

Response to: 'Correspondence on 'Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial' by Cai and Peng

We would like to thank Cai and Peng¹ for the interest they have expressed in our recently published article 'Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial'² and the *ARD* editorial team to give us the opportunity to address their comments.

First, Cai and Peng pinpoint another reason behind the lack of statistical significance of our primary outcome, that is, the shortage of our sample size. As suggested by Cai and Peng we have performed a post-hoc power calculation based on our estimated results (and sample), with $p_1=0.47$ and $p_2=0.36$ (p_1 and p_2 being the proportion of responders in the active arm and control arms, respectively) and an α risk of 5%, the post-hoc-calculated power is 29.9%. However, we have also performed a post-hoc power calculation based on the sample size that we aimed for (ie, 116 patients per arm) and the results observed in the trial: with an α risk of 5% and the p_1 and p_2 mentioned earlier, the power was still 41%, that is, very low. Indeed, in our trial, the difference across arms was only 11.6%; the post-hoc calculation of the sample size needed based on this difference in a classic randomised clinical trial, with an α risk of 5% and a power set at 80%, would be 303 patients *per arm*, that is, 606 patients in total; in the particular case of a cluster-randomised clinical trial (ie, after multiplying the estimated sample size by 1.45, eg, the 'inflation factor' defined as $1+(m-1)\times\rho$ where m is equal to the size of the cluster (in our study, the number of patients per centre=10) and ρ is the intracluster correlation, 0.05³) the sample needed to take the cluster-randomised design into account would be of 880 patients, that is, 440 patients per arm.




Cai and Peng also suggest to present the 95% CI around the point-estimate of the primary and secondary outcomes. Here, we present a table with the estimates at the last visit and their 95% CIs. It is worth of mentioning that in the manuscript we modelled the change in the outcomes over time, not only the estimate at the last visit.

Cai and Peng also refer to contamination bias, which they admit to be almost unavoidable in pragmatic trials. We can only agree with this remark, and indeed that was the reason behind the rationale to run a cluster-based randomised trial: that is, centres underwent randomisation, not patients. This meant that rheumatologists from 'Usual Care' (UC) centres were not aware of the 'T2T/TC' (Tight Control/Treat to target) algorithm, and even participated in separate study meetings during the whole duration of the study. Nevertheless, as pointed out in our manuscript, all participating centres were axSpA expert centres and many of them have participated in the formulation of the recommendations that fed the TICOSPA algorithm^{4,5} and thus it is highly likely that many of the investigators from the UC were indeed consciously or unconsciously applying a TC/T2T approach in their clinics.

Finally, Cai and Peng suggest also to look, particularly for continuous outcomes at the changes from baseline to week 48. This is indeed exactly what was done: mixed models for repeated measures were applied to estimate the changes on the outcomes over time in both groups.

	Estimated outcomes at week 48% and 95% CI	
	TC/T2T	Usual Care
ASAS HI significant improvement	47.3% (95% CI 36.2% to 59.0%)	36.1% (95% CI 25.6% to 46.6%)
ASDAS LDA	76.5% (95% CI 67.2% to 85.8%)	59.5% (95% CI 48.7% to 70.3%)
ASDAS ID	25.9% (95% CI 16.3% to 35.5%)	18.7% (95% CI 10.2% to 27.2%)
ASDAS CII	61.2% (95% CI 50.5% to 71.9%)	46.0% (95% CI 35.1%; 56.9%)
ASDAS MI	16.5% (95% CI 8.4% to 24.6%)	14.9% (95% CI 7.1% to 22.7%)
ASAS40	52.3% (95% CI 41.4%; 63.2%)	34.7% (95% CI 24.3% to 45.1%)
ASAS20	94.9% (95% CI 90.1% to 99.7%)	85.9% (95% CI 78.0% to 93.0%)
BASDAI 50	79.0% (95% CI 70.1% to 87.9%)	43.8% (95% CI 32.9% to 54.7%)
Physician global (0–10)	2.0 (95% CI 1.9 to 2.1)	1.8 (95% CI 1.78 to 1.8)
CRP (mg/L)	3.9 (95% CI 3.6 to 4.2)	3.5 (95% CI 3.2 to 3.8)
BASG (0–10)	2.6 (95% CI 2.5 to 2.7)	3.4 (95% CI 3.3 to 3.5)
BASFI (0–10)	1.7 (95% CI 1.6 to 1.8)	2.4 (95% CI 2.3 to 2.5)
EQ5D-5L	0.7 (95% CI 0.7 to 0.7)	0.8 (95% CI 0.8 to 0.8)
ASAS-NSAID score	1.5 (95% CI 1.0 to 2.0)	−4.9 (95% CI −5.5 to −4.3)

ASAS-HI, ASAS health index; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CII, clinically important improvement; CRP, C reactive protein; EQ5D, EuroQol 5 domains and 5 levels; ID, inactive disease; LDA, low disease activity; MI, major improvement; TC/T2T, tight control/treat to target

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REFERENCES

- 1 Cai G, Peng X. Correspondence on 'Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial' by Molto, *et al.* *Ann Rheum Dis* 2021.
- 2 Molto A, López-Medina C, Van den Bosch FE, *et al.* Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial. *Ann Rheum Dis* 2021;21. doi:10.1136/annrheumdis-2020-219585. [Epub ahead of print: 06 May 2021].
- 3 Hemming K, Girling AJ, Sitch AJ, *et al.* Sample size calculations for cluster randomised controlled trials with a fixed number of clusters. *BMC Med Res Methodol* 2011;11:102.
- 4 Smolen JS, Braun J, Dougados M, *et al.* Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international Task force. *Ann Rheum Dis* 2014;73:6–16.
- 5 van der Heijde D, Ramiro S, Landewé R, *et al.* 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017;76:978–91.