

attenuated calcification progression appears highly speculative.

- (3) Very consistently, all epidemiological studies have noted that the extent of cardiovascular calcifications in HD patients is a potent predictor of cardiovascular outcomes including death. We now have two prospective trials, the 4D study [1] and the AURORA study [2], in which despite excellent LDL cholesterol control with a statin, cardiovascular outcome was not affected in HD patients. If LDL cholesterol were indeed a major determinant of calcification progress, one would have expected to see a benefit, in particular, in high-risk patients such as the diabetic dialysis patients of 4D.

The fact is that we currently have no evidence for a major role of LDL cholesterol in driving cardiovascular calcifications and mortality in HD patients.

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### Azathioprine, the Cinderella in the treatment of lupus nephritis

Sir,

With interest I read the contribution of Dr Joanne Bargman on the use of cyclophosphamide in the treatment of lupus nephritis [1]. Although not fully supported by the data, the i.v. pulses of cyclophosphamide became the gold standard for treatment of proliferative lupus nephritis. In several analyses [2,3], azathioprine gave at least comparable results as cyclophosphamide, but with a much better toxicity profile. Nevertheless, azathioprine became the forgotten Cinderella in this therapeutic scenery and was regarded as second-class treatment. The author then describes that, although it seemed appropriate, the use of azathioprine was not discussed at all in two major nephrology conferences she attended. So it was surprising to note that Dr Bargman did not discuss the only head to head comparison between i.v. cyclophosphamide and azathioprine [4,5]. This randomized controlled trial, comparing i.v. cyclophosphamide with three times three pulses of methylprednisolone and 2 mg/kg azathioprine, in the Netherlands in 87 patients with biopsy-

proven proliferative lupus nephritis showed after a median follow-up of 77 months that

- the occurrence of partial or complete remissions was equal in both arms;
- non-sustained doubling of serum creatinine occurred more frequently in the AZA group (RR 5.2; 95% CI 1.1–25.2;  $P = 0.04$ ) [5];
- renal flares occurred more frequently in the AZA group (RR 4.9; 95% CI 1.6–15.0;  $P = 0.006$ );
- renal flares responded to intensification of treatment in all patients;
- at the last follow-up, there were no differences between the groups in median serum creatinine (82  $\mu\text{mol/l}$ ; IQR: 74–108) and median proteinuria (0.3 g/24 h; IQR: 0.10–0.72);
- in repeat biopsies after 2 years in both groups, the activity index decreased similarly, but the chronicity index decreased slightly in the CY group (2.8–3.0), but in the AZA group, this increase was larger (2.8–3.8;  $P = 0.05$ );
- at the last follow-up, 88% of the patients in the AZA group had been free of cyclophosphamide treatment and had therefore a better prognosis regarding fertility.

These results show that azathioprine is not the first drug of choice for induction treatment in patients with lupus nephritis. However, if a patient chooses not to jeopardize fertility, azathioprine forms an alternative. Also, during pregnancy, azathioprine is relatively safe in contrast to mycophenolate mofetil (MMF) or cyclophosphamide, which are contraindicated. Therefore, azathioprine still has a (limited) place in the induction treatment of lupus nephritis. As maintenance treatment, azathioprine is probably a good choice. In the Euro-Lupus Trial, azathioprine started after 3 months gave comparable results as i.v. cyclophosphamide given for 1 year [6,7]. The upcoming results of the MAINTAIN-trial will give better insight into the comparison of azathioprine with MMF as maintenance treatment [8]. In a recent meta-analysis, the results of azathioprine and MMF during maintenance were comparable, although the number of patients in this analysis was rather low [9].

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## Reply

Sir,

I would like to thank Dr Berden for his response to my editorial 'How did cyclophosphamide become the drug of choice for lupus nephritis?' [1]. As I emphasized in the paper, the editorial did not purport to provide an in-depth review of every study of immunosuppression in lupus nephritis. In particular, I chose not to discuss the study by Grootsoolten *et al.* [2] because of the unbalanced treatment protocol that compared pulsed intravenous cyclophosphamide combined with daily oral prednisone with azathioprine in combination with pulse methylprednisolone. In addition, because the results were reported as relative risks, it was difficult to interpret the outcomes in this cohort of 87 patients.

Although Dr Berden says in this letter that 'non-sustained doubling of serum creatinine occurred more frequently in the AZA groups (RR 5.2; 95% CI 1.1–25.2;  $P = 0.04$ )',

in the actual publication it reports: 'The proportion of patients that reached the primary end point (non-sustained doubling of initial serum creatinine) did not differ significantly between the two arms' [2]. To clarify, it is only in the follow-up renal biopsy study [3] of less than half of the original cohort, published in a rheumatology journal [4], that nine patients reached the end-point of sustained or non-sustained doubling of serum creatinine, and this outcome was more frequent in the azathioprine-treated group. The median chronicity index did increase more in this group, but, as the authors noted, none of the examined pathological variables predicted long-term renal function [3].

Unfortunately, the data in the two studies by Grootsoolten *et al.* are not sufficient to support Dr Berden's conclusion that 'azathioprine is not the first drug of choice for induction treatment in patients with lupus nephritis'. Rather than trying to make a generalized statement about therapy to fit all patients, my editorial is a plea to remember that there exists a choice in treatment, with insufficient evidence to promote one therapy or another as the 'gold standard'.

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