Good Clinical Practice in the use of regenerative medicine in athletes

Buena práctica clínica en el uso de la medicina regenerativa en los deportistas

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As we all know, over the past decade there has been an authentic boom in the use of cellular therapies and products such as Plasma Rich in Growth Factors and its various meanings (hereinafter PRP). The ease of collecting techniques as well as the apparent "harmlessness" or the feeling that they are low-risk techniques has led to a significant increase in the use of these products in fields such as Sports Medicine. Yet it should be considered that just as there is clear legislation regarding the regulation of the use of medicines, surgical treatments and transplants, treatment with biological products (cellular therapy and PRP) is also subject to a legal framework, regarding which unfortunately many professionals are not fully informed or aware. In the case of PRP, as it is a product obtained using lab-based manipulation, it is considered a consolidated medicine (different, for example, to a blood transfusion), and therefore it should be applied in accordance with the usage regulation established by the Spanish Medicine Agency (AEMPS) and the authorities in each Spanish autonomous community[1]. In the case of the different cell types, which are not yet consolidated treatments, the previous authorisation of the Spanish Medicine Agency (AEMPS) should be applied under the provisions of a clinical trial or with compassionate or special uses. In the event that we are unsure whether our product is considered a medicine or not, we should always consult the experts from the Agency, who will provide the answer. However, in many cases clinicians wish to use this type of medicine under their own responsibility and risk - generally under the provisions of information offered by laboratories regarding their products. These include: "quick and easy access to the product means it is not considered a medicine", "it is made in a closed system and does not require authorisation", etc. added to the long list of pathologies that can be treated with these products. These are false concepts that lead to a poor use of these therapies.

When considering the development of this editorial we had the idea of focusing on Good Clinical Practices (GCP) regarding the application of regenerative medicinal products on our athletes, but it is clear that no professionals doubt their ethics and their good clinical criteria in this type of application, and that perhaps the problem lies in the lack of knowledge that many of us have when it comes to discriminating between the different products to which we have access, the legal considerations that are required of each one, as well as how to know which is the most suitable product for treating pathologies. Therefore we have decided to summarise how we define each product.

Cellular types in research used in traumatology/sports medicine

The gold standard tissue used in the field of traumatology for usage in regenerative medicine is bone marrow (BM), mainly collected from the iliac crest. From this, we can obtain various cell types with special characteristics in terms of their capacity to divide and differentiate into tissues that are different from their origin, depending on the microenvironment that surrounds them.

In sports medicine and traumatology, bone marrow is generally collected with the aim of using the mesenchymal stem cells (stem cells) present within it. But it should be considered that they are in a very low concentration. By spinning the sample using methods such as the

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density gradient (Ficoll), we get the part of the bone marrow comprising mononuclear cells, eliminating the plasma, erythrocytes and platelets. These cells include macrophages, lymphocytes, megakaryocytes and haematopoietic progenitor cells, among others. From the whole of this cell group obtained, approximately just 1 from every 1,000/100,000 cells are the much desired mesenchymal cells. If we perform a "bone marrow concentration" (technique very widely used by diverse laboratories and trading houses), we would only be obtaining a concentrated product with a high number of heterogeneous cells, of which very few would actually be mesenchymal cells. From this, if we truly want to obtain mesenchymal cells, we should purify the sample, eliminating the rest of the unwanted cells. To do this, isolation techniques are applied based on the almost exclusive property of mesenchymal cells of adhering to plastic. The cells are cultivated for a specific length of time, and thanks to this property the unwanted cells are eliminated, eventually resulting in the homogeneous sample composed of mesenchymal cells. As a final stage, we should check that these cells meet two more requisites in order to confirm that they are mesenchymal cells, which are: positive phenotype for the markers (≥95%) CD105, CD73 and CD90, and simultaneously negative for (≤ 2%) for CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA-DR; and reveal a capacity to differentiate from osteoblasts, chondroblasts and adipocytes[2].

Only once we have obtained these cells through cultivation, are they considered to be true mesenchymal cells, and if they are not obtained without cultivation it is a group of cells among which there is a very small number of mesenchymal cells, but we can never say that this cell product comprises mesenchymal cells. For example, if we use a bone marrow concentrate (only collected using aspiration and spinning) to treat an avascular necrosis of the femoral head , we cannot say that we are applying mesenchymal cells.

These cells are the most used cells in traumatology, and we can find various publications in national and international research regarding their clinical use, in pathologies such as osteoarthritis in the knee[3-4] and pseudoarthrosis[5]. We should take into account that even with these publications available, the use of mesenchymal cells is still not considered to be consolidated treatment, i.e. their effectiveness is not considered to be proven so their usage should come under the provision of clinical trials, special or compassionate use, and therefore always with the authorisation of the AEMPS.

Another of the tissues used as a cell source is fatty tissue, obtained from liposuctions. With this tissue, after enzymatic digestion, we achieve a cell product called Stromal Vascular Fraction (SVF), which we could compare to mononuclear cells obtained from BM in terms of the heterogeneity of cell types that make up this product. Among these we can find haematopoietic cells, very small fractions of endothelial progenitors, of mesenchymal cells, etc. a product used for example in clinical trials for cardiac regeneration[6] and currently applied by many of our colleagues on patients with a wide range of pathologies in our field, without having, in the majority of cases, scientific proof of the efficiency of these treatments; and more importantly, used as conventional treatment when they are not yet consolidated products nor are they authorised by the AEMPS for their clinical use. For this we are safeguarded, mostly, in that in order to collect them we use closed systems and minimum manipulation, and that these cells are going to have the same purpose as their original tissue, etc. However, we should not forget that in all of these cases it should be the AEMPS that, following consultation, clarifies if the desired product to be used in each case is or is not a medicine, and therefore should comply with the applicable legislation for its use[7].

Just as we have previously explained with the BM, if we put SVF cells in cultivation, given their adhesion to the plastic, we get mesenchymal cells derived from fat, also used in bone regeneration but to a lesser extent. These cells present similar characteristics to those obtained from BM.

The use of rich plasma in growth factors (PRP)

PRP is one of the most used and demanded products in our clinical practice[8,9]. We will not go into more depth here describing PRP, which is widely known by all. We are going to focus on unscientific yet hugely relevant aspects.

As you can see, the PRP has been given a special treatment as it is not an advanced therapy product, the cells are not stem cells. This is a frequently seen news headline every time one of our colleagues applies it to an athlete, with the damage this does to the good use of the medicine. Responsibility for the poor information that is transmitted to the public in general when "to sell more" we give out this kind of information is ours and only ours. Not only when it is released in the press, but also when we are capable of marketing the product as if it were a "magic potion", able to "cure" all kinds of illnesses and which can be applied whenever necessary. The majority of times without much scientific evidence. We should be clear that as it is a medicine, this type of publicity is not allowed. Our obligation as professionals is to comply rigorously with the existing legislation, the base of the Good Clinical Practices that should define professionals in the clinical practice in general.

Another important aspect to consider with our patients is their follow up. Every time that we treat a patient with advanced therapy products or with PRP-type medicines, we should receive help from experts in all the currently applied fields to understand the cases in which its use is recommended[10], and to perform a careful follow up of them. Likewise, in the case of treatment that is classified as medicine, we should notify the pharmacovigilance centres in each autonomous community at the very first suspicions of any adverse reactions. More information about how to do this can be found on the AEMPS website: http://www.aemps.gob.es/vigilancia/medicamentosUsoHumano/home.htm.

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