

A Randomized, Double-Blinded, Placebo-Controlled Trial of Anakinra for Treatment of Acute Gouty Arthritis

A. Study Purpose and Rationale

Acute gout is a common cause of arthritis, affecting approximately 1% of the adult population in the U.S.¹ The acute phase of the disease is characterized by intense, typically monoarticular joint pain, swelling, and erythema and is caused by deposition of monosodium urate crystals in the synovial fluid of large joints. Without proper treatment, progressive insults to joints can lead to chronic gout, characterized by polyarticular involvement, the formation of tophi, decreased quality of life, and irreversible damage to involved joints.

Treatment of acute gout flares has traditionally relied upon the use of NSAIDs, corticosteroids, and colchicine. These medications are regarded as effective medications for acute gout², but are associated with a number of limiting side effects, particularly in patients with chronic gastrointestinal, cardiovascular, and renal disease. NSAIDs are contraindicated in peptic ulcer disease, renal insufficiency, and moderate to severe congestive heart failure. Side effects of corticosteroids include exacerbation of diabetes, hypertension, psychosis, myopathy, osteoporosis, and cataracts. Colchicine is associated with gastrointestinal disturbances, bone marrow suppression, neuropathy, and myopathy.³

Over the past forty years, the incidence and prevalence of gout has been steadily increasing. One of the main factors implicated in this observation is the aging of the general population.² As a consequence, the proportion of elderly patients with medical co-morbidities presenting with acute gouty arthritis is increasing.³ These patients often present with medical co-morbidities that preclude the use of the standard anti-gout medications mentioned above. In addition, a small fraction of elderly patients do not clinically respond to standard therapy, which results in decreased quality of life and increased functional impairment.⁴ Recently, interest in developing novel treatments for acute gout has led to examination of the potential role of interleukin 1 (IL-1) in mediating the inflammatory response responsible for gout.⁵

¹ So A, et. al., "A pilot study of IL-1 inhibition by anakinra in acute gout," *Arthritis Research and Therapy*, 9:R28

² Edwards N., "Treatment Failure Gout: A Moving Target," *Arthritis and Rheumatism*, 58:9, 9/2008

³ Chen K, et. al, "Anakinra's Efficacy is Variable in Refractory Gout: Report of Ten Cases," *Seminars in Arthritis and Rheumatism*, 2010

⁴ Fels E, Sundy J "Refractory gout: what is it and what to do about it?", *Current Opinion in Rheumatology*, 20(2), 198-202, 2008

⁵ Molto A, Olive A "Anti-IL 1 molecules: New corners and new indications," *Joint Bone Spine* 77, 102-107, 2010

IL-1 is a proinflammatory cytokine that has been implicated in the pathogenesis of several chronic diseases. It exists in two forms: IL-1 α and IL-1 β . IL-1 α is thought to serve as an intracellular autocrine messenger. In contrast, IL-1 β is released from phagocytes and is thought to mediate downstream activation of key inflammatory cytokines, including TNF and IL-6.⁶ With regards to gout, precipitated MSU crystals induce activation of the cytopyrin inflammasome, an intracellular protein that cleaves caspase-1 protein. Caspase-1 is responsible for the cleaving of IL-1 β into its mature, biologically active form.⁶ Medications associated with IL-1 blockade have been developed and are currently being investigated as potential therapies in a number of inflammatory diseases.⁵ These drugs include rilonacept, canakinumab, and anakinra.

Anakinra is a commercially produced IL-1 receptor antagonist (IL-1ra) that is currently FDA approved for the treatment of rheumatoid arthritis. IL-1ra is produced endogenously and functions as a competitive receptor antagonist, binding to IL-1 receptors, but not activating target cells.⁷ Of the three anti-IL-1 biologics, it has the shortest half-life and is associated with relatively few side-effects, making it an attractive anti-gout agent. In animal models, anakinra has been found to decrease neutrophil recruitment in mice treated with intraperitoneal injections of MSU crystals.¹ Several case reports have suggested anakinra is effective in the treatment of acute gout.³ A pilot study of anakinra in ten patients with treatment-refractory gout or contraindications to standard therapy found further evidence to support its utility in gout. Patients were given anakinra 100 mg subcutaneously for three days and all had clinical improvement in less than three days.¹ To date, no randomized controlled trials have been published to test the efficacy of anakinra in acute gout.

The purpose of this study is to determine the effectiveness of anakinra as a treatment for acute gout in patients with treatment-refractory gout, or contraindications to standard therapy. Based on previous literature, the underlying hypothesis is that anakinra, by means of IL-1 blockade, will prove to be an effective medication for the treatment of acute gouty arthritis.

B. Study Design and Statistical Analysis

This will be a prospective, randomized, placebo-controlled clinical trial to evaluate the effectiveness of anakinra in patients with acute gouty arthritis who previously failed,

⁶ Terkeltaub R, "The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of placebo-controlled, monosequence crossover, non-randomized, single-blind pilot study," *Ann Rheum Dis*; 68, 2009

⁷ Gratton S et. al, "Case of Anakinra as a Steroid-Sparing Agent for Gout Inflammation," *Arthritis and Rheumatism*, 61-9, 2009

or have contraindications to, standard anti-inflammatory medications. Standard medications are to include colchicine, NSAIDs, and corticosteroids. . Patients admitted to CPMC with a primary or secondary diagnosis of acute gout will represent the potential pool of study participants. Written informed consent will be obtained from all patients enrolled. Randomization will be stratified based on whether patient presents with monoarticular or polyarticular arthritis. Randomization will be generated by the Department of Medical Statistics with a blocked method. In all patients, the diagnosis of acute gout will be confirmed by a rheumatologist using standard American College of Rheumatology (ACR) criteria.

Patients in the treatment group will be treated with anakinra 100 mg subcutaneously daily for three days. Patients in the control group will receive an equivalent volume of placebo delivered by the same route for three days.

The primary outcome measure for the study will be based on a clinical assessment of response to the intervention. Patients will be deemed responders vs. non-responders. Assessment of clinical response will be based on a formal evaluation by a rheumatologist, who will assign each patient into one of the groups. For the purposes of the study, those deemed to be partial responders will be added to the group of responders for statistical analysis. The rationale for this added category is that the study population represent patients who cannot tolerate standard therapy and thus there may be clinically significant to only partial response to therapy. Secondary outcome measures will be the proportion of patients in the responder group who were partial responders and patient responses on the standardized 0-4 Likert pain scale (“no pain” to “extreme pain”) at baseline and at 72 hours, and the incidence of adverse reactions associated with the use of anakinra.

In order to achieve 80% power with an alpha-error rate of 0.05, a sample size of 22 patients for each group was calculated using the Chi-square test, assuming a placebo response rate of 20% and a treatment response rate of 50% (effect size 30%). To account for an estimated 10% attrition rate, 25 patients will be recruited into each arm of the study.

C. Study Procedure

Patients admitted to Columbia-Presbyterian Medical Center or the Allen Hospital with a diagnosis of acute gout will be screened for eligibility. Diagnosis of acute gout will be confirmed by a rheumatologist using standard ACR criteria. Those with a history of cardiovascular disease, chronic renal disease (with a creatinine clearance above 30 ml/min), gastrointestinal bleeding, or with documented or self-reported history of treatment-refractory gout will be consented for enrollment. Written informed consent will be obtained from all patients.

Patients will be treated with anakinra 100 mg subcutaneously daily for a total of three days. The placebo group will receive an equivalent volume of placebo. Participants and clinicians will be blinded as to whether drug or placebo is administered. Clinicians will be required to report any suspected adverse reactions related to the study drug.

Upon enrollment and prior to treatment initiation, patients will complete a standardized 0-4 Likert Pain Scale, in which patients are asked to report the current state of their pain on a 5-point scale: 0- no pain, 1-mild pain, 2-moderate pain 3-severe pain, 4-extreme pain. This assessment will be repeated after three days of treatment are administered. At that time, clinical assessment of treatment response will be made by a participating rheumatologist and patients will be classified as either responders, partial responders, or non-responders.

During the study period, there will be no medication restrictions with regards to treatment of pain. If patients are on chronic corticosteroid therapy, the pre-hospitalization dose will be continued unless otherwise warranted by clinical circumstances. Patients requiring increased doses of corticosteroids or other anti-inflammatory medications during their hospitalization will be automatically considered non-responders to therapy.

Based on enrollment rates of previous studies studying treatment-refractory gout, the duration of the study is estimated to be 15 months.¹

D. Study Drugs

Anakinra is a synthetic, injectable IL-1 receptor antagonist that blocks the effects of IL-1. It is currently FDA approved for use in moderate to severe rheumatoid arthritis or treatment-refractory rheumatoid arthritis. Its use is currently under investigation for a variety of inflammatory conditions including gout.

Standard dosing for anakinra is 100 mg once daily, delivered subcutaneously. The study will use standard dosing for a duration of three days. Side effects include:

- gastrointestinal disturbances (nausea 8%, diarrhea 7%, abdominal pain 5%)
- allergic reaction and anaphylaxis (<1%)
- respiratory infection (upper respiratory tract 13%, sinusitis or flu-like symptoms 7%)
- local skin reactions (pain, inflammation, erythema, or ecchymoses; 70%); usually with four-week therapy)
- decreases neutrophil count (8%), neutrophilia (0.4%), malignant lymphoma (0.12 cases/patient year)

E. Medical Devices

Not applicable

F. Study Questionnaires

Patients will complete standardized 5-point Likert pain scale upon enrollment and after receiving three days of treatment.

G. Study Subjects

Inclusion Criteria:

- patients over 18 years of age
- primary or secondary diagnosis of acute gout
- confirmed diagnosis of acute gout by rheumatologist using ACR criteria
- documented or self-reported intolerance or past failure of standard medications
- patients with medical contraindications to NSAIDs, colchicines, or steroids

Exclusion Criteria:

- polyarticular gout involving more than four joints
- concurrent arthritic disease
- unstable medical condition including active malignancy
- treatment for active infection
- pregnant women
- patients who received NSAIDs within 48 hours of baseline assessment
- patients who received analgesics within six hours of baseline assessment
- patients on TNF inhibitors (infliximab, etanercept, adalimumab)

H. Recruitment of Subjects

All study participants will be recruited from Columbia Presbyterian Medical Center and the Allen Hospital. Primary care physicians will be notified of potential study participation and asked their opinion on patient's suitability for the study.

I. Confidentiality of Study Data

All study materials will be stored in a secure manner, accessible only by the investigators. Patients will be assigned a random numerical identifier for the purposes of protecting confidentiality. No personal numerical identifiers will be used.

J. Potential Conflict of Interest

None

K. Location of the Study

The study will be conducted in the inpatient units at Columbia-Presbyterian Hospital and Allen Hospital.

L. Potential Risks

Risks associated with participation in the study include physical discomfort of treatment injection and potential side effects of the study drug, documented above in the section entitled *Study Drugs* .

Although the efficacy of anakinra has yet to be established in randomized trials, the study population comprises patients who have contraindications or previous failure of standard therapies. Furthermore, no restrictions on medications involving pain management will be made in the study. Thus, the potential risks of the experimental drug are limited only to potential side effects.

M. Potential Benefits

Enrollment in this study may or may not improve the health of the participant. Possible benefits include alleviation of pain and disease burden. As the potential study participants have limited therapeutic options for relieving their symptoms, investigation into novel therapies may help limit symptoms and disease progression.

N. Alternative Therapies

Current medications used in the treatment of acute gout include NSAIDs, colchicine, and corticosteroids. The participants in this study either have contraindications to these medications or have previously failed to achieve clinical resolution with these medications in the past.

O. Compensation to Subjects

Subjects will not be compensated for participation in this study.

P. Costs to Subjects

There will be no costs to subjects in this study.

Q. Minors as Research Subjects

Not applicable

R. Radiation or Radioactive Substances

Not applicable

S. References

- 1) So A, et. al., "A pilot study of IL-1 inhibition by anakinra in acute gout," *Arthritis Research and Therapy*, 9:R28
- 2) Edwards N., "Treatment Failure Gout: A Moving Target," *Arthritis and Rheumatism*, 58:9, 9/2008
- 3) Chen K, et. al, "Anakinra's Efficacy is Variable in Refractory Gout: Report of Ten Cases," *Seminars in Arthritis and Rheumatism*, 2010
- 4) Fels E, Sundy J "Refractory gout: what is it and what to do about it?", *Current Opinion in Rheumatology*, 20(2), 198-202, 2008
- 5) Molto A, Olive A "Anti-IL 1 molecules: New corners and new indications," *Joint Bone Spine* 77, 102-107, 2010
- 6) Terkeltaub R, "The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of placebo-controlled, monosequence crossover, non-randomized, single-blind pilot study," *Ann Rheum Dis*; 68, 2009
- 7) Gratton S et. al, "Case of Anakinra as a Steroid-Sparing Agent for Gout Inflammation," *Arthritis and Rheumatism*, 61-9, 2009
- 8) Sutaria S., et. al, "Effectiveness of interventions for the treatment of acute and prevention of recurrent gout: a systematic review," *Rheumatology*, 45:1422-1431, 2006
- 9) Taylor WJ, et. al, "Assessment of outcome in clinical trials of gout – a review of current measures," *Rheumatology*, 46:1751-1756, 2007