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Oral tacrolimus for pediatric steroid-resistant ulcerative colitis☆

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Abstract

Background: Ulcerative colitis (UC) occurring during childhood is generally extensive and is associated with severe flares that may require intravenous steroid treatment. In cases of corticosteroid resistance is necessary to introduce a second-line treatment to avoid or delay surgery.
Aims: To describe the efficacy and safety of oral tacrolimus for the treatment of severe steroid-resistant UC.
Methods: We performed a retrospective study that included all patients under age 18 suffering from severe steroid-resistant UC treated with oral tacrolimus during the period January 1998 to October 2012 and with a follow-up period after treatment of 24 months or more.
Results: A total of ten patients were included. The age at baseline was 9.4 ± 4.9 years, and the time from diagnosis was 1.3 months (IQR, 1–5.7). Seven of the patients were in their first flare of disease. All of them received an oral dose of 0.12 mg/kg/day of tacrolimus divided in two doses. Trough plasma levels of tacrolimus were maintained between 4 and 13 ng/ml. Response was seen in 5/10 patients at 12 months, colectomy was eventually performed in 60% of patients during the follow-up period.
Conclusions: Tacrolimus is useful in inducing remission in patients with severe steroid-resistant UC, preventing or delaying colectomy, and allowing the patient and family to prepare for a probable surgery. Tacrolimus may also be used as a treatment bridge for corticosteroid-dependent patients until the new maintenance therapy takes effect.

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1. Introduction

Ulcerative colitis (UC) occurring during childhood is generally extensive and is associated with severe flares that may require intravenous steroid treatment. Approximately 60–70% of patients that fail to respond to oral steroid treatment with prednisone will respond to intravenous treatment. Steroid-resistant UC is defined as a lack of response to intravenous steroid treatment at adequate doses in the 3–10 days following the onset of treatment; it is usually found in 34% patients with severe UC.[1] In such cases, it is necessary to initiate a second-line treatment to avoid or delay surgery. Treatment modalities include tacrolimus, cyclosporine (CyA) and antiTNF.[2,3] Tacrolimus is a macrolide that is structurally similar to rapamycin, has a potent immunosuppressive effect and is isolated from the fungus *Streptomyces tsukubaensis*. Its mechanism of action is similar to that of CyA; both bind to a cytosolic protein denoted FK BP12, creating a complex of FK BP12-tacrolimus, calcium, calmodulin, and calcineurin and leading to the inhibition of calcineurin phosphatase activity and prevention of the generation of the nuclear factor of activated T cells (NF-AT), a protein that initiates the transcription of cytokine genes. This, in turn, induces blockage of IL-2 synthesis and consequently the proliferation of T-cells, clonal expansion, and production of the cytokines involved in the immunological chain.[4] Tacrolimus has been used successfully in liver, intestine, lung, heart, pancreas, and renal transplantation,[5–7] in the prevention of graft-versus-host disease after bone marrow transplantation, and in nephrotic syndrome.[8] Its use has also been extended to treat autoimmune chronic hepatitis,[9] primary sclerosing cholangitis, autoimmune enteropathy,[10] and refractory inflammatory bowel disease (IBD).[11]

We provide our experience on the efficacy and safety of oral tacrolimus treatment in children with severe steroid-resistant UC.

2. Patients and method

This was a retrospective study that included patients under age 18 suffering from severe steroid-resistant UC treated with oral tacrolimus during the period January 1998 to October 2012 and with a follow-up period after treatment of 24 months or more.

2.1. Inclusion criteria

In those patients treated before 2007, a severe flare of UC was considered if there was a bad general condition, intense abdominal pain, and loose bloody stools greater in number than five in 24 hours. For patients included after the year 2007, the Pediatric Ulcerative Colitis Activity Index (PUCAI)[12,13] was used; the flare was considered severe if PUCAI $\geq$ 65 points.

2.2. Exclusion criteria

Active intestinal infection, toxic megacolon, intestinal perforation or peritonitis.

Before beginning the treatment, stool samples were obtained for culture and research of Salmonella, Shigella, Yersinia, Campylobacter, *Escherichia coli*, and the presence of *Clostridium difficile* A and B toxins in all cases. Other determinations were the following: blood count, erythrocyte sedimentation rate, C-reactive protein (CRP), sodium, potassium, chloride, transaminases, urea, creatinine, calcium, phosphorus, magnesium and coagulation tests. Active cytomegalovirus (CMV) infection was also excluded. In all cases, informed consent was obtained. Tacrolimus were administered as an off-label medication.

All patients received an oral dose of 0.12 mg/kg/day of tacrolimus (Prograf®, Astellas Pharma, Madrid, Spain) divided in two doses. Daily monitoring during admission included measurement of blood count, urea/creatinine, transaminases, magnesium, blood pressure, and tacrolimus trough levels until the levels reached those expected (5–10 ng/ml). Once such levels were reached, measurements were taken weekly during the first month, every 15 days during the second month and each month thereafter. We administered oral magnesium in cases of hypomagnesemia.

The data collected included age, sex, duration of illness to initiation of treatment with tacrolimus, number of flares, medication administered prior to treatment with tacrolimus, trough levels of tacrolimus (ng/ml), clinical response, duration of treatment, need for surgery, time elapsed until surgery, immunomodulation therapy after tacrolimus in non-colectomised patients and adverse effects observed.

We considered that the patient was responding when the number and characteristics of the stools normalised, the abdominal pain disappeared, the acute phase reactants decreased the hemoglobin increased or when PUCAI dropped over 20 points. The extent of the disease was defined according to the Montreal Classification.[14,15]

3. Statistical analysis

Variables are expressed as the median and interquartile range (IQR) or as the mean and standard deviation based on whether the variables followed a normal distribution. For normally distributed variables, we utilised the Kolmogorov–Smirnoff test. For the comparison of different variables, we used the Fisher exact test, Pearson Chi-square test, or Kruskall–Wallis test. The survival plots were drawn with the Kaplan–Meier method. We considered a $p < 0.05$ as statistically significant.

4. Results

A total of ten patients were included, seven of which were females (Table 1); seven of the patients were in their first flare of disease. The age at baseline was 9.4 ± 4.9 years, and the time from diagnosis was 1.3 months (IQR, 1–5.7). An initial clinical response was achieved in six patients; non-responders required colectomy and, in these cases, surgery was performed in a median of 9 days (IQR, 4.2–25). In the subgroup that initially responded, two of the six patients required colectomy, one at ten months after starting treatment and the other at six years and four months in conjunction with the suspension of immunomodulation therapy and the emergence of a new flare refractory to medical treatment. The three patients who were not in their first flare of the disease responded to tacrolimus. In four patients, surgery was avoided; these patients currently remain in clinical remission with immunomodulation therapy,

Table 1 Patients characteristics n, (%).

Patients	10
Females	7/10 (70%)
Age at tacrolimus started (years)	9.4 ± 4.9
Disease duration (months)	1.3 (IQ 1–5.7)
Flare	
First	7 (70%)
Second	1 (10%)
Third	2 (20%)
Montreal classification	
E3S3	10 (100%)
Baseline PUCAI	68.8 ± 4.8
Previous treatment	
Corticosteroids	10 (100%)
Aminosalicylates	10 (100%)
Azathioprine	2 (20%)
Infliximab	1 (10%)
Days on steroid treatment before starting tacrolimus	7.1 ± 1.6
Tacrolimus trough levels (ng/ml)	4–13
Duration of treatment with tacrolimus in responders (months)	4.7 (IQR, 3.7–6)
Maintenance treatment	
Aminosalicylates	5 (50%)
Azathioprine	4 (40%)
Mercaptopurine	1 (10%)
Surgery during the follow-up	6 (60%)
Time to surgery (days)	
All	20 (IQ, 6.8–773)
Non-responders	9 (IQ, 4.2–25)

more than 24 months after the onset of treatment with tacrolimus.

Trough plasma levels of tacrolimus were maintained between 4 and 13 ng/ml. The median duration of treatment with tacrolimus in the responding group was 4.7 months (IQR, 3.7–6) compared to a duration of treatment in the non-responding group of 0.23 months (IQR 0.13–0.8), p = 0.01.

In responding patients, the steroid dose was reduced after 7–10 days of treatment with tacrolimus and immunomodulation maintenance therapy was started (azathioprine or mercaptopurine). During the duration of the triple immunosuppressive therapy (tacrolimus, steroids and thioguanines), the patients received prophylaxis with trimethoprim–sulfamethoxazole. Tacrolimus was well tolerated in all cases; we observed no adverse effects except for a slight increase in plasma creatinine levels from baseline in one case.

The survival curves (Fig. 1.1) show that, for the patients who initially respond to tacrolimus and whose response is maintained beyond 12 months, the likelihood of colectomy decreases drastically if they continue with immunomodulation therapy. Fig. 1.2 shows that a lack of initial response to tacrolimus inevitably resulted in surgery within the following months; this curve contrasts strikingly with that of the patients who responded initially (p = 0.0001).

5. Discusion

Several definitions of severe UC have been used in the literature. The first and most widely used of these is the classification of Truelove and Witts. In 1977, Werlin and Grand proposed a modification of Truelove's classification, adapting it to children.[12,16] The application of these criteria has never been validated in children with severe UC. Recently, Turner developed a score of UC activity in children. However, this index not only quantifies the degree of disease activity but also predicts the lack of response to steroid therapy and the need to initiate a second-line treatment for severe flare of UC.[12,13]

Steroid-resistant UC is defined as a lack of response to intravenous steroid therapy in adequate doses (1–1.5 mg/kg/day, maximum 60 mg) for 3–10 days. In children, corticosteroid resistance is estimated to occur with an incidence of 34% (CI 95%, 27–41%),[17,18] slightly higher than that observed in adults.[1] Corticosteroid resistance is not a stable situation over time, and genetic[19–21] and environmental factors such as CMV infection have been identified.[22,23]

The introduction of a second-line treatment should ideally be based on ability to recognise those patients likely to fail steroid therapy at an early stage. The PUCAI has proven more effective in children than in adults. Given its sensitivity, when calculating the third day of steroid treatment a PUCAI > 45 points forces the health care provider to plan a second-line treatment and to consult a surgeon. Additionally, due to its high specificity, if after 5 days the PUCAI is >65–70, the provider must begin to administer a second-line treatment.[17] Although treatment with second-line drugs is preferred to surgery for children, once the treatment is established it is necessary to inform the family of the possibility of colectomy if drug treatment is not successful.[24]

CyA is an inhibitor of calcineurin, a molecule that participates in the synthesis of IL-2. The first published work on the use of CyA in adults dates from 1984[25]; the first randomised clinical trial of this drug was halted on ethical grounds because the CyA-treated group had a higher response rate.[26] In a recent published open label RCT, CyA was not more effective than infliximab (IFX) in patients with acute severe UC refractory to intravenous steroids.[27]

There are few published studies on treatment with CyA in children; if we select the studies that include more than five patients, 86 cases treated with different standards have been reported to date.[28–34] The reported studies are heterogeneous in terms of design, sample size, inclusion criteria, remission, and patient follow-up. Some authors use the oral route initially, while others prefer to begin treatment with CyA intravenously and subsequently switch to the oral route when remission is achieved. Analysis of the published data indicates that approximately 80% of patients (IQR, 95%, 70–87%) respond to treatment, although the percentage of cases that are free of colectomy years later is 45% (IQR, 34–57%). Thus, CyA therapy should be used as a bridge between corticosteroids and thioguanines (azathioprine or 6-mercaptopurine), and its use is for duration longer than 3–4 months is not recommended. In two studies in which thioguanines were used routinely in all patients, the sustained response rate was higher and more prolonged.[29,31]

Tacrolimus, which has greater potency than CyA (100 times more in vitro and 10 times more in vivo) due to the high affinity of its complex with FK BP-12 by calcineurin and better bioavailability because its absorption is not hindered by the degree of bowel wall inflammation, was first used in the early 90s as an alternative to CyA in IBD patients.[11] IFX

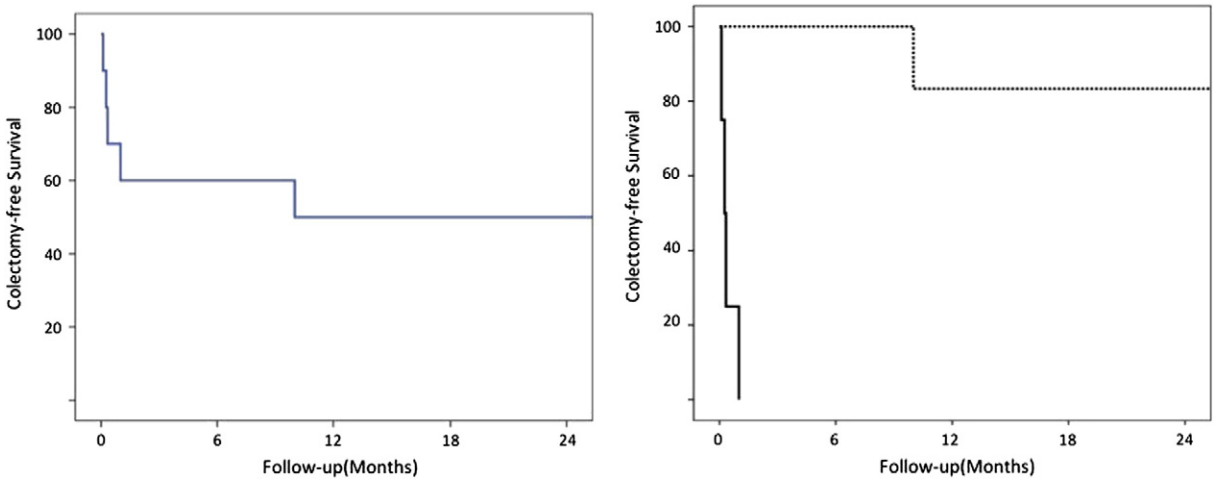

Figure 1 Colectomy-free survival. 1.1. Kaplan–Meier curve. Colectomy-free survival of all patients regardless of initial response. 1.2. Kaplan–Meier curve Colectomy-free survival of patients depending on whether there was initial response (dashed line) or not (solid line). The difference between the survival curves is statistically significant (Log Rank, p = 0.0001).

can also induce remission in patients with severe UC.[35] There are no published studies comparing tacrolimus with CyA or IFX in children.

Experience with tacrolimus in the treatment of pediatric IBD patients is very limited (Table 2). Since the first description by Bousvaros et al. in 1996,[36] a series of studies have been published. Bousvaros et al.[37] conducted a multicentre study that included 14 paediatric patients older than five years old with severe IBD (10 UC, 2 Crohn's disease, and 2 indeterminate colitis) who did not respond to conventional treatment with intravenous steroids. An initial dose of 0.1 mg/kg was administered every 12 h to maintain plasma levels between 10 and 15 ng/ml for 14 days and then between 5 and 10 ng/ml. They found an initial response rate of 65%; the remaining 35% required colectomy. At 12 months follow-up, five patients (38%) were in remission with maintenance therapy and without the need for surgery. The mean duration of treatment in responding patients was 3.4 months.

Ziring et al.[38] studied 18 children with UC (nine corticosteroid-resistant and nine corticosteroid-dependent). The initial dose administered was 0.1 mg/kg every 12 h to maintain levels of 10–15 ng/ml during the first two weeks; thereafter, levels were maintained between 7 and 12 ng/ml. Initially, 94% of patients (17 of 18) responded to tacrolimus. At the time of publication of the study, only 13 of the 18 had had more than one-year follow-up; seven of these (53%) had required colectomy during the first year since the start of tacrolimus.

Turner et al.[2] treated six children with severe UC with calcineurin inhibitors (five of these children received tacrolimus and one CyA) following the treatment protocol published by Bousvaros et al.[37] (unpublished data, information provided by the author). Three of the five patients treated with tacrolimus (60%) responded and were discharged without colectomy. One year after discharge, two patients (40%) continued in remission without colectomy.

Watson et al.[39] published a report on the largest series of patients to date with severe corticosteroid-resistant UC treated with oral tacrolimus. The regimen followed was similar to that used in a previously published study by these authors.[37] The initial response rate was 89% at two years of follow-up, at which time 54% of the patients were free of colectomy.

Table 2 Summary of studies using tacrolimus for the treatment of a severe flare of corticosteroid-resistant ulcerative colitis in children.
Adapted from Turner et al.[17]

Study	N	Dose mg/kg/day	Pl ng/ml	Initial response	% Free of colectomy
Navas (2013)	10	0.12	4–13	6/10 (60%)	5/10 (50%) at 2 years
Watson (2010)[40]	46	0.2	10–15	41/46 (89%)	25/46 (54%) at 2 years
Turner (2008)[2]	5	0.2	10–15	3/5 (80%)	2/5 (40%) at one year
Ziring (2007)[39]	9	0.2	10–15 7–12	8/9 (89%)	0% (<14 months)
Bousvaros (2000)[38]	9	0.2	10–15	5/9 (55%)	2/9 (22 %) at one year
Total (95% IC)	79			79% (68–87%)	43% (32–54%)

Pl: plasma levels (ng/ml).

In our series, six of ten patients (60%) achieved clinical remission with plasma levels of tacrolimus between 4 and 13 ng/ml; after 24 months of follow-up, five of them (50%) had not required surgery. The relation between the tacrolimus dose and plasma trough levels of the drug has been also studied. In a randomised study conducted in 60 adults[40] in which the patients were divided into three groups (plasma levels 10–15 ng/ml; plasma levels 5–10 ng/ml, and placebo), a higher rate of histologic remission and further steroid dose reduction was observed in patients with high plasma levels of tacrolimus (10–15 ng/ml) versus placebo ($p < 0.0001$). If we compare the two groups treated with tacrolimus the difference was not significant ($p = 0.067$), this is likely due to the small sample size. Recently, Ogata et al.[41] published a new study of 62 adults comparing treatment with tacrolimus for two weeks versus placebo; they found a higher response rate and clinical and histological remission in the group treated with tacrolimus. Schmidt KJ et al.[42] treated 130 steroid-resistant UC adult patients with tacrolimus. Colectomy was avoided in the 86% of the patients in the first 3 months of treatment. The tacrolimus median trough level was 6.85 μg/l (range: 1.7–25), although it was only measured in the 60% of the patients. Thiopurines given in parallel to tacrolimus tended to limit colectomy and significantly increased remission in the short-term.[42]

Based on all of the data that has been published to date, tacrolimus could be indicated as second-line therapy in severe steroid-resistant UC and as bridge therapy in severe steroid-resistant or steroid-dependent UC. Ziring et al.[38] showed that not all patients respond in the same way; six of the nine corticosteroid-resistant patients (66%) in that study were operated on within one year after onset, and all underwent surgery prior to four years after starting tacrolimus treatment, unlike the outcome for the series of corticosteroid-dependent patients (22% needed surgery during the follow-up period).

According to the ESPGHAN-ECCO guidelines, CyA or tacrolimus started during an episode of acute severe UC should be discontinued after 4 months, bridging to thiopurines and if disease is still chronically active or frequent flares despite adequate thiopurine treatment, consider IFX therapy (or adalimumab in cases of failure with IFX).[24] In our two patients treated with azathioprine before tacrolimus, we did not use anti-TNF-α because they were not available.

Another recently reported aspect of the treatment of UC is the relationship of the presence of a genetic polymorphism to the response to treatment with tacrolimus. Herrilinger et al.[43] found a higher response rate in patients homozygous for some polymorphisms (1236C > T, 2677G > T, A, and 3435C > T) of the ABCB1 gene (7q21.1). If this determination were readily available, it could be used in choosing a second-line treatment.

In summary, tacrolimus is useful in inducing remission in patients with severe steroid-resistant UC, preventing or delaying colectomy, and allowing the patient and family to prepare for a probable surgery. Tacrolimus may also be used as a treatment bridge for corticosteroid-dependent patients until the new maintenance therapy takes effect.

Conflict of interest statement

The authors acknowledge no conflicts of interest.

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