Title

Comment on: CONVENTIONAL AND BIOLOGIC DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS FOR OSTEOARTHRITIS: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS: Reply

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SIR,

We are grateful to Drs Tecer and Kucuk for their interest and comment on our recent publication on disease-modifying anti-rheumatic drugs (DMARDs) for osteoarthritis (OA).(1)

We agree with the current view that identifying distinct phenotypes in OA, which have different responses to mechanistically diverse treatments, is an important aim in optimising the management of people with OA. In relation to DMARDs, the major endo-phenotypic variable of interest is the presence of joint inflammation.(2) The epitome of OA driven by inflammation is erosive hand OA. We therefore conducted a subgroup analysis of individuals with erosive hand OA and did not find a difference between DMARDs and placebo for this phenotype. Although limited by a small sample size (n=193), the findings were markedly homogenous (I² = 0.0%, p value 0.846). This suggests that inflammation in OA is different from that in RA.

Certainly, it is widely accepted that some individuals with OA report neuropathic-like pain. Its prevalence in people with knee OA varies by population, but generally affects a minority of individuals.(3) In our location in the East Midlands, United Kingdom, the prevalence of neuropathic-like pain in community-derived people with chronic knee pain is 14%.(4) Unfortunately, we were unable to examine people with neuropathic-like pain separately in our meta-analysis as this was not measured or reported for the trials. However, it is unlikely that the presence of this type of pain, estimated to affect 23% of study populations,(3) would explain the lack of efficacy of DMARDs for pain relief in OA. In fact, similar rates of neuropathic-like pain have been reported in rheumatoid arthritis (RA) and other inflammatory arthritides (5) for which DMARDs are commonly used. Therefore the reasons why DMARDs are effective for RA, but not OA, cannot be fully explained by the presence of neuropathic-like pain in OA.

Nevertheless, better characterisation of pain phenotypes in OA patients is important and we suggest that clinical trials should assess important baseline characteristics that may serve as subgroup factors, such as the presence of neuropathic-like pain, synovitis, and pain elsewhere. Such information may not be of primary interest for individual trials, however, its assessment would provide an excellent opportunity for future individual patient data metaanalyses to identify predictors of treatment response.

In conclusion, further research on predictors of response to treatments is important and should be facilitated by the assessment of potential predictors in all clinical trials in OA, irrespective of whether these baseline measures are useful for the individual trials. 1. Persson MSM, Sarmanova A, Doherty M, Zhang W. Conventional and biologic disease-modifying anti-rheumatic drugs for osteoarthritis: a metaanalysis of randomized controlled trials. Rheumatology. 2018:key131-key.

2. Chevalier X, Eymard F, Richette P. Biologic agents in osteoarthritis: Hopes and disappointments. Nature Reviews Rheumatology. 2013;9(7):400-10.

3. French HP, Smart KM, Doyle F, editors. Prevalence of neuropathic pain in knee or hip osteoarthritis: a systematic review and meta-analysis. Seminars in Arthritis and Rheumatism; 2017: Elsevier.

4. Fernandes G, Sarmanova A, Warner S, Harvey H, Richardson H, Frowd N, et al. SAT0670 The prevalence of neuropathic pain-like symptoms and associated risk factors in the nottingham community: a cross-sectional study. BMJ Publishing Group Ltd; 2017.

5. Rifbjerg-Madsen S, Christensen A, Christensen R, Hetland M, Bliddal H, Kristensen L, et al. Pain and pain mechanisms in patients with inflammatory arthritis: A Danish nationwide cross-sectional DANBIO registry survey. PLoS One. 2017;12(7):e0180014.