Chondroprotection Following Acute Joint Injury: Prevention of Osteoarthritis

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Introduction

Disease-modifying therapies to halt or potentially reverse the progression of existing osteoarthritis have been the focus of many research and drug development programs. However, successful registration of a drug for disease modification requires lengthy and expensive clinical trials with structural outcomes such as joint space narrowing and a decrease in signs and symptoms as the main clinical endpoints. In addition, the clinical benefit of any drug will depend on the level of preexisting osteoarthritis at the time therapy is initiated. In many cases, the degree of preexisting osteoarthritis at the time of diagnosis and treatment may be too severe for a significant clinical benefit from a disease-modifying agent. Joint injury is a major factor in the development and progression of secondary osteoarthritis, loss of function, and eventual joint replacement. However, at the time of injury, minimal or no osteoarthritis often exists. As a result, joint injury represents a unique opportunity to evaluate disease-modifying agents in the context of prevention of osteoarthritis rather than the treatment of preexisting osteoarthritis.

Prevalence of Joint Injury

The prevalence of joint injury appears to be increasing worldwide in association with both continued participation in sports in the older population and participation in competitive sports at increasingly younger ages. Surgical treatments for anterior cruciate ligament (ACL) tears and meniscal injuries attempt to reestablish knee joint stability,

but do not directly treat injury to the articular cartilage. In addition, shift in weight bearing to nonadapted cartilage as a result of surgery may put the health of normal noninvolved cartilage surfaces at increased risk for development of osteoarthritis if sufficient time for adaptation is not allowed in the rehabilitation program. Long-term outcome for development of activity-altering osteoarthritis following joint injury can be as high as 50% of cases within 10 to 15 years [4, 5]. Of particular concern are joint injuries in young athletes leading to debilitating osteoarthritis at an earlier age and the eventual necessity for multiple joint replacements in an attempt to relieve pain and restore a semblance of joint function.

Pathophysiologic Responses to Joint Injury

Pathophysiology of acute joint injury includes inflammation (innate response), hemarthrosis, chondrocyte apoptosis, matrix breakdown, and loss of normal joint lubrication (Fig. 1) [1]. Aggrecan fragments associated with matrix breakdown can be significantly elevated immediately following joint trauma [2]. This initial catabolic state can be followed by a later stage anabolic response. As a result of joint injury, cartilage is stressed, but often no osteoarthritis exists at the time of joint injury.

Therapeutic Chondroprotection

Rapid therapeutic normalization of the joint environment following injury may decrease or limit acute phase chondrocyte apoptosis and matrix degradation at the impact sites. Therapeutic normalization of the joint environment may allow physiological adaptation to the new loading environment in nonimpact regions. As a result, therapeutic chondroprotection may decrease or eliminate posttraumatic arthritis in combination with surgical and nonsurgical methods to stabilize joint mechanics.

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Fig. 1. A conceptual framework depicting the immediate cellular responses to acute joint trauma. Catabolic and anabolic processes are involved in the response to the injury and overlap with one another. Reprinted from Anderson et al. [1] copyright 2011, with permission from John Wiley and Sons

Some potential therapeutics that target normalization of the joint following trauma include: lubricin to reestablish normal joint lubrication; aggrecanase, metalloproteinase-13, and iNOS inhibitors to prevent matrix degradation; anti-TNF, anti-IL-1, innate response inhibitors, and TLR4 mAb to limit the acute inflammatory response and associated synovitis; and BMPs to limit chondrocyte apoptosis. Monotherapies, such as aggrecanase inhibitors, might be effective if they are important to the initiation of the catabolic cascade. However, combinations of the above interventions will likely be required to rapidly normalize the joint environment after acute trauma. Treatment could be administered orally, systemically, by intra-articular injection, or in combination. Half-life extension of intra-articular therapies can be achieved through the use of delivery modalities such as microspheres or nanoparticles. Systemically delivered therapies could utilize modalities, such as peptide binding proteins or nanoparticles, to target inflamed joints.

Patient selection for chondroprotection is critical for successful outcome. Due to the complications of more complex joint injuries, ACL injury without focal cartilage defects and meniscal damage or meniscal tears without ACL injury may be the most amenable for evaluation. Articular fractures may also represent a potential indication to evaluate normalization of acute joint injury. Another patient population that could be a rapid proof of concept would be hip dysplasia and femoroacetabular impingement. These conditions are a major cause of osteoarthritis in the young (<40 years old) adult population [3]. Patient stratification would involve age, sex, and potentially the use of genetic markers that could predispose for accelerated development of osteoarthritis.

Outcome measures for normalization of the joint following acute trauma will be quite different than those required for treatment of osteoarthritis. Structural modification, such as joint space narrowing, is rarely associated with acute joint injury, and pain-free function is generally restored following the perioperative period. Surrogate biomarkers would be required for target

engagement and efficacy. Since the goal would be rapid normalization of the joint environment, surrogate markers could include normalization of synovial fluid biomarkers, normalization of synovitis, and prevention of articular cartilage matrix breakdown using imaging biomarkers.

The Food and Drug Administration (FDA) approval for chondroprotection would focus the ability to restore the joint environment and prevent subsequent cartilage damage rather than alteration of the course of preexisting osteoarthritis following treatment with a disease-modifying drug. The general concept for chondroprotection therapies would have the potential advantage of limiting the need for treatment to the peri-injury period in contrast to the prolonged therapy required to treat existing osteoarthritis. Patient registries linking biomarkers to the prevention of osteoarthritis will be critically important. The relevance of chondroprotection therapies as eventual disease-modifying therapies for osteoarthritis could be evaluated as continuation phase 4 studies. Obviously, the commercial viability of pursuing therapies for chondroprotection will be challenging. The pursuit of this indication will likely require creative alternative public-private collaborations involving industry, the Arthritis Foundation, Department of Defense, Professional Sport foundations, FDA, and academic medical centers.

Summary

Developing therapies for chondroprotection offers the potential to prevent debilitating osteoarthritis and associated joint replacement following acute joint trauma. Although many significant challenges must be overcome, in comparison to expensive and time-consuming conventional osteoarthritis clinical trials, therapeutic chondroprotection may provide an easier path to evaluate treatments that have potential as disease-modifying therapies for osteoarthritis.

Disclosures Each author (HS, KG, CF) certifies that he or she has or may receive payments, stock ownership and benefits as employees of a commercial entity (Pfizer Discovery Research) related to this work.

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