

Intravenous methylprednisolone or plasma exchange for adjunctive therapy of severe renal vasculitis?

Original article Jayne DRW *et al.* (2007) Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 18: 2180–2188

SYNOPSIS

KEYWORDS adjunctive therapy, ANCA-associated vasculitis, methylprednisolone, plasma exchange, renal failure

BACKGROUND

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis that presents as advanced renal failure is associated with poor renal outcomes, even when treated with steroids and immunosuppressive agents.

OBJECTIVE

To compare the effects of intravenous methylprednisolone and plasma exchange, when added to oral immunosuppression, on the rate of renal recovery in patients with severe renal ANCA-associated vasculitis.

DESIGN

Adults aged ≤ 80 years who had Wegener's granulomatosis or microscopic polyangiitis; a first episode of biopsy-confirmed, pauci-immune, necrotizing or crescentic glomerulonephritis; and serum creatinine $>500 \mu\text{mol/l}$ ($>5.8 \text{ mg/dl}$) were recruited by the European Vasculitis Study Group from 9 countries. Exclusion criteria included dialysis dependence for >2 weeks and serum creatinine $>200 \mu\text{mol/l}$ ($>2.3 \text{ mg/dl}$) at least 1 year before study entry.

INTERVENTION

After stratification by country and presence of nonoliguria or likely imminent need for dialysis, patients were randomized to receive intravenous methylprednisolone (1 g/day for 3 months) or plasma exchange (7 exchanges of 60 ml/kg within 2 weeks of study entry). In addition, they received oral cyclophosphamide (for 6 months, starting at 2.5 mg/kg/day; subsequently substituted with azathioprine 2 mg/kg/day) and oral prednisolone (for 12 months, starting at

1 mg/kg/day). Participants were assessed at baseline, 6 weeks, 3 months, 6 months, 9 months and 12 months (study end).

OUTCOME MEASURES

The primary end point was renal recovery at 3 months, defined as dialysis-free survival accompanied by a serum creatinine level $<500 \mu\text{mol/l}$ ($<5.8 \text{ mg/dl}$), and analyzed according to the intention to treat principle. Secondary end points included rates of end-stage renal disease, mortality and adverse events.

RESULTS

Of the 151 patients who were screened between March 1995 and October 2002, 137 underwent randomization (67 to intravenous methylprednisolone; 70 to plasma exchange). Baseline demographic, clinical and biochemical characteristics did not differ significantly between the treatment groups. At 3 months, significantly more patients had achieved renal recovery in the plasma exchange group than in the intravenous methylprednisolone group (48 vs 33 [69% vs 49%]; 95% CI for the difference 18–35%; $P=0.02$). This higher rate of dialysis-free survival in the plasma exchange group than in the intravenous methylprednisolone group persisted at 12 months (59% vs 43%; 95% CI for difference 4–40%; $P=0.008$). Compared with methylprednisolone, plasma exchange was associated with reductions in the risk of end-stage renal disease of 22% (95% CI 6–39%) at 3 months and 24% (95% CI 6–41%) at 12 months. There was no significant difference between the two groups in terms of rates of mortality (76% in the methylprednisolone group vs 73% in the plasma exchange group) or severe adverse events (48% and 50%, respectively) at 12 months.

CONCLUSION

Adjunctive plasma exchange is associated with a higher rate of renal recovery in patients with severe renal ANCA-associated vasculitis than is adjunctive therapy with intravenous methylprednisolone.

COMMENTARY

David J Salant

A regimen of initial treatment with high-dose oral prednisolone and oral cyclophosphamide, with substitution of azathioprine for cyclophosphamide 3 months after the induction of remission, is effective at reversing rapidly progressive glomerulonephritis in most patients with ANCA-associated vasculitis.¹ Individuals with vasculitis and severe renal failure, particularly those with oliguria or a requirement for dialysis, fare less well, however.

The current study was designed to determine whether the addition of a two-week course of plasma exchange to standard immunosuppressive therapy would improve the outcome of patients with active renal vasculitis and severe renal failure. The investigators excluded patients who had a serum creatinine >200 µmol/l (>2.3 mg/dl) 1 year or more before study entry, those that had been on dialysis for more than 2 weeks, those with a recurrence of necrotizing or crescentic glomerulonephritis, and those who had previously received substantial immunosuppressive therapy. In other words, the study primarily included patients presenting with recent onset of severe and active glomerulonephritis, in the absence of life-threatening extrarenal manifestations. This observation is corroborated by the fact that 90% of the crescents observed on renal biopsy were cellular and that biopsy tissue samples showed only moderate tubular atrophy, interstitial fibrosis and glomerular sclerosis.

The study results, in terms of renal recovery, are quite impressive. The reduction in the risk of end-stage renal disease attributable to plasma exchange was 24% at 12 months, although patient survival at 12 months was similar in the intravenous methylprednisolone group and the plasma exchange group. Does this mean that some patients died as a result of plasma exchange, thus offsetting the potential renal benefit of this therapy? It is difficult to find evidence that supports this hypothesis among the study data. The death rates in the two treatment groups were similar for the first 3 months—when the effects of plasma exchange were likely to be most pronounced—and only slightly different

at 12 months (27% in the plasma exchange group vs 23% in the methylprednisolone group). Nonetheless, it is sobering that 25.5% of participants died within 1 year and that a high proportion of deaths (54%) were infection-related. Although many of these infections are likely to be attributable to cyclophosphamide and high-dose prednisolone, plasma exchange also has potentially deleterious effects, including depletion of complement, immunoglobulins, and probably other components of the innate immune system.

Many clinicians regard intravenous methylprednisolone as standard therapy for severe vasculitis and renal disease, so one could argue that this agent should have been included in both treatment regimens. If anything, however, exclusion of methylprednisolone from the plasma exchange group biased against a positive result. The trial was also open-label. Mock apheresis of the methylprednisolone group would have reduced the risk of inadvertent investigator bias. Finally, there was no standard protocol for plasma exchange. Nonetheless, given the 'hard' end point of dialysis independence, it is difficult to attribute the positive results of the study to anything other than a real effect.

The results reported by Jayne *et al.* should not be applied indiscriminately to all cases of renal vasculitis. Plasma exchange has not been shown to be more effective than standard therapy in patients with less-severe renal dysfunction than those included in the current study,² or to benefit patients with advanced disease. In otherwise healthy patients with extensive scarring and little or no activity on biopsy, intensive immunosuppression should be avoided because renal transplantation is an excellent option with a low and manageable disease recurrence rate.³

References

- 1 Jayne D *et al.* (2003) A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* **349**: 36–44
- 2 Pusey CD *et al.* (1991) Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. *Kidney Int* **40**: 757–763
- 3 Gera M *et al.* (2007) Recurrence of ANCA-associated vasculitis following renal transplantation in the modern era of immunosuppression. *Kidney Int* **71**: 1296–1301

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Competing interests

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PRACTICE POINT

Patients who have recent onset of active ANCA-associated glomerulonephritis and severe renal failure should receive plasma exchange in addition to standard immunosuppressive therapy