Journal of Crohn's and Colitis (2013) 7, e516–e521

Available online at www.sciencedirect.com

ScienceDirect

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

Jonathan Landy [a], Mahmood Wahed [b], Simon T.C. Peake [a], Mohammed Hussein [a], Siew C. Ng [c], James O. Lindsay [b], Ailsa L. Hart [a,*]

[a] IBD Unit, St Mark's Hospital, Harrow, London HA1 3UJ, UK
[b] Digestive Diseases Clinical Academic Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, UK
[c] Department of Medicine and Therapeutics, Institute of Digestive Disease, Chinese University of Hong Kong, Hong Kong

Received 7 October 2012; received in revised form 13 March 2013; accepted 13 March 2013

KEYWORDS
Tacrolimus;
Inflammatory bowel disease;
Ulcerative colitis

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).

☆ Part of this work was previously presented as an abstract at the British Society of Gastroenterology Meeting Birmingham, 2011.

* Corresponding author at: IBD Unit, 4th Floor, St Mark's Hospital, Harrow, London HA1 3UJ, UK. Tel.: +44 2082354000; fax: +44 2082354093.
E-mail addresses: jonathan.landy@nhs.net (J. Landy), m.wahed@qmul.ac.uk (M. Wahed), simontcpeake@yahoo.co.uk (S.T.C. Peake), mohammed626@hotmail.com (M. Hussein), siewchienng@cuhk.edu.hk (S.C. Ng), james.lindsay@bartshealth.nhs.uk (J.O. Lindsay), ailsa.hart@nhs.net (A.L. Hart).

1873-9946/$ - see front matter
http://dx.doi.org/10.1016/j.crohns.2013.03.008

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).

The median duration of total follow-up was 27 months (IQR 12.7–34 months).

3.1. Patient characteristics (Table 1)

Of the 25 UC patients treated with oral tacrolimus, fifteen were male (60%). Seventeen patients were white British and seven patients were of South Asian ethnicity. The mean age at initiation of tacrolimus was 40.3 years (range 16–75 years). Mean disease duration was 6.4 years (range 2–20 years). Fifteen patients had pancolitis, seven left sided disease and three patients had proctitis. All patients had previously been treated with steroids. Twenty three patients had previously been treated with a thiopurine, ten with methotrexate, two had previously received ciclosporin, five anti-TNF therapy and two patients had previously undergone treatment with leucocyte apheresis. Thirteen patients received prednisolone concurrently with tacrolimus at doses ranging between 5 and 50 mg and six patients were concurrently treated with a thiopurine throughout tacrolimus treatment.

3.2. Long-term outcomes

For all patients initiated on oral tacrolimus, the mean mTW score decreased from 10 +/− 0.5 prior to tacrolimus therapy, to 5.8 +/− 0.8 ($p \leq 0.01$ 95% CI 2.7–5.8) at cessation of treatment or at last follow-up for patients continuing treatment. Four patients ceased treatment prior to six months of tacrolimus therapy due to adverse effects and five patients ceased treatment prior to six months due to lack of response to tacrolimus therapy. Sixteen (64%) patients continued tacrolimus therapy for six months or longer with a mean decrease in mTW score of 5.6 at 6 months, from their baseline ($p \leq 0.01$ 95% CI 3.7–7.5) [Fig. 1]. At six months thirteen of the 25 patients started on tacrolimus therapy (52%) had achieved and maintained clinical response and eleven (44%) were in clinical remission.

Endoscopy data prior to tacrolimus therapy and after six months following was available for fourteen patients. Endoscopy data was not available for the nine patients who had ceased tacrolimus therapy prior to six months or for two patients who continued treatment beyond six months. For those patients where endoscopy data was available, the mean Mayo endoscopy subscore decreased from 2.6 +/− 0.1 to 1.2 +/− 0.2 ($p \leq 0.01$ mean reduction 1.4, 95% CI 0.8–1.9) [Fig. 2]. Nine patients (36%) achieved mucosal healing defined as a Mayo score of ≤ 1.

Six (46%) patients treated with prednisolone concurrently were able to withdraw steroids within 2 months of tacrolimus treatment. Five (38%) of these patients achieved steroid free remission at 6 months and 1 patient had clinical response without steroids at six months. Mean trough tacrolimus level prior to cessation of treatment was 6.6 ng/ml. No differences were found in mean trough tacrolimus levels between responders and non-responders (6.7 ng/ml versus 7.1 ng/ml).

Five patients subsequently received anti-TNF therapy. Eight patients (including one patient in remission who decided on colectomy rather than immunosuppression) (32%) subsequently underwent subtotal or panprocto-colectomy within a mean time of 17 months (range 2–45 months) [Figs. 3 and 4]. Seven of the eight patients undergoing surgery were in the group that did not remain on tacrolimus therapy beyond six months of treatment.

Table 1 Patient characteristics.

Patient characteristic	Number of patients (%)
Gender	
–Male	15 (60%)
–Female	10 (40%)
Mean age at initiation of tacrolimus	40.3 years (range16–75 years)
Ethnicity	
–White British	17 (68%)
–South Asian	7 (28%)
–Other	1 (4%)
Mean disease duration	6.4 years (range 2–20 years)
Disease distribution	
–Proctitis (E1)	3 (12%)
–Left sided (E2)	7 (28%)
–Extensive/pancolitis (E3)	15 (60%)
Extra intestinal manifestations	
–Primary sclerosing cholangitis	1 (4%)
–Arthropathy	2 (8%)
Previous therapies	
–5ASA	25 (100%)
–Thiopurine	23 (92%)
–Methotrexate	10 (40%)
–Cyclosporine	2 (8%)
–Infliximab	5 (20%)
–Leucocytapharesis	2 (8%)

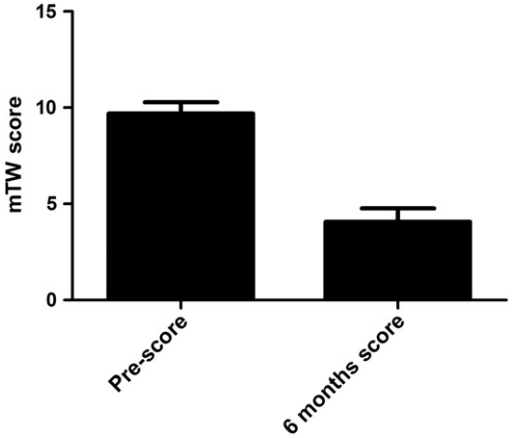

Figure 1 mTW score pre and 6 months post-tacrolimus therapy. mTW score before initiation of tacrolimus and at 6 months for patients treated with tacrolimus for 6 months or longer (n = 16). Mean mTW score decreased from 9.7 +/− 0.6 to 4.1 +/− 0.7; $p \leq 0.01$.

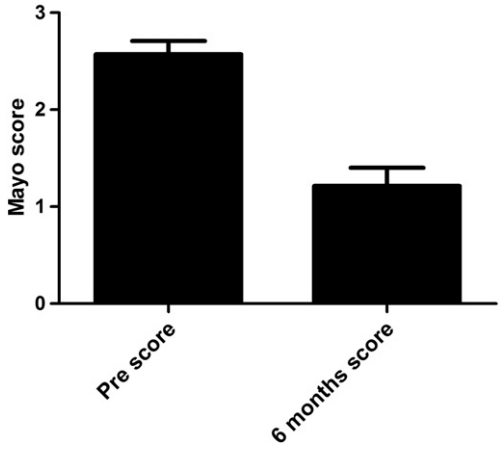

Figure 2 Mayo endoscopy subscore pre and 6 months post-tacrolimus therapy. Mayo endoscopy subscore prior to initiation of tacrolimus treatment and after 6 months of treatment with tacrolimus for patients with endoscopic data available at 6 months following treatment (n = 14). Mean Mayo endoscopy subscore decreased from 2.6 +/− 0.2 to 1.2 +/− 0.2; $p \leq 0.01$.

3.3. Adverse effects (Table 2)

Eleven (44%) patients experienced adverse effects due to tacrolimus. Five patients (20%) ceased treatment with tacrolimus due to adverse effects of the medication. Adverse effects included paraesthesia (n = 2), tremor (n = 3), headache (n = 2), renal impairment (n = 2), leucopenia (n = 2), arthralgia (n = 2) and sepsis (n = 1). Only 1 patient with adverse effects to tacrolimus was found to have supra-therapeutic tacrolimus levels at 13.7 ng/ml. All adverse effects resolved on cessation of tacrolimus. There were no cases of opportunistic infection and no deaths occurred in the patient group studied.

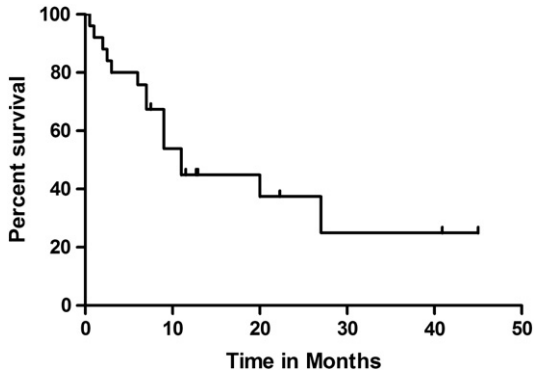

Figure 3 Time to further medical or surgical intervention after tacrolimus initiation. Survival plot showing the time to further medical or surgical intervention after initiating treatment with tacrolimus. The median duration of tacrolimus treatment was 9 months (IQR 3.7–18.2 months). 50% of patients received a further intervention within 11 months after starting tacrolimus treatment.

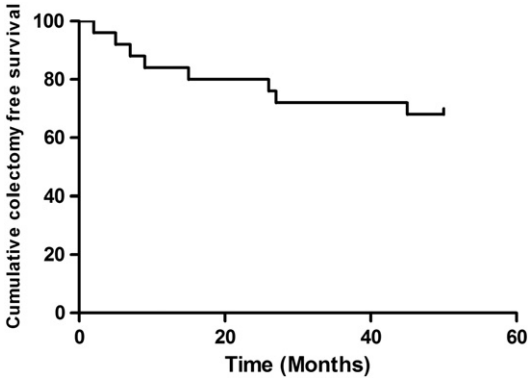

Figure 4 Colectomy free survival after tacrolimus initiation. Colectomy free survival for all patients initiated on tacrolimus treatment. The cumulative colectomy-free survival was estimated as 68%, based on Kaplan–Meier survival analysis at the end of total follow-up.

4. Discussion

The management of refractory UC remains a significant challenge. This group of patients have limited alternative medical treatment options and are at high risk of colectomy. Colectomy and restorative proctocolectomy are associated with potential for immediate and long term complications. Furthermore, some patients despite careful counselling choose not to undergo surgery. Further medical options for the management of steroid and thiopurine refractory UC are needed.

Tacrolimus does not require intravenous administration for the initiation of treatment and may be advantageous for the outpatient maintenance management of this refractory group. The absolute risk reduction for colectomy in ulcerative colitis patients treated with infliximab at one year was 7% in post-study analysis of the ACT-1 and 2 studies.[10]

In this study, 92% of patients had disease refractory to standard therapy with 5ASA, steroids and thiopurines. A significant proportion of patients had also failed to respond to other immunosuppressants and/or biological therapies. This study demonstrated a significant reduction in the mTW score with maintenance tacrolimus therapy. Response and remission rates at 6 months were 52% and 44% respectively. The mean time to colectomy was 17 months. Thirty two percent of patients underwent colectomy. Cumulative colectomy free survival at 24 months following tacrolimus treatment was 80%. This is consistent with previous data.

Table 2 Adverse effects.

Adverse effects frequency	
Paraesthesia	2 (8%)
Tremor	3 (12%)
Headache	2 (8%)
Renal impairment	2 (8%)
Leucopenia	2 (8%)
Sepsis	1 (4%)
Arthralgia	2 (8%)

Four previous retrospective analyses have assessed the long term outcomes of UC patients treated with tacrolimus. All of these include limited numbers of patients, the largest including 40 UC patients.[17] In the previous studies of tacrolimus from Japan,[19,20] the minority of patients had prior exposure to thiopurine treatment and had shorter disease duration. Furthermore, genetic polymorphisms determine tacrolimus response in patients with UC[23] and genetically determined differences between our study population and the Japanese population studied may exist. However, the studies by Benson et al.[18] and Baumgart et al.[17] have similar proportions of patients previously and concurrently treated with thiopurine therapy and comparable duration of disease to the patients in this study, although in these two studies endoscopic scores were not reported.

The duration of tacrolimus treatment and follow-up differs between previous studies. However, remission rates range from 9 to 70% at different time intervals and colectomy rates between 22.5% and 27.5%. Response and remission rates may also be higher in the studies from Japan due to the dose adjustment to higher tacrolimus levels in the initial treatment phase. The first randomised study by Ogata et al. demonstrated an improved dose dependent response at trough tacrolimus levels of 10–15 ng/ml versus 5–10 ng/ml.[15] However, in the study by Baumgart et al.[17] with lower target levels (4–8 ng/ml) high response and remission rates were achieved. Potential consequences of higher levels of tacrolimus may be the frequency of adverse effects necessitating drug withdrawal.

One of the limitations of ciclosporin for maintenance of ulcerative colitis is the rate of adverse effects, in particular, nephrotoxicity. In this study the adverse effect rate was high (44%) with five patients (20%) withdrawing from tacrolimus therapy due to an adverse effect. In only one of these patients was a tacrolimus level greater than 10 ng/ml documented. Renal impairment was seen in only 2 patients in our study. The rate of adverse effects in this study was similar to those in the previous retrospective studies of tacrolimus maintenance therapy.[17–19] All adverse effects resolved on cessation of tacrolimus.

Mucosal healing has not previously been assessed as a long term outcome of tacrolimus treatment for UC. Mucosal healing was demonstrated in both randomised studies of tacrolimus for induction of remission of UC.[15,16] Mucosal healing may be important for the long term clinical outcomes including colectomy rates in UC.[24,25] Early mucosal healing with infliximab has been shown to improve long-term outcomes in UC.[26] Endoscopy data beyond 6 months following tacrolimus initiation was only available in fourteen of the twenty five treated patients in our study. In this subgroup of patients a significant reduction in Mayo endoscopic subscore beyond 6 months after initiation of tacrolimus therapy was demonstrated.

There are a number of limitations to this study. The retrospective design, small number of patients and heterogeneity amongst the patients with regard to prior and concurrent therapies are all significant limitations. Furthermore there was a lack of complete data on all individuals and no comparison group is presented here. Nonetheless this is a subgroup of patients with resistant disease for whom colectomy may be the only option. The retrospective assessment of clinical and endoscopic scores may be subject to bias, but patients were carefully evaluated at each follow-up visit and endoscopy in our IBD centres.

Despite the retrospective design and other limitations of this study the results seem to demonstrate the potential use of tacrolimus as an effective option in the longer-term medical management of patients with refractory ulcerative colitis. Furthermore, the results of the study seem to demonstrate long-term mucosal improvement with tacrolimus therapy that may impact on clinical outcomes including colectomy rates for this group of patients. This study builds on the previous data for maintenance therapy with tacrolimus in UC in the absence of randomised controlled studies, but further studies on larger series of patients are needed.

Conflict of interests

Dr A Hart has been a speaker for and is on the advisory board for Abbot, Shire and MSD.

Dr S Ng has been a speaker for Ferring and Janssen Hong Kong.

Dr J Landy is currently supported by the Eli and Edythe Broad foundation.

Dr S Peake is supported by Abbott and has been a speaker for MSD.

Authors contributions

JL—study data collection, data analysis, statistical analysis, drafting of manuscript.

MW—data collection and writing of manuscript.

SP—data collection and writing of manuscript.

MH—data collection and writing of manuscript.

SN—study conception, data interpretation and writing of manuscript.

JL—study conception, data interpretation and writing of manuscript.

AL—study conception, data interpretation and writing of manuscript.

All authors have read and approved the final manuscript.

Acknowledgements

The authors would like to acknowledge Mr Paul Bassett for statistics advice.

References

1. Cottone M, Scimeca D, Mocciaro F, Civitavecchia G, Perricone G, Orlando A. Clinical course of ulcerative colitis. *Dig Liver Dis* Jul 2008;**40**(Suppl 2):S247–52.
2. Fraser AG, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut* Apr 2002;**50**(4):485–9.
3. Sandborn W, Sutherland L, Pearson D, May G, Modigliani R, Prantera C. Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. *Cochrane Database Syst Rev* 2000;**2**: CD000545.
4. Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2011;**60**(5):571–607.

5. Fraser AG, Morton D, McGovern D, Travis S, Jewell DP. The efficacy of methotrexate for maintaining remission in inflammatory bowel disease. *Aliment Pharmacol Ther* Apr 2002;**16**(4):693–7.
6. Wahed M, Louis-Auguste JR, Baxter LM, Limdi JK, McCartney SA, Lindsay JO, et al. Efficacy of methotrexate in Crohn's disease and ulcerative colitis patients unresponsive or intolerant to azathioprine/mercaptopurine. *Aliment Pharmacol Ther* Sep 15 2009;**30**(6):614–20.
7. Oren R, Arber N, Odes S, Moshkowitz M, Keter D, Pomeranz I, et al. Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology* May 1996;**110**(5):1416–21.
8. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* Dec 8 2005;**353**(23):2462–76.
9. Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* Feb 2012;**142**(2):257–65 [e1-3].
10. Sandborn WJ, Rutgeerts P, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. *Gastroenterology* Oct 2009;**137**(4):1250–60 [quiz 520].
11. Thomson AW, Bonham CA, Zeevi A. Mode of action of tacrolimus (FK506): molecular and cellular mechanisms. *Ther Drug Monit* Dec 1995;**17**(6):584–91.
12. Fellermann K, Ludwig D, Stahl M, David-Walek T, Stange EF. Steroid-unresponsive acute attacks of inflammatory bowel disease: immunomodulation by tacrolimus (FK506). *Am J Gastroenterol* Oct 1998;**93**(10):1860–6.
13. Baumgart DC, Wiedenmann B, Dignass AU. Rescue therapy with tacrolimus is effective in patients with severe and refractory inflammatory bowel disease. *Aliment Pharmacol Ther* May 15 2003;**17**(10):1273–81.
14. Hogenauer C, Wenzl HH, Hinterleitner TA, Petritsch W. Effect of oral tacrolimus (FK 506) on steroid-refractory moderate/severe ulcerative colitis. *Aliment Pharmacol Ther* Aug 15 2003;**18**(4):415–23.
15. Ogata H, Matsui T, Nakamura M, Iida M, Takazoe M, Suzuki Y, et al. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* Sep. 2006;**55**(9):1255–62.
16. Ogata H, Kato J, Hirai F, Hida N, Matsui T, Matsumoto T, et al. Double-blind, placebo-controlled trial of oral tacrolimus (FK506) in the management of hospitalized patients with steroid-refractory ulcerative colitis. *Inflamm Bowel Dis* May 2012;**18**(5):803–8.
17. Baumgart DC, Pintoffl JP, Sturm A, Wiedenmann B, Dignass AU. Tacrolimus is safe and effective in patients with severe steroid-refractory or steroid-dependent inflammatory bowel disease—a long-term follow-up. *Am J Gastroenterol* May 2006;**101**(5):1048–56.
18. Benson A, Barrett T, Sparberg M, Buchman AL. Efficacy and safety of tacrolimus in refractory ulcerative colitis and Crohn's disease: a single-center experience. *Inflamm Bowel Dis* 2008;**14**(1):7–12.
19. Yamamoto S, Nakase H, Mikami S, Inoue S, Yoshino T, Takeda Y, et al. Long-term effect of tacrolimus therapy in patients with refractory ulcerative colitis. *Aliment Pharmacol Ther* 2008;**28**(5):589–97.
20. Yamamoto S, Nakase H, Matsuura M, Masuda S, Inui K, Chiba T. Tacrolimus therapy as an alternative to thiopurines for maintaining remission in patients with refractory ulcerative colitis. *J Clin Gastroenterol* Jul. 2011;**45**(6):526–30.
21. Ng SC, Arebi N, Kamm MA. Medium-term results of oral tacrolimus treatment in refractory inflammatory bowel disease. *Inflamm Bowel Dis* 2007;**13**(2):129–34.
22. Lichtiger S, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* Jun. 30 1994;**330**(26):1841–5.
23. Herrlinger KR, Koc H, Winter S, Teml A, Stange EF, Fellermann K, et al. ABCB1 single-nucleotide polymorphisms determine tacrolimus response in patients with ulcerative colitis. *Clin Pharmacol Ther* Mar 2011;**89**(3):422–8.
24. Ardizzone S, Cassinotti A, Duca P, Mazzali C, Penati C, Manes G, et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. *Clin Gastroenterol Hepatol* Jun 2011;**6**:483–9 [e3].
25. Kobayashi T, Naganuma M, Okamoto S, Hisamatsu T, Inoue N, Ichikawa H, et al. Rapid endoscopic improvement is important for 1-year avoidance of colectomy but not for the long-term prognosis in cyclosporine A treatment for ulcerative colitis. *J Gastroenterol* Nov 2010;**45**(11):1129–37.
26. Colombel JF, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* Oct 2011;**141**(4):1194–201.