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Oral tacrolimus as maintenance therapy for refractory ulcerative colitis—an analysis of outcomes in two London tertiary centres☆

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Abstract

Background: The medical management of refractory ulcerative colitis (UC) remains a significant challenge. Two randomised controlled studies have demonstrated tacrolimus therapy is effective for the induction of remission of moderate to severe UC. However, the long term outcomes of UC patients treated with tacrolimus as maintenance therapy are not certain.
Aims: This study aims to assess the efficacy of tacrolimus maintenance therapy for refractory UC.
Methods: A retrospective review of patients with UC treated with tacrolimus at two London tertiary centres was performed. Clinical outcomes were assessed at six months, at the end of tacrolimus treatment, or at the last follow-up for patients continuing tacrolimus treatment. Modified Truelove–Witts score (mTW) and Mayo endoscopy subscores were calculated.
Results: 25 patients with UC, treated with oral tacrolimus between 2005 and 2011, were identified. The median duration of tacrolimus treatment was 9 months (IQR 3.7–18.2 months). The median duration of follow-up was 27 months (range 3–66 months). At six months thirteen (52%) patients had achieved and maintained clinical response and eleven (44%) were in clinical remission. The mean mTW score decreased from 10 +/− 0.5 before therapy, to 5.8 +/− 0.8 ($p \leq 0.001$ 95% CI 2.7–5.8) at cessation of treatment or last follow-up. Mayo endoscopy subscore decreased from 2.6 +/− 0.1 to 1.2 +/− 0.2 ($p \leq 0.001$ mean reduction 1.4, 95% CI 0.8–1.9). Eight patients (32%) subsequently underwent a colectomy within a mean time of 17 months (range 2–45 months).

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Conclusion: Tacrolimus is effective for the maintenance of refractory UC and can deliver sustained improvement in mucosal inflammation.

1. Introduction

The medical management of patients with refractory ulcerative colitis (UC) remains a significant challenge. Up to one third of patients with UC eventually require surgery.[1] Immunomodulators play a fundamental role in the management of refractory UC, enabling steroid withdrawal and maintenance of disease remission. However, a substantial proportion of patients are either unresponsive or intolerant to thiopurines.[2,3] Ciclosporin is effective for the induction of remission of UC, but long term use is limited due to toxicity and long-term failure rates.[4] Although retrospective analyses have suggested a role for methotrexate in UC,[5,6] a randomised controlled trial for the use of methotrexate for the induction of remission and maintenance of UC demonstrated no benefit[7] and further appropriately powered placebo controlled trials are awaited. Anti-tumour necrosis factor (anti-TNF) drugs are effective for induction of remission and maintenance of remission for UC.[8,9] However approximately 80% of UC patients initially treated do not remain in remission at one year and the absolute risk reduction for colectomy is 7% compared with placebo.[10]

Tacrolimus, like ciclosporin, is a calcineurin inhibitor, which inhibits IL-2 production and T-cell activation.[11] A number of studies have assessed the short term efficacy of oral tacrolimus in inflammatory bowel disease with encouraging results for Crohn's disease and for UC.[12–14] Two randomised double blind studies[15,16] demonstrated that tacrolimus is effective in the induction of remission for steroid refractory moderate to severe UC. In the 2006 study by Ogata et al.[15] patients were randomised to high (10–15 ng/ml) and low (5–10 ng/ml) tacrolimus trough levels. At two weeks clinical response rates were significantly greater in the high and low concentration groups compared with placebo. In addition, 20% of patients in the high concentration group were in remission (defined as a DAI ≤ 2 with no subscore ≥ 1), whilst 10.5% of patients were in remission in the low concentration group, compared with 5.9% in placebo. This study also included a ten week open label extension in which clinical remission was observed in 29% and mucosal healing in 73% of patients with no patients undergoing colectomy.

Short term data appears promising but long term outcomes of tacrolimus in UC remain unclear. To date, five retrospective studies have assessed medium to long-term outcomes in adult patients with inflammatory bowel disease treated with tacrolimus.[17–21] Three of these studies include hospitalised patients initiated on oral and intravenous tacrolimus. The Japanese studies include more thiopurine naive patients with shorter disease duration that might represent a different patient group clinically as well as genetically to a western population. None of the previous studies assess long-term endoscopic outcomes. Here we report our experience of oral tacrolimus as maintenance therapy in 25 patients with chronic refractory UC treated at two London tertiary IBD centres. This is the largest U.K. cohort reported of UC patients treated with tacrolimus. This is also the first study to assess the effect of tacrolimus maintenance therapy on mucosal healing in ulcerative colitis.

2. Methods

All patients with a diagnosis of UC treated with tacrolimus at two London tertiary centres were retrospectively reviewed. Patients treated with tacrolimus between 2005 and 2011 were identified after interrogation of the respective institutions' IBD databases. The case notes were reviewed and the overall outcome was assessed at the end of tacrolimus treatment, at six months following treatment and at the last follow-up for patients continuing tacrolimus treatment.

In all cases a prior diagnosis of UC had been made based on standard clinical, endoscopic and histological assessments. Patients were followed up as outpatients, where clinical data and tacrolimus levels were recorded. Clinical response, remission and adverse effects were determined from case note review. In one half of the patients, case notes were reviewed independently by two investigators (JL, SP) and any inter-observer difference was resolved by consensus. Modified Truelove–Witts scores[22] (mTW) were retrospectively calculated based on case notes' documentation of clinical symptoms and examination. Clinical remission was defined as an mTW score of ≤ 4. Clinical response was defined as a reduction of ≥ 4 points from baseline on the mTW score.

Where available, endoscopic reports and images (baseline and 6-months) were reviewed independently by two investigators to determine endoscopic scores and inter-observer differences were resolved by consensus. Trough tacrolimus levels prior to cessation of tacrolimus were recorded and for patients with ongoing follow-up after tacrolimus therapy was stopped, further medical or surgical interventions were recorded.

All of the patients treated with tacrolimus were outpatients with moderate to severe refractory, but not acute severe ulcerative colitis requiring hospitalisation, at the time treatment was initiated. Oral tacrolimus was initiated at a dose of 0.1 mg/kg/day in two divided doses. Trough blood levels were monitored and the dose adjusted for each patient to achieve a trough level of 5–10 ng/ml.

Statistical analysis was performed using GraphpadPrism® version 5. Paired Student's t-test was used to compare mean clinical and endoscopy scores and data were expressed using 95% confidence intervals. The Kaplan–Meier survival method was used to estimate the cumulative colectomy free survival at 24 months subsequent to the initiation of treatment with tacrolimus. p values ≤ 0.05 were considered statistically significant.

3. Results

25 patients with UC, treated with oral tacrolimus between 2005 and 2011, were identified. The median duration of tacrolimus treatment was 9 months (IQR 3.7–18.2 months).