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Clinical Benefits of Intra-articular Anakinra for Arthrofibrosis

By Christopher A. Brown, MD; Alison P. Toth, MD; Bob Magnussen, MD

Abstract

Postoperative inflammation and stiffness, as well as the struggle to achieve full range of motion (ROM), following knee surgery is a significant clinical challenge. Interleukin-1 is a crucial mediator of the inflammatory response and development of pathological conditions leading to chronic inflammation. We hypothesized that intra-articular injection of intra-articular anakinra, an IL-1 antagonist, would result in sustained improvements of chronic refractory arthrofibrosis and limited arthrofibrosis of the knee joint.

We retrospectively reviewed 8 patients who underwent injection of intra-articular anakinra, 200 mg. Four patients (3 women, 1 man) had intra-articular anakinra for treatment of chronic refractory arthrofibrosis, and 4 patients (4 women) had intra-articular anakinra for limited arthrofibrosis. All 4 of the refractory arthrofibrosis patients had failed conservative treatment with intensive physical therapy, corticosteroid injections, and anti-inflammatory medication. Three of the 4 patients had failed a prior manipulation under anesthesia with lysis of adhesions. All 4 reported improvement in ROM (10°-45°) and swelling, with 75% reporting improvement in pain. Seventy-five percent of these patients returned to prior activity level. All 4 of the limited arthrofibrosis also failed similar attempts at conservative treatment, and 2 of the 4 had failed a prior manipulation under anesthesia with lysis of adhesions. After intra-articular anakinra, all 4 reported improvement in ROM (20°-45°) and swelling, with 80% reporting improvement in pain. Seventy-five percent of these patients were able to return to prior activity level.

We found intra-articular anakinra to be effective in this small cohort of patients with refractory arthrofibrosis and limited arthrofibrosis.

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Motion loss due to arthrofibrosis following knee surgery or injury is a clinical challenge that can be detrimental to patient overall recovery

and functional outcome. Arthrofibrosis represents a wide spectrum of disease, ranging from localized to diffuse involvement of all compartments of the knee and extra-articular soft tissues. There is growing interest to better understand the complex nature of the inflammatory cascade, role of interleukin-1, and possible therapeutic interventions.¹

Because most studies of arthrofibrosis included mixed subsets of patients with loss of motion following an injury or operation, the prevalence of true global arthrofibrosis is difficult to determine. The etiology of motion loss is multifactorial, involving a combination of mechanical and biological factors. Presently, the approach to minimize the likelihood for the development of arthrofibrosis is early preventive strategies and a multimodal approach. Preventive strategies include aggressive postoperative pain control, early passive range of motion (ROM) exercises, and good communication between therapist and physician. Once fibrosis has developed, interventions can range from steroid injections with aggressive physical therapy to surgical intervention with manipulation and arthrolysis. Despite these attempts, studies report that patients continue to have difficulty with continued inflammation, ROM, and swelling.²⁻⁴ This has led investigators to look closer at pathophysiology of arthrofibrosis with regard to the molecular pathways responsible.

The inflammatory cascade is an integral network of signaling between cells and release of cytokines that changes the intra-articular homeostasis. Interleukin-1 has an important role in altering catabolic pathways,⁵ stimulating metalloproteinases,⁶ promoting profibrotic mediators,⁷ and stimulating fibroblast proliferation and chemotaxis.⁸ By upregulating matrix degradation via metalloproteinases and downregulating collagen and proteoglycan synthesis, interleukin-1 promotes a chondrodestructive effect. Postoperative fibrogenesis resulting in poor functional outcomes remains a problem.

Interleukin-1 blockade has shown beneficial effects in many animal disease models¹ as a target for therapeutic treatment of osteoarthritis,^{9,10} juvenile inflammatory arthritis,¹¹ and autoimmune inflammatory syndromes.¹²⁻¹⁴ Anakinra is an interleukin-1 receptor antagonist. A number of studies have evaluated its safety and potential efficacy for the treatment of rheumatoid arthritis and other conditions such as established osteoarthritis.^{9-11,15} The inflammatory microenvironment sustained postoperatively/postinjury suggests that intra-articular delivery of an interleukin-1 receptor antagonist may be useful clinically to alter pro-inflammatory cascade and fibrogenesis.

The senior author (A.P.T.) has made use of the potential therapeutic effects of intra-articular anakinra for treatment of persistent refractory diffuse arthrofibrosis and limited arthrofibrosis over the past 3 years. The goal of this study was to perform a retrospective chart review evaluating the use of this treatment.

Materials and Methods

Between November 2007 and April 2010, the senior author treated 4 patients (3 women, 1 man) ranging in age from 15 to 54 years for treatment of chronic refractory arthrofibrosis and 4 patients (4 women) ranging in age from 19 to 52 years for limited arthrofibrosis of the knee with anakinra. Length of follow-up was patient specific, but for those who returned to sports or regular activities, follow-up ranged from 1 to 10 months.

Chronic diffuse refractory arthrofibrosis was defined as knee arc ROM <110° and failing prior conservative therapies including bracing, corticosteroid injections, intensive physical therapy. It should be noted that 75% of these patients also failed prior manipulation under anesthesia with lysis of adhesions. Limited arthrofibrosis was defined as knee ROM >110° with primarily anterior fat pad fibrosis and poor patella mobility.

A retrospective review of patients' medical records was undertaken after institutional review board approval. Information such as patient demographics, index injury or surgery, date and type of prior failed modalities, any modalities used in association with anakinra, dates of anakinra injection, initial and each additional follow-up clinical examination (pain, ROM, effusion), any additional procedures required after treatment with anakinra, and ultimate outcome (return to sport or prior level of activity, referred to other specialty, ongoing treatment) were recorded.

Data collected were patient demographics, history of prior modalities, dates of anakinra injection, initial and each additional clinical examination (pain, ROM, effusion), additional procedures required after treatment with anakinra, and ultimate outcome (return to sport or prior level of activity, referred to other specialty, ongoing treatment).

All 8 patients had an aspiration of synovial fluid via superolateral approach to the knee, followed by intra-articular injection of a mixture of 200 mg anakinra with 5 mL 1% plain lidocaine into the knee.

Results

All 4 of the refractory diffuse arthrofibrosis patients had failed conservative treatment with intensive physical therapy, corticosteroid injection, anti-inflammatory medication. In addition, 75% of these patients had failed a prior manipulation under anesthesia with lysis of adhesions. Three of 4 patients received anakinra within 2 weeks following manipulation under anesthesia with lysis of adhesions. The other patient had the first anakinra injection 3 months after lysis of adhesions. This patient required an additional lysis of adhesions procedure followed by anakinra. Of these, only 1 required an additional lysis of adhesion followed by treatment with anakinra. All 4 reported improvement in ROM (10°-45°) and swelling after intra-articular anakinra. Pain improved in 2 of 4 patients, while 1 patient never reported any pain and the other was 1/10 during his treatment. Three of 4 of these patients were able to return to sports, or activities of daily living if not previously involved in sports (Table 1).

Table 1
Chronic Arthrofibrosis Patients

Patient No./Sex/ Age, y	Index Injury/ Procedure	No. Anakinra Injections	Pain Score Change	ROM Change	Effusion Change	Helped Patient*	Steroid Injection Failed	No. Prior Procedures	No. Failed LOA Pre-anakinra	Anakinra-associated LOA	No. Procedures During Anakinra Treatment	Final Outcome
1/F/24	Left knee patella tendon repair	4	Worse (1/10)	+10	2+ to 1+	Yes	Yes	6	2	Yes	0	Still under treatment
2/F/22	Meniscus repair	3	No change (1/10)	+45	1+ to 0	Yes	Yes	2	1	Yes	1 LOA before 3rd injection	Returned to sports
3/M/15	ACL BTB	2	No change (0/10)	+20	1+ to trace	No	Yes	1	0	Yes (1st injection 3 months post-ACL; 2nd 1 week post-LOA)	1 LOA before 2nd injection	Returned to sports
4/F/54	Left ACL, untreated	2	Improved (2/10)	+40	2+ to 1+	Yes	Yes	4	1	Yes	0	Referred to rheum for possible underlying autoimmune disorder

Abbreviations: ACL, anterior cruciate ligament; ADL, activities of daily living; BTB, bone-tendon-bone; LOA, lysis of adhesions; rheum, rheumatology; ROM, range of motion.
*Patient opinion.

All 4 of the limited arthrofibrosis patients had failed conservative treatment with physical therapy, corticosteroid injections, and anti-inflammatory medication, while 50% of these patients had failed a prior manipulation under anesthesia with lysis of adhesions. All 4 patients had a lysis of adhesions followed by administration of intra-articular anakinra by 2 weeks of surgery. All 4 reported improvement in ROM (20°-45°) and swelling, with 80% reporting improvement in pain after intra-articular anakinra. Of these patients, 80% were able to return to sports, or activities of daily living if not previously involved in sports (Table 2).

Table 2

Limited Arthrofibrosis Patients												
Patient No./Sex/ Age, y	Index Injury/ Procedure	No. Anakinra Injections	Pain Score Change	ROM Change	Effusion Change	Helped Patient*	Steroid Injection Failed	No. Prior Procedures	No. Failed LOA Pre-anakinra	Anakinra-associated LOA	No. Procedures During Anakinra Treatment	Final Outcome
5/F/19	Left ACL BTB, medial meniscus debridement	2	Improved (1/10)	+20	2+ to 0	Yes	Yes	2	0	Yes	0	Returned to sports
6/F/20	Right knee injury, subsequent fat pad debridement	1	Worse (1/10)	+35	1+ to trace	No	Yes	2	1	Yes	0	Returned to sports
7/F/49	Left plica & hofas fat pad debridement	1	Improved (1/10)	+23	2+ to 0	Yes	Yes	3	2	Yes	0	Referred to rheum/ returned to ADL
8/F/52	Right plica & patella chondroplasty	2	Improved (3/10)	+45	2+ to 0	Yes	Yes	3	0	Yes	0	Returned to ADL

Abbreviations: ACL, anterior cruciate ligament; ADL, activities of daily living; BTB, bone-tendon-bone; LOA, lysis of adhesions; rheum, rheumatology; ROM, range of motion.
*Patient opinion.

Discussion

The majority of our patients had a beneficial effect from intra-articular anakinra. We used intra-articular anakinra for the treatment of refractory arthrofibrosis and limited arthrofibrosis of the knee joint after other standard modalities had failed. Many of the patients in the arthrofibrosis group had numerous procedures prior to treatment with anakinra, including failed lysis of adhesions procedures. All patients in the limited fibrosis group had failed conservative management including steroid injection, and 50% had failed prior surgical lysis of adhesions. All but 1 patient received intra-articular cortisone injection before intra-articular anakinra, and cortisone failed to achieve motion or swelling control.

Prevention through early motion remains the key element in preventing the development of arthrofibrosis in patients. Manipulation under anesthesia and arthroscopic lysis of adhesions remain reliable treatment options for established arthrofibrosis. Some patients do not improve and have recurrent fibrogenesis and poor functional outcomes. This data may suggest that for those patients who have persistent arthrofibrosis or limited arthrofibrosis, intra-articular anakinra may be an additional tool to decrease swelling, improve ROM, and allow the patient to return to sports or activities of daily living.

Although the results of this retrospective study are promising, there are several limitations. The small cohort, lack of control group, and retrospective nature of this study limit the strength of evidence and conclusions that may be drawn. Also, a standard validated knee scoring system was not used to evaluate the patients. Range of motion and effusion were based on clinician estimate. More conclusions may be drawn from future studies that are prospective, blinded, and placebo controlled as to what benefits intra-articular anakinra injection has for patients with persistent arthrofibrosis.

Inflammation is an important homeostatic mechanism that limits postoperative outcomes and rehabilitation from injury. Interleukin-1 is a crucial mediator of the inflammatory response, playing an important part in the body's natural responses and the development of pathological conditions leading to chronic inflammation such as arthrofibrosis. While interleukin-1 production may be decreased or its effects limited by so-called anti-inflammatory cytokines, in vitro interleukin-1 inflammatory effects are inhibited and can be abolished by 1 particularly powerful inhibitor: interleukin-1 receptor antagonist. Reports demonstrate the detrimental effect of interleukin-1 on cartilage homeostasis and a key role for this cytokine in inflammatory cascade.^{5,10,16}

In a retrospective report, in 33 patients with systemic juvenile arthritis, treatment with anakinra was associated with short-term improvements in large joint counts and laboratory parameters of active disease.¹⁷ One study reported that children with mutations that encode for interleukin-1 receptor antagonists allows unopposed action of interleukin-1, resulting in life-threatening systemic inflammation with skin and bone involvement but responded to anakinra treatment.¹⁸ Numerous studies indicate that inflammatory arthritis in experimental animal models is significantly prevented by the blockade of interleukin-1.¹⁵ In an animal study, anakinra therapy inhibited parameters of local and systemic inflammation, and partially reduced local but not systemic bone loss in a rat model.¹⁹

While the specific role of interleukin-1 in wound healing has not been completely elucidated, our review of patients demonstrated no

infections or wound healing complications. Animal studies have indicated that the wound-healing response to concentrations of interleukin-1 may differ depending on the anatomical locations.²⁰ Poor wound healing in interleukin-1 knockout mice has been demonstrated in oral tissue but not dermal wounds.²¹

Conclusion

We found intra-articular anakinra effective in small groups of patients with refractory arthrofibrosis, limited arthrofibrosis, and persistent effusions. There were no adverse clinical reactions or infections. These findings provide support for further study of interleukin-1 inhibition in the management of postoperative fibrosis and inflammation.

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