

Randomized controlled trial of tacrolimus and prednisolone monotherapy for adults with *de novo* minimal change disease

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Running title: Tacrolimus monotherapy for *de novo* minimal change disease

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Abstract

Background and objectives: Minimal change disease is an important cause of nephrotic syndrome in adults. Corticosteroids are first-line therapy for minimal change disease but a prolonged course of treatment is often required, and relapse rates are high. Patients with minimal change disease are therefore often exposed to high cumulative corticosteroid doses and are at risk of associated adverse effects. This study investigated whether tacrolimus monotherapy without corticosteroids would be effective for the treatment of *de novo* minimal change disease.

Design, setting, participants and measurements: This was a multicenter prospective, open-label, randomized controlled trial involving 6 nephrology units across the UK. Adult patients with first presentation of minimal change disease and nephrotic syndrome were randomized to treatment with either oral tacrolimus at 0.05mg/kg twice daily, or prednisolone at 1mg/kg daily up to 60mg daily. The primary outcome was complete remission of nephrotic syndrome after 8 weeks of therapy. Secondary outcomes included remission of nephrotic syndrome at 16 and 26 weeks, rates of relapse of nephrotic syndrome and changes from baseline renal function.

Results: There were no significant differences between the tacrolimus and prednisolone treated cohorts in the proportion of patients in complete remission at 8 weeks, 21 of 25 (84%) for prednisolone and 17 of 25 (68%) for tacrolimus ($p=0.32$, differences in remission rates were 16% (95% CI -10.5% to 40.1%)), at 16 weeks, 23 of 25 (92%) for prednisolone and 19 of 25 (76%) for tacrolimus ($p=0.25$, difference in remission rates 16% (95% CI -7.9% to 38.0%)), or at 26 weeks, 23 of 25 (92%) for prednisolone and 22 of 25 (88%) for tacrolimus ($p=0.99$, difference in remission rates 4% (95% CI -17.4% to 25.4%)). There was no significant difference in relapse rates (17 of 23 (74%) for prednisolone and 16 of 22 (73%) for tacrolimus) for patients in each group who achieved complete remission ($p=0.99$), or in the time from complete remission to relapse.

Conclusion: Tacrolimus monotherapy can be effective alternative treatment for patients wishing to avoid steroid therapy for minimal change disease.

Introduction

Minimal change disease causes up to 25% of nephrotic syndrome in adults¹⁻³. Nephrotic syndrome is associated with significant comorbidities including infections^{4, 5}, thromboembolic events^{6, 7} and hyperlipidaemia⁸. Furthermore, acute kidney injury accompanies the presentation of minimal change disease in up to 25% of cases⁹. Consequently, most clinicians recommend treatment for minimal change disease patients with high doses of corticosteroids. However, this is a rare disease and there is a paucity of data from randomized controlled trials in adults on the efficacy of therapy¹⁰⁻¹². Many adult patients require a prolonged initial course of corticosteroids to enter remission^{9, 13-15}. Additionally, the relapse rate in adults is high at 48-76% and worse in adults younger than 45 years of age^{9, 13}. This necessitates the use of repeated courses of steroids. The resultant high-dose corticosteroid exposure is associated with adverse effects including weight gain, diabetes mellitus, infection, osteoporosis, cosmetic changes and gastrointestinal bleeding^{14, 16}.

Steroid-sparing therapeutic agents have been used to treat patients with frequently relapsing or steroid dependent minimal change disease¹⁷. These include cyclophosphamide, ciclosporin, tacrolimus, mycophenolate and, more recently, rituximab¹⁸⁻²⁹. Tacrolimus is widely available and generally well tolerated and therefore a relatively attractive alternative to corticosteroids for treatment of minimal change disease. Minimal change disease pathogenesis is thought to be dependent on systemic T lymphocyte changes and subsequent cytokine production that impairs glomerular function¹⁷. Tacrolimus is a calcineurin inhibitor which suppresses interleukin 2 (IL-2) transcription and inhibits T-cell activation. Tacrolimus may also reduce proteinuria by directly stabilising podocyte structure³⁰. Additionally, tacrolimus may be associated with a more favourable side effect profile than alternative calcineurin inhibitors such as ciclosporin as well as having fewer side effects than corticosteroids²⁸.

Retrospective case series report successful tacrolimus treatment of frequently relapsing, steroid dependent and steroid resistant minimal change disease^{19, 26}. Likewise, ciclosporin has been used as monotherapy in prospective trials of steroid dependent and steroid resistant minimal change disease treatment^{22, 31}. As significant corticosteroid toxicity can occur from the first, often prolonged, therapeutic course for minimal change disease, as well as from subsequent courses given for relapses, steroid sparing agents such as calcineurin inhibitors and cyclophosphamide are sometimes also used for a first

presentation of minimal change disease. However, there are few data on the effectiveness of steroid free regimens for *de novo* disease.

In kidney transplantation, steroid avoidance or early withdrawal results in improved blood pressure, and lower rates of new-onset diabetes, dyslipidaemia, weight gain and infections³²⁻³⁵. These associations appear to be dose-dependent³⁶. Steroid free regimens may likewise be beneficial in minimal change disease.

This prospective multicentre, randomized, open-label trial compared tacrolimus and prednisolone monotherapy for the treatment of adult patients with minimal change disease and investigated the hypothesis that tacrolimus monotherapy is non-inferior to corticosteroids for inducing remission, has comparable relapse rates but is associated with fewer adverse events. This is the first prospective multicentre trial of steroid-free treatment for *de novo* minimal change disease in adults.

Methods

This was a multicenter, randomized controlled trial which recruited patients from 6 of the 7 units enrolled in the study. The study protocol was registered at the European Clinical Trials Database (EudraCT, number 2009-014292-52) and ClinicalTrials.gov (Identifier: NCT00982072). The trial was conducted in accordance with the Declaration of Helsinki. Ethics approval was obtained from the United Kingdom (UK) National Research Ethics Service Committee (UKNES Reference 09/H0711/68).

The inclusion criteria were; age over 18 years; nephrotic syndrome; and a kidney biopsy showing minimal change disease. We defined nephrotic syndrome as the combination of urine protein creatinine ratio (UPCR) greater than 100mg/mmol and a serum albumin of less than 3.0g/dl. We adopted this level of proteinuria to avoid excluding patients with hypoalbuminemia and significant but non-nephrotic range proteinuria, which may have been subsequent to severe hypoalbuminemia. Only one patient in each cohort had UPCR less than 300mg/mmol, and these patients had UPCR of 249 and 261mg/mmol respectively. Biopsies were examined and reported locally and reviewed by a single histopathologist (Professor H. Terence Cook) if there was diagnostic uncertainty. Patients were excluded if they had any of the following; Hepatitis B, C, or human immunodeficiency virus infection; other untreated infections; females who were pregnant, breast feeding, or at risk of pregnancy; patients who have had

immunosuppression for nephrotic syndrome in the last 18 months or immunosuppression that may affect the outcome of their current episode of nephrotic syndrome; any condition that would cause the study to be detrimental to the patient.

Local responsible clinicians directed the management of hypertension with angiotensin receptor blockers or angiotensin converting enzyme inhibitors and hypercholesterolaemia with statins. Primary venous thromboembolism prophylaxis in the form of subcutaneous low molecular weight heparin while serum albumin was less than 2.0g/dl or aspirin 75mg daily if the serum albumin was 2.0g/dl or more but less than 3.0g/dl³⁷. Patients considered to be at high risk of latent tuberculosis were also prescribed isoniazid 150mg daily and pyridoxine 50mg weekly during immunosuppression treatment.

We randomized patients at a 1:1 ratio to receive either oral tacrolimus or prednisolone. Participants were enrolled by the local principal investigators (PI) at each site. Consecutively enrolled patients were allocated a trial number by the lead site. Before the trial commenced, each trial number was randomized to a treatment arm by computer-generated random permuted blocks (with concealment of block size from the clinical team). Allocation and masking was through computer-generated sheets in opaque, tamper-evident envelopes (one for each trial number) that were stored securely at the lead site and opened by the trial team following each patient enrolment. The intervention assignment was communicated to the local PI. Randomization sequence was not known by the trial investigators. The treatment was non-blinded after intervention assignment. The trial was monitored throughout by the data monitoring committee. Trial recruitment finished after the target study population had been reached and was closed when all patients had completed follow-up.

Patients allocated to tacrolimus received an initial dose of 0.05mg/kg twice daily, with target blood trough levels of 6-8ng/ml. In the event of inadequate clinical response at 8 weeks treatment, the target blood trough level was increased to 9-12ng/ml. Twelve weeks after achieving complete remission, the tacrolimus doses were gradually reduced over 8 weeks and stopped. Patients allocated to prednisolone received initial doses of 1mg/kg/day with a maximum dose of 60mg/day. One week after achieving complete remission, the steroid dose was halved for 4-6 weeks then gradually reduced and stopped over a further 6 weeks ensuring patients received a minimum of 16 weeks of prednisolone. Patients receiving prednisolone were also prescribed omeprazole 20mg and Calcichew D3 two tablets daily.

The primary outcome was the proportion of patients achieving complete remission at eight weeks. We defined complete remission *a priori* as UPCR less than 50mg/mmol. Partial remission was defined as urine protein creatinine ratio reduction of at least 50% from enrolment and a value between 50mg/mmol and 300mg/mmol. The secondary outcomes were the proportion of patients achieving complete remission at 16 and 26 weeks, the proportion who relapsed following complete remission, change in serum creatinine from baseline and the number of adverse events. Relapse was defined as UPCR more than 300mg/mmol in patients who had achieved complete remission. Patients who achieved complete remission were followed up for 78 weeks +/- 2 weeks from complete remission or until relapse. We reviewed patients weekly for 4 weeks, then monthly for 6 months, then every 3 months, or more frequently at the investigators' discretion if clinically indicated. At each review we measured proteinuria (UPCR), and tested blood for full blood count, biochemical profile, non-fasting glucose and trough tacrolimus levels. The per-protocol analysis evaluated patients who completed at least 8 weeks of therapy. We also compared outcomes on an intention to treat basis.

Statistical advice on sample size calculations was provided by the Department of Statistics, Imperial College London. Non-inferiority was assessed by estimating the two-sided 95% confidence interval (CI) for the difference in remission rates between the two groups using the Koopman asymptomatic score³⁸. We aimed to verify that the lower limit of the 95% CI was not lower than 10% (delta value of -0.1). The expected complete remission rate for patients treated with corticosteroids at eight weeks was estimated at 60%²³, and tacrolimus at 84%⁴⁰. Allowing for a 10% drop-out rate, we calculated we needed to enrol 52 patients. We used GraphPad Prism Version 6.00 for Windows for statistical analyses. Normally distributed continuous variables were compared using unpaired t-test. Continuous variables with skewed distribution were compared using Mann-Whitney U test and confidence intervals were calculated using the Hodges-Lehmann method. We compared the proportion of patients in remission and relapse with Fisher's exact test and used the Baptista-Pike method to calculate odds ratio (OR) confidence intervals and the Newcombe/Wilson method with continuity correction for confidence intervals of differences in proportions. We adjusted p-values for differences in remission rates for multiple analyses with the two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli³⁹.

Results

Patients

We enrolled 55 patients from 6 hospitals across the UK. All patients had *de novo* disease. Three patients were excluded after review of their biopsy following electron microscopy determined they had an alternative diagnosis (features of membranous nephropathy in 2 and lupus nephritis in 1 patient). Randomization allocated 27 patients to tacrolimus and 25 patients to prednisolone treatment (Figure 1). Two patients in the tacrolimus group did not complete 8 weeks treatment; 1 patient developed an allergic rash and diarrhea 2 days after starting tacrolimus; 1 patient developed lower respiratory tract infection 8 days into treatment and were withdrawn on the request of the local clinician. 10 patients in each cohort received treatment for hypertension with angiotensin receptor blockers or angiotensin converting enzyme inhibitors (Table 1). The median total treatment time until relapse of nephrotic syndrome, or completion of withdrawal was 36 weeks (inter quartile range (IQR) 26 to 52 weeks) for the tacrolimus cohort compared to 23 weeks (IQR 14 to 29 weeks) for the corticosteroid treated cohort. The median follow-up across the study was 44 weeks (IQR 22 to 82 weeks).

Primary outcome

There were no significant differences between the treatment arms in the proportion of patients in complete remission at 8 weeks, although the results did not meet the *a priori* definition of non-inferiority.

Intention to treat analysis: 21 of 25 (84%) patients in the prednisolone and 17 of 27 (63%) patients in the tacrolimus cohorts were in remission at 8 weeks, $p=0.12$. The difference in remission rates was 21% (95% CI -5.9% to 44.2%).

Per-protocol analysis: Of patients who completed 8 weeks treatment, 21 of 25 (84%) for prednisolone and 17 of 25 (68%) for tacrolimus were in remission at 8 weeks, $p=0.32$. The differences in remission rates were 16% (95% CI -10.5% to 40.1%) (Table 2, figure 2).

Secondary Outcomes:

Remission rates

There were no significant differences between the treatment arms in the proportion of patients in complete remission at 16 or 26 weeks.

Intention to treat analysis: At 16 weeks, 23 of 25 (92%) prednisolone treated and 19 of 27 (70%) tacrolimus treated patients were in complete remission ($p=0.08$, difference in remission rates 22% (95% CI -3.1% to 43.4%)). At 26 weeks, the proportions were 23 of 25 (92%) for prednisolone and 22 of 27 (81%) for tacrolimus ($p=0.71$, difference in rates 11% (95% CI -12.1 to 31.8%)).

Per-protocol analysis: Analysis of patients completing 8 weeks treatment showed 23 of 25 (92%) prednisolone treated and 19 of 25 (76%) tacrolimus treated patients in complete remission at 16 weeks ($p=0.25$, difference in remission rates 16% (95% CI -7.9% to 38.0%)). At 26 weeks, the proportions were 23 of 25 (92%) for prednisolone and 22 of 25 (88%) for tacrolimus ($p=0.99$, difference in remission rates 4% (95% CI -17.4% to 25.4%)) (Table 2, figure 2).

Relapse rates

There was no significant difference between the tacrolimus and prednisolone treated cohorts in the proportion of patients who relapsed after achieving complete remission (Table 2). Relapse following complete remission was recorded in 17 of 23 of the prednisolone, and 16 of 22 of the tacrolimus cohorts ($p=0.99$; difference in relapse rates 1% (95% CI -21.9% to 25.6)). The timings of relapses were similar between the two treatment groups (Figure 3). At 26 weeks from complete remission, 13 of 23 (57%) of prednisolone and 15 of 22 (68%) of tacrolimus cohorts were relapse free ($p=0.54$; difference in relapse rates 11% (95% CI -15.9% to 41.9%)). Two of the patients in remission in the prednisolone group subsequently left the UK and were lost to follow up; one at 36 weeks and one at 40 weeks. At 52 weeks, 7 of 21 (33%) of prednisolone and 9 of 22 (41%) of tacrolimus treated patients were relapse free ($p=0.75$; difference in relapse rates 8% (95% CI -21.1% to 38.1%)). At 78 weeks, 4 of 21 (19%) of prednisolone and 6 of 22 (27%) of tacrolimus treated patients were relapse free ($p=0.72$; difference in relapse rates 8% (95% CI -18.2% to 36.5%)). Most relapses occurred after immunosuppression treatment had been stopped (9 of 17 (53%) relapses in the prednisolone and 9 of 16 (56%) in the tacrolimus treatment cohorts). The duration of remission was not statistically different between the prednisolone and tacrolimus treated cohorts (median time complete remission to relapse 22.0 weeks in the prednisolone and 32.7 weeks in tacrolimus cohort, $p=0.72$).

There were no significant differences in mean serum creatinine between the treatment groups during 12 months follow-up (Figure 4).

Other outcomes

Post-hoc analysis demonstrated a significantly greater proportion of patients treated with prednisolone were in complete remission at 4 weeks. By intention to treat analysis, complete remission rates were 16 of 25 (64%) in the prednisolone and 6 of 27 (22%) in the tacrolimus cohorts ($p=0.005$, difference in remission rates 42% (95% CI 12.2% to 63.3%)). And the per-protocol analysis showed 16 of 25 (64%) patients in the prednisolone and 6 of 25 (24%) in the tacrolimus cohorts were in complete remission at 4 weeks ($p=0.01$, difference in remission rates 40% (95% CI 12.5% to 60.1%)). However, post-hoc analysis of total remission rates (complete or partial remission) at 4 weeks showed no significant difference between treatment arms. By intention to treat analysis, 20 of 25 patients (80%) in the prednisolone and 19 of 27 patients (70%) in the tacrolimus cohort achieved complete or partial remission at 4 weeks ($p=0.53$ difference in remission rates 10% (95% CI -16.5% to 33.8%)). And the per-protocol analysis showed 20 of 25 patients (80%) in the prednisolone and 19 of 25 patients (76%) in the tacrolimus cohort achieved complete or partial remission at 4 weeks ($p=0.99$, difference in remission rates 4% (95% CI -21.6% to 28.8%)).

Post hoc analysis of the per-protocol cohorts showed the mean serum albumin was significantly higher in the prednisolone than the tacrolimus cohort at 4 weeks follow-up (3.24g/dl in the prednisolone and 2.75g/dl in the tacrolimus cohorts, $p=0.03$; difference in means 0.49g/dl, 95%CI 0.05 to 0.93g/dl). No significant difference in albumin was detected at the other time points. Differences in UPCR did not reach statistical significance at 4 weeks follow-up (median prednisolone cohort UPCR 11mg/g (inter quartile range (IQR) 6-109mg/g); median tacrolimus cohort UPCR 58mg/g (IQR 6-216mg/g), $p=0.36$) or at subsequent time points.

Adverse events

Adverse events were recorded from the intention to treat cohorts. Eighteen adverse events were recorded from 25 patients in the prednisolone cohort (0.72 events per patient), and 20 adverse events

were recorded in the 27 patients in the tacrolimus cohort (0.74 events per patient, $p=0.99$ compared to the prednisolone cohort) (Table 3). There were 4 serious adverse events (SAE) that required admission in the prednisolone and 3 in the tacrolimus cohorts ($p=0.99$ for difference in SAE rates between the treatment cohorts). Specifically, there were admissions for perforated diverticular disease, severe headache, traumatic fractured radius, and lower respiratory tract infection in the prednisolone cohort (Table 3). In the tacrolimus cohort, there were admissions for severe hypertension, diarrhoea and rash 2 days into treatment with subsequent withdrawal from the study, and lower respiratory tract infection 8 days into treatment with subsequent withdrawal from the study. There were no deaths during follow-up in either cohort. We recorded a similar number of infective episodes in each cohort (Table 3). We recorded one episode of hyperglycaemia in each cohort, but both were treated with diet alone; we recorded no new cases of diabetes mellitus in either cohort (Table 3).

Discussion

Minimal change disease is a rare disease in adults, and there is a paucity of clinical trials. Corticosteroids are effective in minimal change disease, but the side effects are significant, hence many patients and their physicians would prefer to consider alternative treatments. However, there are few data in the literature on the effectiveness of steroid free regimens in minimal change disease to inform clinicians and allow appropriate counselling of patients on the likely success of alternative regimens. This is the first prospective, multicenter randomized trial of a corticosteroid-free treatment regimen for *de novo* minimal change disease in adults. Although the results did not meet our *a priori* definition of non-inferiority, the lack of significant differences in primary and secondary outcomes between the treatment cohorts demonstrate tacrolimus monotherapy is an effective alternative to corticosteroids for the treatment of minimal change disease. To counter any ambiguity, we have provided intention to treat analysis as well as the per protocol analysis of patient who completed at least 8 weeks of therapy. Post hoc analysis demonstrated more patients treated with prednisolone achieved complete remission at 4 weeks than in the tacrolimus arm. However, the clinical significance of this is not clear, as most patients in both groups had achieved significant reductions in proteinuria ($UPCR < 300\text{mg}/\text{mmol}$) by 4 weeks, and analysis of total remission rates (complete or partial remission) at 4 weeks showed no significant difference between treatment arms. This warrants further study, as it may be relevant in some patients,

especially perhaps those presenting with severe complications of nephrotic syndrome. For patients treated with steroids initially, concomitant tacrolimus treatment, may allow early steroid withdrawal and limitation of steroid associated toxicity, as in the study by Li *et al*⁴²

Rates of complete remission in this trial are comparable to those documented in previous minimal change disease patient series for both steroids and CNIs. Retrospective studies of prednisolone treatment regimens (1mg/kg daily for 4 to 16weeks, and with 24 weeks total treatment) similar to our study, documented remission rates of 70-90% by 16 weeks treatment^{8,9}. In general, calcineurin inhibitor use has predominantly been reported in steroid resistant, steroid dependent and frequently relapsing minimal change disease cases and involved 9 to 12 months treatment, making direct comparison difficult. However, remission rates from these studies were similar at between 60 to 80% with an average time to remission of about 5 weeks⁸. With regards to *de novo* minimal change disease, a single case series of 12 minimal change disease patients with relative contraindications to corticosteroids treated with cyclosporine alone for 12 months documented response rates of 75% and minimal adverse effects²⁴. Data from patients with minimal change disease treated with tacrolimus without prednisolone are limited. However, a number of studies suggest tacrolimus is effective in combination with prednisolone¹⁶ and is better tolerated than cyclosporine as a steroid-sparing agent^{19, 26, 28}. The most comprehensive clinical trial of *de novo* minimal change disease in adults comes from China. In this, Li *et al* compared the use of tacrolimus and prednisolone monotherapy in adults with minimal change disease⁴⁰ after treatment of all patients with high dose daily intravenous methylprednisolone (0.8mg/kg) for ten days⁴⁰. Notably high remission rates were achieved in both cohorts, more than 90% of both treatment cohorts were in remission by four weeks⁴⁰. This may be due to initial use of high-dose intravenous corticosteroids in all their patients, but there may also be a difference in response rates between Chinese and UK patients^{13, 23}.

Relapse rates were similar in our tacrolimus and prednisolone treatment groups and comparable to the 48-76% relapse rates reported in other case series^{9, 13, 14, 41}. Our relapse rate is higher than either of the cohorts in the Li *et al* study⁴⁰. This may also be explained by the use of intravenous methylprednisolone in the Li *et al* study or to racial differences in relapse rates. Other studies have documented relapse rates of 73-76% in predominantly Caucasian patient cohorts compared to 48% in a large cohort from China^{9, 13, 23}. The relapse rates may also reflect treatment regimen durations and doses. At trial design, the sparsity of available data on tacrolimus treatment for minimal change disease led us to adopt a

regimen of modest treatment exposure. We also aimed to use a corticosteroid regimen of similar duration for comparison. This resulted in regimens of relatively modest duration and dosing. Regimens of longer duration and higher dosing may improve relapse rates and should be investigated in future trials.

This study was motivated by the significant adverse effect burden associated with the use of corticosteroids in minimal change disease patients^{11, 42}. Obesity and metabolic syndromes consistently associate with increased all-cause mortality⁴³. There are also significant unpleasant cosmetic side effects associated with steroids such as striae and 'moon facies', which can be especially debilitating for this group of patients, particularly the young adults, and also have an effect on adherence with treatment. Although our study was not powered to demonstrate differences in side-effects, it was reasoned that non-inferiority in terms of remission from nephrotic syndrome in patients with minimal change disease would be likely to portend side-effect benefits for patients treated with tacrolimus compared to corticosteroids. We recorded equal and relatively few adverse events in both treatment regimens. The study by Li *et al* recorded a higher rate of total adverse events (209 adverse events in 119 study patients), and did show an increased adverse event frequency in the prednisolone cohort, particularly osteoporosis and new-onset hypertension⁴⁰. Following intravenous methylprednisolone for ten days, the prednisolone treatment regimen used by Li *et al* provided 1mg/kg oral prednisolone (up to a maximum of 80mg/day) and 22-24 weeks total prednisolone treatment. In comparison our regimen involved no iv methylprednisolone, prednisolone doses up to a maximum of 60mg/day and minimum 16 weeks treatment. The duration and target plasma levels of tacrolimus were similar in the two studies. The lower prednisolone doses and the steroid-free study arm in our study may explain the differences in adverse event burden between the studies. Additional adverse events may be recorded with longer duration of follow up, especially in patients with relapsing minimal change disease who require repeated courses of treatment to achieve and maintain remission.

Our study is relatively small but is none the less important, as most other published data in adults with *de novo* minimal change disease relates to retrospective studies and case series, particularly in Western populations, reflecting the difficulty of conducting studies in this group of patient with a rare disease

Corticosteroids are standard therapy for *de novo* minimal change disease. This study is the first multicentre randomized controlled trial of a steroid free regimen in adults. Based on remission, relapse and adverse event rates, it provides evidence that tacrolimus monotherapy is an effective alternative to corticosteroids for *de novo* minimal change disease. This is highly significant for the treatment of patients with this disease.

Data sharing statement

We are happy to share de-identified collected cohort data and results for comparative and replication research. Additional, related documents such as the study protocol will be available on request. The planned data use must not breach the ethical approval obtained for our study. There is no pre-specified time limit to data availability. Please contact the corresponding author to request access.

Acknowledgements

We thank Tom Walters, Clinical Research nurse for his support and assistance, Bernard North, Department of Statistics, Imperial College London, for advice on calculation of samples size, and Dr Adam Mclean for generating the random allocation sequence.

We acknowledge the NIHR Imperial Biomedical Research Centre (BRC) for support of this study.

Disclosures

B Sood discloses travel sponsorship: Vifor Pharma UK; attending sponsored educational event: Alexion. P Warwicker discloses lecture fees: Alexion. N Turner discloses advisory board member: Otuska, Shire (Takeda), Sanofi Genzyme. J Barratt discloses consultancies: EMD Serono, Omeros, Calliditas, Novartis, Retrophin, Aduro BioTech, Visterra, Alnylam. HT Cook discloses consultancies: Achillion Pharmaceuticals and PsiOxus Pharmaceuticals. J Levy discloses educational advisor: Gilead. L Lightstone discloses research sponsorship: Roche; consultancies: Achillion, Astra Zeneca, Aurinia, Genetech, GSK, Medimmune, Pfizer, Roche, UCB. J Galliford discloses consultancy: Astellas

Pharmaceuticals, and scientific advisor board member: Alexion. M Griffith discloses scientific advisory board member: Vifor Pharma UK. The other authors have no disclosures.

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Figure Legend

Figure 1: Study design and study cohort flow chart. Of 55 patients enrolled, 52 were randomised to treatment, and 25 patients in each cohort completed treatment. Two patients in the tacrolimus group did not complete treatment; 1 patient developed diarrhoea and rash 2 days after starting tacrolimus; 1 patient developed lower respiratory tract infection 8 days into treatment; both were withdrawn from the study to receive non-protocol treatment. These patients are included in the intention to treat and excluded from the per protocol analysis. CR, complete remission.

Figure 2: The proportion of patients achieving completed remission (CR) at weeks from the start of treatment in the prednisolone (grey, solid line) and tacrolimus (black, dashed line) cohorts. The number of patients achieving CR is shown in the table.

Figure 3: The proportion of patients who suffered a relapse following complete remission (CR) in the prednisolone (grey, solid line) and tacrolimus (black, dashed line) cohorts. The number of patients with relapse following CR at 26 week intervals is shown. Two of the patients in remission in the prednisolone group were lost to follow up at 36 weeks and 40 weeks.

Figure 4: Changes in mean serum creatinine, median urine protein creatinine ratio and mean serum albumin from the start of treatment and during follow-up in the prednisolone and tacrolimus treated cohorts. The urine protein creatinine ratio data was non-parametrically distributed.

Tables

Table 1: Patient Characteristics at enrolment

Characteristic		Overall (n=50)	Prednisolone (n=25)	Tacrolimus (n=25)
Male	n (%)	27 (54%)	15 (60%)	12 (48%)
Age	Median (range)	43 (18/74)	39 (18-73)	43 (18-74)
Caucasian	n (%)	33 (66%)	17 (68%)	16 (64%)
Serum creatinine, mg/dl	Median (range)	0.82 (0.53-2.96)	0.81 (0.59-2.33)	0.82 (0.53 -2.96)
Estimated glomerular filtration rate, ml/min/1.73m ²	Median (range)	98 (27-120)	94 (29-120)	99 (27-120)
Urine protein creatinine ratio, mg/g	Median (range)	7310 (2204-15708)	6504 (2310-15708)	7717 (2204-15619)
Urine protein creatinine ratio, mg/mmol	Median (range)	826 (249-1775)	735 (261-1775)	872 (249-1765)
Serum albumin, g/dl	Median (range)	1.6 (0.7-2.9)	1.7 (0.7-2.9)	1.5 (0.7-2.4)
Systolic blood pressure, mmHg	Median (range)	127 (101-145)	128 (101-145)	126 (108-140)
Diastolic blood pressure, mmHg	Median (range)	80 (50-90)	80 (67-89)	73 (50-90)
Antihypertensive treatment	n (%)	20 (40%)	10 (40%)	10 (40%)

Table 2: Primary, secondary and exploratory outcomes

	Overall			Prednisolone			Tacrolimus			p =
Primary outcome	n	Cohort		n	Cohort		n	Cohort		
Complete remission by 8 weeks	38	50	76%	21	25	84%	17	25	68%	0.32 (0.54)
Secondary outcomes	n	Cohort		n	Cohort		n	Cohort		
Complete remission by 16 weeks	42	50	84%	23	25	92%	19	25	76%	0.25 (0.54)
Complete remission by 26 weeks	45	50	90%	23	25	92%	22	25	88%	=0.99 (1.00)
Any relapse following complete remission	33	45	73%	17	23	74%	16	22	73%	=0.99
	n	Median	Range	n	Median	Range	n	Median	Range	
Change in serum creatinine at 12 months (mg/dl)	50	0.02	-1.25 to 0.64	25	0.01	-1.25 to 0.20	25	0.02	-0.47 to 0.64	0.16
Exploratory outcomes	n	Cohort		n	Cohort		n	Cohort		
Complete remission by 4 weeks	22	50	44%	16	25	64%	6	25	24%	0.01 (0.05)
Complete or partial remission by 4 weeks	39	50	78%	20	25	80%	19	25	76%	=0.99 (1.00)
Failed to achieve complete remission	5	50	10%	2	25	8%	3	25	12%	=0.99

Adjusted p-values for multiple analyses are shown in parentheses.

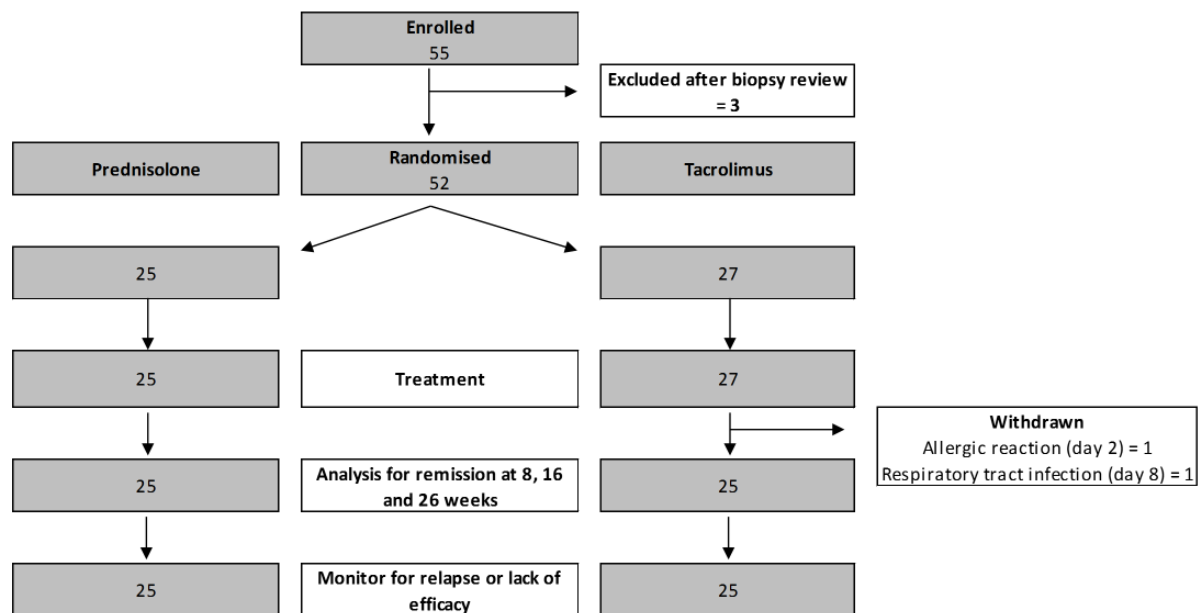
Table 3: Adverse events recorded in the prednisolone and tacrolimus treated cohorts

Adverse Events	Prednisolone (n=25)	Tacrolimus (n=27)
Total	18 (4 SAE*)	20 (3 SAE**)
Infections requiring antibiotics	6	5
- URTI requiring antibiotics	2	3
- LRTI requiring antibiotics	3 (1 SAE)	1 SAE
- Urinary tract infections	1	
- Infective diarrhoea		1
Vaginal candidiasis		1
Musculoskeletal pain		4
GI symptoms	1 SAE	5 (1SAE)
Headache	2 (1 SAE)	1
Gum pain		2
Weight gain	1	
Low mood	2	
Acneiform rash	2	
Hyperglycaemia	1	1
Uncontrolled hypertension		1 SAE
Deranged LFTs	1	
Traumatic limb fracture	2 (1 SAE)	

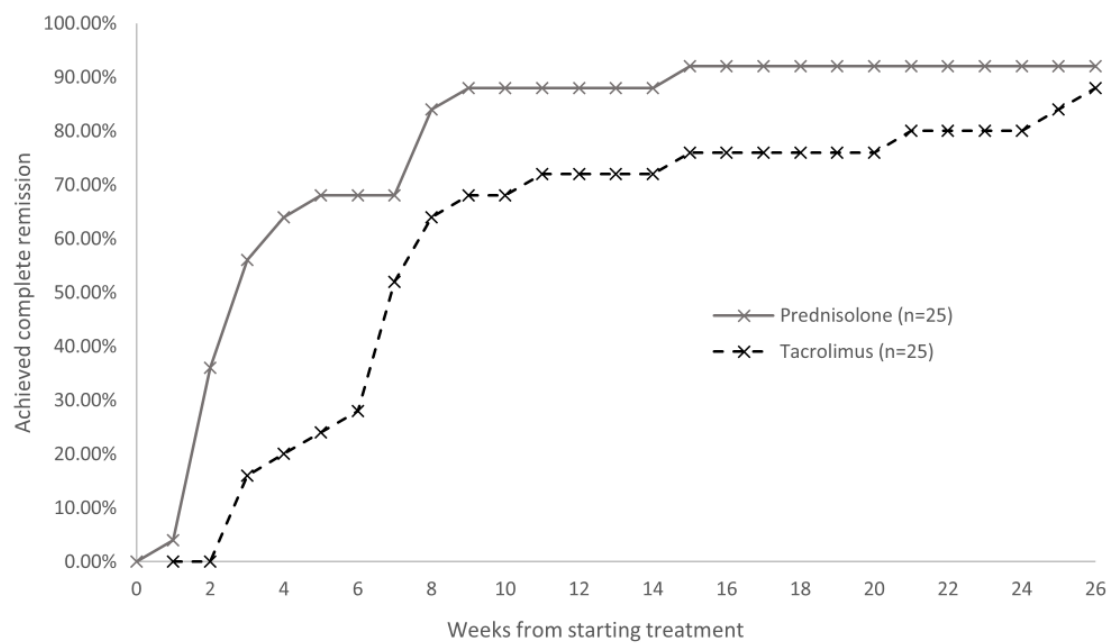
* Serious adverse events (SAE) recorded in the prednisolone cohort were one admission with perforated diverticular ulcer, one episode of severe headache requiring investigation (no organic cause identified), one patient with traumatic fractured radius, and one patient with lower respiratory tract infection requiring intravenous antibiotics and supplemental oxygen.

** The SAE recorded in the tacrolimus treated cohort were one admission with uncontrolled hypertension, one admission with diarrhoea and rash 2 days into treatment, and one admission with lower respiratory tract infection.

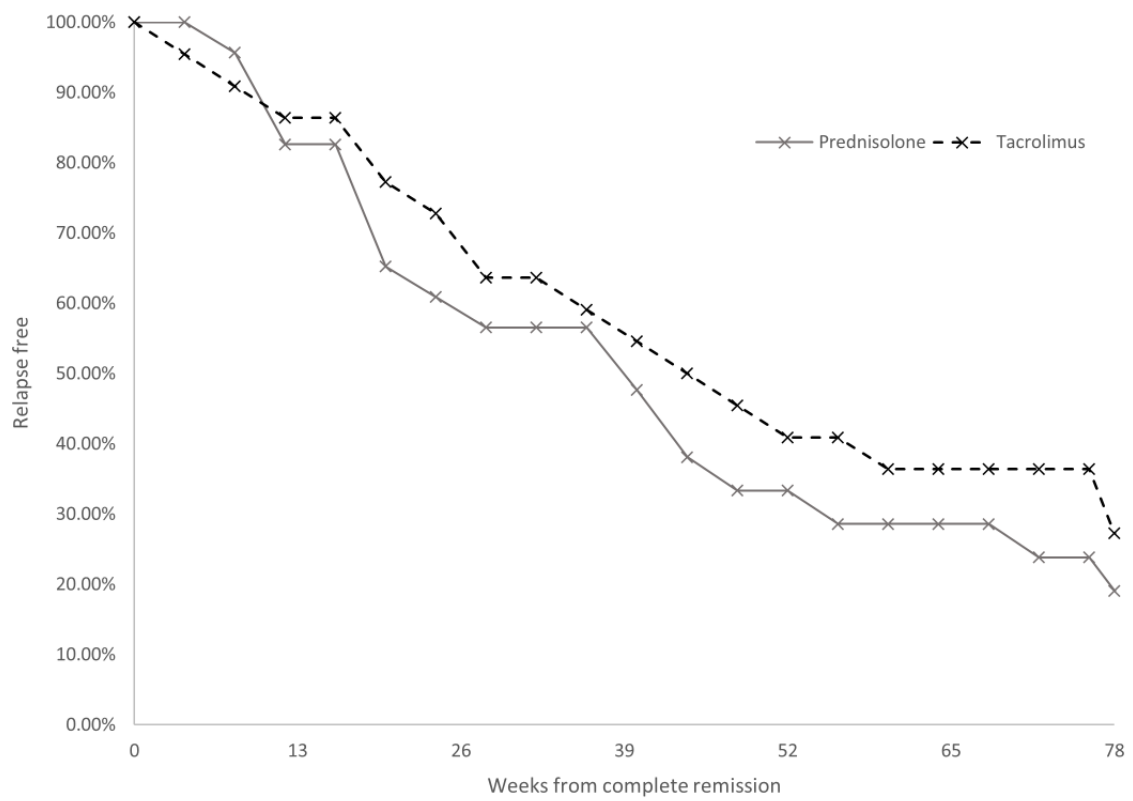
URTI; upper respiratory tract infection. LRTI; lower respiratory tract infection.



Medjeral-Thomas *et al.* Figure 1

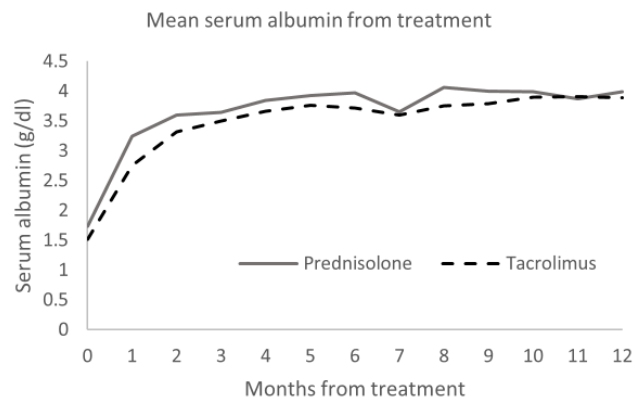
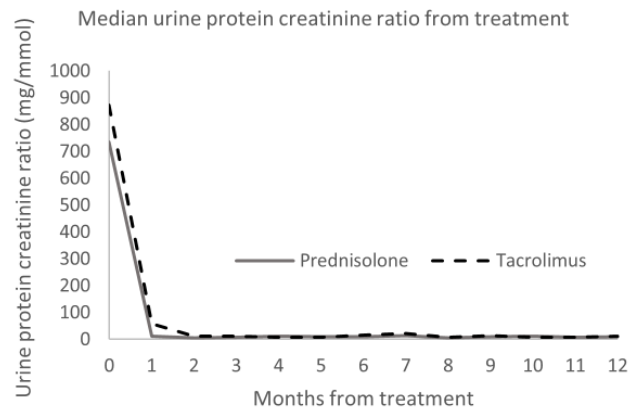
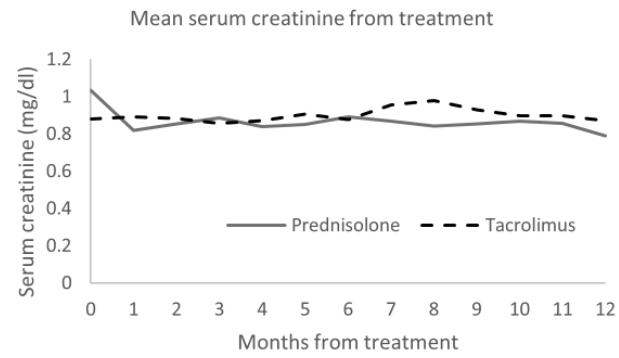


Medjeral-Thomas et al. Figure 2



Weeks from complete remission	0	12	26	52	78
Prednisolone (number followed-up)	22 (23)	18 (23)	13 (23)	7 (21)	4 (21)
Tacrolimus (number followed-up)	22 (22)	19 (22)	15 (22)	9 (22)	6 (22)

Medjeral-Thomas et al. Figure 3



Medjeral-Thomas *et al.* Figure 4