

2020

## IL-1 inhibitor anakinra is an effective alternative to standard treatments for reducing pain due to acute gout flare

Cheryl Craig

Wayne State University School of Medicine, gf8149@wayne.edu

Follow this and additional works at: <https://digitalcommons.wayne.edu/crp>



Part of the [Medical Education Commons](#), [Musculoskeletal Diseases Commons](#), [Rheumatology Commons](#), and the [Translational Medical Research Commons](#)

---

### Recommended Citation

CRAIG C. IL-1 inhibitor anakinra is an effective alternative to standard treatments for reducing pain due to acute gout flare. Clin. Res. Prac. Oct 16 2020;6(2):eP2345. <https://doi.org/10.22237/crp/1593562920>

This Clinical Decision Report is brought to you for free and open access by the Open Access Journals at DigitalCommons@WayneState. It has been accepted for inclusion in Clinical Research in Practice: The Journal of Team Hippocrates by an authorized editor of DigitalCommons@WayneState.

# IL-1 inhibitor anakinra is an effective alternative to standard treatments for reducing pain due to acute gout flare

CHERYL CRAIG, Wayne State University School of Medicine, [gf8149@wayne.edu](mailto:gf8149@wayne.edu)

**ABSTRACT** A clinical decision report appraising Janssen CA, Voshaar MAHO, Vonkeman HE, et al. Anakinra for the treatment of acute gout flares: a randomized, double-blind, placebo-controlled, active-comparator, non-inferiority trial. *Rheumatology*. 2019;58(8):1344-1352. <https://doi.org/10.1093/rheumatology/key402> for a patient with an acute gouty attack refractory to standard treatment.<sup>1</sup>

**Keywords:** *anakinra, acute gout flare*

## Clinical Context

Clarence Bruce [pseudonym] is a 71-year-old African American male presenting to the hospital for suspected NSTEMI with troponin elevation due to acute on chronic CHF exacerbation. Past medical history includes gout, CKD, ischemic cardiomyopathy with combined heart failure EF 15%, DMT2, and HTN. During his five-week hospital stay, Mr. Bruce developed an acute gout flare in his right knee, prompting rheumatology consultation for further management. Physical exam elicited an effused, tender, and erythematous right knee with decreased ROM on extension, limited by pain. In addition, there were two large 1-inch diameter tophi on his bilateral elbows. Blood uric acid level was 12 mg/dL. X-rays showed significant degeneration and erosion of his right knee, bilateral elbows, and bilateral first metatarsals. Patient was not a candidate for colchicine due to his renal impairment and could not be given prednisone because of his CHF with reduced ejection fraction. He was given an intra-articular steroid injection to the right knee and continues to take Norco 7.5mg-325mg Q4 orally for pain management.

Mr. Bruce relies heavily on his wife for transportation and caregiving. He has difficulty ambulating because of joint pain due to his uncontrolled acute and chronic gout. He and his wife have refused placement at subacute rehabilitation, having had previous negative experiences at insurance-covered institutions with the inability of affording more desirable placement. He does not drink alcohol, use drugs, or smoke tobacco with the understanding they can aggravate his gout flares. Chart indicates he is allergic to both allopurinol and febuxostat and he cannot use pegloticase because of box warning of CHF exacerbation. Because of this, he has never taken medications for his chronic gout. Mr. Bruce and wife stated they are concerned about the lack of treatment for his gouty attacks and state that he is in severe pain associated with secondary joint degeneration. Mr. Bruce stated several times that he does not want to continue being a burden to his wife and called for any available treatment that would allow him more independence.

Unable to use the pharmaceuticals traditionally used in the management of acute gout, the rheumatology team considered other options in the treatment of Mr. Bruce's gout flare including use of biologics used in other types of inflammatory arthritis. Anakinra, an IL-1 inhibitor, is used in treatment for rheumatoid arthritis, however, it has

CHERYL CRAIG is a medical student at Wayne State University School of Medicine.



ISSN: 2379-4550

<http://digitalcommons.wayne.edu/crp>, © 2020 The Author(s)

Licensed under [Creative Commons Attribution 4.0 International \(CC-BY-4.0\)](https://creativecommons.org/licenses/by/4.0/)

been hypothesized that it can be utilized to reduce the inflammation associated with an acute gouty flare in patients that are unable to take colchicine, prednisone, and NSAIDs. The rheumatology team wondered if a treatment using anakinra would be as efficacious as the historically used colchicine, prednisone, or NSAIDs for alleviation of pain due to acute gouty attacks.

## Clinical Question

Is IL-1 inhibitor anakinra an effective alternative treatment to colchicine, prednisone, and naproxen for reducing pain in acute gout flares?

## Research Article

Janssen CA, Voshaar MAHO, Vonkeman HE, et al. Anakinra for the treatment of acute gout flares: a randomized, double-blind, placebo-controlled, active-comparator, non-inferiority trial. *Rheumatology*. 2019;58(8):1344-1352. <https://doi.org/10.1093/rheumatology/key402>.

## Related Literature

A literature review using PubMed Advanced Search was completed using the search words (anakinra) AND (gout) and then sorted by best match. 101 articles were found and were then reviewed to evaluate relevance to the clinical question. All case reports, meta-analyses, and review articles were removed from the query. Review articles were used to search for further relevant articles. There were ten total relevant articles found. Seven of the ten relevant articles found in the search were retrospective studies and were discounted because of possibility of researcher bias due to the methodology of chart review and lack of control groups.<sup>2-8</sup> One article, Balasubramaniam et al., was a protocol study for a potential randomized controlled trial with no results published at this time.<sup>9</sup> The remaining two articles were clinical trials. One clinical trial was chosen for critical appraisal.<sup>1</sup> UpToDate was used as an adjunct for additional information about pharmacologic control of acute gout.

So et al. is an open-label clinical trial pilot study testing the efficacy of anakinra use by 10 patients in the treatment of acute gout flares compared to no treatment.<sup>10</sup> Patients given anakinra over a three-day period had a statistically significant decrease in pain. The study was completed on patients who had failed treatment with NSAIDs, colchicine, and corticosteroids, fitting our patient population. However, this study only evaluated 10 patients, which limits the ability to expand results to a greater population. The study was also an open-label clinical trial leaving room for researcher bias in the reported results. In addition, the methodology did not compare anakinra to standard treatments of acute gout.

This critical appraisal focuses on the randomized, double-blinded study by Janssen et al., directly comparing anakinra to colchicine, prednisone and naproxen. Patients that were given anakinra for acute gout flare had a non-inferior reduction in pain as compared to standard treatments. The methodology of this study was superior as compared to the previous stated articles. The study was double-blinded reducing probability of bias that could be present in a retrospective study. The study also had 100% compliance at the conclusion of their study. In addition, they included patients that fit the appropriate patient profile including >90% male participants >18 years old and no exclusion of any comorbidities as seen in our patient.

According to the SORT criteria, the study quality of this publication is Level 1 due to its patient-oriented evidence and high-quality methodology.<sup>11</sup> The Grade of Recommendation is B—limited small studies.

## Critical Appraisal

This study was a randomized, double-blind, placebo-controlled, non-inferiority clinical trial at rheumatology departments at seven hospitals in the Netherlands including a total of 88 patients. All patients were recruited by the attending rheumatologist. It evaluated the efficacy of anakinra for acute gout flares as compared to colchicine, prednisone, and naproxen use. Patients greater than 18 years of age with a diagnosis of an acute gout flare confirmed by microscopy were eligible. Those currently using urate



lowering therapy, on other IL-1 inhibitors, history of liver disease or contraindications to anakinra such as neutropenia or severely reduced creatinine clearance <30ml/min were not included.

A 1:1 randomization was successfully completed. Forty-three patients were randomly allocated to five-day treatment with anakinra plus oral placebo up to three times daily for five days. Forty-five patients were assigned five days of the oral standard of care using colchicine, naproxen, or prednisone as determined by providers and patients prior to the start of the project. All placebo injections and pills were identical in appearance to the anakinra injections and standard pills. Pills and injections were taken under supervision of a study nurse. Patients, providers, pharmacists, and investigators had no knowledge of which medications were being provided. Patients were asked to maintain a gout flare diary for seven days indicating levels of pain, tenderness, and swelling on a five-point scale in the primarily affected joint, as well as evaluation of pain on a 10-point scale and evaluation of treatment response on an 8-point scale. Null hypothesis stated that treatment with anakinra is less effective than standard treatment for acute gout flares by at least 0.4 points on the five-point rating scale. Patients were required to record additional pain killers or anti-inflammatory medication they may have taken daily. Patients returned to clinic on day seven to be evaluated using physical exam, serum uric acid, and CRP.

Researchers evaluated the efficacy of anakinra compared to standard treatment using a difference in pain from baseline to average indicated pain scores at days 2-4 using an ANCOVA model of statistical analysis, with treatment received as a fixed effect and baseline pain scores measured on the five-point rating scale as a covariate. Using ANCOVA they estimated the marginal mean difference between treatments was -0.132 on the five-point rating scale in favor of anakinra. The 95% CI (-0.44,0.18) did not surpass the NI margin of 0.4 suggesting anakinra does not display statistically significant superiority over standard of care, however, maintains efficacy as a potential equivalent treatment.

Although there were several conclusions drawn from this study, the most relevant result to our clinical question lies in the evaluation of pain to improve Mr. Bruce's overall function. They concluded that the use of anakinra was equally as successful as standard treatments for reducing pain, rejecting their null hypothesis. Use of anakinra was non-inferior to using standard treatments of colchicine, prednisone, or naproxen suggesting anakinra has an acceptable level of efficacy for those patients unable to take standard treatment because of comorbidities.

In terms of study design, a double-blinded randomized controlled trial is the best methodology available for determining efficacy of a medication because it eliminates biases of the patients and the researchers. There were few opportunities for detection bias because the pharmacists were also blinded, and the administered treatments were all visually identical. The study had 100% retention indicating no attrition bias. There was no evidence of funding or publication bias as the trial was unsponsored and registered prospectively through the Netherland's Trial Register with no significant deviation from the published study protocol. One limitation of the study was that it only had two arms and lacked a placebo treatment group, limiting the evaluation of the benefit gained from anakinra or standard treatment as compared to no treatment. In addition, the study participants were recruited by the attending rheumatologist, suggesting there may have been underlying bias in the type of recruited patient.

The population of our patient was adequately represented because it included patients with several comorbidities in both treatment groups, including cardiovascular disease, diabetes, hypertension, and renal disorders and included approximately 90% male participants. Average age of the anakinra treatment group was 63.4±12.9, a range accommodating our patient's age and average BMI was 29.5±4.2 matching our patient's BMI of 30. A limitation in terms of patient population includes that only 7% of participants suffered from polyarticular gout like Mr. Bruce which could potentially change the efficacy of anakinra on overall pain reduction based on the severity of the acute gout flare.

## Clinical Application

This study concluded anakinra is an equivalent alternative to the standard treatments of colchicine, prednisone, or naproxen for pain relief in an acute gouty attack. In clinic, anakinra can be used for pain relief in lieu of standard treatment in the event of several comorbidities, allergies, and lack of other options as seen in our patient Mr. Bruce.



In terms of the concerns Mr. Bruce had regarding his pain management and control of his acute gout flares, anakinra is a viable option to provide pain control, allowing Mr. Bruce to be more independent in both ambulation and transportation. Overall, this can reduce the pressure placed on his wife as caregiver and the guilt felt by Mr. Bruce himself. At the conclusion of our conversation with Mr. Bruce, he agreed to try everything possible to control his pain caused by his frequent acute gout flares including diet change, as well as, attempting to get preauthorization for anakinra through his insurance.

The only potential harm from the use of anakinra for an acute gout flare is the lack of studies available proving the safety of short term anakinra use, however, long term safety has been proven via studies of anakinra for rheumatoid arthritis. This critically appraised study by Janssen et al. recorded all complications of the participants over the treatment period and discovered no significant adverse effects, however, a formal research study has not been completed at this time.

## New Knowledge Related to Clinical Decision Science

Clinicians historically use patterns and protocols to diagnose and treat, such that treatments for common conditions become second nature. In the case with Mr. Bruce, these gold standard treatments were unavailable because contraindications and allergies. Conservative measures alone for pain management would be suboptimal to allow him to have the independent lifestyle he desired. The clinician should use their clinical reasoning skills to avoid standard patterns and protocols, exploring lesser known options. This and patient-centered decision-making can improve their patient's quality of life. Because the literature is so limited, Mr. Bruce's care could become a case report after efficacy was evaluated, making clinical decision making more robust for patients like Mr. Bruce.

## References

- Janssen CA, Voshaar MAHO, Vonkeman HE, et al. Anakinra for the treatment of acute gout flares: a randomized, double-blind, placebo-controlled, active-comparator, non-inferiority trial. *Rheumatology*. 2019;58(8):1344-1352. <https://doi.org/10.1093/rheumatology/key402>
- Vitale A, Cantarini L, Rigante D, Bardelli M, Galeazzi M. Anakinra treatment in patients with gout and type 2 diabetes. *Clin Rheumatol*. 2015;34(5):981-984. <https://doi.org/10.1007/s10067-014-2601-7>
- Ottaviani S, Moltó A, Ea HK, et al. Efficacy of anakinra in gouty arthritis: a retrospective study of 40 cases. *Arthritis Res Ther*. 2013;15(5):R123. <https://doi.org/10.1186/ar4303>
- Loustau C, Rosine N, Forien M, et al. Effectiveness and safety of anakinra in gout patients with stage 4-5 chronic kidney disease or kidney transplantation: A multicentre, retrospective study. *Joint Bone Spine*. 2018;85(6):755-760. <https://doi.org/10.1016/j.jbspin.2018.03.015>
- Thueringer JT, Doll NK, Gertner E. Anakinra for the treatment of acute severe gout in critically ill patients. *Semin Arthritis Rheum*. 2015;45(1):81-85. <https://doi.org/10.1016/j.semarthrit.2015.02.006>
- Desmarais J, Chu CQ. Utility of Anakinra in Acute Crystalline Diseases: A Retrospective Study Comparing a University Hospital with a Veterans Affairs Medical Center. *J Rheumatol*. 2019;46(7):748-750. <https://doi.org/10.3899/jrheum.180393>
- Liew JW, Gardner GC. Use of Anakinra in Hospitalized Patients with Crystal-associated Arthritis. *J Rheumatol*. 2019;46(10):1345-1349. <https://doi.org/10.3899/jrheum.181018>
- Chen K, Fields T, Mancuso CA, Bass AR, Vasanth L. Anakinra's efficacy is variable in refractory gout: report of ten cases. *Semin Arthritis Rheum*. 2010;40(3):210-214. <https://doi.org/10.1016/j.semarthrit.2010.03.001>
- Balasubramaniam G, Parker T, Turner D, et al. Feasibility randomised multicentre, double-blind, double-dummy controlled trial of anakinra, an interleukin-1 receptor antagonist versus intramuscular methylprednisolone for acute gout attacks in patients with chronic kidney disease (ASGARD): protocol study. *BMJ Open*. 2017;7(9):e017121. <https://doi.org/10.1136/bmjopen-2017-017121>
- So A, De Smedt T, Revaz S, Tschopp J. A pilot study of IL-1 inhibition by anakinra in acute gout. *Arthritis Res Ther*. 2007;9(2):R28. <https://doi.org/10.1186/ar2143>
- Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *J Am Board Fam Med*. 2004;17(1):59-67. <https://doi.org/10.3122/jabfm.17.1.59>

