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COCHRANE COMMENTARY

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NON-CORTICOSTEROID IMMUNOSUPPRESSIVE MEDICATIONS FOR STEROID-SENSITIVE NEPHROTIC SYNDROME IN CHILDREN

What is this review about?

This systematic review summarized the randomized controlled trials that evaluated the benefits and harms of non-corticosteroid immunosuppressive medications (alkylating agents, levamisole, calcineurin inhibitors, mycophenolate mofetil (MMF), rituximab, azathioprine, mizoribine) in children with frequently relapsing nephrotic syndrome (FRNS) and/or steroid-dependent steroid-sensitive nephrotic syndrome (SDNS).

What are the findings?

In children with FDNS or SDNS, alkylating agents (cyclophosphamide, chlorambucil) compared with prednisone or placebo significantly reduced the risk of relapse at 6–12 months (6 studies, 189 children: relative risk (RR) 0.42, 95% confidence interval (CI) 0.28 to 0.62) (Fig. 1). There was no significant difference in the risk of relapse between cyclophosphamide *versus* chlorambucil (1 study, 50 children: RR 1.31, 95% CI 0.80 to 2.13). Cyclophosphamide administered for 8 weeks compared with 2 weeks reduced the risk of relapse within 12 months (1 study, 22 children: RR 0.25, 95% CI 0.07 to 0.92) but there was no significant difference in the risk of relapse between 8 *versus* 12 weeks of therapy (1 study, 72 children: RR 1.04, 95% CI 0.75 to 1.44). Levamisole compared with prednisone, placebo or supportive therapy significantly reduced the risk of relapse during therapy (7 studies, 375 children: RR 0.47, 95% CI 0.24 to 0.89) (Fig. 1). There was no significant difference in the risk of relapse between levamisole and cyclophosphamide during treatment or after both treatments were ceased (2 studies, 97 children: RR 1.17; 95% CI 0.76 to 1.81) (Fig. 2). Comparing cyclosporine (given for 6 to 12 months) with alkylating agents (given for 6 to 8 weeks), there was no significant difference in the risk of relapse during cyclosporine therapy (2 studies, 95 children: RR 0.91, 95% CI 0.55 to 1.48) (Fig. 2)

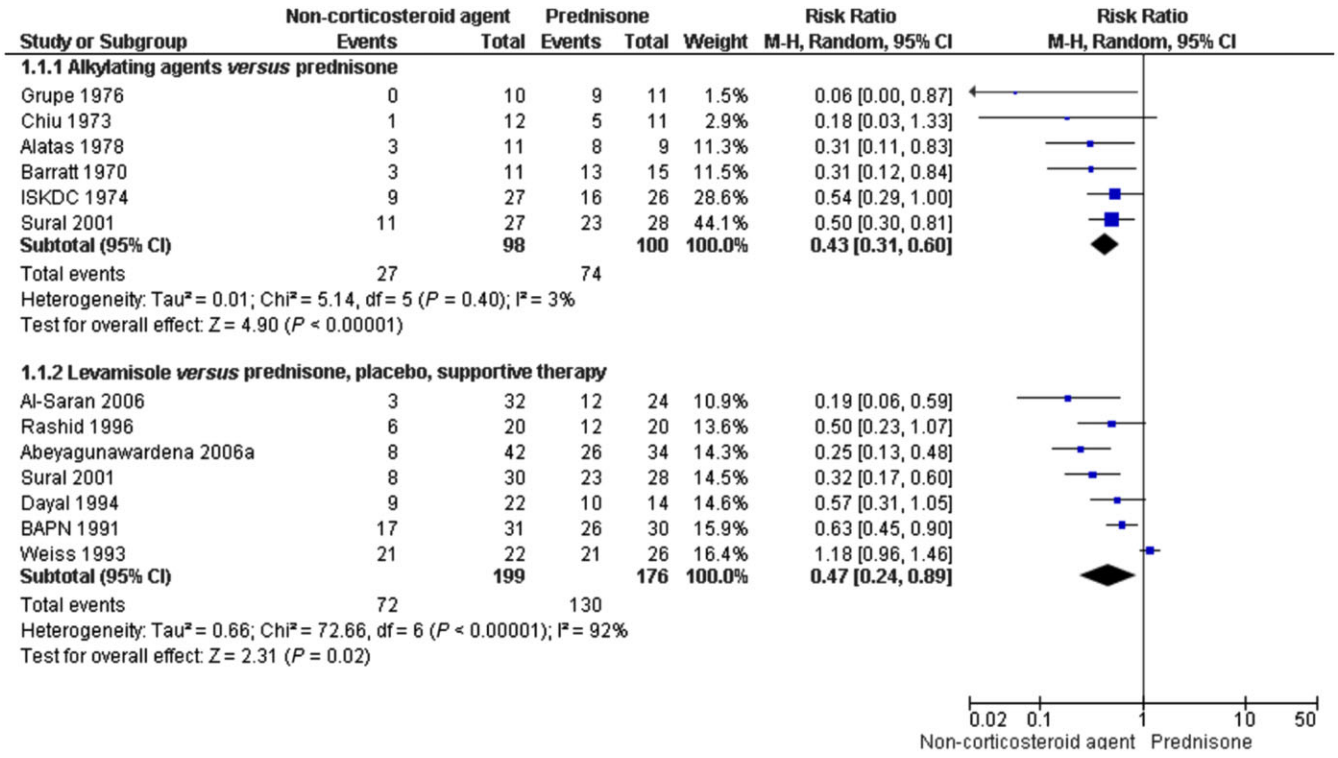

Fig. 1 Risk of relapse with alkylating agents (cyclophosphamide, chlorambucil) or levamisole compared with prednisone, placebo or supportive therapy in children with frequently relapsing or steroid-dependent nephrotic syndrome. CI, confidence interval; df, degrees of freedom; M–H, Mantel-Haenszel statistical method.

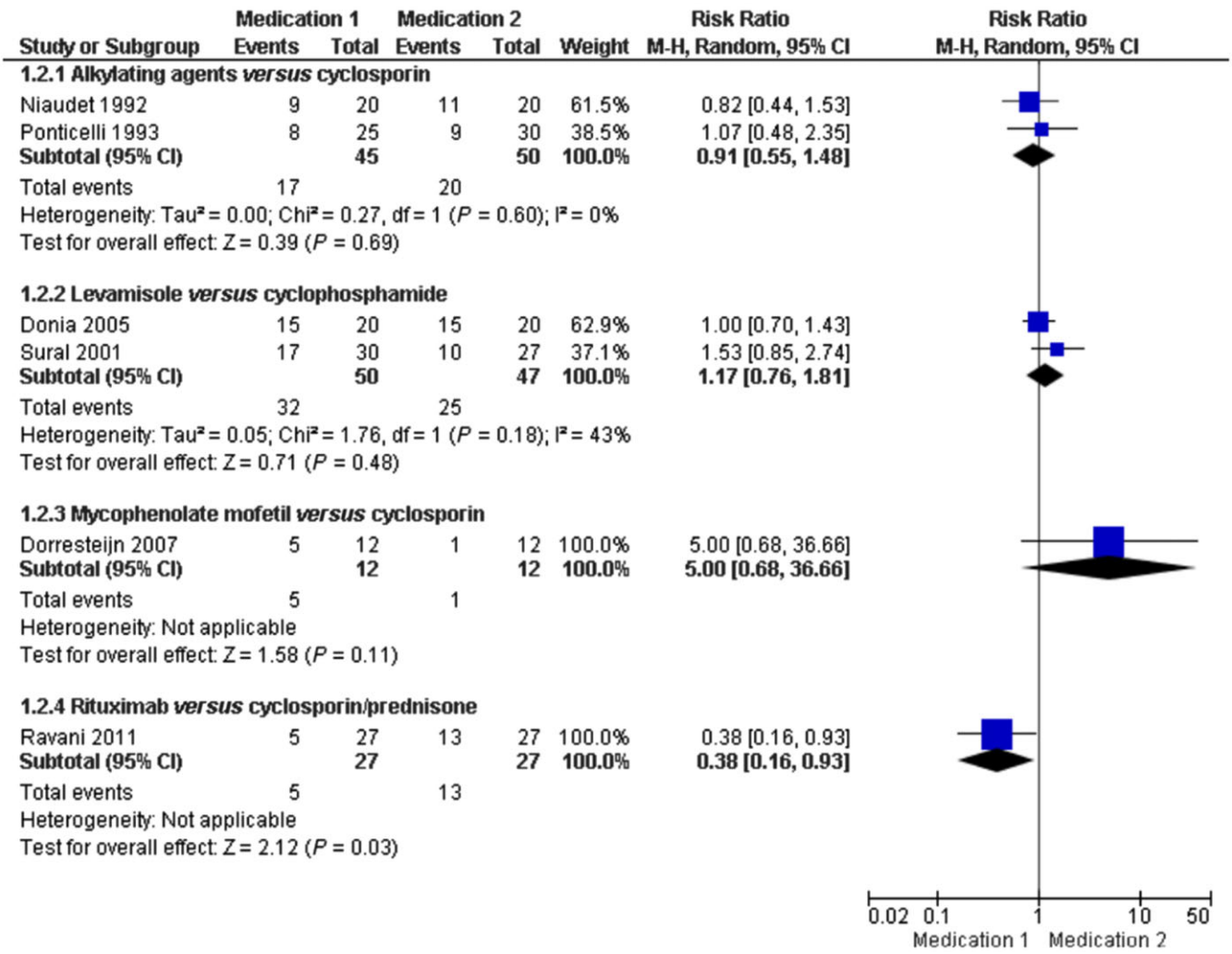

Fig. 2 Risk of relapse in studies comparing different non-corticosteroid immunosuppressive agents (alkylating agents, cyclosporine, levamisole, mycophenolate mofetil, rituximab) in children with frequently relapsing or steroid-dependent nephrotic syndrome. CI, confidence interval; df, degrees of freedom; M–H, Mantel-Haenszel statistical method.

but alkylating agents maintained remission significantly more effectively than cyclosporine after medications were ceased (2 studies, 95 children: RR 0.51, 95% CI 0.35 to 0.74). Two studies have compared MMF with cyclosporine. At 12 months, MMF was less effective *versus* cyclosporine in reducing the risk of relapse though the difference was not significant because of small patient numbers (1 study, 24 children: RR 5.00, 95% CI 0.68 to 36.66) (Fig. 2). However, the relapse rate per year was significantly higher with MMF *versus* cyclosporine (1 study, 24 children: mean difference 0.75, 95% CI 0.01 to 1.49). Preliminary data from a cross-over trial involving 60 children indicate that more children relapsed during treatment with MMF compared with cyclosporine. In prednisone- and cyclosporine-dependent disease, rituximab significantly reduced the risk of relapse at 3 months compared with cyclosporine and prednisone alone (1 study, 54 children: RR 0.38, 95% CI 0.16 to 0.93) (Fig. 2). Compared with prednisone or placebo, azathioprine (1 study, 60 children: RR 0.90, 95% CI 0.59 to 1.38) and mizoribine (hazard ratio of cumulative remission rate 0.79, 95% CI 0.57 to 1.08) did not significantly reduce the risk of relapse. Adverse effects of alkylating agents included serious infection (5%), leucopenia (18%), medication ceased due to leucopenia (7%), hair loss (17% with cyclophosphamide) and cystitis (4% with cyclophosphamide). Adverse effects of cyclosporine included hypertension (13%), reduced kidney function (10%), hirsutism (27%) and gum hypertrophy (23%). Mean glomerular filtration rate at 12 months was slightly but not significantly lower after cyclosporine compared with MMF. Single cases of gastrointestinal upset and leucopenia were reported in two and one levamisole trials respectively. Reported adverse effects following rituximab included bronchospasm, hypotension, fever and skin rashes.

What are the findings based on?

Thirty-two studies (1443 participants) compared different non-corticosteroid immunosuppressive agents with prednisone, placebo or no specific treatment or with other non-corticosteroid immunosuppressive agents in children. Studies were diverse in terms of interventions compared and duration of treatment and follow-up but the primary outcome of relapse was consistent across studies. Most studies were small so that the largest number of studies in any meta-analysis was 7 and the largest number of participants included was 375. Most studies did not differentiate between FRNS and SDNS although there are observational data that children with SDNS have shorter relapse free periods after a course of an alkylating agents compared with children with FRNS. There was significant heterogeneity among studies comparing levamisole *versus* prednisone, placebo or no treatment. This was partially reduced by exclusion of one study (Weiss 1993), which used a much lower dose of levamisole (20 mg/kg per month) compared with the other studies (35 mg/kg per month). Although study data showed that alkylating agents and levamisole were significantly more effective than prednisone, comparative studies between different non-corticosteroid agents were not adequately powered to exclude clinically important differences in efficacy. In particular, we do not have adequate data on the relative efficacies of MMF, calcineurin inhibitors and alkylating agents. Tacrolimus is widely used because of its different adverse effect profile but there are no studies comparing tacrolimus with cyclosporine. Many studies, particularly older studies, were poorly designed. In half of the studies, it was unclear whether the investigators could have influenced the allocation of participants to treatment groups, and over 80% of studies were open-label studies.

Implications for practice

- Compared with prednisolone, alkylating agents and levamisole reduce the incidence of relapse in children with FRNS and SDNS.
- Cyclosporine appears as effective as alkylating agents during therapy. There are no randomized controlled trial data comparing tacrolimus with cyclosporine.
- MMF is probably less effective than cyclosporine but further data are required. There are no randomized controlled trial data comparing MMF and prednisone although there are several before–after studies showing a reduction in relapse rate following the addition of MMF.
- No conclusions can be drawn about which non-corticosteroid immunosuppressive agent should be used as the initial agent in a child with relapsing disease because comparative studies are not powered to exclude important differences.

Clinical perspective

Non-corticosteroid immunosuppressive therapies reduce the risk of relapse in children with FRNS or SDNS. Because comparative studies to date have not demonstrated clear differences in efficacy between therapies, the initial choice of additional therapy will depend on physician, patient and family preferences. Decisions should follow discussion of the benefits and harms of each medication, the need for prolonged courses of cyclosporine, levamisole or MMF compared with short courses of alkylating agents as well as the local availability and cost of medications. Many young people with FRNS or SDNS continue to relapse into adult life, requiring continuing treatment with non-corticosteroid immunosuppressive agents with or without prednisone so are at ongoing risk of adverse effects from these medications.

Pravitsitthikul N, Willis NS, Hodson EM *et al*. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No.: CD002290. DOI: 10.1002/14651858.CD002290.pub4.