Tacrolimus Suppositories in Therapy-Resistant Ulcerative Proctitis

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Keywords

Inflammatory bowel disease · Tacrolimus · Therapy resistant · Topical treatment · Ulcerative proctitis

Abstract

Background: Ulcerative proctitis may often be managed with topical salicylates or steroids alone, but in some patients, symptoms are persistent and severe. We analyzed the efficacy of tacrolimus suppositories in patients who had proven refractory to combined topical and systemic treatment. **Methods:** In this retrospective analysis, ulcerative colitis activity index (CAI), side effects, co-medication and drug levels were assessed in 43 patients with distal ulcerative colitis who received suppositories containing 2 mg of tacrolimus b.i.d. as add-on medication. **Results:** A total of 23 patients with ulcerative proctitis presented to follow-up within ≤50 days (mean 27.0 days) after suppositories were started. A decrease in CAI (from 8.0 to 5.5 points) was observed and 52.3% reached clinical remission (CAI ≤4). In total, 43 patients were available for analysis, of whom 9 had inflammation of the sigmoid colon as well. For the entire cohort, the median treatment duration was 76 days; 60% were in remission on

the last documented visit. Serum measurements revealed a substantial tacrolimus level with a mean of 5.5 ng/mL. We observed one case of mild reversible acute kidney injury.

Conclusions: In ulcerative proctitis, adding tacrolimus suppositories can be an effective and safe option when topical mesalazine, corticoid formulations and concomitant oral or parenteral medications have failed.

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Introduction

Ulcerative colitis limited to the rectum (ulcerative proctitis) seems to have a better prognosis in terms of cancer development than more extensive disease [1] and can often be sufficiently managed with topical mesalazine or steroids such as budesonide alone. Yet in some patients, symptoms can be persistent, severe and have a profound impact on quality of life [2]. In common practice, these patients receive additional systemic therapy in anal-

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ogy to patients with extensive colitis. Nonetheless, many clinicians feel that systemic administration of corticosteroids, immunomodulators, or TNF- α antagonists might expose these patients to an unproportionally high risk of systemic adverse drug effects and potentially life-threatening complications [3].

Local treatment with medications other than mesalazine or steroids thus seems to be an attractive alternative. Along these lines, topical application of the tacrolimus in cases of refractory ulcerative proctitis has been suggested [1, 4]. Tacrolimus is a macrolide that inhibits T-lymphocyte activation and is used after kidney, liver or heart transplantation [5, 6]. In inflammatory bowel disease, tacrolimus has proven to be effective in steroid-dependent or resistant ulcerative colitis [7–9]. Its shorter half-life compared to anti-TNF therapy made it also a choice in fulminant colitis in which proctocolectomy might become inevitable [1].

Yet, numerous adverse drug effects are recognized, ranging from nephrologic and neurologic manifestations to hyperglycemia [10], myelodepression, hypertension or hyperkalemia. Since co-medication of CYP3A4 inhibitors or inducers effect tacrolimus levels, regular monitoring of blood levels is required [6]. In sum, the use of systemic tacrolimus needs to be well weighed against its benefits. The application of tacrolimus directly to inflamed tissues could achieve a local effect and may minimize systemic side effects. Topical formulations of tacrolimus are already used in atopic dermatitis [11] and as an off-label treatment in other dermatologic conditions [12]. Moreover, a study by van Dieren et al. [13] showed that tacrolimus is adsorbed and active in human rectal mucosa. The same authors demonstrated that interleukin-2 can be suppressed in murine colonic (lamina propria) T cells [14] via topical administration of tacrolimus, thus confirming a local mechanism of action. Nonetheless, even with rectal application, raised tacrolimus levels and acute renal injury have been reported [15].

The recommendation for the off-label use of topical tacrolimus in ulcerative proctitis was based on two small studies [13, 16]. Meanwhile, efficacy has also been demonstrated in a randomized, placebo controlled, double-blinded trial using a rectal tacrolimus ointment [17]. Yet, the verum group consisted of only 11 patients, who had either proctitis or protosigmoiditis (i.e., patients with up to 25 cm of inflammation from the anal verge were included).

In this report, we retrospectively summarize our 7 years' experience with add-on therapy of tacrolimus suppositories in a cohort of 43 patients.

Table 1. Patient population, endoscopic diagnosis, and medication at baseline

Patients	43
Gender	
Male	23
Female	20
Age at baseline, years	43.6 (16–80)
Endoscopic diagnosis at baseline	
Mild proctitis	4
Moderate proctitis	11
Severe proctitis	17
Mild proctosigmoiditis	2
Moderate proctosigmoiditis	1
Severe proctosigmoiditis	6
No endoscopic confirmation available	2
Immunosuppression at baseline	
Prednisolone	8
Prednisolone oral + azathioprine	6
Prednisolone + infliximab	1
Azathioprine	6
Azathioprine + tacrolimus (oral)	1
6-Mercaptopurine	2
Methotrexate	1
Oral therapy at baseline	
Mesalazine	22
Lecithin	1
<i>E. coli</i> Nissle	2
Topical therapy at baseline	
Mesalazine	3
Budesonide	6
Betamethasone foam	1
Hydrocortisone foam	7

Data are presented as *n* or mean (range), as appropriate.

Materials and Methods

Patient Population

Patients with ulcerative proctitis have been treated with tacrolimus suppositories in the Department of Gastroenterology at Robert Bosch Krankenhaus in Stuttgart since June 2009. Sufficient data of 43 patients with distal ulcerative colitis was available, and the retrospective chart review ended on June 30, 2016. In all cases, patients had an already known treatment failure of numerous topical therapies, were not able to tolerate/willing to use larger volume enemas or had problems with foams. In addition, several patients had stopped topical therapy on their own when coming back to our out-patient clinic. A proportion of the patients had failed immunomodulators or anti-TNF therapy and was on systemic steroid therapy (Table 1; online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000493979). Four patients stopped and restarted tacrolimus treatment; only the first naïve treatment cycle was considered for analysis. Severity of mucosal inflammation on endoscopy is determined by expert gastroenterologists at Robert Bosch Krankenhaus and reported as mucosal healing, mild, moderate or severe. Extent is classified as proctitis or proctosigmoiditis. As activity index, the clinical part of the ulcer-

ative colitis activity index (CAI) according to Rachmilewitz [18] was calculated at the start of tacrolimus treatment and at follow-up. The index ranges from 0 to 31 points; ≤ 4 is considered remission.

Tacrolimus Suppositories

Tacrolimus suppositories are not commercially available in Germany or other countries. The extemporaneous preparation [19] was carried out locally by the Pharmacy of Robert Bosch Krankenhaus, Stuttgart, Germany, complying with good manufacturing practice guidelines. The content of 5-mg capsules of Prograf® were used to create suppositories containing 2 mg of tacrolimus on a basis of hydrogenated fat. Suppositories were stored at 4 °C until use. Patients were instructed to apply the suppositories b.i.d. (i.e., once in the morning and before going to sleep).

Concomitant Medication

The medication listed represents the time point when the decision to start tacrolimus suppositories was made (baseline) and the medication on follow-up assessment, respectively. Online supplementary Table 1 gives detailed information for every patient.

Safety

Safety laboratory included creatinine, tacrolimus blood levels, complete blood count, C-reactive protein (CRP), glucose and erythrocyte sedimentation rate. Tacrolimus levels were measured in EDTA whole blood with a routine immunoassay (Roche Diagnostics, Germany).

Statistical Analysis

Data analysis and graphs were created with R version 3.4.0 (2017-04-21), using the tidyverse package [20]. Wilcoxon matched-pairs signed-rank test was used to test differences between the CAI values. *p* values are two-tailed. For correlations, Spearman's rank correlation coefficient was calculated.

Results

Patient Population

Table 1 summarizes the main demographic features at baseline, the medication and the endoscopic findings. At the start of treatment (baseline), 9 patients had additional involvement of the sigmoid colon, but the most severe inflammation was localized to the rectum, i.e., up to 16 cm from the anal verge. The decision to use topical tacrolimus in these patients was made when the investigators felt that symptoms were for the most part originating from the inflamed anorectum and thus at least some clinical improvement might be achieved. The pertinent data for each individual patient is provided in online supplementary Table 1.

Concomitant Immunosuppression and Endoscopic Findings

Three patients had a prior failure of anti-TNF therapy, and in 1 patient, infliximab was stopped due to futility upon start of tacrolimus suppositories; 15 patients were

already under therapy with systemic steroids, 8 of whom received a combination therapy. In total, 16 patients took an immunomodulator at baseline. Endoscopic confirmation of distal ulcerative colitis was available for 41 patients (95.3%). An endoscopy was performed within 7 days prior to baseline in 22 patients, and a recent endoscopy within the last 3 months was available for all but 4 patients. Median time from endoscopy to baseline was 3 days (IQR 0–30 days); 23 patients had a severe inflammation at baseline, and 12 showed moderate inflammation.

Overall Efficacy and Course

In the entire cohort of 43 patients, the median duration from baseline to the last documented visit was 76 days (IQR 7–206 days). Clinical course and efficacy of treatment could be assessed only at time points when patients consulted the out-patient clinic, thus follow-up intervals showed a wide range from 7 to 2,157 days (Fig. 1a). Clinical remission (i.e., CAI ≤ 4) was present in 26 of 43 patients (60%) on the last documented visit. Three patients did not have sufficient data for calculation of the CAI, but from the available data, they were clearly not in remission (patients 2, 4 and 38). Mean CAI was 5.1 points (range 0–19). Figure 1b shows individual CAI scores. Remarkably, some patients took the suppositories for an extended period of time, maintaining remission and symptom control (e.g., for up to 1,754 days and 2,157 days).

Short-Term Efficacy

As the treatment duration and follow-up intervals varied considerably in our cohort, we analyzed a more homogeneous subgroup that allowed for assessment of short-term efficacy; 31 patients presented no later than 50 days after baseline. Mean time from baseline to follow-up visit was 28.9 days (range 7–50 days). CAI showed a statistically significant decrease from 7.9 ± 3.3 to 5.7 ± 4.7 points, $p = 0.002$ (Fig. 2a). More important from a patient's perspective, after about 1 month of treatment, clinical remission in terms of CAI was reached in 17 of 31 patients (54.8%). Three patients had a CAI of 0, 3 or 4 at baseline (9.6%).

Excluding all patients who had more proximal disease and the one patient for whom no recent endoscopy result was available left 23 patients. In patients with proctitis, CAI decreased from 8.0 ± 3.1 to 5.5 ± 4.0 points, $p < 0.001$. Mean treatment duration was 27.0 days (Fig. 2b); 12 of 23 patients (52.3%) were in remission after the assessment within 50 days, which we believe to be clinically relevant (2/23 were not in remission at baseline).

Endoscopic follow-up was only available in 6 patients. While none showed worsening of endoscopic findings, 1

Fig. 1.a Duration from start of tacrolimus suppositories to last documented follow-up visit. The histogram with a bin width of 10 therapy days shows the distribution of treatment duration. **b** Colitis activity index at baseline and at last documented follow-up connected by lines. As the follow-up interval had a range from 7 to 2,157 days, we refrained from a statistical comparison.

was unchanged, 3 improved and 2 even improved much. In terms of bleeding, we separately analyzed the bleeding subscore of the CAI, which was available for all patients. Bleeding score showed much improvement in 2 patients and improvement in 9 patients; worsening of bleeding

was not observed. In 12 patients, bleeding score remained the same. Online supplementary Table 1 shows the individual results for all patients.

In contrast, the 7 patients who had more extensive disease did not profit from treatment with the suppositories,

Fig. 2. a Colitis activity index response within 50 days, including all patients with distal ulcerative colitis ($n = 31$). The Wilcoxon matched-pairs signed-rank test was used to test for significant differences between the activity index at baseline and at a given follow-up time point. p values are two-tailed. The underlying jitter plot shows individual scores with corresponding endoscopic diagnosis. Thick horizontal bars are medians. ** $p < 0.01$. **b** Colitis activity index response within 50 days, including only patients with ulcerative proctitis ($n = 23$). The Wilcoxon matched-pairs signed-rank test was used to test for significant differences between the activity index at baseline and at a given follow-up time point. p values are two-tailed. The underlying jitter plot shows individual scores with corresponding endoscopic diagnosis. Thick horizontal bars are medians. *** $p < 0.001$.

Fig. 3. a Tacrolimus blood level and time interval from last dose to blood sampling. All 82 available measurement pairs are shown. The fitted regression line and 95% confidence interval (shaded area) visualize the degree of correlation of blood levels with the length of the time interval. Spearman's $\rho = -0.36$, $p < 0.001$. **b** Correlation of tacrolimus blood level and colitis activity index in patients with proctitis only who presented to follow-up within 50 days (compare Fig. 2b). All available measurement pairs are shown. The fitted regression line and 95% confidence interval (shaded area) visualize the degree of correlation of blood levels with the length of the time interval. Spearman's $\rho = -0.26$, $p =$ nonsignificant.

although their symptoms had initially been judged to originate mainly from the anorectum (mean CAI score of 7 at baseline vs. 6.7 at follow-up, $p = 0.83$).

Tacrolimus Blood Levels

In the entire cohort of 43 patients, 82 measurements of tacrolimus levels with corresponding information about the time interval between application of the suppository and blood sampling were identified. Mean tacrolimus level was 5.5 ± 3.9 ng/mL after a mean of 17.9 ± 10.9 h (range 2–64 h), as illustrated in Figure 3a. Considering the 23 measurements which were taken earlier than 10 h or later than 18 h as genuine trough levels is difficult. Nonetheless, a separate analysis of measurements taken excluding these samples did not significantly change the mean tacrolimus level (5.7 ± 3.9 ng/mL after a mean of 14.9 h).

For the short-term analysis, 26 of 31 patients had available tacrolimus levels on follow-up, and the mean level was 5.6 ± 4.2 ng/mL after 17.0 ± 11.6 h (range 2–48 h).

Correlation of Tacrolimus Levels with CAI and Endoscopic Findings

The height of the individual tacrolimus level did not significantly correlate with simultaneously recorded CAI scores in the short-term efficacy analysis. Spearman's ρ was -0.27 with $p =$ nonsignificant (Fig. 3b). An influence of the severity of inflammation on the tacrolimus levels has been reported. In the small number of patients available for such a correlation, the mean tacrolimus levels in mucosal healing/mild inflammation ($n = 5$) was 5.2 ng/mL versus 3.1 ng/mL in moderate/severe inflammation ($n = 3$).

Laboratory Analyses and Adverse Events

In the vast majority of patients, no baseline CRP was available (34/43, 79%). Seven patients had a normal CRP, and 2 patients showed a slight elevation of CRP. On follow-up, 26 CRP measurements were available, with a mean CRP level of 0.94 mg/dL.

Patient 26, who had no evidence of prior kidney damage, showed an increase to 1.5 mg creatinine/dL after 35 days of treatment. Mesalazine had been well tolerated up to then and another etiology for the decline of renal function could not be found. Kidney function spontaneously normalized after suppositories were discontinued.

We observed 4 cases of hand tremor and 3 cases of headache and unspecific fatigue. Furthermore, new-onset hypertension, dry and scaly skin, nervousity, unrest, whole body pain, arthralgia and dizziness were reported (see online suppl. Table 1).

Discussion

Topical therapy in distal ulcerative colitis is employed with the aim of reducing systemic side effects. Aside from established therapy with mesalazine and steroids, different formulations and agents have been investigated in therapy-resistant cases, including tacrolimus, ciclosporin, nicotine and butyrate enemas, which yielded variable results in small open-labeled cohorts [21].

In this retrospective analysis we evaluated the clinical efficacy of tacrolimus suppositories in 43 patients with distal colitis who had remained symptomatic despite conventional systemic and topical therapy, in most cases including prednisolone or/and immunomodulators like azathioprine (Table 1; online suppl. Table 1). Also, TNF- α therapy had been tried and failed in 4 patients. The median duration of treatment was 76 days (from baseline to the last documented visit). Overall, in 60% of patients, clinical remission according to CAI was eventually reached under the treatment.

Due to the heterogeneous length of treatment in the entire cohort, the key finding of this study is observed in a clearly defined subgroup of patients ($n = 23$) in whom inflammation was confined to the rectum (proctitis) and who presented no later than 50 days after baseline for a follow-up visit. A statistically significant decrease in CAI (from 8.0 to 5.5 points) after a mean of 27.0 days was observed, and 52.3% reached remission. Rectal bleeding improved in 13 patients and did not worsen in any patient. Only 6 patients had a re-endoscopy. While 5 of these 6 patients improved, the small number does not allow for a conclusion with regard to the changes in endoscopic findings.

Topical tacrolimus has already been investigated in ulcerative proctitis in two small clinical trials [13, 16], in pouchitis [22], and most recently, in a small randomized clinical trial [17]. In a pilot study, Lawrance et al. [16] prospectively enrolled 4 patients with ulcerative proctitis (and treated them with 3 mL of ointment containing a total amount of 0.9, 1.5 or 2.4 mg of tacrolimus twice daily over an 8-week period. All patients received oral mesalazine and an immunomodulator, with 2 patients receiving additional rectal mesalazine and 2 systemic steroids. Three patients went into remission. The results of a randomized placebo-controlled double-blinded study with an ointment containing 1.5 mg of tacrolimus b.i.d. in patients with a maximum extent of inflammation of 25 cm became available in 2017 [17]. Although patient numbers were small with 11 patients in the verum arm, 73% reached clinical response and 45% achieved clinical re-

mission after 8 weeks. At week 4, which is closest to the time point assessed in our trial, the partial Mayo score had fallen from 6.3 ± 0.4 to 3.7 ± 0.96 . In terms of concomitant therapy, 72% received mesalazine and 44% azathioprine; 36 and 18% received topical or systemic glucocorticoids, respectively. Earlier investigations from a different group enrolled 12 patients with ulcerative proctitis in a phase I study [13]. Patients were treated with suppositories containing 2 mg of tacrolimus once daily for 4 weeks, and for the most part received concomitant mesalazine and/or immunosuppressive therapy with steroids or azathioprine. Ten of the 12 patients had a decrease in total Mayo score [23] from a mean of 9.4 to 3.6 points and a significant improvement in histopathologic grading and endoscopic appearance. Taken together, our study population was comparable with regard to dose and concomitant therapies, and the outcomes of our short-term efficacy analysis support the existing data of topical tacrolimus in distal ulcerative colitis.

The decision to start topical tacrolimus as well in patients with proctosigmoiditis was based on the assumption that in these patients, at least the symptoms originating from the inflamed anorectum could be ameliorated. Yet, in this subgroup of 7 patients, no clinical benefit could be found. Systemic tacrolimus levels were on average 4.1 ng/mL. Most likely, this level is below the therapeutic range required in extensive disease, and the persistent symptoms may be due to the inflamed mucosa that was not reached by the suppositories.

Our main rationale for the use of topical therapy with tacrolimus was to achieve a local effect, and to avoid double or triple immunosuppression in patients with limited disease extent. Therefore, an important aspect to this study was the blood levels of tacrolimus reached by topical administration, its relationship to clinical outcome and side effects. Rectally applied tacrolimus will bypass the liver, and thus, although extensive first-pass metabolism in the liver and intestine lead to a poor bioavailability of tacrolimus in general, it is not altogether surprising that sizable blood levels were recorded in our cohort.

Tacrolimus trough levels should be drawn 12 h after the last dose [24]. Yet, in our cohort, the mean time interval was actually 17.9 h. Nonetheless, a mean tacrolimus level of 5.5 ng/mL was observed. For comparison, Lawrance et al. [17] reported trough levels of 5.2 ± 2.2 ng/mL with b.i.d. dosing, and they also noted a considerable interpatient variability. In a phase I trial [13] with 2 mg of suppositories once daily, after 6 h tacrolimus levels were already below 2.5 ng/mL and no tacrolimus could be detected after 24 h. The lower tacrolimus levels must be at-

tributed to the dosing interval of 24 h compared to 12 h in our study, which leads to a concentration twice as high in steady state.

Lawrance et al. [17] consider levels below 5 ng/mL as subtherapeutic in ulcerative proctitis, but on the other hand, the goal in renal transplants is 4–8 ng/mL, and thus, such levels need to be considered immunologically relevant. The therapeutic range established for extensive colitis is 5–20 ng/mL [7]. Although trough levels need to be at least 10 ng/mL to reach the best clinical effectiveness, a clinical benefit was still noted with lower levels (5–10 ng/mL). Moreover, maintaining serum levels in this range for 12 weeks after induction therapy proved to be sufficient to increase the rate of clinical remission [8].

In sum, data from Lawrance et al. [17] and our own results show tacrolimus levels high enough to exert clinically relevant systemic immunosuppressive effects. This makes attributing the apparent effectiveness to a local tacrolimus action difficult. Our retrospective analysis cannot sufficiently answer the legitimate question if the clinical response is not the result of systemic immunosuppression. The lack of response in proctosigmoiditis and the missing correlation between tacrolimus levels and the CAI at follow-up nevertheless argue against a solely systemic effect.

Fortunately, our patients reported few adverse effects. Most notably, one patient showed reversible nephrotoxicity that had to be attributed to the suppositories. The remainder of adverse effects was mild and resembles the favorable profile observed by others.

Due to the nature of a retrospective, chart-based investigation, we have to acknowledge some important limitations of our analysis. Firstly, endoscopy was not routinely done at the follow-up visits, precluding an efficacy analysis in terms of mucosal healing. Secondly, we report on individual healing attempts conducted over a period of 7 years, outside the concept of a prospective clinical trial that would have guaranteed, for example, a uniform time to follow-up. Nonetheless, despite the heterogeneity of the patient population, the favorable clinical response in a fairly large number of our patients justified the present analysis. Our data extends the sparse literature that has shown that topical tacrolimus can be beneficial in refractory proctitis. Still, it cannot be excluded that part of the apparent benefit of ointments or suppositories is based on sizable serum levels and therefore “non-local.” Taken together, adding tacrolimus suppositories can be considered a safe and promising alternative if topical mesalazine and corticoid formulations as well as concomitant oral or parenteral immunosuppression have failed.

Statement of Ethics

Tacrolimus suppositories were given on a compassionate use base as an individual therapy attempt, according to legal requirements in Germany. That means that this treatment with an extemporaneous tacrolimus preparation was not given in the context of a clinical study. Therefore, no written informed consent is required in Germany. Patients were informed of the experimental status of this treatment. The possible side effects of tacrolimus therapy and the need for therapeutic drug monitoring were explained and discussed. This retrospective, pseudonymized exploration of data from diagnostic and therapy at Robert Bosch Krankenhaus was approved by the Institutional Review Board (ethics committee) of the University of Tübingen (702/2017BO2) on November 29, 2017.

Disclosure Statement

The authors declare no conflict of interest.

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Author Contributions

S.U.J. wrote the manuscript, organized and acquired data, conducted the chart review, made the statistical analysis, and treated patients. T.K. was involved in the care of the majority of the patients included in this retrospective analysis. K.H. was responsible for documentation of clinical and laboratory data. S.K. was responsible for the extemporaneous preparation of the tacrolimus suppositories. M.E. was involved in the care of the majority of the patients included in this retrospective analysis. N.M. provided clinical expertise and contributed to editing the manuscript. E.S. conceptualized the study, treated patients, and critically revised the manuscript. J.W. contributed to the conception and design of the study, treated patients, provided funding, and critically revised the manuscript.