RESEARCH

Tacrolimus therapy in moderate to subacute ulcerative proctocolitis: a large single-centre cohort study

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ABSTRACT

Objective To explore the 'real world' effectiveness of tacrolimus therapy for refractory ulcerative proctocolitis (UC).

Design Retrospective cohort study using prospectively collated clinical data.

Setting A single district general hospital in Kent, UK. Clinical decisions and regular monitoring were undertaken by a single expert in inflammatory bowel disease.

Patients All patients started on tacrolimus between January 2010 and August 2016 at Tunbridge Wells Hospital.

Interventions Following failure of conventional medication, tacrolimus was commenced at 0.5 mg/kg twice daily. Drug trough levels of 5–20 ng/mL were targeted. Other immunomodulation was stopped and steroids were weaned over 4–6 weeks.

Main outcome measures Treatment duration was measured for each patient. If the drug was stopped, the rationale, including specific side effects, was recorded. The patient's subsequent management plan was noted.

Results Thirty-five patients were started on tacrolimus (range: 18–85, median: 36 years). Disease extent included proctitis to pancolitis. Twenty-five patients derived no benefit. Four patients responded, but drug side effects necessitated withdrawal. Eighteen of these 29 patients (62%) underwent surgery. One patient, who had previously responded, stopped the drug after becoming pregnant (healthy subsequent birth). Therefore, 5 of 35 patients (14%) remain on tacrolimus with sustained clinical response, ranging from 6 to 76 (median: 32) months of treatment. Treatment was most effective for proctosigmoiditis. There were no other demographic or biological markers for success.

Conclusions In line with UK and European guidelines, tacrolimus can be beneficial for refractory UC. With appropriate monitoring, it appears treatment can be continued safely long term.

INTRODUCTION

Ulcerative proctocolitis (UC) is a relapsing–remitting chronic inflammatory illness affecting the rectum and differing lengths of the colon. There are several treatment options depending on severity and extent, patient tolerance and preference. Subacute UC is defined as moderate to severely active disease, based on the Truelove and Witts criteria, which would normally be managed as an outpatient. Treatment initially involves oral systemic corticosteroids; however, failure because of steroid dependence or steroid refractoriness can result in side effects and impact on quality of life.¹ Biological agents, such as the antitumour necrosis factor (TNF)- α monoclonal antibodies infliximab and adalimumab, were approved by the UK's National Institute for Health and Clinical Excellence (NICE) in 2015 for moderately to severely active UC that has failed conventional therapy.² Before these options were available, moderate to subacute UC was a challenging condition to treat, and failure usually led to subtotal colectomy with ileostomy and then, where appropriate, an ileal pouch anal anastomosis.

Tacrolimus is a macrolide immunosuppressant that was discovered in Japan in 1984. It is thought to inhibit the phosphatase activity of the intracellular protein calcineurin, thereby preventing the dephosphorylation and translocation of nuclear factor of activated T cells to the nucleus. This prevents the transcription of genes that encode cytokines such as interleukin-2 and gamma interferon that would normally propagate T cell activation.³ It is widely used to prevent solid organ graft rejection, particularly because of its steroid-sparing effects.⁴

In 2006, Ogata *et al*⁵ reported the first randomised, double-blind, placebo-controlled trial of tacrolimus in 60 patients with refractory UC. The initial 2-week double-blind study demonstrated significant benefit

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in the high trough level (10–15 ng/mL) group compared with placebo with respect to disease activity index (DAI) score, while the low trough level (5–10 ng/mL) group tended towards improvement but did not reach statistical significance. A subsequent 10-week open-label extension reported a significant improvement in the DAI scores of those who had previously been given placebo. A further study by the same Japanese group in 2012 investigated the efficacy of tacrolimus in 62 patients hospitalised with moderate to severe UC who were either steroid resistant or steroid dependent, targeting a high trough level.⁶ For ethical reasons, only a 2-week placebo-controlled study period was used in this group of unwell patients. Nevertheless, significant improvements in clinical response and mucosal healing were demonstrated at week 2. This benefit continued during the 10-week open-label extension, where there was continued improvement in these parameters by week 12. The mean prednisolone dose requirement also decreased. These results provided further support for tacrolimus; indeed, NICE approved its use for up to 12 weeks in steroid-refractory UC in 2013.¹

On the basis of the initial study by Ogata *et al*,⁵ a consultant gastroenterologist with a special interest in inflammatory bowel disease (IBD) (AH) started using tacrolimus for refractory moderate to subacute UC in 2010 to avoid the need for surgery. This practice has continued in carefully selected patients despite the availability of biological agents, and we report outcomes from our consecutive case series.

METHODS

Prospective data were collected for all 35 patients started on tacrolimus (Prograf; Astellas Pharma US, Inc, Northbrook, Illinois, USA) between January 2010 and August 2016 at our district general hospital. This included the extent of disease, clinical response, drug side effects, duration of therapy and subsequent management if tacrolimus failed. Any missing information was obtained from clinic letters. Decision to begin tacrolimus was made by AH. All appropriate conventional medication had been previously tried and either failed or not tolerated, including mesalazine, steroids and a thiopurine, or methotrexate if intolerant, in line with NICE¹ and British Society of Gastroenterology guidance.⁷ Failure was determined by endoscopic examination, biochemical markers or persistence of characteristic symptoms despite previous treatment escalation. On initiation of tacrolimus, other forms of immunomodulation were discontinued, and steroids were weaned to zero over the next 4–6 weeks. The starting dose was 0.5 mg/kg twice daily.

Patients were counselled about contraindications, including pregnancy, and common side effects such as minor gastrointestinal symptoms, headache, muscle cramps and burning or paraesthesiae, as stated within the British National Formulary. The rationale for regular haematological monitoring was also explained, along with advice regarding immunosuppression. All

Table 1 Tacrolimus monitoring algorithm

Blood test	Indication for intervention	Intervention
WCC	Below 3.5 or neutrophil count less than 1.5	Stop tacrolimus Monitor WCC weekly When within normal range, recommence tacrolimus at lower dose
Creatinine	Above 130 µmol/L	Reduce dose of tacrolimus by 1/3 Monitor creatinine weekly If continues to rise, stop tacrolimus Arrange clinic review to assess other causes for possible raised creatinine
Tacrolimus levels	<5 ng/mL >20 ng/mL	Increase dose by 1/3 Decrease dose by 1/3
Drug-related side effects		Decrease dose by 1/3
Blood pressure	Systolic >150 mm Hg	Decrease dose by 1/3

WCC, white cell count.

patients were provided with an information sheet written by AH (see online supplementary material). A telephone contact number and email address were provided. From March 2016, IBD clinical nurse specialists were available to support the service.

Full blood count, renal function, liver function, fasting trough tacrolimus level, blood pressure and body mass were measured pretreatment, at week 2, week 4, monthly for 3 months and then at least 3 monthly throughout treatment. Patients were advised to have their fasting blood tests in the morning and delay their tacrolimus dose until after this. The therapeutic range was 5–20 ng/mL, and doses were adjusted according to response, side effects and renal function⁵ (table 1). AH monitored the results and advised about dose changes or drug cessation by telephone and during clinical review 4 weekly initially and then 12 weekly once stable.

Response was evaluated by AH only using the following parameters: stool frequency and form, fecal urgency, rectal bleeding, abdominal pain and general well-being. Follow-up endoscopy was not standard practice during this period. Tolerance was assessed by specific enquiry about common side effects, including nausea, headache and tingling.

Statistical significance was evaluated using the unpaired t-test on GraphPad Software.

RESULTS

Thirty-five patients were started on tacrolimus between January 2010 and August 2016. Demographic details and disease phenotype are noted in table 2. The drug was stopped when patients became intolerant of side effects or because of lack of clinical effectiveness (figure 1). One patient with ulcerative proctosigmoiditis had good clinical response for 4 months, but then became pregnant, and treatment was discontinued (healthy live birth

Table 2 Patient demographics and extent of disease

Patient characteristics	Number of patients (total=35) (n (%))
Gender	
Male	18 (51)
Female	17 (49)
Age when tacrolimus started (years)	
<20	1 (3)
20–29	8 (23)
30–39	14 (40)
40–49	5 (14)
50–59	3 (9)
≥60	4 (11)
Median	36 years
Age at diagnosis of UC (years)	
<20	3 (9)
20–29	11 (31)
30–39	12 (34)
40–49	4 (11)
50–59	2 (6)
≥60	3 (9)
Extent of disease	
Proctitis	4 (11)
Proctosigmoiditis	13 (37)
Left sided	7 (20)
Extensive/pancolitis	11 (31)

UC, ulcerative colitis.

subsequently). Therefore, 5 of 35 patients currently have a sustained clinical response on tacrolimus. Their duration of treatment ranges from 6 to 76 (median: 32) months.

Of those 29 patients that failed, 18 underwent surgery. The majority of the remaining patients are using biological therapy, including adalimumab (four

Figure 1 Patient outcome flow chart.

Table 3 Comparison between responders and non-responders

	Responders	Non-responders	
Disease extent			
Proctitis (n (%))	1/4 (25)	3/4 (75)	
Proctosigmoiditis (n (%))	6/13 (46)	7/13 (54)	
Left sided (n (%))	2/7 (29)	5/7 (71)	
Extensive/pancolitis (n (%))	1/11 (10)	10/11 (90)	
Duration of UC pretacrolimus (mean/years)	4.10 (n=10)	3.28 (n=25)	P=0.61
Age at UC diagnosis (mean/years)	29.7 (n=10)	37.0 (n=25)	P=0.21
Drug levels (mean/ng/mL)	10.35 (n=8)	9.3 (n=21)	P=0.54
Blood markers of inflammation			
WCC (mean/ $\times 10^9$ /L)	7.73 (n=9)	7.60 (n=23)	P=0.91
ESR (mean/mm/hr)	27.2 (n=5)	39.1 (n=15)	P=0.53
CRP (mean/mg/L)	10.0 (n=7)	18.8 (n=21)	P=0.41
Endoscopy			
Baron score pretacrolimus initiation (mean)	2.4 (n=5)	2.6 (n=16)	

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; WCC, white cell count.

patients, 14%), infliximab with concomitant methotrexate (two patients, 7%), vedolizumab (two patients, 7%) and methotrexate monotherapy (one patient, 3%). One patient has stable disease off treatment, and one patient has been lost to follow-up.

Those with proctosigmoiditis had a higher rate of response compared with other disease phenotypes (table 3). There were no significant differences between responders and non-responders when comparing other clinical parameters. Two of the 10 patients (20%) who responded had previously been treated with biologicals (both infliximab).

The two main reasons for withdrawal due to side effects were renal failure (persisting rise in creatinine above 130 μ mol/L despite dose reduction) and gastrointestinal side effects (table 4). Following drug cessation, all patients' creatinine levels normalised. The mean duration of treatment for this group was 4.3 months, and the mode was 1 month. There was no difference in drug levels between those who tolerated tacrolimus (15 had levels checked) and those who withdrew due to adverse effects (n=14) (means/ng/mL: 9.60 vs 9.63, P=0.98).

CONCLUSION

Tacrolimus was shown in randomised controlled trials to be of short-term benefit in patients with refractory moderate to severe UC. NICE recommends its use, although for up to 12 weeks, in appropriate patients,¹ and the recent European Crohn's and Colitis Organisation (ECCO) guidelines advise it as an option for

Table 4 Reasons for drug withdrawal due to side effects (not mutually exclusive)

Reason for withdrawal	Number of patients (total=35) (n (%))
Renal failure	10 (29)
Abdominal pain/nausea	4 (11)
Sensorimotor neurological symptoms (eg, twitching, paraesthesiae and burning sensation)	4 (11)
Headache	2 (6)
Recurrent urinary tract infections	1 (3)
Hypertension	1 (3)
Non-specific side effects	2 (6)

moderate disease refractory to oral steroids.⁸ Our experience over the past 6 years in a district general hospital suggests that, with close monitoring, tacrolimus may be used safely and effectively. Fourteen per cent of 35 patients had a sustained clinical response which, though modest overall, has prevented the need for surgery in this group. Many patients started the drug before infliximab was available. However, even after this, some opted for tacrolimus because of concerns about 8-weekly hospital attendances and long-term side effects. A further appeal was its fast onset time, allowing early assessment of efficacy, and its quick excretion.

This is the largest UK single-centre, prospective, consecutive report of the use of tacrolimus in patients with UC. A particular strength is that the decision to start treatment and subsequent close monitoring was undertaken by a single experienced consultant specialising in IBD. Standard clinical criteria were used during regular clinic review to assess response or the need for treatment withdrawal in the case of dangerous or intolerable side effects. There are a number of limitations with this study. First, the data are uncontrolled. Second, the monitoring of tacrolimus therapy is time intensive, and we relied on an enthusiastic consultant to monitor this. Third, mucosal healing was not assessed, and last, there was no corroboration of clinical assessment by another expert. However, we think that our findings are a useful, informative addition to the relatively sparse literature on tacrolimus therapy particularly outside of tertiary referral centres and clinical trials.

There is relatively little data on the use of tacrolimus in patients with UC. Other than the aforementioned randomised placebo-controlled trials by Ogata and colleagues in Japan,^{5,6} most of the clinical information is limited to retrospective studies. The most comparable UK report is from two tertiary IBD centres in London where 25 patients were initiated on tacrolimus for moderate to severe refractory UC between 2005 and 2011.⁹ On retrospective analysis, 19 patients had been treated concurrently with either prednisolone or a thiopurine. Eleven patients (44%) experienced adverse effects, including tremor (three patients, 12%),

headache and renal failure (affecting two patients, 8%, each). At 6 months, 11 patients (44%) were in clinical remission, and five of these (20% of the original cohort) were in steroid-free remission; this is analogous to our findings.

A retrospective review from Germany of 130 patients taking tacrolimus for refractory UC has also shown benefit. Fourteen per cent required surgery at week 12,¹⁰ which may be augmented with thiopurine cotreatment. Side effects were infrequent and reversible on drug cessation, and none were deemed serious. The most common were tremor and paraesthesiae. The report details the first 12 weeks of treatment, but patients have been continued on it indefinitely with appropriate regular monitoring (*personal communication, Dr E. Stange*).

In studies comparing tacrolimus with anti-TNF biologicals, similar clinical outcomes have been demonstrated. A recently reported retrospective analysis of 122 patients with moderate to severe UC treated with tacrolimus (n=64) or infliximab (n=58) showed a statistically insignificant difference in remission at week 14.¹¹ This supports previous similar findings.^{12,13}

With recent NICE approval of biologicals for moderate to subacute UC, the emergence of new biological therapies and the availability of generic anti-TNF therapy, one could assume that there is little to be gained from tacrolimus with its side effect profile and possibly limited therapeutic benefit. However, we still feel that it has an important role in the management of UC for the following reasons.

First, the intention-to-treat benefit from biological agents in patients with refractory UC is limited. The Active ulcerative colitis trial 2 (ACT 2) study randomised patients with moderate to severe UC to placebo, 5 mg/kg infliximab or 10 mg/kg infliximab with the continuation of previous immunosuppressive medication.¹⁴ It reports that, at 30 weeks, 25.6% were in clinical remission. The Ulcerative colitis long-term remission and maintenance with adalimumab 2 (ULTRA 2) trial compared adalimumab with placebo for moderate to severe UC.¹⁵ Clinical remission was achieved in only 8.5% of patients at week 52. The double-blind GEMINI 1 study compared vedolizumab, a monoclonal antibody targeting the gut-specific $\alpha_4\beta_7$ integrin, against placebo for the treatment of moderately active UC.¹⁶ At week 52, on an intention-to-treat basis, only 21% had durable clinical remission.

Second, all the current biological therapies require parenteral administration, with associated inconvenience and cost implications. Third, side effects are common. Up to 29% of patients on anti-TNF therapy were found to have developed skin lesions in a recent retrospective study, including eczema in over 50% of cases.¹⁷ These may be delayed (median: 1.9 years from initiation) and can cause troublesome pain, pruritus and disfigurement. Treatment cessation was required in 10% of patients.

Biological treatment may not, therefore, be the *holy grail* of treatment for UC that was hoped. Despite

some patients having excellent, life-changing clinical outcomes, many will ultimately fail all medical therapy and require surgery. There may, therefore, be a role for tacrolimus, which has shown positive results in several studies. Our 'real world' data suggest that those with disease limited to the sigmoid colon have the highest chance of benefit. Though success was more common in biological-naïve patients, 20% of the responders had been previously treated with infliximab. Our findings did not demonstrate any other predictors of success, such as age at diagnosis, drug levels, serological markers or endoscopic findings. An approach may therefore be to offer tacrolimus to those with limited disease who are able to engage with regular monitoring but decline or do not tolerate biologicals, or hope to avoid surgery. Side effects, including renal failure, seem to be fully reversible but clearly need to be discussed in detail before treatment.

In our uncontrolled cohort of patients treated with tacrolimus for moderate to severe UC, 14% of the 35 patients had sustained clinical response on a twice daily oral medication regimen with good drug tolerance. Following our experiences, and in line with NICE⁶ and ECCO⁷ guidance, we recommend that tacrolimus is considered in suitable patients with UC.

Significance of this study

What is already known on this topic

Randomised placebo-controlled trials have shown tacrolimus to be beneficial in ulcerative colitis (UC) that is refractory to conventional therapy. However, despite being recommended in current National Institute for Health and Clinical Excellence and European Crohn's and Colitis Organisation guidelines, it is infrequently used, often, it seems, due to concerns about side effects and efficacy and the advent of biological therapy.

What this study adds

Our single-centre cohort study—to our knowledge, the largest such consecutive cohort in the UK—demonstrates that tacrolimus can be useful in such patients. Side effects including renal failure and sensorimotor disturbances were fully reversible. Five patients of our 35-patient cohort (14%) have sustained steroid-free clinical response, comparable with steroid-free outcomes for biologicals, ranging from 6 to 76 (median 32) months. Treatment was most effective for proctosigmoiditis, but there were no other demographic or biological markers for success.

How might it impact on clinical practice in the foreseeable future

Tacrolimus should be considered in patients with refractory UC, in accordance with national and international guidance. Our data suggest that, with appropriate monitoring, it can be safely used long term. Patients can achieve sustained steroid-free clinical remission with a twice daily oral medication.

Contributors AS performed retrospective data collection, data analysis and interpretation and wrote the manuscript. AH performed prospective data collection, advised about data analysis and interpretation and reviewed draft versions of the manuscript.

Competing interests None declared.

Ethics approval As this work is a prospective quality assurance audit, ethics committee approval is not required.

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Data sharing statement No additional unpublished data are available.

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