Comment on moving toward targeting the right phenotype with the right platelet-rich plasma formulation for knee osteoarthritis

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Dear Editor,

We have read with great interest the review by Andia *et al.*[1] about the search for the most optimal PRP application protocol for knee osteoarthritis (KOA). The authors very successfully address the question of the importance of the KOA phenotype when choosing the most appropriate blood-derived product to reach the best possible clinical result. Indeed, the future of these treatments lies in achieving optimal personalization and fit between the patient, their pathology, the product chosen and the application protocol, so as to develop a tailor-made treatment. As Andia *et al.*[1] rightly say, new blood-derived products are being developed from platelet rich-plasma (PRP) by selecting specific molecules that could show a clear cause–effect relationship in KOA, such as alpha-2-globulin or IL-1Ra. In the case of PRP, it is difficult to define this relationship or the concrete mechanism of action, due to the multitude of molecules present in this biological cocktail, making it challenging to understand and standardize. This molecular complex is one of its main limitations, but also one of its virtues, and we must bear in mind the complexity of a pathology such as KOA.

Far from considering KOA as a pathology in which only the cartilage is involved, it should be considered a disease of the entire joint, as if it were one more organ in our body.[2] There is a deep interaction between the different structures, namely the cartilage, synovial membrane, subchondral bone, meniscus, and ligaments, which is not only physical (mechanical), but also chemical and biological. KOA patients presented meniscus with increased vascularization and nerve terminals, an unstructured extracellular matrix, abnormal cell organization, and cell death.[3] Ligaments of KOA patients showed calcifications and disorganized collagen fibers.[4] Pro-inflammatory molecules, such as tumor necrosis factor or interleukin 1 beta produced by cell populations of the synovial membrane, are released into the joint space, contributing to cartilage degeneration.[5] The excessive accumulation of transforming growth factor-beta (TGF-β) or vascular endothelial growth factor in subchondral bone causes dysfunctional processes, such as neurovascular tissue overgrowth, aberrant cell proliferation, and structural malformations in the bone marrow and subchondral bone that alter load distribution, stressing the cartilage.[6,7] On the other hand, TGF-β is also key to preventing the degeneration of articular cartilage.[8] These are just a few examples of the still unfamiliar and complex network of interactions that exists within the knee, responsible for both its correct performance and its degeneration.

Bearing this in mind, given the different joint structures involved in the triggering and development of KOA, it is reasonable to assume that the application of the product in the various tissues could improve clinical outcomes. Thus, the data obtained following PRP applications that combine administration in the intra-articular space with other structures, such as the subchondral bone or ligaments, are promising, although, as the authors say, further studies are needed. Second, it currently seems extremely difficult for the administration of a single molecule to reverse the degenerative process brought about by KOA. Although this is a fascinating challenge for the future, current knowledge suggests that the

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administration of products with several molecules involved in the different biological processes could be the most viable approach.

However, the search for blood-derived products, such as PRP, that meet the best characteristics for a given patient with a given pathology is also currently a challenge. The fact that most of the blood-derived products used in tissue repair are grouped under the term PRP makes it impossible to draw solid conclusions from the studies carried out. In their review, Andia *et al.*[1] already mention how PRP can vary, for example, depending on the absence or not of leukocytes, but also on the presence of erythrocytes, platelet concentration or platelet activation. These and other variables generate a great variety of PRP products whose composition and the consequent result are logically different, avoiding an adequate comparative analysis among different studies. Because of this, it is the responsibility of all (authors, reviewers, editors) to raise the quality standard of our work and to provide as much information as possible about the PRP used in our studies in order to define the product used, as suggested in the last consensus reached regarding classification and information in studies with PRP.[9] Only thus will we be able to move in the right direction for the optimization of our products and protocols, and customize them as effectively as possible to the patient and his or her pathology, as indicated by Andia *et al.*[1]

Finally, the article mentions that the application of these treatments does not delay total knee arthroplasty (TKA). The authors refer to the work of Rajan *et al.*,[10] which describes an insightful and revealing cost-effectiveness analysis to assess the value of PRP in delaying knee replacement. However, and only concerning the matter of PRP, the model of this work contemplates the delay of TKA by only 1 year. To expand on this question, we would like to mention a study recently conducted by our group in which we involved more than 1000 patients. The results of this study showed that 74.1% of the patients in the retrospective study achieved a delay in TKA of more than 1.5 years, with a median delay of 5.3 years.[11] Although this work also has limitations, such as its retrospective nature, it opens up the possibility that PRP becomes a cost-effective treatment for certain assumptions according to the model applied in the work of Rajan *et al.*[10] Other studies in joints such as the elbow and ankle also observed a reduction in the need for surgical intervention.[12,13] These data justify further studies to collect adequate information on patients, pathology, product, and application protocol. Taking these four cornerstones into consideration, we may be closer to developing a tailor-made treatment capable of inducing disease-modifying effects in KOA.

Conflict of interest statement

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