Response to: 'MYCYC, unravelling the long road ahead in ANCA-associated vasculitis' by Jain *et al*

In their letter to the editor, Jain *et al* raised some issues regarding our recent paper. We appreciate their interest in our study and their positive comments.[1]

Jain *et al* highlight the fact that the presenting glomerular filtration rate (GFR) did not improve considerably during the study and were concerned that this raised the suspicion that there was a component of chronicity associated with the underlying disease. This is unlikely; at study entry it was an inclusion criteria that all patients had newly diagnosed disease, not relapsing disease and had not received either rituximab therapy or more than one intravenous pulse of cyclophosphamide or more than 2 weeks daily oral cyclophosphamide. Renal vasculitis can present in a number of different ways; from microscopic haematuria with a normal renal function to the syndrome of rapidly progressive glomerulonephritis necessitating dialysis. The stability of GFR over the course of the study reflects the facts that GFR at entry was relatively high (51 mL/min), that patients with a clinical syndrome of rapidly progressive glomerulonephritis were excluded (defined as a 20% fall in GFR over a 2 weeks), that patients with a GFR <30 mL/min were excluded and that active renal vasculitis was not a requirement for entry. Eighty-one per cent of patients had active renal vasculitis at study entry and the lack of change in GFR is very likely a reflection of less severe renal disease rather than more chronic renal disease. Change in GFR demonstrated includes all patients from the study and is not a subgroup analysis of patients with active renal vasculitis at entry.[2] However, we did not collect data on time from diagnosis to inclusion in the study and we have not analysed renal biopsies in this study to determine chronicity of the lesions present in those who had a renal biopsy performed.

The indication for additional treatments intravenous methylprednisolone (MP) and plasma exchange or initiation of oral steroids, and cyclophosphamide (CYC) in the 2 weeks before study entry were not recorded; however, these treatments were permitted prior to enrolment as these are standard treatments initiated for severe disease and reflect usual clinical practice.[3] Exclusion of patients receiving these treatments would have restricted the study population to those with milder disease, thus limiting generalisability of results. Recognising that intravenous MP or plasma exchange may affect short-term outcomes, use of these additional treatments was a stratification factor in the randomisation process to ensure groups were balanced in this regard.

Jain *et al* were interested in predictors of relapse but the study was an induction trial and not designed to investigate relapse of disease. The study was not powered for this endpoint and follow-up duration was short, with only 18 months follow-up. We do not feel it appropriate to report risk factors of relapse in this manuscript. Jain *et al* are concerned that mycophenolate mofetil (MMF) dosing may have impacted on treatment efficacy and risk of relapse, however, a number of patients receiving different doses of MMF are too small to investigate this; only 12 patients received <2 g and 4 patients received >2 g.

Clarification was requested on relapses relating to patients with Proteinase 3-anti-neutrophil cytoplasm antibody (PR3-ANCA)-associated disease. We were unable to detect a statistical difference in relapse rates between MMF and CYC in Myeloperoxidase (MPO)-ANCA disease, the increase in relapse rate was accounted for by patients with PR3-ANCA positivity. However, we have not included this statistical data in the manuscript as the study was underpowered to test this hypothesis. We are concerned about an overinterpretation of our data if this is stated. We, therefore, tested for an interaction of MMF and disease type and could show no evidence that the effect of MMF on relapse differed by ANCA subtype, this is included in the manuscript.

Jain *et al* were concerned that the p value for the incidence risk ratio (IRR) for relapse rates in MMF versus CYC is <0.05 even though the lower limit of 95% confidence intervals (CI) crosses 1 (IRR 1.97, 95% CI 0.96 to 4.23, p=0.049). This is not a factual error as Jain *et al* suggest. The CI and p value are derived from different models, so it is possible that these disagree particularly in a 'borderline' case like this. Relapse rate was a secondary outcome in this study which was not powered to give robust evidence on relapse. The abstract published in 2013 was based on preliminary findings and was submitted before final adjudication of the data and analysis. The final analysis of the study is as published in *Annals of Rheumatic Diseases*, and the study met the primary endpoint as stated.

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We agree that the steroid dosing in MYCYC may have contributed to remission and relapse outcomes, and for this reason was standardised across treatment groups and compliance with steroid taper was a component of the primary remission outcome definition. We also agree that remission efficacy observed with MMF and steroids in this study should not be interpreted as MMF efficacy alone or with lower steroid regimen without further randomised data.

We agree with Jain *et al* that there remain many questions about the management of ANCA associated vasculitis (AAV) with regard to steroids and maintenance therapy but these are out with the realms of this publication.

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Handling editor Josef S Smolen

Contributors LH and RBJ both wrote and approved the response.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Harper L, Jones RB. *Ann Rheum Dis* 2020;**79**:e58.

Received 27 February 2019
Accepted 28 February 2019
Published Online First 20 March 2019

► http://dx.doi.org/10.1136/annrheumdis-2019-215241

Ann Rheum Dis 2020;**79**:e58. doi:10.1136/annrheumdis-2019-215254

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