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Letter to the Editor

Towards a correct timing and dosage in PRP applications

Dear Editor,

A letter you have recently published makes reference to "*Concerns about fibrosis development after scaffolded PRP therapy of muscle injuries*" [1], and in our humble opinion, several errors require address.

In their reference to our article "Muscle repair: platelet-rich plasma derivates as a bridge from spontaneity to intervention" [2] Robi and Matjaz make an inaccurate statement when they note "they combine PRP with a liquid-to-gel fibrin-based scaffold. . .". In fact, there is no combination of two elements. Rather, the autologous enriched platelet plasma liquid has progressed to its more gel-like formulation which makes it a natural fibrin based scaffold in the infiltrated site. This transition from liquid PRGF (plasma rich in growth factors) formulation to gel form is accomplished with the simple addition of calcium chloride. In this form, platelets are activated and fibrinogen is cleaved, and in this way the polymerization of fibrin is achieved [3]. This liquid-to-gel fibrin-based scaffold conveys growth factors, cytokines, morphogens, and even exosomes contained in the platelets, as well as fibrinogen and other plasmatic proteins in a biologically balanced aggregate, managed and delivered in a physiological manner [4].

We would again point out to authors that PRGF muscle infiltrations are aimed at recruiting, activating and mobilizing satellite cells and resident macrophages which contribute to muscle reparation processes by cell signalling soluble factors in addition to the already activated endothelial cells, macrophages, and platelets in the injured area [5–7]. Furthermore, the gradual activation and homogeneous tissue distribution supported by a PRGF liquid-to-gel transition 3D (three dimensional) injectable scaffold may well serve as a highway for mechanical energy to transit from the environment to the cell, bring about cell-to-cell transition, promote multicellular assembly, provide mechanical support and plastic–elastic stiffness which has a drastic impact on the fate of muscle stem cells [8,9].

The author's concern about the development of fibrosis mediated by TGF-β is widely shared with many other biologists and practitioners, and it is underpinned by ample research data in most of which TGF-β was applied alone [10]. Although transient fibrogenesis, collagen synthesis and deposition, mainly driven by the TGF-β family are crucial processes for structural and functional muscle regeneration, one of the most unsuccessful and nonfunctional outcomes of muscle regeneration is the formation of fibrotic scarring [11]. The application of PRGF in damaged tendons exhibited an absence of scarring [12,13] which might be attributed to the concurrent presence of TGF-β1, VEGF, IGF-1 and HGF within PRGF thereby rendering this therapeutic system an anti-fibrotic formulation [14–17].

The authors mention the excellent study conducted by Reurink et al. [18] who reported no benefit for intramuscular PRP injections, as compared with isotonic saline injections, in patients with acute hamstring injuries. However, we have already suggested that the delayed application and low dosage may well have rendered PRP application ineffective as this initial window of 5 days is the time purported to shorten treatment, and appears to be crucial to muscle repair [19,20]. By the time of PRP application (a window of 5 days post injury), many of the injured microenvironmental biological targets of PRP, have either disappeared or undergone a phenotypic shift (myoblasts, endothelial cells, macrophages). Three in vivo studies, in which the treatment started either a few hours or two days after injury, reported histological acceleration or functional improvement in the treated group [21–23]. The total GF dosage applied at the site of injury throughout the treatment in these three studies was at least 2 times as high as that in the trial by Reurink et al. [18]. This is not caused by any difference in GF concentration of different PRPs (insulin-like growth factor 1 [IGF-1], 100,000 pg per millilitre versus 90,000 pg per millilitre, platelet-derived growth factor [PDGF], 20,000 pg per millilitre versus 20,000 pg per millilitre), but rather due to the fact that each application conveyed a higher GF dosage (2.5 millilitres versus 1 millilitre) and were greater in number (4–5 injections versus 2 injections).

Conflict of interest

EA and SP are scientists at BTI Biotechnology Institute ImasD, a biotechnology company that investigates the biological potential of PRGF.

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[1]The authors declare the following competing financial interest(s): E. Anitua is the Scientific Director and S. Padilla are scientists at BTI Biotechnology Institute, a dental implant company, that investigates in the fields of oral implantology and PRGF-Endoret technology.

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