Rilonacept in the treatment of subacromial bursitis: a randomized, non-inferiority, unblinded study versus triamcinolone acetonide

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ABSTRACT

Introduction: Subacromial bursitis is caused by inflammation of the bursa that separates the superior surface of the supraspinatus tendon from the overlying coraco-acromial ligament and acromion. While multiple cytokines are implicated, interleukin-1 beta appears to play a prominent role. Rilonacept, an interleukin-1 trap, may be an alternative to corticosteroid injection for the management of this condition.

Methods: This single center, randomized, non-inferiority, unblinded study recruited 33 subjects over 9 months. Twenty subjects received 160 mg intra-bursal injection of rilonacept and 13 received a 6 mL mixture of lidocaine, bupivacaine, and 80 mg triamcinolone acetonide. QuickDASH, subject reported pain, and adverse events were recorded at time of injection, 2 days later, 2 weeks later, and 4 weeks later. Primary outcome was improvement in QuickDASH 4 weeks post-injection. Secondary outcomes were improvement in subject reported pain and occurrence of adverse events at 4 weeks.

Results: Both study groups were equally matched for age, gender, ethnicity, and site of bursa injection. Both medications demonstrated a statistically significant improvement in QuickDASH 4 weeks post-injection, but triamcinolone acetonide injection offered greater improvement ($p=0.004$). Both medications demonstrated improvement in subject reported pain but between group comparison at 4 weeks showed that triamcinolone was superior ($p=0.044$). No statistically significant differences in adverse events were noted between groups, but subjects who received rilonacept experienced more episodes of diarrhea and headache.

Conclusions: While improvement in QuickDASH and pain was noted with a single intra-bursal injection of rilonacept at 4 weeks, injection with triamcinolone acetonide was more efficacious.

This trial was registered with www.clinicaltrials.gov (NCT01830699)

Key Words: Subacromial bursitis, rilonacept, triamcinolone acetonide

Introduction

The subacromial bursa is a synovial membrane located beneath the acromion. The membrane extends above the humeral head to form a bursa between the humeral head and the overlying acromial process. Subacromial bursitis is a condition caused by inflammation of the bursa that separates the superior surface of the supraspinatus tendon from the overlying coraco-acromial ligament, acromion, coracoid (the acromial arch) and from the deep surface of the deltoid muscle. The subacromial bursa helps the motion of the supraspinatus tendon of the rotator cuff in activities such as overhead work.

The pathophysiology of subacromial bursitis describes inflammation as the main cause of symptoms. Patients with subacromial bursitis commonly present for treatment with concomitant shoulder problems such as arthritis, rotator cuff tendonitis, and rotator cuff tears. This generally occurs due to microtrauma of adjacent structures, particularly the supraspinatus tendon. The inflammatory process causes synovial cells to multiply, increasing collagen formation and fluid production within the bursa and reduction in the outside layer of lubrication. Microarray analyses for gene expression and immunohistochemistry have demonstrated that the expression of several cytokine genes (TNF, IL-1alpha, IL-1beta, and IL-6) are increased in patients with subacromial bursitis when compared with control specimens. Furthermore, the expression of metalloproteases (MMP-1 and MMP-9) and cyclooxygenases (COX-1 and COX-2) in the bursitis group was found to be increased as compared with controls [1]. An earlier study also histochemically demonstrated a significant presence of proinflammatory cytokines to include IL-1beta [2]. Inflammatory subacromial bursitis is usually the result of repetitive injury to the bursa and develops in response to complex factors thought to cause shoulder impingement symptoms.

While a variety of non-surgical treatment modalities are readily available to treat subacromial bursitis they are not always sufficient for successful management of this disorder. A corticosteroid injection, when conservative therapy fails or is not feasible, can be used to decrease inflammation which subsequently leads to improvement of bursitis symptoms. Though corticosteroid injections are an effective short-term treatment for relief of subacromial bursitis symptoms and helps substantially decrease pain while improving motion, both key to successful rehabilitation, such injections have potential side effects.

Over the last decade, several potential alternative agents for the treatment of subacromial bursal inflammation have been studied but to date no large trials have been performed looking at whether or not intra-bursal injection of an IL-1 antagonist provides pain relief similar to that of a corticosteroid injection. The subcutaneous injection of anakinra, an IL-1 receptor antagonist, in patients with shoulder pain due to rotator cuff tendonitis and subacromial bursitis was efficacious in relieving pain but the data presented was a case series, so a true cause and effect relationship of the medication remains unclear [3]. Intra-articular administration of anakinra in patients with Osteoarthritis of the knees demonstrated no efficacy when compared to placebo. Multiple criticisms of this trial have been made, however, specifically that anakinra has a short half-life, the patients received only one injection, and an excess of IL-1 receptor antagonists naturally occurs in the synovial fluid [4]. Based mainly on the data from the intra-articular administration of anakinra, there have not been any adverse trends in outcomes or safety to suggest that intra-bursal injection of IL-1 blocking medications would carry an increased risk of adverse events or be associated with aberrant safety signals. Based on this information, we hypothesized that rilonacept, a longer acting IL-1 “trap”, would be non-inferior to traditional injection consisting of triamcinolone acetonide (the most frequently injected corticosteroid at our facility).

Methods

Subjects for this study were recruited from the Internal Medicine (IM) Clinic or IM Subspecialties Clinic from our academic community hospital between March and December 2013. To participate in this study subjects had to be at least 18 years of age or older, report at least a 2 week history of shoulder pain, report moderate to severe pain in this area, and on examination by any of the study investigators have tenderness to palpation over the subacromial bursa. All subjects underwent a clinically directed but reasonably thorough history and physical examination of the affected shoulder at the time of their enrollment. We also carried out active and passive range of motion and assessed where pain was noted in the arc of movement on abduction and forward flexion. Regardless of the underlying condition responsible for the subject's shoulder pain (impingement syndrome, rotator cuff tendinopathy, bicipital tendonitis, etc.), so long as the subject satisfied the inclusion criteria they could potentially be enrolled. Subjects were excluded if they reported having an allergy to lidocaine, bupivacaine, triamcinolone acetone, or rilonacet. They were also excluded if they were experiencing a flare of an inflammatory arthritis (including but not limited to conditions such as Rheumatoid Arthritis or a Seronegative Spondyloarthropathy) at the time of enrollment, had signs or symptoms of an active infection, were actively being treated for cancer (with the exception of non-melanoma skin cancer), were actively experiencing a myocardial infarction, had clinical and/or radiographic evidence of a clavicular or humeral fracture, were pregnant, or were breastfeeding. Female subjects of childbearing potential were screened with a pregnancy test prior to undergoing rilonacet injection to confirm they were not pregnant at the time they received this medication.

Upon confirmation by one of the study investigators that the subject satisfied the inclusion criteria and met none of the exclusion criteria, the subject was then randomized to receive either 160 mg of rilonacet ("rilonacet arm") or a mixture of 2 mL of 1% lidocaine without epinephrine, 2 mL of 0.5%

bupivacaine, and 2 mL of triamcinolone acetonide (40 mg/mL) (“triamcinolone arm”). Randomization was performed using a random number generator in blocks of 10. Once randomized, the subject underwent “blind” intrabursal injection of the medication to which they were assigned using a lateral/posterolateral approach, injecting the study medication into the site of maximal pain. Neither the subject nor the study investigator were blind to the medication that was administered in the subacromial bursa because it was unknown what effect on the potency diluting the riloncept to a volume of 6 mL would have. Additionally, we anticipated some difficulty with maintaining blinding when one syringe would have a white, cloud-like color consistent with triamcinolone (the steroid of choice in our clinics) and the other would be clear (riloncept). One patient was randomized to riloncept but declined the medication. She was still enrolled in this study but entered the triamcinolone arm.

The primary endpoint of this study was to assess improvement in pain from subacromial bursitis using the QuickDASH questionnaire 4 weeks after their injection. The QuickDASH is a shortened version of the Disabilities of the Arm, Shoulder, and Hand (DASH) Outcome Measure. This questionnaire has been validated for use in clinical and research settings and utilizes 11 items to measure physical function and symptoms in people with musculoskeletal disorders of the upper limb. The score ranges from 0 – 100 with higher scores indicating greater disability [5]. Changes in reported pain 4 weeks after the injection of the study medication and the frequency and severity of adverse events were the two secondary endpoints studied. Pain was reported by the subject as ranging from 0 – 10, with 0 meaning no pain and 10 meaning the worse pain of their life. At the time of the injection ($t = 0$) of the study medication, the study investigator asked the subject about their pain (ranging from 0 – 10), had the subject accomplish a QuickDASH questionnaire, and asked about pain medication use. All of this information was collected prior to the administration of the study medication. The QuickDASH questionnaire, pain score, adverse events that the subject experienced potentially related to the medication, and pain medication use were

ascertained by phone interview 2 days after injection (t = 2 days), 2 weeks after injection (t = 2 weeks), and then at the primary endpoint of 4 weeks (t = 4 weeks).

For our statistical analysis, setting $\alpha=0.05$, the study power to 0.8, and initially assuming an effect size of 0.2 we anticipated that a total of 138 subjects would have to be recruited. At our first analysis of the data, with a larger than expected effect size of 1.01 calculated, the false positive rate was preserved and power was calculated at 1.0, so the study was stopped. Mean with standard deviations are used to describe continuous variables. Within group comparisons (comparing time points with day of injection) were made using repeated generalized linear models. Between group comparisons (comparing rilonacept with triamcinolone) were made using an independent t-test. Categorical variables were compared using Chi-squared testing with the Fisher exact test when $n < 5$. A 'p' value of < 0.05 was considered statistically significant.

All data collection and recording was performed by the study investigators (the authors of this article) and research assistants. Written informed consent was obtained from all the study participants and the study was approved by the institutional review board at our medical facility.

Results

Thirty four subjects gave written consent to participate in this study. One subject in the triamcinolone arm was excluded as they were lost to all follow-up after they underwent injection, bringing the number of subjects for whom data was analyzed to 33. Over 96% of all potential data points were recorded at study conclusion, with only 2 data points not collected 2 days after injection, 1 data point missed 2 weeks after injection, and 2 data points missed 4 weeks after injection.

Baseline demographics for the 33 subjects analyzed are shown in table 1. The majority of subjects were Caucasian females with an average age of approximately 66 years old. There were 20 subjects randomized to the rilonacept arm. Of these 8 were male and 12 were female with 14 being injected in the right subacromial bursa while the remaining 6 were injected in the left subacromial bursa. There were 13 subjects randomized to the triamcinolone arm. Of these 5 were male and 8 were female with 6 injected in the right subacromial bursa and 7 injected in the left subacromial bursa. There were no statistically significant differences in the baseline demographics between the two treatment arms.

The primary outcome of this study was improvement in QuickDASH scores 4 weeks after injection. QuickDASH scores at each of the four time points studied are listed in Table 2 with a graphic representation shown in Figure 1. QuickDASH scores ($\pm$ 95% Confidence Interval (CI)) at time of injection, 2 days, 2 weeks, and 4 weeks after injection for rilonacept were 56.37 ($\pm$ 6.33), 46.7 ($\pm$ 9.23), 37.21 ($\pm$ 11.70), and 38.52 ($\pm$ 11.00), respectively. QuickDASH scores ($\pm$ 95% CI) at time of injection, 2 days, 2 weeks, and 4 weeks after injection for triamcinolone arm were 53.51 ($\pm$ 9.84), 33.05 ($\pm$ 10.62), 27.28 ($\pm$ 8.76), and 15.92 ($\pm$ 9.09), respectively. Comparing QuickDASH scores between treatment arms, there was a statistically significant difference appreciated only 4 weeks after injection ($p = 0.004$), demonstrating that triamcinolone was superior to rilonacept. For within group comparisons of QuickDASH(R) scores, when compared to time of injection, all points afterwards demonstrated statistically significant reductions for both rilonacept and triamcinolone (P-value data not shown).

The secondary outcome measurements included the between group comparison of reported pain scores (on a scale of 0 – 10) and frequency of adverse events at 4 weeks. Changes in reported pain scores at each of the four time points studied are listed in Table 3 with a graphic representation shown in Figure 2. Reported pain scores ($\pm$ 95% CI) at time of injection, 2 days, 2 weeks, and 4 weeks after

injection for rilonacept arm were 5.65 (+/- 0.84), 3.56 (+/- 1.00), 3.92 (+/- 1.20), and 3.85 (+/- 1.20), respectively. Reported pain scores (+/- 95% CI) at time of injection, 2 days, 2 weeks, and 4 weeks after injection for triamcinolone arm were 5.67 (+/- 1.47), 3.54 (+/- 0.77), 3.84 (+/- 1.39), and 2.27 (+/- 0.84), respectively. Comparing reported pain scores between treatment arms, there was a statistically significant difference noted only at 4 weeks after injection ($p = 0.044$), demonstrating that triamcinolone was superior to rilonacept. For within group comparisons of reported pain scores, when compared to time of injection, all points afterwards demonstrated statistically significant reductions for both rilonacept and triamcinolone (P-value data again not shown).

Monitoring for adverse events, 2 subjects were hospitalized during the study period. One subject in the rilonacept arm was hospitalized for diarrhea, heme-occult positive stool, and an INR of 3.4. One subject in the triamcinolone arm was hospitalized for shortness of breath for which an etiology was never identified. During the review of these hospitalizations by the study investigators it was thought that neither hospitalization was due to the medication received. Less serious adverse events were diarrhea in 3 subjects, headache in 2 subjects, and a case of generalized stiffness, hand tingling, and bronchitis in the rilonacept arms. In the triamcinolone arm, one subject experienced a mild injection site reaction and one subject experienced oral thrush which needed to be treated. At none of the 4 time points of the study was a statistically significant difference in adverse events noted.

Discussion

To our knowledge this is the first study to test whether or not rilonacept, an IL-1 beta neutralizing medication typically administered subcutaneously, was effective when injected into the subacromial bursa. The impetus for this study was to find a medication that would have the same clinical effect as an intrabursally administered corticosteroid but with few side effects. While injection of a corticosteroid

into the subacromial bursa to provide pain relief is reasonably safe, corticosteroids can cause side effects such as transient hyperglycemia in patients with diabetes, adrenal suppression, skin hypopigmentation, fat atrophy, facial flushing, and tendon rupture [6]. A review of the literature on corticosteroid injection for athletic injuries yielded complication ranging from facial flushing (0.6%) , skin depigmentation (0.8%), to skin atrophy (2.4%) [6]. A medication that would be free from these side effects would be desirable. Other investigators have evaluated the subacromial bursal injection of sodium hyaluronate weekly for 5 weeks. As compared with saline placebo, the weekly injections of sodium hyaluronate provided improvement in pain and function in subjects enrolled without significant adverse effects [7]. A similar experience was noted with sodium hyaluronate injected weekly for 3 week by another study group (as compared with saline placebo) [8] and 2 injections of sodium hyaluronate 14 days apart (as compared with physical therapy) [9]. Experiences to date with plasma rich fibrin matrix have not demonstrated an effect, although these trials administered plasma rich fibrin matrix intra-operatively and did not have a placebo injection [10,11]. These investigations highlight the ongoing desire to have an alternative injectable medication to control pain and improve function. Rilonacept, while this medication had an observable effect, was inferior to triamcinolone acetonide.

Our study had several strengths. First, a randomized design was used to study the efficacy of rilonacept compared to a standard of care medication (triamcinolone acetonide). Second, despite ultimately being inferior to triamcinolone acetonide at the primary endpoint of this study, a biologic effect was observed with rilonacept. This effect was also noted across a variety of conditions such as impingement, rotator cuff tendinopathy, partial rotator cuff tears, etc. Subjects that received rilonacept reported pain improvement of about 40% two days post injection and at every time point after. Rilonacept subjects also experienced an improvement in the QuickDASH at 2 weeks and 4 weeks that exceeded the minimal clinically important difference of 15.91 [12]. Third, no short-term adverse safety signals were noted with the use of rilonacept in this study. Subjects that reported diarrhea and

headache experienced side effects consistent with those known to be related to use of the medication subcutaneously. Finally, this study demonstrated that rilonacept can safely be administered as an intrabursal injection into an area of pain where IL-1 plays a prominent role in the pathophysiologic process.

Our study had several limitations. First, since neither the study investigator nor the subject were blinded to the medication they were randomized to which, potentially introduces bias. Lack of blinding would introduce a recall bias, specifically a participant expectation bias, as participants might have expected more from the routinely administered triamcinolone injection because of the volume and color of the medication they would have watched being drawn up in clinic [13]. We did not attempt blinding in this trial as the rilonacept injection was prepared by our hospital pharmacy whereas the triamcinolone injection was prepared in our clinic, at the patient's bedside. Second, our trial did not have a placebo for comparison, so it is possible that neither the triamcinolone nor the rilonacept injections had any true effect beyond placebo. This may be unlikely as a trial comparing triamcinolone 40 mg and 20 mg subacromial injections to placebo demonstrated efficacy of both triamcinolone doses in function and pain improvement when compared with placebo [14]. The placebo arm of this trial also had no improvement in pain, function, or range of shoulder motion at any time point tests (up to 8 weeks after injection), whereas in this study we demonstrated improvement in pain and function in both arms at various time points, thus again supporting biologic efficacy of both injections [14]. Third, an 80 mg dose of triamcinolone acetonide was administered with lidocaine and bupivacaine. In a review of musculoskeletal injections in 2009 the recommended dose for triamcinolone acetonide injection into a bursa was between 2.5 – 5 and 5 – 15 mg [6]. A recent trial compared 20 mg of triamcinolone acetonide to 40 mg of triamcinolone acetonide, with 20 mg considered a "medium dose" and 40 mg considered a "high dose" [15]. In our institution, however, it is routine practice to administer 80 mg of triamcinolone acetonide. The 80 mg triamcinolone acetonide dose that we used generated an effect size of 2.22

whereas the effect size in the rilonacept arm was smaller at 0.89. This discrepancy in effect size thus favored success of triamcinolone and a future trial should consider a lower triamcinolone dose. Less clear is the effect that the 2 mL of 1% lidocaine that was co-administered with triamcinolone might have had on the results of this study. The volume and concentration of lidocaine typically used in subacromial bursa injection are based on clinical experience with volumes ranging from 1 – 5 mL and concentrations ranging from 0.5 – 4% [6]. While lidocaine co-administered with triamcinolone acetonide in this trial was 2 mL of 1%, in a recent trial 5 mL of 0.5% lidocaine was administered [16]. While it is possible that different volumes and concentrations of lidocaine may have different pain relief effects, we did not observe any differences in the QuickDASH or reported pain between the two arms at 2 days post-injection. Lidocaine was not mixed with rilonacept because it was unknown what effect, if any, it might have on the active medication. We were also interested in observing the biologic effect of rilonacept alone and did not want to confound any clinical changes by adding lidocaine. Fourth, in both arms the medications injected in the subacromial bursa were administered without ultrasound guidance. This could have resulted in administration of either study medication in the wrong location and thus negated any true effect that would have been observed if the medication was administered in the correct location. In one trial which compared the blind injection of medication into the subacromial bursa compared to ultrasound guided injection, both of which were followed immediately afterwards by MRI, accuracy of injection was 65% for ultrasound guided injection and 70% for blind injection [17]. This difference between the two arms was not statistically significant and at the study endpoint of 6 weeks, regardless of whether or not the injection was accurate, pain relief was obtained in all the subjects [17]. Finally, the cost of rilonacept at the current time prohibits routine use, even if rilonacept was equivalent or superior to therapy with triamcinolone acetonide.

In conclusion, this study was the first of its kind to assess the clinical efficacy of IL-1 β neutralizing medication, rilonacept, in the treatment of loss of function and pain due to subacromial bursitis. While

intrabursal rilonacept was inferior to the current standard of care corticosteroid 4 weeks after injection, rilonacept did demonstrate a modest, short lived biologic effect without serious safety signals. While additional studies could be performed to study whether repeat injections or a higher dose would be as effective as corticosteroids, the current cost of rilonacept remains prohibitive.

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Table 1: Demographics

Demographics*		Rilonacept (n=20)	Triamcinolone (n=13)
Age (mean +/- SD)		64.5 +/- 12.1	66.7 +/- 13.8
Ethnicity	African American	0	1
	Caucasian	19	11
	Asian	1	0
	Pacific Islander	0	1
Gender (M : F)		8 : 12	5 : 8
Site (left : right)		14: 6	6 : 7
Key: SD = Standard Deviation, M = male, F = female * -There were no statistically significant differences between the two treatment arms in any areas recorded			

Table 2: QuickDASH scores

	Time of injection	2 days post-injection	2 weeks post-injection	4 weeks post-injection
Rilonacept (Score +/- 95% CI)	56.37 +/- 6.33	46.77 +/- 9.23	37.21 +/- 11.70	38.52 +/- 11.00
Triamcinolone (Score +/- 95% CI)	53.51 +/- 9.84	33.05 +/- 10.62	27.28 +/- 8.76	15.92 +/- 9.09
'p' value	0.619	0.067	0.231	0.004
Key: CI = Confidence Interval QuickDASH data shown for each time point during the study for each treatment arm. P-values given for comparisons between the two treatment arms at each individual time point.				

Table 3: Reported Pain Scores

	Time of injection	2 days post-injection	2 weeks post-injection	4 weeks post-injection
Rilonacept (Score +/- 95% CI)	5.65 +/- 0.84	3.56 +/- 1.00	3.42 +/- 1.20	3.85 +/- 1.20
Triamcinolone (Score +/- 95% CI)	5.67 +/- 1.47	3.54 +/- 0.77	3.84 +/- 1.39	2.29 +/- 0.84
'p' value	0.984	0.980	0.902	0.044
Key: CI = Confidence Interval Reported pain scores for each time point during the study for each treatment arm shown. P-values given for comparisons between the two treatment arms at each time point. Subjects reported pain on a scale from 0 to 10, with 0 being no pain and 10 being classified as the worst pain of their life.				

Figure 1: QuickDASH Scores

Key: QuickDASH scores presented with 95% Confidence Interval bars. Time is in reference to numbers or days after undergoing subacromial injection.

* - $p = 0.004$

Figure 2: Reported Pain Score

Key: Reported pain scores presented with 95% Confidence Interval bars. Time is in reference to the number of days or weeks after receiving subacromial injection. Subjects reported pain on a scale from 0 to 10, with 0 being no pain and 10 being classified as the worst pain of their life.

* - $p = 0.044$