Response to 'Correspondence to viewpoint 'Defining refractory rheumatoid arthritis' by Buch' by Roodenrijs *et al*

I would like to thank Roodenrijs *et al*¹ for their thoughtful comments on my viewpoint 'Defining refractory rheumatoid arthritis'² and appreciate their acknowledgement of this important subgroup of patients with unmet clinical needs.

The authors highlight their description and recent review of 'difficult to treat RA'³ that in contrast to my viewpoint includes refractory rheumatoid arthritis (RA) in the presence of persistent inflammation and in its absence. I acknowledge this approach is more inclusive in encompassing the breadth of reasons that contribute to challenging RA treatment decision making in real-world practice and as such would consider 'difficult to treat RA' more of an umbrella term.

In my viewpoint, I *a priori* focused on the concept and subgroup of intrinsic refractory RA *disease* that (as with other diseases such as refractory cancer) tacitly implies persistent (RA) pathology (be it local±systemic) in the face of available therapeutic interventions. Such a subgroup is likely to be rare; the majority of biological refractory individuals demonstrate both inefficacy and intolerance to successive therapeutic interventions (as illustrated in a first report from the British Society of Rheumatology Biologic Register⁴). The viewpoint was thus necessarily more directed and discussed how best to identify the rare refractory disease group to deliver on the overarching objective of its biological characterisation and mitigate against inclusion of solely non-inflammatory drivers. Precision medicine principally relies on a pathogenesis-driven approach to treatment selection. Ultimately, final treatment decisions in clinical practice would be an integration of such a pathologically driven rationale, with consideration of the wider patient profile (lifestyle and comorbidity) and indeed contextual factors that may also coexist and contribute to 'difficult to treat RA'.

I would acknowledge that distinguishing such refractory disease through presence or absence of antidrug antibody (ADA) is clinically problematic. There remains a continued knowledge gap in how best to translate the profusion of ADA data into clinical practice, with issues in assay robustness and standardisation, the definition of cut-off values to define ADA and therapeutic drug levels as well as its interpretation.⁵ Nevertheless, as part of this ongoing research agenda, it remains important to evaluate for ADA when otherwise refractory RA disease may be erroneously ascribed to incorrect drug targeting.

In summary, I would consider my viewpoint as complementary to Roodenrijs *et al*'s comments and prior review. I welcome the

European League Against Rheumatism initiative as a pragmatic and important first step towards improving the understanding and management of the wider concept of 'difficult to treat' RA. It is likely that further iterations will be needed as more of an evidence base emerges, with refined evaluation of specific areas such as refractory RA disease.

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REFERENCES

- 1 Roodenrijs NMT, de Hair MJH, van der Goes MC, *et al*. Response to viewpoint 'Defining refractory rheumatoid arthritis' by Buch. *Ann Rheum Dis* 2019;**78**:e105.
- 2 Buch MH. Defining refractory rheumatoid arthritis. *Ann Rheum Dis* 2018;**77**:966–9.
- 3 de Hair MJH, Jacobs JWG, Schoneveld JLM, *et al*. Difficult-to-treat rheumatoid arthritis: an area of unmet clinical need. *Rheumatology* 2017. doi: 10.1093/rheumatology/kex349. [Epub ahead of print 4 Oct 2017].
- 4 Kearsley-Fleet L, Davies R, De Cock D, *et al*. BSRBR-RA Contributors Group. Biologic refractory disease in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann Rheum Dis* 2018;**77**:1405–12.
- 5 Vincent FB, Morand EF, Murphy K, *et al*. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. *Ann Rheum Dis* 2013;**72**:165–78.