Treatments for children with idiopathic steroid-resistant nephrotic syndrome

The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review

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Executive summary

Health Technology Assessment 2007; Vol. 11: No. 21

Health Technology Assessment
NHS R&D HTA Programme
www.hta.ac.uk

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Executive summary

Background

Nephrotic syndrome is a collection of signs and symptoms, including protein in the urine, low blood protein levels, high cholesterol levels and swelling. First line treatment is with oral corticosteroids, but some children do not respond to this treatment. The optimal treatment of steroid-resistant nephrotic syndrome (SRNS) is uncertain.

Objectives

The objectives of this review were to assess the clinical effectiveness and cost-effectiveness of treatments for children with idiopathic SRNS.

Methods

Data sources

Electronic databases were searched from inception to February 2006. Bibliographies of included studies and related papers were checked for relevant studies. Experts were contacted for advice and peer review and to identify additional studies.

Study selection

Titles and abstracts were screened for eligibility by one reviewer and checked by a second. Inclusion criteria were applied to the full text of selected papers by two reviewers, with differences resolved though discussion. Inclusion criteria were:

- intervention: high-dose steroids, immunosuppressive agents, alkylating agents, plasma exchange therapy, angiotensin-converting enzyme inhibitors or fish oils
- patients: children aged 1–18 years with idiopathic SRNS
- studies: systematic reviews of randomised controlled trials (RCTs), RCTs, controlled clinical trials, prospective cohort studies with concurrent controls and economic evaluations; abstracts were considered if sufficient information was presented; non-English-language studies were excluded
- outcomes: remission rates, relapse rates, renal function, adverse effects, long-term renal survival, quality of life, costs and cost-effectiveness.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second, with differences resolved though discussion. The quality of included studies was assessed using criteria from the NHS Centre for Reviews and Dissemination.

Data synthesis

The clinical effectiveness data were synthesised through a narrative review with full tabulation of results. Meta-analysis was undertaken, where appropriate, using the random effects model. Where data allowed, subgroup analysis was undertaken according to renal histopathology [e.g. minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS)].

Results

Number and quality of studies

Two systematic reviews and 11 trials were included in the systematic review of clinical effectiveness. The quality of reporting and methodology of the included studies was generally poor. No economic evaluations were identified.

Summary of benefits and risks

No statistically significant difference in remission rates was found between cyclophosphamide plus prednisone and prednisone alone for all children [relative risk (RR) 1.15, 95% confidence interval (CI) 0.65 to 2.05] or those with FSGS (RR 1.01, 95% CI 0.43 to 2.37). Time to response was statistically significantly less with cyclophosphamide [38.4 days (range 6–80) versus 95.5 days (range 61–129), $p < 0.05$]. Death occurred in five patients. Remission rates were not statistically significantly different between intravenous and oral cyclophosphamide. Vomiting was common with intravenous cyclophosphamide, while pneumonia and alopecia occurred in the oral group.

Ciclosporin statistically significantly increased the number of children (both MCNS and FSGS included) with complete remission compared with placebo or supportive treatment (RR 7.66, 95% CI 1.06 to 55.34), but not for the FSGS subgroup (RR 5.83, 95% CI 0.75 to 45.09). One trial ▶

did not contribute to the summary statistic as no patient in either group had remission. One study reported no major side-effects. Adverse effects including infection and hypertension differed little between groups.

No differences were found between azathioprine and placebo, with about 13% of each group having remission.

Complete or partial remission occurred in six out of seven patients on the 18-month methylprednisolone regimen and three out of five patients on the 6-month regimen. Renal function improved in both groups. Adverse events such as hypertension and frequent infections occurred in both groups. One death occurred.

Intravenous dexamethasone and methylprednisolone produced similar complete remission rates (35.1%, 95% CI 22.9 to 48.9, versus 33.3%, 95% CI 14.6 to 46.9) and partial remission rates (12.3%, 95% CI 5.0 to 23.7 versus 14.3%, 95% CI 3.0 to 36.3). Median time to response (about 10 days) and total number of adverse events were also similar. The most common adverse event was hypertension. There was a statistically significant decrease in median urine to albumin creatinine ratio in both groups.

Six-hour urinary albumin and urinary albumin to creatinine ratio decreased statistically significantly with high-dose but not low-dose enalapril. The difference in the urine albumin to creatinine ratio reduction percentage between the two groups was statistically significant in the period before cross-over only. A small number of patients experienced dry cough.

Tuna fish oil was not associated with any statistically significant improvements in proteinuria, creatinine clearance, serum creatinine or lipid profiles compared with placebo.

Summary of costs

A very limited literature was found on costs associated with SRNS in children. Costs consisted of treatment costs, longer term monitoring and management costs, and longer term costs for patients who progress to end-stage renal failure. The pharmaceutical cost of treatment varied considerably: an 8-week course of cyclophosphamide cost less than £6, while a course of ciclosporin cost almost £900 per year. Treatment with tacrolimus, an alternative to ciclosporin, was estimated to cost in excess of £3400 per year. In addition to pharmaceutical costs, healthcare medical management costs were estimated; varying by treatment strategy, they ranged from £250 to £930 per year in patients not experiencing complications. Other longer term costs may be incurred; these may comprise the cost of care for longer term side-effects and complications, and costs associated with the onset and management of renal failure. Children who fail to respond to treatment are at high risk of developing end-stage renal failure, the costs of which are considerable.

Summary of cost-effectiveness

No published evidence on the cost-effectiveness of treatments for SRNS in children was identified. Subsequent searches were undertaken to identify economic evaluations and economic evidence for SRNS in adults. The current data are sparse and the modelling of the cost-effectiveness of current treatments for SRNS is not feasible at present. It is clear that in future cost-effectiveness analysis it would be inappropriate to compare interventions with a 'no treatment' alternative. It is suggested here that ciclosporin be used as the comparator strategy in future cost-effectiveness analysis, and that the appropriate patient group for analysis may be those patients either not indicated for cyclophosphamide treatment and/or not responding to cyclophosphamide, who would typically be treated with ciclosporin. Where appropriate data on clinical effectiveness were available, a framework for the assessment of the cost-effectiveness of treatment for SRNS was identified in the current review.

Conclusions

Implications for healthcare

The clinical effectiveness literature on treatments for idiopathic SRNS in children is very limited. The available evidence suggests a beneficial effect of ciclosporin on remission rates and of cyclophosphamide on time to remission; however, the strength of the conclusions drawn is limited by the poor quality of the included studies. The other treatments included in this review were each evaluated by only one study, and none found a statistically significant effect. There is insufficient evidence to determine whether or not there is a clinically significant difference. No economic evaluations were identified. The available data on costs and outcomes are sparse and do not permit the ▶

reliable modelling of the cost-effectiveness of treatments for SRNS at present. A modelling framework is suggested, should more relevant data become available.

Recommendation for future research

A well-designed adequately powered RCT comparing ciclosporin with other treatments in children with SRNS without genetic mutation is required.

Publication

Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS. The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review. *Health Technol Assess* 2007;**11**(21).

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The research reported in this monograph was commissioned by the HTA Programme as project number 05/37/01. The contractual start date was in September 2005. The draft report began editorial review in March 2006 and was accepted for publication in January 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.