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CASE SERIES

Intra-articular Anakinra for the Treatment of Persistent Inflammation and Arthrofibrosis following Anterior Cruciate Ligament Reconstruction

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ABSTRACT

Purpose: Postoperative inflammation and arthrofibrosis remain difficult problems following ACL reconstruction. Interleukin-1 (IL-1) is a potent driver of intra-articular inflammation and arthrofibrosis following injury and surgery. Anakinra (Kineret, Amgen, Thousand Oaks, CA) is an IL-1 receptor antagonist. We hypothesize that postoperative intra-articular anakinra use decreases inflammation and subsequent arthrofibrosis, reducing the need for arthroscopic debridement and manipulation under anesthesia.

Methods: Four patients (ages 15-56) who were treated with anakinra for persistent postoperative inflammation and scarring within 4 months of ACL reconstruction were retrospectively reviewed. Anakinra was utilized when patients were unable to obtain full extension and at least 90° of flexion 1 month postoperatively in association with persistent effusions or decreased patellar mobility.

Results: Anakinra injection was performed between 36 and 97 days postsurgery. All four reported improvements in range of motion and decreased pain and effusions within 10 days of injection. One patient, who did not receive anakinra until more than 3 months postsurgery, required eventual arthroscopic debridement of a cyclops lesion but none of the patients required frank lysis of adhesions or manipulation under anesthesia. No adverse reactions to anakinra occurred.

Conclusion: Based on previous experience, we believe that all of these patients would have required arthroscopic debridement of scar tissue and manipulation under anesthesia to regain motion were not for the anakinra treatment. Clearly, the concept of IL-1 inhibition in the postoperative knee requires further research, but early results are promising for this unique treatment of a difficult clinical problem.

Keywords: Anakinra, Anterior cruciate ligament, Arthrofibrosis, Inflammation, Interleukin-1.

INTRODUCTION

The anterior cruciate ligament (ACL) is frequently injured and its reconstruction is among the most commonly performed orthopaedic surgical procedures. Although reconstruction yields good results in many cases, recovery can be hampered by the development of postoperative arthrofibrosis.[1] The last three decades have witnessed numerous surgical advances that have significantly decreased the incidence of this complication. The development of arthroscopic techniques has eliminated the need for a formal arthrotomy, significantly decreasing scarring.[2] The utilization of more secure graft fixation devices has allowed "accelerated" rehabilitation protocols to help regain motion postoperatively.[3,4] Finally, numerous authors have demonstrated a higher incidence of arthrofibrosis following reconstruction within 4 weeks of an acute ACL tear.[5-7] This finding has led surgeons to delay reconstruction until good preoperative range of motion is restored. In spite of these advances, postoperative motion loss continues to be a frequent complication of ACL reconstruction. Patients who fail to regain motion following aggressive physical therapy frequently require arthroscopic debridement and manipulation.

Work by Mayr et al suggests the presence of inflammation in the knee rather than timing of surgery is the key predictor of the development of postoperative arthrofibrosis.[8] They demonstrated that a persistent effusion beyond 4 weeks following reconstruction is correlated with an increased risk of arthrofibrosis. It is therefore desirable to avoid prolonged joint inflammation following ACL reconstruction. Traditionally, ice and nonsteroidal anti-inflammatory drugs, and more recently oral corticosteroids,[9] have been used for this purpose.

Growing literature demonstrates the key role of interleukin-1 (IL-1) in inflammation and the development of arthrofibrosis.[10,11] IL-1 is released in the acute inflammatory response following injury or surgery and leads to increased expression of adhesion molecules and leukocyte infiltration.[12] More importantly, it acts as an "alarm cytokine," stimulating increased production of other proinflammatory cytokines, including interleukin-6 (IL-6), transforming growth factor beta-1 (TGF-β1) and tumor necrosis factor-alpha (TNF-α).[12,13]

TGF-β1 along with platelet-derived growth factor (PDGF) is a profibrotic cytokine with a key role in the development of progressive tissue fibrosis through the stimulation of myofibroblasts and fibroblasts to cause extracellular collagen accumulations.[14-17] IL-1 is also able to stimulate fibroblasts directly, and thus drives fibrogenesis directly and indirectly.[18]

The key role of IL-1 in postsurgical inflammation suggests that targeting IL-1 may be an effective therapy for decreasing excessive postoperative inflammation and preventing postoperative arthrofibrosis. Anakinra (Kineret, Amgen, Thousand Oaks, CA) is an IL-1 receptor antagonist (IL-1ra) approved for subcutaneous daily use in rheumatoid arthritis. Although anakinra was developed for the treatment of rheumatoid arthritis, a number of studies have evaluated its safety and potential efficacy for the treatment of other conditions.[19-21] In addition, anakinra has been used safely via intra-articular administration in patients with established osteoarthritis of the knee.[22]

The senior author has utilized intra-articular anakinra injections for the treatment of persistent postoperative inflammation and arthrofibrosis following ACL reconstruction over the last 3 years. We hypothesize that in patients with persistent postoperative inflammation and scarring following ACL reconstruction, intra-articular anakinra injection decreases this inflammation and lessens the need for subsequent surgical manipulation and debridement of scar tissue.

MATERIALS AND METHODS

Patient Selection

Between May 1, 2007 and April 30, 2010, the senior author treated four patients with anakinra for persistent postoperative inflammation and scarring within 4 months of ACL reconstruction. Anakinra was utilized when patients were unable to obtain full extension and at least 90° of flexion one month postoperatively in association with persistent effusions or decreased patellar mobility. All patients had associated knee injuries addressed surgically at the time of reconstruction. One patient underwent meniscal repair, one patient had a posterolateral corner injury reconstructed and two patients were treated for grade 3 medial collateral ligament injuries with posteromedial capsular insufficiency (one patient was treated with primary repair and one patient with an allograft MCL reconstruction). The four patients (one male and three females) ranged in age from 15 to 56 years.

Data Collection

After permission was obtained from our institutional review board, a retrospective review of these patents' medical records was undertaken. Preoperative information (patient demographics, date and mechanism of injury), operative information (time from injury to ACL reconstruction, associated injuries noted and concomitant procedures performed at ACL reconstruction, reconstructive technique and graft choice), postoperative information (details of rehabilitation, pain scores and range of motion at follow-up) and information regarding treatment for postoperative inflammation and stiffness were recorded from the patients' electronic medical records.

Surgical Technique

ACL reconstruction was performed between 18 and 50 days postinjury after resolution of any postinjury effusion. All patients had full range of motion compared to the contralateral limb prior to surgery with the exception of one patient who lacked 5° of terminal extension (Table 1). A primary ACL reconstruction was performed in three patients while one patient underwent revision ACL reconstruction with either hamstring autograft or patellar tendon allograft and standard fixation techniques. The femoral tunnel was drilled with a transtibial technique in one case and through an independent outside-in technique in three cases. Associated injuries included meniscal and chondral pathology, posterolateral corner injury and medial collateral ligament injury, all of which were treated with standard techniques (Table 2).

Rehabilitation

Rehabilitation protocol was varied due to the high incidence of associated injuries in this series of patients. The patient who underwent concomitant meniscal repair was limited in therapy to 90° of flexion for 6 weeks postoperative but allowed to weight bear as tolerated immediately. The patient with a posterolateral corner injury and the two patients with MCL and posteromedial capsular insufficiency were kept non-weightbearing for 3 weeks then advanced to weightbearing as tolerated. They were placed in a hinged knee brace postoperatively but were allowed to flex 90° by 4 weeks postoperative and full range of motion thereafter with the exception of hyperextension, which was blocked with the brace for 8 weeks.

Table 1: Preoperative patient information

Patient	*Age*	*Sex*	*Mechanism of injury*	*Preoperative range of motion (extension-flexion)*	*Preoperative effusion*
1	24	Female	Flag football	0-130	None
2	27	Male	Martial arts	5-135	None
3	56	Female	Skiing	0-135	None
4	15	Female	Soccer	0-135	None

Table 2: Surgical information

Patients	*Time from injury to reconstruction*	*Principal procedure*	*Graft*	*Graft fixation*	*Femoral tunnel technique*	*Additional findings*	*Additional procedures*
1	18 days	Primary ACL reconstruction	Hamstring autograft	Femoral: Endobutton Tibial: Staple and absorbable screw	Independent	Medial and lateral meniscus tears	Medial meniscus repair
2	50 days	Primary ACL reconstruction	Hamstring autograft	Femoral: Endobutton Tibial: Staple and absorbable screw	Independent	Posterolateral corner injury Lateral meniscus tear	Posterolateral corner reconstruction
3	32 days	Primary ACL reconstruction	BTB allograft	Both: Absorbable interference screws	Independent	MCL tear Posteromedial capsular insufficiency Medial meniscus tear	MCL reconstruction Posteromedial capsular repair Partial medial meniscectomy
4	45 days	Revision ACL reconstruction	BTB allograft	Both: Absorbable interference screws	Transtibial	MCL tear Posteromedial capsular insufficiency	MCL primary repair Posteromedial capsular repair

ACL – Anterior cruciate ligament; BTB – Bone-patellar tendon-bone; MCL – Medial collateral ligament

Anakinra Administration

Intra-articular anakinra administration was performed in all patients via a superolateral approach. Aspiration of synovial fluid confirmed intra-articular position in all patients and 200 mg of anakinra was injected into the supra-patellar pouch in all four patients.

CASE REPORTS

Patient 1

The patient is a 24-year-old female who underwent ACL reconstruction and medial meniscus repair without complication. Postoperative motion was initially progressing, but by postoperative day 40, she lacked 5° of terminal extension and could only flex to 70°. Her patellar mobility was decreased to 1 quadrant or less in four directions. Anakinra injection was performed on postoperative day 41. She noted sudden improvement in her motion within 48 hours of the injection. Three weeks later, her knee range of motion had improved to 2 to 125° and her patellar mobility had improved considerably. Motion continued to improve and by 4 months postoperative was equal to the contralateral limb.

Patient 2

The patient is a 27-year-old male who underwent ACL reconstruction and posterolateral corner reconstruction. The patient's knee was initially stiff postoperatively, but by 5 weeks his postoperative motion had improved to 5 to 110°. However, over the next 6 weeks he could not improve his terminal extension and his range of motion, 90 days postoperative, was 10 to 115°. Anakinra injection was given on postoperative day 97. He reported improvement in his flexion and decreased pain within the first week following injection. After 4 weeks, his motion had improved to 5 to 130° but he continued to lack terminal extension and developed a palpable "pop" when he extended the knee. He was taken to the operative room and scar was debrided from the anterior compartment. Postoperatively, he had full extension, and by postoperative day 31 had range of motion from 0 to 130°.

Patient 3

The patient is a 56-year-old female who underwent ACL reconstruction with associated medial collateral ligament reconstruction and partial medial meniscectomy. She was noted to lack extension two weeks postoperatively and by postoperative day 36, her range of motion was 5 to 90° with associated decreased patellar mobility. Anakinra injection was given on postoperative day 38. Two weeks later, her patellar mobility had improved to normal and her range of motion was 0 to 110°. Six months postoperatively, she had equivalent range of motion to the contralateral limb.

Patient 4

The patient is a 15-year-old female who underwent revision ACL reconstruction and medial collateral ligament primary repair. She had significant difficulty with knee flexion post-operatively and by postoperative day 34, had range of motion of 0 to 50° with decreased patellar mobility. Anakinra injection was given on postoperative day 36. She and her physical therapist noted improvement in her knee range of motion within 3 days of injection. Four weeks later, her patellar mobility had improved and her range of motion was 0 to 120°. Three months postoperatively, her knee motion was nearly equal to the contralateral limb.

RESULTS

Anakinra injection was performed in all four patients between 36 and 97 days postsurgery. Minimum follow-up was six months (range 6-15 months). All four patients noted decrease in their effusions. All reported decreased pain and improvements in range of motion within 10 days of injection. The three patients noted to have decreased patellar mobility prior to injection had resolution of this finding. One patient required eventual arthroscopic cyclops lesion debridement due to persistent extension deficit and clicking in the front of the knee with active extension. None required manipulation under anesthesia or formal lysis of adhesions. All patients were noted to have a nearly normal Lachman postoperatively, which remained unchanged following anakinra administration. All patients with pain noted improvement in their pain following anakinra injection (Table 3). No adverse reactions to anakinra were noted in this series.

DISCUSSION

This case series represents the first published report of the intra-articular use of an IL-1 inhibitor to treat arthrofibrosis following ACL reconstruction. Based on previous experience, we believe that all of these patients would have required arthroscopic debridement of scar tissue and manipulation under anesthesia to regain motion were not for the anakinra treatment. Previous reports have documented an increased risk of arthrofibrosis following ACL reconstruction in patients with associated injuries.[23,24] In our case series, one of the patients required arthroscopic debridement in spite of anakinra treatment. This patient required debridement of limited scar tissue in the anterior compartment that was limiting extension and causing palpable clicking in the joint, but did not require manipulation under anesthesia to regain motion. This patient received anakinra considerably later in his postoperative course (97 days) than the other three patients in whom repeat arthroscopy was avoided (36, 38 and 41 days). Perhaps anakinra is more effective in preventing arthrofibrosis when given earlier in the postoperative course.

Previous efforts to decrease joint inflammation following ACL reconstruction have been limited to ice, elevation and oral anti-inflammatory medications. Intra-articular corticosteroid injections have generally been avoided in the early postoperative period due to concerns of inhibition of graft healing. While the specific role of IL-1 in wound healing has not been completely elucidated, *in vitro* studies have demonstrated that high concentration of IL-1 have deleterious effects on porcine meniscal healing.[25,26] In animal studies, wounds in different locations demonstrate differential responses to IL-1 concentration. IL-1 knockout mice demonstrated poor healing of oral wound compared to controls, but dermal wound healing is unaffected.[27] Similarly, increased IL-1 concentration has been associated with poor healing of skin in mice.[28] Thus, elevated levels of IL-1 seem to be detrimental to healing, so blockade of IL-1 may be advantageous postoperatively.

In Europe, autologous conditioned serum (ACS), which contains high levels of IL-1receptor antagonist (IL-1ra), has been investigated as a method for decreasing the deleterious actions of IL-1 in post-ACL reconstruction patients. These actions include increased osteoclastic activity leading to tunnel widening.[29] There have no reports of inhibited ACL graft healing with ACS administration. *In vitro*, ACL fibroblasts have been noted to proliferate in response to platelet-derived growth factor (PDGF) and basic fibroblast growth factor, but not in response to IL-1.[30] Several authors have noted an increased concentration of IL-1 in ACL deficient knees, which correlates with the degree of chondral injury.[31] Decreased native IL-1ra levels in the synovial fluid have been noted in these same knees.[32] Increases in synovial fluid levels of IL-1 have been noted following ACL reconstruction as well.[29] Restoration of a more normal IL-1 to IL-1ra balance via anakinra administration may in fact be advantageous to the ACL reconstruction.

No adverse reactions to anakinra injection were noted in this series. The senior author has utilized intra-articular anakinra injections on nearly 100 occasions without complication. Specifically there have been no instances of allergic reaction, systemic effects or wound complications. Other authors have reported similarly low complication rates with intra-articular anakinra use.[22]

This study has numerous weaknesses. Primarily, the small number of patients severely limits the conclusions that can be reached from this data. Clearly, the concept of IL-1 inhibition in the postoperative knee requires further research. Additionally, the retrospective nature of the study limits which variables can be collected and limits our knowledge of the reliability of certain data points. Specifically, ranges of motion data were likely not quantified with a goniometer in all cases but rather represent the clinician's estimate of the range of motion in some cases. Follow-up is quite short; however, it far exceeds the time period that anakinra would be expected to present in the joint (less than 1 week) and we have noted no recurrence of stiffness. Longer follow-up will be critical to verify successful recovery. Perhaps the most significant limitation of the study is the lack of a control group that did not receive anakinra. Future investigations into this topic should include a prospective,

Table 3: Treatment of postoperative inflammation

Patients	*Postoperative day*	*Intervention*	*Range of motion (degree) (Extension-flexion)*	*Effusion*	*Pain score**	*Lachman*	*Other physical exam findings*
1	12		0-90	Minimal	1	Near normal	
	40		5-70	Minimal	1	Near normal	Decreased patellar mobility
	41	Anakinra injection				Near normal	Improved patellar mobility
	75		2-125	None	0		
	103		–2-130	None	0	Near normal	
	143		–5-135	None	0	Near normal	
	199		–5-143	None	0	Near normal	
2	11		20-90	Moderate	6	NR	
	39		5-110	Moderate	2	Near normal	
	90		10-115	Moderate	2	Near normal	
	97	Anakinra injection					
	125		5-130	Minimal	1	Near normal	Palpable “pop” noted at 40° of extension
	134	Arthroscopic debridement					
	146/12		0-110	Minimal	1	Near normal	
	165/31		0-130	Minimal	1	Near normal	
3	13		5-90	Moderate	4	NR	
	36		5-90	Moderate	3	Near normal	Decreased patellar mobility
	38	Anakinra injection					
	55		0-110	Minimal	NR	Near normal	Improved patellar mobility
	146		0-130	None	1	Near normal	
	218		–5-135	None	1	Near normal	
4	11		0-30	Minimal	1	Near normal	
	18		0-40	Minimal	1	Near normal	
	34		0-50	Minimal	0	Near normal	Decreased patellar mobility
	36	Anakinra injection					
	63		0-120	None	0	Near normal	Improved patellar mobility
	95		–2-135	None	0	Near normal	
	132		–5-130	None	0	Near normal	
	188		–5-130	None	0	Near normal	
	473		–5-135	None	0	Near normal	

*Self-reported pain scale ranging from 0 (no pain) to 10 (worst pain imaginable); NR – Not reported

blinded, placebo controlled trial to determine whether anakinra injection can help patients to avoid postoperative arthrofibrosis following ACL reconstruction.

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