

Regenerative medicine in osteoarthritis

-A new chance for knee osteoarthritis patients

Editorial

There have been many exciting breakthroughs over the last years in medical research in terms of regenerative treatments for degenerative joint disorders in Humans, among which we can mention:

- **Mesenchymal stem cells (MSCs)**, whose benefits to date are essentially clinical and modest, for a high cost of treatment and without histological evidence of definite efficacy [1]. According to the FDA, manipulations prior to the ex vivo cell expansion may represent a significant risk in addition to the potential in vivo secondary transformation of these stem cells or even their differentiation towards an osteogenic lineage [2].
- **Three-dimensional biomaterial scaffolds** (Biomaterials for Tissue Engineering) supplemented with growth factors, more or less cellularized, or chemotactic biomaterials for MSCs represent promising directions for future research. Advanced biocompatible materials mimicking the three-dimensional organization of joint cartilage incorporate stem cells and growth factors either produced locally, or by biotechnological techniques. The future will tell us if this research axis of tissue bioengineering will be one of the therapeutic options for osteoarthritis. It seems however misleading to implant such systems in diffuse osteoarthritic lesions for which the preferred route remains intra-articular-injections [3].
- The local application of **Bone Marrow Cell concentrates** (BMC) harvested by bone puncture, often combined with a Hyaluronic Acid (HA)-based scaffold soaked in Platelet-Rich Plasma (PRP) or even associated with the microfracture technique, has only been described in case reports or small case series on localized cartilage defects so far. On one hand, it

is difficult to determine the specific effect of BMC in these multiple therapeutic combinations and, on the other hand, the second-look arthroscopy shows only dubious results with a neocartilage more fibrocartilaginous than natural hyaline. This histological result is similar to those observed with chondrocyte grafts for the treatment of osteochondritis dissecans [4].

- **Superfactors** such as Prostaglandin Factor 2 (PGF2), involved in regulating PPAR γ expression (protective effects of the peroxisome proliferator-activated receptor gamma) or Fibroblast Growth Factor 18 (FGF18), referred to as Sprifermin, are currently being studied [5]. The promising work conducted in 2014 on cartilage thickness following cycles of 3 injections per week administered every 6 to 12 months of Sprifermin seems to be supported by the post-hoc analysis performed in 2018 [6].

At this stage of our knowledge, we wanted to remain consistent in this special issue and focus on the **PRP/HA combination (CM-PRP-HA)** obtained using a dedicated medical device: Cellular Matrix A-CP-HA kit. Treatment with CM-PRP-HA has the advantage of being a validated simple, inexpensive and clinically effective procedure in terms of pain, stiffness and joint function, while remaining non-invasive and safe [7]. Interestingly, it was recently demonstrated that CM-PRP-HA was structurally effective using both ultrasound and high field MRI.

But, how does it work ?

The rationale underlying the use of a combination of PRP and HA is attractive, the patient being his «own treatment». CM-PRP-HA exerts its anti-inflammatory and regenerative effects through the compounds of the platelet secretome in a three-dimensional network of HA.

W-H Chen et al [8] investigated in vitro the dual biochemical mode of action of the

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combination of PRP and HA, with its anti-inflammatory and potentially regenerative effects on articular cartilage.

In this special issue, Dr. JL Renevier's publication demonstrates the long-lasting clinical efficacy of the CM-PRP-HA combination in patients who had unsuccessful response to previous treatment with HA alone (9). The HA present in the combination seems to improve the biological action of the PRP and to bring superior results than standard treatments with HA alone [10].

Dr. P Adam's publication demonstrates the interest of treating, with this product, degenerative meniscal lesions at an early stage, which otherwise are the precursors of the more advanced stages of knee osteoarthritis.

The clinical and structural effects of this new therapeutic approach for knee osteoarthritis treatment are proved in two studies. Dr B Barac and Dr JF Marc, demonstrate, following repeated injections of the CM-PRP-HA, the quantitative increase of cartilage thickness by ultrasound in 53 patients (90 knees) and the qualitative improvement in proteoglycan (PG) content in cartilage areas by 3 Tesla MRI in 6 patients, respectively.

S Vischer and al, explain the interest of the concept of combining PRP and HA treatment using a specific medical device. Cellular Matrix is the first medical device that has been designed and certified for the preparation of PRP combined with HA (CM-PRP-HA) in compliance with regulations and good practices for class III medical devices and for the therapeutic use of biological tissues for autologous therapy.

To conclude this special issue, the medico-economic study of Dr S Landi describe the significant savings to be expected from this type of treatment for the French national social organizations protecting the health of citizens. This data could be useful for a future consideration of reimbursement of this therapy for patients suffering from osteoarthritis.

However, in the context of evidence-based medicine, it is of key importance to confirm with a larger number of patients the results obtained in the structural proof-of-concept study. It is also crucial to standardize the injection protocol of CM-PRP-HA. A structural clinical study with various injection protocols is, therefore, already underway to clarify these two points.

In practice, and in the primary interest of patients, the place of Cellular Matrix, which is registered in Europe and many other countries, is to be part of the conservative

medical management of osteoarthritis as a first-line treatment and concomitantly with both non-pharmacological (weight loss, physical activity, orthoses, physical rehabilitation) and pharmacological treatment options (analgesics, short-term AINS for inflammatory flares, slow-acting anti-rheumatic drugs).

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