Cyclosporin for Severe Ulcerative Colitis

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Abstract

Background: About one-third of patients with severe ulcerative colitis do not respond to conventional therapy and require urgent colectomy. It was recently shown that cyclosporin is effective in some of these patients.

Objectives: To review the current experience of six hospitals in central Israel that used cyclosporin in patients with severe ulcerative colitis.

Methods: The files of all 32 patients treated with cyclosporin for corticosteroid-resistant ulcerative colitis were reviewed. Activity of disease was measured by a clinical activity, index colonoscopy and laboratory tests.

Results: The average duration of treatment with intravenous cyclosporin was 12.7 days (range 9–28) after which the disease activity index dropped from an average of 14.22 to 4.74. The mean time for response was 7.5 days (4–14). Twelve patients (40%) required surgery within 6 months and another 6 patients (18.8%) were operated on after more than 6 months. Twelve patients (37%) maintained remission for at least 6 months and did not require surgery. In one patient treatment was stopped because of non-compliance and one was lost to follow-up. There were numerous side effects, but in only one case with neurotoxicity was treatment withdrawn.

Conclusions: Cyclosporin is a relatively safe and effective treatment for severe ulcerative colitis. It induced long-term remission in 37% of the patients, and in those who required surgery the treatment resulted in an improved clinical condition before the operation.

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Ulcerative colitis has a wide clinical spectrum, ranging from a mild disease controlled with 5-aminosalicylates and small intermittent doses of steroids, to a severe and life-threatening condition. Treatment of such severe attacks consisted traditionally of hospitalization, nil per os, intravenous fluids and electrolytes, and high dose corticosteroids both rectally and intravenously [1]. About 30% of patients with severe ulcerative colitis do not respond to this treatment and require urgent total colectomy [2]. It was recently shown that cyclosporin is effective in this group of patients. However, experience is limited and the numbers of patients reported are relatively small. The aim of this study was to review the experience with cyclosporin for the treatment of severe ulcerative colitis in six hospitals in Israel.

Patients and Methods

The files of all 32 patients treated with cyclosporin for ulcerative colitis in six hospitals in central Israel were reviewed. Data collected from the files included past history, history of the index attack for which cyclosporin was given, clinical follow-up and laboratory tests. Disease activity was measured by a clinical activity index described by Lichtiger et al. [3], which included the number of daily stools, presence or absence of nocturnal diarrhea, percent of bowel movements with visible blood, presence or absence of fecal incontinence, abdominal pain, general well being, and abdominal tenderness [Table 1]. A score of 10 or more indicated active disease. Patients were given a score the day before starting cyclosporin treatment, the day when intravenous treatment was completed and oral treatment begun, and once a month during follow-up thereafter. The endpoints were proctocolectomy or continuous remission (defined as disease activity index of 7 or less) during a follow-up of not less than 6 months. Before the start of therapy permission was obtained from the ethics committee of the Ministry of Health for the use of cyclosporin for an as yet non-registered indication. The nature of the therapy and alternative methods of treatment were explained to the patients or their parents. All consented to cyclosporin therapy.

The 32 patients comprised 18 females and 14 males with an average age of 25.8±12 (range 11–50 years). The mean duration of the disease from the diagnosis to the attack requiring cyclosporin treatment (the index attack) was 35.9 months (range 1–180), and the mean duration of

Table 1. Disease Activity Index

Symptom	Score
Diarrhea (no. of daily stools)	
0-2	0
3-4	1
5-6	2
7-9	3
10 or more	4
Nocturnal diarrhea	
No	0
Yes	1
Stool with visible blood (%)	
0	0
< 50 %	1
>50 %	2
100 %	3
Fecal incontinence	
No	0
Yes	1
Abdominal pain	
None	0
Mild	1
Moderate	2
Severe	3
General well being	
Perfect	0
Very good	1
Good	2
Average	3
Poor	4
Terrible	5
Abdominal tenderness	
None	0
Mild and localized	1
Moderate and diffuse	2
Severe or rebound	3

the index attack was 1.6 months (1 week to 8 months). Mean weight loss was 4.8 kg, mean albumin 35 g/L (range 24–46 g/L) and mean hemoglobin 10.5 g/dl (7.6–12.9 g/dl). Eleven of the 32 patients had total colitis on colonoscopy, 3 had colitis to the transverse colon, 2 had proctosigmoiditis, and 17 patients only underwent rectosigmoid examination.

All patients received steroids intravenously for at least 2 weeks before cyclosporin treatment was begun. Three patients were steroid dependent and had been given steroids for periods of 72, 52 and 24 months respectively. Lack of response to steroid treatment was defined as a disease activity index of 10 or more on the day before commencement of the cyclosporin treatment. Cyclosporin was started intravenously at 5 mg/kg for an average of 10 days (range 8–28). All patients continued to receive steroids during the IV cyclosporin treatment. Three were taking azathioprine and 9 received metronidazole together with cyclosporin. Response to cyclosporin was defined as a drop in disease activity index below 6. In those who responded well, cyclosporin treatment was continued orally at a dose of 6–8 mg/kg/day. If the disease activity index did not drop to below 8 or if it rose again during follow-up, patients were referred for proctocolectomy. Cyclosporin doses were adjusted to obtain a whole blood level of 200–300 ng/ml, the mean level being 276.06±312 ng/ml (mean ± SD). The total period of cyclosporin treatment was 5 to 12 months (average 7.25 months).

Results

Initial response

The average disease activity index was 14.22 (range 10–21) on the day before cyclosporin was started. By the end of the intravenous treatment it had dropped to 4.74 (range 0–13) [Figure 1]. In 25 patients (78%) a remission was achieved during intravenous cyclosporin treatment, and 7 patients (22%) did not respond and were referred for immediate surgery [Figure 2]. There was no correlation between the initial disease activity index and the clinical response to therapy [Figure 1]. All patients who went into remission continued to receive cyclosporin orally for at least 5 more months or until they relapsed. The mean time for response was 7.5 days (range 4–14).

Despite the good initial response, five patients required surgery within 6 months of starting cyclosporin treatment, while still receiving oral cyclosporin. Treatment was stopped in one patient because of non-compliance, but this patient did not require an operation. One patient left the country and was lost to follow-up.

Long-term response

After 6 months of treatment, 18 ulcerative colitis patients were symptom free and in clinical remission. Follow-up revealed that 12 of them remained in remission for an average of 17.4 months (6–40 months) [Figure 2]. All the patients who remained in remission had also received steroids (10–40 mg prednisone for at least 4 months) during the period of oral cyclosporin treatment; 6 had also been treated with azathioprine (50 mg/day), 2 with methotrexate (12.5 mg/week), and one with 6-mercaptopurine (50 mg/day). Six patients relapsed during the follow-up period and were referred for proctocolectomy. Thus at the time of submission of this article, 18 patients (56%) eventually required an operation.

No correlation was found between the patients' response to treatment and their age, gender, duration of disease, nutrition during treatment, or albumin or hemoglobin level. Side effects were numerous, but treatment had to be stopped in only one patient who developed severe neurotoxicity. One patient developed hypertension that responded well to hydralazine. One patient developed a rash that was treated successfully with steroids. Two patients had pneumonia that resolved after antibiotic treatment. Three patients complained of paresthesia, tremor and a burning sensation that were reversible when the drug dose was lowered. Eight patients complained of hirsutism. One patient who developed mild transient renal failure was found to have urolithiasis, but kidney function returned to normal after a stone was passed. One patient

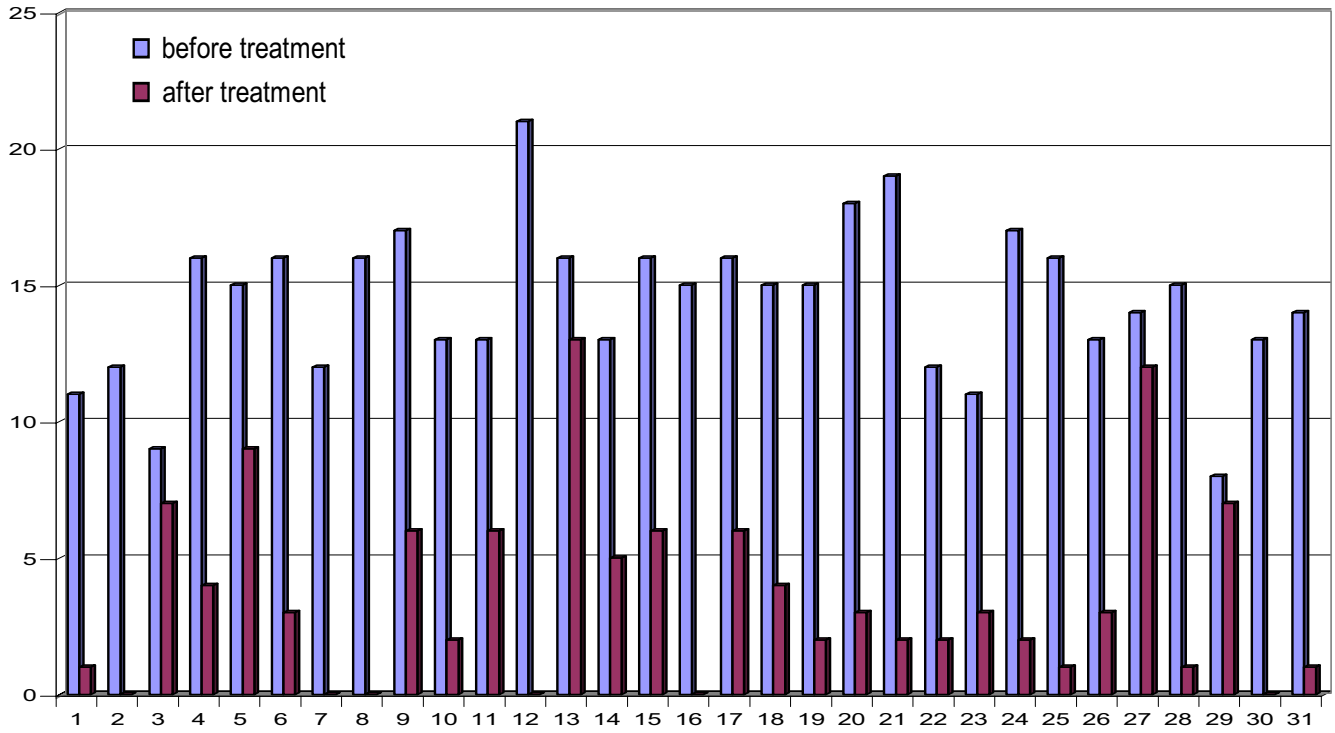

Figure 1. Disease activity index in 31 patients before and at the end of intravenous cyclosporin treatment

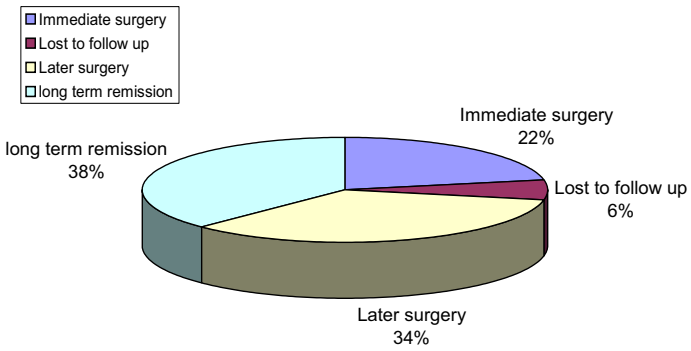

Figure 2. Final outcome of cyclosporin treatment

had a deep leg venous thrombosis. In one patient treatment had to be stopped because of non-compliance, and one patient left the country and was lost to follow-up.

Discussion

Cyclosporin is an immunosuppressive drug that inhibits T cell proliferation and interleukin-2 production. It has been used in a variety of immune-mediated disorders including graft rejection, rheumatoid arthritis [4], psoriasis [5], Behcet's syndrome [6], and many others [7]. In view of the success of cyclosporin treatment in these settings, it seemed logical to investigate its efficacy in inflammatory bowel disease [8–10]. We retrospectively studied the clinical experience accumulated in central Israel of using cyclosporin to treat severe ulcerative colitis. Although this is a retrospective summary of clinical experience, all centers used a similar clinical approach: namely cyclosporin was given intravenously to patients with severe non-steroid responsive disease, and all patients received the same dose of cyclosporin, aiming at the same blood levels. Those who responded continued to receive cyclosporin orally, and for those patients who relapsed the policy in all the centers was to recommend surgery. The centers did vary with regard to the introduction of additional immunosuppressive therapy.

In our study, 78% of patients showed a good initial response, with rapid resolution of their symptoms as measured by disease activity index. This is similar to reports in other studies [3,8,11] that have also shown rapid improvement within 1 to 2 weeks in about 80% of patients given cyclosporin intravenously.

During a mean follow-up of 17 months, 18 of our ulcerative colitis patients (56%) relapsed and required surgery, however in 12 patients (37%) surgery was avoided. By the time surgery was undertaken the patients' condition had improved, including serum levels of albumin and hemoglobin and the clinical status. Two additional patients have fallen out of the study. Similar results were reported by Lichtiger and coworkers [3] who observed sustained improvement in 18 of 32 patients (50%) during a mean follow-up of 2.6 years. Van Gossum et al. [9] also reported short-term efficacy in 20 of 29 patients (69%), but after 12 months follow-up only 13 of 29 patients (45%) had not had a colectomy. Other investigators reported relapses necessitating surgery in almost all patients within 4 to 8 months after discontinuation of cyclosporin [12]. In another retrospective study published recently, 23 of 32 patients (73%)

with severe ulcerative colitis required colectomy by the end of 12 months follow-up [13]. That study also included patients with very active disease and even toxic megacolon. In our study, patients were included if they had severe non-steroid-responsive colitis but without the need for imminent surgery.

Numerous side effects, mostly mild, were observed, and treatment had to be stopped in only one patient with severe neurotoxicity. Nephrotoxicity, a common and serious complication of cyclosporin treatment, did not occur. Hypertension, when present, responded readily to medical treatment, and a rash and paresthesia were managed by dose adjustment or steroids. This relative absence of side effects seems to be due to the low dose used in this study – 5 mg\kg\day – a dosage known to be associated with a low level of toxicity [14]. In another study, Carbonnel and colleagues [13] reported severe complications, including one perforation and one perioperative death. This high complication rate seems to be due to the inclusion of patients who were too ill for medical treatment, such as patients with toxic megacolon.

We conclude that in young patients with severe ulcerative colitis, a trial of cyclosporin should constitute part of the treatment before surgery is offered. This treatment can avert surgery in some of the patients; and in those requiring surgery their clinical condition at operation is improved. More studies are needed to evaluate the role of combining early additional immunosuppressive treatment in an attempt to keep the patients in remission from stopping cyclosporin therapy.

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