'Lower anti-drug antibodies with etanercept biosimilar: can Ctrough explain the differences?'

I read with great interest Emery *et al*'s¹ article on SB4 phase III study and subsequent response to comments from Meacci *et al*.² As per the results of SB4 study,¹ there was significantly lower ($p<0.001$) incidence of antidrug antibodies (ADA) in the biosimilar etanercept (SB4) group (0.7%) compared with reference etanercept (ETN) group (13.1%). While it is known that product-specific factors such as product origin (foreign or human), product aggregates, impurities and container closure system could affect the immunogenicity of biopharmaceuticals,^{3–5} their contribution in terms of lower immunogenicity of SB4 has not been described.¹

As explained lucidly by Emery *et al*,¹ the possibility of ADA assay underestimating the incidence of immunogenicity to SB4 is unlikely, since the study used SB4-tagged single-assay approach. Also the study employed Meso Scale Discovery electrochemiluminescence technique, which is considered to be a more sensitive method for ADA detection than conventional ELISA assay.² While it may be possible that the drug concentrations in the assay can influence ADA levels for detection, it is highlighted by Emery *et al*² that acid dissociation technique (that dissociates drug-ADA immune complexes and improves drug tolerance of the assay) was used to measure total ADA levels.² Given the higher sensitivity of the methodology used for ADA detection in SB4 study, it is reasonable to assume that the differences observed in the incidence of ADA between SB4 and ETN may not have been confounded by inability of assay to detect ADAs against SB4 or against ETN.

On this background, I was bewildered to read the observations of European Medicines Agency Assessment Report⁶ on the same study that attributed the differences in ADA incidence to different trough concentrations (Ctrough) observed in SB4 and ETN groups, suggesting that it 'may have caused a bias in the ADA results'. However, as per Emery *et al*,¹ the Ctrough was comparable at each time point between SB4 (ranging from 2.419 to 2.886 µg/mL in weeks 2–24) and ETN (ranging from 2.066 to 2.635 µg/mL in weeks 2–24). In the absence of any valid quantitative correlation being established between Ctrough and ADA incidence, would it be possible to accept such an explanation based on an assumption that the drug-ADA complex has been missed out from measurement, leading to lower incidence for SB4? Particularly when the pharmacokinetics (PK) were estimated only in a subset of patients ($n=79$ out of 596 randomised patients) in the SB4 phase III study, who may have been different from patients who developed ADA.¹

Therefore, the opinions of Emery *et al*^{1 2} would provide valuable insights whether Ctrough levels can lead to a differential estimation of ADA incidence as seen in SB4 example, particularly when total ADAs have been estimated by employing specialised techniques for sample preparation such as acid dissociation. A lack of clarification on this important scientific matter could lead to an unprecedented expectation of regulatory agencies from biosimilar developers to correlate Ctrough with ADA incidence.

Chirag A Shah

Correspondence to Dr Chirag A Shah, Department of Medical Research, Community Welfare Foundation of India, Sangli 416416, India; chiirag@gmail.com

Citation: Emery P, Vencovsky J, Kang JW, *et al*. Confirmation on the immunogenicity assay used in the SB4 phase III study: response to the comments by Meacci *et al*. *Ann Rheum Dis* 2016;75:e40.

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.

CrossMark

To cite Shah CA. *Ann Rheum Dis* 2016;75:e60.

Received 21 June 2016

Accepted 23 June 2016

Published Online First 7 July 2016

► <http://dx.doi.org/10.1136/annrheumdis-2016-210114>

Ann Rheum Dis 2016;75:e60. doi:10.1136/annrheumdis-2016-210089

REFERENCES

- Emery P, Vencovsky J, Sylwestrzak A, *et al*. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2015; Published Online First: 6 Jul 2015. doi: 10.1136/annrheumdis-2015-207588
- Emery P, Vencovsky J, Kang JW. Confirmation on the immunogenicity assay used in the SB4 phase III study: response to the comments by Meacci *et al*. *Ann Rheum Dis* 2016;75:e40.
- Singh SK. Impact of product-related factors on immunogenicity of biotherapeutics. *J Pharm Sci* 2011;100:354–87.
- Hermeling S, Crommelin DJ, Schellekens H, *et al*. Structure-immunogenicity relationships of therapeutic proteins. *Pharm Res* 2004;21:897–903.
- Rosenberg AS. Effects of protein aggregates: an immunologic perspective. *AAPS J* 2006;8:E501–7.
- European Medicines Agency: EMA/CHMP/819219/2015- Assessment report -Benepali 2015. 17 June 2016. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004007/WC500200380.pdf