Immunoglobulin therapy in inflammatory bowel disease

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DS LEVINE. Immunoglobulin therapy in inflammatory bowel disease. *Can J Gastroenterol* 1993;7(2):187-195. A pilot, open-label study was carried out to determine if intravenous immunoglobulin (Ig) produces clinical improvement in patients with inflammatory bowel disease (IBD). Twelve consecutive patients with idiopathic ulcerative colitis (n=9) or Crohn's colitis (n=3) were enrolled. Eleven patients were refractory to medical treatment, including adrenocorticosteroids in all cases, and were symptomatic for at least six months with endoscopically moderate or severe mucosal inflammation; one patient had relapsed repeatedly during withdrawal of steroid therapy. Six patients had pancolitis and four patients had colitis to the right flexure or transverse colon. Nine patients required hospitalization for treatment of colitis. Intravenous Ig was administered in one or two induction phases (2 g/kg over two or five days) followed by a maintenance phase (200 to 500 mg/kg every two weeks for 12 or 24 weeks). Tapering of adrenocorticosteroid therapy was attempted, but oral aminosalicylates and retention enema medications for idiopathic colitis were continued. Treatment response was assessed clinically, as well as endoscopically and histologically whenever possible. Intravenous Ig therapy was well tolerated and biochemical abnormalities were not detected. For all 12 patients, statistically significant reductions were achieved in subjective symptoms, as quantified by a colitis activity score, and in daily doses of prednisone. Five of six patients who completed the treatment protocol improved clinically. Four of five who underwent post treatment colonoscopic and biopsy evaluations had unequivocal reductions in the intensity of colonic mucosal inflammation. Three patients who had objective improvement with intravenous Ig experienced relapses of colitis after discontinuation of this therapy. Of six patients who did not complete the treatment protocol, two required surgical intervention and four withdrew to undergo elective colectomy. Intravenous Ig may be beneficial in some patients with idiopathic colitis. The results of this pilot study justify the undertaking of prospective, randomized controlled trials to investigate the therapeutic efficacy and mode of action of intravenous Ig in different subsets of patients with idiopathic IBD. (*Pour résumé, voir page 188*)

Key Words: Autoimmune disease, Crohn's disease, Idiopathic inflammatory bowel disease, Immunoglobulin therapy, Immunomodulation, Immunotherapy, Ulcerative colitis

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CURRENT TREATMENT OF PATIENTS with idiopathic inflammatory bowel diseases (IBD) is based on hypotheses concerning the etiology of these disorders. Immunoregulatory, autoimmune and infectious mechanisms have been proposed for IBD (1-3), leading to the use of anti-inflammatory drugs, immunomodulating agents and antibiotics in these disorders (4,5). Unfortunately, not all patients with IBD respond to standard therapies and surgical intervention often is not accepted by patients. Suboptimal responses to drug treatments, especially in those with severe disease, and a desire to avoid surgery has prompted investigations of many new therapeutic agents.

Intravenous immunoglobulin (Ig) is used successfully and safely in patients with primary and secondary immune deficiencies and immunoregulatory disorders such as autoimmune thrombocytopenic purpura, Kawasaki disease and graft-versus-host disease following bone marrow transplantation (6-11). The rationale for intravenous Ig use in patients with primary immunodeficiency diseases is to provide specific antibodies against pathogens (7,9,11). Other mechanisms of action for intravenous Ig have been demonstrated or hypothesized for immunoregulatory disorders, including decreasing auto-antibody production by the infusion of anti-idiotypic antibodies that are present in the intravenous Ig preparations, altering B cell function, increas-

Traitement de la maladie intestinale inflammatoire par les immunoglobulines

RÉSUMÉ: Une étude pilote ouverte a été menée afin de déterminer si l'immunoglobuline (Ig) intraveineuse produit une amélioration clinique chez les patients atteints de maladie intestinale inflammatoire. Douze patients consécutifs porteurs de colite ulcéreuse idiopathique (n=9) ou de colite de Crohn (n=3) ont été admis. Onze patients étaient réfractaires aux traitements médicamenteux, y compris aux adrénocorticoïdes dans tous les cas et étaient symptomatiques depuis au moins six mois avec une inflammation de la muqueuse de modérée à sévère à l'endoscopie. Un patient avait rechuté à plusieurs reprises durant le sevrage du traitement stéroïdien. Six patients présentaient une pancolite et quatre présentaient une colite à l'angle droit du côlon transverse. Neuf patients ont nécessité une hospitalisation pour le traitement de la colite. L'Ig intraveineuse a été administrée en une ou deux phases d'induction (2 g/kg sur deux ou cinq jours) suivies d'une phase d'entretien (200 à 500 mg/kg aux deux semaines durant 12 à 24 semaines). La réduction graduelle du traitement adrénocorticoïde a été tentée, mais les aminosalicyles oraux et les médicaments par lavement retenu pour la colite idiopathique ont été poursuivis. La réponse thérapeutique a été évaluée au plan clinique, endoscopique et histologique dans la mesure du possible. Le traitement par Ig intraveineuse a été bien toléré et aucune anomalie biochimique n'a été décelée. Pour les douze patients, des réductions statistiquement significatives ont été atteintes au plan des symptômes subjectifs mesurés par un barème d'activité de la colite et par les doses de prednisone administrées quotidiennement. Cinq patients sur six qui ont complété le protocole thérapeutique se sont améliorés au plan clinique. Quatre des cinq patients qui ont subi une coloscopie après le traitement et des évaluations par biopsie présentaient des réductions nettes de l'intensité de l'inflammation de la muqueuse du côlon. Trois patients qui présentaient une amélioration objective grâce à l'Ig intraveineuse ont présenté des rechutes de la colite après l'interruption du traitement. Sur les six patients qui n'ont pas terminé le protocole thérapeutique, deux ont nécessité une intervention chirurgicale et quatre ont abandonné pour subir une colectomie élective. L'Ig intraveineuse peut être profitable chez certains patients qui présentent une colite idiopathique. Les résultats de cette étude pilote justifient la mise en oeuvre d'essais contrôlés randomisés prospectifs pour mesurer l'efficacité thérapeutique et le mode d'action de l'Ig intraveineuse chez différents groupes de patients atteints de maladie intestinale inflammatoire idiopathique.

ing natural killer and suppressor T cell activity, inhibiting cytokine release, enhancing clearance of antigen-antibody complexes, and interfering with Fc receptors on reticuloendothelial system cell membranes (6-15).

The immunoglobulin molecules present in intravenous Ig preparations have an extraordinary variety of idiotypic specificities, are of adequate mass to produce measurable, lasting increases in serum Ig levels, and have distinct Fc receptor reactivities (12). In theory, these properties of intravenous Ig could, in patients with IBD, produce ameliorative effects that are mediated by a variety of mechanisms, including primary immunoregulatory effects, neutralization of antigens, suppression

or enhancement of T and B cell functions, and anti-inflammatory actions. In practice, the therapeutic action of intravenous Ig has been suggested by clinical observations of improvement in small numbers of patients with ulcerative colitis and Crohn's disease (16-21). However, the observed clinical improvement may have reflected spontaneous remissions of IBD because the degree of refractoriness to standard medical therapies, the proximal extent of colonic disease, and the intensity of mucosal inflammatory change in the responders were not clearly described in all cases.

To assess further its therapeutic potential in IBD, intravenous Ig was administered to patients with active

and extensive idiopathic colitis who had not responded to standard medical therapies or who were dependent on systemic adrenocorticosteroids to remain in clinical remission. Responses to intravenous Ig therapy were monitored clinically, as well as endoscopically and histologically whenever it was feasible, in order to assess the results of treatment as objectively as possible in this open-label study (22-25). This article is adapted from a previous publication (26) and previous presentations at the annual meeting of the American Gastroenterological Association in San Antonio, Texas, May 1990 (27), and the Third Conference on Immunotherapy With Intravenous Immunoglobulins in Interlaken, Switzerland, May 1990 (28).

MATERIALS AND METHODS

Patients: Twelve consecutive patients (eight women, four men) with idiopathic ulcerative colitis (n=9) or Crohn's disease of the colon (n=3) were enrolled (Table 1). Eleven patients had active symptoms for at least six months before enrollment and were referred for enrollment because of refractory colitis despite standard medical therapy, including systemic adrenocorticosteroids in all cases. One patient required oral prednisone therapy to remain in clinical remission. All patients were reluctant to receive other immunosuppressive therapy or have surgical intervention at the time of enrollment into the study. Nine of the 12 patients had been hospitalized for treatment of severe colitis within one year of initiating intravenous Ig therapy. The study protocol was approved by the University of Washington Human Subjects Division in 1987.

Clinical evaluations: All patients had interval medical histories, physical examinations and clinical assessment of colitis symptoms during the course of the study. Diaries were issued to patients for recording the colitis symptoms. Colitis activity scores adapted from a previously published index (29) were calculated based on these records by adding point values for different symptoms (Tables 2,3). Blood pressure, pulse, respiratory rate and body

TABLE 1
Patient data and treatment with intravenous immunoglobulin (Ig)

Patient	Sex	Age (years)	Diagnosis	Previously hospitalized	Duration of disease (years)	Intravenous Ig treatment phase	
						Induction [†]	Maintenance [‡]
1	Female	16	UC	Yes	1.1	x 2	12 weeks (200-500 mg/kg)
2	Female	20	Crohn's	No	1.1	x 1	12 weeks (400 mg/kg)
3	Male	66	UC	No	3.2	x 1	12 weeks (400 mg/kg)
4	Female	23	UC	Yes	1.3	x 1	12 weeks (400 mg/kg)
5	Male	17	UC	Yes	0.6	x 1	24 weeks (400 mg/kg)
6	Male	7	UC	Yes	3.0	x 1 (2 days)	24 weeks (400 mg/kg)
7	Female	42	Crohn's	Yes	10.0	x 1	2 weeks (200 mg/kg)
8	Female	29	Crohn's	Yes	10.0	x 1	4 weeks (200 mg/kg)
9	Male	51	UC	No	8.5	x 1	2 weeks (400 mg/kg)
10	Female	17	UC	Yes	2.0	x 1 (plus 1 g per kg/2 days)	0 weeks
11	Female	10	UC	Yes	4.0	x 2	0 weeks
12	Female	17	UC	Yes	0.5	x 1	6 weeks (400 mg/kg)

UC Ulcerative colitis; Crohn's Crohn's disease of the colon; [†] Intravenous Ig 2 g/kg administered over five days, except as noted; [‡] Intravenous Ig infused every two weeks

temperature were carefully monitored during intravenous Ig infusions and patients were observed for the development of any adverse effects (7,8).

Laboratory evaluations: Standard laboratory tests were performed pre-treatment and after completing the induction and maintenance phases of intravenous Ig therapy. These tests included complete blood count, white blood cell count and differential, erythrocyte sedimentation rate, liver enzymes, a battery of blood chemistries, quantitative serum immunoglobulin (IgG, IgA, IgM and IgE) concentrations and serum IgG subclass levels. Trough and peak total serum IgG levels were respectively measured before administration of intravenous Ig infusions and 10 mins after completing infusions.

Colonoscopic evaluations: The proximal extent and intensity of inflammation was assessed within one week of initiating intravenous Ig therapy by direct inspection of the colonic mucosa during total colonoscopy in adults

(patients 2 to 5, 7 to 9 and 12) and limited colonoscopies in pediatric patients (patients 1, 6, 10 and 11) (Table 4). Follow-up colonoscopies were performed in patients who completed the treatment protocol 12 and 24 weeks after initiating intravenous Ig therapy (Table 1). Endoscopic inflammation was scored as follows: severe – multiple erosions and ulcers, exudate and spontaneous hemorrhage; moderate – mucosal friability and erosions; mild – edema and loss of the normal vascular pattern; no inflammation – intact mucosa with a normal vascular pattern. Colonoscopic biopsies were obtained in adult patients from four quadrants at 10 to 20 cm intervals for histopathological examination.

Colonic biopsy evaluations: The histological intensity of inflammation in the colon was assessed in adults in 12 to 32 biopsies obtained during each colonoscopy performed within one week before and 12 and 24 weeks after initiating intravenous Ig therapy (Table 4). All

biopsies were oriented, fixed, processed, step-serial sectioned at 4 µm thickness, and stained with hematoxylin and eosin alone, and with hematoxylin and eosin, saffron and Alcian blue at pH 2.5. Histopathological examination was performed independently on coded slides to blind the pathologist to all clinical patient data and the anatomical site of the biopsies. Histological inflammation was scored as follows: severe – ulcerated mucosa with granulation tissue; moderate – numerous crypt abscesses; mild – scattered crypt abscesses or cryptitis; no inflammation – uninfamed mucosa with abnormalities of crypt architecture consistent with quiescent ulcerative colitis.

Immunoglobulin treatment protocol:

Intravenous Ig therapy began after completion of the above pretreatment evaluations. Two lots of intravenous Ig (Sandoglobulin, lots #73712710 and #83711310, provided by Sandoz Pharmaceuticals, New Jersey) were used throughout the study. Variation in

TABLE 2
Tabulation of colitis activity score for patients receiving intravenous immunoglobulin

Symptom parameter	Description or severity	Point score*
General health	Well	0
	Fair	1
	Poor	2
Abdominal pain	Absent	0
	Present	1
Stool frequency	Number/day	1 per stool
Stool form	Formed	0
	Loose to formed	1
	Watery to loose	2
Rectal bleeding	Absent	0
	Present	1
Extraintestinal manifestations	Arthralgias	1
	Uveitis or iritis	1
	Erythema nodosum	1
	Aphthous ulcers	1
	Pyoderma gangrenosum	1
	Fistula	1
	Abscess	1

*The sum of the points equals the colitis activity score

dosing regimens resulted from attempts to optimize the administration of intravenous Ig and to adjust therapy based on individual clinical circumstances. Intravenous Ig was prepared as a 6% solution and was infused at a rate of 1 mL/kg/h (60 mg/kg/h) during the first 15 mins of the infusion and subsequently at a rate of 3 mL/kg/h during induction and maintenance phases of therapy. The intravenous Ig dosing and infusion rates for patients with idiopathic colitis were comparable to those used for patients with other disorders (6-11).

During the induction phase, a total of 2 g/kg intravenous Ig usually was infused over a five-day period (400 mg/kg/day). Induction phase therapy was repeated in three patients two to eight days after completing the initial induction course (2 g/kg over five days in patients 1 and 11; 1 g/kg over two days in patient 10). Within two weeks of completing the induction phase, maintenance phase therapy began with 200 to 500 mg/kg intravenous Ig administered on one day every two weeks. The duration of maintenance therapy was scheduled to be 12 weeks (six infusions) and was completed in four patients (patients 1 to 4). Maintenance

therapy was extended to 24 weeks (12 infusions) in two patients (patients 5 and 6) (Table 1). The remaining six patients (patients 7 to 12) withdrew from the study before either starting or completing 12 weeks of maintenance phase therapy.

Other medical therapy for idiopathic colitis: Oral or intravenous systemic adrenocorticosteroids, oral sulphasalazine, oral or parenteral antibiotics and retention enemas of topically active anti-inflammatory drugs were being taken by patients at the time of enrollment into the study. Every effort was made to discontinue systemic adrenocorticosteroids and antibiotics, whereas therapy with sulphasalazine and retention enemas was continued during the course of intravenous Ig therapy.

Assessment of treatment response: Patients who experienced an objective, beneficial therapeutic response to intravenous Ig had an unequivocal reduction in the length and area of colonic mucosa involved by colitis based on colonoscopic inspection and/or reduction or elimination of histological inflammation (Table 4). The colitis activity score and daily prednisone dose is reported for all patients

before treatment with intravenous Ig and at the study's completion (24 weeks after initiating intravenous Ig therapy or at the time of withdrawal from the treatment protocol) (Table 3).

RESULTS

Patient participation: Patients 1 to 6 completed the study. The other six (patients 7 to 12) withdrew before completing the treatment protocol (two required urgent surgical intervention and four withdrew to undergo elective surgery). Patient 7 failed to respond and required emergency colectomy for limited colonic perforations. Patient 8 had extensive perirectal abscesses at the time of enrollment and required a diverting ileostomy seven weeks after initiating intravenous Ig. Patient 9 elected to have a colectomy just four weeks after initiating intravenous Ig. Patient 10 received two induction courses of intravenous Ig but elected to have a colectomy before maintenance therapy began. Patient 11 responded clinically after the induction phase but decided to have a colectomy prior to beginning maintenance phase therapy. Patient 12 was steroid-dependent at the time of enrollment, withdrew from the treatment protocol during maintenance phase therapy because her clinical symptoms worsened, and had an elective colectomy.

Safety of immunoglobulin therapy: No biochemical abnormalities developed with intravenous Ig therapy. Mild clinical side effects (headache, chills, chest tightness) developed during intravenous Ig infusions in either the induction or the maintenance phases (patients 1, 5, 6, 9 and 12) and resolved promptly after slowing the infusion rates.

General clinical response to immunoglobulin therapy: Significant reductions in the colitis activity score were achieved by the group of six patients who completed the treatment protocol and by the entire study group of 12 patients (Table 3). Prednisone therapy was completely discontinued in patients 1, 2, 3 and 5. Patient 4 had brittle, insulin-dependent diabetes mellitus and her clinical improvement was based largely on a reduction of fluctuat-

TABLE 3
Clinical results in patients receiving intravenous immunoglobulin

Patient	Colitis activity score		Prednisone dose, mg/day	
	Baseline	Completion	Baseline	Completion
1	14	2	40	0
2	8	3	25	0
3	15	7	40	0
4	17	7	20	5
5	13	3	75	0
6	13	6	50	6
7	12	13	50	60
8	6	6	50	0
9	12	12	60	20
10	11	11	75	40
11	13	6	60	40
12	3	11	20	11

(Mean $\pm$ SE for different patient groups):

1-6	13.3 $\pm$ 1.2	4.7 $\pm$ 0.9*	41.7 $\pm$ 8.0	1.9 $\pm$ 1.2*
7-12	9.5 $\pm$ 1.6	9.8 $\pm$ 1.3†	52.5 $\pm$ 7.5	28.5 $\pm$ 9.0‡
1-12	11.4 $\pm$ 1.1	7.3 $\pm$ 1.1‡	47.1 $\pm$ 5.5	15.2 $\pm$ 5.9*

* $P < 0.001$ compared to baseline, Student's paired *t*-test; † $P > 0.05$ (NS) compared with baseline, Student's paired *t*-test; ‡ $P < 0.05$ compared with baseline, Student's paired *t*-test

ing diarrhea, a part of which could be ascribed to the diabetes. Patient 6 showed improvement during the maintenance phase of intravenous Ig therapy and substantially reduced his dose of prednisone. Of those patients who withdrew from the treatment protocol, patient 11 had clinical improvement following the induction phase of intravenous Ig therapy.

Laboratory evaluations: IgG subclass deficiencies (IgG, less than 375 mg/dL; IgG2 less than 90 mg/dL; IgG3 less than

30 mg/dL; IgG4 less than 3 mg/dL) were found in six patients before initiating intravenous Ig therapy: IgG1 in patients 7 and 9; IgG2 and IgG3 in patients 1, 3, 4 and 5; and IgG4 in patients 1 and 7. Pretreatment total IgG levels were decreased in patient 1 (574 mg/dL) and were increased in patients 10 (1810 mg/dL) and 11 (1700 mg/dL). Pretreatment IgA, IgM and IgE levels were normal in all patients.

Eleven patients showed a marked increase in total serum IgG levels during

intravenous Ig therapy (post treatment data on patient 6 not available). The mean pretreatment total IgG level $\pm$ SE of 1076 $\pm$ 124 mg/dL differed significantly from the mean post treatment level of 3378 $\pm$ 183 mg/dL following completion of the induction phase of intravenous Ig therapy ($P < 0.001$, Student's paired *t* test). For patients 1 to 5, the mean pretreatment total IgG level of 893 $\pm$ 126 mg/dL differed significantly from both the mean trough and peak total IgG levels (measured at the completion of the maintenance phase of intravenous Ig therapy) of 1391 $\pm$ 198 mg/dL and 1851 $\pm$ 199 mg/dL, respectively ($P < 0.01$ and $P < 0.001$, respectively, Student's paired *t* test).

Pretreatment white blood cell counts exceeded $10 \times 10^9/L$ in patients 1, 5, 6, 8, 10 and 11, and normalized after intravenous Ig treatment in patients 1, 5, 6 and 8. Pre- and post treatment values for erythrocyte sedimentation rate and hemoglobin did not vary significantly.

Endoscopic and histological evaluations: Results of colonoscopic and biopsy evaluations performed before initiating intravenous Ig therapy and at the completion of the study protocol are summarized in Table 4. Examples of the colonic distribution of inflammation before, during and after intravenous Ig therapy, as assessed histologically, are depicted for patients 3 and 5 in Table 5.

TABLE 4
Endoscopic and histological results in patients receiving intravenous immunoglobulin (Ig)

Patient	Proximal extent of colitis		Endoscopic intensity of inflammation		Histological intensity of inflammation	
	Baseline	Completion*	Baseline	Completion	Baseline	Completion
1	Transverse†	(Refused F/U)	Severe	(-)	Moderate-severe	(-)
2	Pancolitis	Pancolitis	Moderate	Mild	Mild	None
3	Right flexure	Sigmoid	Severe	Moderate	Mild-severe	Mild
4	Pancolitis	Pancolitis	Mild-moderate	Moderate	Mild-severe	Mild-severe
5	Pancolitis	Proctitis	Moderate-severe	None	Mild-moderate	Mild
6	Transverse†	Transverse	Severe	Mild-moderate	(No biopsies)	(No biopsies)
7	Pancolitis	(Colectomy for perforation)	Moderate-severe	(-)	Severe	(-)
8	Rectal abscess	(Diverting ileostomy)	Severe	(-)	(No biopsies)	(-)
9	Pancolitis	(No F/U)	Mild-severe	(-)	Moderate-severe	(-)
10	Left flexure†	(No F/U)	Severe	(-)	Severe	(-)
11	Transverse†	(No F/U)	Severe	(-)	Severe	(-)
12	Pancolitis	(No F/U)	Mild-moderate	(-)	Mild	(-)

*Information in parentheses regarding lack of data: refused F/U - refused follow-up colonoscopic evaluation; no F/U - no follow-up on individuals who withdrew from intravenous Ig maintenance treatment protocol and underwent elective colectomy. †Proximal extent determined only to limits of colonoscopic examination.

TABLE 5

Examples of distribution of colonic inflammation (histological assessment) before, during and after therapy with intravenous immunoglobulin

Patient	Site of biopsies (cm from anus)	Histological inflammation scores for each biopsy		
		Baseline	12 weeks	24 weeks
Patient 3	Cecum (70 cm)	0000	0000	0000
	Ascending (60 cm)	0000	0000	0000
	Right flexure-transverse (50 cm)	0001	0001	0000
	Left flexure (40 cm)	1111	0001	0000
	Descending (30 cm)	2233	1111	0011
	Sigmoid (20 cm)	2233	1333	1111
	Rectum (10 cm)	3333	1111	0000
Patient 5	Ascending (75-80 cm)	1111	0000	----
	Right flexure-transverse (55-60 cm)	1222	0000	----
	Descending (35-40 cm)	1222	0000	0000
	Rectosigmoid (15-20 cm)	1222	0000	0000
	Rectum (10 cm)	2222	----	1111

— No biopsies taken; 3 Severe; 2 Moderate; 1 Mild; 0 None (see text)

Four of the six patients who completed the treatment protocol had objective improvement based on direct inspection of the colonic mucosa (patients 2, 3, 5 and 6), and three of the six patients had evidence of histological improvement based on examination of endoscopic mucosal biopsies (patients 2, 3 and 5). Colonoscopies performed at 12 weeks showed intermediate improvement in patients 2, 3 and 6, and complete resolution in patient 5 (Table 5). No objective change in the proximal extent or intensity of colitis was demonstrated in patient 4. Patient 1 refused to have follow-up colonoscopy. Endoscopic evaluation was not performed on patients who withdrew from the treatment protocol (patients 7 to 12).

Clinical follow-up after completion of maintenance phase immunoglobulin therapy: Patient 1 remained in clinical remission while off oral prednisone. Patient 2 was asymptomatic while off adrenocorticosteroids for three months before she relapsed and required reinstitution of oral prednisone. Patient 3 relapsed after four months and underwent elective colectomy four months later. Patient 4 died of complications related to her diabetes after eight months. Patient 5 redeveloped colitis after one month and required reinstitution of oral prednisone before ultimately undergoing elective colectomy. Patient 6 required low dose oral prednisone to keep symptoms controlled.

DISCUSSION

Intravenous Ig therapy can be administered safely to patients with idiopathic colitis and may be therapeutically beneficial in a subset of such IBD patients. For this preliminary study 12 consecutive, medically refractory, moderately or severely ill patients with extensive idiopathic colitis were enrolled. Of these, five developed reversible, mild, adverse clinical effects associated with the intravenous Ig infusion rate. In many patients induction therapy with intravenous Ig successfully induced subjective symptomatic improvement. Of the six patients completing 12 or 24 weeks of maintenance phase intravenous Ig therapy, five had unequivocal clinical improvement, four had significant, albeit incomplete reduction in colonic mucosal inflammation as assessed by colonoscopy and biopsies, and all six discontinued or significantly decreased their systemic adrenocorticosteroid therapy.

It is of interest that pretreatment serum IgG subclass deficiencies were detected in half of the patients, and that two of the three patients who relapsed following completion of maintenance phase intravenous Ig therapy had pretreatment IgG subclass deficiencies. However, it is not clear whether or not the response to intravenous Ig in these patients was in any way related to these observations. Serum IgG subclass deficiencies are certainly not typical in IBD patients

(30,31), although altered expression of IgG subclasses by intestinal mucosal cells from IBD patients has been reported (32-36). The observations of serum IgG subclass deficiencies in the present study may reflect either IBD disease chronicity or chronic treatment with systemic adrenocorticosteroids (35,37) at the time serum was obtained for analysis.

The study was confounded by six patients who did not complete at least 12 weeks of maintenance phase intravenous Ig therapy. In these patients, intravenous Ig was not promptly effective or could not be objectively evaluated. Two patients with Crohn's disease were true treatment failures because they required surgical intervention within four to seven weeks of initiating intravenous Ig. However, four patients withdrew from the study in order to undergo elective colectomies before beginning or well before completing maintenance phase therapy.

The rationale for using intravenous Ig in the treatment of IBD is based on the hypothesis that these disorders are caused by an abnormal immune response to gut-associated antigens, an autoimmune mechanism, or an infectious agent. The apparent therapeutic efficacy of intravenous Ig in some patients with idiopathic colitis may be due to its immunomodulating or antimicrobial properties, as demonstrated in other diseases (6-15). The manifestations of idiopathic colitis have been

postulated to result from immunologic mechanisms based on the colonic histopathology, response to immunosuppressive drugs and extraintestinal complications that are observed in IBD patients (1-3,31,38). A variety of humoral and cell-mediated immune abnormalities have been demonstrated in patients with IBD, and whether these represent primary immunoregulatory abnormalities or secondary epiphenomena is vigorously debated. Nevertheless, intravenous Ig may produce therapeutic improvement by modulating disordered immunoregulation regardless of whether it is a primary process or a secondary manifestation that leads to intestinal tissue damage in IBD. Altered immunoreactivity may be responsible for the disease manifestations of IBD based on identification of disease-specific autoantibodies (39-41) and evaluations of B cell function and immunoglobulin secretion (30,32-36,42), T cell function (43-46), elaboration of cytokines and cytokine receptors (47-54), complement activation (55) and generation of prostaglandins and leukotrienes (56-58).

The mechanisms of therapeutic action of intravenous Ig in IBD may be similar to those in other diseases (6-15) and involve direct or indirect systemic immunoregulatory activities. The recent demonstration of gut localization of technetium-labelled immunoglobulin in IBD patients (59) suggests that intravenous Ig also may affect local gut mucosal immunoregulation. Potential mechanisms of action of intravenous Ig in IBD include: provision of specific antibody (eg, producing neutralization of a pathogenic antigen, specific anti-CD4 or anti-interleukin receptor antibodies); immune modulation of anti-idiotypic antibodies; immune modulation of activated macrophages and T cells; and ultimately altered regulation of local generation of inflammatory mediators. Intravenous Ig preparations derived from large pools of plasma may contain antibodies to an unknown etiologic agent that is important in the pathogenesis of IBD. Alternatively, anti-idiotypic antibody present in intravenous Ig may down-regulate autoantibody synthesis

(6-15,60,61). Increased interleukin-1 production by activated intestinal lamina propria mononuclear cells obtained from patients with IBD was recently demonstrated (48). Therefore, the recent finding that intravenous Ig may interfere with the excess production and secretion of interleukin-1 in Kawasaki disease (62) also may be of relevance for IBD.

Approaches to treatment of patients with IBD have long included anti-inflammatory and immunomodulating agents. Many patients respond to intermittent or continued use of systemic adrenocorticosteroids and immunosuppressive agents such as azathioprine or 6-mercaptopurine (1,2,4,37). More recently, other immunomodulating drugs have been found to be effective in subsets of patients with IBD, including methotrexate (63) and cyclosporine A (64,65). The ultimate immunosuppressive therapy – removal of lymphocytes by leukapheresis – is associated with considerable morbidity and is not practical as a long term treatment strategy (66).

The results of this pilot, open-label trial of intravenous Ig, although encouraging in some patients, must be considered preliminary. These observations justify the undertaking of a prospective, randomized controlled trial in IBD patients who are carefully selected or stratified into different disease categories in order to assess most objectively the therapeutic effectiveness of intravenous Ig. The variety of potential mechanisms of action of intravenous Ig in IBD should invite investigations of the relationships between treatment response and various factors that ultimately could be predictive of the effectiveness of this treatment modality, including: IBD diagnosis (ulcerative colitis versus Crohn's disease); colitis disease activity (proximal extent and intensity of mucosal inflammatory change); duration of disease; adrenocorticosteroid dosing; IgG subclass deficiencies; and perhaps other immunological markers. The possible need for extended treatment periods as well as increased dosages of intravenous Ig must be evaluated because of the significant im-

provement in, but incomplete resolution of, colitis in responders, the tendency for responders to relapse following completion of maintenance courses of intravenous Ig therapy, and the costs for such therapy. Intravenous Ig therapy may be shown to produce long remissions of disease in selected patients or provide a satisfactory temporizing measure in severely ill patients who are destined for surgical intervention. Investigation of the mechanisms underlying the therapeutic response to intravenous Ig could lead to the design of more practical, less expensive and more effective immunomodulatory therapies. The devastating nature of IBD and the evidence supporting the immunopathogenesis of these disorders justifies continued investigation of immunomodulating therapeutic agents for affected patients.

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