FOLLOW-UP PREDNISOLONE DOSAGE IN RAPIDLY PROGRESSIVE CRESCENTIC GLOMERULONEPHRITIS SUCCESSFULLY TREATED WITH PULSE METHYL PREDNISOLONE OR PLASMA EXCHANGE

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Summary

Of nineteen patients with RPCGN who responded promptly to initial treatment with PMP or PX, and who were subsequently maintained on oral immuno-suppression with prednisolone (reducing dosage from 30mg/day) and azathioprine/cyclophosphamide (1–3mg/kg/day), five showed progressive loss of renal function within one year of responding to treatment. Both the daily dose at four weeks and the cumulative dose of prednisolone at six months were significantly lower (p<0.01) in the group whose renal function deteriorated. We suggest that the follow-up dosage of prednisolone may be critical in maintaining continued stable renal function in the first few months after starting PMP or PX.

Introduction

The poor immediate prognosis usually associated with rapidly progressive crescentic glomerulonephritis (RPCGN) has been shown in an earlier communication to be reversible in >70 per cent of cases by early aggressive therapy with pulse methylprednisolone (PMP) or plasma exchange (PX) [1]. The long-term outcome, however, is uncertain, with some patients showing progressive loss of renal function within one year of responding to initial treatment. The factors associated with relapse following initial response to PMP or PX were investigated and are reported in this paper.

Patients and methods

Twenty-six patients with RPCGN were treated with PMP or PX between 1976–1983 at the Regional Renal Unit, Liverpool, United Kingdom as previously described [1]. RPCGN was diagnosed when rapidly progressive renal failure was associated with normal sized kidneys and histologically confirmed severe crescentic glomerulonephritis (>50% crescents). Patients with lupus nephritis, post
Figure 1. Follow-up renal function of 19 patients with RPCGN who responded to treatment with PMP/PX
streptococcal disease, malignant hypertension and anti-glomerular basement membrane disease were excluded. Nineteen patients made a prompt initial response to PMP/PX and form the basis of this study. All were maintained on a reducing dose of prednisolone (initially 30mg/day) and azathioprine and/or cyclophosphamide 1–3mg/kg/day according to the white cell count. Relapse was defined when a progressive loss of renal function lead to a doubling of the plasma creatinine concentration from the trough level reached after PMP/PX, whilst still on maintenance prednisolone and azathioprine/cyclophosphamide, and in the absence of infection, hypertension, nephrotoxic drugs or obstruction.

Results

Fourteen patients had stable renal function between 24 and 78 months after PMP/PX. In five others, renal function deteriorated within the first year, and all progressed ultimately to death or dialysis (Figure 1) despite further treatment with PMP in three. There was no difference in age, extra-renal manifestations, the presenting plasma creatinine, oligo-anuria or histological severity between the five patients who relapsed within 12 months and 14 whose renal function remained stable (Table I). In four of the five relapsing patients however, the dosage of prednisolone was reduced to 20mg/day or less four weeks after PMP/PX, contrasting with 10 of the stable patients who continued to take 30mg of prednisolone daily for six to eight weeks. The mean dosage of prednisolone in the five relapsing patients four weeks after PMP/PX, 20.5 ± 4.5mg daily, was significantly lower than in patients with stable renal function, 28.4 ± 3.6mg daily (p<0.01).

TABLE I. Characteristics of 19 patients with RPCGN who responded to treatment with PMP/PX

<table>
<thead>
<tr>
<th></th>
<th>Relapsed within 12 months</th>
<th>No relapse</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.2 ± 18.13 (18–65)</td>
<td>58.79 ± 10.97 (43–72)</td>
</tr>
<tr>
<td>Sex (%)M</td>
<td>100%</td>
<td>86%</td>
</tr>
<tr>
<td>% Crescents</td>
<td>69.2 ± 14.6 (53–85)</td>
<td>69.3 ± 15.9 (50–91)</td>
</tr>
<tr>
<td>Plasma creatinine</td>
<td>730 ± 454 (237–1376)</td>
<td>917 ± 284 (456–1400)</td>
</tr>
<tr>
<td>Oligo-anuric</td>
<td>60%</td>
<td>43%</td>
</tr>
<tr>
<td>ERM</td>
<td>60%</td>
<td>71%</td>
</tr>
</tbody>
</table>

ERM: presence of extra renal manifestations

Values expressed as means ± SD with ranges in parentheses

The rate at which the dose of prednisolone was reduced thereafter was lower in the stable patients than in patients who relapsed (Figure 2). Three months after PMP/PX, four of the five patients were taking 10mg or less of
Figure 2

DAILY PREDNISOLONE DOSAGE (mg/day) VALUES EXPRESSED AS MEAN ± S.E.

MONTHS FOLLOWING PMF/PX THERAPY

• Non relapsing patients
○ Relapsing patients

p < 0.01

Graph showing the decline in daily prednisolone dosage over months following PMF/PX therapy, with a significant difference indicated by the star.
prednisolone daily, by contrast with nine stable patients who took 15 mg or more. At one year, the dosage of prednisolone averaged 7.3 ± 3.3 mg/day in stable patients whereas the two remaining, but slowly relapsing, survivors were taking only 2.5 and 5 mg of prednisolone daily. By six months the cumulative steroid dosage was 3.18 ± 0.55 g and 2.12 ± 0.47 g in the stable and relapsing groups of patients respectively \((p<0.01)\). There was no difference in the daily or cumulative dosage of azathioprine or cyclophosphamide received by either group. Steroid side effects were infrequent and not severe in either group with no deaths attributable to the immunosuppression. Indeed three of the five patients who relapsed died subsequently of progressive disease.

Two other patients who had been stable for several months also showed sensitivity to their steroid dosage. One discontinued his maintenance prednisolone after nine months and his renal function deteriorated rapidly, the plasma creatinine rising from 260 μmol/L to 500 μmol/L in four weeks. He responded promptly to a second course of PMP and his renal function remains stable with a plasma creatinine of 375 μmol/L on maintenance steroids/azathioprine after three years. The other patient who had Wegener’s granulomatosis also suffered loss of renal function 24 months after PX when her plasma creatinine rose from 180 μmol/L to 300 μmol/L in association with a recurrence of nasal and ocular symptoms. These responded and her renal function improved when she was given a short course of high dosage oral prednisolone and her maintenance dosage increased from 5 mg to 10 mg daily. She experienced a further relapse when another attempt was made to reduce her prednisolone dosage, but this proved refractory to further aggressive treatment, and maintenance dialysis was necessary.

Discussion

Rapidly progressive crescentic glomerulonephritis of this histological severity carries a poor immediate prognosis and although the deterioration in renal function may be halted or reversed by early aggressive treatment with PMP/PX, the long-term results are uncertain. It is not known how long immunosuppression should be continued nor how quickly prednisolone dosage should be reduced. In most studies prednisolone dosage was tapered to the lowest effective dose as judged by the clinical course \([2-4]\). However, relapse after prolonged remission has been reported as long as 28 months after initial treatment, 8–20 months after maintenance prednisolone was discontinued \([5]\). Although all patients recovered following further PMP/PX, renal function was re-established at a higher plasma creatinine concentration, as in one of our own patients.

In our patients, relapse in the first year was not associated with age, severity of disease at presentation or extra-renal manifestations. It did appear that the maintenance prednisolone dosage was critical, and that in those patients who relapsed the prednisolone may have been tapered too quickly despite their favourable clinical course. Our results suggest that patients should be given prednisolone 30 mg daily for at least one month after PMP/PX and that the dosage thereafter should be reduced to 15–20 mg daily at three months, 10–15 mg daily at six months and 5–10 mg daily at one year in addition to
continuing azathioprine and/or cyclophosphamide. Some patients may require maintenance prednisolone indefinitely even in the absence of associated disease such as polyarteritis nodosa or Wegener’s granulomatosis.

References

1 Stevens ME, McConnell M, Bone JM. Proc EDTA 1982; 19: 724
3 O’Neill WM, Etheridge WB, Bloomer HA. Arch Intern Med 1979; 139: 514