The efficacy and safety of tacrolimus suppositories in patients with localized ulcerative colitis

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Abstract

Background

Tacrolimus is a calcineurin inhibitor used for the treatment of 5-Amino-salicylic acid (5-ASA) and systematic corticosteroid refractory ulcerative colitis. However, systemic administration of tacrolimus could lead to many adverse events. Therefore, we used tacrolimus suppositories as a local therapeutic agent and examined its efficacy and safety with strict blood concentration monitoring.

Methods

Sixteen patients with ulcerative colitis were administered a 0.5-mg tacrolimus suppository once daily. In cases with an insufficient clinical effect, additional amounts, at an increment of 0.5 mg of tacrolimus, were administered. The blood concentration was measured two weeks after the start of treatment or any dose change and every four weeks thereafter.

Results

The partial Mayo score was 5.31 before the start of treatment, and it decreased significantly after 2 *(*2.56, *P = 0.001)*, 4 *(*1.53, *P < 0.001)*, and 8 *(*1.47, *P = < 0.001)* weeks of treatment. The median duration of tacrolimus treatment was 24 (range 2–96) weeks, and 6 patients were treated continuously for more than one year after the pMayo score improved. No exacerbation of adverse events during the treatment regimen was observed. The effects and safety of tacrolimus suppositories were verified with strict blood concentration monitoring.

Conclusions

Our findings suggest that the application of tacrolimus suppositories is safe and effective in the treatment of patients with ulcerative colitis.

Background

Tacrolimus is a macrolide antibiotic that can be isolated from the soil bacterium *Streptomyces tsukubaensis* [1]. It inhibits T-cell activation and proliferation by reducing the transcription of interleukin-2 (IL-2), which is essential for T-cell activation and proliferation. Specifically, tacrolimus binds to the immunophilin FK binding protein and forms a complex, which binds to calcineurin and prevents the dephosphorylation of the nuclear factor of activated T-cells (NF-AT). Subsequently, NF-AT moves to the nucleus and induces transcription of IL-2 [2]. Thus, tacrolimus suppresses inflammatory cytokines and thereby causes immunosuppression and could be used for immunosuppression post-transplantation and for various inflammatory diseases. In patients with ulcerative colitis, oral tacrolimus is used for the

treatment of oral corticosteroid refractory states [3]. However, systemic administration could lead to many problems such as infection arising from immunosuppression [4, 5]; nephrotoxicity, cardiotoxicity, and neurotoxicity; hyperglycaemia; and other complications [5–9]. In contrast, a topical tacrolimus therapy could be used in cases with atopic dermatitis, and efficacy and safety are already well established [10]. Suppositories, used as a topical therapeutic agent for ulcerative colitis, could be an alternative treatment option for steroid therapy as the next step from mesalazine. Recently, the efficacy of tacrolimus suppositories as a topical preparation has been reported; however, few studies have measured the blood concentration of tacrolimus. Since the possibility of systemic administration could not be ruled out, the value of a topical formulation remained elusive. Therefore, we developed a relatively low-dose tacrolimus transanal agent and examined its efficacy and safety by strictly monitoring the blood concentration of tacrolimus.

Methods

Sixteen cases of ulcerative colitis (proctitis and distal colitis) were treated with tacrolimus at our hospital between June 1, 2014 and August 30, 2018. Two cases were investigated in this study. The subjects included a male and female with ulcerative colitis (proctitis and distal colitis) who were both at least 20 years old, and informed consent was be obtained from all patients prior to their inclusion in the study. This study was approved by the Institutional Review Board (No. 17) and conducted in compliance with the guidelines of the Helsinki Declaration. In the formulation of the tacrolimus suppository, 1 mg of Prograf (manufactured by Astellas Pharma) was unshelled and combined with a base to prepare a 0.5-mg suppository, which was transanally administered once per day. The blood concentration was measured two weeks after the start of the therapy and every four weeks thereafter. The administration of tacrolimus suppositories was continued as long as the trough value was below the detectable limit. In cases with an insufficient clinical effect, additional amounts, at an increment of 0.5 mg of tacrolimus, were administered. The blood concentration was measured 2 weeks after the dose was increased and every 4 weeks thereafter. The tacrolimus blood concentration was measured by Chemiluminescent enzyme immunoassay using ARCHITECT® (Abbott Diagnostics, USA). A blood concentration of 2.0 ng/ml was defined as the lower limit of measurement. The clinical disease score was evaluated using the partial Mayo score (pMayo score) [11]. Two weeks after the start of the administration of tacrolimus suppositories, patients with an improvement of 2 points or more were regarded as having a therapeutic effect. If the observed effect was insufficient at a particular visit, the dose was sequentially increased, and the blood concentration was measured 2 weeks after such an increase and every 4 weeks thereafter. If the blood concentration was below the lower limit of detection, the treatment was discontinued. All other topical preparations used at the start of the therapy were eventually replaced with tacrolimus suppositories. For oral 5-ASA preparation, thiopurine preparation, or steroid administration, the dosage was not changed during the administration period. No concomitant use with oral tacrolimus was performed. Dosing was continued for the biological product without any change or discontinuation. At the start of the administration of the tacrolimus suppositories, hepatitis B (HB) surface (s) antigen, HBs antibody, hepatitis C virus antibody, and the presence of cytomegalovirus and tuberculosis infection were

determined to screen for any infectious diseases. The administration of tacrolimus suppositories was not performed if such tests were positive. Two weeks after the start of therapy and every four weeks thereafter, a blood test and the presence or absence of proteinuria were evaluated in each patient. Additionally, the timing of bowel movements, presence or absence of blood in the stool, general condition, and the pMayo score were evaluated. Endoscopy was proposed at the start and 8 weeks after therapy. In patients with improved clinical symptoms, therapy was continued even after improvements were observed, and the effect of maintenance with tacrolimus suppositories was verified.

Statistical analysis

Statistical analyses were performed using SPSS statistics 24 for Windows (SPSS Inc., Chicago, IL). Qualitative and quantitative variables were analysed using the chi-square test or Fisher's test and Student's t-test or non-parametric (Wilcoxon) test, respectively. The Kruskal–Wallis test, by ranks, was used for comparing multiple groups. P-values < 0.05 were considered statistically significant.

Results

A total of 16 cases (6 males and 10 females) were included in this study, and the median age was 38 (range 20–56) years. In these cases, the type of ulcerative colitis was proctitis (10 cases) and distal colitis (6 cases). The median weight was 53.5 (range 40–84) kg. The median duration of illness was 9 (0.5–16) years, and 11 cases had been treated with systemic steroids, but none had been treated with systemic steroids from the start of the disease. None of the cases had a history of using biologics. Oral salazopyrine, sulfasalazine (SASP), or 5-ASA preparations were administered in all cases, and seven patients received azathioprine; no changes were made during the administration period. Of the 9 cases that switched from topical preparations to tacrolimus suppositories, five cases were treated with topical mesalazine, and four cases were switched to topical steroids with tacrolimus suppositories (Table 1). The pMayo score was 5.31 before the start of treatment, and it decreased significantly after 2 *(*2.56, $P = 0.001$*)*, 4 *(*1.53, $P < 0.001$*)*, and 8 *(*1.47, $P = < 0.001$*)* weeks of treatment (Fig. 1). In 12 of the 16 cases, the pMayo score, after 2 weeks, decreased by 2 points or more. Of the remaining 4 patients with no improvement in the pMayo score, 1 and 2 patients were treated again 2 and 8 weeks later, respectively. In the remaining 1 patient, treatment continued up to 28 weeks; however, the medication was discontinued due to an insufficient therapeutic effect. No statistically significant differences in laboratory data at baseline and 2, 6, and 10 weeks after the start of treatment were observed (Table 2). In addition, no cases with proteinuria were observed. At the start of this study, colonoscopy was performed in four cases, which showed inflammation with Mayo endoscopic sub-scores (MES) of 2–3.

Table 1
Patients' characteristics

Sex (male/female)	**6 / 10**
Age (median [range]) (years)	38 (20–56)
Weight (median [range]) (kg)	53.5 (40–84)
Disease duration (median [range]) (years)	9 (0.5–16)
Type of ulcerative colitis	
Proctitis (%)	10 (62.5%)
Distal colitis (%)	6 (37.5%)
Concomitant oral medication	
Salazosulfapyridine or Mesalazine (%)	16 (100%)
Immunosuppressant (Azathioprine) (%)	7 (43.8%)
Topical therapy at baseline	
Mesalazine	5 (31.3%)
Steroid	4 (25%)
Past history of systemic steroids (%)	11(68.8%)

Table 2
The mean value of different parameters after the start of treatment

	Pre administration	**Two weeks after starting treatment**	**Six weeks after starting treatment**	**Ten weeks after starting treatment**	***P*-value**
WBC	5743	5538	5775	5300	0.767
Hb	13	12.9	12.7	12.7	0.987
Plt	26.7	27.5	27.8	28.1	0.792
Alb	4.4	4.5	4.5	4.5	0.966
AST	21.9	19.6	17.6	17.8	0.266
ALT	16.4	16	14.4	13.5	0.81
Cre	0.7	0.67	0.65	0.65	0.858
CRP	0.16	0.07	0.12	0.1	0.869

WBC: white blood cell, Hb: haemoglobin, Plt: platelets, Alb: albumin, AST: aspartate aminotransferase, ALT: aspartate aminotransferase, Cre: carbapenem-resistant Enterobacteriaceae, CRP: C-reactive protein

Endoscopy at follow ups was performed in two of these cases after the start of treatment, which revealed endoscopic mucosal healing and MES of 0. In another case, endoscopy was not performed at the start of the administration of tacrolimus but rather when no clinical effect was observed. This endoscopic study showed that severe inflammation (MES 2) was retained; however, it was sparse in the rectum near the anus (Fig. 2). The maximum dose of tacrolimus administered was 0.5 g in 10 cases, 1.0 g in 3 cases, 1.5 g in 1 case, and 2 g in 2 cases. The tacrolimus blood concentration exceeded the lower limit of measurement (2.1 ng/ml) in two patients; one patient received 1.5 g, and the other patient received up to 1.0 g of tacrolimus. In both cases, due to an insufficient therapeutic effect, the blood was collected two weeks after administering the maximum dose. The blood concentration of tacrolimus was 2.1 and 3.4 ng/ml in these cases, respectively, and the administration of tacrolimus suppositories was stopped. Nine out of ten patients who received 0.5 g of tacrolimus showed sufficient therapeutic effects, and the blood concentration was below the lower limit in these cases. The remaining 1 patient had poor improvement in efficacy, refused to undergo treatment with an increase in the amount of tacrolimus, and dropped out of this study. Of the 6 patients who received more than 1 g of tacrolimus, 3 patients showed an improvement in symptoms, 2 patients discontinued treatment as the tacrolimus blood concentration was above the lower limit, and 1 patient had a poor therapeutic effect. In 9 patients where topical formulations were replaced with tacrolimus suppositories, 6 (2 steroids and 4 mesalazine suppositories) showed improvement in the pMayo score. However, no such improvements were seen in the remaining 3 cases (2 steroids and 1 mesalazine suppositories). The median duration of tacrolimus treatment was 24 (range 2–96) weeks, and 6 patients were treated continuously for more than one year after improvements in the pMayo score were observed. No exacerbation of adverse events was observed during the treatment regimen in any patient. Additionally, the pMayo score did not improve in 4 cases after the administration of the tacrolimus suppositories, and as described above, 3 of those cases were switched from other enema preparations. Two of these cases were rescued by switching to a steroid enema. Two other patients, who had used a steroid enema before tacrolimus induction, were treated with cytapheresis or biologics, both of which resulted in clinical remission.

Discussion

In cases of ulcerative colitis where inflammation is limited to the rectum or distal colon, suppositories or enemas with 5-ASA, SASP, and steroids are used as topical preparations in addition to oral 5-ASA and SASP preparations [12]. In particular, foam formulations of steroids have been widely used and have become an effective treatment for local ulcerative colitis [13]. However, there are some cases in which these treatments fail to induce a response. Currently, the next-stage treatments include the systemic application of steroids, azathioprine, and biological agents, which are associated with many complications [14–16]. Systemic treatment of ulcerative colitis, which is localized to proctitis or distal colitis, could be an excessive measure. Therefore, in this study, we focused on tacrolimus as a new topical formulation. Some reports showed that tacrolimus, as a topical preparation, has therapeutic effects in the treatment of localized ulcerative colitis [17–19]. However, transrectal drug administration could lead to absorption through the mucous membrane. In a previous report, many cases with elevated

blood levels of tacrolimus were registered, and the value of local therapy has not been strictly examined. In another study, tacrolimus was orally or transanally administered to normal volunteers, and the blood concentration was measured. In this study, the duration and amount of the maximum blood tacrolimus concentration were lower in cases with transanal administration than in those cases with oral administration; however, a certain amount of tacrolimus was absorbed into the bloodstream in both cases. Thus, transanal administration of tacrolimus could lead to clinically relevant systemic exposure [20]. Furthermore, absorption efficiency is considered to be higher in patients with ulcerative colitis who have erosions or ulcers in the rectum. As such, blood level monitoring is required for a rigorous evaluation of the safety and efficacy of the transanal administration of tacrolimus as local therapy. Therefore, in this study, we measured the blood concentration of tacrolimus 2 weeks after the start of the administration of the tacrolimus suppositories and every 4 weeks thereafter and verified the effect of the drug by closely monitoring the blood concentration. The therapeutic effect in this study was seen as a significant improvement in the pMayo score between baseline and 2 or 4 weeks after the initiation of therapy, indicating the usefulness of tacrolimus suppositories. The therapeutic effect was seen in 12 out of 16 cases, where the blood concentration of tacrolimus did not exceed the detectable limit of 2.0 ng/ml. On the other hand, even when the blood concentration of tacrolimus is below the detectable limit, a small amount of tacrolimus could be absorbed, and such a low dose could produce therapeutic benefits in ulcerative colitis. Although an accurate evaluation of this was difficult to achieve in this study, we showed that, even when there is no improvement in symptoms, inflammation is reduced on the anus side of the rectum, and the range of topical drug delivery could be reached (Fig. 2). This observation highlights the value of tacrolimus suppositories as a topical formulation.

Regarding the optimal dose of tacrolimus, 9 out of 16 cases showed an improvement with 0.5 g of tacrolimus, which was the minimum dose used in this study. As none of these cases exceeded the measurable serum level of tacrolimus, we recommend treatment at this dose. Symptom improvement was seen in 3 out of the 6 cases when the tacrolimus suppository was increased to 1 g or more. However, in one of these cases, the blood concentration was higher than the lower limit of measurement, and the administration of tacrolimus was discontinued. In 3 other cases, no effect was seen even when the dose was increased to 1 g or more. Transanal tacrolimus doses of 1 g or more could also be considered for the treatment of ulcerative colitis after evaluating the risks and benefits. However, no adverse events were observed in any cases during the study period, including cases with elevated blood tacrolimus concentrations. We believe that adverse events were prevented because appropriate measures such as discontinuation and dose reduction were judiciously implemented. Additionally, in one case, the administration of tacrolimus was continued up to 96 weeks but no exacerbation of adverse events was observed, further demonstrating the safety of transanal tacrolimus administration with appropriate blood concentration monitoring. Furthermore, regarding the position of tacrolimus suppositories as a topical preparation, a single comparative study of transanal tacrolimus and steroids reported that tacrolimus suppository formulations were comparable to transanal steroids therapy [21]. In this study, topical preparations were not used in 7 patients at the start of the study, and 6 out of 7 patients showed improvement with tacrolimus suppository administration. Of the five cases that switched from topical

mesalazine preparations, 4 cases showed improvement with tacrolimus suppository administration. In contrast, of the 4 cases that switched from topical steroid preparations, 2 cases showed improvements with tacrolimus suppository administration. Although the number of cases was small and could not be considered statistically relevant, tacrolimus was highly effective in cases where topical drugs were not used or switched from the mesalazine suppository, while its therapeutic effect was limited in cases where steroids were previously used. This observation is consistent with those reported in previous studies. Steroid suppositories were effective in some cases where tacrolimus suppositories were ineffective. The effect of tacrolimus suppositories was superior and similar to that of mesalazine topical preparation and steroids suppository, respectively. Further studies are required to validate this observation.

Conclusions

In conclusion, the efficacy and safety of tacrolimus suppositories were verified with strict blood concentration monitoring. The pMayo score significantly improved in patients treated with tacrolimus suppositories, and no exacerbation of adverse events was observed, thereby confirming the efficacy of this treatment. Thus, tacrolimus suppositories, as topical preparations, are useful, and we hope to verify these findings in the future. In order to establish the position of this drug, a comparative study with a topical steroid preparation is warranted. We believe that tacrolimus suppositories will become a new option for the treatment of local ulcerative colitis that is resistant to existing treatment modalities. To the best of our knowledge, this is the first study on the safety and efficacy of tacrolimus suppository in Japanese ulcerative colitis patients with strict blood concentration monitoring.

Abbreviations

IL2, interleukin-2

NF-AT, nuclear factor of activated T-cells

pMayo, partial Mayo score

HB, hepatitis B

S, surface

SASP, sulfasalazine

MES, Mayo endoscopic sub-scores

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (No. 17) and conducted in compliance with the guidelines of the Helsinki Declaration. All participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Fukuyama Medical Center (No. 17).

Authors' contributions

Conception and design of study: Shizuma Omote, Tatsuya Toyokawa.

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Figures

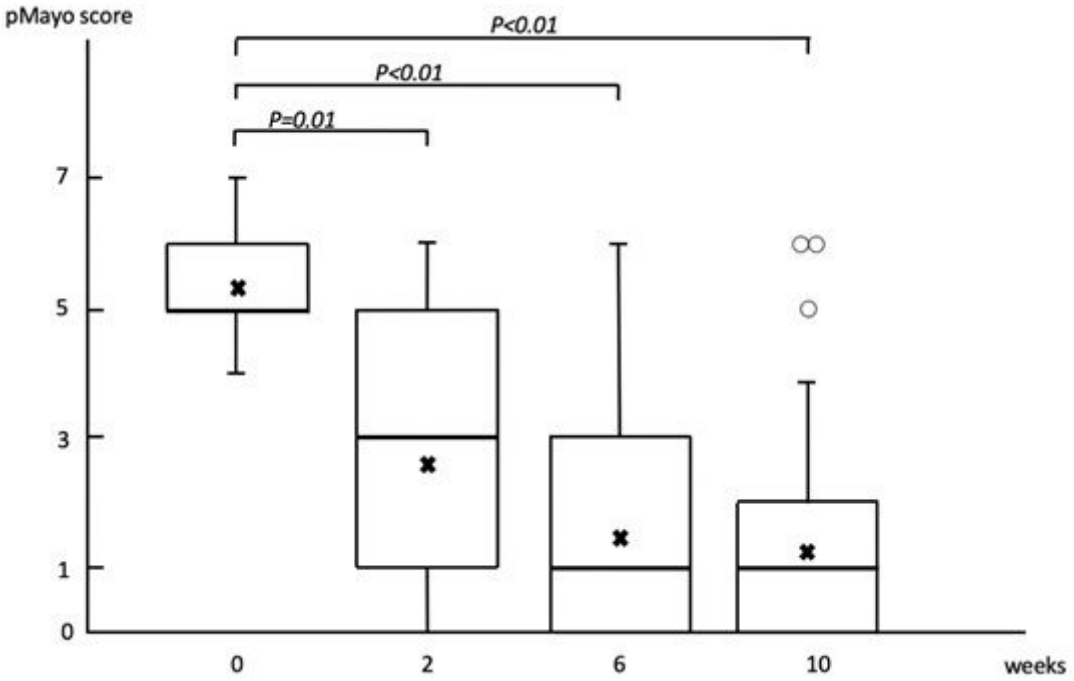

Figure 1

Changes in the partial Mayo score after tacrolimus suppository administration Box plot showing the partial Mayo score at baseline and 2, 6, and 10 weeks after the administration of tacrolimus. The mean at each time point is indicated with a cross.

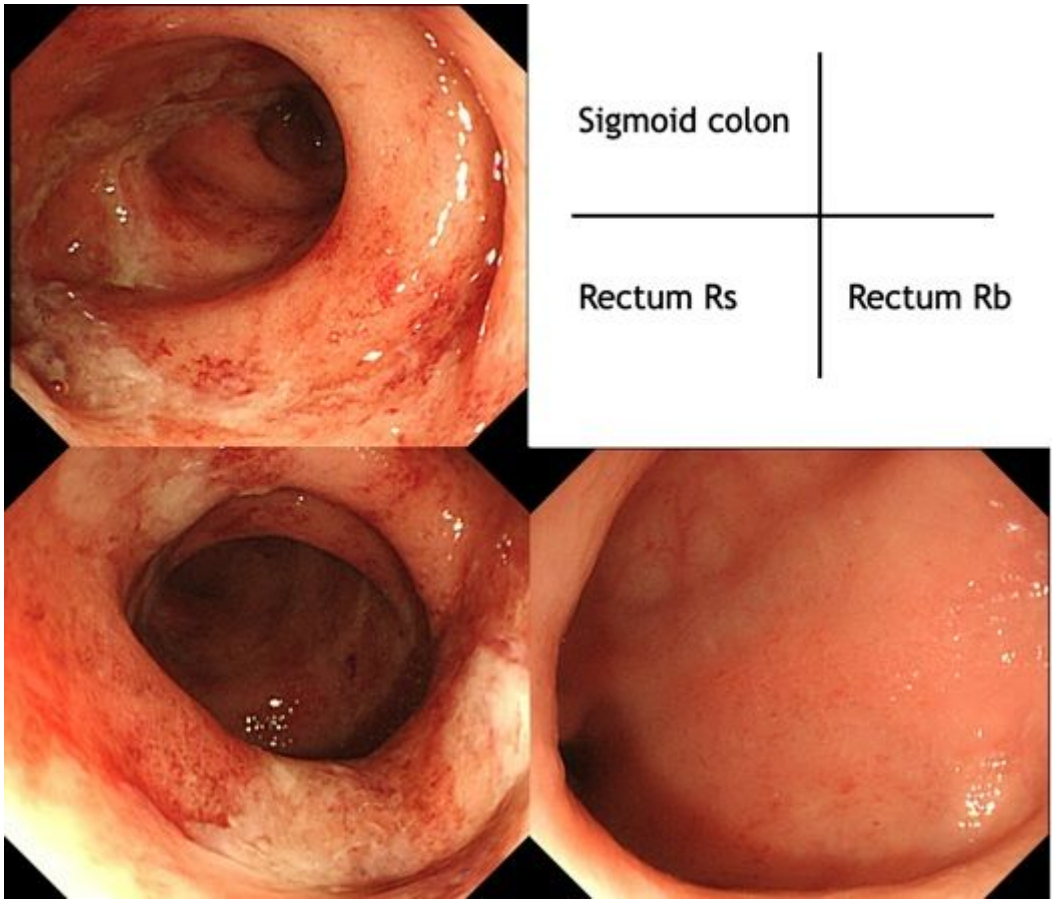

Figure 2

Endoscopic findings in a case where no clinical effect was found