

## Response to: 'Not all drugs (and routes) are same' by Zanwar and Gandhi

We would like to thank Zanwar and Gandhi<sup>1</sup> for their comments regarding our paper.<sup>2</sup> We are aware of the long-term results of the European Vasculitis Society (EUVAS) trial: patients treated with daily oral (DO) cyclophosphamide experienced fewer relapses than those given pulse intravenous cyclophosphamide for induction therapy.<sup>3</sup> At 18 months, no significant between-group differences were seen and long-term follow-up indicated fewer relapses only for the DO cyclophosphamide group. However, as mentioned by the authors, the study was retrospective and approximately 10% of the data were missing, which might have modified their results. The DO versus pulse difference in relapse rates could be explained by those groups' different cumulative (median (IQR) cyclophosphamide doses, respectively: 15.9 (11–22.5)g vs 8.2 (5.95–10.55)g). The excess relapses in the pulse arm were not associated with higher mortality or more renal damage. In light of the well-known increased risk of adverse events when DO cyclophosphamide is prescribed (infertility, malignancies, infections), we no longer recommend it as first-line therapy. Since the demonstration of rituximab non-inferiority to oral cyclophosphamide to induce antineutrophil cytoplasm antibody (ANCA)-associated vasculitis remission,<sup>4</sup> we have modified our cyclophosphamide use strategy. We prescribe DO cyclophosphamide only for patients with refractory disease, after pulse cyclophosphamide and rituximab have failed. In the MAINRITSAN2 trial, only one patient in the fixed-schedule infusion arm received oral cyclophosphamide for induction versus none in the individually tailored arm.

Based on the post-hoc analysis of the RAVE trial data, Fussner *et al*<sup>5</sup> reported that higher antiproteinase-3 ANCA titres were associated with relapses only in patients who had received rituximab as induction therapy; this group of patients did not receive any maintenance therapy. No ANCA-titre–relapse association was found for patients taking DO cyclophosphamide followed by azathioprine. We do not think that their observed association could affect MAINRITSAN2 results because, after remission was obtained with different induction regimens, all patients received rituximab for maintenance at randomisation, thereby rendering the population homogeneous.

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