Disease-activity in ANCA-associated vasculitis

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Maintenance therapy for vasculitis associated with antineutrophil cytoplasmic antibodies

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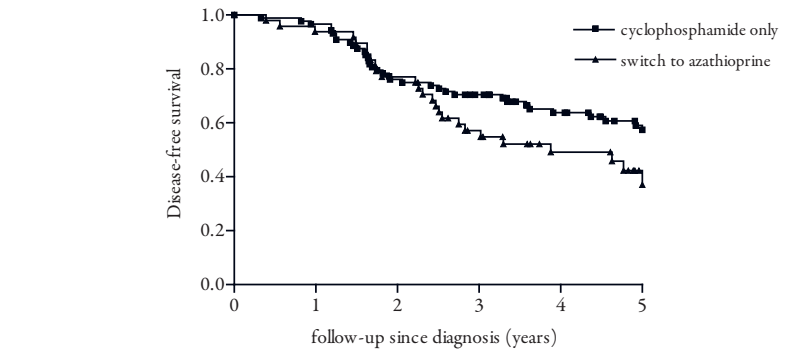
In their report on maintenance therapy for vasculitis associated with autoantibodies to neutrophil cytoplasmic antibodies (ANCA) (July 3 issue), Jayne et al. conclude that the level of exposure to cyclophosphamide can be safely reduced in patients with ANCA-associated vasculitis by switching to azathioprine once remission has been achieved [1]. As the authors point out, and as is noted in the accompanying Perspective article by Langford, follow-up was limited to 18 months [1, 2]. It was thought unlikely that extended follow-up would reveal significant differences in rates of relapse. We present some data, that may challenge this assumption.

From 1990 through 1996 new patients at our center were treated with oral cyclophosphamide (2 mg/kg/day, tapered every 3 months by 25 mg), whereas from 1997 to 2001, patients were increasingly switched to azathioprine (1.5-2.0 mg/kg/day, tapered every 3 months by 25 mg), after three months of remission achieved with cyclophosphamide therapy. In both schemes treatment is discontinued after 18 to 24 months. Overall, 88 patients received cyclophosphamide only, and 48 were switched to azathioprine. Treatment with prednisolone was similar in both cohorts. The mean age at diagnosis was 53 years (mean, range 14-83); there was renal involvement in 104 patients (76%); the mean (±SD) Birmingham Vasculitis Activity Score was 23 ± 9; ANCA against proteinase 3 and myeloperoxidase were detected in 102 (75%) and 34 (25%) patients, respectively. These characteristics did not differ between both cohorts and are similar to the clinical characteristics in the study by Jayne et al.

We analyzed the actuarial rates of relapse-free survival among patients treated with cyclophosphamide only and among those who were switched to azathioprine (Figure 1). Data of patients who did not have a relapse were censored on May 1st 2003, or at the time of death. In the cyclophosphamide-group three patients died, without experiencing relapse or findings compatible with active vasculitis (one died of myocardial infarction and two of disseminated carcinoma of the colon). At 18 months, the rate of relapse-free survival was 88.6 percent in the cyclophosphamide group and 89.6 percent in the azathioprine group, results that are similar to those reported by Jayne et al (86.3 percent and 84.5 percent, respectively). However, at five years of follow-up, relapse-free survival was 42.3 percent in the azathioprine group as compared with 57.4 percent in the cyclophosphamide group. The difference between the curves nearly reached statistical significance (log-rank test: RR 1.51, 95% CI 0.92-2.68; p=0.099).

These data indicate that relapses in ANCA-associated vasculitis predominantly occur after therapy has been discontinued, as reported by Hoffman et al [3]. Moreover, our data challenge the conclusion by Jayne et al. that switching cyclophosphamide to azathioprine after three months of remission does not lead to an increase in the rate of relapse, since their

follow-up may have been too short. We recently found that the persistence of ANCA at the time when a patient is switched to azathioprine is a risk factor for relapse [4]. Whether extending treatment with azathioprine in some or all patients might reduce the number of relapses without increasing treatment-related toxicity should be studied.



Numbers at risk						
cyclophosphamide only	88	86	68	60	47	36
switch to azathioprine	48	46	37	25	17	9

Figure 1. Disease-free survival among 136 patients with ANCA-associated vasculitis, according to treatment with cyclophosphamide only (■) or switched to azathioprine after 3 months of remission on cyclophosphamide (▲). Logrank test: RR 1.51, 95% CI 0.92-2.68; p=0.099.

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