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REGENERATIVE THERAPIES FOR TREATMENT OF OSTEOARTHRITIS (OA) IN DOGS. REVIEW

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ABSTRACT

Osteoarthritis is a degenerative joint disease characterized by destructive changes in articular cartilage and formation of new bone tissue - osteophytes. OA is the most common degenerative joint disease in humans and animals. OA affects the entire joint and is characterized by inflammation, remodeling of bones and progressive destruction of constitutive cartilage components.

The main purpose in the treatment of osteoarthritis is aimed at relieving pain, maintaining joint mobility, improving the quality of life of the patient, slowing down the development of degenerative changes. Over the last decades, on the basis of a number of studies, the beneficial effects of regenerative medicine in the treatment of injuries in all tissues in the body, in particular, the treatment of osteoarthritis, have been proven.

The most commonly used regenerative therapies for the treatment of osteoarthritis are platelet-rich plasma (PRP), bone marrow (BM), and stem cells. These methods are obtained from the patient's own blood or tissues. These therapies have an anti-inflammatory, analgesic, reparative and antidegenerative effect.

Key words: Platelets-Rich Plasma (PRP), bone marrow, stem cells, osteoarthritis, dog.

Introduction

Osteoarthritis (OA) is a complex disease affecting all joint structures. Usually, it is diagnosed lated in the irreversible stages of the disease. Until now, there is no known therapy to modify disease and block the pathways for disease progression (Mobasheri & Henrotin 2010). Studies on treatment options focused on therapies such as cytokine inhibitors, genetic therapy, and the use of growth factors that would have the potential to preserve the normal joint homeostasis or to reverse structural disorders in degenerative joints (Johnston et al., 2008; Spakova et al 2012). Primary OA therapy aims to provide pain relief (Mobasheri & Henrotin 2010), maintaining joint motility, improving patients' quality of life, and delaying the disease progression (Gigante & Callegari 2011).

Materials and Methods

Modern therapy methods include:

Non-steroidal anti-inflammatory drugs are most commonly used in OA in dogs. Prolonged use of NSAIDs has been associated with good pain control and improved joint mobility (Innes et al., 2010b). These agents inhibit nitric oxide in the articular cartilage and thus, most likely slow down cell death and disease progression (Innes et al., 2010b).

NSAIDs can be combined with other analgesic agents in treatment of chronic pain. They can not only help control pain in severe cases but also help reduce NSAIDs doses (Lamont & Mathews 2007). Possible analgesic adjuvants are tramadol, amantadine, gabapentin and amitriptyline (Lamont & Mathews 2007).

Another pharmacological option is the use of polysulfate glycosaminoglycan and pentosan polysulphate (Innes 2012).

Intraarticular therapy

One of the most commonly used agents for intra-arterial therapy is corticosteroids. The exact mechanism of action still remains unclear. Their action is believed to be mediated by inhibiting the activity of phospholipase A leading to the reduction of cyclooxygenase and lipoxygenase production (Schulz 2007; Gege et al., 2012). They reduce the number of inflammatory cells, such as lymphocytes, macrophages and mastocytes, and thus reduce phagocytosis – the release of lysosomal enzymes and inflammatory mediators (Lavelle et al., 2007). Corticosteroids, cytokines and enzymes involved in articular cartilage degeneration in OA joints reduce the release of leukotrienes and prostaglandins and the expression of two of the most important mediators of cartilage degradation interleukin-1 (IL-1) and tumor necrosis factor-α (TNF -a) (Caron 2005; Lavelle et al., 2007). Corticosteroids protect joint cartilage by lowering the activity of metalprotein (Schulz 2007).

Hyaluronic acid is administered intra-articularly to improve the viscosity and elasticity of synovial fluid and suppress joint pain (Henrotin et al., 2005; Larsen et al., 2008; Gomis et al., 2009; Kwon & Park 2012). In-vitro studies show that hyaluronic acid has anti-inflammatory, anti-septic and chondroprotective effects (Colen et al., 2010; Edwards 2011).

Mesenchymal stem cells (MSCs)

MSCs are defined as undifferentiated cells with the ability to transform into differentiated cells and in regenerative tissue (Mafi et al., 2011, Fortier & Tuan 2012). The three major stem cell classes are embryonic stem cells, fetal stem cells and mature stem cells (Fortier & Tuan 2012).

It is currently unclear whether MSCs can differentiate into specific tissue cells or their potential therapeutic effect is mediated by secretion of immunomodulators and trophic factors such as cytokines and growth factors that affect the surrounding cells and alter the local inflammatory response (Black et al. Fortier & Travis 2011; Fortier & Tuan 2012).

Autologous conditioned serum.

Catabolic-conditioned interleukin 1 (IL-1) is the most potent catabolic mediator destroying articular cartilage and an important inflammatory mediator in joint diseases (Frisbie et al., 2009; Baltzer et al., 2009). Interleukin 1 (IL-1Ra) antagonist prevents the interaction of IL-1 cell surface receptors and thus, the inflammatory cascade initiated by IL-1 (Baltzer et al., 2009). In order to prevent the effect of IL-1, the ratio between IL-1Ra and IL-1 should be too high.

Platelets-rich plasma (PRP)

Platelets were initially thought to be involved only in the blood clotting process. Later, it was found that they also contained growth factors and cytokines that are essential for the recovery of soft tissues and bone mineralization. Many of the thrombocyte-released bioactive proteins attract macrophages, mesenchymal stem cells and osteoblasts and thus play a significant role in tissue regeneration and healing processes (Sampson et al., 2010).

Platelet growth factors such as platelet growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), fibroblast growth factor (FGF), insulin-like growth factor 1 (IGF-1), and epidermal growth factor (EGF) have been shown to take part in the regulation and synthesis of articular cartilage. They are also the source of cytokines, chemokines

and other proteins that stimulate chemotaxis, cell proliferation and model the inflammatory response (Kon et al., 2011a).

It has been shown that high platelet concentrations lead to high concentrations of said growth factors and thus, they accelerate and stimulate the healing processes normally following the trauma (Sampson et al., 2010; Stief et al., 2011; Spakova et al., 2012). Intra-articular administration of PRP may slow the progression of OA by stimulating cartilage anabolism (Stief et al., 2011).

Bone Marrow (BM)

Adult stem cells, also known as somatic stem cells, are found in different tissues and are responsible for the maintenance and recovery of tissues from which they originate. For example, adult stem cells are polypotential and have the ability to differentiate into mesodermal cells in the muscles, bones, tendons, cartilage and adipose tissue (Lee EH, and Hui JHP 2006).

These cells can be stimulated to irreversibly alter their cell lines in a process called transdifference, where the cells are transformed into a different cell type. (Lee EH, and Hui JHP 2006; 4. Song L, and Tuan RS, 2004).

The bone marrow aspirate concentrate (BMAC) has the potential to be a source of MSCs and key growth factors that can be used in treatment of chondral injuries.

In order to overcome the significant financial costs of in-vitro multiplication of MSCs, untreated BM is used as a source of MSCs. There are a number of potential areas for obtaining BM. Hyer et al., compare the iliac crest, tibia and calcareous, and evaluate the number of obtained MSCs (45. Hyer CF, et al., 2013). The iliac crest provides a high average concentration of MSCs compared to the other locations. However, with increasing age, there is a decrease in the absolute number of MSCs (47 Stolzing A et al., 2004). Muschler et al., show that since the aspirate volume of the iliac crest rises from 2 to 4 ml, the number of MSCs decreases by 50%. A recent study in horses by Peters A.E. and Watts A. E. (2016) shows that inserting a needle from 5 mm to three times as much in depth could increase the percentage of MSCs, although subsequent depth penetrations are not as helpful (50). This is probably due to hemodilution with aspirated blood. Approximately 0.001% of the nuclear BM cells are MSCs (51 Kasten P, et al., 2008; Ross A. Hauser and Amos Orlofsky, 2013) when using intra-articular injection of whole tibial BM to treat a series of patients with joint disease.

The use of whole bone marrow (WBM) aspirators potentially combines elements from several regenerative therapy methods. Unlike the previous therapies discussed in this article, the BM is not fractionated and therefore, the potentially supportive chondrogen component in the plasma of the brain is retained.

The administration of a natural, uncultivated, fresh and non-reduced volume autologous BM aspirator containing stem cells is considered to be potentially successful source of proliferative elements for the following reasons:

- avoiding tissue rejection problems;
- the heterogeneous BM aspirate composition containing both stem cells and other cells with regenerative potential has a synergistic effect, and has been shown to enhance the effect of various cell-based therapies when administered;
- rich source of adipose cells, extracellular matrix and growth factors, all of which coordinate interactions between different cell types;

- it does not require in-vivo cultivation of stem cells, which may lead to potential changes and instability in their genetic or epigenetic potential;
- the need for strictly standardized protocols in the production of material is avoided as the resulting BM aspirates are autologous and the possibility of transmission of possible trasmissible infections or other diseases is avoided.

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