Treatment of the Pre-Osteoarthritic Joint Disease: Is there a role for DMOADs (disease-modifying osteoarthritis drugs)?

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Treatment of the pre-osteoarthritic joint disease is a new concept, which emphasizes the need for preventive strategies that will modify the course of a disease. Hip dysplasia, FAI (femoroacetabular impingement), joint trauma, meniscus and ACL injuries are considered conditions that will accelerate the development of OA (osteoarthritis).

The current approach to the clinical treatment of OA is the palliation of symptoms arising from late-stage disease. Early-stage disease or pre-osteoarthritis disease is clinically silent in that structural changes typically precede clinical signs and symptoms of pain, deformity, functional limitations, and disability. Metabolic changes in articular cartilage, synovium, and subchondral bone may represent the earliest measurable changes in pre-OA conditions. As such, identification and validation of biomarkers for pre-OA states and at-risk joints may have wide application in clinical trials of new intervention strategies, in routine screening, as well as in activity-modification programs and return to-play evaluations. The ability to observe early and reversible cartilage damage supports development of disease-modifying therapies.

In vitro studies suggest that there is a role for use of disease-modifying therapies after articular cartilage injury, when progressive chondrocyte death and apoptosis have been observed within minutes to days. In vitro, prevention of cell death following a cartilage injury can be obtained using anti-apoptotic drug therapies, such as P-188 or anti-caspases (Figure 1a-b). Matrix metalloproteinases (MMPs), a diverse family of proteolytic enzymes involved in the maintenance of the extracellular matrix, were initially seen as attractive drug targets for the treatment of OA. However, the development of MMP inhibitors has been limited by their tendency to elicit various undesirable musculoskeletal pathologies in both preclinical models and in the clinic, at efficacious blood concentration. A human clinical trial involving knee OA patients receiving the MMP inhibitor PG-116800 (PG-530742) (NCT00041756) was unfortunately terminated due to musculoskeletal toxicity. Although these highly specific MMP inhibitors may offer significant therapeutic potential, no such molecules have yet been approved for use in the clinic and concerns remain that the muscle toxicity may be due to the molecule class. Yet, there are new research efforts to use siRNA (small interfering RNA) to inhibit MMP-13, one of the key MMPs responsible for collagen degradation, as anti-MMP therapy. Currently, the relative contribution of ADAMTS-4 and ADAMTS- 5 proteinases to aggrecan loss and early cartilage erosion in OA has been established. Developing pharmacological aggrecanase inhibitors into the clinic has proven difficult due to poor pharmacokinetic (PK) properties with this class of inhibitor resulting in poor systemic exposure unless potency is compromised. Exploring the potential synergistic efficacy of combining an aggrecanase inhibitor with a selective MMP inhibitor or siRNA against MMP-13 and ADAMTS-4, or indeed a pro-anabolic drug may be one way forward in achieving an efficacious therapeutic drug with suitable PK properties. Targeting anabolic pathways to promote cartilage repair is an alternative strategy for preventing cartilage degeneration. Many laboratories also focus on the potential of naturally present products (resveratrol, green tea, and other) as future DMOADs for joint injuries.

It will be necessary to stratify patients concerning clinical, biomechanical, genetic and epigenetic profiles. For example, patients with symptomatic FAI (femoroacetabular impingement) could be stratified using biomarkers of cartilage disease and high-resolution MRI sequences combined with quantitative MR techniques that will provide accurate assessment of the cartilage tissue biochemistry. These patients, if shown that they have already developed a “pre-osteoarthritic condition”, could then be offered surgical treatment together with DMOADs (disease-modifying osteoarthritis drugs) that could reverse their cartilage to a healthy state. The chances that these patients will have improvement in symptoms and prevent future OA will be higher than untreated patients with a pre-osteoarthritic condition.

Figures:

Anti-apoptotic drugs applied immediately following acute injury reduce the development of post-traumatic cartilage degeneration and promote cell survival after a single impact to human ankle cartilage

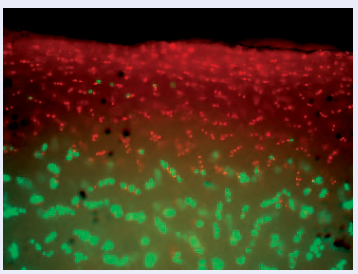

Fig1a: Cartilage explant 7 days post injury. Note the great amount of dead cells (red cells), evident in all superficial, medial and deep layer.

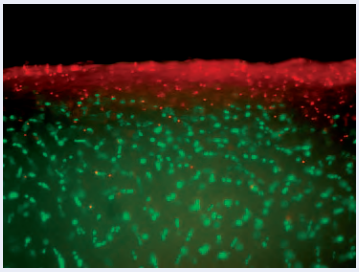

Fig. 1b. When cartilage was pre-treated with P-188 before trauma, the dead cells are only evident in the superficial layer, suggesting the potential for prevention of cartilage degeneration after cartilage trauma.