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Commentary

Interventions for renal vasculitis in adults

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What is this review about?

Induction and maintenance therapy for renal vasculitis.

What are the findings?

Plasma exchange used as adjunctive treatment to immunosuppression reduced the risk of end-stage renal failure at 3 (two studies; 147 participants; Relative Risk (RR) 0.43; 95% CI 0.23–0.7; $I^2 = 0\%$; Number Needed to Treat (NNT) = 5) and 12 months (six studies; 235 participants; RR 0.45; 95% CI 0.29–0.72; $I^2 = 0\%$; NNT = 5) (Fig. 1). Pulse cyclophosphamide is as effective as continuous cyclophosphamide in remission induction but leads to an increased risk of relapse (four studies; 235 participants; RR 1.79; 95% CI 1.11–2.87; $I^2 = 0\%$; Number Needed to Harm (NNH) = 5) (Fig. 2). Rituximab is as effective as cyclophosphamide for remission induction with a similar side effect profile. Mycophenolate is possibly more effective than cyclophosphamide for

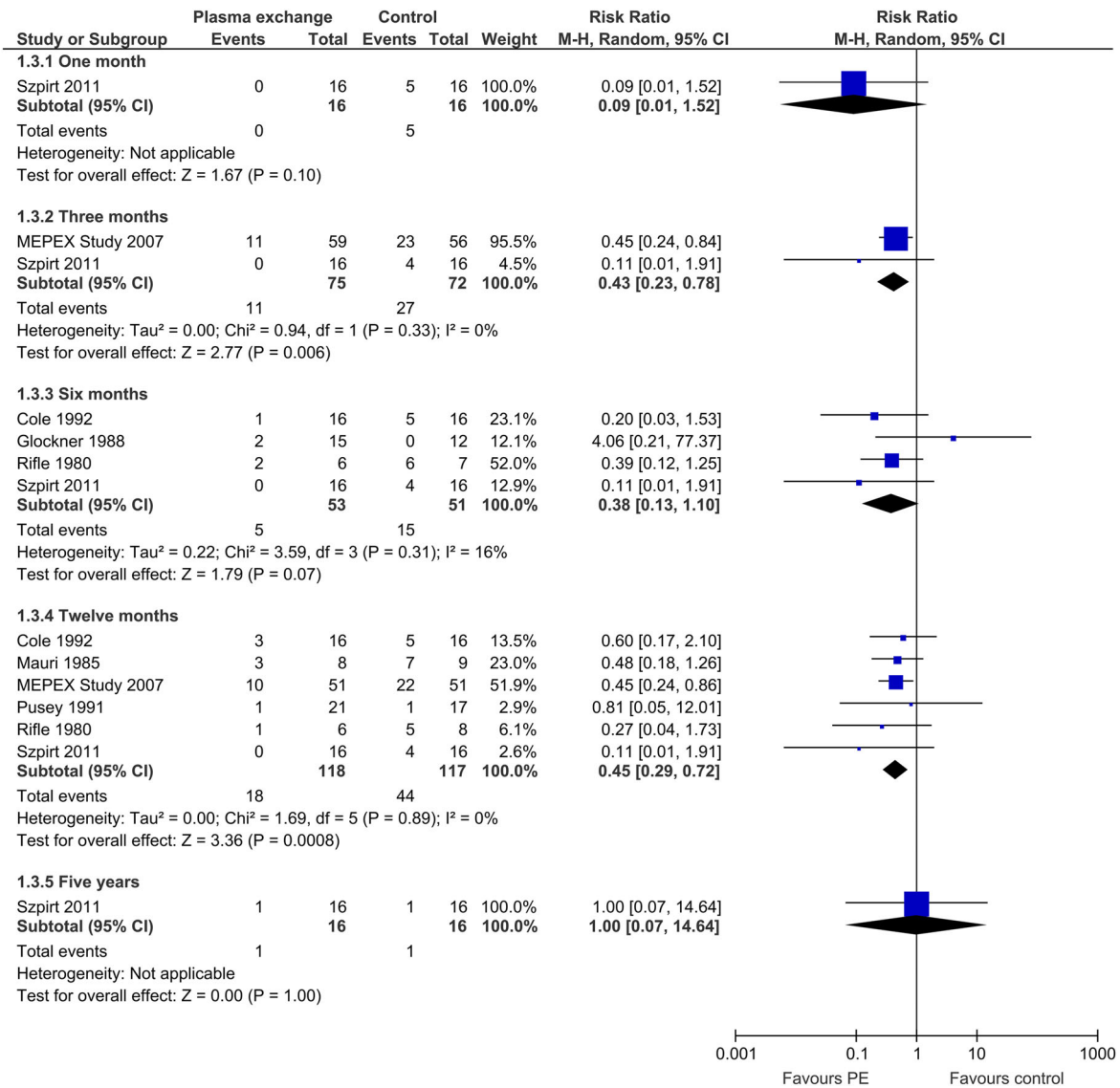

Fig. 1 The effect of plasma exchange on end-stage renal failure.

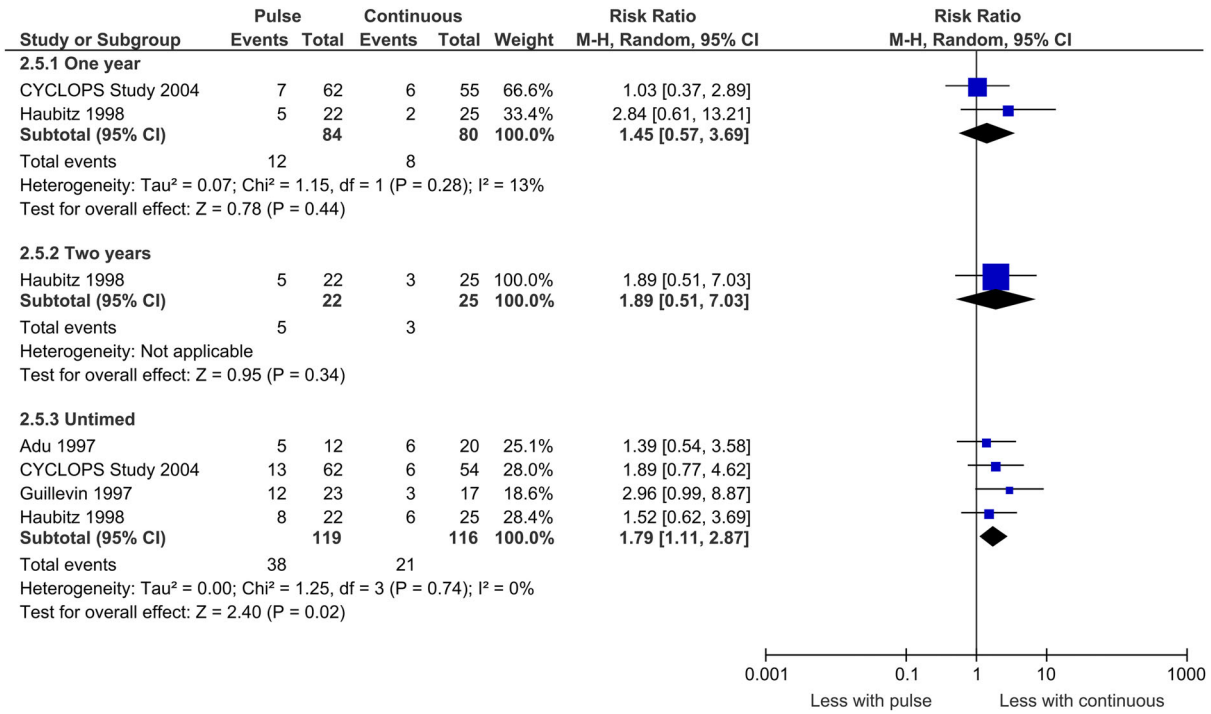

Fig. 2 Comparison of pulse and continuous cyclophosphamide. Effect on relapse rate.

remission induction at 6 months (three studies; 217 participants; RR 1.17; 95% CI 1.02–1.35; $I^2 = 4\%$) but resulted in a shorter time to relapse compared with azathioprine when it was used as a maintenance agent (one study; 156 participants; RR 1.47; 95% CI 1.04–2.09). In maintenance therapy, azathioprine is equivalent to cyclophosphamide. Mycophenolate, methotrexate and leflunomide are all potential alternatives for maintenance.

What are the findings based on?

Thirty-one studies (2217 participants) were included in the review. Twenty-two studies investigated treatments for induction of remission, and nine studies investigated maintenance therapy. Eight studies assessed the use of plasma exchange in remission induction. Four studies compared pulse with continuous cyclophosphamide. Ten studies compared other agents such as rituximab, mycophenolate and IVIg. Maintenance treatment was investigated by nine studies comparing agents such as azathioprine, mycophenolate, leflunomide and methotrexate.

Heterogeneity for the main results was low, as reflected in the I^2 scores. Risk of bias was low on more than 50% of the scored domains. Older studies generally had a higher risk of bias.

Implications for practice

- Plasma exchange is indicated for renal vasculitis in patients with significant renal damage, reducing the number of patients requiring renal replacement therapy by half.
- Pulse cyclophosphamide is equivalent to continuous cyclophosphamide for remission induction, but patients are more likely to relapse.
- Rituximab is effective as an induction agent, but there is no evidence for its superiority over cyclophosphamide.
- Mycophenolate is an effective induction agent, but is untested in severe renal failure.
- Azathioprine is the first-line agent for maintenance treatment, but mycophenolate, methotrexate or leflunomide are potential alternatives.

Clinical perspective

This review establishes the place of plasma exchange in the prevention of end-stage kidney disease for patients with renal vasculitis. A previous review combined death and end-stage renal failure as a composite endpoint and reported a non-significant result, arguing that the data did not support any impact on hard outcomes. Plasma exchange has no impact on death, so in combining a death endpoint with end-stage kidney disease, this had the effect of making the composite non-significant. This review clearly demonstrates a highly significant effect on End Stage Kidney Disease (ESKD). The PEXIVAS study is currently recruiting, and synthesis may change once PEXIVAS results are incorporated.

Pulse cyclophosphamide, whilst giving a good remission rate, resulted in a significantly higher number of relapses. It is also notable that twice as many patients were left on dialysis after pulse therapy, and although this did not reach statistical significance, it is clinically important and needs further clarification.

Mycophenolate induced more remissions at 6 months compared with cyclophosphamide. This effect is currently demonstrated at a single time point and needs further confirmation for the longer term. Rituximab is shown to be equivalent to cyclophosphamide for remission induction, but did not show any improvement in side effect profile. Whilst avoidance of infertility in women of child-bearing age is an advantage, there is no hard data to otherwise justify its expense. There no comparative data between rituximab and mycophenolate.

In maintenance therapy, Azathioprine is the clear first-line agent. In second-line choices, the design of the various studies makes it difficult to establish a clear ranking of agents. Methotrexate is cheap and easy to use, but contraindicated in renal and hepatic impairment. Mycophenolate is a good induction agent and can be continued in maintenance with little disadvantage. Leflunomide is widely used in rheumatoid arthritis and helpful if other agents are not able to be employed.

Future research is already addressing the use of rituximab in maintenance therapy. The interesting questions will be what sort of improvements in clinical care come and at what cost.

Walters G, Willis NS, Craig JC. Interventions for renal vasculitis in adults. Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD003232. DOI: 10.1002/14651858.CD003232.pub3.