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No Superiority of Tacrolimus Suppositories vs Beclomethasone Suppositories in a Randomized Trial of Patients With Refractory Ulcerative Proctitis

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BACKGROUND & AIMS: **Ulcerative proctitis (UP) refractory to 5-aminosalicylic acid (5-ASA) suppositories is a challenge to treat, often requiring step up to immunomodulator or biological therapy. Topical tacrolimus is effective and safe in patients with refractory UP. However, it is not clear how tacrolimus suppositories fit into in the treatment algorithm of UP.**

METHODS: **We performed a randomized controlled, double-blind study at 8 hospitals in the Netherlands and Belgium from 2014 through 2017. Eighty-five patients with refractory UP (65% women) were randomly assigned to groups given once daily tacrolimus suppositories (2 mg; n = 43) or beclomethasone (3 mg; n = 42) for 4 weeks. The primary outcome was clinical response (decrease in Mayo score of 3 or more). Secondary outcomes included clinical remission, endoscopic response and remission, adverse events and quality of life. Outcomes were compared using Fisher's exact test and Mann-Whitney U test.**

RESULTS: **Proportions of patients with clinical responses were 63% in the tacrolimus group and 59% in the beclomethasone group ($P = .812$); proportions of patients in clinical remission were 46% and 38%, respectively ($P = .638$). Proportions of patients with an endoscopic response were 68% and 60% in the tacrolimus group and in the beclomethasone group ($P = .636$); proportions in endoscopic remission rates were 30% and 13%, respectively ($P = .092$) Median increases in the inflammatory bowel disease questionnaire score were 18.0 in the tacrolimus group and 20.5 in the beclomethasone group ($P = .395$). Adverse event rates did not differ significantly between groups.**

CONCLUSIONS: **In a 4-week randomized controlled trial, tacrolimus and beclomethasone suppositories induce comparable clinical and endoscopic responses in patients with UP refractory to 5-ASA. There were no significant differences in adverse events rates. Tacrolimus and beclomethasone suppositories are therefore each safe and effective treatment options for 5-ASA refractory disease. EUDRACT 2013-001259-11; Netherlands Trial Register NL4205/NTR4416.**

Keywords: IBD; Ulcerative Colitis; Refractory Proctitis; Immune Suppression.

[a]Authors contributed equally to the study.

Abbreviations used in this paper: CRP, C-reactive protein; IBDQ, inflammatory bowel disease questionnaire; UP, ulcerative proctitis.

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Up to 40% of newly diagnosed patients with ulcerative colitis have disease limited to the rectum and are considered incident cases of ulcerative proctitis (UP).[1] Adequate therapy for UP may not only be important for symptom control and quality of life[2] but may also reduce the risk of progression of disease extent. Epidemiologic and retrospective studies have shown that in patients with UP progression of disease extent occurs in 50% of patients,[3,4] whereas in retrospective studies the risk of progression seems to be higher in patients with persistent or recurrent disease activity.[5]

The first step in the current treatment scheme for UP consists of topical mesalamine therapy, usually in suppository form. Although mesalamine has a remission induction rate of 65%,[6] maintenance of remission occurs in only 50% of patients. Current guidelines advise locally administered corticosteroids in these refractory patients,[7] although this therapy induces remission in only 46% of patients[8] and comes with risks of systemic side effects, such as suppression of the hypothalamic-pituitary-adrenal axis.[9] When UP is refractory to mesalamine and corticosteroids, step-up to systemically administered immunosuppressive drugs, such as thiopurines and biologicals, is recommended in the guidelines.[7] However, robust data regarding these drugs in UP are lacking, because patients with UP are usually excluded from clinical trials. Furthermore, the use of these systemically administered drugs might be associated with side effects and higher costs, particularly in the case of biological therapies,[10] Therefore, a proven effective topical therapy will expand the current therapeutic possibilities.

Systemically applied calcineurin inhibitors, such as ciclosporin and tacrolimus, are already established therapeutic options for steroid-refractory ulcerative colitis.[7] Several pilot studies have shown that topical tacrolimus is a safe and effective induction therapy in refractory UP, with clinical response rates up to 80%.[11,12] Recently, the results of a double-blind, randomized controlled trial were published, showing highly significant differences between rectal tacrolimus and placebo at the interim analysis.[13] The response and remission rates were similar to the pilot studies, further reinforcing the basis of this study. These studies formed the basis for this randomized controlled trial comparing tacrolimus suppositories with beclomethasone suppositories for the treatment of patients with mesalamine-refractory UP.

What You Need to Know

Background

Achieving timely remission in patients with active ulcerative proctitis may prevent disease progression. Topical tacrolimus effectively induces remission in these patients, but it has not yet been studied versus an active comparator in a randomized trial.

Findings

Treatment with tacrolimus suppositories was effective and safe in patients with 5-ASA refractory proctitis as was the use of beclomethasone suppositories. Both drugs are able to induce remission within 4 weeks after initiation.

Implications for patient care

Both tacrolimus and beclomethasone suppositories are viable treatment options for 5-ASA refractory ulcerative proctitis, and should be considered before step-up to systemic therapies.

Materials and Methods

Study Design

A randomized controlled, double-blind multicenter study was performed in 8 hospitals in Belgium and the Netherlands from 2014 to 2017. The study protocol was approved by the institutional review board and ethics committee of the Erasmus MC University Medical Center (MEC-2013-300) and by the institutional review boards and ethics committees from each participating site, and all enrolled patients provided written informed consent. Patients were treated with suppositories for 4 weeks and were randomly assigned to either beclomethasone 3 mg once daily or tacrolimus 2 mg once daily. All study procedures were conducted in accordance to the Declaration of Helsinki. This trial was registered at the Netherlands Trial Register (NL4205, NTR4416). All authors had access to the study data and reviewed and approved the final manuscript.

Patients

Patients were aged ≥18 years with endoscopically proven active UP, with disease activity up to 20 cm beyond the anal verge. Active disease was defined as either a Mayo endoscopic severity subscore[14] of at least 2, or a histologic inflammation grade (Geboes score[15]) of at least 2, regardless of total Mayo score. Additional inclusion criteria were either mesalamine-refractory UP (defined as a failure to at least the use of mesalamine suppositories of a maximum of 1 g for at least 21 days) or recurring UP (defined as a relapse within 3 months after stopping adequate local mesalamine therapy). Concomitant treatment with oral mesalamine, thiopurines, methotrexate, or biologicals was allowed if used at a stable dose for at least 12 weeks before enrollment.

Key exclusion criteria were: signs of bacterial pathogens in a stool sample (ie, *Clostridium difficile*, *Salmonella* sp, *Shigella* sp, *Yersinia* sp, *Campylobacter jejuni*), local inflammatory bowel disease therapy with mesalamine enemas within 14 days before randomization, any previous tacrolimus treatment, treatment with topical beclomethasone 12 weeks before randomization, or any other steroid use 4 weeks before randomization.

Additionally, other significant medical issues, such as poor renal function (estimated glomerular filtration rate <30 mL/min), poor liver function, leucopenia, and thrombopenia, were reasons for ineligibility. Finally, pregnant or lactating women were excluded.

Randomization and Blinding

Randomization was performed centrally by an independent clinical research bureau. Participating sites were to fax or e-mail a request for randomization, which would then be provided within 24 hours of the request. Randomization occurred per study site, using a 1:1 randomization schedule with various block sizes. To ensure blinding, the investigational drugs were custom made for this trial and were of identical appearance and weight (Tiofarma BV, Oud-Beijerland, the Netherlands). Patients, treating physicians, endoscopists, and investigators remained blinded throughout the study. Tacrolimus serum levels were centrally measured during the study and were thus unavailable to the investigators.

Study Procedures

After providing written informed consent, a screening period of up to 2 weeks before randomization started. During this period the index endoscopy had to be performed, confirming the key inclusion criterion of active proctitis as described previously. Additionally, baseline laboratory tests and stool cultures were performed to ensure eligibility. On eligibility, patients visited the study site for baseline clinical activity measurements and subsequently the study drugs were provided to the patients. Follow-up visits occurred after 2 and 4 weeks of treatment. During these visits adverse events were registered, drug accountability was performed, and blood samples were acquired. Additionally, a second clinical and endoscopic evaluation was scheduled after 4 weeks of treatment.

Outcome Measures

Clinical activity was measured using the Mayo score[14] (Supplementary Materials), which consists of 3 clinical variables and 1 endoscopic variable, all rated from 0–3. The total score therefore varies between 0 and 12, with a higher score indicating more severe disease. Additionally, histologic inflammation was graded using the Geboes score, which ranges from 0 (structural changes only) to 5 (erosions or ulcers).[15] Grades 0 and 1 are considered remission, whereas grades 2–5 are considered active disease.

The primary outcome of this study was clinical response after 4 weeks of treatment, defined as an absolute decrease in Mayo score of ≥3 points, with a relative decrease of ≥30% of the total score and at least ≥1 point decrease in the rectal bleeding subscore or an absolute rectal bleeding subscore of 0 or 1.

Secondary outcomes were combined clinical and endoscopic remission. Clinical remission was defined as a Mayo score ≤2, and endoscopic remission as no visible inflammation (ie, Mayo subscore 0). Additional secondary outcomes were endoscopic response, defined as a decrease in Mayo subscore of ≥1 and/or a decrease in extent of inflammation of ≥5 cm, changes in histologic inflammation grade, changes in C-reactive protein (CRP) and leucocyte counts, adverse events, and quality of life using the Dutch version of the inflammatory bowel disease questionnaire (IBDQ).[16]

Statistical Analyses

A power analysis was performed using Pearson chi-square test for 2 proportions. Under the assumptions of a 50% response rate for topical steroids and 80% response rate for topical tacrolimus, and with a 1-sided alpha of 0.025, >80% power could be achieved with 40 patients in each arm. To account for possible loss to follow-up, it was decided to include an additional 10% of patients, resulting in a total of 88 study patients.

For the statistical analysis the IBM SPSS Statistics for Windows, Version 24.0 (Armonk, NY) was used. Descriptive statistics were used to summarize the data. Medians with the range were calculated for continuous data and percentages were calculated for categorical data.

Apart from missing data, no adjustment for confounders was performed. Categorical data in unrelated groups were compared by the Fisher exact test, and categorical data in related groups were analyzed by McNemar test. The Mann-Whitney test was used to compare continuous data. For paired test, the paired sample Student *t* test was used. Correlations were assessed using Spearman rho. For all these results, 1- or 2-sided (as appropriate) P values $< .05$ were considered significant. Analyses were performed according to both intention to treat and per protocol principles. Because there were no meaningful differences between these analyses, the per protocol results were reported in this manuscript.

As for missing data, only missing data in the IBDQ were imputed. At baseline, imputation was only performed if up to 3 missing subscores were present and no more than 1 subscore was missing from the "systemic symptoms" or "social functioning" domains, because these domains consist of only 5 questions. In case of a missing subscore, the lowest possible score (1 point) was imputed. For the IBDQ at Week 4, missing values were carried forward from baseline where available, or similarly imputed.

Results

Patient Characteristics

Between February 2014 and November 2017, a total of 88 patients were enrolled in this study. However, 1 patient was subsequently excluded because of protocol

Table 1. Baseline Characteristics

	Tacrolimus (n = 43)	Beclomethasone (n = 42)
Female, n (%)	27 (62.8)	28 (66.7)
Age, *y* (median, range)	39.6 (18.3–75.1)	43.2 (18.6–76.4)
Disease duration, *y* (median, range)	5.8 (0.3–36.7)	7.4 (0.3–47.8)
Concomitant medication use, n (%)		
Oral mesalamine	15 (34.9)	24 (57.1)
Immunomodulators	10 (23.3)	6 (14.3)
Biologicals (anti-TNF n = 8; vedolizumab n = 1)	4 (9.3)	5 (11.9)
Smoking status, n (%)		
Current	4 (9.3)	5 (11.9)
Former	17 (39.5)	19 (45.2)
Never smoked	21 (48.8)	17 (40.5)
Total Mayo score (median, range)	7 (3–12)	7 (3–12)
Mayo endoscopic subscore, n (%)		
0	0 (0)	0 (0)
1	4 (9.3)	2 (4.8)
2	26 (60.5)	29 (69.0)
3	13 (30.2)	11 (26.2)
Disease extent, *cm* (median, range)	10 (2–20)	13 (1–20)
C-reactive protein (median, range)	2.5 (0.3–248.0)	2.0 (0.0–44.0)
IBDQ (median, range)	146 (91–211)	145 (87–210)

IBDQ, inflammatory bowel disease questionnaire; TNF, tumor necrosis factor.

violations (on monitoring, concomitant use of corticosteroids was discovered). Additionally, 2 patients were excluded because of low Mayo scores at baseline, resulting in 85 patients for per protocol analysis (Supplementary Figure 1). In total, 43 patients received tacrolimus and 42 received beclomethasone (Table 1). Fifty-seven patients were female (64.7%), median age was 42.3 years (range, 18.3–76.4 years), and median disease duration was 7.0 years (range, 0.25–47.83 years). Concomitant medication included oral mesalamine in 39 patients (45.9%), immunomodulators in 16 patients (18.8%), and biologicals in 9 patients (10.6%). The available data are also summarized in Supplementary Figure 1. The study ended after the last follow-up visit from the last patient, in December 2017.

Clinical Response

In the tacrolimus group, the median baseline Mayo score was 7 (range, 3–12); in the beclomethasone group the median baseline Mayo score was also 7 (range, 3–12).

After 4 weeks of treatment, in the tacrolimus group 22 out of 35 patients (62.9%) achieved the primary outcome of clinical response, compared with 22 out of 37 (59.5%) patients in the beclomethasone group, a nonsignificant difference ($P = .812$) (Figure 1*A*).

At the end of the study, in the tacrolimus group the median Mayo score decreased to 3 (range, 0–12; median change, -3.0 points) and in the beclomethasone to 3 (range, 0–11; median change, -3.5 points; $P = .638$).

The secondary outcome of clinical remission was achieved in 16 of 35 patients (45.7%) in the tacrolimus group and 15 of 39 patients (38.5%) in the beclomethasone group, which was not a statistically significant difference ($P = .638$) (Figure 1*B*).

Endoscopic Response

At baseline, 39 patients (90.7%) in the tacrolimus group and 40 patients (95.3%) in the beclomethasone group had moderate or severe disease activity. The remaining patients had mild endoscopic disease activity, but were included because of severe histologic inflammation. Median baseline disease extent was 10 cm (2–20) in the tacrolimus group and 12 cm (1–20) in the beclomethasone group.

At the end of the study, endoscopic response was achieved in 25 of 37 patients (67.6%) in the tacrolimus group and 24 of 40 (60.0%) patients in the beclomethasone. This difference was not statistically significant ($P = .636$) (Figure 1*C*).

The difference in endoscopic remission rate was not significantly different ($P = .092$), with remission occurring in 11 of 37 patients (29.7%) in the tacrolimus group and in 5 of 40 patients (12.5%) in the beclomethasone group (Figure 1*D*). The change in length of inflamed colon was also not significantly different between both groups ($P = .139$).

Histologic Response

The baseline biopsies showed a median inflammation grade of 3 (range, 1–5) in the tacrolimus group and 4 (range, 0–5) in the beclomethasone group. At the end of the study, the median inflammation grade decreased to 2 (range, 0–5) for both groups. Histologic remission was seen in 11 tacrolimus patients (40.7%) and 8 beclomethasone patients (27.6%), which was not a statistically significant difference ($P = .299$).

Biochemical Parameters

At the start of the study, the median CRP levels in the tacrolimus and beclomethasone groups, respectively, were 2.5 (range, 0.3–248.0) and 2.0 (range, 0.0–44). At the end of the study the medians were, respectively, 2.0 (range, 0.3–31.0) and 1.6 (range, 0.0–17.0), which was not significantly different ($P = .554$).

Median leucocyte counts at baseline in the tacrolimus and beclomethasone groups, respectively, were 7.2 (range, 2.7–13.5) and 6.9 (range, 3.0–10.2). After 4 weeks, the medians, respectively, changed to 7.5 (range,

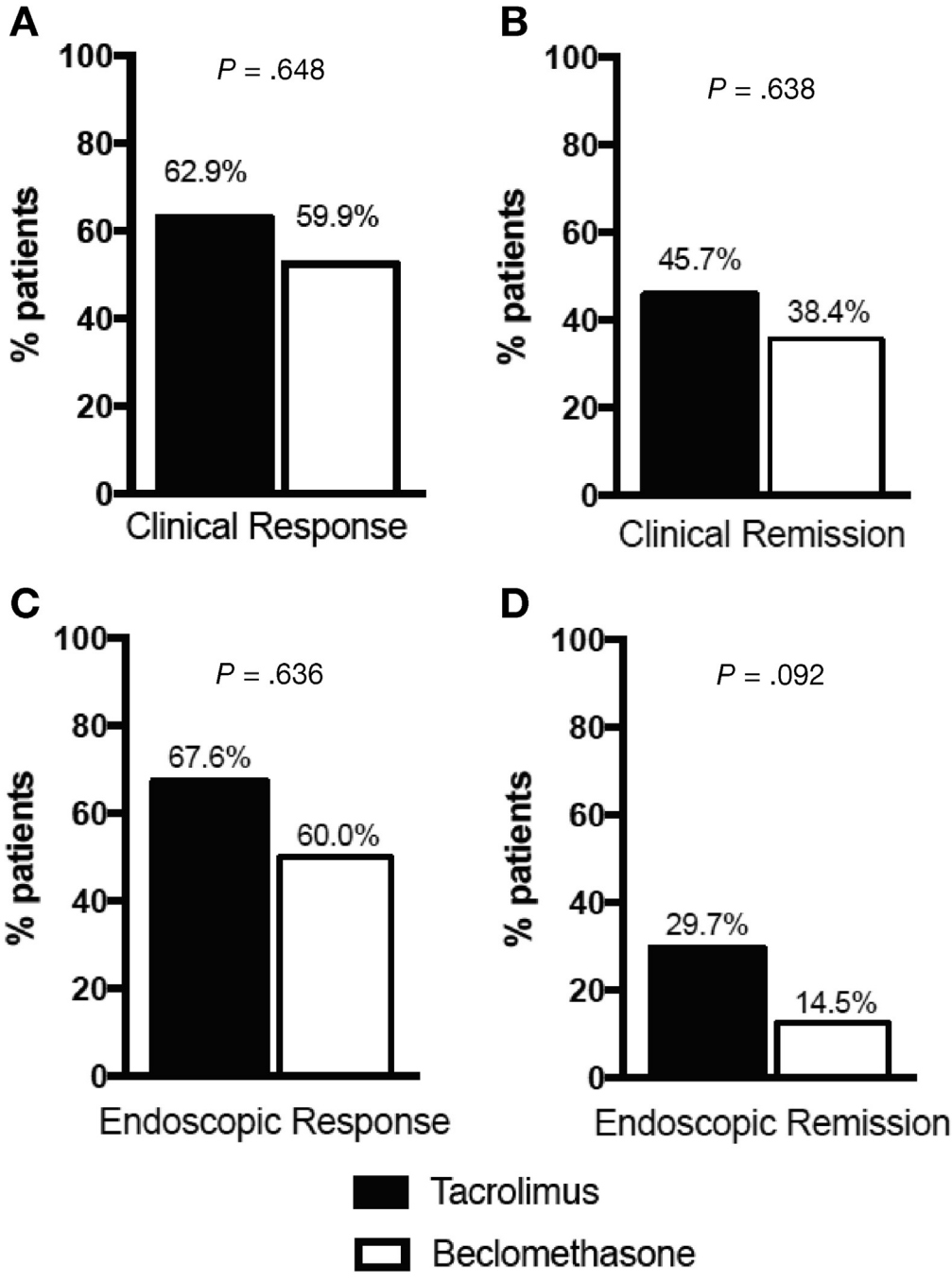

Figure 1. Main study results. (*A*) Proportion of patients with a clinical response. (*B*) Proportion of patients with clinical remission. (*C*) Proportion of patients with endoscopic response. (*D*) Proportion of patients with endoscopic remission.

2.8–13.4) and 7.3 (range, 3.0–11.7), which was also not significantly different ($P = .476$).

Quality of Life

At the start of the study, the median IBDQ scores for the tacrolimus and beclomethasone groups were 147 (range, 91–211) and 145 (range, 87–210), respectively. After treatment, the median increases in IBDQ scores were 18 (range, -18 to 93) and 20.5 (range, -13 to 71), leading to median IBDQ scores of 175 (range, 57–214) and 165 (range, 80–214), for the tacrolimus and beclomethasone groups, respectively, which was not significantly different ($P = .733$).

Additionally, changes in the IBDQ were significantly correlated with changes in the total Mayo score ($R^2 = 0.151$; $P < .001$), endoscopic severity ($R^2 = 0.104$; $P = .007$), and endoscopic disease extent ($R^2 = 0.164$; $P < .001$), but not to changes in CRP, leucocyte count, or histologic inflammation grade ($P = .766$, .575, and, .108, respectively).

Tacrolimus Levels and Adverse Events

Sixty-two tacrolimus levels were available from 37 of tacrolimus-treated patients. The mean tacrolimus level was 4.2 ± 3.4 μg/L (range, 0.0–13.6) at Week 2 and 2.7 ± 2.8 μg/L (range, 0.0–12.8) at Week 4. Although

tacrolimus levels did not represent trough levels, 46 of the levels (74.2%) were undetectable or subtherapeutic (<5 μg/L). The remainder were within the low therapeutic range (5–20 μg/L). There was no correlation between tacrolimus levels and clinical and endoscopic outcome.

Forty-eight adverse events were reported that were judged to be at least possibly related to the study drugs (Table 2). Eighteen adverse events occurred in 14 patients (33.3%) of the beclomethasone group, whereas 29 events were seen in 21 patients (48.8%) in the tacrolimus group, which was not significantly different ($P = .188$). Within the tacrolimus group, serum tacrolimus levels were not associated with the occurrence of adverse events ($P = .611$).

No serious adverse events were reported; nevertheless, 1 patient discontinued the study because of an adverse event possibly related to the study drug. Specifically, this patient was randomized to tacrolimus and developed a clostridium infection after 2 weeks.

Discussion

In this randomized controlled trial comparing tacrolimus suppositories with beclomethasone suppositories as induction therapy for mesalamine-refractory UP, no superiority of tacrolimus was shown over beclomethasone. After 4 weeks of treatment, clinical and endoscopic response (62.9% vs 59.9% and 67.6% vs 60%) and clinical and endoscopic remission (45.7% vs 38.5% and 29.7% vs 14.5%) were equal.

Thus, both study drugs managed to induce clinical and endoscopic response in most patients. Furthermore, both treatments resulted in improvements in histologic inflammation and quality of life. Adverse event rates were similar in both groups.

Table 2. Adverse Events

	Tacrolimus	Beclomethasone	Both
Abdominal pain/worsening of symptoms	3	3	6
Arthritis	0	1	1
Perianal effects (burning/itching/hemorrhoid/fissure)	9	3	12
Clostridium infection	1	0	1
Cytomegalovirus	1	0	1
Nausea/dizziness/weakness	2	1	3
Skin (flushing, erythema, itchiness)	3	4	7
Flatulence	5	2	7
Headache	2	1	3
Rectal urgency	1	0	1
Night sweats	1	0	1
Palpitations	1	1	2
Upper airway infection	0	2	2
Total	29	18	47

To our knowledge, this is the first head-to-head controlled trial examining the effects of tacrolimus and beclomethasone suppositories in patients with ulcerative colitis. The clinical response and remission rates of 60% and 40%, respectively, are comparable with the rates of other topical corticosteroids,[9] although some of these studies examined a combination of patients with UP and patients with left-sided disease.[17,18]

Topical tacrolimus has been investigated in only few studies. When comparing our study with the randomized controlled trial of Lawrance et al,[13] certain differences in the reported outcomes warrant consideration. In their 8-week trial comparing rectal tacrolimus with placebo in patients with therapy-refractory UP, they observed a clinical response rate of 73%. Our 4-week study finds a somewhat lower clinical response rate of 62.9% in the tacrolimus group, and finds no statistically significant difference when compared with another active drug. The clinical remission rates are more similar, with Lawrance et al[13] reporting 45% and our study finding 45.7%. However, mucosal healing (defined in their study as an endoscopic Mayo score of 0 or 1) was reported in 73% of their patients, whereas using this criterium it was seen in only 58% of tacrolimus-treated patients in our study.

Possible explanations for the differences in clinical response rate and mucosal healing are the differences in baseline characteristics between the patients of these 2 studies. Specifically, we had a greater proportion of female patients, had more current smokers, and patients used more concomitant immunosuppressive and biological drugs. This may reflect more refractory disease in the patients enrolled in our trial, because current guidelines recommend the use of these agents only for refractory UP.

A notable difference between our study and Lawrance et al[13] is a shorter treatment duration (4 weeks compared with 8 weeks). Additionally, Lawrance et al[13] used a different treatment regimen, consisting of twice-daily rectally applied ointment with a total daily dose of 3 mg of tacrolimus. In our study we decided to use once-daily suppositories containing only 2 mg of tacrolimus, based on our previous phase 1 study.[11] In that study, low but measurable serum levels of tacrolimus were found with the use of once-daily 2-mg tacrolimus suppositories. Thus, to prevent systemic exposure to higher tacrolimus levels, the same dose was used in our current study. Concerning serum tacrolimus levels, Lawrance et al[13] also find measurable serum levels, and similar to our study, they find no correlation between serum levels and efficacy or adverse events. Of note, the tacrolimus serum levels in our study do not represent true trough levels; nevertheless, most tacrolimus levels were subtherapeutic. Therefore, the true tacrolimus trough levels would probably be even lower than currently measured. These differences in treatment duration, regimen, and patient characteristics may partly explain the differences seen between these studies in the reported clinical response and mucosal healing rates.

No serious adverse events were reported during the study period, and only a single adverse event, possibly related to the study drugs, caused patients to discontinue the study. Nevertheless, mild adverse events, particularly perianal itching and burning, were frequently reported, more often in patients treated with tacrolimus.

Systemically applied calcineurin inhibitors are already approved for use in steroid-refractory acute severe ulcerative colitis.[7] The optimal position of topical tacrolimus within the step-up scheme for treatment of UP is currently unclear. Topical mesalamine is the first-line therapy for patients with UP because of the robustly proven efficacy and side effect profile. Given the results of our study and of previous studies, using either topical tacrolimus or topical corticosteroids as the second step in UP therapy seems safe and viable options, and both therapies should be considered before step-up to immunomodulators or biologicals.

Despite the randomized controlled and triple blinded design, there are limitations to this study. First, patients were mostly enrolled in tertiary centers. This may have resulted in the inclusion of patients with more severe disease than seen in general clinical practice.

Second, the inclusion criteria of our study were primarily based on the presence of endoscopic disease activity. Although this was intended to ensure objective disease activity at the start of the study, some of the included patients had surprisingly low Mayo scores at inclusion. These low baseline scores may have reduced the number of patients who could achieve the predefined 3-point decrease in the Mayo score to achieve the primary outcome of clinical response, thus resulting in a study with less power than initially designed.

Third, this study only examined an induction treatment period of 4 weeks, thus the value of a longer induction period or (intermittent) maintenance therapy remains unclear. Initially, a study period of 8 weeks was considered, but because of concerns regarding side effects related to long-term rectal corticosteroid therapy a 4-week study period was chosen.

In summary, among mesalamine-refractory patients with UP, the use 4 weeks of tacrolimus suppositories was not superior to treatment with beclomethasone suppositories. Furthermore, no significant differences between tacrolimus and beclomethasone were seen regarding the secondary outcomes and both treatments seem to be safe. Therefore, both tacrolimus suppositories and beclomethasone suppositories seem to be viable treatment options for mesalamine-refractory disease. Topical treatment with tacrolimus should be considered before step-up to thiopurines or biologicals in mesalamine-refractory UP.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.09.049.

References

1. van den Heuvel TRA, Jeuring SFG, Zeegers MP, et al. A 20-year temporal change analysis in incidence, presenting phenotype and mortality, in the Dutch IBDSL Cohort: can diagnostic factors explain the increase in IBD incidence? J Crohns Colitis 2017; 11:1169–1179.
2. Argyriou K, Kapsoritakis A, Oikonomou K, et al. Disability in patients with inflammatory bowel disease: correlations with quality of life and patient's characteristics. Can J Gastroenterol Hepatol 2017;2017:11.
3. Meucci G, Vecchi M, Astegiano M, et al. The natural history of ulcerative proctitis: a multicenter, retrospective study. Gruppo di Studio per le Malattie Infiammatorie Intestinali (GSMII). Am J Gastroenterol 2000;95:469–473.
4. Hochart A, Gower-Rousseau C, Sarter H, et al. Ulcerative proctitis is a frequent location of paediatric-onset UC and not a minor disease: a population-based study. Gut 2017; 66:1912–1917.
5. Kim B, Park SJ, Hong SP, et al. Proximal disease extension and related predicting factors in ulcerative proctitis. Scand J Gastroenterol 2014;49:177–183.
6. Lie M, Kanis S, Hansen B, et al. Drug therapies for ulcerative proctitis: systematic review and meta-analysis. Inflamm Bowel Dis 2014;20:2157–2178.
7. Harbord M, Eliakim R, Bettenworth D, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: current management. J Crohns Colitis 2017;11:769–784.
8. Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. Gut 1997; 40:775–781.
9. Sandborn WJ, Boswort B, Zakko S, et al. Budesonide foam induces remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis. Gastroenterology 2015;148:740–750.
10. van der valk ME, Mangen MJ, Severs M, et al. Evolution of costs of inflammatory bowel disease over two years of follow-up. PLoS One 2016;11:e0142481.
11. van Dieren JM, Van Bodegraven AA, Kuipers EJ, et al. Local application of tacrolimus in distal colitis: feasible and safe. Inflamm Bowel Dis 2009;15:193–198.
12. Lawrance IC, Copeland TS. Rectal tacrolimus in the treatment of resistant ulcerative proctitis. Aliment Pharmacol Ther 2008; 28:1214–1220.
13. Lawrance IC, Baird A, Lightower D, et al. Efficacy of rectal tacrolimus for induction therapy in patients with resistant ulcerative proctitis. Clin Gastroenterol Hepatol 2017; 15:1248–1255.
14. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987; 317:1625–1629.
15. Geboes K, Riddell R, Ost A, et al. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut 2000;47:404–409.
16. Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology 1989;96:804–810.

17. Lindgren S, Löfberg R, Bergholm L, et al. Effect of budesonide enema on remission and relapse rate in distal ulcerative colitis and proctitis. Scand J Gastroenterol 2002; 37:705–710.
18. Gross V, Bar-Meir S, Lavy A, et al. Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. Aliment Pharmacol Ther 2006;15(23):303–312.

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Conflicts of interest
The authors disclose no conflicts.

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Supplementary Material: Mayo Score

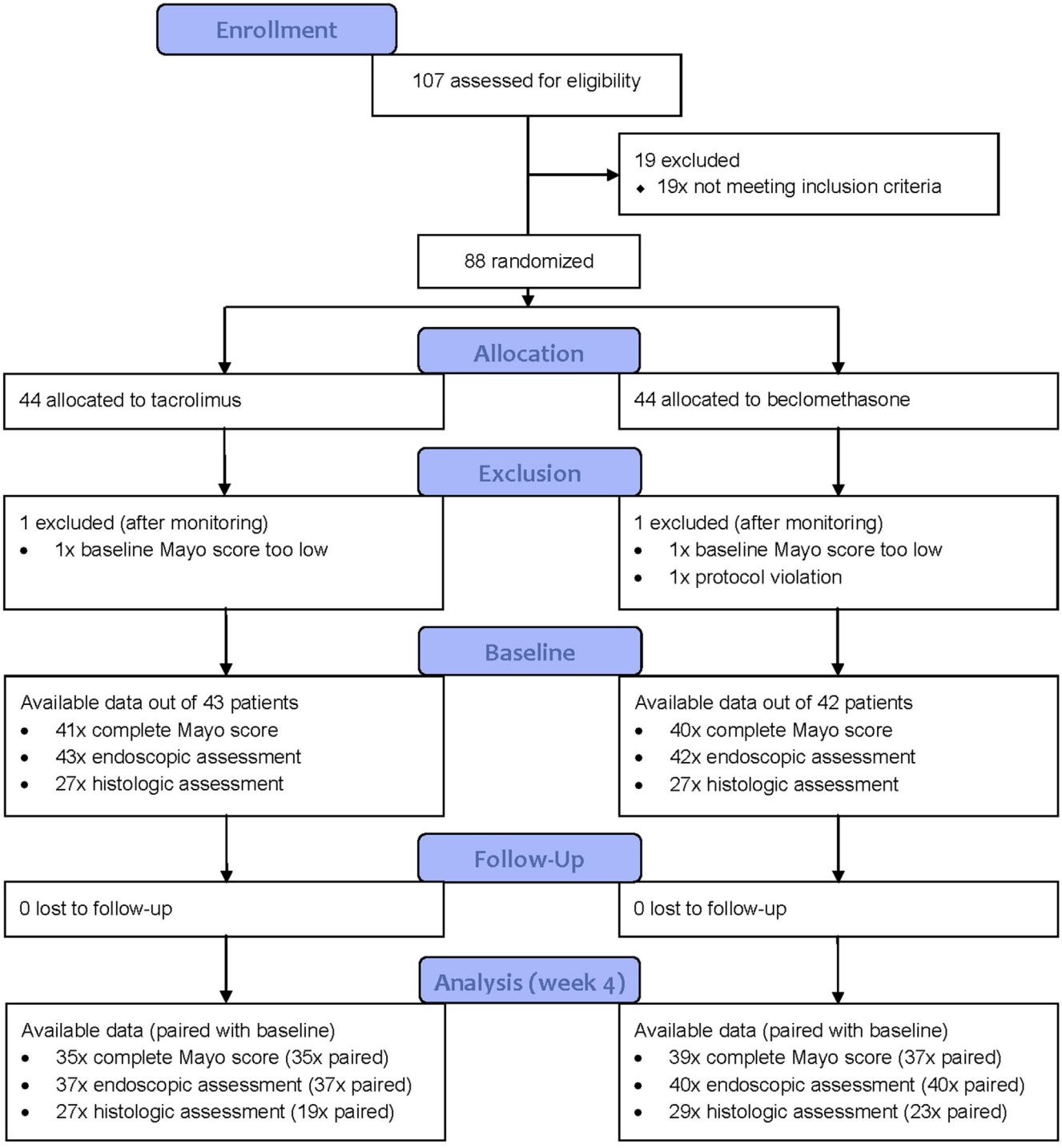
Stool frequency[a]
- 0 = normal number of stools for this patient
- 1 = 1–2 stools more than normal
- 2 = 3–4 stools more than normal
- 3 = 5 or more stools than normal

Rectal bleeding[b]
- 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

Findings of flexible proctosigmoidoscopy
- 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[c]
- 0 = normal
- 1 = mild disease
- 2 = moderate disease
- 3 = severe disease

Adapted from reference 14.
[a]Each patient served as his or her own control subject to establish the degree of abnormality of the stool frequency.
[b]The daily bleeding score represented the most severe bleeding of the day.
[c]The physician's global assessment acknowledged the other criteria; the patient's daily record of abdominal discomfort and general sense of well-being; and other observations, such as physical findings and the patient's performance status.



Supplementary Figure 1. CONSORT flow diagram of screened and included patients, and available study data per timepoint.