Mycophenolate mofetil: a step forward in the induction treatment of ANCA-associated vasculitis? Comment on the article by Jones *et al*

We have read with interest the results of the MYCYC trial showing that mycophenolate mofetil (MMF) is not inferior to intravenous cyclophosphamide (CYC) in achieving a primary remission in the treatment of ANCA-associated vasculitides (AAV).¹ We would like to address several comments.

First, in a previous report of the MYCYC trial in 2013, the authors could not establish a non-inferiority of MMF compared with CYC because the lower bound of the 90% CI of the absolute risk difference (RD) crossed the prespecified non-inferiority margin of -12% (MMF: $n=46/70$ (66%) vs CYC: $n=48/70$ (69%), RD=-3%, 90% CI -16% to 10%, $p=0.06$).² In the current publication, the reported primary remission rates at 6 months are slightly different compared with the princeps abstract (MMF: $n=47/70$ (67%) vs CYC: $n=43/70$ (61%)), leading this time to a non-inferiority of MMF compared with CYC regarding the primary endpoint (RD=5.7%, 90% CI -7.5% to 19%, p value=not reported). As the number of included patients are equal in each group between the two publications, suggesting that the study populations are the same, we would be interested to learn what can explain these discrepancies in results.

Beyond these statistical issues, these results could impact future AAV guidelines by expanding the recommendation of MMF use to cases more severe than the non-life or non-organ threatening mentioned in EUVAS/EULAR guidelines (which state that MMF is an alternative to oral methotrexate in such patients).³ Indeed, patients included in the MYCYC trial display a level of severity similar to those from the RAVE study⁴ in terms of renal involvement. In MYCYC, median eGFR was 51 mL/min/1.73 m² in both arms whereas in the RAVE study, median eGFR was 54 and 69 mL/min/1.73 m²

in the rituximab (RTX) and the CYC arms, respectively. The renal exclusion criteria in MYCYC were an eGFR <15 mL/min/1.73 m² or a rapidly declining renal function, whereas the RAVE trial stated a creatininemia above 4 mg/dL. The comparison between activity scores of the two trials is hampered by the use of BVAS V.2003 in MYCYC versus BVAS-WG in RAVE (see [table 1](#) for the comparison between the two studies).

The statement that MMF and RTX are both non-inferior to CYC should be interpreted with caution, in particular, in anti-PR3-AAV patients who are at high risk of relapse and hence—as highlighted by the authors—would not represent good candidates for an induction treatment with MMF, as it is associated with a higher risk of relapses than CYC.² These results confirm those of the IMPROVE trial, showing that—contrary to lupus nephritis maintenance treatment and prevention of solid-organ graft rejection—MMF was associated to more relapses than azathioprine.⁵ Conversely, in a post hoc analysis of RAVE, patients with anti-PR3-AAV responded better to RTX than to induction with CYC followed by maintenance with azathioprine, whereas no association between treatment and complete remission were observed in the anti-MPO-AAV patient subset.⁶

Finally, in severe patients (at least with anti-PR3 ANCA), one could still prefer RTX or CYC to MMF because RTX, the maintenance treatment that has shown the best efficacy in the MAINRITSAN 1 trial,⁷ has only been used in maintenance after an induction with either CYC⁷ or RTX (RITAZAREM study — unpublished results).

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Table 1 Comparison between MYCYC¹ and RAVE⁴

	MYCYC	RAVE
Design	Unblinded RCT	Blinded RCT
Non-inferiority margin	12%	20%
Excluded patients	<ul style="list-style-type: none"> Imminent life-threatening eGFR<15 mL/min/1.73 m² and/or rapidly declining renal function 	<ul style="list-style-type: none"> Creatinine>4 mg/dL Alveolar haemorrhage requiring mechanical ventilation
Comparator	Intravenous CYC (EUVAS scheme)	Oral CYC
Median eGFR (mL/min/1.73 m ²)	51 for both arms	54 (RTX arm) and 69 (CYC arm), $p=0.04$
Median BVAS 2003	19 (MMF arm) and 18 (CYC arm)	Not applicable
Median BVAS-WG	Not applicable	8.5 (RTX) and 8.2 (CYC) (NS)
Renal involvement	81% for both arms	66% for both arms
Serious adverse events (SAE)	73 for 70 patients (MMF arm) versus 64 for 70 patients (CYC arm) (NS)	Only SELECTED SAE: 31 for 99 patients (RTX arm) versus 33 for 98 patients (CYC arm) (NS)
Primary endpoint definition:		
Complete remission (CR) rate at month 6 with adherence to prednisone tapering scheme	<ul style="list-style-type: none"> BVAS 2003=0 PDN=5 mg/day at month 6 	<ul style="list-style-type: none"> BVAS-WG=0 PDN=0 mg/day at month 6
Definition of CR		
Objective of tapering		
Primary endpoint achievement	67% for the MMF arm 61% for the CYC arm (p value for non-inferiority not reported)	64% for the RTX arm 53% for the CYC arm ($p<0.001$ for non-inferiority)

BVAS, Birmingham Vasculitis Activity Score; BVAS-WG, BVAS-Wegener; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; EUVAS, European Vasculitis Study Group; MMF, mycophenolate mofetil; NS, Not significant; PDN, Prednisone; RCT, randomised controlled trial; RTX, rituximab; SAE, serious adverse events.

Contributors I hereby certify that both the authors have brought a significant contribution in the content of this manuscript.

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