Daily low-dose prednisolone to prevent relapse of steroid-sensitive nephrotic syndrome in children with an upper respiratory tract infection: PREDNOS2 RCT

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Scientific summary

The PREDNOS2 RCT

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Scientific summary

Background

Idiopathic nephrotic syndrome is the most common glomerular disease of childhood, with an incidence of 2 per 100,000 children in the UK. However, it is up to six times more common in children of South Asian ethnic origin. Most children respond to treatment with high-dose prednisolone and the disease is then known as steroid-sensitive nephrotic syndrome (SSNS). At least 80% of children with SSNS will relapse, and these relapses are associated with a risk of significant complications, including sepsis, thrombosis, dyslipidaemia and malnutrition. The treatment of relapses with high-dose prednisolone is associated with major short- and long-term adverse effects. Around half of children with SSNS will commence non-corticosteroid treatment with drugs such as levamisole, cyclophosphamide, ciclosporin, tacrolimus, mycophenolate mofetil or rituximab to prevent relapses.

Previous studies have shown that at least 50% of relapses follow from upper respiratory tract infections (URTIs). Furthermore, in children with relapsing SSNS, half or more URTIs will trigger a relapse. Four trials have shown that low-dose daily prednisolone given for 5–7 days when an URTI is diagnosed reduces the risk of ensuing relapses. These studies were, however, relatively small (with 36–100 participants), not all were blinded and all but one study included only those children already taking maintenance alternate-day prednisolone. One trial comprised children with a history of frequently relapsing steroid-sensitive nephrotic syndrome (FRSSNS), but who were taking no maintenance treatment at the time of recruitment. Two studies were a crossover design, raising questions about the independence of response after the treatment arm was changed. Some trials excluded participants when they showed evidence of non-adherence. Others excluded patients if their background therapy changed. The 2020 update of the Cochrane systematic review demonstrated risks of bias for all of these studies (Hahn D, Samuel SM, Willis NS, Craig JC, Hodson EM. Corticosteroid therapy for nephrotic syndrome in children. *Cochrane Database Syst Rev* 2020;**8**:CD001533).

All of these studies were carried out in South Asia or the Middle East, and often incorporated a broader range of intercurrent infection that included lower respiratory tract infection and gastroenteritis. The epidemiology of infections is different in Europe, where the most common intercurrent infections are URTIs.

To determine if children living in temperate climates who are on a range of maintenance treatments for relapsing SSNS would benefit from taking daily low-dose prednisolone at the time of an URTI, a large, placebo-controlled, double-blinded, randomised controlled trial was needed.

Objectives

The primary objective was to determine whether or not a 6-day course of low-dose daily prednisolone reduced the incidence of upper respiratory tract infection-related relapse (URR) in a population of children with relapsing nephrotic syndrome on different background medication.

The secondary objectives were to compare the overall rate of relapses, the incidence of escalations or reductions in background therapy and the cumulative dose of prednisolone over 12 months; and assess corticosteroid adverse effects, including behaviour and quality of life, and treatment costs.

Methods

A Phase III randomised parallel-arm placebo-controlled double-blind trial, including a cost-effectiveness analysis, was undertaken in 122 UK paediatric departments. Children aged 1–18 years were eligible if they had relapsing SSNS (defined as having experienced two or more relapses in the preceding 12 months). Exclusions included children with steroid-resistant nephrotic syndrome; children receiving, or within 3 months of having completed, a course of oral or intravenous cyclophosphamide or rituximab; and children on daily prednisolone therapy at the time of recruitment or an alternate-day dose of > 15 mg/m^2 at the time of recruitment.

Participants were randomised in a 1 : 1 ratio and minimised by background therapy (i.e. no background treatment, maintenance prednisolone only, maintenance prednisolone and non-corticosteroid immunosuppression, and non-corticosteroid immunosuppression only) to receive either low-dose daily prednisolone or placebo for 6 days at the time of an URTI. For children not taking background prednisolone, the intervention arm received a dose of 15 mg/m^2. Those already taking maintenance prednisolone made up their usual dose to 15 mg/m^2 daily or to their alternate-day dose, whichever was the higher. Placebo tablets were used to maintain blinding.

An URTI was defined as presence of at least two of the following for at least 24 hours: sore throat, ear pain/discharge, runny nose, cough, hoarse voice or fever > 37 °C (measured using a tympanometric electronic thermometer).

The primary outcome was the incidence of the first URR following any URTI during the 12-month follow-up period. Secondary outcomes were the overall rate of URRs, overall rate of relapses (URTI and non-URTI related), escalations or reductions in background treatment, cumulative dose of prednisolone over 12 months, rates of serious adverse events (SAEs), incidence of corticosteroid adverse effects, change in behaviour measured with the Achenbach Child Behaviour Checklist (ACBC), quality of life and a health cost analysis. The analysis was by intention-to-treat (ITT) principle.

Children were seen every 3 months for 12 months and, at each trial visit, information was collected on relapses, medication and corticosteroid adverse effects. Behavioural effects of corticosteroids were assessed objectively using the ACBC questionnaire and quality of life was assessed using the Pediatric Quality of Life Inventory (PedsQL), Child Health Utility 9D (CHU-9D) and EuroQol-5 Dimensions (EQ-5D) questionnaires.

In children with FRSSNS, the development of an URTI results in relapse in around 50% of instances. To detect an absolute difference of 17.5% (i.e. 35% proportional reduction) in URR rate (i.e. from 50% to 32.5%), with 80% power and an alpha of 0.05, required 250 children in total. To allow for attrition, the original sample size was inflated by between 10% and 20%, meaning that between 280 and 320 children were required. Therefore, we planned to recruit 300 children, 150 to each arm. During the trial, it became apparent that a larger number of participants (28%) were completing the 12-month trial without experiencing an URTI. The Trial Steering Committee recommended increasing the sample size to 360 patients, based on a revised attrition rate of 30%, which would provide the 250 patients needed to detect the difference as per the original sample size calculation.

Analyses were based on a modified ITT population, which included only those participants who had an URTI over the 12-month follow-up period. Binomial and linear regression models, with the minimisation variable (i.e. background therapy at randomisation) and baseline scores (where available) included in the model as covariates, were used to obtain estimates of treatment effects, along with two-sided 95% confidence intervals (CIs). *p*-values are reported from two-sided tests at the 5% significance level.

A decision-analytic model was developed to undertake a cost–utility analysis alongside the PREDNOS2 (PREDnisolone in NephrOtic Syndrome 2) trial. The model structure was informed by clinical input and the pathways followed by participants within the trial. All model parameters were based on the trial data.

The economic evaluation was conducted using an outcome of cost per quality-adjusted life-years (QALYs), measured using the CHU-9D and/or the EQ-5D, depending on the age of the participant. For participants aged < 5 years, a published mapping algorithm was applied to predict utility values from the PedsQL instrument. Two analyses were conducted, reflecting a 1-year and 16-year time horizon.

Results were reported using incremental cost-effectiveness ratios and a probabilistic sensitivity analysis (PSA) was conducted to reflect the uncertainty in the results and to generate cost-effectiveness acceptability curves.

Results

Between February 2013 and January 2019, 365 children with relapsing SSNS were recruited from 91 paediatric centres. Their mean age at recruitment was 7.6 (standard deviation 3.5) years and 63.8% were white. Eighty children completed 12 months of follow-up without experiencing an URTI. Thirty-two children were withdrawn (8.8%), of whom 14 were withdrawn before having an URTI. This left a modified ITT population of 271 children (134 children in the prednisolone arm and 137 children in the placebo arm), which was the analysis population. Treatment was commenced at the time of an URTI for 85.4% of URTIs in the prednisolone arm and 89.2% of URTIs in the placebo arm.

There were 384 URTIs and 82 URRs in the prednisolone arm, and 407 URTIs and 82 URRs in the placebo arm. The number of children who experienced an URR was 56 (42.7%) in the prednisolone arm and 58 (44.3%) in the placebo arm (adjusted risk difference −0.024, 95% CI −0.14 to 0.09; $p = 0.70$). There was no evidence that the treatment effect differed when the data were analysed by predefined subgroups according to background treatment, but there was a small difference in response when the data were analysed post hoc by ethnicity [South Asian ethnicity risk ratio 0.66 (95% CI 0.40 to 1.10) vs. other ethnicity risk ratio 1.11 (95% CI 0.81 to 1.54)]. However, the numbers are small and this was not a planned subgroup analysis.

There were no significant differences in secondary outcomes between treatment arms. There were 216 (URTI and non-URTI related) relapses in 91 children in the prednisolone arm and 237 relapses in 98 children in the placebo arm (adjusted risk difference −0.053, 95% CI −0.16 to 0.06; $p = 0.33$). Background treatment was escalated on at least one occasion in 58 (44.6%) children in the prednisolone arm, compared with 57 (44.5%) children in the placebo arm ($p = 0.96$). Fifty-five (43%) children in the prednisolone arm had at least one treatment reduction during the trial, compared with 62 (48.1%) children in the placebo arm ($p = 0.42$). The median cumulative dose of prednisolone over 12 months was 2060 mg [interquartile range (IQR) 1127.5–3355 mg] in the prednisolone arm and 1880 mg (IQR 1115–3295 mg) in the placebo arm ($p = 0.72$). There were no significant differences between trial arms in the number of SAEs or specific corticosteroid adverse effects. There were no differences in behaviour scores when measured with the ACBC or in quality of life when measured with the PedsQL.

At 1 year, giving daily prednisolone at the time of an URTI led to a reduction in overall health care costs (£252 vs. £254) and an improvement in QALYs (0.9427 vs. 0.9424), compared with standard care, and was, therefore, the 'dominant' treatment option. This result was robust to the deterministic sensitivity analysis. The PSA showed that at a willingness-to-pay threshold of £20,000 per QALY, there was an 80% and 90% probability of daily prednisolone being cost-effective over a 1- and 16-year time horizon, respectively.

Conclusions

In a large and methodologically robust trial, PREDNOS2 has shown that giving 6 days of daily low-dose prednisolone at the time of an URTI does not reduce the risk of relapse of nephrotic syndrome in UK children. However, the economic analysis showed that giving low-dose prednisolone at the time of an URTI leads to less overall health-care cost and is more effective (in QALYs) than standard care, both in the short and longer term.

Further work is needed to investigate interethnic differences in treatment response, the pathogenesis of individual viral infections and their effect on nephrotic syndrome, and the effect of different corticosteroid regimens in treating relapses along with the role of the adrenal axis.

Trial registration

This trial is registered as ISRCTN10900733 and EudraCT 2012-003476-39.

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This report

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