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PLASMA EXCHANGE IN LUPUS NEPHRITIS

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Summary

Thirty patients with lupus nephritis were treated with plasma exchange and immunosuppressive drug therapy. The indications included failure of drug treatment (15), severe systemic vasculitis (12) and drug toxicity (3). Clinical improvement occurred in eight of 15, six of 12 and one of three respectively. A response was more likely in those with less severe renal impairment, those without marked glomerular sclerosis or hypertensive changes on biopsy, and those receiving cyclophosphamide as concomitant drug therapy. There was a significant fall in anti-DNA antibody and a rise in the C_3 component of complement following plasma exchange, and these changes were maintained at one month and at six months.

Introduction

The treatment of systemic lupus erythematosus remains a matter of debate. Steroid therapy is associated with a historical improvement in outcome [1], and the addition of azathioprine or cyclophosphamide may confer additional benefit [2]. The role of plasma exchange has yet to be defined, although it may be of value in certain patients and controlled trials are now in progress. In this report we describe our retrospective experience of the use of plasma exchange in 30 patients with lupus nephritis.

Patients

Thirty patients (27 female and 3 male), with ages ranging from 14–45 years, were treated between 1976–1984. Diagnosis was made on the basis of elevated levels of antibodies to double stranded DNA, together with clinical features characteristic of lupus. Twenty-five had renal biopsies which were consistent with the diagnosis of systemic lupus erythematosus, and the remainder had

contraindications to biopsy at the time of referral; in these the diagnosis of nephritis was made on the basis of urinary protein excretion and urine microscopy.

Management

Plasma exchange was introduced in three different clinical situations: firstly, in patients whose nephritis had failed to respond to conventional drug therapy (15); secondly, in those with severe multisystem involvement, e.g. cerebral or pulmonary vasculitis (12); and thirdly in three patients with major drug toxicity. A mean of seven 4L exchanges for plasma protein fraction was performed on a daily basis, using fresh frozen plasma only when clinically indicated. Plasma exchange represented the only change in treatment in 18 patients, and in these cases the drug regimen had been stable for at least one week (usually 2 weeks to 3 months). Concomitant drug therapy varied, depending upon the clinical indications, and comprised prednisolone alone (9), prednisolone and azathioprine (9), prednisolone and cyclophosphamide (8) and all three agents (4). Maintenance therapy consisted of tapering doses of prednisolone together with azathioprine in most cases; those patients who had received cyclophosphamide were generally transferred to azathioprine after eight weeks.

Serial assessment of renal function was made by regular measurements of plasma creatinine, creatinine clearance, 24 hour urinary protein excretion and microscopy of urine for red cells and casts. The C_3 and C_4 components of complement were measured antigenically by radial immunodiffusion, CH_{50} by a haemolytic plaque assay, antibodies to double stranded DNA by a modification of the Farr assay, and immune complexes by C1q and rheumatoid factor binding assays.

Results

The outcome of treatment at the time of discharge is shown in Table I, which relates response to the indications for plasma exchange and severity of renal

TABLE I. Initial outcome related to indication for plasma exchange and renal function

	Patients	Improved	No response	Death
Indication				
Failure drugs	15	8	5	2
Vasculitis	12	6	1	5
Toxicity	3	1	2	0
Creatinine (μmol/L)				
<500	14	11	2	1
>500	6	2	3	1
RDT	10	2	3	5

RDT=regular dialysis therapy

impairment. Improvement in renal function was defined as the discontinuation of dialysis therapy, or at least a 25 per cent improvement in plasma creatinine or creatinine clearance, or the disappearance of an active urinary sediment and reduction in proteinuria to less than 1g/day in those with normal renal function. Overall, there was an improvement in 15 of 30 patients, and in six of 18 treated by the addition of plasma exchange alone. A response was more often observed in those with less severe renal failure (Table I), and also in those without evidence of marked glomerular sclerosis or severe hypertension on biopsy (data not shown). An initial improvement was observed in nine of 12 cases treated with cyclophosphamide as concomitant drug therapy, as compared with six of 18 treated with other drugs. It is apparent that the majority of non-responders treated principally for nephritis went on to regular dialysis, whereas non-responders with multisystem involvement died early. Seven patients died during the initial admission, five of infection ± systemic disease, one of lung haemorrhage and one from cerebral hypoxia.

On follow-up to six months, 14 of the 15 with an initial response maintained their improvement and one deteriorated following a relapse. Of eight non-responders, two remained stable, three (all with creatinine >500μmol/L and marked glomerular sclerosis on biopsy) became dialysis dependent and three remained on dialysis. Full follow-up data was available in 21 patients and their renal function is shown graphically in Figure 1.

The initial response to anti-DNA antibody and C_3 to treatment is shown in Figure 2. There was a significant fall in anti-DNA antibody (taken between

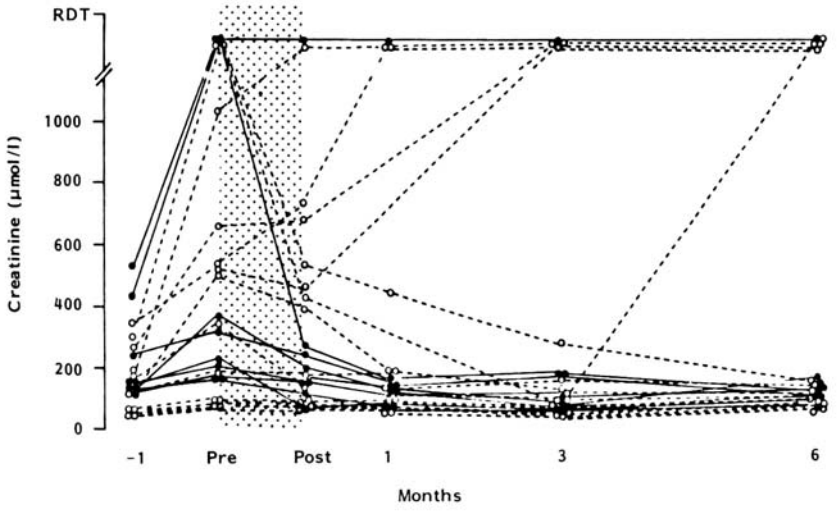

Figure 1. Plasma creatinine in 21 patients, showing response to plasma exchange and follow-up for six months. Concomitant treatment was with prednisolone + cyclophosphamide (●–●) or prednisolone ± azathioprine (○- - -○). Period of exchange indicated by stippled area. RDT=regular dialysis therapy

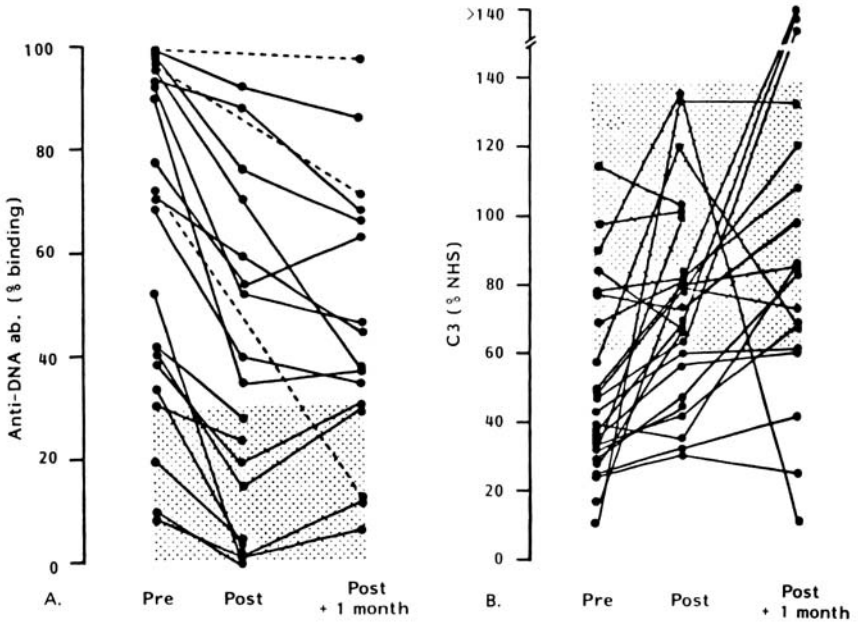

Figure 2. A. Anti-DNA antibody levels in 21 patients, showing response to plasma exchange. There was a significant fall ($p<0.01$) which was maintained at one month. B. C_3 complement levels in 24 patients, showing response to plasma exchange. There was a significant rise ($p<0.01$) which was maintained at one month. Normal ranges are shown by the stippled areas

3 and 7 days following the last exchange) and this was maintained at one month; there was also a significant rise in C_3 post exchange and at one month (similar results were obtained for C_4 and CH_{50}). Further assessment of anti-DNA antibody and C_3 at three and six months show that this improvement was maintained. Immune complexes were not routinely measured, but were detected in 14 of 16 patients, and became undetectable after plasma exchange in 13 of 14.

Discussion

From this retrospective study it is possible to make a number of observations relevant to the use of plasma exchange in patients with lupus nephritis, although no firm conclusions can be drawn. Whatever the indication for plasma exchange, improvement occurred most commonly in those patients with less severe renal failure at the time of presentation, and in those whose renal biopsy showed an active glomerulonephritis (generally diffuse proliferative), without the presence of chronic glomerular changes. As reported by other groups [3], the importance of the glomerular changes in determining renal outcome is reflected by the fact that of those six patients who were dialysis dependent at six months, four had marked sclerosis on biopsy. The superimposition of malignant hypertension appears to be an additional adverse factor as regards renal outcome. It is of note

that 50 per cent of surviving cases in whom PE was introduced as the only additional treatment showed an improvement in renal function. Although it is possible that a late response to drugs could have occurred in certain patients, this provides some evidence for the additional benefit of plasma exchange. The high early mortality, particularly in those treated for systemic vasculitis, reflects the severity of disease and prolonged use of high dose steroids in many patients at the time of admission.

Although there is considerable controversy over the most appropriate immunosuppressive regimen in severe lupus nephritis it is generally agreed that the addition of a cytotoxic agent confers some benefit over steroids alone; there are recent data to support the use of cyclophosphamide in addition to azathioprine [3]. In our experience, the use of cyclophosphamide, together with plasma exchange, was associated with a higher initial response rate, and this combination was also found to be more effective in the long term in a review of 70 cases [4].

It is of interest that there was a sustained improvement in indices of disease activity such as C_3 and anti-DNA antibody, for at least six months after exchange. Although immunological parameters have been recorded as improving following plasma exchange in lupus [5], such prolonged improvement is unusual. In one controlled trial in mild systemic lupus erythematosus, which demonstrated no clinical benefit, anti-DNA antibodies fell after each exchange but returned to normal shortly thereafter [6]; however, in this trial plasma exchange was not combined with cytotoxic therapy. It seems likely that a combination of intensive plasma exchange and cyclophosphamide will be required to produce any long term immunological improvement in systemic lupus erythematosus, as suggested by Jones et al [5], and by our own experience of anti-GBM antibody synthesis in Goodpasture's syndrome [7]. It should be remembered, however, that other effects of plasma exchange, for example depletion of inflammatory mediators and improvement in reticulo-endothelial function, may be important in determining the outcome in this disease [8].

Our observations indicate that plasma exchange may have a role in the management of severe lupus nephritis when it is associated with severe systemic vasculitis, or when drug therapy is ineffective or contraindicated. We have tried to identify those clinical situations in which this approach is likely to be successful, although this is difficult in view of the heterogeneity of such patients. Adequate definition of the role of plasma exchange in lupus nephritis must await the results of prospective controlled trials, in which patients are carefully matched and the amount of exchange and concomitant drug treatment is adequate.

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