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Mucosal healing with oral tacrolimus is associated with favorable medium- and long-term prognosis in steroid-refractory/dependent ulcerative colitis patients

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Abstract

Background: Oral administration of tacrolimus is an effective remission induction therapy for steroid-refractory/dependent ulcerative colitis (UC).
Aim: This study aimed to evaluate the short- as well as medium- and long-term effectiveness of tacrolimus therapy.
Methods: The medical records of 51 patients treated with tacrolimus for UC at our hospital between July 2009 and December 2011 were reviewed retrospectively. Clinical remission and improvement were defined as a Lichtiger score of 4 or less and as a Lichtiger score of ≤ 10 and a reduction in the score of ≥ 3 compared with the baseline score, respectively. Endoscopic findings were evaluated based on the endoscopic activity index and Mayo endoscopic score.
Results: The clinical effectiveness combining clinical remission and improvement was observed in 62.7% of the patients at 3 months. Thirty-six patients underwent colonoscopy at 3 months, and 12 (33.3%) and 10 patients (27.8%) showed Mayo endoscopic scores of 0 and 1, respectively. On Kaplan–Meier analysis, the overall percentage of event-free survivors, who did not require colectomy nor switching to other induction therapy such as infliximab, was 73.0% at 6 months, 49.9% at 1 year, and 37.8% at 2 years. Patients with a Mayo endoscopic score of 0–1 at 3 months showed significantly better medium- and long-term prognosis than those with a score of 2–3 ($p < 0.01$). All adverse events, including infections in 2 patients, were reversible.

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Conclusions: Tacrolimus therapy was effective for inducing clinical and endoscopic remission of steroid-refractory/dependent UC. Endoscopic improvement was associated with favorable medium- and long-term prognosis.

1. Introduction

Ulcerative colitis (UC) is a form of chronic inflammatory bowel disease and is characterized by periods of remission and episodes of relapse. The pathogenesis of UC remains unclear and, therefore, radical therapy has not yet been established. 5-Aminosalicylates (5-ASA), immunomodulators (IMs) and corticosteroids have been employed as therapeutic options for UC for decades. Although steroids are an effective induction therapy, approximately 20% of patients fail to show improvement with steroid treatment.[1,2] Lichtiger et al.[3] reported the effectiveness of intravenous cyclosporine A (CSA), which inhibits calcineurin activity, for steroid-refractory UC in 1994. Several studies also reported that oral tacrolimus, another calcineurin inhibitor, could be an effective induction therapy for steroid-refractory or steroid-dependent UC.[4–7] Ogata et al.[8,9] clearly showed the short-term efficacy of oral tacrolimus for steroid-refractory UC in randomized prospective studies in 2006 and 2011. Recently, a German group reported a large retrospective analysis of patients treated with tacrolimus showing the short-term efficacy and safety of tacrolimus therapy in steroid-refractory UC patients.[10] Interestingly, the same group suggested the possibility that ABCB1 single-nucleotide polymorphisms may be a predictive factor for short-term efficacy of tacrolimus.[11] Thus far, this is the only report of a factor to predict the efficacy of tacrolimus.

Some retrospective studies also showed the medium- and long-term effectiveness of oral tacrolimus therapy in adults and children.[12–17] Yamamoto et al.[18] reported the potential of administering tacrolimus as a maintenance therapy. However, in those studies, the number of subjects was limited, and endoscopic improvement was not assessed.

In this study, we retrospectively evaluated the clinical and endoscopic effectiveness of oral tacrolimus therapy and the medium- and long-term prognosis of UC patients after induction therapy with oral tacrolimus. To our knowledge, this is the first report that assesses the endoscopic improvement and its impact on the medium- and long-term prognosis after tacrolimus therapy. The data obtained from our experience and detailed endoscopic analysis of a large patient population treated with tacrolimus would offer valuable information for the treatment of intractable UC patients.

2. Methods

2.1. Patients and treatment protocol

Oral tacrolimus has been approved for the treatment of steroid-refractory UC and steroid-dependent UC since July 2009 in Japan. Between July 2009 and December 2011, 51 patients with UC were treated with tacrolimus at Keio University Hospital. We reviewed their medical records retrospectively.

The clinical disease activity of the patients was assessed by trained physicians and scored according to the Lichtiger clinical activity index.[3] The Lichtiger index is composed of the following items: the number of daily bowel movements, entity of abdominal pain and tenderness, use of antidiarrhoics, blood in stools, general well-being, fecal incontinence and nocturnal diarrhea. In this scoring system, a higher score indicates more severe disease (score range 0–21).

We assessed the patients with colonoscopy at 3 months after the introduction of tacrolimus. We employed the endoscopic activity index (EAI)[19] and Mayo endoscopic score to evaluate endoscopic severity. The EAI is scored using the following six items: ulcer size, ulcer depth, redness, bleeding, edema, and mucus exudates. A score of zero to two or three is given to each item and a higher score indicates more severe endoscopic activity (score range 0–16).[19] In the Mayo endoscopic score, normal or inactive disease is scored as 0 and mild, moderate or severe disease is assigned a score of 1, 2 and 3, respectively.[20] We used EAI to demonstrate the change of endoscopic severity before and after the therapy, because EAI has been reported to be able to detect improvement after therapeutic intervention more quantitatively than other endoscopic indices.[19]

At our hospital, when starting oral tacrolimus, all patients were hospitalized and the initial dose of tacrolimus was 5 mg/body/day in two divided doses. We adjusted the trough level of tacrolimus in the whole blood based on the report by Ogata et al.[8], with a range of 10–15 ng/ml for the initial 2 weeks and subsequently a range of 5–10 ng/ml.

2.2. Definition and evaluation of effectiveness

Clinical response was assessed using the Lichtiger index. "Clinical remission" was defined as a score of 4 or less. "Improvement" was defined as a score of ≤ 10 and a reduction in the score of ≥ 3 compared with the baseline score before tacrolimus administration. All other cases were defined as "No response". We evaluated the clinical effectiveness at 3 months. Mucosal healing was defined as a Mayo endoscopic score of 0 or 1.

We defined patients who did not need colectomy or whose medication was not switched from tacrolimus to other induction therapy including infliximab (IFX) as "event-free survivors".

2.3. Statistical analysis

The evaluation of changes in EAI was carried out by Wilcoxon signed-rank test. In the analysis of predictive factors for

prognosis, univariate analyses for interval scale and comparisons of proportions between groups were performed by Mann–Whitney *U* test and Fisher exact test, respectively. Multivariate logistic regression analysis was also performed. The event-free survival rate was assessed using Kaplan–Meier analysis. Factors that contribute to the event-free survival rate were estimated by Log-rank test. IBM SPSS Statistics version 18 (SPSS, Chicago, IL, USA) was employed for statistical analyses. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Patient demographics

The clinical background of the 51 patients with UC is shown in Table 1. The patients consisted of 27 males and 24 females, with a median age of 39 years (range 18–67 years). The median age at onset was 33 years old (range 15–64 years old), and the median duration of the disease was 7.0 years (range 0.5–28 years). Thirty-eight and 13 patients were classified as having total colitis or left-sided colitis, respectively. Eighteen and 30 patients were prednisolone (PSL)-dependent or -resistant, respectively and the other 3 patients refused the administration of PSL. The median duration of tacrolimus therapy was 7.0 months (range 0.2–27 months). The median follow-up period after tacrolimus induction was 16 months (range 3–29 months).

Table 1 Clinical background of the patients treated with tacrolimus.

Sex	
Male	27
Female	24
Age at tacrolimus (years)	39 (18–67)
Age at onset (years)	33 (15–64)
Duration of disease (years)	7.0 (0.5–28)
Extent	
Total	38
Left-sided	13
Clinical phenotype	
First attack	7
Chronic continuous	21
Relapse remitting	23
Response to prednisolone	
Dependent	18
Resistant	30
Naïve	1
Others	2
Duration of tacrolimus treatment (months)	7.0 (0.2–27)
Follow-up period (months)	16 (3–29)
Medications at administration of tacrolimus	
5-Aminosalitylate	46
Prednisolone	33
Thiopurines	24

Values are shown as the median (range).
Prednisolone resistance was defined as unresponsiveness to oral or intravenous prednisolone at a dose of more than 30 mg for 5 days.

Before starting tacrolimus, 46 (90.2%), 33 (64.7%) and 24 (47.1%) patients had been treated with 5-ASA, PSL, or thiopurines, respectively.

3.2. Clinical effectiveness

The mean period to reach the target trough concentration of tacrolimus was 4.9 days (range: 2 to 13 days).

The mean Lichtiger score at baseline was 11.5. At 3 months, 20 (39.2%) and 12 patients (23.5%) demonstrated clinical remission or improvement, respectively. Two patients (3.9%) required switching to IFX treatment and colectomy was performed in 4 patients (7.8%) 3 months after starting tacrolimus administration (Fig. 1). Thus, clinical effectiveness combining clinical remission and improvement was obtained in 62.7% of the patients with tacrolimus therapy. Among 20 patients with clinical remission, 19 patients achieved steroid-free remission and one patient was tapering the dose of PSL. The mean Lichtiger score at 3 months of the patients without colectomy was 5.3.

3.3. Endoscopic effectiveness

We next assessed endoscopic improvement by the EAI in 35 patients who underwent colonoscopy at our hospital both before and 3 months after the introduction of tacrolimus. The EAI significantly improved from a mean of 12 (range 9–16) to 7 (range 0–16) ($p < 0.001$) (Fig. 2a). Among those patients, the median Mayo endoscopic score at base line was 3 (range 1–3) and 29 (82.9%), 4 (11.4%), and 2 (5.7%) had a score of 3, 2, 1,

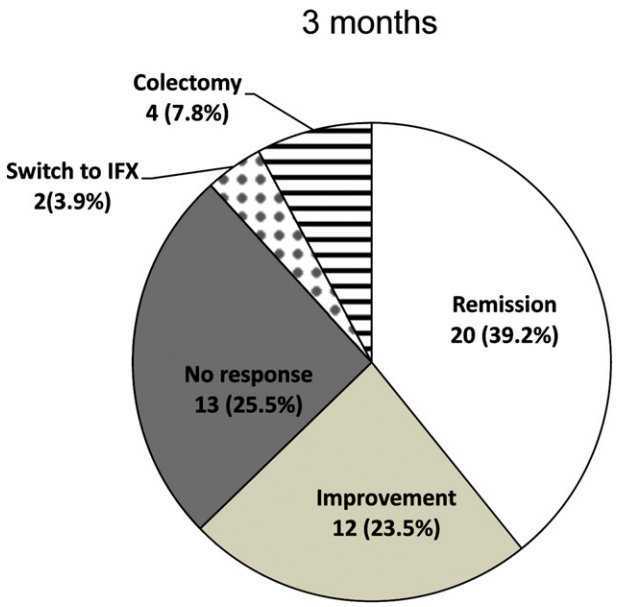

Figure 1 Outcomes of tacrolimus therapy. Clinical responses were assessed by the Lichtiger index at 3 months. Remission was defined by a score of 4 or less and improvement was defined by a score of ≤ 10 and a reduction in the score of ≥ 3 compared with the baseline score before tacrolimus administration. IFX: infliximab.

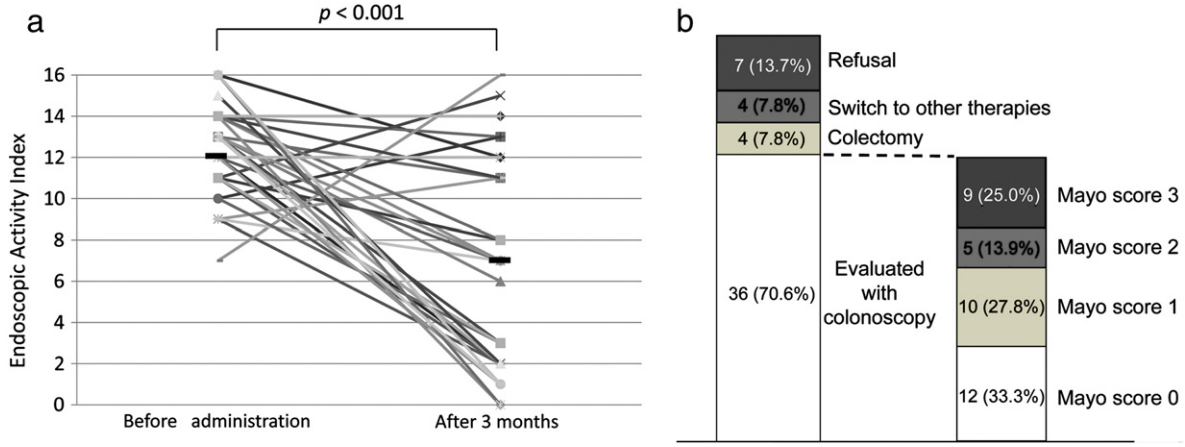

Figure 2 Endoscopic improvement by tacrolimus therapy. (a) Endoscopic severity was assessed by the endoscopic activity index before tacrolimus therapy and after 3 months. (b) Endoscopic findings were evaluated by Mayo endoscopic score at 3 months.

respectively. At 3 months, the median Mayo endoscopic score was 1 (range 0–3).

We did not evaluate 15 patients with colonoscopy at 3 months because of colectomy in 4 patients, switching to other therapies in 4 patients, and refuse to the examination in 7 patients. Consequently, 36 patients were assessed with endoscopy at 3 months. Among the 36 patients, 12 (33.3%), 10 (27.8%), 5 (13.9%), and 9 (25.0%) patients showed Mayo endoscopic scores of 0, 1, 2 and 3, respectively (Fig. 2b).

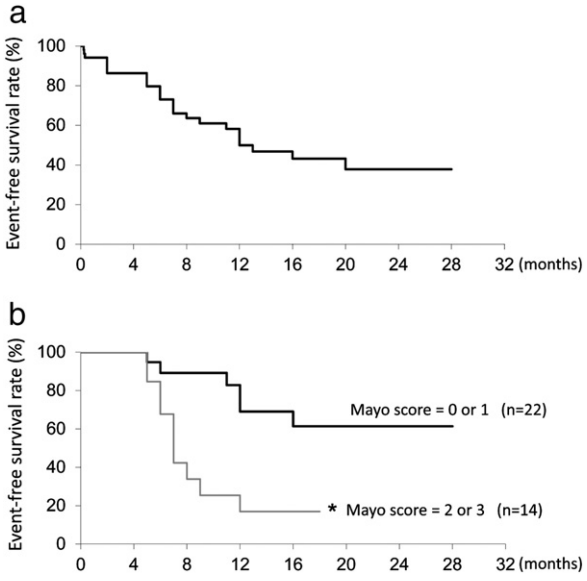

Figure 3 Medium- and long-term prognosis of patients treated with tacrolimus. (a) The Kaplan–Meier analysis showed event-free survival in the overall patient population. (b) Medium- and long-term prognosis was analyzed in patients with a Mayo endoscopic score of 0 or 1 and those with a Mayo endoscopic score of 2 or 3. The event-free survival rate was defined as the percentage of patients who had not required surgery or switch to infliximab treatment.

3.4. Medium- and long-term prognosis

We examined the medium- and long-term prognosis of patients treated with tacrolimus therapy using Kaplan–Meier analysis. The overall percentage of event-free survivors, who had not required surgery or switching to other induction therapy including IFX, was 73.0% at 6 months, 49.9% at 1 year and 37.8% at 2 years (Fig. 3a). We next analyzed predictive factors for the medium- and long-term prognosis in 36 patients who underwent colonoscopy at our hospital at 3 months after the introduction of tacrolimus. Univariate analyses showed that the clinical remission (Lichtiger index ≤ 4) and mucosal healing (Mayo endoscopic score = 0 or 1) at 3 months were associated with the event-free prognosis in follow-up periods ($p = 0.01$ and $p = 0.02$, respectively) as shown in Table 2. At multivariate logistic regression analysis, the clinical remission was correlated with favorable medium- and long-term prognosis ($p = 0.04$; OR 5.64; 95% CI 1.09–29.14). As mucosal healing is emerging as a new therapeutic target, we next examined the impact of endoscopic improvement on the medium- and long-term prognosis using Kaplan–Meier analysis. The patients were stratified based on the Mayo endoscopic score at 3 months: one group of patients with a score of 0 or 1

Table 2 Predictive factors for medium-and long-term prognosis.

	Events		
	(−)	(+)	*p* value
Sex (male/female)	11/9	11/5	NS
Age (years)	39.0	42.5	NS
CRP at 3 months (mg/l)	0.30	0.90	NS
Concomitant medication of thiopurines (yes/no)	9/11	8/8	NS
Continuous administration of tacrolimus (yes/no)	15/5	13/3	NS
Lichtiger index at 3 months ($\leq 4/>4$)	13/7	3/13	0.01
Mayo endoscopic score at 3 months (0–1/2–3)	16/4	6/10	0.02

Values are shown as the median.
Events: colectomy, and switching to other induction therapy.

(n = 22) and the other group of patients with a score of 2 or 3 (n = 14). The overall percentage of event-free survivors in the group with a score of 0 or 1 was 89.2% at 6 months, 69.0% at 1 year and 61.3% at 2 years. In contrast, the overall percentage in the group with a score of 2 or 3 was 67.7% at 6 months and 16.9% at 1 year. The group with mucosal healing showed dramatically better prognosis than the group without mucosal healing ($p < 0.01$) (Fig. 3b).

3.5. Adverse events

The adverse events that were encountered in our series of patients are shown in Table 3. All adverse events developed during the early period after starting tacrolimus administration and were reversible. Twenty seven patients (52.9%) showed hypomagnesemia (≤1.4 mEq/l). One patient (2.0%) developed renal dysfunction when the trough concentration of tacrolimus was 21.2 ng/ml. One patient showed hyperglycemia, defined as the fasting plasma glucose level more than 126 mg/dl or casual plasma glucose level more than 200 mg/dl. Two patients (3.9%) contracted infectious diseases. One patient developed both Pneumocystis pneumonia (PCP) and *Clostridium difficile* associated diarrhea (CDAD) and the other developed CDAD.

4. Discussion

The goals of the treatment for UC are the induction and maintenance of remission. Moreover, not only clinical remission but also endoscopic remission, i.e., mucosal healing, has recently been emphasized. In this study, we assessed the clinical as well as endoscopic effectiveness of oral tacrolimus therapy in the daily clinical setting.

Ogata et al.[9] reported that a clinical response was observed in 50.0% of patients with tacrolimus treatment at 2 weeks, and that 28.6% of patients with continuous tacrolimus treatment showed clinical remission at 12 weeks. In that randomized controlled study, no patients required colectomy, and the study population might have consisted of patients with moderate UC rather than severe UC. Similarly, Yamamoto et al.[15] reported that 77.8% of 27 patients responded to tacrolimus therapy within 30 days and the study population seemed to consist of patients with moderate UC rather than severe UC according to the disease activity at baseline which they showed (the median modified Truelove–Witts severity index was less than 12). In our study, four patients (7.8%) required colectomy at 3 month and 2 patients required switching to IFX. Also, the proportion of severe patients with severe UC with a Lichtiger score >10 at the time of introduction of tacrolimus was 62.5% (the mean Lichtiger score at baseline was 11.5) in our study. Collectively, these data suggest that our study cohort represents the real-world patient population. In this setting, tacrolimus was effective in 62.7% of patients at 3 months after its introduction. The clinical remission rate was 39.2% at 3 months. The effectiveness was similar regardless of disease severity. These data confirmed that tacrolimus is effective in patients with moderate as well as severe UC. Schmidt et al.[10] recently reported that clinical remission was achieved in 72% of 130 patients after 3-month tacrolimus therapy and the remission rate at 3 months was significantly higher in patients with a Lichtiger score at baseline ≥12 (82%) than in patients with the score <12 (57%). The remission rate in their study was much higher than our result. We suspect that the fact that the rate of patients who take any concomitant immunosuppressive medications at baseline was higher in their study (64.6%) than in our study (47.1%) may affect this difference. They reported that patients concomitantly treated with tacrolimus and purine analogs showed better remission rate than patients treated with tacrolimus alone in their study.

In this study, we assessed the endoscopic effectiveness at 3 months using the EAI, which was reported to be useful to quantitatively assess endoscopic improvement in patients with severe UC.[19] We clearly demonstrated that oral tacrolimus therapy significantly improves endoscopic findings at 3 months ($p < 0.001$). We also presented that 36 patients were evaluated with colonoscopy at 3 months, and 22 (61.1%) showed mucosal healing.

We next evaluated the medium- and long-term prognosis of patients treated with tacrolimus. Our data showed that the overall percentage of survivors who did not undergo surgery and who were not switched to IFX treatment was 73.0% at 6 months, 49.9% at 1 year and 37.8% at 2 years. When it comes to the overall cumulative colectomy-free survival rate, Yamamoto et al.[15] reported that it was estimated as 62.3% at 65 months, while it was 69.0% at 2 years in our study. Their Kaplan–Meier analysis data seemed more favorable than ours at 2 years and it may be affected by the difference in study population as discussed above. In this study, we clearly demonstrated that patients with endoscopic remission of UC had significantly good prognosis. This is the first report to suggest that endoscopic assessment at 3 months is important for predicting the future clinical course.

There are several limitations of this analysis. First, the duration of tacrolimus administration varied among the patients. Our healthcare insurance permits 3-month use of tacrolimus, but tacrolimus had to be continued in some patients beyond 3 months (average 8.7 months). Secondly, the concomitant use of IM as maintenance therapy was not uniform in our population. We did not have a sufficient

Table 3 Adverse events after tacrolimus administration.

	Cases	%
Tremor	9	17.6
Hypomagnesemia	27	52.9
Renal dysfunction (Cre > 1.3 mg/dl)	1	2.0
Hyperpotassemia	4	7.8
Hyperglycemia	1	2.0
Myalgic pain	1	2.0
Infection	2	3.9
PCP	1	
CDAD	2	

Hypomagnesemia was defined as a serum magnesium level lower than or equal to 1.4 mEq/l.
Hyperglycemia was defined as the fasting plasma glucose level more than 126 mg/dl or casual plasma glucose level more than200 mg/dl.
PCP: Pneumocystis pneumonia.
CDAD: *Clostridium difficile* associated diarrhea.

number of patients to analyze those confounding factors separately.

Despite a favorable medium- and long-term prognosis of UC patients who received tacrolimus treatment, it is still a challenge to rescue patients who fail to respond to tacrolimus. In our study population, 13 patients who did not respond to tacrolimus required switching to IFX administration. As a result, 11 patients (84.6%) could avoid colectomy. Considering the potential increased risk of infectious complications, further studies are necessary to examine the possibility of IFX as a rescue therapeutic option for tacrolimus failures.

Finally, we assessed the adverse events in patients who received tacrolimus. In this study, all adverse events were non-lethal and reversible. However, we experienced one case of PCP and two cases of CDAD. We must keep in mind that tacrolimus can increase the risk of infectious diseases.

In conclusion, we reported data on tacrolimus use in intractable UC patients. We demonstrated that tacrolimus therapy is effective for inducing clinical as well as endoscopic remission in steroid-refractory or -dependent UC patients. Endoscopic assessment is important to predict the medium- and long-term prognosis.

Conflict of interest

T. Hibi received donation for general research activities in his division from Astellas Pharma Inc. Other authors declared no conflict of interest.

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