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Alimentary Tract

Tacrolimus induction followed by maintenance monotherapy is useful in selected patients with moderate-to-severe ulcerative colitis refractory to prior treatment

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ABSTRACT

Background: Tacrolimus in refractory ulcerative colitis often serves as a bridge to long-term maintenance therapy with thiopurines. Our aim was to review efficacy and safety of tacrolimus in active ulcerative colitis resistant to conventional therapies, including anti-tumour necrosis factor.
Methods: Charts of consecutive outpatients with refractory ulcerative colitis, in whom tacrolimus was orally administered as a 12 week-induction (target trough levels 10–15 ng/mL) followed by a maintenance therapy (target trough levels 5–10 ng/mL), were retrospectively reviewed. Clinical remission and response at weeks 4, 12 and 52 as well as adverse events within 1-year therapy were reported.
Results: Twelve (40%) and six (20%) of the 30 patients included (14 males, mean age 37.1 ± 1.4 years) achieved a clinical remission and response, respectively, at week 12. Three responders to tacrolimus initiation experienced drug-related adverse events requiring discontinuation. Among the 18 remaining initial responders who tolerated tacrolimus, 8 (27%) were in clinical remission at week 52, whereas the remainder either experienced adverse events requiring drug withdrawal ($n = 4$) or relapsed ($n = 6$). Overall adverse events were recorded in 14 patients (46%), mainly finger tremor and urinary infections.
Conclusion: Oral monotherapy with tacrolimus may be a valuable long-term therapeutic option in selected patients with moderate-to-severe active refractory ulcerative colitis.
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1. Introduction

Cyclosporin (CsA) is a potential rescue medical therapy for intravenous steroid-resistant severe ulcerative colitis (UC) and has been shown to be also effective in case of chronic active UC [1–3]. However, the narrow therapeutic index of CsA and its potential side-effect profile have strongly limited its use and acceptability in UC in a long-term care setting. Tacrolimus (also called FK506) is a macrolide antibiotic with strong immunosuppressant effects isolated from *Streptomyces tsukubaensis* [4]. It primarily affects T cell activation and proliferation and also T cell function by binding to the FK binding proteins (FKBP) and mediates immunosuppression (i) by inhibiting calcineurin, a calcium and calmodulin-dependent phosphatase, leading to an interruption of T cell signal transduction pathways and (ii) by affecting key transcription factors as NFAT and NF-κB leading to inhibition of transcription of the early activation genes coding for cytokines such as tumour necrosis factor alpha (TNFα), interleukin 2 (IL-2) and interferon γ (IFNγ). Intestinal absorption of tacrolimus is assumed to be greater than that reported with CsA even in case of intestinal damage and, although its cell target is similar to that of CsA, accumulating experimental evidence show that its immunosuppressive properties could be greater both *in vitro* and *in vivo* when compared with CsA [4].

Tacrolimus is currently approved for the prevention of allograft rejection in patients undergoing liver or kidney transplantation in whom it is considered to be a more effective immunomodulator than CsA [5,6]. Tacrolimus is effective to treat various colitis in animal models of inflammatory bowel disease (IBD) [7,8]. In humans,

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tacrolimus has been reported to be effective for patients with fistulizing and refractory Crohn's disease (CD) [9,10]. In steroid-refractory or dependent UC, evidence on efficacy and safety of tacrolimus come from case-series, open-label or retrospective studies performed in adults and in children with often mixed data including patients with UC, CD and pouchitis [11–18]. A short-term treatment by tacrolimus is effective in patients with steroid-refractory or steroid-dependent UC but data in anti-TNF refractory patients with UC are scarce. Recently, Schmidt KJ et al. reported a large retrospective survey in 130 patients with steroid-refractory UC, in whom a clinical remission under tacrolimus was achieved in 72% at 12 weeks [16]. Ogata et al. [19,20] performed two short controlled studies and reported a significant benefit of tacrolimus over placebo at 2 weeks in steroid-refractory or -dependent UC patients when tacrolimus was adjusted to trough levels of 10–15 ng/mL.

In most of the studies investigating the efficacy of tacrolimus in UC patients, tacrolimus is used as a "bridge" to long-term maintenance with thiopurines or in association with thiopurines [11,14,16,17,20,21] and a high proportion of patients are unable to wean off steroids [12,14,15,19,20]. However, in contrast with CsA, tacrolimus seems to be better tolerated in long-term care settings [22] and could be therefore used as long-term monotherapy in patients resistant to conventional treatments, including steroids, thiopurines and anti-TNF agents.

Up to date, results of long-term monotherapy with oral tacrolimus without combination or switch to thiopurines for moderate to severe UC refractory to all conventional drugs remain scarce and tacrolimus-related adverse-event profile in this setting still warrants additional data. We report here the first multicenter, retrospective, observational French experience about effectiveness and safety of induction and long-term maintenance monotherapy with tacrolimus in patients with moderate to severe active UC refractory to conventional treatment, including anti-TNFα.

2. Patients and methods

2.1. Patients

The medical charts of outpatients with moderate to severe active UC, who did not respond to conventional medical therapies including steroids, immunosuppressants and anti-TNFα agents and treated with oral tacrolimus between July 2007 and June 2012, were retrospectively reviewed from 3 referral French IBD centres using the same pre-defined tacrolimus protocol for treatment and surveillance. All patients were defined (i) steroid-refractory when they kept an active disease despite prednisone (0.75 mg/kg/day) over a period of 4 weeks and (ii) immunosuppressor-refractory when they stayed with an active or steroid-dependent disease in spite of appropriate dose of azathioprine (2–2.5 mg/kg/day), mercaptopurine (1–1.5 mg/kg/day) or methotrexate (15–25 mg/week) for at least 6 months and (iii) anti-TNF-refractory when they kept an active disease for at least 6 months despite an optimization (infliximab to 10 mg/kg every 4 weeks or adalimumab 40 mg every week in mono or combo therapy). Diagnosis of UC was based on the usual clinical, biological, endoscopic and histological criteria, according to the Lennard–Jones parameters [23]. Concurrent therapies included 5-ASA and corticosteroids in 18 and 4 patients out of 30, respectively. None had concomitant immunosuppressant and biologics given that all the patients had failed to respond to such previous drugs.

Clinical and biological data were extracted from a database. Disease activity was assessed using the abbreviated UC-DAI (partial Mayo score defined as the Mayo score without endoscopy), including number of bowel movements/day (more than normal) based on average of last 3 days, rectal bleeding and physician global assessment [24]. A moderate active UC was defined by an abbreviated UC-DAI score of 4–6 points and a severe active UC by an abbreviated UC-DAI score between 7 and 9 points. No patient exhibited signs of fulminant colitis. Clinical remission was defined as an abbreviated UC-DAI of 2 points or less without rectal bleeding. Clinical improvement was defined as a decrease in the abbreviated UC-DAI of more than 2 points below baseline. Treatment failure included the absence of clinical remission or response to therapy, recurrence of symptoms and a drug-related adverse event requiring withdrawal of tacrolimus. In case of clinical remission or improvement occurring within the 12 weeks of the induction phase, tacrolimus was continued as a maintenance regimen.

2.2. Tacrolimus treatment modalities

Before beginning tacrolimus therapy, superinfection was systematically ruled out by stool cultures and *Clostridium difficile* toxin testing. Tacrolimus was started orally at an initial dose of 0.10–0.15 mg/kg body weight per day in two divided doses aiming for a serum drug target trough levels of 10–15 ng/mL during the first 12 weeks (induction phase). In patients who responded to tacrolimus and who had no adverse event requiring withdrawal, tacrolimus was then continued with a dose aiming at a target trough levels ranging from 5–10 ng/mL (maintenance phase), as previously recommended by Yamamoto et al. [25,26]. Blood assays to assess drug trough levels and drug tolerance were determined twice a week for 2 weeks, weekly for the following 4 weeks and then once a month for the remaining treatment period. The dose of tacrolimus was checked and adjusted using drug target trough levels. The disease outcome was clinically assessed during scheduled follow-up visits (at week 4, 12 and every 12–14 week intervals until week 52) using the abbreviated UC-DAI in association with routine laboratory tests (including serum C-reactive protein, glycaemia, magnesemia and liver function). Renal function was evaluated with creatinine clearance before starting tacrolimus and during the follow-up at week 4, 12 and every 12–14 weeks. At each visit, patients underwent physical examination with vital signs, concomitant medications and adverse events including clinical and biological events were recorded. Given the fact that tacrolimus was used as a monotherapy, no prophylaxis against opportunistic infections, including *Pneumocystis jiroveci*, was administrated as recommended [27].

2.3. Assessment and statistical analysis

Effectiveness was primarily assessed by the clinical improvement and clinical remission rates at 4 weeks, 12 weeks and 52 weeks after tacrolimus onset. The secondary endpoints were steroid withdrawal and treatment safety. Statistical analysis was performed using the nonparametric Mann–Whitney test (unpaired comparisons) and the Fisher's exact test (paired data) as appropriate. Data were expressed as median or mean ± SEM when appropriate. Statistical analysis was performed using the Statistical Package GraphPad software Inc. (San Diego, CA). All the tests were two-sided and a p-value less than 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 30 patients (14 males, 46.7%), mean age 37.1 ± 1.4 years (range: 22–61 years) were included. The median duration of UC at the initiation of tacrolimus treatment was 96 months, range [36–336]. The baseline abbreviated UC-DAI score ranged

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