

Plasma-exchange and immunosuppression in the treatment of Goodpasture's syndrome

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Eight patients with Goodpasture's syndrome, all of whom demonstrated circulating antibody to glomerular basement membrane (GBM) as detected by radioimmunoassay, were treated by a regime of intensive plasma-exchange, cytotoxic drugs and steroids. Four patients had some renal function at presentation and in three of these there was improvement in renal function and termination of antiGBM antibody synthesis following this therapeutic regime. The fourth patient, at present in the second week of treatment, is showing improvement in renal function and fall in antiGBM titre. The other four patients were anuric at presentation and all had extensive changes on renal biopsy. No return of renal function occurred in this group and antiGBM antibody levels, although reduced by the combination of plasma-exchange, cytotoxic agents and steroids, remained elevated. Pulmonary haemorrhage was a feature at presentation in six patients and in one was severe and life-threatening. In this patient and four others lung bleeding was arrested soon after starting therapy. In a further patient, currently undergoing therapy, haemoptysis has stopped after one week's treatment. The 'deglobulinating' effect of plasma-exchange using purified protein fraction, leading to depletion of fibrinogen, complement and immunoglobulins will be discussed.

Commentary by John Feehally

I was in my first medical house job when I admitted a young man with a devastating illness I did not understand; he died of exsanguinating pulmonary haemorrhage a few days later in the local renal unit during his first haemodialysis just after the renal biopsy had confirmed crescentic GN with linear IgG. At almost the same time, this abstract was presented at the Renal Association. The regimen developed at Hammersmith Hospital was soon published in the Lancet, and by the time I began a new life as a renal registrar four years later, this treatment regimen had become a familiar mantra, rapidly gaining sway throughout the UK, and rather more slowly elsewhere.

Note that it gained pre-eminence soon after this abstract reporting only 8 patients without a randomised controlled trial [always likely to be a challenge in such a rare disease]. This is not surprising since the disease had been spectacularly and rapidly fatal before this regimen was described – fulminant lung haemorrhage taking its toll even if dialysis was offered – and the outcome for some patients at least was immediately transformed. Furthermore the regimen had the attraction of its logical basis – remove the circulating antibody by plasma exchange, and prevent further antibody synthesis by potent immunosuppression – building on the transfer experiments of Lerner, Glasscock, & Dixon reported in 1967¹ which provided unequivocal evidence that the circulating antibody is indeed pathogenic.

What can be said after 35 years with the wisdom of hindsight?

1 Lerner RA, Glasscock RJ, Dixon FJ. The role of anti-glomerular basement membrane antibody in the pathogenesis of human glomerulonephritis. J Exp Med 1967; 126: 989

As in many other renal diseases we have struggled to decide what to call it. The authors refer to these patients as having Goodpasture's syndrome, which in modern parlance is used for a broader spectrum of patients presenting with immune-mediated lung haemorrhage and rapidly progressive GN usually associated with systemic vasculitis, reserving Goodpasture's disease for those patients with circulating anti-GBM antibodies and linear IgG deposits on the glomerular capillary wall. There has also been a vogue over the years for preferring the term 'anti-GBM disease' not least because Ernest Goodpasture's original descriptions were very likely of patients with fulminant lung and kidney disease of aetiologies other than anti-GBM antibody.

Some might regard as disproportionate, given its rarity, the research budget devoted to Goodpasture's disease over the last 35 years. One justification is that such investment had a high chance, since the antibody is undoubtedly pathogenic, of unravelling more broadly applicable mechanisms of initiation and control of auto-immunity; and that has proven a remarkable success.

The second justification for investment was that the knowledge gained of disease mechanisms would soon translate into novel therapies for Goodpasture's and other auto-immune diseases which by virtue of precise targeting would provide better outcomes while lessening the substantial burden of toxicity from the immunosuppressive regimen then deployed. I doubt that even the most pessimistic of us would have predicted that this regimen with little or no modification would still today be standard therapy for Goodpasture's disease 35 years later. But the search for precise targeted therapies has foundered against the multiplicity and redundancy of renal inflammatory pathways, and the sheer sophistication of the mechanisms by which auto-immunity and tolerance are controlled. The very 'crudity' of the treatment - high dose corticosteroids to suppress a broad range of inflammatory pathways, cyclophosphamide to switch off many immune responses besides the one which is life threatening, plasma exchange removing many unidentified mediators as well as the antibodies - has proven to be a virtue, though not of course without risk.

For my part, the frustration I felt at my complete inability to understand the illness of the young man I met in 1975, or to do anything to save his life, was one powerful factor in convincing me to be a nephrologist.