A Biological Approach to Orthopaedic Surgery: Are They Lost in Translation?

To the Editor:

Despite the care and seriousness with which Ruiz-Moneo et al.[1] conducted their study "Plasma Rich in Growth Factors in Arthroscopic Rotator Cuff Repair: A Randomized, Double-Blind, Controlled Clinical Trial," there are methodologic and conclusive issues that we believe would affect the outcomes in this recently published study.

It is now commonplace to apply plasma rich in growth factors (PRGF-Endoret) in the treatment of musculoskeletal injury as a magic bullet instead of adopting a biological approach. The traditional triangular conception of tissue repair known as the regenerative triad encompasses cells, 3-dimensional scaffolds, and signaling molecules. The healing process in any tissue is driven by those specific cells that, when triggered by signaling factors, will generate an optimum microenvironment for the tissue to recover and eventually resume its mechanical functions.

The application of PRGF to rotator cuff tears is intended to provide the damaged structure with 1 of the 3 elements involved in the repair stage, namely the growth factors and cytokines as signaling molecules. However, it is not enough to add a storm of growth factors to a tendon that for years has been undergoing a degenerative process and, as a consequence, barely possesses healing capacity.

Every time we tackle a surgical or conservative repair procedure with a biological approach, we should ask the following question: Where do the cells come from that will synthesize collagen and other molecules that make up the extracellular matrix? There is a growing body of evidence showing that mesenchymal stem cells (MSCs) play an important role in skeletal tissue repair.[2] Moreover, the MSCs in this specific area of rotator cuff lie mainly in anatomic sites such as the spongy bone of the humerus and acromion, in the myotendinous junction, and in the subacromiodeltoid bursa. Besides these MSCs, perivascular cells, or pericytes, have been suggested to function as immunomodulatory and trophic MSCs. These pericytes, which reside on endothelial tubes, might be mobilized to the injured site and proliferate and differentiate to repair the tissue.[3]

Drawing on the aforementioned biological evidence, our team has developed a procedure for arthroscopic repair of rotator cuff tears assisted by PRGF-Endoret, descriptions of which are included in our recently published book.[4] In addition, a clinical trial on this topic is currently under way. This procedure involves 5 sites where the PRGF is infiltrated: into the body and sutured tendon, into the myotendinous junction, into the subacromiodeltoid bursa, into the spongy bone of the humerus, and finally, into the subacromial space. Beside these intraoperative local applications of PRGF, our approach includes patient follow-up, which consists of adding an ultrasound evaluation 3 and 6 weeks after the intervention, after which we proceed to ultrasound-guided infiltration of PRGF into the reconstructed tendon.

As it pertains to the outcomes of the experimental study by Ruiz-Moneo et al.,[1] we take exception to the claim that ". . . the efficacy of PRGF is unproven and controversial in orthopaedic surgery . . . ." There is, in fact, a great deal of research showing the safety and efficacy of PRGF in the field of medicine and, specifically, in orthopaedic surgery.[5] Last but not least, the authors themselves acknowledge that the weakness in their study arises from a lack of standardization in both preparation and application of PRGF. Indeed, were these methodologic weaknesses addressed as we recommend, we respectfully suggest that the outcomes would have been different.

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Authors' Reply

We read with interest the letter from Anitua et al. in response to our randomized, blinded, controlled, clinical trial evaluating the use of plasma rich in growth factors (PRGF) in the repair of the rotator cuff, recently published in *Arthroscopy* (January 2013). We are grateful for their contribution to improve the discussion on the topic, because we acknowledge that for the design of our randomized controlled trial (RCT), we took into consideration their previous results on the application of PRGF in maxillofacial surgery and orthopaedics and, thereafter, we strictly followed their guidance to prepare the PRGF and their advice for its use in the surgery.[1,2]

As we stated, the aim of our RCT was to evaluate a proposed surgical practice through the appropriate methodology (RCT) in response to the recommendation for the use of platelet-rich plasma (PRP) in orthopaedics without sufficient evidence. In this sense, we are very surprised by the statement in the letter of Anitua et al. that they have developed a method and published it in a book (without peer review), pending the results of a clinical trial! In our opinion, the appropriate method is just the opposite: before one suggests a therapeutic intervention, it is absolutely necessary to show efficacy and safety applying the appropriate methodology.

We agree about the important role of mesenchymal stem cells in the tissue repair procedure[3] and about the low cellularity present in the repaired rotator cuff tendon. Anitua et al. recommended the infiltration of PRGF in the sites in which lie more mesenchymal stem cells (cancellous bone of the humerus, myotendinous junction, and subacromial deltoid bursa). As such, the use of PRGF in our trial is consistent with their recommendations. As described in our report, we infiltrated PRGF at the repair site and the myotendinous transition. Moreover, at the end of the procedure, without liquid, we deposited PRGF in the subacromial-deltoid bursa. We do not understand the benefit of infiltration of PRGF in the cancellous bone of the greater tuberosity. Instead, a bleeding surface was created with a 4.5-mm bur on the greater tuberosity before the repair. However, and according to our previously stated opinion, any innovation should be supported by the appropriate study.

Another issue is the recommendation of Anitua et al. for an ultrasound-guided infiltration of PRGF. However, they recognize that the criteria to make this recommendation are largely arbitrary and, again, based only on their clinical experience.[4] So, they will agree that, at present, there is not any scientific evidence to support such a recommendation. Moreover, one cannot ignore that repeated infiltrations increase the risk of infection, and therefore the recommendation should be balanced with regard to risk and benefit. A study by Bergeson et al.[5] found a 10% infection rate in the group who received PRP; and the role of PRP injection cannot be discarded.

Regarding the mentioned lack of standardization, it seems that Anitua et al. have misunderstood our statement: All the preparations for the trial were prepared strictly in accordance with the methodology described in our article, maintaining consistency during the trial. PRGF was prepared with strict adherence to guidelines previously described by Anitua and colleagues[6,7] and using the same equipment and material. Our mention of the lack of standardization refers to the different methodology used by diverse authors.

Finally, we think that orthopaedic surgeons must consider how we are using this type of unproven treatment. Currently, there are no studies with high levels of evidence to support firmly the effectiveness of PRP in the rotator cuff. The unregulated massive application of PRP implies, at a minimum, a huge monetary cost. So, in our opinion, future recommendations about the use of these therapies must be made only after (and never before) the benefit-risk ratio has been established through randomized clinical trials.

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