Emerging Ideas

Prevention of Posttraumatic Arthritis Through Interleukin-1 and Tumor Necrosis Factor- α Inhibition

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Abstract

Background Despite surgical and mechanical stabilization of an acutely injured joint through ligament reconstruction, meniscus repair, or labral repair, the risk of posttraumatic arthritis remains high. Joint injury triggers three phases of pathogenic events: the early (acute) phase involves joint swelling, hemarthrosis, expression of inflammatory cytokines (especially interleukin-1 [IL-1] and tumor necrosis factor- α [TNF- α]), and biomarkers of cartilage catabolism; an intermediate phase is characterized by reduction of joint inflammation, ongoing joint catabolism, but no evidence yet for typical features of radiographic

osteoarthritis (OA); and a late phase characterized by radiographic OA.

Hypotheses We hypothesize that the early phase of acute knee injury represents a window of opportunity for providing biologic treatment to promote healing and to slow or prevent a subsequent cascade of destructive joint processes leading to OA.

Proposed program We propose a phase II, randomized, placebo-controlled, double-blinded, clinical trial to treat acute knee injuries with intraarticular injection of an IL-1 inhibitor. Patient-centered outcomes will include pain reduction and improvement of knee function. MR imaging and measurement of biochemical markers will be monitored during the subsequent 2 years to determine if the structural response to injury can be reversed.

Significance If this model is validated, modulation of the molecular pathways responsible for articular cartilage breakdown will augment current reconstructive procedures in the treatment of acute joint injuries and prevent the development of injury-related arthritis.

Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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Hypothesis

We hypothesize that blocking IL-1 will reduce the breakdown of articular cartilage normally seen after traumatic injury.

Background

Traumatic knee injuries increase the risk of arthritis five- to 17-fold [12, 36]. Unfortunately, restoration of mechanical stability with ACL reconstruction or meniscus repair does not prevent future arthritis [6, 10, 23, 27, 38]. Evidence is accumulating that molecular mechanisms regulate inflammation and breakdown of articular cartilage and menisci after injury [9, 18, 19, 29, 30, 34, 35, 37]. IL-1 and TNF- α are proinflammatory cytokines produced in response to injury by chondrocytes, meniscocytes, synoviocytes, and macrophages [15, 16, 31]. Animal models support the dominant role of IL-1 early in the development of arthritis, and overexpression of IL-1 alone can create arthritis [13, 14, 32, 33]. In patients with acute ACL injury, IL-1 and TNF- α levels increase substantially, and native interleukin-1 inhibitor (IL-1Ra) decreases sixfold [2, 8, 9]. With decreased IL-1Ra, the inflammatory response cannot be buffered efficiently [4, 7, 17]. Within 1 month after joint injury in humans, Lohmander et al. documented synovial fluid elevations of proteoglycan fragments and metalloproteinases [22], collagen fragments [21], and persistent

elevations of these molecules over decades [20, 24–26, 28]. These data suggest a model (Fig. 1) whereby trauma causes an initial inflammatory response in the joint. This inflammatory response, mediated ultimately through IL-1 and TNF- α , then leads to a state of cartilage breakdown.

We became intrigued with cytokine blockade for prevention of posttraumatic arthritis noting chondral preservation with IL-1Ra administration in a dog ACL transection model [3] and TNF- α inhibition in a rat ACL tear model [9]. IL-1 and TNF- α inhibition also improve rat meniscus healing in vitro [29, 30]. In patients, knee injections of IL-1Ra and a TNF- α inhibitor have been reported for OA and inflammatory arthritis [1, 5, 11]. As acute knee injury is characterized by increased articular levels of IL-1 and TNF- α , which play a central role in joint damage, we suggest this early phase of injury represents a window of opportunity for providing biologic treatment to promote healing and to slow or prevent a cascade of joint destructive processes leading to OA.

Proposed Program

To assess the effect of IL-1 inhibition on cartilage breakdown, a double-blind, placebo-controlled trial will be conducted with intraarticular administration of an IL-1 inhibitor after traumatic knee injury. The functional and metabolic state of the injured joint will be followed with time to assess the effect of blocking IL-1 during the initial

Fig. 1A–B Proposed models of interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α) in the development of posttraumatic arthritis are shown. (A) Before major traumatic injury, high levels of interleukin-1 receptor antagonist (IL-1Ra) buffer the downstream effects of any proinflammatory responses. (B) After injury, increased

macrophages in the synovial lining reinforce proinflammatory responses and decreased IL-1Ra is available to buffer this inflammatory response. MMPs = matrix metalloproteinases; GM-CSF = granulocyte-macrophage colony-stimulating factor; PGE₂ = prostaglandin E₂; COX2 = cyclo-oxygenase 2.

proinflammatory state after injury. A homogenous injury population with isolated ACL tears will be studied and functional outcome will be assessed clinically with patient-based outcome scores, pain assessment, ROM, and functional recovery tools. Because the development of cartilage damage substantial enough to cause radiographic evidence of arthritis takes many years, the metabolic status of the articular cartilage will be followed with time with intraarticular and serum-based biomarkers of cartilage breakdown, such as serum hyaluronan (HA). Intraarticular and serum cytokine profiles, including IL-1 α , IL-1 β , IL-1RA, and TNF- α , also will be followed with time to assess any change in response to administration of the IL-1 inhibitor. Finally, qualitative MRI, for example, dGEMRIC and T2 mapping, will be used to assess for early matrix changes typical of arthritis.

Preliminary data in a small pilot trial showed that intraarticular administration of a short acting IL-1 inhibitor, anakinra (Swedish Orphan Biovitrum Sverige AB, Stockholm, Sweden), substantially decreased pain and improved clinical outcomes compared with saline placebo. Although inflammatory profiles did not change considerably, biomarkers of cartilage breakdown did suggest that IL-1 inhibition could protect against major cartilage breakdown.

Limitations

The presence of prior traumatic knee injuries and the variability in the treated injury pattern are major limitations with the use of human subjects. The timing of administration of the IL-1 inhibitor is also a limitation as the time of presentation and diagnosis are not uniform. Recruitment and followup also sometimes are difficult. However, although these limitations present challenges in the interpretation of the data, they also represent the reality of treatment if IL-1 inhibition is to have widespread clinical use. Resorting to a large animal model would be the most plausible alternative approach.

Biomarkers and qualitative MR imaging to assess cartilage breakdown after injury remain unproven surrogate outcome measures to predict the development of arthritis. Ultimately long-term followup studies will be needed to determine if IL-1 inhibition can truly alter the natural history of traumatic joint injuries.

The pharmacokinetics of intraarticular delivery of the medications may limit their effectiveness, especially when compounded with the variability in patient presentation. Although a longer-acting dimeric IL-1 receptor inhibitor, an IL-1 tartrate-resistant acid phosphatase (TRAP), riloncept (Arcalyst, Regeneron Pharmaceuticals, Inc, Tarrytown, NY), has been developed and may show

improved response because of its longer half-life, it is possible that polymerized, depot, or nanoparticle preparations may be needed to provide sustained intraarticular delivery. Gene therapy strategies also may sustain intraarticular levels of inhibitors and prevent the development of arthritis [39].

Next Steps

To fully translate these findings to clinical practice, investigators will have to address many challenges. First, we will need to determine the ideal timing of IL-1 inhibition. To determine this, a more-detailed assessment of the postinjury inflammatory response and the effect that modulation of that response has on the metabolic state of the articular cartilage will be necessary. These investigations also will help answer the second critical question, namely, the duration of the inhibitory effect required to prevent cartilage breakdown. As indicated above, preparations with different pharmacokinetics, or alternative strategies, such as gene therapy approaches may need to be developed to make this technology a viable clinical tool. Finally, depending on the critical timing issues, the general approach to treatment of traumatic joint injuries may require rethinking. It may be that the initial few hours after the injury are the most critical to prevent long-term arthritis. If this is the case, healthcare-delivery systems will have to think of traumatic joint injuries as emergencies, not unlike how we treat stroke or myocardial infarction.

Implications and Future Directions

Even if current IL-1 or TNF- α inhibitors are not able to prevent the development of arthritis after traumatic joint injuries, the preclinical studies showing the dramatic chondroprotective effects of these agents underscore the primary role that the molecular mechanisms regulating cartilage breakdown play in the development of arthritis after injury. Although mechanical derangement clearly leads to arthritis, it appears to exert this response through alterations in the cellular and molecular mechanisms regulating cartilage metabolism. Understanding the cellular interactions and the molecular pathways at play in this process and developing tools to manipulate them promise to have a dramatic effect on preventing arthritis.

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References

- Boesen M, Boesen L, Jensen KE, Cimmino MA, Torp-Pedersen S, Terslev L, Koenig M, Danneskiold-Samsøe B, Rogind H, Bliddal H. Clinical outcome and imaging changes after intra-articular (IA) application of etanercept or methylprednisolone in rheumatoid arthritis: magnetic resonance imaging and ultrasound-Doppler show no effect of IA injections in the wrist after 4 weeks. *J Rheumatol*. 2008;35:584–591.
- Cameron M, Buchgraber A, Passler H, Vogt M, Thonar E, Fu F, Evans CH. The natural history of the anterior cruciate ligament-deficient knee: changes in synovial fluid cytokine and keratan sulfate concentrations. *Am J Sports Med*. 1997;25:751–754.
- Caron JP, Fernandes JC, Martel-Pelletier J, Tardif G, Mineau F, Geng C, Pelletier JP. Chondroprotective effect of intraarticular injections of interleukin-1 receptor antagonist in experimental osteoarthritis: suppression of collagenase-1 expression. *Arthritis Rheum*. 1996;39:1535–1544.
- Carter DB, Deibel MR Jr, Dunn CJ, Tomich CS, Laborde AL, Slightom JL, Berger AE, Bienkowski MJ, Sun FF, McEwan RN, et al. Purification, cloning, expression and biological characterization of an interleukin-1 receptor antagonist protein. *Nature*. 1990;344:633–638.
- Chevalier X, Giraudeau B, Conrozier T, Marliere J, Kiefer P, Goupille P. Safety study of intraarticular injection of interleukin 1 receptor antagonist in patients with painful knee osteoarthritis: a multicenter study. *J Rheumatol*. 2005;32:1317–1323.
- Daniel DM, Stone ML, Dobson BE, Fithian DC, Rossman DJ, Kaufman KR. Fate of the ACL-injured patient: a prospective outcome study. *Am J Sports Med*. 1994;22:632–644.
- Eisenberg SP, Evans RJ, Arend WP, Verderber E, Brewer MT, Hannum CH, Thompson RC. Primary structure and functional expression from complementary DNA of a human interleukin-1 receptor antagonist. *Nature*. 1990;343:341–346.
- Elsaid KA, Fleming BC, Oksendahl HL, Machan JT, Fadale PD, Hulstyn MJ, Shalvoy R, Jay GD. Decreased lubricin concentrations and markers of joint inflammation in the synovial fluid of patients with anterior cruciate ligament injury. *Arthritis Rheum*. 2008;58:1707–1715.
- Elsaid KA, Machan JT, Waller K, Fleming BC, Jay GD. The impact of anterior cruciate ligament injury on lubricin metabolism and the effect of inhibiting tumor necrosis factor alpha on chondroprotection in an animal model. *Arthritis Rheum*. 2009;60:2997–3006.
- Ferretti A, Contedua F, De Carli A, Fontana M, Mariani PP. Osteoarthritis of the knee after ACL reconstruction. *Int Orthop*. 1991;15:367–371.
- Fisher BA, Keat A. Should we be using intraarticular tumor necrosis factor blockade in inflammatory monoarthritis? *J Rheumatol*. 2006;33:1934–1935.
- Gelber AC, Hochberg MC, Mead LA, Wang NY, Wigley FM, Klag MJ. Joint injury in young adults and risk for subsequent knee and hip osteoarthritis. *Ann Intern Med*. 2000;133:321–328.
- Ghivizzani SC, Kang R, Georgescu HI, Lechman ER, Jaffurs D, Engle JM, Watkins SC, Tindal MH, Suchanek MK, McKenzie LR, Evans CH, Robbins PD. Constitutive intra-articular expression of human IL-1 beta following gene transfer to rabbit synovium produces all major pathologies of human rheumatoid arthritis. *J Immunol*. 1997;159:3604–3612.
- Ghivizzani SC, Lechman ER, Kang R, Tio C, Kolls J, Evans CH, Robbins PD. Direct adenovirus-mediated gene transfer of interleukin 1 and tumor necrosis factor alpha soluble receptors to rabbit knees with experimental arthritis has local and distal anti-arthritis effects. *Proc Natl Acad Sci USA*. 1998;95:4613–4618.
- Goldring MB. The role of the chondrocyte in osteoarthritis. *Arthritis Rheum*. 2000;43:1916–1926.
- Goldring MB. Update on the biology of the chondrocyte and new approaches to treating cartilage diseases. *Best Pract Res Clin Rheumatol*. 2006;20:1003–1025.
- Hannum CH, Wilcox CJ, Arend WP, Joslin FG, Dripps DJ, Heimdal PL, Armes LG, Sommer A, Eisenberg SP, Thompson RC. Interleukin-1 receptor antagonist activity of a human interleukin-1 inhibitor. *Nature*. 1990;343:336–340.
- Hubbard JR, Steinberg JJ, Bednar MS, Sledge CB. Effect of purified human interleukin-1 on cartilage degradation. *J Orthop Res*. 1988;6:180–187.
- Le J, Vilecek J. Tumor necrosis factor and interleukin 1: cytokines with multiple overlapping biological activities. *Lab Invest*. 1987;56:234–248.
- Lohmander LS. The release of aggrecan fragments into synovial fluid after joint injury and in osteoarthritis. *J Rheumatol Suppl*. 1995;43:75–77.
- Lohmander LS, Atley LM, Pietka TA, Eyre DR. The release of crosslinked peptides from type II collagen into human synovial fluid is increased soon after joint injury and in osteoarthritis. *Arthritis Rheum*. 2003;48:3130–3139.
- Lohmander LS, Dahlberg L, Ryd L, Heinegard D. Increased levels of proteoglycan fragments in knee joint fluid after injury. *Arthritis Rheum*. 1989;32:1434–1442.
- Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am J Sports Med*. 2007;35:1756–1769.
- Lohmander LS, Hoerner LA, Dahlberg L, Roos H, Björnsson S, Lark MW. Stromelysin, tissue inhibitor of metalloproteinases and proteoglycan fragments in human knee joint fluid after injury. *J Rheumatol*. 1993;20:1362–1368.
- Lohmander LS, Hoerner LA, Lark MW. Metalloproteinases, tissue inhibitor, and proteoglycan fragments in knee synovial fluid in human osteoarthritis. *Arthritis Rheum*. 1993;36:181–189.
- Lohmander LS, Neame PJ, Sandy JD. The structure of aggrecan fragments in human synovial fluid: evidence that aggrecanase mediates cartilage degradation in inflammatory joint disease, joint injury, and osteoarthritis. *Arthritis Rheum*. 1993;36:1214–1222.
- Lohmander LS, Ostergren A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. *Arthritis Rheum*. 2004;50:3145–3152.
- Lohmander LS, Roos H, Dahlberg L, Hoerner LA, Lark MW. Temporal patterns of stromelysin-1, tissue inhibitor, and proteoglycan fragments in human knee joint fluid after injury to the cruciate ligament or meniscus. *J Orthop Res*. 1994;12:21–28.
- McNulty AL, Moutos FT, Weinberg JB, Guilak F. Enhanced integrative repair of the porcine meniscus in vitro by inhibition of interleukin-1 or tumor necrosis factor alpha. *Arthritis Rheum*. 2007;56:3033–3042.
- McNulty AL, Weinberg JB, Guilak F. Inhibition of matrix metalloproteinases enhances in vitro repair of the meniscus. *Clin Orthop Relat Res*. 2009;467:1557–1567.
- Ochi M, Uchio Y, Okuda K, Shu N, Yamaguchi H, Sakai Y. Expression of cytokines after meniscal rasping to promote meniscal healing. *Arthroscopy*. 2001;17:724–731.
- Pelletier JP, Caron JP, Evans C, Robbins PD, Georgescu HI, Jovanovic D, Fernandes JC, Martel-Pelletier J. In vivo suppression of early experimental osteoarthritis by interleukin-1 receptor antagonist using gene therapy. *Arthritis Rheum*. 1997;40:1012–1019.
- Pelletier JP, Mineau F, Ranger P, Tardif G, Martel-Pelletier J. The increased synthesis of inducible nitric oxide inhibits IL-1 α synthesis by human articular chondrocytes: possible role in

- osteoarthritic cartilage degradation. *Osteoarthritis Cartilage*. 1996;4:77–84.
34. Pettipher ER, Higgs GA, Henderson B. Interleukin 1 induces leukocyte infiltration and cartilage proteoglycan degradation in the synovial joint. *Proc Natl Acad Sci USA*. 1986;83:8749–8753.
35. Pratta MA, Di Meo TM, Ruhl DM, Arner EC. Effect of interleukin-1-beta and tumor necrosis factor-alpha on cartilage proteoglycan metabolism in vitro. *Agents Actions*. 1989;27:250–253.
36. Roos EM. Joint injury causes knee osteoarthritis in young adults. *Curr Opin Rheumatol*. 2005;17:195–200.
37. Saklatvala J. Tumour necrosis factor alpha stimulates resorption and inhibits synthesis of proteoglycan in cartilage. *Nature*. 1986;322:547–549.
38. von Porat A, Roos EM, Roos H. High prevalence of osteoarthritis 14 years after an anterior cruciate ligament tear in male soccer players: a study of radiographic and patient relevant outcomes. *Ann Rheum Dis*. 2004;63:269–273.
39. Wang HJ, Yu CL, Kishi H, Motoki K, Mao ZB, Muraguchi A. Suppression of experimental osteoarthritis by adenovirus-mediated double gene transfer. *Chin Med J (Engl)*. 2006;119:1365–1373.