PREDNOS
END OF STUDY REPORT

Title	Full Title: Long-term tapering versus standard prednisolone (steroid) therapy for the treatment of the initial episode of childhood nephrotic syndrome: national multicentre randomised double blind study Short Title: PREDnisolone in NephrOtic Syndrome: The PREDNOS study
EudraCT number	2010-022489-29
CTA Number:	21761/0255/001-0001
Sponsor protocol code	RG_08-015
ISRCTN number	ISRCTN16645249
Co-sponsor details	University of Birmingham and Central Manchester University Hospitals NHS Foundation Trust
REC reference number	10/H1008/122
Funder	National Institute for Health Research Health Technology Assessment programme (NIHR HTA) Ref: 08/53/31
NIHR CRN Study ID:	9617
Date 1st patient randomised:	2nd Aug 2011
End of study	7th April 2017

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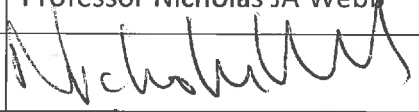
Signature	
Date	28/02/2018

This report was prepared by the Chief Investigator and Renal Team Leader on behalf of the Co-Sponsors.

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Section 1 Abstract

Background

The optimal corticosteroid regimen for treating the presenting episode of steroid sensitive nephrotic syndrome (SSNS) remains uncertain. The majority of UK centres use an eight week regimen despite previous systematic reviews indicating that longer regimens reduce risk of relapse and frequently relapsing nephrotic syndrome (FRNS).

Objectives

Primary objective was to determine whether an extended 16 week course of prednisolone increases the time to first relapse. Secondary objectives were to compare the relapse rate, FRNS and steroid dependent nephrotic syndrome (SDNS) rates, requirement for alternative immunosuppressive agents, corticosteroid-related adverse events (AEs), including behaviour and costs.

Design

Randomised double-blind parallel group placebo-controlled trial including a cost-effectiveness analysis.

Setting

One hundred and twenty-five UK paediatric and paediatric nephrology departments.

Participants

Two hundred and thirty-seven children presenting with first episode of SSNS. Participants aged one to <15 years were randomised in a one-to-one ratio according to a minimisation algorithm to ensure balance of ethnicity (South Asian, White, Other) and age (≤5, ≥6 years).

Interventions

Control group received standard course (SC) prednisolone therapy: weeks 1-4: prednisolone 60mg/m^2/day (max. 80mg), weeks 5-8: prednisolone 40mg/m^2 (max. 60mg) on alternate days, weeks 9-16: matching placebo on alternate days (total 2240mg/m^2).

Intervention group received extended course (EC) prednisolone therapy: weeks 1-4: prednisolone 60mg/m^2/day (max. 80mg), weeks 5-16: starting at prednisolone 60mg/m^2 (max. 80mg) on alternate days tapering by 10mg/m^2 every two weeks (total 3150mg/m^2).

Main Outcome Measures

Primary outcome measure was time to first relapse (Albustix positive proteinuria 3+ or greater for three consecutive days or the presence of generalised oedema plus 3+ proteinuria). Secondary outcomes were relapse rate, incidence of FRNS and SDNS, use of other immunosuppressive therapy, rates of serious adverse events (SAEs) and AEs and the incidence of behavioural change (using Achenbach Child Behaviour Checklist (ACBC)). A comprehensive cost-effectiveness analysis was performed. Analysis was by intention to treat. Participants were followed for a minimum of 24 months.

Results

There was no significant difference in time to first relapse between the SC and EC groups (Hazard Ratio: 0.87, 95% Confidence Interval: 0.65-1.17; log-rank p=0.3). There were also no differences in

the incidence of FRNS (SC: 50% vs. EC: 53%; p=0.7), SDNS (44% vs. 42%; p=0.8) or requirement for other immunosuppressive therapy (56% vs. 54%; p=0.8). Total prednisolone dose received following completion of study medication was 5475mg vs. 6674mg; p=0.07. SAE rates were not significantly different (25% vs. 17%; p=0.1), nor were AEs with the exception of poor behaviour which was lower in the EC group. There were no differences in ACBC scores. EC therapy was associated with a mean increase in generic health benefit (0.0162 additional Quality-Adjusted Life Years (QALYs)) and cost savings (£4,369 vs. £2,696).

Limitations

Study drug formulation may have prevented some younger children unable to swallow whole or crushed tablets from participating.

Conclusions

PREDNOS has not shown any clinical benefit for EC prednisolone therapy in UK children; however it has shown this to be cheaper and more effective in QALY terms.

Future work

Studies investigating EC vs. SC therapy in younger children and further cost-effectiveness analyses are warranted.

Section 2 Plain English Summary

Steroid sensitive nephrotic syndrome (SSNS) is one of the commonest childhood kidney diseases. The kidney filters leak protein into the urine, resulting in low levels of protein in the blood and generalised swelling. If untreated this can lead to serious complications, including infection and blood clots. The disease responds well to prednisolone, a steroid drug; however it is very common for disease to recur (called a relapse).

Doctors are uncertain how long prednisolone should be given for to treat children when they first present with nephrotic syndrome. In the United Kingdom (UK), a two month course has traditionally been used. However, a number of research studies have suggested that giving three months or more of prednisolone may reduce the number of children who relapse and also those who develop lots of relapses (called frequently relapsing nephrotic syndrome; FRNS).

We recruited 237 children presenting with SSNS. Half were given an eight week standard course (SC) of prednisolone and the other half a 16 week extended course (EC). We used placebo (dummy tablets) so the participants and doctors did not know which treatment group they were in. Participants were followed for a minimum of 24 months and monitored for the development of relapses and prednisolone side-effects, including behavioural problems. A cost analysis was performed.

Giving EC prednisolone did not delay the development of disease relapse. There was also no difference in the number developing FRNS or steroid dependent nephrotic syndrome or needing to be given other treatments. The rate of prednisolone side-effects was the similar in the two treatment groups. EC treatment was, however, cheaper by £1,673.

We therefore conclude that there is no clinical benefit associated with the administration of EC prednisolone therapy in UK children presenting for the first time with SSNS. However, EC therapy was cheaper.

Section 3 Scientific Summary

Background

Idiopathic nephrotic syndrome (INS) is the commonest glomerular disorder of childhood, with an incidence of 2 per 100,000 child population in the United Kingdom (UK). The disease presents at a median of two to three years of age and is twice as common in boys. There is ethnic variability in the disease incidence, with a four to six fold higher incidence in the UK South Asian population.

In excess of 90% of children who present with INS will respond to a course of high-dose corticosteroid therapy. For this reason, the large majority are treated empirically with a course of corticosteroids without a renal biopsy being performed. Those who are corticosteroid responsive are given a diagnostic label of steroid sensitive nephrotic syndrome (SSNS).

Following initial successful treatment with corticosteroids, around 80% of children with SSNS develop disease relapses necessitating further courses of high-dose prednisolone, and around 50% develop frequently relapsing nephrotic syndrome (FRNS), defined as two or more relapses within the first six months following presentation or four relapses within any 12 month period. Similar to the presenting episode, nephrotic syndrome relapses are associated with a risk of significant complications, including sepsis, thrombosis, dyslipidaemia and malnutrition. The treatment of relapses with repeated courses of high-dose prednisolone is associated with major adverse effects, including hip avascular necrosis, growth failure, hypertension, obesity, diabetes and behavioural problems. Where complications of repeated courses of corticosteroids develop or where they are anticipated, a range of immunosuppressive strategies are employed in an attempt to reduce the frequency of disease relapses. These include the use of long-term low-dose alternate day prednisolone, as well as a range of non-corticosteroid immunosuppressive agents, including levamisole, cyclophosphamide, ciclosporin, tacrolimus, mycophenolate mofetil and rituximab.

There remains uncertainty about the ideal corticosteroid regimen for the treatment of the child presenting with SSNS. The majority of UK centres have continued to use the eight week regimen first described by the International Study of Kidney Disease in Children in the 1960s. At the time of commencement of the PREDNOS study, a total of six randomised controlled trials (RCTs) had compared two months of prednisolone with a variety of different regimens of three months or longer in duration. A 2005 Cochrane review concluded that intensification of the initial corticosteroid therapy at disease presentation significantly reduced the rate of relapse at 12 to 24 months (risk ratio 0.7, 95% confidence interval (CI): 0.58-0.84). There was an inverse linear relationship between treatment duration and risk of relapse (risk ratio=1.26-0.112 duration; p=0.03). Furthermore, there was a significant reduction in the number with FRNS and the mean relapse rate per participant per year. However, significant concerns have been raised about a number of methodological issues relating to these six studies. There thus remains significant clinical equipoise, with the UK, parts of North America and other countries continuing to use the eight week ISKDC regimen, whilst Germany, France and other countries use a regimen of three months or longer in duration.

The PREDNOS study was designed to determine the optimum treatment regimen for UK children presenting with SSNS.

Objectives

Primary Objective: To determine whether an extended 16 week course of prednisolone increases the time to first relapse in children presenting with SSNS compared with the standard eight week course.

Secondary Objectives: To determine whether an extended course of prednisolone reduces relapse rate, the proportion of participants who develop FRNS or steroid dependent nephrotic syndrome (SDNS) and the requirement for second and third line immunosuppressive agents, is associated with an increased incidence of corticosteroid-related adverse events (AEs) including behavioural problems and is more cost-effective than standard course therapy.

Methods

A double-blind RCT was undertaken across 125 UK National Health Service district general hospitals and tertiary paediatric nephrology units comparing an eight week standard course (SC) of prednisolone therapy with a 16 week extended course (EC) of prednisolone therapy in children presenting with their first episode of SSNS. Children were eligible if they had urine albumin:creatinine ratio >200mg/mmol or protein:creatinine ratio >200mg/mmol on an early morning urine sample, had a serum or plasma albumin level <25g/L, were aged one to <15 years at the time of diagnosis, had not previously received therapy with corticosteroids, immunosuppressive or cytotoxic agents for any form of renal disease, had no evidence of underlying systemic disorder or exposure to agents known to be associated with newly presenting SSNS, and provided informed consent. Children with histological changes other than minimal lesion glomerulonephritis (where renal biopsy has been undertaken), prior history of poor adherence with medical therapy, or known allergy to prednisolone were excluded.

Participants were randomised in a one-to-one ratio to either the SC or EC group in accordance with a minimisation algorithm to ensure balance of ethnicity (South Asian, White, Other) and age (≤5, ≥6 years). The SC (control) group received prednisolone 60mg/m2 daily (max. 80mg) for four weeks followed by 40mg/m2 (max. 60mg) on alternate days for four weeks. The EC group received prednisolone 60mg/m2 daily (max. 80mg) for four weeks, followed by a further 12 weeks of alternative day prednisolone starting at 60mg/m2 (max. 80mg) and tapering by 10mg/m2 every two weeks. In both groups, treatment in the first four weeks was open-label and then blinded in the following 12 week phase, with matching-placebo in the control group.

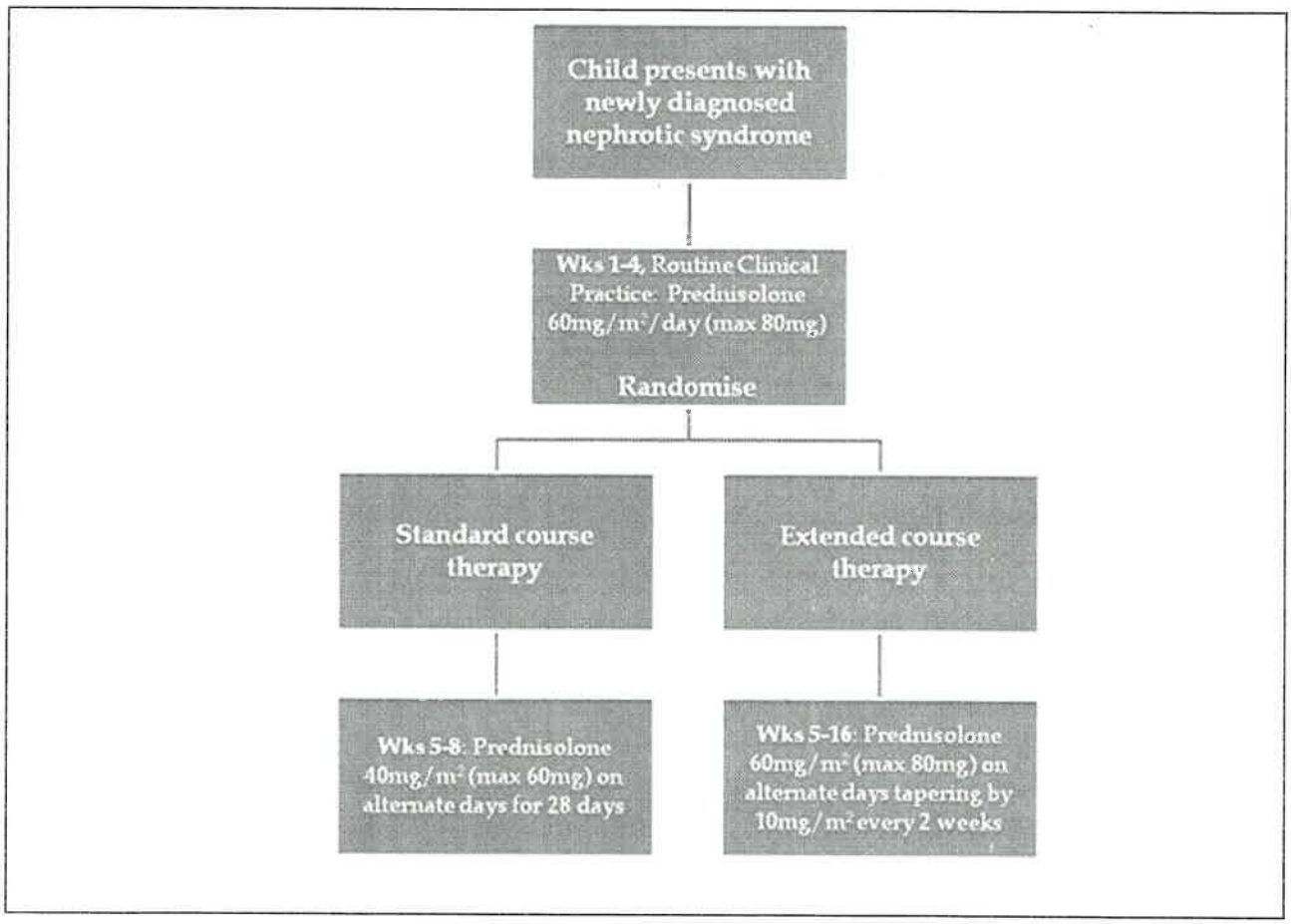
The primary outcome measure was time to first relapse. Relapse of proteinuria was defined as Albustix positive proteinuria (+++ or greater) for three consecutive days or the presence of generalised oedema plus 3+ proteinuria. Secondary outcomes were relapse rate, incidence of FRNS (two or more relapses in the first six months or four or more relapses within any 12 month period) and SDNS (relapses on or within 14 days of discontinuation of corticosteroid therapy), use of other immunosuppressive therapy, rates of serious adverse events (SAEs) and AEs and the incidence of behavioural change (using Achenbach Child Behaviour Checklist (ACBC)). A comprehensive cost-effectiveness analysis was performed.

Participants were followed-up with visits at 4, 8, 12 and 16 weeks, and then at 5, 6, 8, 10, 12, 18, 24, 30, 36, 42 and 48 months after commencing open-label prednisolone. Participants were followed-up for a minimum of 24 months and up to a maximum of 48 months; the study completed when the last participant had completed 24 months of follow-up. At each trial visit information was captured on relapses, treatments for relapse, AEs (including SAEs), use of health services and trial treatment

adherence. The ACBC was used to assess behaviour change as a potential adverse effect of corticosteroid use. The Paediatric Quality of Life Inventory (PedsQL) and Child Health Utility (CHU-9D) questionnaires were used to assess quality of life to inform the health economic analysis. Questionnaires were completed at 4 and 16 weeks, and then at 12, 24, 36 and 48 months.

Analyses were of all randomised participants, except for those who, following randomisation, were subsequently found to be corticosteroid resistant, using the intention to treat (ITT) principle. The primary outcome measure was the time from the start of open-label treatment to first relapse. Kaplan-Meier survival curves were constructed for visual presentation of the time to first relapse. The primary analysis of time to first relapse was assessed across the two treatment groups and compared using a log-rank test. A Cox-proportional hazard model was fitted to obtain a hazard ratio (HR) and a 95% CI.

Trial Schema



Results

Two hundred and thirty-seven participants were recruited into the study from 86 UK centres between 2nd August 2011 and 7th October 2014; 118 were randomised to SC and 119 to EC therapy. Fourteen participants (SC: 9 vs. EC: 5) were withdrawn during the first few weeks of the trial (following randomisation) as per the protocol due to the development of corticosteroid resistance following an initial response to open-label prednisolone therapy, leaving an ITT population of 223 participants. During the trial, 15 participants (6%) had their consent to participate in the study

withdrawn, 11 (5%) became lost to follow-up and four participants (2%) withdrew from the study for other reasons. For these 30 participants, data collected up until the time of their withdrawal from the study were included in the analysis. Therefore, in total 44 (19%) participants were withdrawn from the trial (20 vs. 24).

The mean (standard deviation) age at randomisation of the ITT population was 4.9 (3.1) years, 65% were male and 20% were of South Asian origin. The median body mass index percentile was 87.5 and the mean open-label prednisolone dose was 58.2 mg/m2/day.

Eighty-six (39%) of the 223 participants did not complete their course of study medication. The number of participants discontinuing study medication was greater in the SC group (50% vs. 28%; p=0.001). The predominant reason for discontinuation was the development of relapse (79 relapses) during the 12 week period when double-blind study medication was being administered. The number of participants who discontinued due to relapse was higher in the SC group (n=50) compared with the EC group (n=29), which was mainly due to the SC group being on placebo from week eight. Where relapses developed during this period of study drug administration, the protocol stated that study medication was to be discontinued and relapse treatment commenced.

Adherence with study medication was generally high, with only a small proportion of participants (13%) reporting missed doses. Attendance rates for follow-up study visits were high as were submission rates of clinical data and participant questionnaires (>90% of expected forms received at each time-point).

The number of participants who reported a relapse during the trial was 179, with 88/109 (81%) in the SC group compared with 91/114 (80%) in the EC group. There was no significant difference in time to first relapse between the SC and EC groups (Hazard Ratio: 0.87, 95% CI: 0.65-1.17; log-rank p=0.3). When pre-specified subgroup analyses were performed for the primary outcome for the two minimisation variables of ethnicity (South Asian, White, Other) and age (≤5 years, ≥6 years), there was no clear evidence to suggest that the treatment effect differed between the different participant subgroups.

The number of relapses per participant ranged from zero to 15; there were eight participants in the SC group and nine in the EC group who experienced ten or more relapses. The mean number of relapses did not differ between groups (SC: 3.61 vs. EC: 3.98, Incident Rate Ratio: 1.09, CI: 0.86-1.39; p=0.5). There was also no significant difference between the two groups in the proportion of participants developing FRNS (50% vs. 53%; p=0.7), SDNS (44% vs. 42%; p=0.8) or requiring other immunosuppressive therapy (56% vs. 54%, p=0.8). The total dose of prednisolone received during the trial (following completion of study medication) was greater in the EC group (5475mg vs. 6674mg; p=0.07).

There were 67 SAEs reported in 46 participants (21%); 39 SAEs in 27 participants in the SC group and 28 SAEs in 19 participants in the EC group (SC: 25% vs. EC: 17%; p=0.1). The most common reason for SAE reporting was admission for treatment of or because of haemodynamic complications of a disease relapse (16 vs. 15). Bacterial infection necessitating antibiotic therapy was responsible for admission of four participants in the SC group and seven in the EC group. Six of the 39 SAEs in the SC group and six of the 28 SAEs in the EC group were, in the opinion of the Principal Investigator, related to study drug, though none resulted in study drug discontinuation. There was one accidental death unrelated to the trial.

The most common AEs reported were increased appetite, poor behaviour (parent reported), Cushingoid facies, hypertrichosis and abdominal pain. In the first 16 weeks of the trial, increased appetite was reported in 87% of participants (SC: 87% vs. EC: 86%), poor behaviour in 83% (90% vs. 76%), Cushingoid facies in 67% (66% vs. 68%), hypertrichosis in 26% (23% vs. 30%) and abdominal pain in 26% (28% vs. 25%). By 24 months, these had increased to 94% (94% vs. 93%) for increased appetite, 87% (93% vs. 82%) for poor behaviour, 72% (71% vs. 73%) for Cushingoid facies, 39% (38% vs. 39%) for hypertrichosis and 45% (47% vs. 43%) for abdominal pain. At 16 weeks, and 6, 12 and 24 months, there were no significant differences between the groups in the cumulative number of participants reporting any of the AEs, except for poor behaviour which was lower in the EC group. In the first 16 weeks, 90% in the SC group reported poor behaviour compared with 75% in the EC group (relative risk (RR): 0.85, 95% CI: 0.76-0.96). Differences were also seen at six months (91% vs. 81%, RR: 0.90, 95% CI: 0.82-1.00), 12 months (92% vs. 82%, RR: 0.90, 95% CI: 0.82-0.98) and 24 months (93% vs. 83%, RR: 0.90, 95% CI: 0.82-0.98). There were no differences in ACBC scores.

Cost-effectiveness analysis showed EC therapy to be associated with a mean increase in generic health benefit (0.0162 additional Quality-Adjusted Life Years (QALYs)) and cost savings (£4,369 vs. £2,696).

Conclusions

The PREDNOS study has not shown any clinical benefit associated with the administration of EC prednisolone therapy in UK children presenting for the first time with SSNS. There was no difference between EC and SC regimens in the incidence of prednisolone-related AEs. Cost-effectiveness analysis showed EC therapy to be cheaper and more effective in QALY terms.

Section 4 Discussion

The PREDNOS study has not shown any clinical benefit for an extended 16 week course of prednisolone compared with the standard eight week ISKDC course in UK children presenting with SSNS. There was no significant difference between the two treatment groups in time to first relapse of nephrotic syndrome, or in any other of the clinically important secondary endpoints, including the number of relapses experienced, the proportion of participants who went on to develop FRNS or SDNS, or requirement for alternative non-corticosteroid immunosuppressive therapies. However, despite showing no clinical benefit, we did find that the extended 16 week course was cheaper and more effective in QALY terms.

These findings differ from the six studies published prior to the commencement of the PREDNOS study, which had compared the ISKDC regimen with prednisolone regimens of greater than three months duration. A Cochrane review of these studies performed in 2005 showed a benefit of longer course prednisolone therapy, with a lower rate of relapse at 12 to 24 months, and a significant reduction in the number of children with FRNS.26 Based upon this, a recommendation was made that children presenting with SSNS should be treated with a minimum of three months of prednisolone therapy. This did not, however, lead to international consensus, and significant clinical equipoise and variation in practice persisted.

More recent studies have reported results that are consistent with PREDNOS. A Japanese study of 255 participants which compared the ISKDC regimen with a six month course of prednisolone found no benefit associated with longer duration prednisolone therapy.37 Yoshikawa et al. chose a primary endpoint of time to the development of FRNS, a clinically important endpoint identifying those children who have developed a complicated disease course and who are likely to develop disease and treatment-related morbidity, and therefore require alternative more potent immunosuppressive therapies. There was no difference in FRNS, and the time to first relapse and the incidence of adverse effects were also similar in the two groups. An Indian study comparing three and six months of prednisolone did not show any benefit associated with increased duration of prednisolone,36 nor did the Dutch study by Teeninga et al. which also compared three and six months of therapy. When these three well-designed studies were included in a 2015 update of the Cochrane review, they changed the overall conclusions. It was noted that these studies of long versus shorter duration of corticosteroids had heterogeneous treatment effects, with the older higher risk of bias studies tending to over-estimate the effect of longer course therapy, compared with the more recently published lower risk of bias studies. Among studies at low risk of bias, there was no significant difference in the risk for FRNS between prednisone given for two or three months and longer durations or total dose of therapy, indicating that there is no benefit of increasing the duration of prednisone beyond two or three months in the initial episode of SSNS. However, when the meta-analysis was restricted to those addressing the same question as the PREDNOS study, comparing the eight week ISKDC regimen with regimens of three months or longer (i.e. adding the study of Yoshikawa et al. to the six studies reported in the original Cochrane review), there remained a benefit for the longer three months or more treatment regimen, though this only just reached statistical significance. The risk of FRNS was significantly lower (RR: 0.68, 95% CI: 0.47-1.00), as was the number of participants relapsing by 12 to 24 months (RR: 0.8, 95% CI: 0.64-1.00). It is likely that once the results of the PREDNOS study are added to the Cochrane review, that the overall result will show no difference in outcome between the ISKDC and longer treatment regimens.

The data reported in our study are similar to those reported in previous studies. The proportion of participants experiencing a relapse was 80.3% (179/223) over a median follow up of 37 months which is comparable to the rate of 60-90% reported in the literature. Teeninga et al. reported a relapse rate of 78.6% (99/126) in a European population with a median follow-up of 47 months, with a median time to first relapse of six months for the three month prednisolone group and eight months for the six month group. Sinha et al. reported a lower relapse rate of 57.8% (104/180), however participants were only followed up for 12 months. In the Japanese study, the overall relapse rate was not stated; however the median time to relapse was 242 days and 243 days in the two month and six month groups respectively, significantly later than the 87 days for the SC group and 139 days for EC group observed in the PREDNOS study. Noteworthy is the fact that they used urine dipstick values of ++ or higher as their definition of relapse, though if anything this would have over-diagnosed relapse and reduced the time for first relapse.

We also found similar rates of FRNS (50% and 52%) to those previously reported. Using the same ISKDC definition as used in PREDNOS, Sinha et al. reported a rate of FRNS at last follow-up of 50.4% in the six month group and 60.4% in the three month group. The time to FRNS was 23.0 months and 17.6 months respectively. Teeninga et al. reported FRNS in 45% of the three month prednisolone group and in 50% of the six month prednisolone group, commenting that this was higher than anticipated. In previous studies, FRNS has been reported in 32-78% of participants who received a two month course of prednisolone and 18-44% of those who received prednisolone for three months. It has been proposed that this variation may in part be explained by regional differences or variations in definitions of FRNS, length of observation and relapse treatments.

Interestingly, although we found no clinical benefit for the EC prednisolone treatment regimen, we did find that this regimen was cheaper and more effective in QALY terms. The cost-analysis showed that over a 24 month period, the EC treatment regimen cost less due to a lower rate of hospital admission; a shorter duration of hospital stay; fewer hospital emergency visits; and fewer outpatient and primary care visits, and therefore, on average, was cheaper by £1,673 per patient, when compared to the SC treatment regimen. Furthermore, the EC treatment regimen produced more QALYs, compared to the SC treatment group. Using commonly applied threshold values for how much society is WTP for a QALY gain, the EC treatment regimen is cost-effective. At first glance, this result may seem surprising as the clinical outcomes have shown little or no benefit for extending prednisolone treatment, yet the economics reveals evidence of cost-effectiveness. These differences, in part, relate to the differences in cost and QALYs, but also to the different methods of analysis adopted in the economic and clinical evaluations.

Unlike the objectives of the clinical evaluation which are about testing if extending the prednisolone therapy leads to an improved patient outcome relative to the control group, the objectives of the economic evaluation are to provide an estimation of the value of the extended therapy reflecting both efficiency and equity – and thus an estimate of whether the difference in cost between the treatment groups, is worth the difference in effect, taking into account the opportunity cost of that investment, and the fact that the resources could have been invested elsewhere across all parts of the NHS.

The key thing to note is that small insignificant clinical benefits can be cost-effective. The economics focus is about comparing two things: costs and effects. For the economic analysis, the effects are measured using QALYs which reflect societal values incorporating preferences for domains of quality

of life. These values are measured using preference based QoL instruments which was in this study, the CHU-9D. Measuring cost differences between different treatment therapies has no meaning until these are offset against differences in effects: it is the simultaneous consideration of costs and effects and therefore the joint density of cost and effect differences that is the focus for economic evaluation.

Within the PREDNOS study, the clinical analysis quantified the difference in time to first relapse, at the individual participant level, using statistical inference. The economic analysis measured the difference in cost for extended versus standard therapy which was on average £1673 cheaper per participant, and the difference in QALYs which was on average 0.0162 more QALYs per participant for the EC group. When the costs and QALY differences are assessed separately these differences are not statistically significant, however, when assessed simultaneously, the incremental cost-effectiveness ratio (the ratio of the mean cost and the mean QALY difference) produces a cost-effective result as the EC group is cheaper, and produces more QALYs, on average. It is therefore dominant as it is not only more effective in QALY terms, but also saves health care resources, relative to the SC group.

Furthermore, there are different methods within the economic analysis for representing the uncertainty in the cost and QALY differences. QALYs and cost data tend to have unusual distributional properties often being skewed, exhibiting ceiling effects or having a bimodal distribution and because of this, the stochastic bootstrapping method was applied. Bootstrapping generates multiple samples of joint cost and effect estimates from the same trial data and these cost and effect pairs are then represented on a scatter plot on an incremental cost effectiveness plane. Plotting bootstrapped cost and QALY pairs from the PREDNOS study shows that most of the pairs lie in the south-east quadrant indicating that there are cost-savings, and QALY gains from the extended therapy versus the standard therapy, there are however some points spread within the north-east quadrant (indicating that the extended therapy is more costly), and in the south-west quadrant (indicating that the extended therapy leads to a QALY loss). This reflects some uncertainty regarding the cost-savings, and QALY-gains from having extended therapy versus standard therapy, which is consistent with the finding of a non-significant difference for both costs and effects, when considered independently, between the two treatment groups.

To account for the uncertainty in the cost and effect pairs, the proportion of points falling above and below a WTP threshold line are simply counted, and then the threshold line is varied to produce a CEAC. Cost effectiveness acceptability curves are regarded as an alternative method to calculating CIs and indicate the probability that the extended therapy is cost-effective, compared to the standard therapy, for different threshold WTP values for a QALY gain. Using the PREDNOS trial data, the probability that the extended therapy is cost-effective, at the commonly applied threshold value of £20,000 per QALY is 0.988. So, despite there being no statistically significant differences in costs and effects for extended therapy versus standard therapy, the CEAC shows there is very little uncertainty over the choice to treat patients with EC therapy compared to SC therapy from a cost-effectiveness perspective. It is also worth noting that regardless of benefit measured in QALYs, parents and children value avoidance of hospital admission. This is also valued by clinicians and reduces demand pressures on the NHS.

Previous studies have been somewhat inconsistent in their reporting of the adverse effects associated with using corticosteroids, however, the most recent (2015) Cochrane review found no

significant differences in the risk of adverse events between extended duration and two or three months of prednisolone. We found no differences in the adverse effect profiles between the two treatment groups, with the exception of parentally reported poor behaviour which was significantly more common in the SC group. At 24 months, the cumulative incidence of poor behaviour was 93% in the SC group compared with 82% in the EC group (RR: 0.90, 95% CI: 0.82-0.98). There was no difference in the incidence of any other adverse effects including Cushingoid facies, striae, hypertrichosis, acne, increased appetite, glycosuria, cataract and abdominal pain. These findings are broadly comparable with those of multiple other larger-scale and smaller trials addressing this same clinical question; the large majority of these have found no significant difference in the incidence of adverse effects, however there was significant heterogeneity in the extent to which these were monitored. Most adverse events were transient and occurred relatively early during the course of treatment, when the prednisolone dose was at its highest. We detected a minor increase in bacterial infection resulting in hospital admission in participants in the EC group.

We were particularly interested in the impact of the two prednisolone regimens on behaviour, as expert clinical opinion and advice from our PPI group indicated that this was the adverse effect of greatest prevalence and significance to families. When the PREDNOS study was designed, no previous study had objectively and systematically investigated this using a quantitative measure. In PREDNOS, we collected quantitative data on behaviour using the ACBC. Although parentally reported poor behaviour was significantly more common in the SC group, when behaviour was assessed objectively through the ACBC questionnaire completed by the parents, there was no significant difference in either the total behaviour score or T score. The proportion of participants assessed as having abnormal behaviour by the ACBC was also no different between the two groups and varied between 21% and 31% at different time-points throughout the study. Parents reported a higher proportion of participants with poor behaviour than had scores outside the normal ACBC range. This provides some reassurance to parents that perceived poor behaviour is generally within normal bounds and is not greatly impacted by corticosteroid treatment, a finding of relevance in other paediatric conditions treated with corticosteroids. Teeninga et al. assessed behaviour using visual analogue scales. Compared with baseline, participants scored significantly higher on eating, overactive behaviour and aggressive behaviour at three months follow-up ($p<0.01$), however these scores returned to baseline within one year in both groups. Scores for happiness temporarily dropped in the first six months, while scores for sleeping remained relatively stable over the entire observation period.

Subgroup analyses showed that there was no clear evidence to suggest that the treatment effect differed according to ethnicity, age or gender, though we were not powered to detect differences in subgroups. For age, there may be some suggestion that the time to first relapse was extended in those in the EC group in participants aged 5 years or under, with no difference between the two groups in participants aged 6 years or over. This remains a topic of some debate, as a number of studies have reported young age at diagnosis to be associated with an increased risk of FRNS and/or corticosteroid dependence, whereas others have not reported this association. In a post-hoc analysis of Sinha's study, Cox regression suggested participants aged three years or younger benefited from prolonged therapy with reduced risk for first relapse, but not for frequent relapses, and Poisson regression confirmed a higher relative relapse rate in younger participants. Other reports have strongly argued that age may be a predictor of disease severity, including FRNS, corticosteroid dependence and response to cyclophosphamide therapy. A few non-randomised studies have

investigated the role of gender in the disease course, and have reported males to be at a disadvantage. Cox regression analysis in the study of Teeninga did not identify boys at being significantly greater risk for developing FRNS. We found also no evidence of a difference in treatment effect according to gender.

Systolic and diastolic blood pressure Z scores were similar in both treatment groups throughout the course of the study. Z scores were relatively high at the time of the week 4 visit, presumably as a result of the high-dose of prednisolone being administered at this point. However, the Z scores decreased progressively during study follow-up. These observations are entirely consistent with the findings of other similar studies.

Interestingly, over the course of the study, following an initial slight fall during the first 16 weeks, the height Z scores increased in both treatment groups. This is an interesting observation given the fact that these participants received multiple courses of prednisolone for treatment of relapses, a treatment which is known to have a negative impact on linear growth. Previous studies have also reported a fall in height velocity during the first few months of high-dose prednisolone treatment, with a subsequent return to baseline by 12 months. Others have described a dose-dependent effect of corticosteroids on growth in children with SSNS. A small number of studies have noted the baseline height SDS to be relatively low in children presenting with SSNS, though no satisfactory explanation has been found for this observation. We did not observe this in PREDNOS study. Weight Z scores were relatively constant throughout the study, and BMI Z scores decreased over time.

The main strengths of the PREDNOS study are its randomised, double-blind, placebo-controlled design. This ensured a low risk of selection, performance, detection and selective reporting bias. Inclusion criteria were defined to ensure that the study population was representative of the population of children presenting with SSNS in the UK. Outcomes were assessed using internationally accepted ISKDC definitions. Our primary outcome measure of time to first relapse was felt by UK clinicians to be of clinical importance and previous studies have shown a link between timing of first relapse and subsequent clinical course. Baseline features were well balanced and there was a low rate of attrition. Regular safety assessment was ensured through regular clinical review. Prior to the commencement of PREDNOS, previous studies had been small (largest 184 participants) and no previous double-blind placebo controlled RCTs had ever been conducted in children with SSNS. PREDNOS successfully recruited 237 participants from 124 sites throughout all regions of the UK into a double-blind placebo controlled RCT. Since then, the studies of both Teeninga33 and Sinha36 were double-blinded, though one further study comparing the ISKDC regimen with longer duration therapy was not blinded. The authors acknowledged that this may have introduced preconception bias, however proposed that as their design was a non-inferiority trial with regular visits with relapses being measured objectively, they could not assume positive placebo effects. It must be remembered that this would not have been the case with the reporting of AEs, where there is considerable scope for bias.

The sample size calculations for the study were based on detecting an absolute difference of 20% in relapse rate at one year from 60% in the SC group to 40% in the EC group using a log-rank test (80% power, α=0.05). The one year relapse rate observed in the SC group was 77%. This means that the study has over 85% power to detect an absolute difference of 20% between groups (i.e. from 77% to 57%) using a log-rank test. This makes the likelihood of our results being the result of a type 2 statistical error small.

An additional strength of the PREDNOS study is the generalizability of its findings. We recruited participants with a first presentation of INS from across the UK with broad inclusion criteria. We selected an age range of one to 14 years as this is the range in which the large majority of patients present and are treated empirically with a course of corticosteroids without recourse to renal biopsy. One of the key purposes of the PREDNOS study was to ascertain the optimal prednisolone treatment regimen for UK children by comparing the eight week SC ISKDC regimen with a longer 16 week EC regimen. We chose the ISKDC SC regimen for one group as this was the regimen in use in the very large majority of UK centres at the time of the planning of the PREDNOS study, and chose a 16 week EC regimen as a comparator as longer duration treatment regimens have previously been shown to result in lower rates of relapse and FRNS. The ethnic mix of the study population broadly represented that of the wider population of children with nephrotic syndrome, including significant representation from the South Asian community. We recruited 44 participants (20% of the study population) from families of South Asian origin and 31 (14%) from families recorded as other non-White ethnic origin. This is a very similar figure to that reported in the study of Teeninga et al, which included 35% of participants of non-Western European descent. This is an important achievement, as the UK South Asian community in particular is significantly over-represented in the SSNS population, the incidence being around six times greater than in the UK white population. Furthermore, the UK South Asian population is generally under-represented in clinical trials and recruitment poses a number of particular challenges. Finally, whilst formal screening logs were requested, in keeping with other studies these were not kept well, however, based on known epidemiological data, we estimate that we have managed to include 34% of newly presenting patients over a three year and two month recruitment period. This indicates a high level of acceptability of the trial amongst both families and clinicians.

One of the greatest challenges in setting up the PREDNOS study was facilitating the recruitment of participants in District General Hospitals. Children with INS have traditionally been, and continue to be investigated and managed within District General Hospitals rather than tertiary paediatric nephrology centres. Referral to tertiary centres generally only takes place where the presenting features are atypical or where investigation or management proves problematic. As such, any study that recruited solely within tertiary centres would not reach the large majority of potential participants and would risk sampling a preselected somewhat atypical group of participants. In the early 2000s, when the PREDNOS study was being planned, there was little paediatric experience in the conduct of RCTs involving an investigational medicinal product, and little funded infrastructure to support this work. Our Kidney Research UK and Kids Kidney Research jointly-funded pilot study confirmed that there was great willingness amongst PIs to participate in the study and similarly interest in the study from participants from both the White and South Asian communities. The pilot study allowed the trial design and infrastructure to be tested, including aspects such as the provision of study medication from a single national clinical trials pharmacy with delivery direct to the participant, attendance rates for study visits and the completion of questionnaires and the study case report forms. The success of the pilot study was significantly enhanced by the development of the NIHR Clinical Research Network: Children (formerly the NIHR MCRN), which commenced operating in 2005. The PREDNOS pilot study was one of the first studies to be adopted onto the MCRN study portfolio and the infrastructure put in place facilitated study set-up and participant recruitment in many sites. The main PREDNOS study was also adopted onto the study portfolio and similarly benefited.

Possible weaknesses of the study include the possibility that the choice and preparation of study drug might have influenced the age profile of the population under study, with a potential trend towards the relative over-inclusion of older participants. Because the PREDNOS study drug was supplied in crushable tablet-form rather than in suspension or in a soluble or dispersible form, this may have resulted in smaller children not participating in the study because of inability or perceived inability to swallow this. The initial ISKDC studies reported that the median age of presentation of MCD nephrotic syndrome was threè years and a UK series from the county of Yorkshire reported the incidence to be greatest in the one to four year old age group. The mean age of participants in our study was 4.9 years, with 65% of the study participants being under six years of age. This rather suggests that there was a trend towards the recruitment of slightly older participants, perhaps as a result of this study medication formulation issue. However, our study participant age profile is broadly comparable with those reported in the three most recent RCTs of corticosteroid therapy in SSNS by Teeninga et al. (median (IQR) age 4.2 years, 3.2 to 6.2 years), Yoshikawa et al. (mean (SD) age 6.7 (4.1) years in the SC group and 6.3 (4.1) years in the EC group) and Sinha et al. (42.4 months in three month treatment group and 44.2 months in the six month treatment group).

The parents of two participants recruited at the Chief Investigator's site commented that they felt that they knew which group their child had been randomised to because their child had noticed slight differences in taste between the active prednisolone and placebo tablets. Prednisolone and other oral corticosteroids tend to have a somewhat bitter taste and it may be that other study participants noticed this same phenomenon. This was not, however, reported by other PIs and it therefore seems unlikely that this would have had a significant impact on the study results.

One further potential minor limitation is the fact that study participants were in the majority of cases observed and treated at their local hospital, where the study visits took place. As such, observation and scoring of adverse effects in the study was performed by multiple observers. To avoid this issue would have meant all study participants travelling to a single or small number of centres, which would have proved a very significant barrier to participation. Randomisation was not minimised by centre, as individual centre contributions were difficult to predict.

In designing the study, we wanted to ensure that we objectively and comprehensively collected prednisolone-related AEs to adequately compare the two treatment regimens. Earlier studies lacked consistency in the level of information that was recorded and none reported quantitative data regarding behavioural change. Our adverse event reporting was, however, somewhat less comprehensive than that in some more recent studies and this warrants some further discussion. Yoshikawa et al. performed formal ophthalmological assessment, including measurement of intraocular pressure, which was found to be elevated in 32 of 246 participants (13%). In the study of Teeninga et al., participants underwent formal ophthalmological assessment at diagnosis and after six months, specifically looking for evidence of cataract and glaucoma. No cases of glaucoma were detected and only one single case of posterior sub capsular cataract was detected in the three month prednisolone group. In the PREDNOS study, we did not ask for participants to have a formal ophthalmological review, though PIs screened participants for cataract on an annual basis. Only one case of cataract was detected in each group, a similar frequency to the single case in the study of Sinha et al. On the basis of their observations, Teeninga et al. commented that cataract and glaucoma have been reported with much greater frequency in cohorts of Japanese children than those from other races and that their findings indicate that routine ophthalmological screening was not indicated at an early stage in Dutch children.

Yoshikawa additionally performed regular blood tests and detected minor abnormalities of liver function tests and plasma amylase in up to 21% of participants. We elected not to perform regular blood tests as part of the study protocol principally because this is not routine clinical practice in the UK; children with SSNS generally have very few blood tests performed unless they are commenced on alternative immunosuppressive therapies mandating monitoring of drug levels or adverse effects. Furthermore, we were of the opinion that the introduction of regular blood tests into the study protocol would negatively impact upon study participation. We did include a single episode of blood sampling for the purpose of collecting a DNA samples for a separate study aiming to identify potential genetic changes associated with SSNS. A recommendation was made that this be performed at the time of venepuncture for other clinical reasons if this occurred, though our Research Ethics Committee approval permitted us to perform a stand-alone venepuncture solely for this sample. Sampling was successfully performed in 173 study participants.

In Teeninga's study of Dutch children, lumbar spine bone mineral density was measured using dual energy x-ray absorbitiometry (DXA) at baseline and after six months. We did not perform this investigation, principally because there is little in the published literature that indicates that significant abnormality of bone mineral density is likely to occur within the first 24 months of treatment, particularly in an unselected cohort of newly presenting SSNS patients. Whilst our own work has reported a minor reduction in trabecular bone mineral density in adult 'survivors' of childhood relapsing nephrotic syndrome, such changes required the use of peripheral quantitative CT, which is not widely available and would not have been detected using DXA alone. Many of the District General Hospitals participating in PREDNOS would additionally have experienced difficulties in providing DXA services for paediatric study participants. Furthermore, a high quality prospective study examined 60 children with INS and 195 controls and found no deficits in spine or whole body bone mineral content. In Teeninga's study no difference was detected in bone mineral density from baseline to six months in either group, and they were not able to achieve bone assessment in all participants.

Conclusion

On the basis of the results of the PREDNOS study, it can be concluded that extending the duration of prednisolone beyond the two month ISKDC regimen that is currently being used in the large majority of UK centres does not result in a reduction in the time to first relapse, the number of participants developing FRNS or SDNS or the total dose of prednisolone administered. There were no differences between the two treatment regimens in the incidence of corticosteroid AEs. However, the cost-effectiveness analysis showed EC therapy to be cheaper and more effective in QALY terms and therefore on the basis of the economic analysis alone, is the recommended treatment of choice.

Future research recommendations

Our results, whilst not adequately powered to show a difference, suggest that children presenting with SSNS under six years of age may benefit from receiving EC therapy and this requires further investigation. This observation has previously been reported in other RCTs36 and is currently being investigated in an Indian trial which is ongoing (personal communication Professor A Bagga). This is of particular importance given the fact that younger children appear to be at increased risk of FRNS and SDNS.

The lack of benefit of EC compared with SC therapy raises the issue as to whether further studies should investigate whether it is safe and efficacious to use even shorter corticosteroid regimens.

This strategy has only once been previously addressed in a RCT which showed the relapse rate and incidence of FRNS to be higher in those who received shorter course rather than SC therapy many of the earlier studies in this disease group, this was, however, at significant risk of a number of areas of trial bias. Finally, the disparate results between the health economic analysis and the clinical analysis requires further evaluation; the difficult question here is whether further RCTs comparing SC and EC are justified given the clear lack of clinical benefit.

Acknowledgements

The PREDNOS investigators would like to thank the NIHR for funding this study and Kidney Research UK and Kid's Kidney Research, who funded the pilot study. We thank the North West 7 Research Ethics Committee ethics committee for all of their input and guidance. We thank all the parents and participants who agreed to enter the study, the investigators who contributed to the trial and the NIHR Clinical Research Network: Children for their support with study set-up and recruitment. We also thank the Service Users Group from the UK Nephrotic Syndrome Trust (NeST) and the Renal Patient Support Group, in particular Mrs Wendy Cook, Mrs Samantha Davies-Abbott and Dr Shahid Muhammad who provided valuable input regarding trial design and conduct and reviewed the plain English summary. The support of the British Association for Paediatric Nephrology and the Royal College of Paediatrics and Child Health is much appreciated.

Section 5 Publication and Dissemination

The study results were initially presented at the European Society of Paediatric Nephrology 50th Anniversary conference in Glasgow 6th -9th September 2017.

The final version of the HTA publication following reviewer and editorial comments was submitted in January 2018.

The BMJ publication is currently being prepared for initial submission.

Following the publication of the HTA report and the BMJ paper the trial results will be disseminated to all study collaborators. The plain English summary of the study results will be sent to all participants and/or their parents via their responsible clinician. The summary will also be available on the UK Nephrotic Syndrome Trust (NeST) website and the PREDNOS study website (http://www.birmingham.ac.uk/prednos).