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Original article

# 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 intrabursal 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 intrabursal injection of rilonacept at 4 weeks, injection with triamcinolone acetonide was more efficacious.
This trial was registered with www.clinicaltrials.gov (NCT01830699).


## 1. 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.

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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 help 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 intrabursal 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 intrabursal 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).

## 2. 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 acetonide, or rilonacept. 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 rilonacept 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 rilonacept ("rilonacept 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 rilonacept 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 (rilonacept). One patient was randomized to rilonacept 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 $Chi^2$ 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.

## 3. Results

Thirty-four subjects gave written consent to participate in this study. One subject in the triamcinololne arm was excluded as they