LETTERS TO THE EDITOR

Changes in Renal Biopsies during Low Dosage Cyclosporin Treatment

Sir,

The efficacy of cyclosporin (Sandimmun®) in treatment of psoriasis (1) has been thoroughly documented and cyclosporin has also been shown to be useful in cases of severe progressive systemic sclerosis (2). But because cyclosporin is a known nephrotoxic drug (3) there is legitimate concern about both short- and long-term toxicity. Due to our concern about potential long-term renal toxicity in spite of a low-dosage regime, we studied pre- and posttreatment renal biopsies in 8 cases (5 psoriatics, and 3 patients with systemic sclerosis). The patients were treated from 6 to 18 months with between 2.5 and 5 mg cyclosporin/kg/day; one patient, however, received 7 mg/kg/day for a period of 2 weeks in order to control her severe psoriasis. The dosages are shown in Table I.

All patients had normal serum creatinine and normal serum creatinine clearances prior to treatment. Five patients (4 psoriatics and 1 scleroderma patient) had increases in serum creatinine to pathological values, which led to dosage reductions. The average increases in serum creatinine are shown in Table I. These increases were all reversible, as were several non-significant increases in blood pressure which did not require treatment. Two patients had moderate changes in their prekidney biopsy; one of these (no. 6) had previously suffered an acute renal failure necessitating dialysis during the course of a severe infectious hepatitis. All 3 scleroderma patients — and possibly 3 patients with psoriasis — showed changes in their renal biopsies which were conceivably related to therapy. The findings developing between the two biopsies were slight to moderate hyalinosis and sclerosis of arterioles, slight to moderate tubular atrophy, and slight focal fibrosis.

One of us (T.S.O.) performed a blind morphometric evaluation of the biopsies using a point count method (4). This investigation showed an increase in the average amount of interstitial connective tissue, from 34 to 44% (p = 0.03) using a blind, semiquantitative scoring, a non-significant increase in hyaline arteriolosclerosis (average score increase from 0.9 to 1.9), and in numbers of sclerotic glomeruli (from 3 to 9%).

The findings in the renal biopsies follow the pattern known from the literature from investigations in patients treated with higher dosages of cyclosporin (5-6). None of our biopsies from scleroderma patients had acute arterial or arteriolar lesions characteristic of systemic sclerosis, such as mucoid intimal proliferation or arteriolar fibrinoid necrosis, and no severe intimal fibrosis was found in the arteries.

Table I. Serum creatinine and kidney biopsies in low-dose Sandimmun treatment

<table>
<thead>
<tr>
<th>Pat. no.</th>
<th>Sex/Age</th>
<th>Diagnosis</th>
<th>Dosage (mg/kg)</th>
<th>Serum creatinine</th>
<th>Prebiopsy</th>
<th>Postbiopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Before (mmol/l)</td>
<td>Average during treatment (mmol/l)</td>
<td>Prebiopsy ±</td>
<td>Postbiopsy ±</td>
</tr>
<tr>
<td>1</td>
<td>F/44</td>
<td>S</td>
<td>3</td>
<td>63</td>
<td>23</td>
<td>+F</td>
</tr>
<tr>
<td>2</td>
<td>M/47</td>
<td>S</td>
<td>3.5</td>
<td>65</td>
<td>18</td>
<td>+F</td>
</tr>
<tr>
<td>3</td>
<td>F/27</td>
<td>S</td>
<td>2.5-4</td>
<td>78</td>
<td>15</td>
<td>++F + AH</td>
</tr>
<tr>
<td>4</td>
<td>F/39</td>
<td>P</td>
<td>3.5-5(7)</td>
<td>78</td>
<td>0</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>F/21</td>
<td>P</td>
<td>2.5-5</td>
<td>76</td>
<td>32</td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>F/42</td>
<td>P</td>
<td>2-3</td>
<td>94</td>
<td>14</td>
<td>++F ++ AH</td>
</tr>
<tr>
<td>7</td>
<td>M/37</td>
<td>P</td>
<td>2-5</td>
<td>87</td>
<td>45</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>M/43</td>
<td>P</td>
<td>2-2.5</td>
<td>102</td>
<td>7</td>
<td>N</td>
</tr>
</tbody>
</table>

*S = Systemic sclerosis. P = Psoriasis.

*Blind, semiquantitative evaluation. N = Normal biopsy; F = Fibrosis and tubular atrophy; AH = Arteriolar hyalinosis. + = slight. ++ = moderate.
Tubular atrophy and interstitial fibrosis may occur in systemic sclerosis, but tend to depend on the severity of sclerosis-associated vascular changes. Although we cannot entirely rule out that an increase in interstitial connective tissue in the scleroderma patients could be disease-related rather than treatment-related, this does not appear to be the case for the psoriasis patients. Kidney biopsies in uncomplicated psoriasis have been found normal (7).

The present preliminary study gives no information concerning the clinical relevance of the minor changes we have found hitherto, and does not exclude the use of cyclosporin A in severe psoriasis or severe systemic sclerosis when necessary. But we feel it important that long-term renal toxicity should also be taken into consideration in so-called low-dose cyclosporin therapy of these diseases.

REFERENCES

Received March 19, 1990.

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Oral Hairy Leukoplakia

Sir,

Reggiani & Pauluzzi reported a case of oral hairy leukoplakia in a liver transplant patient (1). Although hairy leukoplakia was first described exclusively in patients infected with the human immunodeficiency virus (HIV), the virus was never found in the lesions, but the absence of Langerhans’ cells indicates a dysfunction of the immune system (2). On the other hand, Epstein-Barr virus (EBV) is a regular finding and hairy leukoplakia is considered today to be an opportunistic infection of the tongue by EBV (2). Since EBV can be found in oropharyngeal excretions in immunosuppressed as well as in healthy people (3) and EBV receptors are present in the parakeratinized oral mucosa (4), it is not surprising that several cases of hairy leukoplakia in immunosuppressed patients without evidence for HIV infection have been reported recently (Table 1) (5-9). However, EBV-DNA has never been detected in hairy leukoplakia-like lesions in individuals without immunosuppression (10). Therefore, in individuals lacking evidence of HIV infection, hairy leukoplakia-like lesions should be confirmed by detection of EBV-DNA.

REFERENCES
4. Corso B, Eversole LR, Hutt-Fletcher L. Hairy leu-