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Letter to the Editor

Osteoarthritis and Cartilage

Title: Corticosteroids and osteoarthritis progression: a confounded issue

Dear Dr Block

I read with interest the article from Dr Zeng and colleagues investigating the effects of intra-articular corticosteroids (IACs) on osteoarthritis (OA) progression[1]. This is a hugely important issue given the paucity of effective pharmacological treatments for OA pain and the need for us to optimise the use of existing therapies with strong analgesic effect sizes, such as IACs. As the authors state, previous *in vivo* and clinical retrospective studies have raised questions about potential IAC toxicity that remain unanswered. To add to the confusion, the *in vivo* studies referenced by the authors were performed in normal joints, and it is unclear how they relate to OA joints with pre-existing cartilage loss, inflammation and abnormal cell metabolism. Indeed, results from in *vivo* studies across a variety of species demonstrated that IACs did not induce damage in osteoarthritic joints, and in some cases produced a protective effect[-4]. The randomized clinical study referenced in Zeng et al as providing evidence for deleterious effects of IACs, as highlighted by the authors, demonstrated a very small cartilage volume change based on 8 IAC injections over a 2-year period, where injections were repeated irrespective of clinical response[5]; it is unclear how this reflects usual clinical care.

Unfortunately this recent analysis also leaves us with major uncertainty. It is very possible that people with 'true' structural progression (progression more than measurement error) have more pain and require IACs. The authors have discussed the potential for unaccounted confounders, but it is impossible to fully adjust for these even using the excellent Osteoarthritis Initiative dataset, where pain is measured annually and the timing of injections in relation to subsequent radiographic assessment is not clear. The current analysis used a radiographic grade at the "nearest visit prior to the "index [injection] visit"", which highlights the difficulty the authors had with the dataset.

It is worth noting that these analyses were applied in a relatively small number of patients, far fewer than would be required in a clinical DMOAD trial to assess progression. The duration of follow-up for cases was very short indeed: only 44/148 (30%) and 27/104 (26%) of KL and rJSW worsening cases were included with 2 years of follow-up.

Very importantly, this study uses radiographic endpoints with their known limitations[6,7], Kellgren-Lawrence grading has been a great tool for epidemiologic studies, however each KL grade comprises a range of pathologies and hence quantitative radiographic joint space width (rJSW) outcomes are preferred for assessing knee progression when using X-ray outcomes[6,7]. However even rJSW is a composite endpoint including meniscal damage and extrusion[8], which is why directly assessing tissues of interest with MRI quantitative cartilage measurements have been employed in modern trials in order to understand who is a real progressor in terms of cartilage loss. It is unclear from the current paper whether the KL and rJSW progressors were the same knees (people) but it seems unlikely – supporting questions about the radiographic outcomes as described here.

Taken together, the issue of IAC detrimental effects on cartilage remains confounded and worthy of further investigation, but we should be very careful about sending any message to practicing clinicians on the basis of the existing evidence.

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