TREATMENT FOR EQUINE JOINT DISEASE WITH REGENERATIVE MEDICINE PRODUCTS

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DEGENERATIVE JOINT DISEASE (DJD)

DJD is the most prevalent joint pathology in horses. It is a chronic, irreversible degenerative process, based on progressive cartilage erosion, joint space narrowing, subchondral bone remodeling, marginal osteophytosis, synovitis and joint capsule fibrosis.

OBJECTIVES

- To assess the advantages and disadvantages of using different origin mesenchymal stem cells (MSCs) and compare their effectiveness in the horse with DJD.
- To establish an own judgement of clinical use, as well as a treatment proposal.

CLINICAL SIGNS

- Lameness
- Thickening of joint capsule
- Pain on manipulation
- Progressive loss of joint function
- Muscle atrophy
- Behavioural changes
- Decrease in athletic performance

PATHOPHYSIOLOGY

INTERLEUKIN IL-1 + MATRIX METALLOPROTEINASES (MMPs) + EZ PROSTAGLANDINE + B4 LEUKOTRIENE + NITRIC OXIDE (NO) → DJD CLINICAL SIGNS

STEM CELLS

DEFINITION

A stem cell is an undifferentiated cell capable of dividing indefinitely and differentiate into several specialized cell types, not only morphologically but also functionally. Stem cell main features are:

1. Self-renewal due to telomerase activity
2. Pluripotentiality: ability to differentiate into other cell types

CLASSIFICATION

ACCORDING TO ORIGIN:

- Embryonic stem cells (ESCs): properties of self-renewal and pluripotency, offer the possibility of an unlimited, renewable source of cells that can be induced to differentiate into any cell of the body.
- Adult stem cells: found within the majority of tissues. MSCs hold the greatest therapeutic potential.
- IPCS: generated from adult, terminally differentiated cells, re-programme cells into very similar ESCs by the introduction of four genes (Oct4, Sox2, cMyC and KIf4).

ACCORDING TO POTENTIAL DIFFERENTIATION:

- Totipotent: able to create an entire organism
- Pluripotent: capable of differentiating into cells of the 3 germ lines (endoderm, mesoderm and ectoderm)
- Multipotent: capable of differentiating into a limited lineages but also more specialised cell types
- Unipotent: capable of differentiating into a unique cell type.

MSCS TISSUE COLLECTION AND DIFFERENTIATION IN VITRO

MSCs EFFECT ON CARTILAGE REPAIR

A study of the literature makes it apparent that MSCs injected intraarticularly do not enrol into the endogenous cartilage and directly affect repair. Nevertheless, they do appear to have anabolic and chondroprotective benefits retarding the progression of cartilage destruction by reducing inflammation. Treatment timing seems to be a key factor in the degree to which MSCs modulate the progression of cartilage destruction.

However, recent advances in tissue engineering technologies have allowed to create scaffolds for regenerative medicine, such as HR007, which is composed of sulphated glycosaminoglycans (sGAGs) and hyaluronic acid (HA). HR007 scaffolds induce cell proliferation, enhance the expression of specific gen markers, induce the tissue production and have chemotactic effects over the MSCs.

MSCs + PRP COMBINED THERAPY

A study compared the conventional regenerative therapies based on the use of PRP or native MSCs alone, with the combined treatment (MSCs + PRP). The results shown that PRP enhances MSCs proliferation and chondrogenic differentiation.

AUTOLGOUOS VS ALLOGENOUS MSCS

Autologous MSCs are obtained from the individual donor. The main disadvantage is that their expansion process takes 10-21 days, so the treatment start is delayed and difficult as a result of the growth kinetic variations. In addition, some collection techniques are invasive and might not be suitable for all patients.

Allogeneic MSCs are obtained from a different donor. They allow immediate treatment of acute orthopedic lesions. Some security studies done in horses by intrarticular administration in healthy joints, have shown promising prospects due to the similar response to autologous MSCs.

CONCLUSIONS

- Allogeneic MSCs are safe even administrating more than a single dose. They allow us to establish an early treatment without having to wait for their expansion.
- Patients age and exposure to invasive techniques become irrelevant.
- BM-MSCs are characterized by a great rate of isolation, good regenerative behaviour, the shortest culture period and tri-potential differentiation capacity.
- AT-MSCs are characterized by great immunomodulatory behaviour. It would be interesting to combine with BM-MSCs to determine possible synergistic effects.
- PRP enhances MSCs proliferation and chondrogenic differentiation so it improves the regenerative results short (6-12weeks) and long term (6-12months) when combined.
- Tissue engineering based on sGAGs and HA might allow horse MSCs to engrat cartilage, decrease the expression of matrix degradation factors and make chondrogenic differentiation.

TREATMENT STUDY PROPOSAL

Combined intrarticular administration of BM-MSCs + AT-MSCs + PRP charged in a biocompatible matrix.