Sixteen-week versus standard eight-week prednisolone therapy for childhood nephrotic syndrome: the PREDNOS RCT

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Declared competing interests of authors: Nicholas JA Webb has served on advisory boards within the past 5 years for AbbVie Inc. (North Chicago, IL, USA), Alexion Pharmaceuticals (New Haven, CT, USA), AMAG Pharmaceuticals Inc. (Waltham, MA, USA), Astellas Pharma Inc. (Tokyo, Japan), Raptor Pharmaceuticals (Novato, CA, USA), Takeda Pharmaceutical Company (Osaka, Japan) and UCB (Union Chimique Belge) (Brussels, Belgium). These have related to the design and conduct of early-phase trials in childhood kidney disease. None has been related to the treatment of corticosteroid-sensitive nephrotic syndrome. Since August 2018, Nicholas JA Webb has been Translational Medicine Discovery Director, Renal and Transplantation, at Novartis Institutes for BioMedical Research. Carole Cummins has received grants from Kidney Research UK and Kids Kidney Research.

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Scientific summary

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Background

Idiopathic nephrotic syndrome (INS) is the most common glomerular disorder of childhood, with an incidence of 2 per 100,000 child population in the UK. The disease presents at a median age of 2 to 3 years and is twice as common in boys as in girls. There is ethnic variability in the disease incidence, with a fourfold to sixfold 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 having steroid-sensitive nephrotic syndrome (SSNS).

Following initial successful treatment with corticosteroids, around 80% of children with SSNS experience 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 6 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. When complications of repeated courses of corticosteroids develop, or when they are expected, 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 a child presenting with SSNS. The majority of UK centres have continued to use the 8-week regimen first described by the International Study of Kidney Disease in Children (Nephrotic syndrome in children: a randomised controlled trial comparing two prednisolone regimens in steroid responsive patients who relapse early. *J Pediatr* 1979;**95**:239–43) in the 1960s. At the time of commencement of the PREDnisolone in NephrOtic Syndrome (PREDNOS) study, a total of six randomised controlled trials (RCTs) had compared 2 months of prednisolone with a variety of different regimens of ≥ 3 months in duration. A 2005 Cochrane review (Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. *Cochrane Database Syst Rev* 2005;**1**:CD001533) 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 to 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 of children 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. Thus, there remains significant clinical equipoise, with the UK, parts of North America and other countries continuing to use the 8-week International Study for Kidney Disease in Children (ISKDC) regimen, while Germany, France and other countries use a regimen of ≥ 3 months in duration.

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

Objectives

The primary objective was to determine whether or not a 16-week extended course (EC) of prednisolone increases the time to first relapse in children presenting with SSNS compared with the standard 8-week course.

The secondary objectives were to determine whether or not an EC of prednisolone reduces relapse rate; reduces the proportion of participants who develop FRNS or steroid-dependent nephrotic syndrome (SDNS); reduces 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 (SC) therapy.

Methods

A double-blind RCT was undertaken across 125 UK NHS district general hospitals and tertiary paediatric nephrology units comparing an 8-week 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 a urine albumin-to-creatinine ratio of > 200 mg/mmol or protein-to-creatinine ratio of > 200 mg/mmol on an early-morning urine sample, had a serum or plasma albumin level of < 25 g/l, were aged between 1 and 15 years at the time of diagnosis, had not previously received therapy with corticosteroids or 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 (when renal biopsy has been undertaken), who had prior history of poor adherence with medical therapy or who had a known allergy to prednisolone were excluded.

Participants were randomised in a 1 : 1 ratio to either the SC or EC group in accordance with a minimisation algorithm to ensure balance of ethnicity (South Asian, white or other) and age (≤ 5 or ≥ 6 years). The SC (control) group received a 60 mg/m^2 dose of prednisolone daily (maximum 80 mg) for 4 weeks, followed by 40 mg/m^2 (maximum 60 mg) on alternate days for 4 weeks. The EC group received a 60 mg/m^2 dose of prednisolone daily (maximum 80 mg) for 4 weeks, followed by a further 12 weeks of alternate-day prednisolone starting at 60 mg/m^2 (maximum 80 mg) and tapering by 10 mg/m^2 every 2 weeks. In both groups, treatment in the first 4 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® (Siemens Healthcare Limited, Frimley, UK)-positive proteinuria (+++ or greater) for 3 consecutive days or the presence of generalised oedema plus +++ proteinuria. Secondary outcomes were relapse rate, incidence of FRNS (two or more relapses in the first 6 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 Pediatric Quality of Life Inventory and Child Health Utility 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.

Results

Two hundred and thirty-seven participants were recruited into the study from 86 UK centres between 2 August 2011 and 7 October 2014: 118 were randomised to SC and 119 to EC therapy. Fourteen participants (SC, $n = 9$; EC, $n = 5$) were withdrawn during the first few weeks of the trial (following randomisation), as per the protocol, owing 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 participants (5%) became lost to follow-up and four participants (2%) withdrew from the study for other reasons. For these 30 participants, data that were 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 (SC, $n = 20$; EC, $n = 24$).

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/m^2/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 than in the EC 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 because of relapse was higher in the SC group ($n = 50$) than in the EC group ($n = 29$), which was mainly because the SC group was on placebo from week 8. When relapses developed during this period of study drug administration, the protocol stated that study medication was to be discontinued and relapse treatment commenced.

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

The number of participants who reported a relapse during the trial was 179: 88 out of 109 (81%) in the SC group and 91 out of 114 (80%) in the EC group. There was no significant difference in time to first relapse between the SC and EC groups (HR 0.87, 95% CI 0.65 to 1.17; log-rank $p = 0.3$). When prespecified subgroup analyses were performed for the primary outcome for the two minimisation variables of ethnicity (South Asian, white, other) and age (≤ 5 or ≥ 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 0 to 15; there were eight participants in the SC group and nine in the EC group who experienced ≥ 10 relapses. The mean number of relapses did not differ between groups (SC 3.61 vs. EC 3.98; incidence rate ratio 1.09, 95% CI 0.86 to 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 than in the SC group (5475 mg vs. 6674 mg; $p = 0.07$).

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 reasons for SAE reporting were admission for disease relapse or bacterial infection. Five out of the 39 SAEs in the SC group and six out of the 28 SAEs in the EC group were, in the opinion of the principal investigator, related to study drug, although none resulted in study drug discontinuation. There was one accidental death that was 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% (SC 90% vs. EC 75%), Cushingoid facies in 67% (SC 66% vs. EC 68%), hypertrichosis in 26% (SC 23% vs. EC 30%) and abdominal pain in 26% (SC 28% vs. EC 25%). By 24 months, these had increased to 94% (SC 94% vs. EC 93%) for increased appetite, 87% (SC 93% vs. EC 82%) for poor behaviour, 72% (SC 72% vs. EC 73%) for Cushingoid facies, 39% (SC 38% vs. EC 39%) for hypertrichosis and 45% (SC 47% vs. EC 43%) for abdominal pain. At 16 weeks, and at 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 to 0.96]. Differences were also seen at 6 months (91% vs. 81%, RR 0.90, 95% CI 0.82 to 1.00), 12 months (92% vs. 82%, RR 0.90, 95% CI 0.82 to 0.98) and 24 months (93% vs. 82%, RR 0.90, 95% CI 0.82 to 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 (£4369 vs. £2696)].

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 suggested that EC therapy may be cheaper, with the possibility of a small QALY benefit.

Trial registration

This trial is registered as ISRCTN16645249 and EudraCT 2010-022489-29.

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