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Efficacy of cyclosporin in severe ulcerative colitis attack

Ciddi ülseratif kolit ataklarında siklosporinin etkinliği

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Background/aims: *Cyclosporin-A is used as a alternative medical therapy in steroid resistant ulcerative colitis with severe activity. In spite of its known efficacy, the long term effects of are not entirely clear.* ***Methods:*** *The records of 13 steroid resistant patients treated with cyclosporin-A were retrospectively assessed. Cyclosporin-A had been prescribed orally at a dose of 8mg/kg/day in four patients and intravenously, 4mg/kg/day in nine patients. Intravenous therapy was changed to oral therapy after one week and patients also received 5-ASA and azathioprine. Steroid treatment was tapered.* ***Results:*** *Ten patients responded to treatment in a mean of nine days (range: 2-30 days). Three patients who did not respond underwent total colectomy on day seven, 11 and 19 of therapy. The 10 patients who initially responded received the drug for an average of 4.9 months; four of these relapsed during and one relapsed soon after discontinuation of therapy. Four of the five patients who relapsed underwent colectomy and the one patient who did not accept surgical intervention continued medical therapy. The remaining five patients (38% of the total group; 50% of the patients who initially responded) remained in remission at the end of an average 17 month follow up period.* ***Conclusions:*** *Cyclosporin-A therapy in severe ulcerative colitis that is resistant to steroids, provides initial remission in 80% of patients and allows 40% to retain their colon for one year.*

Key words: Cyclosporin-A, ulcerative colitis, remission, colectomy.

Amaç: *Siklosporin-A steroide yanıtsız, ciddi aktiviteli ülseratif kolitli hastaların tedavisinde, alternatif bir tedavi şeklidir. Siklosporin-A nın etkinliği oldukça bilinmesine rağmen uzun dönem tedavi sonuçları bu gün için net değildir.* ***Yöntem:*** *Çalışmamızda siklosporin-A kullanan steroide dirençli 13 hastanın sonuçları retrospektif olarak değerlendirildi. Hastalardan 4 üne siklosporin-A 8 mg/kg/gün oral, 9 una 4 mg/kg/gün intravenöz olarak başlandı. Siklosporin-A nın intravenöz başlandığı hastalarda, bir hafta sonra oral uygulamaya geçildi. Hastalara eş zamanlı 5-ASA ve azatioprin verildi, kortikosteroid azaltılarak kesildi.* ***Bulgular:*** *Vakaların 10 u ortalama 9 (2-30) gün içinde tedaviye cevap verdi. Tedaviye cevapsız 3 hastaya 7, 11 ve 19. günlerde total kolektomi uygulandı. İlk cevabın alındığı 10 hastada ilaca ortalama 4,9 ay devam edildi. Bu hastalardan 4 ünde siklosporin almaya devam ederken, 1 inde ilacın kesilmesinden hemen sonra alevlenme meydana geldi. Dört vakaya total kolektomi uygulandı. Cerrahi girişimi kabul etmeyen bir hasta medikal tedavi ile takip edilmektedir. Geri kalan 5 hasta (total grubun %38'i; ilk cevap verenlerin %50'si) ortalama 17 aylık takip sonunda remisyonda kalmaya devam ettiler.* ***Sonuç:*** *Steroide dirençli ciddi aktiviteli ülseratif kolit ataklarında siklosporin-A tedavisi hastaların yaklaşık %80'inde ilk remisyonu sağlamakta, %40 ında da sonraki 1 yıl içinde kolektomiden korumaktadır.*

Anahtar kelimeler: Siklosporin-A, ülseratif kolit, remisyon, kolektomi

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease with periods of remission and relapse, and is characterized by inflammation and ulceration of the innermost lining of the colon. Steroids are agents of choice in the treatment of patients with acute, severe UC, but in around 30-40% of patients, the disease is resistant to treatment with high-dose glucocorticoids (1) and there is no clear-cut treatment strategy in such cases. The introduction of cyclosporin A (CyA) for use in patients with severe, steroid-resistant UC has provided an effective medical alternative to patients previously faced with only surgical options (2,3).

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Table 1. Baseline features of study group

Gender	7 male; 6 female
Mean age	33.5 (16-50) yr
Mean disease duration	64.5 (8-180) months
Disease location	10 pancolitis; 3 left sided
Initial CyA application route	9 IV; 4 oral
Truelove-witts clinical actitvity index	All severely active

Cyclosporin A is a fungal metabolite and an immunosuppressant agent which mainly effects cellular immunity. It reduces the production of IL-2 and inhibits stimulation of T cells (4).

The aim of this study to assess the efficacy and long term effects of CyA therapy in patients with severe, steroid resistant UC.

MATERIALS AND METHODS

Between January 1999 and 2002, the records of patients with severe, steroid resistant UC, treated with CyA were retrospectively reviewed. Persistence of symptoms and abnormal laboratory values despite parenteral (2x20mg methyl prednisolone) or oral (32mg methyl prednisolone) high dose steroid therapy for an average of 15 (range 10-18) days, was accepted as being resistant to steroids. A total of 13 patients with these criteria were included in assessment. Seven (53.8%) were male, with a mean age of 33.5 years (range:16-50) at the time of initiation of therapy (Table 1). Three patients had left sided colitis and ten patients had pancolitis. Disease activity was severe in all patients according to Truelove and Witts activity index (5). No patient had fulminant colitis. Cyclosporin A was started orally at a dose of 8mg/kg/day in four patients and IV, 4mg/kg/day as a, continuous infusion in nine patients. The IV therapy was changed to oral therapy, 8 mg/kg, after one week. Steroid treatment was tapered. All patients were also receiving concomitant therapy with 5-ASA products and azathioprine (both drugs prescribed of at least five months at least). During CyA treatment, detailed information on symptoms, findings of physical examination, laboratory results, serum levels and complications of CyA was recorded. Serum levels of CyA were measured twice a week initially and twice a month later (first measurement at second day). Trough levels of cyclosporin were within the target therapeutic range of 150 to 250 mg/ml for all patients in this study. A decrease in clinical symptoms and normalisation of laboratory values within 10 days of commenting treatment was accepted as a response to CyA.

Statistical analysis was performed using Mann-Whitney U test and Yates' correction chi-square test.

RESULTS

The mean duration of disease was 64.5 months (range: 8-180 months). Ten patients (76.9%) responded to treatment in mean of nine days (2-30). Three patients who did not respond underwent colectomy, two owing to persistence of severe symptoms and one due to development of toxic colonic dilation. Features of these three patients are summarized in Table 2. Cyslosporin A was given for a median of 4.9 (range: 2-6) months in the 10 patients who initially responded, but five of them developed clinical and laboratory features which indicated and were accepted as relapse. Of these, three relapsed during therapy and underwent colectomy, one relapsed during therapy and did not accept surgical intervention and one relapsed within two a few days of CyA discontinuation and underwent colectomy. The remaining five patients, 38% of the total group and 50% of patients who initially responded to CyA, maintained their remission at the end of an average 17 month follow up period. Figure 1 summarizes the

Table 2. Features of three patients with lack of initial response

Name	*gender*	*age yr*	*disease duration*	*location*	*CyA Appl. route*	*reason and day of colectomy*
FY	F	16	12 months	Pancolitis	lV	Toxic megacolon, 7th day
ZÖ	F	49	36 months	Pancolitis	lV	Unresponsiveness, 11th day
MY	M	30	48 months	Left sided	lV	Unresponsiveness, 19th day

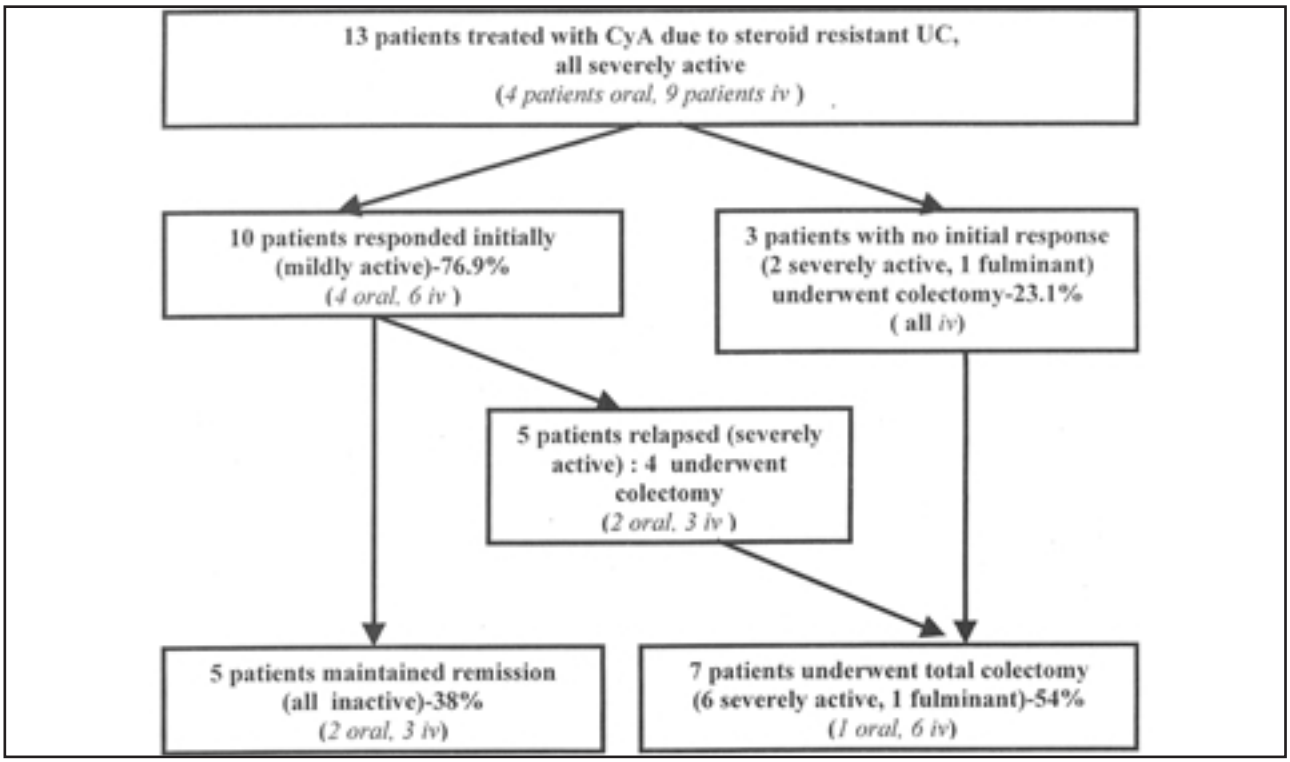

Figure 1. Cyclosporin A treated patients: summary of outcome

results of CyA treatment in patients with steroid resistant, active UC. A total of seven patients (54%) underwent total colectomy. It was statistically determined that gender, age, disease extent and duration did not affect the response to CyA.

Three patients (23%) experienced an adverse event after commencing CyA treatment. A 16 year old female patient who underwent colectomy on the seventh day of therapy due to toxic megacolon, had a generalized seizure which started focally. Despite normal serum CyA levels, the seizure was thought to be due to drug neurotoxicity as there was no other apparent cause. Another 28 year old male patient received CyA for a total of four months and remained in remission, but developed herpetic conjunctivitis with 80% loss of vision. The third patient suffered from minor adverse effects as nausea and mild skin eruptions; CyA was continued, however and these and complaints resolved spontaneously.

DISCUSSION

The efficacy of CyA in patients with severe and steroid resistant UC is well established (6,7). According to a quality of life analysis that compared patients treated with CyA to those underwent colectomy, CyA patients did not score worse than their surgical counterparts (8). Cohen et al. reported an initial response rate of 86% (7) and our rate of 79.6% was consistent with these results. The present authors suggest that intravenous cyclosporin is a rescue therapy in resistant, acute and severe UC as reported formerly (9). Since all of the patients in this study, received concomitant therapy with 5-ASA products and azathioprine, it would be accurate to say that CyA is a safe adjunctive therapy. The long term results of CyA attract attention more than efficacy. In our study, at the end of an average 17 month follow up period, the rate of remission was 38% of the total group and 50% of initially responding patients. This rate seems to be lower than previously reported results (10) and we think this inconsistency may be due to the smaller size of the study group.

In this study the colectomy rate was 54% and rate of maintenance of response was 38%. However, the patient who relapsed but did not consent to colectomy affected the expected results.

It has been previously reported that there was no

increased incidence of perioperative complications associated with the use of intravenous cyclosporin rather than steroids in acute severe UC (11). All colectomies were performed in the surgical department of our hospital and to date no perioperative complications caused by preoperative use of CyA have been reported.

We also assessed the safety of CyA. Fleshner reported complications associated with the use of intravenous cyclosporin (9) but we observed no side effects and no opportunistic infections associated with the use of either intravenous or oral CyA in the treatment of acute, severe UC there was also no mortality. In our study, the rate of adverse effects was 23% (herpetic conjunctivitis, convulsion, nausea-vomiting and mild skin eruption in three patients) which is higher than previous reports. We thought this high rate of adverse effects was due to the small study group and would decrease if the numbers were higher. Intravenous CyA can cause convulsions and this may be exacerbated by hypocholesterolemia. We observed a convulsion in one patient who underwent colectomy due to toxic megacolon, but serum cholesterol and CyA levels were within normal limits. In our unit, all patients receiving CyA, whether intravenously or orally, undergo close monitoring of renal function, blood pressure, and drug levels. No patients included in this study had impairment of renal function or drug-associated hypertension.

In conclusion, this study indicated a high initial response rate to CyA therapy, allowing 40% of patients to retain their colon for one year. This result, and the relative safety of the drug when properly monitored, suggests that CyA therapy should be considered as an option for patients with severe, steroid UC.

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