Cyclosporin for the prevention of disease reactivation in relapsing ANCA-associated vasculitis

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Abstract

**Background.** In patients with ANCA-associated vasculitis the frequent development of relapses after successful initial treatment remains a major therapeutic problem. Thus a long-term prophylactic therapy with low side-effect potential is needed. As recent data suggest an involvement of T cells in the pathogenesis of ANCA-associated vasculitis, the prophylactic value of therapy low-dose cyclosporin was investigated in seven patients (three with Wegener’s granulomatosis, four with microscopic polyangiitis, all with renal involvement) who had developed at least one relapse during cyclophosphamide (CP) treatment or in the first 4 months after the end of CP therapy.

**Methods.** After remission had been achieved for 6 months using CP and prednisolone, the CP dose was reduced (3 months 75%, 3 months 50%) and cyclosporin was added concomitantly (dose adjusted to whole blood levels 60–90 ng/ml). Cyclosporin therapy was continued for 1 year after the end of CP treatment.

**Results.** During a mean follow-up of 24 months no patient developed a relapse. Two patients developed a herpes zoster infection. No severe bacterial infection occurred.

**Conclusions.** These preliminary results indicate that cyclosporin can be successfully used to sustain remission in patients with a relapsing course of ANCA-associated vasculitis and renal involvement.

Key words: ANCA-associated vasculitis; cyclosporin; relapse

Introduction

In patients with systemic vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA), short-term remission can be achieved using prednisolone (PR) and cyclophosphamide (CP) in about 80–90% of the patients [1,2]. About half of the patients develop relapses, often in the first months after cessation of the CP therapy. Therefore a lengthy immunosuppressive treatment (>1 year) is frequently administered [1,3,4]. The prolonged use of CP to sustain remission, cannot be recommended without reserve, however, since serious short- and long-term side-effects, like bone-marrow toxicity, opportunistic infections, gonadal toxicity, and an increased risk of malignancies are frequent events [1]. A long-term prophylactic therapy with low side-effect potential is therefore needed. Methotrexate has been shown to be effective in sustaining remission [5] but cannot be used in patients with impaired renal function. Recently Nowack et al. [6] reported the successful use of mycophenolate mofetil, a new immunosuppressive drug which acts mainly on B cells, for maintenance therapy in four patients with systemic vasculitis. However, there is substantial evidence that, apart from providing help for autoantibody production, T cells play an important role in the pathogenesis of ANCA-associated vasculitis. Patients with ANCA-associated vasculitis and autoantibodies directed to proteinase 3 (PR3) and myeloperoxidase (MPO) respectively, showed T cell proliferation in vitro in response to the autoantigens [7,8]. Activated T cell subsets have been found in patients with Wegener’s granulomatosis (WG) and microscopic polyangiitis (MP) [9,10]. Moreover, elevated levels of soluble IL-2 receptor as a marker of T cell activation have been described in the serum of patients with relapses of WG [11]. In consideration of these findings, and since cyclosporin acts on T cells and indirectly on B cells [12], we investigated the prophylactic value of a low-dose cyclosporin therapy in patients with relapsing ANCA-associated vasculitis.

Subjects and methods

**Patients**

Cyclosporin was given prospectively for 18 months to seven patients (selected consecutively) after informed consent and institutional ethical approval had been obtained (three had WG and four had MP, all with renal involvement). Diagnosis
was based on the definition of the International Consensus Conference at Chapel Hill [13]. All patients had had at least one relapse of the vasculitis during CP treatment \( (n = 4) \) or in the 4 months following the end of CP therapy given for at least 12 months \( (n = 3) \). Patient characteristics are shown in Table 1.

### Treatment protocol

Cyclosporin administration started after remission had been achieved for 6 months using PR (starting with 0.5–1 mg/kg BW/day, doses tapered down to \( \leq 10 \) mg/day and CP (i.v. CP \( (n = 3) \) 500–750 mg/m\(^2\) every fourth week; oral CP \( (n = 4) \) 1–2 mg/kg BW). The cyclosporin dose (2 mg/kg BW initially) was adjusted to whole-blood trough levels of 60–90 ng/ml. Concomitantly, the CP dose was reduced as follows: oral CP treatment was continued for 3 months with 75% of the last CP dose, followed by 3 months treatment with a further reduction of the dose to 50% using i.v. CP therapy, intervals between the pulse administrations were extended from 4 to 6 weeks (3 months), followed by a further extension to 8 weeks (3 months). Cyclosporin therapy was continued for a year after the end of CP treatment.

### Results

#### Clinical outcome

During a mean follow-up period of 24 months after the end of CP treatment, no patient developed a relapse (recurrence or first appearance of disease activity sufficient to warrant an increase in therapy). After the addition of cyclosporin, ANCA titre decreased by one to four steps in five patients, one patient remained negative and the ANCA titre was stable in another patient. Mean prednisolone dose given decreased from 6.1 \( \pm \) 3.2 mg to 2.3 \( \pm \) 2.5 mg.

#### Side-effects

The mean cyclosporin dose in the seven patients was 2.9 mg/kg BW. Two patients developed a herpes zoster infection. Cyclosporin therapy was discontinued in one patient. Both patients were treated with acyclovir orally. No severe bacterial infection occurred. In three patients a moderate increase in blood pressure (up to 20 mmHg systolic and 10 mmHg diastolic) occurred, and in two of these patients a diuretic drug was given. In three patients cholesterol and triglyceride levels tended to increase and in one of them a HMG-CoA reductase inhibitor was administered. No other side-effects were seen.

### Discussion

In order to sustain remission in patients with ANCA-associated vasculitis, a lengthy immunosuppressive therapy with low side-effect potential is needed. Our study provides evidence that low-dose cyclosporin therapy is an effective prophylactic tool in this patient group. This finding is particularly remarkable since our patients had experienced relapses in the past, and therefore probably represent a high risk population for repeated vasculitis activity. The side-effects of cyclosporin therapy were moderate, probably due to the low dose chosen.

The results are supported by our experience in patients with Wegener’s granulomatosis and kidney transplantation, who received cyclosporin and PR therapy to prevent graft rejection. In these patients the relapse rate decreased significantly after transplantation as compared to the period on chronic dialysis treatment [14].

The reason for the efficacy of cyclosporin is probably its predominant influence on T cells, which are thought to be involved in the pathogenesis of ANCA-associated vasculitis [7–11]. Beside evidence from \textit{in vitro} studies [7–11] (see above), \textit{in vivo} results point to the importance of T cells in these autoimmune diseases. A therapeutic use of anti-thymocyte globulin was effective in patients with active Wegener’s granulomatosis who were untreated with CP and steroids [15]. Other reports have indicated a beneficial effect of therapy with anti-CD4 and anti-CD52 in patients with severe systemic vasculitis [16]. One of the possible mechanisms of these anti-T-cell treatment strategies may be the depletion of autoreactive T cells. However, these ‘rescue therapy protocols’ cannot be used on a long-term basis because of potential severe side-effects like prolonged lymphocytopenia, serum sickness, and infec-

### Table 1. Patient characteristics, organ manifestation and follow-up

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>ANCA-antigen</th>
<th>Organ manifestation Initially</th>
<th>Follow-up after CP (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>64</td>
<td>M</td>
<td>WG</td>
<td>PR3</td>
<td>K-L-ENT-A-O-B</td>
<td>15</td>
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<tr>
<td>56</td>
<td>M</td>
<td>WG</td>
<td>MPO</td>
<td>K-L-ENT-B</td>
<td>17**</td>
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<tr>
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<td>M</td>
<td>WG</td>
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<td>K-L-ENT-Ey-A-O-B</td>
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<tr>
<td>62</td>
<td>F</td>
<td>MP</td>
<td>MPO</td>
<td>K-A-B</td>
<td>16</td>
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<tr>
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<tr>
<td>33</td>
<td>M</td>
<td>MP</td>
<td>PR3</td>
<td>K-A-S-B</td>
<td>31</td>
</tr>
</tbody>
</table>

*Chronic dialysis patient; K, kidney; L, lung; ENT, ear, nose, throat; Ey, eye; S, skin; A, arthralgia; O, other organs; B, B symptoms (fever, weight loss, fatigue). **Patient received a kidney transplant after 17 months.
tious complications [15,16]. Cyclosporin represents a therapeutic option, with low side-effect potential, as it inhibits calcineurin, resulting in a failure to activate genes required for T cell proliferation and for B cell help [12]. It is usable in patients with severe renal involvement to whom methotrexate cannot be given and where trimethoprim/sulphamethoxazole, in contrast to its beneficial effects in the upper respiratory tract [17], is probably not effective [5,18].

In summary, cyclosporin successfully sustained remission in ANCA-associated vasculitis with renal involvement, even in patients who had experienced relapses in the past. Prospective randomized studies are necessary further to confirm the beneficial role of cyclosporin for the sustainment of remission in this patient group.

References

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