Tacrolimus—finally!

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Tacrolimus appears to be at least comparable to ciclosporin in refractory ulcerative colitis in terms of tolerability and efficacy but the oral route of administration and reliability of drug levels are advantageous

Tacrolimus is a new calcineurin inhibitor widely used in transplantation medicine. Similar to ciclosporin, tacrolimus inhibits the calmodulin sensitive serine phosphatase calcineurin, thereby reducing NF-AT activation. In this issue of *Gut*, Ogata and colleagues¹ present the first randomised controlled trial of tacrolimus in patients with “refractory” ulcerative colitis (see page 1255). Two tacrolimus arms with low and high trough levels were compared with a placebo group. Oral dosing was adjusted to trough levels by an external board to secure blinding. The primary end point was the proportion of patients with improvement after two weeks based on a disease activity index (DAI) score, a composite of clinical and endoscopic findings, with a range of 0–12 points. Sixty patients were included in the efficacy analysis, of whom only 15 had been “steroid resistant”. Improvement (decrease in DAI score by ≥ 4) was achieved in 68%, 38%, and 10% in the high trough, low trough level, and placebo groups, respectively. Remission (DAI score ≤ 2) was achieved in 20%, 11%, and 6%, respectively. Open label tacrolimus extension for another 10 weeks in 58 patients yielded an improvement in 55% and remission in 29%. Endoscopic healing was achieved in 73% and a steroid taper was possible in both steroid resistant and dependent cases. Adverse events were tolerable, with a case of severe viral gastroenteritis and one with acinetobacter sepsis but no mortality.

Although this trial is well designed and results are convincing, there are several limitations. The randomised part of the study was ultrashort, with only two weeks’ duration, possibly for ethical reasons. However, the previous uncontrolled trials with longer duration^{2–4} as well as the uncontrolled extension period in the present study are in line with those results. Sample size in the present phase II trial was too small to prove outcome differences between the high and low trough groups. Although a dose ranging study of tacrolimus in

ulcerative colitis has not yet been performed, levels in the range of the low trough group (4–6 $\mu\text{g/ml}$) were associated with an excellent outcome in a recent trial.⁴ In our previous study, drug levels achieved by intravenous or oral application were similar and stable over time.³ Therefore, intravenous administration of tacrolimus is avoidable. Remission was achieved in 13/38 patients while the colectomy rate was 50% in patients with a follow up of at least two years. Thus about half of a tacrolimus treated cohort benefit from this medication (that is, the glass is half full (or half empty)).

Another issue is disease severity. Surprisingly, in the present trial, none of the patients enrolled underwent colectomy, in contrast with failure rates with the need for colectomy in the earlier ciclosporin and tacrolimus series ranging from 10% to 50%. Thus it is questionable whether disease in the present study was comparably severe or, alternatively, Japanese surgeons are remarkably conservative. Indeed, the majority of patients were “refractory” only to low doses of corticosteroids (<30 mg/day, mean 15 mg/day) and may well have responded to higher doses. The term “steroid dependent” for these patients is a misnomer because they had active disease. In a truly steroid dependent cohort, azathioprine, which was not used in the study by Ogata *et al*, is an important option.⁵ Finally, it remains unknown why some patients experience endoscopic but not clinical remission, but this may be due more to the limitations of end point definitions than a weakness of the study.

What are the alternatives in such a patient group? The benefit of ciclosporin was initially demonstrated in a short and even smaller randomised controlled trial in patients with severe steroid refractory disease.⁶ The intravenous dose of 4 mg/kg per day was high. Trough blood levels varied markedly both inter- and intraindividually and were approaching toxic ranges resulting in serious adverse events (for example,

renal insufficiency and seizures). Another trial compared methylprednisolone with ciclosporin in moderate to severe ulcerative colitis and demonstrated similar efficacy in the short term.⁷ However, in the long term, ciclosporin was superior to steroids with regard to remission maintenance. Van Assche *et al* were able to reduce the ciclosporin dose to 2 mg/kg/day, reducing adverse events with similar efficacy compared with the standard dose of 4 mg/kg.⁸ Avoiding the intravenous route by administration of oral micro-emulsion ciclosporin preparations seems to be equally effective.⁹ Several larger retrospective analyses confirmed the findings of the initial study by Lichtiger and colleagues.^{10–13} Overall efficacy in the short term, determined by prevention of colectomy, ranged between 60% and 90%. Long term colectomy free survival was lower, with again about half of the patients undergoing proctocolectomy beyond three years and still 42% retaining their colon after seven years.¹³ However, addition of purine analogues to the ciclosporin regimen apparently increased efficacy, indicating additive effects in maintenance of remission.¹⁴ Thus ciclosporin or tacrolimus appear to be useful for rapid induction of remission until the effect of purine analogues kicks in.

Similar to the previous uncontrolled observations, tolerability in the present trial was excellent, even in the high trough level group. The only frequent side effect was tremor. It has to be mentioned that follow up was short. In comparison, a retrospective analysis of more than 300 patients with inflammatory bowel disease treated with ciclosporin reported additional frequent side effects, including paresthesia, hypertrichosis, and arterial hypertension.¹⁵ Deterioration of renal function is another serious adverse effect, reported in approximately 6% of patients treated with ciclosporin. From the uncontrolled series on tacrolimus, the frequency of slight and reversible renal impairment tended to be within the same range.³ Thus with the possible exception of diabetes (not observed in the present trial), tacrolimus appears to be at least comparable to ciclosporin in terms of tolerability and efficacy but the oral route of administration and reliability of drug levels are advantageous. However, triple immunosuppression with steroids, purine analogues, plus a calcineurin inhibitor such as ciclosporin or tacrolimus may be associated with an increased risk of serious and possibly lethal infections, including pneumocystis carinii.¹²

Are biologicals a reasonable alternative? Infliximab, originally tested and

approved for Crohn's disease, failed in a first placebo controlled trial in moderately active ulcerative colitis¹⁶ but was effective in a second trial with more severe disease. In this trial patients received a single infusion of infliximab or placebo in case of steroid refractoriness.¹⁷ Colectomy or death at three months were chosen as tough end points which 71% in the infliximab group avoided whereas 67% of the placebo patients lost their colon. Notably, those with fulminant colitis did not benefit from infliximab, only those with less severe disease. Meanwhile, two large randomised controlled trials have been conducted showing efficacy in moderate to severe disease.¹⁸ Although "response" rates were satisfactory with almost 70% responding and remission rates ranged from 30% to 40% in the short term, long term exposure was characterised by loss of response and sustained remission was maintained in only one of five patients at one year. Mucosal healing was observed in approximately 60% by week 8. There was a death from histoplasmosis. Therefore, provided those cohorts were comparable, short term remission rates and mucosal healing are quite similar to tacrolimus. Toxicity, including severe adverse events (for example, tuberculosis and sepsis) with mortality ranging up to 2%,¹⁹⁻²⁰ is a major drawback of infliximab and highlights the need for critical consideration of the indication. Other antibodies have been proposed, such as basiliximab (anti-CD25), natalizumab (anti- $\alpha 4\beta 7$ integrin), or daclizumab (anti-IL2R), but controlled trials are still lacking. Only visilizumab (anti-CD3) has been investigated in a randomised controlled trial and the study awaits closure. Preliminary data suggest efficacy comparable with infliximab but this drug seems to cause considerable side effects due to cytokine release.

Considering the fact that we published the first series of tacrolimus treated ulcerative colitis patients in 1998, why did it take so long to perform the controlled trial? Because of commercial considerations, the pharmaceutical company producing the drug was not interested in this indication. Therefore, it is of paramount importance that institutions other than pharmaceutical companies accept the task of financing appropriate investigator driven randomised controlled trials for certain indications. These could include health insurance providers and research foundations which have been reluctant to fund "clinical trials". Otherwise,

promising and time honoured drugs such as cyclophosphamide,²¹ leflunomide,²² or mycophenolate mofetil²³⁻²⁵ will never be subjected to critical appraisal in well conducted studies. In the end, both the patient and his physician will have to take what the profit oriented pharmaceutical industry supported by their national drug administration agencies will offer and not what is effective and safe as well as economical.

What is best clinical practice in refractory ulcerative colitis in view of the present study? Based on the route of application and the reliable as well as stable drug levels, we believe that tacrolimus may have an advantage over cyclosporin although a direct head to head comparison is urgently needed. In the short term, tacrolimus seems to be comparable if not better than infliximab; both tolerability and costs are favourable. Since the trial by Ogata and colleagues¹ was restricted to patients without thiopurine therapy, the additive effect and safety of these agents remains to be determined. With its rapid onset of action, tacrolimus should probably best be used as a bridging therapy to the delayed onset azathioprine.

Gut 2006;**55**:1224-1225.

doi: 10.1136/gut.2006.093302

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Conflict of interest: None declared.

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