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## EDITORIAL

### Can I continue to use platelet-rich-plasma on my patients? How do I use it legally?☆



### ¿Puedo seguir aplicando plasma rico en plaquetas a mis pacientes? ¿cómo hacerlo legalmente?

Professionals who have been using PRP for decades in their practices and others who wish to use it to treat their patients are faced with these and other questions. In this editorial we attempt to shed some light on the most controversial aspects of the use of PRP and comment some possible solutions for the successful application of the treatment, considering its legal framework.

It is generally known that, in recent years, the application of “growth factors” in all their forms, and specifically platelet rich plasma (PRP), for multiple pathologies has undergone a boom, leading to their indiscriminate use in many cases. It is also true that, due to this considerable increase, there is a lack of scientific evidence regarding the benefits of this product and the standards for the best method of obtaining it. Therefore, there is significant controversy in both aspects. This situation has led numerous professionals, represented by their scientific societies (Sports Traumatology professionals represented by SETRADE and the TERCEL Cell Therapy Network), to address the Spanish Agency for Medicines and Health Products (AEMPS) in order to request clarification on the use and application of PRP. Following consultations, the final decision was to elaborate a joint report (between AEMPS technicians and professionals harboring concerns about the misuse of PRP) which attempted to clarify and define the “Autologous use of Platelet Rich Plasma”.<sup>1</sup> This report clarified data and established criteria for the use of autologous PRP, hitherto diffuse and in a limbo in which it seemed that everything was acceptable. The report “gathered the framework for the autologous use of PRP in Spain, the obligations to be met by manufacturers and the minimum information to be given to patients undergoing the

treatment”.<sup>a</sup> Nevertheless, there still remain some unresolved issues and we are currently going through an active period of collaboration between experts and scientific societies involved in the preparation and application of PRP therapies and AEMPS, in an attempt to answer and resolve all the doubts which continue to appear regarding the necessary facilities, the regulations to be met in all cases, the definition of pathologies in which this product is applicable, the publication of more scientific studies which support the use of these products, etc.

Even taking into account the doubts inherent to the implementation of new legislation in a complex field, some issues are already very clear. In the report, AEMPS classifies PRP as a *drug for human use*, according to the definition of Directive 2001/83/EC, of 6 November, establishing a EU code on drugs for human use, and Law 29/2006, from July, on the guarantees and rational use of drugs and healthcare products, with different regulatory aspects which are directly applicable and must be enforced. Among them, we should note that the use of PRP must be *prescribed by a physician, dentist or podiatrist within the scope of their respective competencies, with prescription by other healthcare or non-healthcare professionals not being permitted*. Therefore, the choice of product that best suits the condition being treated and the best way to obtain it remain the responsibility of the prescriber. Furthermore, this professional should have experience in the treatment being applied. Since the drug should only be dispensed under a restricted medical prescription, it may only be used in specific and specialized facilities: healthcare centers or services, which are duly authorized to carry out such activities in accordance with the applicable regulations of each Regional

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<sup>a</sup> The report does not address the allogeneic use of PRP (plasma from a different donor). The use of this type of product should be subject to consultation with experts from AEMPS about the requirements that must be met in each case.

Government, assisted by technicians and specialists from AEMPS, the authority which will ultimately issue the authorization. The objective for the coming months will be to work on defining the types of facilities required to obtain a quality product, the contents of the product, a list of applications, methods of application, etc.

Another important aspect to consider is that, like any other prescription medication, any type of advertising regarding the product and the pathologies to be treated which targets the general public is prohibited. The latter is important because of the numerous establishments, clinical and non-clinical, which advertise these treatments with great fanfare. We only need to enter the term into an Internet search engine and, within seconds, we will be overwhelmed by a vast amount of advertising about it, most of it misleading.

Always bearing in mind that PRP is a medicine, the report establishes the minimum guarantees required for its use. We will attempt to present these assurances as clearly as possible.

### Minimum quality assurance in production

Since there are different techniques to obtain PRP (production), a minimum quality assurance should be established for these processes. In this sense, there are significant doubts regarding the minimum facilities required. The report from AEMPS groups these techniques into two main categories: open and closed, giving different guidelines about the necessary facilities required to use one or the other. In both cases, the prescribing physician will be ultimately responsible for ensuring that the process employed, despite being performed by a third party, complies with these guarantees.

Using one technique or the other for the processing of PRP remains a decision for the prescriber. The person responsible should be aware that *open techniques* are those in which any of the products is exposed to "open air" during the process (opening of peripheral blood tubes, pipetting to collect different types of plasma, etc.). In this case, the competent authority must be requested to conduct an inspection in order to verify that the facilities are optimal for obtaining a quality product. When *closed techniques* are used, usually with disposable kits, it will not be necessary to obtain a certificate of appropriateness of the facilities, provided that the kits are CE marked for their intended use and that they are truly closed, that is, that at no stage in the process is the product exposed to open air (opening of connections, tubes, etc.). Inspections by the authorities will be performed when they are considered appropriate by those using these techniques. In both cases, EU good manufacturing practices (GMP) will be taken as a reference in order to maintain quality assurance.

Considering the quality of the product obtained, there must be some kind of analysis which determines whether or not the product meets the prescriber's requirements in order to "repair" the lesion, including a specific number of platelets, product sterility, etc. These characteristics must be defined by the prescriber and will help to carry out a better analysis of the effectiveness of the product used in each treatment.

### Effectiveness assurance

As previously discussed, PRP is a commonly used treatment in a wide range of medical specialties. However, there are no clinical trials of sufficient quality to demonstrate efficacy in any of them. Hence, AEMPS, in collaboration with the experts and scientific societies involved, will develop a list of the different applications in which there is some evidence of a positive benefit/risk to patients and those where well-designed clinical trials are required to establish levels of evidence which support the use of different PRPs in each of the pathologies studied.

### Traceability assurance

Since these products are derived from blood, despite being autologous they require control, monitoring and traceability measures which prevent the transmission of infectious diseases. The prescribing physician will be responsible for complying with these measures. In practical terms, the prescriber must comply with Royal Decree 1088/2005, of 16 September, which establishes the technical requirements and minimum conditions for blood donation and transfusion services and centers,<sup>2</sup> in addition to conducting the mandatory analytical tests on patients (donors) described in Annex III of Royal Decree 1088/2005. Blood group determination is excluded in the present scenario (patient-donor of PRP), with the focus being on the identification of infectious agents.

### Pharmacovigilance assurance

The prescriber should monitor every patient following treatment with PRP, promptly notifying any suspected adverse reactions that may have been caused by the drug to the Pharmacovigilance Centers of the appropriate Regional Government. Information about how to report these adverse reactions can be obtained through the AEMPS website: <http://www.aemps.gob.es/vigilancia/medicamentosUsoHumano/home.htm> (in Spanish).

### Information assurance

Since PRP does not have a technical data sheet or a prospectus authorized by the AEMPS, the prescribing physician will be responsible for providing adequate information to each patient in order to ensure compliance with the requirements regarding product quality, effectiveness aspects for the pathology being treated, advantages of using this product over any other existing alternatives, known risks and methods for reporting any adverse reaction. In this sense there is a commitment by AEMPS, along with the scientific societies involved, to determine and publish minimum information criteria for each indication.

In conclusion, we can continue to apply PRP to our patients, but we must not forget that it is a drug, so we must comply with existing legislation. If we harbor doubts, we must study the product to be applied and for what condition, what facilities are available and what we need to obtain the

product, considering whether we should request authorization or not. Since the legislation is new, it would be useful to have a roadmap which reflected all the legal aspects and steps to be followed in relation to the request and authorization for the processing and application of PRP, as well as the minimum criteria for processing facilities for each of the assumptions that would be necessary to use autologous PRP as a treatment, while complying with all the requirements established by the V1/23052013 report published by AEMPS. This information will certainly become available in the coming months through the different scientific societies. However, until we have this information, we must appeal to ethics and good clinical practice which, by definition, should always be applied by professionals employing these treatments. We must never forget that the person primarily responsible for the correct preparation, implementation and monitoring of this drug is the prescriber, who should place the clinical benefit that the patient may obtain through its use before any other benefit.

## References

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