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Short-term efficacy of tacrolimus in steroid-refractory ulcerative colitis – experience in 130 patients

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This article is dedicated to Jörg Emmrich.

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SUMMARY

Background
Steroid-refractory ulcerative colitis (UC) remains a challenging condition warranting surgery upon failure of pharmacological treatment. Calcineurin inhibitors or infliximab are alternatives in this situation. Data on the efficacy and safety of tacrolimus in this setting are limited.

Aim
To study the short-term efficacy and safety of tacrolimus in moderate-to-severe steroid-refractory UC. The role of thiopurines in this situation and predictors of colectomy were evaluated.

Methods
In three centers, all charts from tacrolimus-treated patients with steroid-refractory UC were reviewed. Efficacy was assessed by colectomy-free survival and clinical remission at 3 months.

Results
We identified 130 patients with pancolitis in 75 (59%), left-sided disease in 35 (27%) and proctitis in 18 patients (14%) (disease localisation not obtainable in two patients). The median age was 40 (range: 18–81). Clinical activity according to the median Lichtiger score decreased from 13 (range: 4–17) at baseline to 3 (0–14) at week 12. Eighteen patients underwent colectomy within the first 3 months of treatment with tacrolimus (14%). Clinical remission was achieved in 94 patients (72%) in this period. Thiopurines given in parallel to tacrolimus tended to limit colectomy and significantly increased remission ($P = 0.002$) in the short-term. No other predictors of colectomy or remission were identified. Side effects were noticed in 53% of patients and no severe events occurred.

Conclusion
This large survey confirms the efficacy and safety of tacrolimus in patients with steroid-refractory ulcerative colitis.

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INTRODUCTION

The introduction of steroids for the treatment of ulcerative colitis (UC) several decades ago has changed the outcome of patients dramatically.[1] Mortality and morbidity declined significantly, whereas life expectancy and quality of life improved. Nevertheless, a relevant proportion of patients still have to face surgery. To date, about 20–30% of patients receiving steroids will have to undergo colectomy within their first year of disease[2, 3] with higher numbers for extensive and active disease.[4]

The pharmacological repertoire for the steroid-refractory situation is limited. Present guidelines recommend the use of calcineurin inhibitors, i.e. ciclosporin or tacrolimus as well as infliximab and adalimumab, chimeric TNF-α blockers. Among these, only the latter have gained approval by the FDA and EMA in UC.

The question arises whether infliximab or calcineurin inhibitors should be chosen as first line treatment. Both drugs have recently been compared in a retrospective analysis. At 3 months, colectomy-free survival was 67% in the infliximab cohort vs. 93% in the ciclosporin cohort ($P = 0.002$).[5] In contrast, a controlled trial by Laharie *et al.* observed no difference in the efficacy of ciclosporin compared to infliximab in steroid-refractory patients. With regards to the primary endpoint treatment failure at 98 days, 60% failed on ciclosporin and 54% in the infliximab arm. Immediate response was identical and the colectomy rate was 18% and 21%, respectively, within 3 months.[6] Infliximab has a long biological half-life and can be detected in the serum for at least 8 weeks after application.[7] Thus, patients who fail to respond to infliximab might theoretically be at risk of overt immunosuppression perioperatively, whereas calcineurin inhibitors are rapidly eliminated.

Some open-label trials report on the efficacy and safety of tacrolimus, as a rapid acting option in UC.[8–11] Short-term efficacy has been stated to be in the range of 70–80%. Two placebo-controlled trials confirmed these results, although the sample size of steroid-refractory patients was low.[12, 13] Thus, more evidence is mandatory, although the efficacy seems to be in the same range as reported for ciclosporin. Typical ciclosporin related side effects, such as gingival hyperplasia and hypertrichosis, do not occur with tacrolimus.

In Crohn's disease, the SONIC trial suggested a benefit of a combined therapy with infliximab and azathioprine over infliximab alone already in the first months of treatment.[14] Accordingly, so far unpublished results from the SUCCESS trial indicate a better outcome at week 16 for concomitant infliximab and azathioprine use in UC patients with steroid failure.[15] Thus, slow acting thiopurines enhance the efficacy of rapid acting drugs in the short term. Thiopurines have been shown to be effective in the long-term in patients initially receiving tacrolimus or ciclosporin for severe UC.[16, 17] Data on possible prevention of early colectomy in severely affected patients are lacking.

Outcome after proctocolectomy and ileoanal pouch repair is fairly good, but patients are at risk for pouch-related morbidity and pouch failure. Thus, an improvement of the therapeutic strategies in the steroid-refractory situation is important. In a large cohort of steroid-refractory patients, we aimed to provide further evidence for the short-term efficacy and safety of tacrolimus. In particular, the impacts of coadministered thiopurines on the need for colectomy as well as predictors of tacrolimus failure were evaluated.

MATERIALS AND METHODS

This three centre retrospective analysis was performed at the Department of Internal Medicine I, University of Schleswig-Holstein, Campus Lübeck, the Department of Internal Medicine II, University Rostock and the Department of Gastroenterology, Hepatology and Endocrinology, Robert-Bosch-Hospital, Stuttgart, Germany.

Patients

One hundred and thirty adult patients with moderate to severely active steroid-refractory UC and tacrolimus treatment were identified. Their charts were retrospectively reviewed for a period of 3 months after initiation of tacrolimus. Diagnosis of UC was based on established standard endoscopic, histological and radiological criteria. An infectious origin had been ruled out by stool cultures, serology, immunohistochemistry and/or blood CMV-DNA analysis. Tacrolimus was started orally at a dose of 0.1 mg/kg per day (b.d.). In a minority of patients, it was administered intravenously at 0.01 mg/kg with a fast switch to the oral route. The daily dose was subsequently adjusted according to clinical requirements under the discretion of the treating physician. All patients had a steroid-refractory course of UC defined as unresponsiveness to 7 days of prednisolone at a daily dose of 1 mg/kg bodyweight or at least 30 mg/day. Steroids were tapered individually. In a few patients, who experienced a steroid-refractory flare in their history, tacrolimus was started without the addition of steroids. In some cases, prednisolone was tapered under the threshold of 30 mg/day already at the beginning of ta-

crolimus due to side effects. Pre-existing treatment with azathioprine (2–2.5 mg/kg/day) or mercaptopurine (1–1.5 mg/kg/day) was continued. Purine analogue naïve patients or patients with effective treatment in the past were amenable to receive thiopurines *de-novo* in addition to tacrolimus. Treatment was started in parallel already at the very beginning. Methotrexate (15–25 mg/week) was used in four patients with known intolerance or ineffectiveness of purine analogues in the past.

Analysis of efficacy

Efficacy was primarily assessed by the colectomy free survival after 12 weeks of treatment. Disease activity was calculated at baseline and week 12 using the Lichtiger index.[18] Clinical remission was consistent with a score of ≤ 3. Lacking data precluded a complete calculation of the Lichtiger score in some patients. The patients were regarded as 'not obtained' in the particular analysis and highlighted accordingly. In these patients, clinical remission was assumed if stool frequency was normal and rectal bleeding absent.

Statistics

Data are reported as median and range. Colectomy free survival is illustrated in Kaplan–Meier plots. Differences between groups were tested using log-rank test (Cox–Mantel), Pearson Chi-Squared test, and Fisher's exact test. Selected data are presented in summarised tabulated form.

RESULTS

Patient characteristics and treatment

Baseline demographics and disease characteristics of the 130 patients included in our analysis are presented in detail in Table 1. In 70 males and 60 females, UC was diagnosed at a median age of 27.5 years (range: 10–77) and tacrolimus was started at a median age of 40 years (range: 18–81). Median time from diagnosis to start of tacrolimus was 4 years (range: 0.1–33). The median Lichtiger score at baseline was 13 (range: 4–17). Disease distribution was as follows: pancolitis (E3) in 75 (59%), left-sided (E2) in 35 (27%) and proctitis (E1) in 18 patients (14%). In two patients, the extent of colonic inflammation could not be determined.

Tacrolimus was administered orally in 118 patients (91%) and intravenously in 10 patients (8%). In two patients, data were insufficient to assess the initial route of application or the dose of tacrolimus. The median daily oral dose was 8 mg (range: 3–21) according to 0.12 mg (0.05–0.46) per kg bodyweight. In case of intravenous administration the total daily dose was 1.1 mg (range: 0.56–1.8). Tacrolimus whole blood levels within the first 4 weeks of treatment were measured in 78 patients (60%), the median level was 6.85 μg/L (range: 1.7–25). Subsequent whole blood levels were obtained infrequently. One hundred-fifteen patients (88%) concomitantly received corticosteroids with a median daily dose of 50 mg prednisolone (range: 15–160 mg/d). Seventy-five patients (58%) were given additional immunosuppression with azathioprine (median dose 150 mg, range: 75–250), five patients (4%) received mercaptopurine (median dose 75 mg, range: 50–100) and four patients (3%) methotrexate (median dose 25 mg, range: 15–25) in parallel. CRP-levels were obtained in 117 of 130 patients (90%) at baseline. The median CRP-level was 4.3 mg/L (range: 0–256).

Efficacy of tacrolimus

Overall eighteen of 130 patients (14%) had to undergo colectomy within the 3 months period after initiating tacrolimus treatment. Of these 18 patients, 11 underwent surgery within the first 4 weeks.

The Lichtiger index was obtainable in 126, 109, and 80 of 130 patients at baseline, week 4 and week 12 respectively (Figure 1). At baseline, the median Lichtiger score was 13 (range: 4–17) and decreased to 3 (range: 1–16 and 0–14) at weeks 4 and 12. Overall clinical remission, based on a Lichtiger score ≤ 3 or subject to clinical judgment with normal stool frequency and absence of blood, was achieved in 94 patients (72%) after 3 months. Patients who were in remission at week 4 were highly likely to stay in remission at week 12. According to the Lichtiger score available, indicating remission with ≤ 3, 39/45 patients at week 4 maintained remission up to week 12 (87%). Overall remission was achieved at week 4 in 57 patients and was maintained up to week 12 in 48 of these patients (84%). Thus, a substantial surplus amount of patients achieved remission later than week 4. Remission at week 12 was observed in 82% of patients with a Lichtiger score at baseline ≥ 12 ($n = 89$) in contrast to 57% with a score <12 ($n = 37$) (Chi-squared test $P = 0.003$). At week 12, remission rates were about similar in patients with elevated CRP-levels at baseline ($n = 56$; remission in 73%) compared with those with a normal CRP ($n = 61$; remission in 72%) (Chi-squared test $P = 0.867$).

Table 1 | Patient's baseline characteristics

n (%)	Overall 130 (100%)	PA >3 months*,† 28 (22%)	PA de-novo*,† 47 (36%)	no PA 46 (35%)
Age at tacrolimus initiation [median (range)]	40 (18–81)	40.5 (18–68)	33 (18–81)	44 (21–79)
Disease duration prior tacrolimus [median (range)]	4 years (0.1–33)	5 (0.5–22)	3 (0–21)	4 (0.5–33)
Gender [*n* (%)]				
Men	70 (53%)	17	29	21
Women	60 (47%)	11	18	25
Bodyweight in kg [median (range)]	65 (41–148)	70.5 (48–105)	65 (41–99)	65 (46–148)
Disease distribution [*n*/%)]‡				
Pancolitis, E3	75 (59%)	15 (54%)	30 (64%)	25 (55%)
Left–sided, E2	35 (27%)	10 (36%)	10 (21%)	13 (28%)
Proctitis, E1	18 (14%)	3 (10%)	7 (15%)	6 (13%)
Lichtiger at baseline [median (range)]	13 (4–17)	12 (8–17)	12 (5–17)	14 (6–17)
Steroids in mg/d at baseline [median (range)]	50 (15–160)	60 (20–150)	60 (15–150)	50 (15–160)
n (%)	115 (88%)	23 (82%)	47 (100%)	41 (89%)
Tacrolimus dose in mg/d initial [median (range)]‡				
po	8 (3–21)	8 (4–16)	8 (4–16)	8 (2–21)
n (%)	118 (91%)	26	43	40
iv	1.1 (0.56–1.8)	1.5 (1.2–1.8)	0.9 (0.6–1.2)	1.0 (0.56–1.0)
n (%)	10 (8%)	2	4	4
Tacrolimus dose in mg/kg bodyweight [median (range)]	0.12 (0.05–0.46)	0.13 (0.08–0.26)	0.1 (0.05–0.21)	0.12 (0.05–0.46)
Concomitant immunosuppression				
Azathioprine in mg/d [median (range)]	150 (75–250)	150 (75–250)	150 (100–200)	–
n (%)	75 (58%)	27 (96%)	44 (86%)	–
Mercaptopurine in mg/d [median (range)]	75 (50–100)	100 (100–100)	50 (50–75)	–
n (%)	5 (4%)	1 (4%)	3 (6%)	–
Methotrexate in mg/d [median (range)]	25 (15–25)	–	–	–
n (%)	4 (3%)	–	–	–

Baseline characteristics of the complete cohort and the three groups (PA longer than 3 months prior to tacrolimus, PA de-novo to tacrolimus, no PA). An assignment to one of these groups was not feasible in five patients based on nonobtainable data and four patients were treated with methotrexate in parallel to tacrolimus. Disease distribution and initial tacrolimus dose was not obtainable in two patients respectively (PA, purine analogues; bw, bodyweight; po, per os; iv, intravenous).

* Assignment in one of the PA group was not obtainable in five patients (four patients with azathioprine and one patient with mercaptopurine).

† Methotrexate in four patients.

‡ Not obtainable in two patients.

Efficacy of concomitant immunosuppression with purine analogues

The impact of additional thiopurines was analysed by defining three subgroups. The first group consisted of 28 patients (22%) who received purine analogues for at least 3 months prior to tacrolimus [27 patients on azathioprine (median dose 150 mg/d, range 75–250) and one patient on mercaptopurine (100 mg/day)]. The second group contained of 47 patients (36%) in whom purine analogues were started in parallel to tacrolimus [44 patients on azathioprine (median 150 mg/day, range: 100–200) and three patients on mercaptopurine (median 50 mg/day, range 50–75)]. The third group consisted of 46 patients (35%) who were treated without concomitant thiopurines. In five patients (4%), the timing of thiopurine initiation remains unclear and they were excluded from this analysis. In four patients, methotrexate was started in parallel to tacrolimus (25 mg/day, range: 15–25 mg).

Demographic characteristics, the disease course with respect to duration, extent and severity, steroid dosing as well as the baseline CRP-levels did not differ significantly between the three groups. Median trough levels of tacrolimus were comparable. The patients initially receiving iv administration of tacrolimus were equally distributed. At baseline, the median Lichtiger score was 12 (group 1), 12

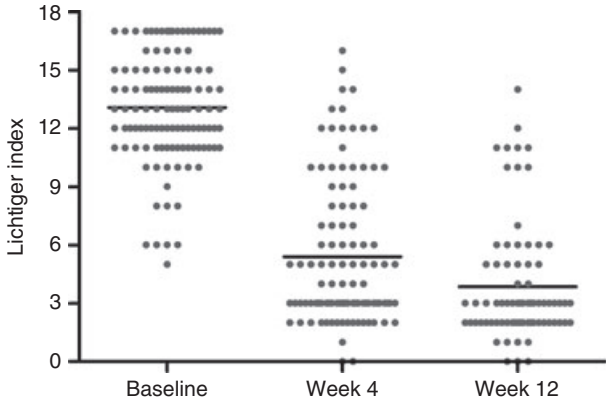

Figure 1 | Lichtiger Index of the complete cohort at week 0 (126 of 130 patients), week 4 (109/119) and week 12 (80/112). Every patient is shown as a single dot and median of the cohort as a line. Data were not obtainable in 4, 10 and 32 patients at week 0, 4 and 12. Ten and 18 patients underwent colectomy at week 4 and 12.

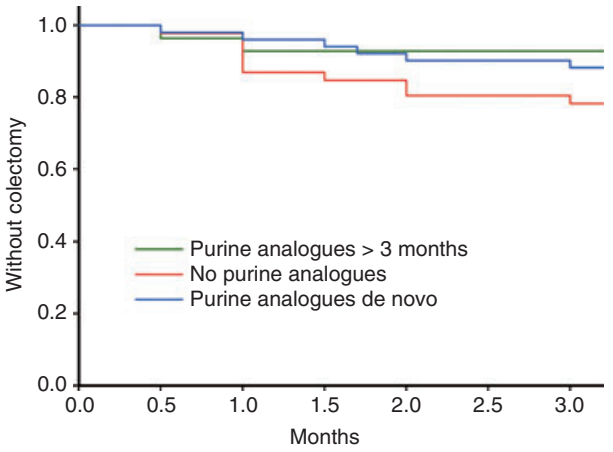

Figure 2 | Kaplan–Meier analysis of colectomy-free survival. Kaplan–Meier curve of colectomy-free survival separated in the subgroups (PA longer than 3 months prior to tacrolimus, PA de-novo to tacrolimus, no PA) within the first 3 months of tacrolimus treatment. PA, purine analogues.

(group 2) and 14 (group 3). Detailed information is given in Table 1.

Colectomy within the observed 3 months was necessary in 2 of 28 patients (7%) in the first, in 6 of 47 patients (13%) in the second and in 10 of 46 patients (22%) in the third group (log rank test $P = 0.183$; Figure 2). Clinical remission occurred in 86% (24/28 patients), 85% (40/47) and 61% (28/46) of the patients at week 12 (Chi-squared test $P = 0.009$). We pooled the first two groups to compare colectomy and remission rates between patients concomitantly treated with thiopurines (either pre- or *de-novo* treated) and those patients without purine analogues. The Kaplan–Meier analysis showed a trend towards improved outcome in the thiopurine group with regard to colectomy (log-rank test $P = 0.076$). Remission was significantly more often achieved with concomitant thiopurines (85% vs. 61%, Chi-squared test $P = 0.002$). Lichtiger score was available in 69/80 patients treated with purine analogues and 37/46 without azathioprine/mercaptopurine. At week 4, Lichtiger score ≤ 3 was found in 46% and 38% respectively. However, the median score was 4 in the first and 3 in the second group. Adverse events did not significantly differ among patients additionally exposed to thiopurines compared to those patients without combined immunosuppression. Four patients were treated with methotrexate de-novo in parallel to tacrolimus. Colectomy in this small group was required in one patient. Median Lichtiger index at baseline, week 4 and 12 was 6, 5 and 10. Remission was achieved in one patient.

Duration of disease

A long-term course of the disease and consecutive chronic structural alterations of the gut might bear a negative impact on the efficacy of tacrolimus as rescue therapy in UC. We divided our cohort into those patients who experienced duration of disease of less vs. more than 1 year until start of tacrolimus (33 patients (25%) <1 year vs. 94 patients (72%) >1 year). In three cases, the time of first diagnosis remained unclear. Both groups were characterised with regard to age, sex, severity and extension of UC and treatment regimens. Demographics and clinical activity at baseline according to the Lichtiger index disclosed no relevant differences. The localisation of colonic inflammation differed significantly. E3 and E2 were more prominent in UC lasting longer than 1 year, whereas E1 was found to be more often in UC established less than 1 year ($P = 0.017$). The use of steroids and tacrolimus was consistent in both groups. Patients receiving concomitant immunosuppression with purine analogues were more prevalent in early UC (70% vs. 55%, $P = 0.148$), although not statistically significant. Colectomy was indicated in three (9%) patients in the group shorter than 1 year UC duration compared to 15 (16%) patients in the other group ($P = 0.331$). The analysis of clinical remission showed a trend towards improved outcome of patients with a short-term

duration (85% vs. 69%) that did not reach statistical significance ($P = 0.08$).

Surgery vs. no surgery

Colectomy was carried out in 18 of 130 patients (14%) within the first 12 weeks after initiating tacrolimus treatment. We intended to identify parameters at baseline related to the risk for early colectomy in steroid-refractory UC patients exposed to tacrolimus. Patients undergoing colectomy were not different with regards to age, sex and duration of disease when compared to those without surgery. At baseline, the median Lichtiger score was 12 vs. 13. Extent of colonic inflammation was equally distributed between both groups. No differences were found with respect to treatment and dose of steroids or tacrolimus. In the colectomy group, 44% (8/18 patients) were on additional immunosuppression with purine analogues or methotrexate ($n = 1$) in contrast to 65% (72/112 patients) with purine analogues or methotrexate ($n = 3$) in patients with colectomy free survival ($P = 0.108$).

Safety of tacrolimus

Adverse reactions to tacrolimus were generally mild, none sustaining and controlled by conservative measures in all three centers. No opportunistic infections and no deaths occurred while on tacrolimus. Overall adverse events due to tacrolimus were observed in 69 patients (53%). Only in two cases, tacrolimus therapy had to be discontinued because of an increase in serum creatinine and drug intolerance respectively. The most frequent adverse events were tremour and paraesthesia in 50 patients (38%) followed by hyperglycaemia in 13 patients (10%). A clinically relevant elevation of creatinine levels was documented in eight patients (6%) and abdominal discomfort or nausea was observed in five patients (4%). We found no relevant differences in reference to add on given purine analogues, duration of disease and necessity of surgery. A detailed analysis of adverse events is presented in Table 2.

Table 2 | Adverse events during tacrolimus therapy

	Complete cohort *n*/130 (%)	PA*,† *n*/75 (%)	Ø PA*,† *n*/46 (%)
Overall	69 (53%)	41 (55%)	26 (57%)
Tremor/paresthaesia	50 (38%)	30 (40%)	18 (39%)
Hyperglycaemia	13 (10%)	9 (12%)	4 (7%)
Increased creatinine level	8 (6%)	4 (5%)	4 (7%)
Abdominal discomfort	5 (4%)	1 (1.3%)	3 (4%)

Data of adverse events due to tacrolimus treatment of the complete cohort and separately in patients with or without concomitant purine analogues. Data obtained within the first 3 months of tacrolimus treatment are given in absolute and relative numbers. No significant differences were obtained between these groups. PA, purine analogues.

* Assignment in one of the PA group was not obtainable in five patients (four patients with azathioprine and one patient with mercaptopurine).

† Methotrexate in four patients.

DISCUSSION

Approximately 20% of patients with UC will experience a steroid-refractory course of disease. An increasing colectomy rate of up to 40% is found in patients with one or more admissions due to acute severe colitis.[19, 20] In patients with a complete response, colectomy is reported in 15% compared to 85% with an incomplete response.[21] Steroid response has to be assessed at an early stage. The rate of colectomy is 85% if more than 8 bloody stools or a CRP >45 mg/L in conjunction with 3–8 bloody stools on day 3 are present.[22] Hence, day 3 assessment is critical and in case of a nonresponse, alternative medical or surgical options should be considered.[23]

The efficacy and safety of infliximab in patients with moderate-to-severe active ulcerative colitis was demonstrated in the two ACT trials by Rutgeerts *et al.* Almost 70% achieved clinical response with infliximab at week 8 maintained in 45% until week 54.[24] Another randomised clinical trial has shown a reduced need for colectomy in a 3-month-period after a single infusion of infliximab compared with placebo in steroid-refractory patients (29% vs. 67%, $P = 0.017$).[25]

The broad experience with intravenous ciclosporin in steroid-refractory UC, based on retrospective and controlled prospective data, is summarised in a recent review with remission rates between 50 and 80% and an 80% success in avoiding early colectomy.[26] Despite the lack of a head-to-head comparison, studies available point to a similar efficacy of tacrolimus in this clinical setting. In a retrospective analysis, Fellermann *et al.* reported colectomy within 1 month after initiation of tacrolimus in 3 of 38 UC patients, the largest survey addressing short-term colectomy in the steroid-refractory situation so far.[9] The placebo-controlled prospective trial conducted by Ogata *et al.* demonstrated no need for colectomy in 32 tacrolimus treated steroid-refractory UC patients at week two.[13] In this rather short period, clinical remission, defined as a DAI score ≤ 2 with an individual subscore of 0 or 1, was found in 9.4%.[14] Our results obtained in a steroid-refractory cohort of 130 patients are in accordance with the existing data for calcineurin inhibitors. We observed

a requirement for surgery in 14% of the patients at week 12. Clinical remission, subject to a Lichtiger score ≤ 3 or a normal stool frequency without any visible blood, was found in 72%. In patients with a Lichtiger score >12 at baseline, remission was even found in 82%. However, elevated CRP-levels at baseline appear not to be predictive for remission.

Deep ulcers at an index colonoscopy have been retrospectively shown to be associated with a risk for colectomy in 93% of severely affected UC patients opposed to 26% without these findings.[27] In severe or fulminant colitis, no predictors for early colectomy under treatment with calcineurin inhibitors or infliximab have been established so far. Our analysis did not encounter any significant differences in demographics or clinical factors between patients with vs. those without a need for colectomy receiving tacrolimus. Those patients in our cohort with a history of UC shorter than 1 year revealed a trend towards a higher remission rate compared with those with a more longstanding disease ($P = 0.08$) and a lower, although not significant, need for colectomy (9% vs. 16%). Of note, a more frequent use of concomitant immunosuppression was notified in early UC patients. Although the level of statistical significance was missed, our patients in the cohort without colectomy in the 3-months period exhibited a higher percentage of a combined use of tacrolimus and thiopurines (65% vs. 44%, $P = 0.108$). This might argue in favour of an increased short-term efficacy of tacrolimus given in parallel with purine analogues. However, the retrospective character of our survey and the few numbers of colectomy might have hampered a more valid statistical analysis and definitive conclusions. Furthermore, our data did not allow analysis of biomarkers or endoscopic variables.

The concept of combined therapy in Crohn' disease has been transferred to steroid-refractory UC in the SUCCESS trial. According to preliminary results, azathioprine given in addition to infliximab significantly improved the clinical course. Patients who received both drugs went into remission in 40% at week 16 in contrast to 22% solely treated with infliximab ($P < 0.05$).[15] In agreement with the SONIC trial,[14] the overall safety was found to be similar. Baumgart *et al.* reported long-term remission on thiopurines after successful tacrolimus rescue in UC.[16] Long-term observational data by Cohen *et al.* with ciclosporin treatment already demonstrated the usefulness of thiopurines for maintenance of remission during a follow-up period of 5.5 years.[17] Our study now yields first data for a potential benefit of an early combination of tacrolimus and thiopurines in steroid-refractory UC. Although without statistical significance, the Kaplan–Meier analysis clearly depicts the trend towards a better outcome with respect to colectomy in the 3-months period. A higher percentage of remission at week 12 in those patients concomitantly treated with tacrolimus and purine analogues opposed to tacrolimus alone (85% vs. 61%, $P = 0.002$) strengthens this finding. Although both groups were comparable with regard to co-medication, severity and extension of the disease, the individual choice to avoid thiopurines might represent a bias. Consistent with the data obtained for infliximab and azathioprine, our analysis detected no increase in side effects under combined immunosuppression. Remarkably, no opportunistic infections and no deaths occurred.

In patients already on azathioprine while experiencing a steroid-refractory flare of UC, the long-term need for colectomy increased to 59% compared with 31% in patients starting azathioprine de-novo in parallel with ciclosporin.[28] Although our study did not detect obvious differences between these two cohorts addressing early colectomy, the data of Moskovitz *et al.* might argue against the use of calcineurin inhibitors in UC patients failing thiopurines. In contrast to the retrospective analysis of Sjöberg *et al.* and a prospective controlled study conducted by the GETAID,[6] reported no advantage of ciclosporin over infliximab in steroid-refractory UC after 12 weeks. While calcineurin inhibitors might be preferable in thiopurine naïve patients, infliximab may be used in case of thiopurine failure or intolerance.

We are aware of limitations of the study, as it was retrospective. Hence, data assessment was incomplete and lacked biological and endoscopic variables. Nonetheless, this is to date the largest evaluation of the efficacy and safety of tacrolimus in a cohort of steroid-refractory UC patients. Our retrospective data confirm the potential and safety of this drug in the short-term with a colectomy free survival of 86%. In the absence of controlled trials, our data suggests that the remission rates with tacrolimus in this setting are higher in patients also prescribed thiopurines.

AUTHORSHIP

Guarantor of the article: Klaus J. Schmidt.

Author contributions: Schmidt, Herrlinger, Emmrich, Barthel, Koc, Stange and Fellermann collected the data. Schmidt and Fellermann analysed the data. Schmidt, Herrlinger, Fellermann and Büning contributed to the design of the study and wrote the paper. All authors approved the final version of the submitted manuscript.

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