Utility of Anakinra in Acute Crystalline Diseases: A Retrospective Study Comparing a University Hospital with a Veterans Affairs Medical Center

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ABSTRACT. ***Objective.*** To evaluate the efficacy and safety of anakinra in inpatient management of acute gout and pseudogout.

Methods. Hospitalized patients with acute gout (n = 77) or pseudogout (n = 11) or both (n = 3) were analyzed for response to anakinra and adverse effects.

Results. Half of all patients had comorbidities limiting the treatment choice. Anakinra was well tolerated, and 92% of gout flares and 79% of pseudogout flares responded to treatment.

Conclusion. Anakinra is an effective and safe treatment for acute gout and pseudogout in hospitalized patients, particularly in those with comorbidities. (J Rheumatol First Release November 15 2018; doi:10.3899/jrheum.180393)

Key Indexing Terms:
GOUT PSEUDOGOUT ANAKINRA

Anakinra is a recombinant interleukin 1 (IL-1) receptor antagonist that blocks IL-1 activity, used off-label to relieve acute inflammation from gout and pseudogout. Monosodium urate and calcium pyrophosphate crystals activate the NALP3 (NACHT, LRR, and PYD domains–containing protein-3) inflammasome, which leads to caspase 1 activation and conversion of pro-IL-1β to active IL-1β[1]. The efficacy and safety of blocking IL-1β activity in the inpatient setting, however, has not been well evaluated. Small open-label studies have shown promise, with 3 doses of anakinra used in acute inpatient gout[2]. Two small retrospective studies of 10 and 26 patients, respectively, showed good outcomes in acute gout treatment in the outpatient and inpatient settings[3,4]. Another retrospective review of 40 patients documented good relief for acute gout, with 30 receiving anakinra for 15 days or less for an acute flare[5]. The use of anakinra to treat pseudogout has limited evidence, but a study of 16 patients in the outpatient setting showed 2/3 of patients had a good response[6]. In a smaller study, 3 patients with crowned dens syndrome (2 with pseudogout, 1 with hydroxyapatite deposition disease) responded well to anakinra, though a longer course of 9–11 days was needed[7]. Anakinra use has been described in calcific tendonitis in 5 patients as well[8].

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One of the challenges that providers encounter in the inpatient setting is that comorbidities limit the choice of medications to treat acute crystalline arthritis. The use of anakinra in gout patients with diabetes, for example, was reported regarding glycemic control over 6 months[9]. Anakinra is a reasonable option when comorbidities limit use of other agents such as oral steroids and/or nonsteroidal antiinflammatory drugs (NSAID), and has been used in inpatient gout for this reason[10]. Here we report our experience in using anakinra for hospitalized patients with acute gout or pseudogout.

MATERIALS AND METHODS

Institutional review board approval was obtained for this study (00015685). A retrospective chart review was included of patients with crystalline arthritis hospitalized at Oregon Health & Science University (OHSU) Hospital and the VA Portland Health Care System (VAPORHCS) who had received anakinra while inpatient. Dates of hospitalization from January 1, 2008, to November 30, 2016, were evaluated. All the patients had a diagnosis of gout or pseudogout made by a rheumatologist. Of the 77 patients with gout, 69 had crystal-proven or tophaceous disease, and the rest (n = 8) had elevated uric acid and consistent clinical examination. All but 2 patients with pseudogout were crystal-proven, because 2 had refused aspiration but had consistent imaging. Inclusion criteria were patients over 18 years of age who received 1 or more doses of anakinra while inpatient for an acute crystalline arthritis flare. Patients were identified by searching inpatient medication administration databases for anakinra. Data analyzed were patient characteristics, comorbidities, reasons for anakinra use, number of doses of anakinra (1 dose was 100 mg subcutaneous injection), adverse events, and response to treatment. A re-dose was defined as needing more anakinra after having not received this medication for 72 h.

A pain scale response to treatment was defined as improvement of 50% at 0–10 visual analog scale (VAS) from day of anakinra administration. Functional improvement such as ability to bear weight on affected limbs when unable to initially, or a documented clinical response such as "great improvement" was collectively called "clinical response." Cases with inadequate documentation to assess for response were noted. Patients who clearly

did not have VAS improvement or clinical response were considered nonresponders. For evaluating pain improvement on VAS, a Student t test was used to calculate significance.

RESULTS

A total of 91 patients who had 115 flares of crystalline arthritis were identified. The average patient age with gout or pseudogout was 64 (61 at OHSU, 69 at VAPORHCS). At both OHSU and the VAPORHCS, around half of all patients had comorbidities such as diabetes, congestive heart failure, and chronic kidney disease that affected the choice of their crystalline arthritis treatment (Table 1). All anakinra prescriptions were with rheumatology consult or prior use of anakinra with rheumatologists. House staff monitored for response. Anakinra was used first-line in some patients, but other treatments were used as well during hospitalization and emergency department course. Among patients with gout, 39% received colchicine, 15% intraarticular corticosteroids, 5% NSAID, and 40% prednisone. Among patients with pseudogout, 14% received colchicine, 14% intraarticular corticosteroids, 36% NSAID, and 14% prednisone.

A total of 77 patients with 98 gout flares were treated with anakinra. At OHSU, there were 38 patients with 47 flares. At VAPORHCS, there were 39 patients with 51 flares. At OHSU the average number of anakinra doses for treating gout was 4.6 (range 2–29), while at the VAPORHCS it was 3.5 (range 2–12). Of the 47 patient flares at OHSU, 42 (89%) had a clear response that took about 2.2 days, 4 had inadequate documentation, and 1 did not respond. Of the 42 with a clear response, 12 had improvement in VAS by 50% and 30 had clinical response. In the 1 nonresponder, it took about a week for the flare to improve clinically; it was not clear whether anakinra shortened the flare or whether it self-resolved. At VAPORHCS, there were 51 flares, of which 48 clearly responded (94%) with an average time of 1.8 days, and 3 had inadequate documentation. Of the 48, 21 had a VAS improvement by 50% and 27 had a clinical response. One day after anakinra was administered, at both institutions there was a significant decrease in pain score ($p < 0.01$; Figure 1).

At the VAPORHCS, 3 patients had both gout and pseudogout on joint aspiration. All 3 patients responded to anakinra treatment by VAS score, with an average of 1 dose, and an average 1.3 days to 50% VAS improvement.

There were a total of 11 patients with pseudogout who had 14 flares. There were 6 patients at OHSU who had 8 flares. Of the 8 flares, 7 had an adequate response to treatment with an average of 2 doses of anakinra, and 1 patient had inadequate documentation. At VAPORHCS, there were 5 patients with 6 episodes of pseudogout. Of the 6 episodes, 4 were responders, 1 was unclear, and 1 patient did not respond to treatment. The nonresponder received 3 days of anakinra and had a history of chronic pain with ongoing high pain scores, though it was documented that his pain was well controlled with the addition of oral narcotics, and he was discharged home without further intervention. The average number of doses of anakinra at OHSU was 2, while at VAPORHCS it was 4. Together, 11 patients had 14 flares, with 11/14 episodes (79%) responding to anakinra, requiring 2–4 doses of anakinra.

Anakinra was well tolerated. One patient may have had a rash on the back due to anakinra, but received diphenhydramine prior to the third dose and tolerated a 5-day course. No other adverse reactions were reported.

DISCUSSION

Treating both gout and pseudogout in acutely hospitalized patients can be difficult owing to patient comorbidities. Because of the limitations by which patients cannot receive oral corticosteroids, colchicine, or NSAID, providers are searching for other options to help with disease control. This retrospective study evaluated the use of an IL-1 blocking medication to assess the clinical viability of this option.

Anakinra appears to work well for acute gout. In our cohort, 92% of gout flares and 79% of pseudogout flares responded to treatment. The reason for the good outcomes in our study may have been the acute character of the gout flares. Of note, the inpatient anakinra prescriptions increased over the study period, which suggests its better acceptance among providers.

Table 1. Patient baseline characteristics.

	OHSU, n = 44	VAPORHCS, n = 47
Percent male	73	94
Average age	61	69
Comorbid conditions, n (%)	DM 21 (48%), CKD 25 (57%), CHF 21 (48%), transplant 5 (11%; 3 heart, 2 kidney)	DM 25 (53%), CKD 29 (62%), CHF 32 (68%), transplant 2 (4%; both kidney)
Average no. joints involved	Gout: 4; pseudogout: 3.1	Gout: 3.8; pseudogout: 5.2
Prior crystalline arthritis diagnosis	Gout: 95%; pseudogout: 50%	Gout: 88%; pseudogout: 60%
Average duration of diagnosis, yrs	4.2	3.9

Duration of crystalline arthritis diagnosis was calculated at time of first anakinra use. OHSU: Oregon Health & Science University; VAPORHCS: VA Portland Health Care System; DM: diabetes mellitus; CKD: chronic kidney disease; CHF: congestive heart failure.

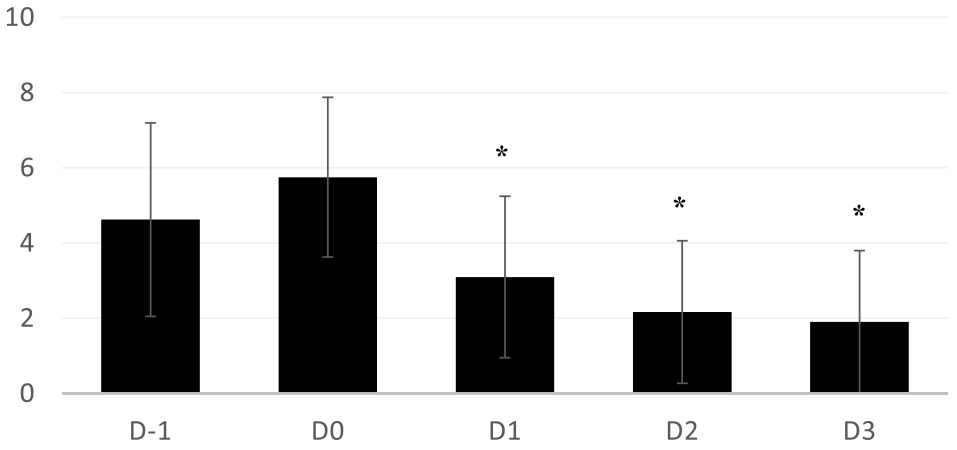

Figure 1. Visual analog scale pain scores, by day of treatment. * $p < 0.01$ in comparison with the pain score at D0.

There is a paucity of information about the use of anakinra in pseudogout, which our study addresses. In the inpatient setting, we found that patients on average received between 2–4 doses for their flares, with good results. The shorter course of anakinra administration in our study reflected that our patients had pseudogout flares in peripheral joints, because none of the patients had crowned dens that required longer courses of anakinra[7]. Other studies have found that pseudogout would flare again after anakinra was stopped[6], though in our study none of the patients needed to be re-dosed.

Our study has several limitations, mostly inherited from the retrospective design of the study. Assessment for response was based on clinical response and pain scores as listed in patient vital signs. The patient pain scores were used where possible, and were recorded at the VAPORHCS more frequently than at OHSU. Because this study focused on patients who were acutely hospitalized, those who had adverse reactions to anakinra postdischarge or who had another flare of disease may have not been identified.

A short course of anakinra is an effective and safe medication for treating acute flares of gout and pseudogout in hospitalized patients, particularly in those who have comorbidities that would limit the use of other acute gout medications.

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