

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)

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Acknowledgements To PNSResearch for organising the logistics of implementing the study in the three countries.

Contributors AM performed the statistical analysis and drafted the manuscript. DvdH, FEVD and MD critically reviewed the manuscript.

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.

Disclaimer UCB provided an unrestricted grant for this study, but had no role in providing any drug, or in the study design, data collection, data analysis, data interpretation, or writing of the report.

Competing interests AM reports grants from UCB during the conduct of the study; personal fees from Abbvie, grants and personal fees from UCB, personal fees from BMS, grants and personal fees from Pfizer, grants and personal fees from MSD, personal fees from Novartis, personal fees from Gilead, personal fees from Lilly, outside the submitted work. DvdH reports personal fees from AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Cystone, Daiichi, Eisai, Eli-Lilly, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, UCB Pharma, outside the submitted work; and Director of Imaging Rheumatology bv. FEVD reports personal fees from Abbvie, personal fees from Celgene, personal fees from Eli Lilly, personal fees from Galapagos, personal fees from Janssen, personal fees from Novartis, personal fees from Pfizer, personal fees from UCB, outside the submitted work. MD reports grants from UCB, during the conduct of the study; grants and personal fees from ABBVIE, grants and personal fees from PFIZER, grants and personal fees from LILLY, grants and personal fees from NOVARTIS, grants and personal fees from ROCHE, grants

and personal fees from BMS, grants and personal fees from MERCK, outside the submitted work.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study was approved by the ethics committee CPP Ile de France III (Réf. Am7156-1-S.C.3394). All patients gave their informed consent.

Provenance and peer review Commissioned; internally peer reviewed.

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To cite Molto A, van der Heijde D, Van den Bosch FE, *et al.* *Ann Rheum Dis* 2023;**82**:e167.

Received 9 June 2021

Accepted 11 June 2021

Published Online First 29 June 2021



► <http://dx.doi.org/10.1136/annrheumdis-2021-220904>

Ann Rheum Dis 2023;**82**:e167. doi:10.1136/annrheumdis-2021-220913

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