

## MYCYC: unravelling the long road ahead in ANCA-associated vasculitis

We read with great interest the article on ‘Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomized, non-inferiority trial’ by Jones *et al.*<sup>1</sup> The trials of mycophenolate mofetil (MMF) for induction in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) done previously were single-centre studies mostly restricted to patients with microscopic polyangiitis (MPA), predominantly from South East Asia.<sup>2,3</sup> We commend the authors for including a large population of patients with AAV of different age groups, with true representation of both granulomatosis with polyangiitis, and patients with MPA from different countries, thus overcoming the limitations of previous studies and possibly bringing us closer to the true estimate of efficacy of MMF as an induction agent in AAV. However, certain aspects of this study require clarification and discussion.

First, median baseline estimated glomerular filtration rate (eGFR) of 51 mL/min/m<sup>2</sup> of the trial patients did not improve considerably at 6 or 18 months in either of the two arms (online supplementary figure 1B of the paper). Non-reversibility of renal dysfunction with immunosuppressive therapy raises a suspicion of a component of chronicity to the underlying renal disease. Since patients with recent decline (eGFR fall >20%) in renal function in previous 2 weeks were excluded, the baseline renal dysfunction at entry could be reflective of previously unrecognised or relapsing/refractory renal disease. Thus, although newly diagnosed (within 6 months) patients were included in the trial, it might be prudent to examine the duration of disease (taken from onset of first AAV-related symptom) at the time of recruitment. Were the recently diagnosed patients with AAV included in the study recruited at first presentation or at a relapse?

It would be interesting to see the predictors of relapse in the study, and whether there was any correlation with the dose of MMF used for induction or the dose of steroids at the time of relapse. Was there any incremental benefit of increasing the MMF dose to 3 g/day in terms of remission and subsequent relapse rates? Did the 18% patients who received MMF <2 g/day relapse more? In today's world where we are gradually attempting a transition towards low or no steroid use in AAV, knowledge of a correlation (or a lack thereof) between steroid dose and risk of relapse would be quintessential. Since a sizeable number (26) of patients in each arm were not on maintenance azathioprine by the end of 18 months, did this correlate with an increased risk of relapse? With the post hoc subgroup analysis showing that most relapses in the MMF arm occurred in patients with PR3-ANCA, further clarification on the subsequent comment by the authors, ‘There was no evidence that the effect of MMF on relapse differed by ANCA subtype (p=0.52 for interaction)’ may be helpful.

We could not help but notice a few factual errors and text-table discrepancies. Two withdrawals or loss to follow-up by 6 months in the MMF group (figure 1 of the paper) versus three in the text. The p value for the incidence rate ratio (IRR) for relapse rates in MMF versus cyclophosphamide (CYC) is <0.05 even though the lower limit of 95% CI crosses 1 (IRR 1.97, 95% CI 0.96 to 4.23, p=0.049). Interestingly, as per the results of the primary efficacy analysis in the same data set presented at the 16th International Vasculitis and ANCA workshop and published in abstract form in the *La Presse*



*Medicale* in 2013, the non-inferiority endpoint was not met.<sup>4</sup> The primary remission endpoint occurred in 46/70 (66%) MMF vs 48/70 (69%) CYC, with the risk difference being -3% (90% CI -16% to 10%), leading to a p value of 0.06 for non-inferiority.

It would be interesting to know the indication for prerandomisation treatment with plasmapheresis or pulse methylprednisolone. With 24% patients in the MMF arm receiving one dose of pulse CYC, 59% receiving intravenous pulse methylprednisolone and 11% receiving plasma exchange before randomisation, the efficacy estimates of MMF, and the time taken for remission are prone to overestimation, although the prerandomisation treatment did not differ between the two arms

The steroid dosage protocol followed in the MYCYC mimics the current standards of practice in AAV. Higher remission rates at 6 months irrespective of steroid compliance compared with those with steroid compliance, along with comparable remission rates of most induction agents in AAV, make one wonder if the efficacy estimates of second induction agents in AAV in MYCYC and other induction trials like CYCLOPS, RAVE, RITUXVAS or NORAM have been confounded by the use of background steroids. Although the preliminary results of the PEXIVAS have found reduced dose (<60%) glucocorticoids (GC) to be non-inferior to standard dose GC in terms of efficacy,<sup>5</sup> the exact contribution of steroids in the currently used steroid-based combination induction regimens in AAV should be clearer with the results of low-steroid induction trials in AAV like the LoVAS.<sup>6</sup>

With the documented efficacy of MMF in advanced proliferative lupus nephritis and the inclusion of a small subset of patients with AAV with severe renal involvement in the study by Han *et al.*,<sup>3</sup> comparison of MMF versus CYC in this cohort of patients represents an unmet need that needs to be studied in systematically designed prospective studies.

Finally, with a statistically significant increase in relapse rates in the MMF arm after 18 months of follow-up in the current study, it would be interesting to see if the long-term outcome of this cohort of patients parallels the NORAM trial.<sup>7,8</sup> With the still uncertain way of handling steroids during induction and maintenance of AAV and the expanding therapeutic armamentarium for AAV, these certainly are challenging although exciting times in the management of AAV.

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