Title:

Use of anakinra in hospitalized patients with crystal-associated arthritis

Running head:

Anakinra for crystal-associated arthritis

Authors:

Jean W. Liew, MD[1]

Gregory C. Gardner, MD[1]

[1]Division of Rheumatology, Department of Medicine, University of Washington, Seattle, Washington

Corresponding Author

Jean W. Liew, MD

University of Washington

1959 NE Pacific St, BB561

Seattle, WA 98195

Office: 206-685-9950

Fax: 206-685-9397

Email: jwliew@uw.edu

Orcid ID: https://orcid.org/0000-0002-8104-2450

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ABSTRACT

Objective: In this retrospective observational study, we assess the efficacy and safety of the interleukin-1 receptor antagonist anakinra in medically complex, hospitalized patients with acute gout and calcium pyrophosphate crystal arthritis.

Methods: Adult inpatients patients treated with anakinra from 2014-2017 were identified for inclusion. Charts were reviewed for demographics, comorbidities, laboratory data, pain scores, joint involvement, prior treatment, dosing and response to anakinra, concurrent infections, and surgical interventions. Response to anakinra treatment was determined from review of provider documentation, as well as recorded pain scores on a numeric scale.

Results: We identified 100 individuals accounting for 115 episodes of arthritis. This population was 82% male, with an average age of 60 years. Comorbidities included renal disease (45%) and history of organ transplantation (14%). Twenty-nine episodes of arthritis occurred in the perioperative setting. Concurrent infection was present in 34 episodes. Eighty-four episodes of arthritis had partial or complete response to anakinra within four days of treatment initiation; 66 episodes had partial or complete response within one day of anakinra administration. Anakinra was well-tolerated.

Conclusion: This is the largest observational study of anakinra use in the inpatient setting for the acute treatment of crystal-associated arthritis. We observed a rapid response to anakinra, with 75% of episodes significantly improving or completely resolving within four days of the first dose. Our data also support the use of this biologic agent in individuals with infections, as well as perioperative individuals and immunosuppressed transplant recipients.

INTRODUCTION

Gout is an inflammatory condition in which the precipitation of monosodium urate (MSU) crystals within joints results in recurrent attacks of arthritis. Calcium pyrophosphate (CPP) crystal arthritis, also known as pseudogout, is a similar condition that more commonly affects older individuals or those with certain metabolic disorders such as hemochromatosis.

The prevalence of gout in the United States is estimated to be 3.9% [1]. Comorbidities are common and in one study, the prevalence of hypertension was 74%, chronic kidney disease (CKD), 53%, diabetes mellitus, 26%, and congestive heart failure, 11% [2]. Gout is independently associated with higher medical comorbidity, and increases in both primary care and inpatient utilization [3-4].

Both gout and CPP crystal arthritis are chronic diseases marked by acute arthritic attacks. The pharmacologic management of both conditions is similar, and per the most recent American College of Rheumatology (ACR) guidelines, include nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine as first line agents. In monoarticular flares, an intraarticular glucocorticoid injection may be administered. Polyarticular flares may be treated with systemic glucocorticoids if NSAIDs and colchicine are contraindicated, as in individuals with CKD or end stage renal disease (ESRD), or in the elderly [5]. However, glucocorticoids should be used with caution in individuals with end stage or refractory heart failure, or diabetes with poor glycemic control.

In these medically complex individuals, the IL-1 receptor antagonist, anakinra, may be considered. Anakinra blocks the downstream effects of the NLRP3 (NOD, LRR, and pyrin

domain-containing 3) inflammasome. This protein complex is activated by both MSU and CPP crystals, resulting in the caspase-1 cleavage of pro-IL-1β to active IL-1β, an inflammatory cytokine [6-7]. The standard anakinra dosing is derived from the pilot study by So, et al, in which individuals with acute gouty arthritis were given anakinra 100mg subcutaneously daily for three doses [8]. Several observational studies, including one from our center, have demonstrated the rapid efficacy of anakinra on pain and swelling in acute gout attacks [10-18]. The observational data for CPP crystal arthritis has been more limited, but anakinra has also been shown to be effective for acute episodes as well as maintenance therapy [14; 19-24].

In the current single center, retrospective, observational study, we assessed the efficacy and safety of anakinra in medical complex, hospitalized patients with acute gout and CPP crystal arthritis. The 26 patients reported in our prior publication were not included in the current study.

METHODS

Adult patients hospitalized at the University of Washington Medical Center (UWMC) and Harborview Medical Center (HMC) and who were treated with anakinra during their admission were identified for inclusion through the Leaf application, the interface for the University of Washington's deidentified clinical data repository. Information was available for admissions from January 2014 to the date of the analysis, 10 December 2017. A total of 120 individual patients were identified. We conducted a chart review and excluded patients who received anakinra for indications other than gout or CPP crystal arthritis; the remaining 100 patient charts were reviewed for basic demographic information, comorbidities, laboratory data, pain scores, joint involvement, prior treatment, anakinra dosing and frequency, response to anakinra

treatment, concurrent infections and surgical interventions, and adverse effects of anakinra administration. The diagnoses of gout and CPP crystal arthritis were defined as follows: by joint aspiration yielding MSU or CPP crystals; and/or clinical diagnosis by a rheumatologist; and/or acute joint pain and swelling in the setting of prior gout or CPP crystal arthritis diagnosis, with alternative diagnoses excluded. At UWMC and HMC, the administration of anakinra was not restricted to the rheumatology consultation service.

Infections and surgical interventions were considered concurrent if they occurred during the index hospitalization within a month of anakinra treatment. Infections were considered concurrent and unrelated to anakinra administration unless they were attributed as such in the discharge summary.

Response to anakinra treatment was determined from chart review of inpatient provider documentation, as well as recorded pain scores (0-10 on a numeric scale). Responses were rated on a scale of no response, partial response, significant response, and complete resolution. Partial response was denoted by documented clinical response by the clinician, such as commentary in the chart that the patient had “modest,” “some,” or “mild” improvement; or situations in which one joint was improved but another was not. Significant response was denoted by any combination of the following: functional improvement, such as ability to walk or bear weight on the affected joint; movement or range of motion of the affected joint with minimal pain; improved swollen or tender joints on exam; or documented clinical response such as “dramatic” or “significant” improvement. If there was no documentation of the above, then a change in the average daily pain score by at least two points was considered a significant response [25].

Complete resolution was denoted by chart documentation stating that the patient's flare was completely resolved. Cases of incomplete documentation were denoted as "NA."

An IRB for this study (STUDY00003614) was approved by the University of Washington Human Subjects Division.

RESULTS

We identified 100 individuals hospitalized at UWMC or HMC between January 2014 and December 2017, who received anakinra for the acute treatment of gout or CPP crystal arthritis while inpatient. These individuals accounted for a total of 115 separate episodes of arthritis. Baseline data are shown in Table 1. The population was 82% male, with an average age of 60 years. The majority were white (64%); 19% were black, 15% were Asian or Pacific Islander, 1% were Native American, and 1% did not report a race or ethnicity. Comorbidities included heart failure in 43%, CKD or ESRD in 45%, diabetes mellitus in 27%, chronic anticoagulation use in 22%, and a history of organ transplantation requiring anti-rejection immunosuppression in 14%. Fifty-eight percent of individuals had two or more of these comorbid conditions. The average serum creatinine measured proximately to the episode of arthritis was 1.9 mg/dl.

Ninety-three of the patients had gout, of which 22 were crystal-proven during the index admission. Of the seven patients who had CPPD, five were crystal-proven. Of the remaining patients who did not have a confirmatory synovial fluid analysis during their index admission, approximately 10% reported a prior crystal-proven diagnosis of gout. The average serum uric

acid level at the time of the flare was 8.6 mg/dL and was available for 90 episodes. Patients had an average pain score of 4.1 on a numeric pain scale (range 0-10).

Monoarthritis was seen in 43 episodes, oligoarthritis in 56, and polyarthritis in 15; one episode presented as a systemic inflammatory response alone in the absence of joint manifestations. The knee was involved in 37 episodes, the ankle in 35, the first metatarsophalangeal joint in 25, the wrist in 25, the elbow in 22, and the small joints of the hand in 21. The back and shoulder were involved in one episode each.

Concurrent infection was present in 34 arthritis episodes. This included cellulitis or abscess in seven, bacteremia in six (three with *Staphylococcus*, one with *Pseudomonas*, two with *Klebsiella*), septic arthritis in six, urinary tract infection in five, *Clostridium difficile* colitis in five, pneumonia in three, cytomegalovirus viremia in one, and infectious endocarditis in one.

Recent surgical intervention was found associated with 29 arthritis episodes. This included articular washout in five, incision and drainage or debridement in four, other orthopedic procedures in four, cardiac procedures in four (either a valvular surgery or placement of a left ventricular assist device), transplantation in three (two orthotopic heart and one orthotopic liver transplantations), video-assisted thoracic surgery in three, endovascular procedures in two, neurosurgical procedure in one, and three procedures classified as other.

Other treatment for the acute arthritis (Table 2) included: NSAIDs for two episodes (one day of treatment in one case; greater than two days in the other case); colchicine for 26 episodes (two or

fewer doses in 19; more than two doses in seven); oral prednisone of 10mg daily or more in 23 episodes (one received one day of treatment; the rest received two or more days of treatment); intraarticular glucocorticoid injection for seven episodes; and operative washout in three episodes. No other treatment apart from anakinra was given for 55 episodes.

The decision to treat with anakinra was due to the patient's underlying comorbidities in 84% of episodes, and due to failure of other therapies in 48% of episodes; some patients had both indications for the use of anakinra. The average duration of the arthritis episode prior to receiving anakinra was 4.8 days. Various dosing regimens of anakinra were used (Table 3). Twenty-four episodes were treated with a single dose; 100mg daily for two doses was given for 13 episodes; 100mg daily for three doses was given for 52 episodes; 100mg daily for more than three doses was given for eight episodes; 100mg every other day (renally dosed) for two doses was given for four episodes; 100mg every other day for three doses was given for 13 episodes; and 100mg every other day for more than three doses was given for one episode.

Response to anakinra is shown in Table 4. Eighty-four episodes of arthritis had partial or complete response to anakinra within four days of the first dose. Sixty-six episodes had partial or complete response within one day of administration of the first dose. There was only a partial response in seven episodes and no response in six. There was insufficient information to determine the response in 14 episodes. In 36 episodes, patients discharged from the hospital within four days of receiving the first dose of anakinra.

Overall, anakinra was well tolerated. Two individuals had leukopenia attributed to anakinra administration (one new, one with worsening of preexisting white blood cell counts). Worsening of bicytopenia, injection site reaction, and nausea occurred in one individual each.

DISCUSSION

This is the largest observational study of anakinra use in the inpatient setting for the acute treatment of crystal-associated arthritis. Our findings build upon our earlier study, in which 26 individuals were treated for a total of 40 episodes with few adverse events [10]. In the current study, we observed a rapid response to anakinra, with 75% of episodes significantly improving or completely resolving within four days of the first dose, and 57% of episodes within one day of the first dose. These data also support the use of this biologic agent in those with active or recent infections, those who are peri- or post-operative, and in those immunosuppressed for transplant rejection purposes.

The first-line agents for the treatment of acute gout or CPP crystal arthritis are NSAIDs, colchicine, and glucocorticoids. These are agents that may fail or be poorly tolerated in a medically complex patient population with multiple comorbidities that includes diabetes, CKD, and congestive heart failure. Prior observational studies of anakinra have shown its efficacy in this population. Other IL-1 inhibitors, canakinumab and rilonacept, have been shown in trials to be effective for the treatment of acute and chronic gout, as well as for flare prophylaxis while initiating urate-lowering therapy [26-28].

Forty-five percent of the patients in our study had CKD or ESRD. In most of these cases, anakinra was dose-reduced to 100mg every other day, as described in prior studies [29]. We observed the safety of anakinra in these patients with renal dysfunction, complementing the findings of Loustau, et al in their retrospective study of 25 patients with CKD [30].

With regard to safety, our study identified 29 episodes in which individuals received anakinra in the setting of concurrent infection. These infections ranged from localized infections such as cellulitis, to systemic infections such as bacteremia. In many of these cases, the decision to initiate anakinra was made following multidisciplinary discussions with the infectious disease consultants regarding the risks and benefits. All individuals received appropriate antibiotic coverage. There was no indication of worsening of infection in these patients that could be attributed to the anakinra administration. This finding is in agreement with other observational studies that included individuals with active infection [10, 12, 13, 15].

Twenty-six episodes of anakinra administration were in the setting of recent surgical intervention, without evidence for subsequent surgical complications. Our study also identified 14 patients with a history of solid organ or stem cell/bone marrow transplantation, including three who had transplantations during their index hospitalizations. No complications were attributed to the administration of anakinra. Prior published cases of transplant recipients receiving anakinra for crystal-associated arthritis include 10 individuals with renal transplants [15;30-31] and two with orthotopic liver transplants [15]. The safety of anakinra in a bone marrow transplant recipient has been described in a case report of familial Mediterranean fever

[32]. We add to these reports two individuals who received heart transplants during the same admission that they were given anakinra.

Although we are unable to determine the impact of anakinra administration on the length of stay, we did note that in 31% of episodes, patients discharged from the hospital within four days of the first anakinra dose. We could extrapolate that these patients experienced significant enough responses that that they were able to leave the hospital. Given the rapid efficacy of anakinra, this treatment may be more cost-effective in those who are refractory to other less costly treatments. Our findings are supported by a case-control study by Singh, et al in which 16 patients receiving anakinra for acute crystal-associated arthritis, who were matched with 32 controls receiving conventional therapy, were found to have a length of stay that was two days shorter, on average [33]. The partial or nonresponse to anakinra seen in some of our patients may be explained by the short half-life of anakinra (4-8 hours), other involved cytokines, or by patient selection as discussed below.

This study has its strengths in the number of patients included, and the high prevalence of comorbidities. However, as a retrospective observational study, it has limitations. About half of the patients did not have a crystal-proven diagnosis; a non-crystal-associated arthritis may have been misclassified as gout or CPPD, thus accounting for poor or inadequate anakinra response as discussed. Our previous observational study response rates were 67% of patients had a one-day significant response rate and 90% achieved a significant response within four days (compared to 57% and 75%, respectively, in the current study). Since the first study was published, the efficacy of anakinra for gouty arthritis is widely recognized within our institution and anakinra

therapy can now be instituted by the primary inpatient team without rheumatology involvement. In 20 cases of anakinra administration, the order was initiated prior to, or without the involvement of, the rheumatology consult service. This may impact the number of patients who actually have crystal-associated arthritis since few were crystal-proven. In addition, there was no control population to serve as a comparison for efficacy of anakinra therapy. These patients had significant comorbidities that limited their use of other pharmacological therapies to treat their acute arthritis; thus, they cannot easily be compared to a less medically complex population who did not receive anakinra. As there were no formal standards of documentation of improvement of arthritis flares, the response criteria we employed cannot account for inaccuracies of over- or underestimating response. We cannot account for all possible adverse events attributable to the anakinra, as these may not have been captured or documented in the discharge summaries. Further adverse events may have occurred following the hospitalization, which may not have been documented in the electronic medical record.

Controlled trials are required to solidify the efficacy of anakinra for use as an acute therapy for gout or CPP crystal arthritis, particularly in medically complex inpatients who may have concurrent infections or recent surgical procedures.

CONCLUSION

Acute attacks of gout or CPP crystal arthritis can be highly symptomatic and frequent complications of inpatient admissions, particularly in a medically complex patient population, for whom standard therapies are contraindicated, poorly tolerated, or unsuccessful. Anakinra should be considered in these patients, as it has a rapid onset of action and is well tolerated. Our

large retrospective study supports its use in hospitalized patients, including those with concurrent infections, transplant recipients, or those who have undergone recent surgical interventions.

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Table 1. Baseline demographics

Age (years), mean ± SD	60 ± 15
Gender	82% male
Race/ethnicity	64% white
	19% black
	15% Asian or Pacific Islander
	1% Native American
	1% unknown
Comorbidities	45% chronic kidney disease or end stage renal
	43% heart failure
	27% diabetes mellitus
	22% chronic anticoagulation
	14% history of transplantation
Infection within the same admission	34 episodes
Operation within the same admission	29 episodes
Serum uric acid (mg/dl), mean ± SD[a]	8.6 ± 4.1
Serum creatinine (mg/dl), mean ± SD[b]	1.9 ± 1.9
Pain score (0-10), mean ± SD[c]	4.1 ± 2.8
Duration of gout flare (days), mean ± SD	4.8 ± 5.3
Indication for anakinra[d]	84% due to comorbidities
	48% due to failure of other therapies
	8% with reason not documented

[a]Serum uric acid obtained most proximately to episode of arthritis

[b]Serum creatinine obtained most proximately to the administration of anakinra. ESRD patients not included.

[c]Average of pain scores on a numeric pain scale (0-10) obtained at initiation of anakinra

[d]Indications for anakinra administration could be multiple and overlapping within the same individual

Table 2. Prior treatments, by episode

NSAID	
One day	1
More than one day	1
Colchicine	
Two or fewer doses	19
More than two doses	7
Prednisone	
One day	1
More than one day	22
Intraarticular glucocorticoid	7
Operative washout	3
No other therapy	55

Table 3. Anakinra dosing regimens, by episode

100mg, once	24
100mg daily	
Two doses	13
Three doses	52
More than three doses	8
100mg every other day	
Two doses	4
Three doses	13
More than three doses	1

Table 4. Responses, by episode

Significant response or complete resolution by 4 days	86
Delayed response > 4 days	2
Partial response	7
Non-response	6
Insufficient information	14