Regarding "Intra-Articular Injections of Hyaluronic Acid or Steroid Associated With Better Outcomes Than Platelet-Rich Plasma, Adipose Mesenchymal Stromal Cell, or Placebo in Knee Osteoarthritis: A Network Meta-analysis"

We have read with interest the paper authored by Han et al.,[1] who performed a network meta-analysis of randomized controlled trials (RCTs) dealing with intra-articular injections for knee osteoarthritis (OA). The authors compared the outcomes and safety profile of different injectables adopted in clinical practice, such as steroids, hyaluronic acid, platelet-rich plasma (PRP), adipose-derived mesenchymal stem cells (a-MSCs), and placebo. The great effort in analyzing 43 trials should be commended, but we would like to raise some concerns both on the interpretation of the results and on the clinical indications proposed by Han et al. We think that the paper contains incongruencies, making it difficult for readers to conclude how different substances compare with each other, and caution is required when making clinical recommendations based upon the study's findings.

In the "*Comparative Effects on Pain Relief*" paragraph, the authors write that "although most treatment were not significantly superior to one another, ... all of the listed intervention showed statistically significant pain relief over placebo." So, it seems that no treatment is superior to others, but, a few lines after, they suggest that steroid is "most likely the best treatment, followed by HA." The authors should reconcile these differences.

Later, in the *Conclusions*, they state that "single PRP, multiple PRP, and adipose MSC do not result in a reduction of joint pain nor improvement of joint function compared to placebo." This finding further contradicts existing literature, including RCTs and systematic reviews,[2-4] that have shown a-MSCs[5] and particularly PRP have a significant role in pain reduction and functional recovery in knee OA, with results even superior to those of HA.[6] Therefore, we are left confused by these arguments, and authors should clearly indicate, based on their analysis, which substances works or not.

With regard to the "*Comparative Effects on Function Improvement*" paragraph, the authors focused on the analysis of the function subscale of the Western Ontario and McMaster Universities Osteoarthritis Index score. Existing trials analyze functional recovery by multiple validated questionnaires (e.g., International Knee Documentation Committee-subjective, Knee Injury and Osteoarthritis Outcome Score, Lequesne score, etc.), and a comprehensive evaluation should have analyzed all scores separately. Often, there are differences in outcomes based on the score considered as published in previous meta-analyses on a similar topic.[6] Instead, the authors extracted "other functional scores" only in case of absence of the Western Ontario and McMaster Universities Osteoarthritis Index function subscale. It remains unclear how they managed and pooled these data since different subjective scores cannot be compared. In particular, there are 3 papers[7-9] where they extracted Tegner Scale, which is not a subjective functional score, but rather a scale to evaluate the level of sport practice and is not the most appropriate tool for the purposes of the meta-analysis, especially considering that the same papers[7-9] included International Knee Documentation Committee and Knee Injury and Osteoarthritis Outcome Score scores.

In the same paragraph on functional evaluations, the authors write again that "most treatments were not significantly superior to one another" and that "multiple PRP injections are better than placebo." A few lines after that, they say that "steroid is most likely the best treatment followed by placebo, whereas multiple PRP ranked last." We question how PRP ranks last when the authors specifically stated that PRP was better than placebo. Related to this, we also question how placebo is the second best after steroids: this statement seems completely detached from clinical reality, as we know that placebo can have positive effects,[10] but there is no known published data supporting HA or PRP to be inferior compared with placebo. In contrast, there is an abundance of literature demonstrating better outcomes for HA and PRP,[11,12] and it is unlikely clinicians would ever propose intra-articular saline injection to their patients as a first line treatment.

Going back to the role of steroids, in the *Discussion* it is underlined that steroids can provide pain relief and functional improvement for "at least 26 weeks": we question how the authors set this time point based upon the absence of this time frame in the literature.

The authors should have also compared the effects on longer-term time points since that is the key when considering these treatments. In the following lines, another significant issue involves the role of multiple PRP injections, which are considered by the authors the "least effective treatment" (together with a-MSCs), with no beneficial effect even compared with a single PRP injection. To the best of our knowledge, the majority of trials currently available adopted multiple PRP administrations and, despite the paucity of data, no study has shown superiority of a single PRP injection compared with multiple administrations.[13] We also noticed that in Figures 4, 5, and 6, there are many forest plots with just 2 or even a single study analyzed, and in forest plots 4H, 5H, 6G, and 7C where we have the comparison between HA and "single PRP," actually many of the included studies deal with multiple PRP injections (e.g., Cole et al., Filardo et al., Vaquerizo et al., Sanchez et al., etc.): this requires a clarification, especially considering the previous statements on multiple PRP injections.

Other incongruencies are present also in the "*Safety*" paragraph, where the authors stated that "single PRP demonstrated a statistically significant lower amount of adverse events (AE) compared to other interventions" and a few sentences later they again affirm that the best treatment in terms of AE is steroid, followed by HA. We don't understand how this statement can be supported and, furthermore, looking at Table 5, there are just a few significant differences, and particularly the one between multiple and single PRP injections, which, based on our experience, is more a statistically valid finding versus a true clinical concern. Lastly, in the *Discussion*, the authors stated that "either steroid, HA or placebo had a lower probability of AE compared to single and multiple PRP," which is in complete contrast with what they said previously in the *Results*. This needs to be clarified by the authors.

Moreover, we were surprised by the analysis of severe AE, where authors included pneumonia, transient ischemic attack, cardiac arrest, progressive joint disease (which is not a severe AE, but rather the natural history of OA), and cancer. All of these are clearly unrelated to the specific substance injected, and no clinician would ever consider the risk of cancer following hyaluronic acid or steroid injection, or the risk of pneumonia following PRP injection. It would have been more pertinent to focus on the risk of joint infection[14] or the long-term side effects of corticosteroids, noting the risk of inducing osteonecrosis,[15] or, in case of a-MSCs, to elucidate the potential complications following liposuction, which could be very serious and deserve discussion to properly inform clinicians.

We acknowledge that the field of nonsurgical approaches for the treatment of knee OA varies widely and is in constant evolution and new therapeutic options are emerging, such as polynucleotides,[16] bone-marrow derived MSCs,[17,18] and oxygen-ozone, whose role has been investigated in 11 RCTs to date,[19] and perhaps should have been included in the present study: in this regard, it is worth noting that only 2 RCTs (with 84 patients in total) on a-MSCs were included in the meta-analysis, thus showing the paucity of data on this novel technique, which limits the ability to compare it with other, more established treatments.

Given the importance of the topic, we believe that clinicians should base their decision on unambiguous and reliable data. The paper by Han et al.[1] could be a relevant reference for the field, provided that they elucidate the uncertainties we have highlighted and better explain some methodologic aspects in their work. The *Conclusion* of the meta-analysis is mainly focused on the SUCRA (surface under the cumulative ranking curve) evaluation, but, despite the complexity of this statistical method, readers are left in doubt as to the clinical impact of their findings. The authors themselves recognize that statistical significance does not imply clinical significance and, based upon this premise, their title could be misleading for readers. The disconnect between statistics and "real-world" experience must be reconciled.

Berardo Di Matteo, M.D.
Department of Biomedical Sciences
Humanitas University
Milan, Italy
Humanitas Clinical and Research Center (IRCCS)
Milan, Italy
First Moscow State Medical University
Sechenov University
Moscow, Russia

Diego Delgado, Ph.D.
Advanced Biological Therapy Unit
Hospital Vithas San José
Vitoria-Gasteiz, Spain

Mikel Sánchez, M.D.
Advanced Biological Therapy Unit
Arthroscopic Surgery Unit
Hospital Vithas San José
Vitoria-Gasteiz, Spain

Brian J. Cole, M.D.
Department of Orthopaedics
Rush University Medical Center
Chicago, Illinois, U.S.A

Scott A. Rodeo, M.D.
Orthopaedic Soft Tissue Research Program
Hospital for Special Surgery
New York, New York, U.S.A

Elizaveta Kon, M.D.
Department of Biomedical Sciences
Humanitas University
Milan, Italy
Humanitas Clinical and Research Center (IRCCS)
Milan, Italy

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