. The IBDQ and RFPIC parameters revealed no improvement in health-related quality of life and no serious adverse events were encountered. However, the small number of patients with draining fistulae included in our pilot study and Korzenik's randomized trial limit our conclusions about the potential therapeutic effect and safety of sargramostim in fistulizing CD. A larger, placebo-controlled study with particular attention to patients with fistulizing CD would better define the role of sargramostim within the

limited therapeutic armamentarium against this chronic and debilitating gastrointestinal disease.

Resumen

Objetivos: Evaluar la seguridad y efectividad de sargramostin (factor estimulante de colonia granulocito-macrófago) en pacientes con enfermedad de Crohn fistulizante que no han respondido a terapia médica convencional o que han desarrollado reacción adversa a infliximab requiriendo descontinuar el medicamento. Trasfondo: En la búsqueda de descubrir la patogénesis de la enfermedad inflamatoria de intestino se ha postulado que pueda existir una disfunción de las células neutrofílicas, en donde la inhabilidad para controlar la respuesta hacia las bacterias y sus productos desatan una cascada inflamatoria. Se ha observado que algunas enfermedades genéticas en donde predomina la disfunción neutrofílica exhiben síntomas gastrointestinales similares a la enfermedad de Crohn. Los tratamientos con factores estimulantes de colonia granulocito-macrófago han sido exitosos en estas condiciones genéticas ya que ayudan a mejorar la función de las celulas neutrofílicas y macrófagos. Estudios en los que se ha utilizado sargramostin en pacientes con enfermedad de Crohn sugieren tener efectividad en la actividad de la enfermedad, incluyendo enfermedad fistulizante. Estudio: Los pacientes con enfermedad de Crohn fistulizante fueron reclutados en las clínicas de enfermedad inflamatoria de intestino. Durante un periodo de 8 semanas se les administró sargramostin 6µg/kg subcutaneo diariamente. Las visitas de seguimiento incluían examen físico, evaluación de las fístulas, laboratorios, índice de actividad de la enfermedad de Crohn(CDAI score), efectos adversos, cumplimiento con la terapia, evaluación sobre calidad de vida, y resonancia magnética abdomino-pélvica al comenzar y al finalizar el tratamiento. Resultados: Tres pacientes participaron en el estudio. Hubo un total de 4 fístulas perianales, 7 fístulas enterocutáneas y múltiples fístulas enteroentéricas. Dos pacientes completaron 8 semanas de tratamiento y 1 fue descontinuado en la semana 5 al desarrollar reacción de hipersensibilidad. Sargramostim fue inefectiva en los tres pacientes. Conclusiones: El número reducido de pacientes y la severidad de su enfermedad no permitieron llegar a una conclusión definitiva sobre la efectividad del medicamento. Se necesitan estudios placebo-control, tal vez con pacientes menos complicados, para mejor definir el efecto de esta terapia en pacientes con la enfermedad de Crohn fistulizante.

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