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Cyclosporin treatment of anal and perianal lesions associated with Crohn's disease

Crohn hastalığına bağlı anal ve perianal lezyonların siklosporin ile tedavisi

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Background/aims: *To analyse the long-term effect of cyclosporin on anal-perianal lesions associated with Crohn's disease. Methods:Twenty patients (15 females and 5 males); having Crohn's disease with anal-perianal involvement and resistant to conventional treatment were evaluated. The following criteria of diagnosis and evaluation were applied to all patients: onset of Crohn's disease, description of anal-perianal lesions according to Cardiff classification after proctological examination, onset of symptoms and their aggravation, and previous agents and surgical interventions. Cyclosporin was administered orally following intravenous treatment for 7 days (4 mg/kg/day). Dose adjustments' target was to achieve a cyclosporin level of 100/200 ng/mL. The efficacy of treatment was assessed by proctologists on days; 15 and 30, so-called acute period, and at 3, 6, 7, and 20 months, so-called chronic period. Patients were also seen between these two periods as needed, based on the condition ofpatients and their symptoms. At each examination, patients were scored according to Cardiff classification and the anatomical localisation of lesions, with the scores recorded subsequently.* ***Results:*** *Symptomatic improvements were seen in 80-85% ofpatients while proceeding from acute to chronic period. Oral treatment was continued for 3-7 months. In acute period (in the follow-up assessments: on days 15 and 30), 16/20 (80%) patients had symptomatic improvements, 5/20 (25%) had improvements in all anal-perianal lesions, 11/20 (55%) had regression of lesions, and 4/20 (20%) had worsening of lesions. In chronic period (range, 1-20 months; mean, 5 months), no complication occurred and no patient showed reactivation. In chronic period, the observation was that; 45% offistulae were closed and 70% of ulcers healed. During treatment, 3 (15%) patients underwent a definitive ileostomy and 4 patients underwent surgical drainage of abscess of ano-vaginal and ano-perianal fistula.* ***Conclusions:*** *In treatment of anal-perianal lesions associated with Crohn's disease, cyclosporin is an important agent in providing regression and healing of lesions in cases refractory to standard treatment. It should be considered an alternative treatment particularly in restorative surgical interventions. Comparisons are needed versus newer agents and cyclosporin for efficacy and superiority.*

Key words: Crohn's disease, cyclosporin-A, anal-perianal lesion

Amaç: *Siklosporinin uzun dönemde Crohn hastalığına bağlı anal-perianal lezyonlar üzerindeki etkisini analiz etmek.* ***Yöntem:*** *Anal-perianal tutulumu olan geleneksel tedaviye direnç gösteren 20 Crohn'lu hasta (15 kadın, 5 erkek) değerlendiriliyor. Bütün hastalar için şu diyagnostik ve değerlendirme kriterleri uygulanıyor; CH başlangıç tarihi, proktolojik muayene yapılarak Cardiff klassifikasyonuna göre anal-perianal lezyonlarının deskripsiyonu, semptomların ne zamandan beri başladığı ve ağırlaştığı, daha önceden kullanılan ajanlar ve yapılan cerrahi müdahaleler. Ciclosporin önce 7 gün boyunca İ. V yolla veriliyor (4 mg/kg/'gün), daha sonra oral devam ediliyor ciclosporinemi düzeyi 100-200 ng/ml olacak şekilde doz ayarlaması yapılıyor. Tedavinin etkinliği uzman proktologlar tarafından akut dönem olarak kabul edilen 15. ve 30. günde ve kronik dönem olarak kabul edilen 3., 6., 7., 20. aylarda değerlendiriliyor. Ayrıca hastanın ve semptomların durumuna göre hastalar bu periyotlar arasında gerekirse arada görülüyor. Hasta her görüldüğünde Cardiff klasifikasyonuna ve lezyonlarm anatomik durumuna göre skorlanarak kaydediliyor.* ***Bulgular:*** *Akut dönemden kronik döneme geçiş sürecinde semptomatik olarak %80-85 hastada iyileşme görülüyor. Oral tedavi 3 ile 7 ay arası devam ediliyor. Akut dönemde (15. ve 30. gün yapılan kontrollerde) 16/20 (%80) hastada semptomatik iyileşme, 5/20 (%25) hastada bütün anal-perianal lezyonlarında iyileşme, 11/20(%55) hastada lezyonlarda gerileme ve 4/20 (%20) hastada lezyonlarda kötüleşme gözlemleniyor. Kronik dönemde ise (l ile 20 ay arası ortalama 5 ay)herhangi bir komplikasyon olmuyor, hiçbir hastada tekrar aktifleşme görülmüyor. Yine kronik dönemde fistüllerin kapanma oranı %45 ve ülserlerin iyileşme oranı %70 olarak gözlemleniyor. Tedavi boyunca 3(%15) hastada definitifolarak üeostomi ve 4 hastada ano-vajinal ve ano-perianal fistüllerden dolayı abse drenajı gerçekleştiriliyor.* ***Sonuç:*** *Crohn hastalığına bağlı anal-perianal lezyonlarının tedavisinde standart tedaviye direnç gösteren vakalarda ciclosporin lezyonlarm geriletilmesinde ve iyileştirilmesinde önemli bir ajandır. Özellikle reparasyona yönelik cerrahi müdahalelerde alternatif tedavi olarak düşünülmelidir. Yeni ajanların etkinliği ve üstünlüğü ciclosporin ile karşılaştırılmalıdır.*

Anahtar kelimeler: Crohn hastalığı, siklosporin-A, anal-perianal lezyon

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INTRODUCTION

Crohn's disease (CD) is a disorder which may segmentally involve any part of digestive system, notably terminal ileum. It often starts acutely, has a course with exacerbations, and lasts for all patient's life. Its incidence is 2.3-6.6/100.000. It is encountered more often in north hemisphere and peak age is 20-30 years (12). Since Crohn described the disease (3), many treatment protocols have been experimented for treatment and prevention of acute exacerbations. Management of the disease is pharmacological, diet, and surgical in sequence. The aim of pharmacological treatment is to control symptoms, to provide healing at anatomical level, to improve the condition of patients to an extent that a natural nourishment could be provided, and to avoid surgery. CD may involve the entire digestive system, but particularly terminal ileum and proximal colon. Regarding the localisation, 30% of cases involve small intestine, especially terminal ileum; 20% show colonic involvement and 50% involve ileocolic segment.

Incidence of ano-perianal (APA) lesions associated with CD varies; these lesions are ulcerations, fistulas, and stenoses. APA lesions are the initial manifestations leading to diagnosis of CD in 25% of cases. The more distally CD is localised, the higher the incidence and severity of APA lesions are. In Crohn's disease, APA lesions are observed in 30% of cases with ileal involvement, in 50% of cases with proximal colonic involvement, and in 75% of cases with recto-sigmoid involvement (5,6). Management of APA lesions includes medical and surgical treatment. While numerous treatment modalities have been tested, none of them has provided complete healing. Although metronidazole and ciprofloxacin are the first choice of drugs, there are disadvantages with their use, including side effects, a very high cost in chronic administration (4-6 weeks), and a low efficacy. Currently, immunosuppressants hold an important place in treatment of CD; this class of drugs is frequently used in treatment of APA lesions associated with CD. Cyclosporin, tacrolimus, cytostatic drugs (azathioprine, mercaptopurine, methotrexate) and lately introduced anti-TNFa antibodies are the examples of agents included in this class (7-8). In fistulous CD, none of the immunosuppressive treatments can provide complete healing. Indications for surgical treatment are fairly limited because it results in significantly high morbidity. It is only indicated for completely formed suppurations. However, restorative surgical treatment plays an important part in treating, without any sequela, APA lesions in controlled CD. The disease must be controlled by pharmacological therapy prior to restorative surgical treatment. Interestingly, cyclosporin administered before surgical treatment has shown activity in fistulous CD in a short term. However, the long-term efficacy of cyclosporin on APA lesions is still unknown. Our objective in this study was to analyse the long-term efficacy of cyclosporin on APA lesions associated with Crohn's disease.

MATERIALS AND METHODS

1- Patients

Twenty patients (15 females and 5 males, range of age: 21-54 years, mean age: 32.9 years) treated for APA lesions associated with CD between July 1992 and October 1999 in our clinics were included in this study (Table 1). Prior to cyclosporine treatment, all patients had been refractory to standard therapy (metronidazole, ciprofloxacin, azathioprine, corticosteroid) for at least two months. Diagnosis of CD was made according to the standard criteria (9). All patients were examined by proctologists and scored according to Cardiff classification and Harvey-Bradshaw clinic index (by giving scores between 1 and 10 according to the severity of pain, discharge, bleeding, and incontinence). Follow-up of patients varied in length (3-20 months). After the onset of cyclosporin treatment, 5 patients were followed up for more than 1 year, 6 were followed up for more than 6 months, and 9 were followed up for more than 3 months. Fourteen of these patients had undergone surgery for APA lesions or a gastrointestinal disorder (surgical drainage of fistula or fistulotomy in 8 patients, ileostomy in 2, ileocaecal resection in 1, ilecolonic resection in 1, colonic resection in 1, and anal canal dilatation in 1). All patients had undergone colonoscopy before cyclosporin treatment. At baseline, 15 patients were found to have recto-colic involvement and active lesions; 3 patients had no rectal involvement. In proctological examination, most numerous superficial ulcerations were seen in anal region (in 19 patients, 57 ulcerations). Fourteen patients had 19 fistulas (5 perineal, 4 anavulver, 4 anovaginal, 4 intersphincteric, 1 rectovaginal, and 1 abdominal complex fistulae) and 3 patients each

had anal canal stenosis. All patients had normal renal function.

2- Methods

2.1 Treatment with cyclosporin

Treatment was given intravenously at 4 mg/kg/day for the first week, followed by an oral administration at 8 mg/kg/day. In order to make adjustments for the adaptation dose of 100-200 ng/mL, cyclosporinemia was initially measured 48 hours after the oral administration, and once every week thereafter. Dose adjustments were made by phone contact or during consultation. Cyclosporin was not discontinued in any patients because of surdosage or side effects, and no other treatment was initiated while on cyclosporin treatment or during follow-up.

2.2 Evaluation criteria:

Patients were evaluated by gastroenterologists experienced in proctological examination at baseline and during treatment. This evaluation was done according to Harvey-Bradshaw index and Cardiff classification. Complete healing was described as disappearance of all lesions, closure of fistulas, and improvement in patient's general condition. Partial healing was described as an improvement in patient's general condition with decreased number of ulcers and fistulas; unresponsiveness was described as the lack of reduction in the number of ulcers and fistulas and absence of any change in general condition.

All patients were examined at least 3 times (on days 15 and 30, at 3, 6, 7, and 20 months, and also later as needed).

RESULTS

Results were assessed over 2 periods; the time from the onset of treatment to day 30 was considered acute period, whereas the interval between months 1 and 20 was considered chronic period.

1- Acute period:

Symptomatic improvement was seen in 16 (80%) patients. In proctological examination, complete or partial healing was noted in 16 (80%) patients (5 with complete remission, and 11 with partial remission). No healing was seen in 4 (20%) patients (Table 2); four fistulas completely closed and all ulcers healed in patients with complete response. Of these patients, 3 are still on corticosteroids, 2 on metronidazole, and 2 on azathioprine. In patients with partial improvement, 1 patient had closure of fistula, 2 had ulcer healing, and 9 had reduced number of ulcers. There was no difference in gender, history of CD and APA, and type of lesion between responders and non-responders. Despite 1 month of cyclosporin treatment, 1 of 4 non-responders had worsening after the day

Table 1. Patients characteristics, history of Crohn's disease, localisation of intestinal involvement, extraintestinal findings and continued treatment status

No	G	Age	HCD	HAPL	BMI	L	NGISI	CT
1	f	40	3y	3y	22.2	colon	-	metronidazole, mesalazine, azathioprine,corticosteroid
2	f	32	2y	ly	26.7	ileo-colic	-	metronidazole, corticosteroid, mesalazine,
3	f	23	2y	2y	17.5	colon	-	mesalazine, corticosteroid
4	f	46	4y	ly	20.7	colon	-	azathioprine
5	f	35	ly	ly	20.3	colon	-	azathioprine, mesalazine, corticosteroid
6	f	23	5y	ly	22.1	ileum	-	azathioprine
7	m	21	9y	5y	14.7	ano-perianal	erythema nodosum	mesalazine
8	f	31	3mo	Imo	18.5	colon	pyoderma gangrenosum	mesalazine, corticosteroid
9	f	33	15y	10y	17.1	colon	-	mesalazine, corticosteroid
10	m	24	6y	6mo	21.5	colon	-	corticosteroid, mesalazine
11	m	29	8y	8y	19	pancolon	-	enteral nutrition, azathioprine, corticosteroid
12	f	47	7y	ly	20.2	colon	-	corticosteroid, mesalazine
13	m	21	5y	4y	24.8	ileo-colic	-	corticosteroid, ciprofloxacin
14	f	34	13y	3y	16.9	ileo-colic	-	corticosteroid
15	m	54	15y	32	21.8	ileo-colic	arthropathy	mesalazine, corticosteroid
16	f	27	4y	5	18.3	ileo-colic	-	corticosteroid, amoxicillin+clavulanic acid
17	f	38	ly	2	22.7	colon	anterior uveitis	corticosteroid
18	f	30	11y	9y	25.5	colon	arthropathy	mesalazine, corticosteroid
19	f	38	20y	ly	16.8	colon	-	corticosteroid, azathioprine, amoxicillin+clavulanic acid
20	f	30	9y	ly	20.3	ileo-colon	-	mesalazine, metronidazole

G: Gender, HCD: History of Crohn's Disease, HAPL: History of Anal-Perianal Lesion, BMI: Body Mass Index, L:Localisation, NGISI: Non-Gastrointestinal System Involvement, CT: Continued Treatment, f: female, m: male, y: year

Table 2. Results of acute period

Before cyclosporin				Results obtained 1 month after treatment with cyclosporin			
Patient	*APAo*	*HBIo*	*GGDo*	*LAP1*		*GGS1*	*Response*
		5	*8*	Ux3,Fo	5	4	P
1	Ux2,Fxl	1	*2*	Uo,Fo	0	1	C
2	Uxl.Fxl	6	4	-	9	9	F
3	Ux8,Fxl	6	4	Uo,Fo	3	2	C
4	Ux4,Fxl	7	8	Uo,Fxl,Dl	3	3	P
5	Uxl,Fxl,Dl	5	8	Uo,Fo,Dl	3	5	C
6	Uo,Fx3,Dl	14	9	Ux4,Fo,Sl	2	2	p
7	Ux2,Fo,Sxl	8	7	Uxl,Fxl,Dl	3	3	p
8	U5,Fxl,Dl	7	8	Uo,Fo,S,Dl	4	2	C
9	Uxl,Fx2,S,Dl	7	8	Uxl,Fx3,D2	5	2	F
10	Uxl,Fx3,Dl	10	9	Uxl,Fo,Dl	3	3	P
11	Ux8,Fo,Dl	13	3	Ux3,Fxl,Dl	4	3	P
12	Ux3,Fxl,Dl	6	9	Ux2,Fx2,D2	12	10	F
13	Ux2,Fx2,Dl	7	7	Ux2,Fo,Dl	3	3	P
14	Ux3,Fo,Dl	6	7	Uxl,Dl	3	2	P
15	Ux3,Fo,Dl	24	8	Ux2,Fo,Dl	6	4	P
16	Ux3,Fo,Dl	10	8	Uxl,Fxl,Dl	4	3	P
17	Ux3,Fxl,Dl	15	9	Ux6,Fxl,S,D2	8	10	F
18	Ux7,Fo,Sl,Dl	8	6	Uo,Fo,Dl	4	2	C
19	Ux5,Fo,Dl	5	5	Uxl,Fxl,Dl	4	3	P
20	Ux2,Fxl,Dl						

U: Ulcer, F: Fistula, Di: Inactive lesion, D2: Active lesion APA: Anal-Perianal, HBI: Hervey Bradshaw Index,
GGD: Global General Status (0: the best, 10 the worst) P: Partial response, C: Complete response, F: Failure
5/20 (25%) complete response
11/20 (55%) partial response
4/20 (20%) worsening

15, which required proctocolectomy. Nineteen patients were followed up in chronic period.

2- Chronic period:

Cyclosporin treatment was continued for 3-12 months (mean,7.2 months).

2.1- The course of the patients who exhibited complete healing at completion of the first month:

There were 5 patients in this group. Two of these patients remained in remission as long as they were on cyclosporin treatment (number 6 for 6 months, number 9 for 4 months); in 2 patients the disease worsened after the sixth month (number 2 underwent surgery for rectovaginal fistula, number 4 was applied discharge ileostomy), and 1 patient remained in remission during 14 months of follow-up (number 19) (Table 3).

2.2- The course of patients in partial remission:

There were 11 patients in this group; 3 of them had disappearance of APA lesions after 3 months of treatment and remained in complete remission during follow-up (3-20 months). In 4 patients APA lesions worsened after 3-6 months, which required discontinuation of cyclosporin treatment. One of these patients underwent proctocolectomy; in the other 3 patients there was no major treatment amendment. Four patients had stable APA lesions after 3-6 months of follow-up. One of them underwent surgical abscess drainage after termination of cyclosporin treatment. For the other 3 patients, no other treatment was added as they felt well and had stable APA lesions in clinical examination, as well as they were still on azathioprine treatment.

2.3 The course of non-responders

Two of patients underwent surgical intervention (coloproctotectomy); 2 patients underwent surgical drainage of fistula, and 1 patient was placed on parenteral nutrition with subsequent surgical abscess drainage (number 13). No change in treatment was made in other patients.

2.4 Synthesis of results

As a result of cyclosporine treatment there were symptomatic improvements in 17 (80%) of patients. At the level of APA lesions, 45% of ulcerations and 70% of fistulas showed healing. No effect of cyclosporin on anal stenosis was seen.

Table 3. Results at the end of treatment

	Before cyclosporin			After cyclosporin				
Patient	*APAo*	*HBIo*	*GGSo*	APA2	*HBI2*	*GGC2*		*RSDC*
1	Ux2,Fxl	5	8	Ux2,Fo	5	4	4months	P
2	Uxl.Fxl	1	2	Uxl,Fxll	0	1	6months	F
3	Ux8,Fxl	6	4	worsening	-	–	–	F
4	Ux4,Fxl	6	4	Ux4,Fo	6	2	6months	F
5	Uxl,Fxl,D	7	8	Uo,Fxl,Dl	7	3	6months	P
6	Uo,Fx3,Dl	5	8	Uo,Fo,Dl	5	5	6months	C
7	Ux2,Fo,S	14	9	Ulax3,Fo,S	14	2	5months	F
8	U5,Fxl,Dl	8	7	Uo,Fo,So,Dl	8	3	12months	C
9	Uxl,Fx2,S,Dl	7	8	Uo,Fo,S,Dl	7	4	5months	C
10	Uxl,Fx3,Dl	7	8	Ux2,Fxl,D2	7	2	6months	F
11	Ux8,Fo,Dl	10	9	U2b,Fo,D2	10	3	6months	F
12	Ux3,Fxl,Dl	13	3	Uo,Fo,Dl	3	4	4months	C
13	Ux2,Fx2,Dl	6	9	Ux2,Fx2,Dl	6	10	1month	F
14	Ux3,Fo,Dl	7	7	Ux2,Fo,Dl	7	3	4months	F
15	Ux3,Fo,Dl	6	7	Uxl,Fo,Dl	6	2	4months	P
16	Ux3,Fo,Dl	24	8	Uxl,Fo,Dl	24	2	4months	P
17	Ux3,Fxl,Dl	10	8	Uxl,Fo,D2	10	3	5months	F
18	Ux7,Fo,Sl,Dl	15	9	Ux6,Fxl,S,D2	15	7	3months	F
19	Ux5,Fo,Dl	8	6	Uo,Fo,Dl	8	2	5months	P
20	Ux2,Fxl,Dl	5	5	Uo,Fo,Dl	5	4	6months	C

U: Ulcer, F: Fistula, Di: Inactive lesion, D2: Active lesion APA: Anal-Perianal, HBI: Hervey Bradshaw Index, GGS: Global General Status, DCU: Duration of Cyclosporin Use, RSDC: Response Status After Discontinuation Cyclosporin P: Partial response, C: Complete response, F: Failure
5/19 (26%) complete response
5/19 (26%) partial response
9/19 (48%) worsening

DISCUSSION

In this non-randomised retrospective study of patients with anal and perianal involvement associated with Crohn's disease resistant to standard therapy, treatment with cyclosporin led to regression of functional complaints in 80% of patients and complete anatomical healing (scarring of ulcers, closure of fistulas) in 25%. In half of patients, the healing started in acute period, but only 26% of these patients continued to respond in chronic period. Our study constitutes the largest series in the literature on cyclosporin treatment of APA lesions associated with Crohn's disease. Crohn's disease is a chronic and inflammatory pathology, and treatment with immunosuppressants is important for provision of disease regression, prevention of worsening, and arrest of anatomical destruction. Investigations show that an average of 30% of patients may achieve a long-term remission; and there is no curative treatment for APA lesions associated Crohn's disease (10). Corticosteroid treatment remains to be important in Crohn's disease with intestinal involvement, especially if there is rectal involvement. However, long-term use of this treatment produces important side effects and is not very effective in providing regression of APA lesions. The efficacy of treatment with immunosuppressants (mercaptopurine, azathioprine..) is unquestionable. The disadvantages of this group of drugs are slow onset of action and a likelihood as high as 50% of disease reactivation upon termination of treatment (11,12). Treatment success of antibiotics (metronidazole, ciprofloxacin...) is very limited; the treatment is expensive and requires at least 2 months of use. In plasebo-controlled studies, the rate of disease reactivation is about 75% with metronidazole and ciprofloxacin treatment (13,14). As with the discharge ileostomy and colostomy, the objective of enteral and parenteral nutrition is to provide bowel rest for gastrointestinal system as well as ano-rectal segment. Investigations comparing these methods versus medical therapies have not been managed. Taking their cost-effectiveness into consideration, these methods currently seem to be the last option to choose. An effective medical therapy for APA lesions, especially prior to restorative surgical

intervention is of great importance. Among currently used drugs, administration of cyclosporin to control active APA lesions has significant advantages. Cyclosporin is a cyclic polypeptide composed of 11 amino acids, demonstrating immunosuppressive activity. It inhibits production and liberation of lymphokines, especially of interleukin-2. Unlike other cytostatic agents, it does not suppress haematopoiesis and alter phagocytic functions. Its elimination is primarily via biliary system and it does not have an important side effect. Cyclosporin is used to prevent graft-versus-host reaction after organ transplantation and in a variety of immune system disorders. Use of cyclosporin in Crohn's disease with and without anal-perianal involvement has been addressed in many studies (15, 17). It has been used as monotherapy or in combination with corticosteroids or other immunosuppressive agents (azathioprine, mercaptopurine, methotrexate). There is a rapid response with cyclosporin treatment (2-4 days). In a study by Present et al. (16) on 16 patients refractory to conventional treatment (especially mercaptopurine), cyclosporin was initially given intravenously, followed by oral administration; a rapid symptomatic improvement in i.v. period was seen in 88% (16/88) of patients, and closure of fistula was observed in 44% (7/16). After oral administration started, 56% (9/16) of patients maintained their initial response whereas 3 patients had a severe disease reactivation. In another study with similar design (17), similar results were obtained with 4 patients demonstrating complete healing after switching to oral form. In other 2 studies with cyclosporin (18,19), a healing rate of 78-100% in i.v. administration period was reported. In our study, we observed that one in every 4 patients responded in the first days of treatment. This outcome appears to be less successful than in the above-mentioned studies. One of the reasons for this is that criteria for response to therapy were strict (healing of ulcers, closure of fistulas) and the patients had complex APA lesions. It should be stated that APA lesions entirely disappeared in 3 patients after a long time. However, overall success rate is about 40% (8/20) and this result reflects a success comparable with the other studies (16-19). The rate achieved in our study is unquestionably high when compared to plasebo (10-20%). It is reported that two other agents, talidomide and infliximab, gave good results. In a study with talidomide which is a very old agent, a success rate of over 40% was reported (20). A comparative study between talidomid and cyclosporin has not been performed so far. On the other hand, in a study comparing infliximab with plasebo, the rate of closure of fistulae was found to be 55% compared to 13% with plasebo (21). Although this treatment seems to be more effective than cyclosporin, a study comparing treatment cost-effectiveness between these two agents is needed. In Crohn's disease with APA involvement, cyclosporin should consistently be regarded as one of the main treatment options in that it provides healing and regression in lesions in 25% of patients, particularly in those getting prepared for surgery. As shown in this study and literature, an average of 50% of patients treated with cyclosporin have disease reactivation in long-term or upon termination of treatment. However, the question here to ask is: Is it cyclosporin or its dosage ineffective? While the cyclosporin level (100-200 ng/ml) and its dose appear to be well-adjusted in our study, it is impossible to give a definite answer to this question. Ultimately this blood level was accepted anticipatingly, and there may be an disproportionateness between the dose required by patients and the biodisponibility of cyclosporin. Cyclosporin is a well-tolerated agent with an established efficacy in treatment of anal-perianal lesions associated with Crohn's disease. Compared to infliximab which was indicated as the reference treatment in our study, an efficacy not less than that of infliximab, a considerably reduced cost of treatment, and the lack of very serious side effects constitute the indisputable advantages of cyclosporin.

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