INFLAMMATORY BOWEL DISEASE

A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis

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Background and aims: Immunosuppressive therapy with intravenous ciclosporin is an alternative treatment option to total colectomy for patients with ulcerative colitis (UC), while the benefits of oral administration of tacrolimus are not well defined and are based on reports of several uncontrolled studies.
Methods: Patients with refractory active UC were randomly assigned to a high trough concentration (10–15 ng/ml) group (HT group) (n = 21), low trough concentration (5–10 ng/ml) group (LT group) (n = 22), or placebo group (n = 20). Patients received an initial oral dose of 0.05 mg/kg tacrolimus or placebo twice daily. Efficacy was evaluated in 60 patients based on a disease activity index (DAI) score. Fifty eight patients had additional treatment with tacrolimus and were evaluated for efficacy in a 10 week open label extension.
Results: An improvement in DAI score (⩾4 points, all categories improved) was observed for 68.4% of cases in the HT group compared with 10.0% in the placebo group ($p<0.001$). In the HT group, 20.0% of patients had clinical remission and 78.9% had mucosal healing. In the open label extension, 55.2% of all patients had an improved DAI score at week 10. Mean dose of prednisolone was reduced from 19.7 mg/day at study entry to 7.8 mg/day at week 10. The incidence of side effects in the HT group was significantly higher than that of the placebo group ($p = 0.043$). The most common event was mild finger tremor.
Conclusions: Our findings demonstrate dose dependent efficacy and safety of oral tacrolimus for remission-induction therapy of refractory UC. The optimal target range appears to be 10–15 ng/ml in terms of efficacy with two week therapy.

Tacrolimus (FK506) is an immunosuppressive macrolide isolated from fermentation broth of *Streptomyces tsukubaensis*. It potently inhibits helper T lymphocyte activation. In fact, tacrolimus has been shown to inhibit transcription of the early activation genes for cytokines such as interleukin 2 (IL-2), tumour necrosis factor α (TNF-α), and interferon γ (IFN-γ) in T cells. Its immunosuppressive effect appears to be mediated, in part, through inhibition of IL-2 synthesis and release, as well as a decrease in the number of IL-2 receptors on activated lymphocytes.[1 2]

Furthermore, in vitro studies have demonstrated that steroid resistance is due to the intrinsic properties of T lymphocytes and involves IL-2 and the IL-2 receptor, with steroid resistant lymphocytes producing higher levels of IL-2.[3] Although its mode of action is similar to that of ciclosporin (CsA), the immunosuppressive effect is 30–100 times greater in vitro and 10–20 times greater in vivo than that of CsA.[4] Also, its intestinal absorption is more consistent even in the presence of gastrointestinal disease.[5] In renal transplantation, tacrolimus is associated with fewer acute rejections, lower steroid requirements, fewer graft failures, and a better adverse event profile than CsA.[6 7]

Intravenous CsA is an alterative treatment option to surgery for patients with severe steroid refractory ulcerative colitis (UC).[8–10] In contrast, high intra- and interpatient variability in blood levels limits the efficacy of oral CsA , although a new formulation (microemulsion CsA) has reported to be useful in a limited number of studies.[11] Recently, the anti-TNF-α, infliximab which is administered intravenously, has been proved to be a useful biological therapy for the treatment of moderately to severely active UC.[12–18] Any drug requiring intravenous administration has a higher potential for serious adverse events and prolonged hospitalisation than those administered orally.

Tacrolimus has been reported to be effective for patients with Crohn's colitis and intestinal fistulae.[19–22] To date, several uncontrolled studies have shown that tacrolimus can induce remission in adults[5 23–25] and in children[26] with steroid refractory UC. We report the results of a placebo controlled double blind study of oral tacrolimus therapy designed to assess the efficacy and safety of two target tacrolimus blood concentration ranges and its open label extension in patients with refractory moderately/severely active UC.

METHODS

Patient selection

Patients with moderately/severely active UC were eligible for this study. UC was defined by standard symptomatic, radiographic, and endoscopic criteria.[27] All patients in this study were hospitalised and afflicted with left sided colitis (except for proctosigmoiditis) or pancolitis. The extent of colonic involvement was determined by total colonoscopy. Before the start of treatment, infectious diarrhoea was ruled out by stool cultures and *Clostridium difficile* toxin testing. Endoscopies were done within one week prior to the first dose of study drug.

Steroid resistance was defined as unresponsiveness to oral or intravenous corticosteroid therapy (equivalent to a daily dose of more than 30 mg of prednisolone) over at least two

Abbreviations: UC, ulcerative colitis; DAI, disease activity index; IL-2, interleukin 2; TNF-α, tumour necrosis factor α; IFN-γ, interferon γ; CsA, ciclosporin; ESR, erythrocyte sedimentation rate; CRP, serum C reactive protein; C12h, blood trough concentration at 12 hours; C24h, blood trough concentration at 24 hours; HT group, high trough concentration (10–15 ng/ml) group; LT group, low trough concentration (5–10 ng/ml) group

weeks, and steroid dependency was defined as either chronic active UC for more than six months or frequent recurrence (more than once a year, or three times or more every two years regardless of intensive medical therapy). Patients were permitted to continue taking drugs containing 5-aminosalicylic acid or steroids during the study as long as the dosage of these drugs was not adjusted during the period two weeks prior to the start of the study through to the end of the study.

Patients with known renal or severe hepatic dysfunction, and pregnant women were excluded. Pretreatment evaluations included a history and physical examination, complete blood count, chemistry screening panel, and urinalysis.

Azathioprine or 6-mercaptopurine was prohibited for concomitant use after initiation because the indication of UC is not covered by healthcare insurance for these drugs in Japan. Patients taking azathioprine, 6-mercaptopurine, CsA, or other immunosuppressants within three months prior to entry were excluded from evaluation of the efficacy and safety for tacrolimus. In addition, cytapheresis within 28 days prior to entry was also a reason for exclusion.

Protocol review

The study protocol was reviewed and approved by each institutional review board. Each patient read and signed a consent form before enrolment into the study.

Study design

We conducted a two week, placebo controlled, double blind, randomised study in which patients with active UC were administered either placebo or tacrolimus at an oral dosage to achieve and maintain one of two target blood concentrations, followed by an open label 10 week extension in which all patients received tacrolimus. The total study period was therefore 12 weeks.

Administration and monitoring of study drug

The tacrolimus capsule used (tacrolimus; Astellas Pharma Inc., successor in interest to Fujisawa Pharmaceutical Co. Ltd, Japan) contained 0.5 mg or 1 mg of FK506.

The initial oral dose of tacrolimus was 0.05 mg/kg per day twice daily. Blood was collected for determination of tacrolimus whole blood trough concentration at 12 hours (C12h) or 24 hours (C24h) after the initial dose. Dosage was adjusted in order to maintain whole blood concentrations within the assigned target range. To preserve the blindness of the study, blood trough levels were measured by SRL Inc. (a third party organisation independent of the study physicians or sponsor) and values were forwarded to Control Center (Bellsystem24, Inc.; a third-party organisation independent of the study physicians or sponsor). Dosages were calculated with the trough level at the Control Center and clinical sites were informed of the subsequent dosage by fax twice or three times in two weeks. Patients in the placebo group were pseudo-dose adjusted to preserve study blindness. Patients in the tacrolimus "high trough" (HT) and "low trough" (LT) groups were dose adjusted to achieve and maintain trough levels of 10–15 ng/ml and 5–10 ng/ml, respectively. Dose adjustment at the Control Center was carried out using the equations shown in table 1; these equations were created based on the known pharmacokinetic profile of tacrolimus in healthy volunteers (data not shown).

In the open label extension, the trough level was adjusted to 5–15 ng/ml during the initial stage of tacrolimus administration, and 5–10 ng/ml after attaining remission at the treating physician's discretion. Dosage reduction was allowed when adverse drug reactions were observed.

Symptom assessment and study end points

The primary end point was the proportion of patients with improvement (combination of patients with partial response and patients with complete response) on the basis of the disease activity index (DAI) score[28 29](table 2). The DAI score includes an objective assessment of the mucosal appearance and patient questionnaire components. Patients recorded the frequency of their stools, abdominal pain, and blood in stool on diary cards. A complete response was defined as complete resolution of all symptoms (all assessment scores were zero). A partial response was defined as a reduction in DAI of more than 4 points with improvement of all categories, but not a complete response. In the event any assessment score was noted to worsen or not change, despite improvement in other scores, the patient was considered to have had a treatment failure. Patients whose symptoms worsened at any time or did not improve for more than one week (in the case of a total DAI score $\geqslant$10 at baseline) were considered to be treatment failures if the investigators assessed that the study drug could not be continued. DAI was evaluated at weeks 0 and 2 in the double blind study, and at week 10 in the open label extension.

The secondary end points were changes from baseline in each category of DAI score, clinical response, and mucosal healing. Clinical remission was defined as a DAI score $\leqslant$2, with no individual subscore $>$1, and mucosal healing was defined as an endoscopy subscore ($\geqslant$2 at entry) of 0 or 1.[18] Prednisolone dose was allowed to be tapered at the treating physician's discretion when clinical symptoms improved after the open label extension started. Other observations included the number of bowel movements, visible blood in stool, abdominal pain, body temperature, pulse rate, haemoglobin, erythrocyte sedimentation rate (ESR), and serum C reactive protein (CRP) level.

Statistical analysis

For demographic and other baseline variables, the χ^2 test or Kruskal-Wallis test was used to assess comparability among the three treatment groups. Variables that exhibited imbalance ($p<0.15$) among treatment groups were included as

Table 1 Dose adjustment of tacrolimus (FK506)

Trough concentration used for dose adjustments	Dosage calculation method
C12h*	0.025 mg/kg × target trough concentration (12.5 or 7.5)†/(C12h × 4)‡
C24h*	0.025 mg/kg × target trough concentration (12.5 or 7.5)†/(C24h × 2.5)‡
Both C12h and C24h	0.025 mg/kg × target trough concentration (12.5 or 7.5)†/(average of C12h and C24h × 3)‡

*Blood trough concentration analysed at 12 hours (C12h) or 24 hours (C24h) after initial administration of the drug.
†The target trough concentration was 12.5 ng/ml when the desired trough range was 10–15 ng/ml, and 7.5 ng/ml when the range was 5–10 ng/ml.
‡The estimated trough concentration at steady state.

Table 2 Scoring system for assessment of ulcerative colitis activity*

Stool frequency†
- 0 = Normal number of stools for this patient
- 1 = 1–2 stools more than normal
- 2 = 3–4 stools more than normal
- 3 = 5 or more stools more than normal

Rectal bleeding‡
- 0 = No blood seen
- 1 = Streaks of blood with stool less than half the time
- 2 = Obvious blood with stool most of the time
- 3 = Blood alone passed

Mucosal appearance
- 0 = Normal or inactive disease
- 1 = Mild disease (erythema, decreased vascular pattern, mild friability)
- 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
- 3 = Severe disease (spontaneous bleeding, ulceration)

Physician's global assessment§
- 0 = Normal
- 1 = Mild disease
- 2 = Moderate disease
- 3 = Severe disease

*Referred from Schroeder and colleagues[28] and Sutherland and colleagues.[29]
†Each patient served as his or her own control to establish the degree of abnormality of the stool frequency.
‡The daily bleeding score represented the most severe bleeding of the day.
§A score of zero in physician's global impression meant there were no symptoms of colitis, the score of bowel movements, blood in stool, and endoscopic findings was zero. A score of 1 indicated mild symptoms or endoscopic findings that were mildly abnormal. A score of 2 reflected more serious abnormalities, and endoscopic and symptom scores of 1 to 2. A score of 3 indicated that endoscopic and symptom scores were 2–3.

covariates in a secondary analysis (logistic regression) of the primary variable to assess the effect of the imbalance.

Dunnett-type multiple comparisons was used to compare each of the tacrolimus groups (HT group or LT group) and placebo group for improvement rate of DAI scores, each category of DAI scores, and other efficacy measures. Fisher's exact test or the Mann-Whitney U test was used for comparison between the two tacrolimus groups (that is, HT group and LT group). The Wilcoxon signed rank test was used for comparison between baseline and each time point within each group.

Logistic regression analysis was used to explore the effect of demographic factors on the primary end point. All statistical tests were two sided with a significance level of 0.05, unless otherwise specified.

Sample size

Improvement in DAI score with tacrolimus was assumed to be 80% based on previous results in a pilot study. Improvement in the placebo was to be 20% based on Schroeder and colleagues.[28] Based on these assumptions and a two sided alpha 0.025 and power of 0.9, 20 randomised patients per group was estimated using normal approximation to be sufficient to show a difference in efficacy between placebo and tacrolimus.

RESULTS

Patient population

This study was performed between June 2002 and September 2003. A total of 65 patients in 17 centres were enrolled. Two patients were not administered study drug after enrolment because they failed to show confirmed visible bloody stool, resulting in a safety population of 63 patients. Three patients who received study drug were excluded from the efficacy analyses; two failed to show confirmed visible bloody stool at the start of the study and one underwent cytapheresis therapy within the previous 28 days. Therefore, the efficacy analysis set for the double blind study consisted of 60 patients. Six patients in the placebo group and one patient in

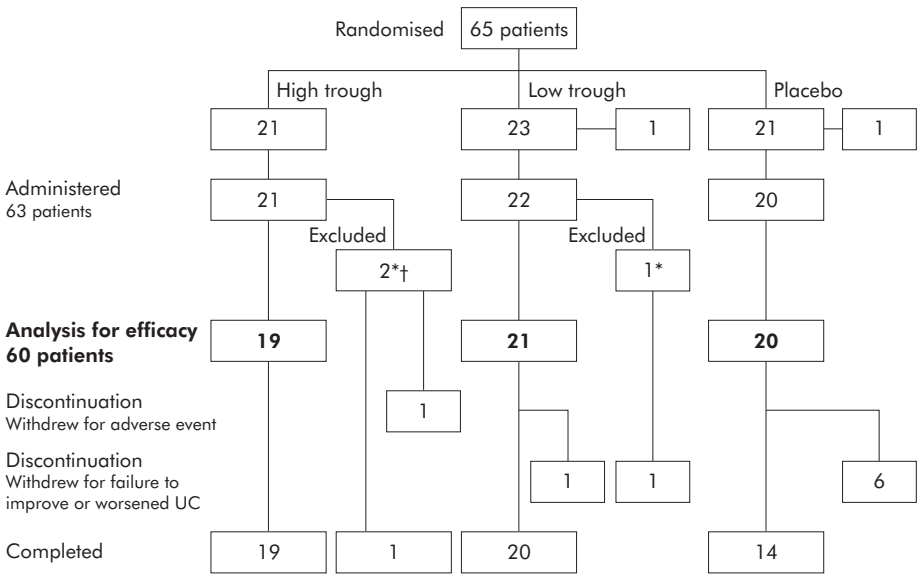

Figure 1 Trial profile of patients with active ulcerative colitis (UC) who received tacrolimus (FK506) or placebo in this randomised double blind study. *Failed to show confirmed active UC. †Cytapheresis therapy within 28 days.

Table 3 Demographic data on 60 patients included in the two week efficacy analysis of tacrolimus (FK506) for treatment of ulcerative colitis (UC)

Variable	High trough group	Low trough group	Placebo group	p Value
No of patients	19	21	20	
Sex (M/F)	9/10	11/10	9/11	0.890*
Age (y) (mean (SD))	33.3 (10.3)	31.2 (10.8)	30.0 (6.4)	0.645†
Weight (kg) (mean (SD))	53.0 (12.9)	50.9 (8.2)	53.6 (9.3)	0.758†
Disease duration (y) (mean (SD))	7.0 (6.3)	4.8 (3.5)	6.0 (3.5)	0.470†
Extent of disease				
Pancolitis	12	14	10	0.522*
Left sided	7	7	10	
DAI total score				
6	0	2	1	
7–9	13	9	8	
10–12	6	10	11	
Mean (SD)	9.2 (1.2)	9.2 (1.8)	9.4 (1.5)	0.845†
Steroid resistant/dependent				
Resistant*	5	5	5	0.983*
Dependent	14	16	15	
Previous treatment (within 6 months)				
Azathioprine	5	1	2	0.150*
Cytapheresis	4	4	7	0.445*
Concomitant medication				
Prednisolone (⩾10 mg/day)	19	21	20	–
5-Aminosalicylates	19	21	18	0.126*
Immunosuppressants	0	0	0	–
Cytapheresis	0	0	0	–

*Steroid resistance was defined as unresponsiveness to oral or intravenous corticosteroid therapy (equivalent to a daily dose of more than 30 mg of prednisolone) over at least 2 weeks.
*χ^2 test.
†Kruskal-Wallis test.

the tacrolimus groups (0 HT group, 1 LT group) withdrew due to lack of efficacy (flare of symptoms or no improvement/worsening) (fig 1).

The characteristics of the patients at baseline are shown in table 3 and were similar in all groups. Mean duration of disease was 4.8–6.6 years in each group. Enrolled patients showed a total DAI score of 6 or more. Eight patients showing lack of efficacy or relapse with azathioprine and 15 patients showing little or no improvement after cytapheresis within the previous six months were enrolled in the study.

Sixty one of 63 patients were given study medication in the open label extension except for two patients who developed serious adverse events (gastroenteritis and sepsis). Fifty eight patients continued to receive oral tacrolimus for 10 weeks in the open label extension study. Three patients withdrew before 10 weeks for failure to improve, adverse event (headache and fever), or patient request. No patient underwent colectomy during the 12 week study period.

Drug exposure

In the double blind study, target tacrolimus blood trough concentrations were achieved by day 10 in both tacrolimus treatment groups and maintained until the end of the study (fig 2). Thus, by using the dosage adjustment method for this study under blind conditions, a tacrolimus trough level was achieved at the target trough level and was well controlled.

A smooth transition into the open label extension was achieved. Mean trough levels were 10.1 (3.9) ng/ml at week 2, 8.5 (2.5) ng/ml at week 6, and 8.8 (3.9) ng/ml at week 10, respectively.

Clinical response

Double blind study

As shown in table 4, improvement in DAI score (⩾ 4 points, all categories improved) was observed in 68.4% (13/19) of patients in the HT group, in 38.1% (8/21) in the LT group, and in 10.0% (2/20) of patients in the placebo group. Significantly

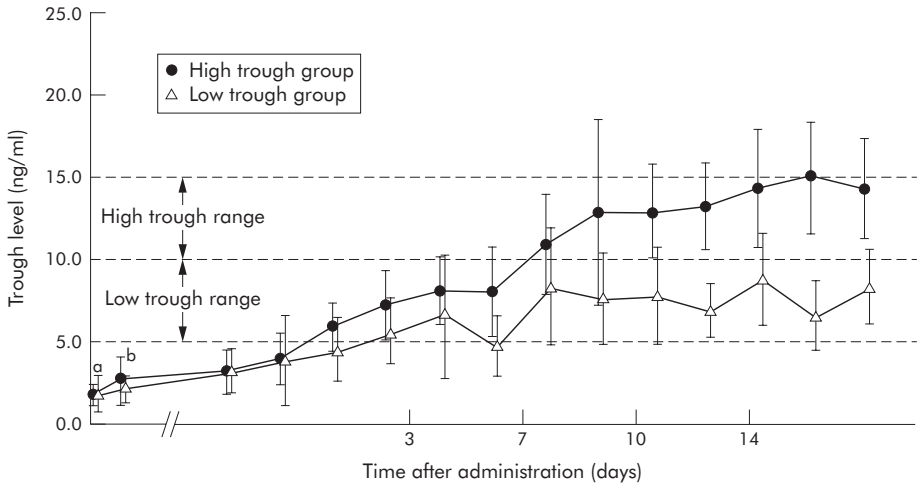

Figure 2 Mean trough levels in both tacrolimus groups. [a]12 hours; [b]24 hours.

Table 4 Clinical responses to therapy in the two week double blind study

Clinical response*	High trough group	Low trough group	Placebo group
No of patients (%)			
(n=60)†	19	21	20
Complete	0 (0)	0 (0)	0 (0)
Partial	13 (68.4) (p<0.001§)	8 (38.1) (p=0.067¶)	2 (10.0)
None	6 (31.6)	13 (61.9)	18 (90.0)
Severe patients (DAI score 10–12)			
(n=27)	6	10	11
Complete	0 (0)	0 (0)	0 (0)
Partial	4 (66.7) (p=0.086§)	5 (50.0) (p=0.219¶)	2 (18.2)
None	2 (33.3)	5 (50.0)	9 (81.8)
Moderate patients (DAI score 6–9)			
(n=33)	13	11	9
Complete	0 (0)	0 (0)	0 (0)
Partial	9 (69.2) (p=0.002§)	3 (27.3) (p=0.155¶)	0 (0)
None	4 (30.8)	8 (72.7)	9 (100.0)
Steroid resistant‡			
(n=15)	5	5	5
Complete	0 (0)	0 (0)	0 (0)
Partial	4 (80.0) (p=0.106§)	2 (40.0) (p=0.718¶)	1 (20.0)
None	1 (20.0)	3 (60.0)	4 (80.0)
Steroid dependent			
(n=45)	14	16	15
Complete	0 (0)	0 (0)	0 (0)
Partial	9 (64.3) (p=0.002§)	6 (37.5) (p=0.074¶)	1 (6.7)
None	5 (35.7)	10 (62.5)	14 (93.3)

*Complete was defined as complete response, all assessment DAI scores were zero; partial, a partial response, a reduction in the disease activity index (DAI) of more than 4 points with improvement of all categories, but not a complete response; and none, no response, other than the above.
†Two patients in the high trough group were excluded from administered patients; one failed to show confirmed visible bloody stool at the start of the study and another underwent cytapheresis therapy within 28 days before initiation. One patient who failed to show confirmed visible bloody stool before initiation in the low trough group was excluded from administered patients. The patient with cytapheresis therapy was judged as ''partial'' and two patients without bloody stool were as ''none'' in the administered population.
‡Steroid resistance was defined as unresponsiveness to oral or intravenous corticosteroid therapy (equivalent to a daily dose of more than 30 mg of prednisolone) over at least two weeks.
§Dunnett-type multiple comparison was used to compare the high trough group and placebo group.
¶Dunnett-type multiple comparison was used to compare the low trough group and placebo group.

more patients in the HT group demonstrated improvement compared with the placebo group ($p<0.001$). The rate of partial responders in patients with severe disease with a DAI score of 10–12 was 66.7% (4/6) in the HT group, 50.0% (5/10) in the LT group, and 18.2% (2/11) in the placebo group. Partial response rates in steroid resistant patients were 80.0% (4/5) in the HT group, 40.0% (2/5) in the LT group, and 20.0% (1/5) in the placebo group.

A significantly greater percentage of patients had improvement in each DAI score evaluation parameter (bowel movements, blood in stool, endoscopic findings, and physician's global impression) in the HT group compared with those in the placebo group. A significantly greater percentage of patients in the LT group compared with those in the placebo group experienced improvement with respect to bowel movements, blood in stool, and physician's assessment (table 5). Clinical remission was observed in 20.0% (4/20) and 10.5% (2/19) of the HT and LT groups compared with 5.9% (1/17) in the placebo group at week 2. Mucosal healing was achieved in 78.9% (15/19) and 44.4% (8/18) of patients in the HT and LT groups, respectively, compared with 12.5% (2/16) in the placebo group at week 2.

The percentage of patients with improvement in the number of bowel movements per day, visible blood in stool, ESR, and CRP level was significantly greater in both tacrolimus groups compared with placebo. There were no statistically significant differences among treatment groups with respect to abdominal pain, body temperature, pulse rate, or haemoglobin during the two week therapy period (data not shown).

Open label extension

The improvement rate for the former placebo group significantly increased with therapy from 10.0% (2/20) to 57.9% (11/19) at week 10 ($p = 0.012$). Improvement in DAI score at week 10 was observed in 55.2% (32/58) of patients who received tacrolimus treatment. Clinical remission was observed in 29.3% (17/58) and mucosal healing in 72.7% (40/

Table 5 Improvement in each disease activity index (DAI) assessment parameter in the two week double blind study (No of patients (%))

	High trough group		Low trough group		Placebo
n=60					
Bowel movement	17/19 (89.5)	(p=0.001)	15/21 (71.4)	(p=0.031)	8/20 (40.0)
Blood in stool	16/19 (84.2)	(p=0.001)	15/21 (71.4)	(p=0.015)	8/20 (40.0)
Endoscopic findings	16/19 (84.2)	(p=0.002)	10/20 (50.0)	(p=0.154)	4/17 (23.5)
Physician's global impression	16/19 (84.2)	(p=0.010)	14/20 (70.0)	(p=0.050)	6/17(35.3)

p Value: Dunnett-type multiple comparison of difference in DAI score between end of treatment and baseline was used to compare each of the tacrolimus groups (high trough or low trough group) and placebo group.

Table 6 Clinical responses* of tacrolimus in the open label extension study at week 10 (No of patients (%))

	High trough group	Low trough group	Placebo group†	Total
n = 58	19	20	19	58
Complete	1 (5.3)	1 (5.0)	1 (5.3)	3 (5.2)
Partial	10 (52.6)	9 (45.0)	10 (52.6)	29 (50.0)
None	8 (42.1)	10 (50.0)	8 (42.1)	26 (44.8)

*Complete was defined as a complete response, all assessment disease activity index (DAI) scores were zero; partial, a partial response, a reduction in DAI of more than 4 points with improvement of all categories, but not a complete response; and none, no response, other than the above.
†Patients who received placebo in the two week double blind study

55) of patients at week 10. Mean dose of prednisolone was reduced from 19.7 (11.5) mg/day at study entry to 7.8 (5.9) mg/day at week 10 in all patients ($p<0.001$), from 33.8 (6.2) mg/day to 9.5 (5.4) mg/day in steroid resistant patients ($p<0.001$) and from 14.7 (8.4) mg/day to 7.2 (5.9) mg/day in steroid dependent patients ($p<0.001$) (tables 6, 7).

Adverse events to therapy

Safety was evaluated for the 63 patients who received at least one dose of study drug. In the double blind study, adverse events that occurred in more than 5% of patients and serious adverse events are shown in table 8. There was no statistically significant difference between the HT and placebo groups ($p = 0.215$) in the overall incidence of adverse events but there was a statistically significant difference ($p = 0.043$) with respect to overall related events. Finger tremor was the most common adverse event in the tacrolimus groups

One patient in the HT group developed serious viral gastroenteritis on day 4; tacrolimus was discontinued and the patient recovered with symptomatic therapy after four days. Another patient in the LT group developed acinetobacter sepsis on day 14 and recovered with symptomatic therapy after eight days. Both events were considered by the investigator to be possibly related to tacrolimus. No other serious adverse events were observed.

No serious adverse events were reported during the 10 week extension. The most common study drug related adverse events in patients who received tacrolimus for 10 weeks were finger tremor and headache. The incidence of adverse events did not increase remarkably in the open label extension study (table 8).

Decreases in serum magnesium and increases in serum creatinine are known as common adverse drug reactions of tacrolimus.[30] Serum magnesium was decreased in seven of 21 patients (33.3%) and in three of 22 patients (13.6%) in the HT and LT groups in the double blind study, respectively, and in seven of 61 patients (11.5%) who received tacrolimus in the open label extension study. However, the change was considered to be mild by the investigators. Increase in serum creatinine levels to >30% above baseline occurred in 4.8% (1/21) of patients in the HT group and in 4.5% (1/22) in the LT group in the double blind study, and in 14.8% (9/61) in the open label extension study. One patient had an increase from baseline to a value ⩾1.5 mg/dl[22] (1.9 mg/dl) but the patient also had diarrhoea and dehydration. There were no other clinically important differences among each of the treatment groups with respect to changes in laboratory assessments.

Table 7 Steroid sparing effects of tacrolimus in the open label extension study (mean dose of prednisolone (mg/day))

	At entry	At week 10
Steroid resistant*	33.8 (6.2)	9.5 (5.4) (p<0.001†)
Steroid dependent	14.7 (8.4)	7.2 (5.9) (p<0.001†)

Values are means (SD).
*Steroid resistance was defined as unresponsiveness to oral or intravenous corticosteroid therapy (equivalent to a daily dose of more than 30 mg of prednisolone) over at least two weeks.
†Wilcoxon signed rank test.

Factors affecting clinical response

Multifactorial analysis of the various demographic factors based on logistic regression showed no significant effect of the patient's age (divided into the following groups: 15–30 years, 31–45 years, and >45 years), sex, or total disease duration on clinical outcome.

Compliance

During this trial, patients were questioned by the investigator about compliance. Although pills were not counted, there were no identifiable cases of non-compliance.

DISCUSSION

This study was designed to assess the efficacy and safety of an oral tacrolimus preparation in patients with refractory moderately/severely active UC. The size of the study groups was designed to permit determination of any statistically significant difference in response rates between the HT group and the placebo group, and a possible trend towards a difference between the LT group and placebo groups, as to identify statistically significant differences in response rates among all three treatment groups would have required a prohibitively large number of patients.

Oral tacrolimus, adjusted to a target blood trough concentration of 10–15 ng/ml, resulted in a greater percentage of patients with a partial response than placebo. Although there was no complete responders to this treatment, several patients experienced clinical remission. The LT group achieved a rate of improvement nearly four times that observed with placebo but the difference did not reach statistical significance. This may have been due to a smaller improvement in endoscopic findings although clinical symptoms such as diarrhoea or bloody stool in the LT group were improved or resolved as well as that observed in the HT group. Indeed, the ratio of patients with no visible blood in stool was 52.6% (10/19) in the HT group, 52.4% (11/21) in the LT group, and 15.0% (3/20) in the placebo group.

Our data suggest that oral tacrolimus is effective for patients with severely active UC, as well as for patients with moderately active UC. Follow up data in the open label extension study suggest that tacrolimus has steroid sparing effects.

Most CsA protocols recommend continuous intravenous infusion whereas tacrolimus achieved therapeutic levels if given orally twice a day. This oral therapy might be an effective alternative to other intravenous immunosuppressive agents, such as CsA or Infliximab. These therapies will reduce the number of patients who require colectomy.

Table 8 Adverse events to therapy

	Double blind study						Open label extension
	High trough (n = 21)		Low trough (n = 22)		Placebo (n = 20)		Tacrolimus (n = 61)
No of patients (%)	12 (57.1)*		11 (50.0)‡		7 (35.0)		
	Related 10 (47.6)†	Unrelated 2 (9.5)	Related 5 (22.7)§	Unrelated 6 (27.3)	Related 3 (15.0)	Unrelated 4 (20.0)	Related 29 (47.5)
Serious adverse events							
Gastroenteritis	1 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sepsis	0 (0)	0 (0)	1 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events occurring in >5% of patients in at least one of the treatment groups							
Tremor finger	4 (19.0)	0 (0)	2 (9.1)	0 (0)	0 (0)	0 (0)	9 (14.8)
Sleepiness	2 (9.5)	0 (0)	0 (0)	0 (0)	1 (5.0)	0 (0)	0 (0)
Hot flush	2 (9.5)	0 (0)	1 (4.5)	0 (0)	0 (0)	0 (0)	1 (1.6)
Headache	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.0)	1 (5.0)	5 (8.2)
Queasy	0 (0)	0 (0)	0 (0)	2 (9.1)	0 (0)	2 (10.0)	3 (4.9)
Stomach discomfort	1 (4.8)	1 (4.8)	0 (0)	0 (0)	0 (0)	1 (5.0)	1 (1.6)

*Fisher's exact test p = 0.215 versus placebo, p = 0.763 versus low trough.
†Fisher's exact test p = 0.043 versus placebo, p = 0.116 versus low trough.
‡Fisher's exact test p = 0.366 versus placebo.
§Fisher's exact test p = 0.700 versus placebo.

Tolerance of the drug was acceptable. Adverse reactions limited therapy in only 1 of 43 patients receiving active medication. Previous studies on the use of tacrolimus in inflammatory bowel disease[5 19–26] reported a high frequency of adverse events such as tremor, hyperglycaemia, hypertension, opportunistic infections, and impaired renal function. The rate of whole adverse events in our study was similar to that in previous reports. However, there was no serious adverse event observed in our study other than gastroenteritis, while severe adverse events such as thrombocytopenia or bicytopenia were reported in UC[23] or cardiothoracic transplantation.[31] The incidence of adverse reactions did not increase remarkably in the open label extension study. Therefore, this therapy was well tolerated for three months.

As in transplantation, trough concentration monitoring was a reliable means of maintaining appropriate tacrolimus blood levels in order to individualise dosing for each patient. Median tacrolimus doses at week 2 were 0.20 mg/kg/day (10.0 mg/day) (min 0.08–max 0.30 mg/kg/day) in the HT group and 0.14 mg/kg/day (6.0 mg/day) (min 0.03–max 0.29 mg/kg/day) in the LT group. The calculation method for dose adjustment provided in this study appeared to be useful for determining the required dose of tacrolimus to maintain optimal blood concentrations.

To our knowledge this is the first report of a placebo controlled, double blind, randomised trial on the efficacy of tacrolimus in remission induction in refractory UC. The optimal target blood trough concentration range of tacrolimus appears to be 10–15 ng/ml in terms of efficacy with two week therapy. Longer term tacrolimus treatment (>3 months) is now under investigation.

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Conflict of interest: None declared.

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EDITOR'S QUIZ: GI SNAPSHOT

Robin Spiller, *Editor*

Catastrophic lower gastrointestinal complications following spinal surgery

Clinical presentation

A 42 year old man was admitted for surgical excision of a malignant vascular spinal (cervical) tumour. There was no smoking, alcohol, past medical, or family history. Regular medications on admission were: paracetamol, diclofenac, opioids, dexamethasone, and omeprazole. Postoperatively he had abdominal pain, torrential fresh and altered bleeding per rectum, with haemodynamic instability.

Urgent investigations revealed the following: haemoglobin 6.9 g/dl, white cell count 20.3×10^9/l, erythrocyte sedimentation rate 19, albumin 18 g/l, and negative vasculitis screen. Gastroscopy revealed a chronic duodenal ulcer with no stigmata of bleeding while flexible sigmoidoscopy showed altered blood with obscured views. Mesenteric angiogram showed normal superior mesenteric and coeliac arteries but the inferior mesenteric artery could not be cannulated. The day following his angiogram the patient developed features of peritonitis on abdominal examination. After an urgent abdominal computed tomography (CT) scan (fig 1), an extended Hartmann's procedure (specimen shown in fig 2) was performed at laparotomy that day. Following surgery the patient did not complain of any further gastrointestinal symptoms.

Question

What does the CT of the abdomen (fig 1) and the colonic specimen (fig 2) show to be the cause of this patient's symptoms?

See page 1289 for answer

This case is submitted by:

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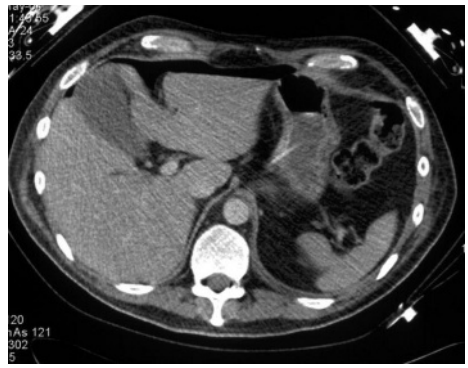

Figure 1 Computed tomography scan of the abdomen performed just prior to laparotomy.

Figure 2 Part of the resected specimen showing the sigmoid colon.

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