Clinical Rheumatology (2019) 38:425–430
https://doi.org/10.1007/s10067-018-4272-2

ORIGINAL ARTICLE

Efficacy and tolerance of anakinra in acute calcium pyrophosphate crystal arthritis: a retrospective study of 33 cases

Marion Thomas[1] · Marine Forien[1] · Elisabeth Palazzo[1] · Philippe Dieudé[1] · Sébastien Ottaviani[1]

Received: 17 May 2018 / Revised: 8 August 2018 / Accepted: 20 August 2018 / Published online: 25 August 2018

Abstract

Calcium pyrophosphate (CPP) deposition is a frequent joint disease with increased prevalence in older people in whom treatment of acute CPP arthritis with conventional therapies such as colchicine or non-steroidal anti-inflammatory drugs could be contra-indicated or not used at an optimal dose. As recommended in gout, anakinra might represent an alternative treatment for arthritis. We aimed to analyze the efficacy and safety of anakinra in acute CPP arthritis in a large reported series. We retrospectively included all patients receiving anakinra for acute CPP arthritis between January 2011 and 2017. The following data were collected before and 4 days after the first anakinra injection: swollen joint count (SJC), tender joint count (TJC), pain score on a visual analog scale (VAS, 0–100 mm), and C-reactive protein (CRP) level. A good response was defined according the evaluation of the physician. We included 33 patients (24 women; mean age 79.2 ± 12.8 years). The number of good responders was 27 (81.8%). At day 4, patients showed decreased mean VAS pain score (from 64.8 ± 26.5 to 21.2 ± 19.7 mm, $p < 0.0001$), TJC (5.8 ± 5.0 to 1.0 ± 1.0, $p < 0.0001$), SJC (3.9 ± 2.7 to 0.9 ± 1.0, $p < 0.0001$), and CRP level (116.1 ± 71.6 to 26.0 ± 23.1 mg/l, $p < 0.0001$). Anakinra was well tolerated, without skin complications. Only one patient had pneumonitis that was resolved with oral antibacterial agents. Anakinra could be a relevant alternative for managing acute CPP arthritis when conventional therapies are ineffective or contraindicated.

Keywords Acute arthritis · Anakinra · Calcium pyrophosphate dehydrate · Treatment

Introduction

Calcium pyrophosphate deposition (CPPD) is a joint disease caused by deposition of CPP crystals. Although often asymptomatic, CPPD can be associated with acute mono- or polyarticular arthritis. The prevalence of CPPD increases with age, and acute CPP arthritis is frequently observed in older people [1, 2]. The European League Against Rheumatism (EULAR) recommends treating CPP arthritis with corticosteroids injection, oral non-steroidal anti-inflammatory drugs (NSAIDs), or colchicine [3]. Parenteral or oral corticosteroids are useful alternative treatment modalities for patients with polyarticular involvement or with acute CPP arthritis, non-response or unsuitability of other treatments.

Evidence to support the use of these treatments for acute CPP arthritis is mainly from the treatment of gouty attacks [4]. However, side effects can occur with NSAIDs (e.g., gastrointestinal bleeding, cardiovascular events, renal impairment) [4] and colchicine (e.g., myopathy or diarrhea) [5]. Diabetes can also limit the use of corticosteroids. These drugs may be also contraindicated or cannot be used at an optimal dose, especially among older patients with renal impairment. Thus, other therapeutic options are often required in clinical practice.

The main mechanism of crystal arthritis (including monosodium urate and CPP arthritis) is mature interleukin-1β (IL-1β) secretion. The pyrin domain-containing 3 (NLRP3) inflammasome mediates caspase-1 activation and subsequent secretion of IL-1 [6, 7]. IL-1 blockers such as anakinra and canakinumab have been evaluated in gout for treating acute arthritis [8–11]. Considering the role of IL-1 in the pathophysiology of inflammation during crystal diseases and the efficacy of IL-1 inhibitors in gouty arthritis, EULAR has allowed the use of such therapeutic agents for treating gout

Marion Thomas and Marine Forien contributed equally to this work.

✉ Marine Forien
marine.forien@aphp.fr

[1] Service de Rhumatologie, Hôpital Bichat, APHP, Université Paris Diderot, 46 rue Henri Huchard, 75018 Paris, France

flares in patients with frequent flares and with contraindications to conventional therapies [4].

In contrast to studies of anakinra in gout, only a few short case series and case reports have focused on its efficacy in CPP arthritis [12–17]. The aim of this study was to analyze the efficacy and safety of anakinra in acute CPP arthritis in a larger reported series.

Methods

Patient selection

In this monocenter retrospective study, we included all patients who received anakinra for CPP arthritis between January 2011 and 2017. All patients received anakinra because of insufficient response to others treatments among colchicine, corticosteroids, and/or NSAIDs. Among this population, eight patients included were previously reported in a multicenter pilot study [17]. As recommended [3], the diagnosis of CPPD was confirmed by the identification of CPP crystals in synovial fluid (SF) when available and/or the presence of typical imaging features of CPPD. Exclusion criteria were age < 18 years and concomitant gout. Medical history data including hypertension, diabetes mellitus, cardiovascular disease, history of gastroduodenal ulcer, renal impairment, and concomitant treatments including anticoagulants or antiplatelet drugs were collected.

Evaluation

Disease data collected were symptom duration, involved joints, and medications received before anakinra: corticosteroids (oral, parenteral, injection), colchicine, NSAIDs. For all patients, we collected data on the clinical evaluation before the first injection of anakinra (day 0), with swollen joint count (SJC) and tender joint count (TJC), patient evaluation of pain on a visual analog scale (VAS; 0–100 mm), and laboratory tests with C-reactive protein (CRP) level and creatinine clearance according to Modification of the Diet in Renal Disease.

To evaluate the efficacy of anakinra, we collected the following items 4 days after the first anakinra injection (day 4) if available: SJC and TJC, VAS pain score and CRP level. A good response was defined according to the evaluation of the physician or documentation in the chart of the phrase "good response" after anakinra treatment.

Statistical analysis

Data are reported as mean ±SD or number (%). Wilcoxon test was used to compare quantitative data. A two-tailed $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 33 patients (24 women) with acute CPP arthritis were included. The clinical characteristics of patients at baseline are summarized in Table 1. Mean age was 79.2 ± 12.8 years. At baseline (first injection of anakinra), mean duration of acute arthritis 13.2 ± 12.9 days. CPP arthritis was confirmed by the presence of CCP crystals in SF in 28/33 (84.8%) patients. For the remaining 5 patients, the diagnosis was confirmed by CPPD features seen on imaging. CPPD features were confirmed on radiography for 27 patients and ultrasonography for 26. At baseline, 18 patients had polyarticular involvement. Associated comorbidities were hypertension ($n = 24$), heart disease ($n = 19$), previous gastroduodenal ulcer ($n = 3$), diabetes mellitus ($n = 11$), and renal impairment ($n = 18$) with mean clearance 68.6 ± 23.9 ml/min/1.73 m^2. Concomitant medications with potential interaction with conventional therapies were oral anticoagulants ($n = 9$) and low-dose aspirin as an antiplatelet drug ($n = 10$). Mean VAS pain score was 64.8 ± 26.5 mm. Mean TJC and SJC were 5.8 ± 5.0 and 3.9 ± 2.7, respectively, and mean CRP level was 116.1 ± 71.6 mg/l (Fig. 1).

Treatment of CPP arthritis

Corticosteroids, NSAIDs and colchicine were previous treatments, without significant improvement in 27 patients. Among them, 13 were treated with colchicine (4 were treated with low dose of colchicine in prevention of acute CPP arthritis), 2 with NSAIDs, 4 with corticosteroids, 3 patients received colchicine and corticosteroids, 3 patients corticosteroids and NSAIDs, and 2 patients received NSAIDs, colchicine, and corticosteroids. Conventional therapies were contraindicated for the 6 remaining patients. The mean dose of corticosteroids was 20.8 ± 8.2 mg/day.

Among the 33 patients, 24 received the following protocol proposed by So et al. [18]: anakinra, 100 mg, administered subcutaneously (s.c.) daily for 3 days. For the remaining 9 patients, anakinra, 100 mg, was given s.c. daily for 1 to 6 days. The mean number of anakinra injections was 3.3 ± 0.8 per patient. For all patients, NSAIDs and colchicine were discontinued at the start of anakinra treatment.

Efficacy and safety of anakinra (Fig. 1)

Among the 33 patients, 32 had a documented visit at day 4; 27 (81.8%) showed good response. At day 4, patients showed decreased VAS pain score (from 64.8 ± 26.5 to 21.2 ± 19.7 mm, $p < 0.0001$), TJC (5.8 ± 5.0 to 1.0 ± 1.0, $p < 0.0001$), SJC (3.9 ± 2.7 to 0.9 ± 1.0, $p < 0.0001$), and

Table 1 Baseline characteristics of patients receiving anakinra for acute calcium pyrophosphate (CPP) arthritis ($n = 33$)

Clinical characteristics	
Age (years), mean ± SD	79.2 ± 12.8
Male, *n* (%)	9 (27.2)
Duration of present flare (days), mean ± SD	13.2 ± 12.9
Monoarticular involvement, *n* (%)	2 (6.1)
Oligoarticular involvement, *n* (%)	13 (39.4)
Polyarticular involvement, *n* (%)[a]	18 (54.5)
Comorbidities, *n* (%)	
Hypertension	24 (72.7)
Heart disease	19 (57.5)
Previous gastroduodenal ulcer	3 (9.1)
Diabetes mellitus	11 (33.3)
Renal impairment	18 (54.5)
Medications, *n* (%)	
Oral anticoagulants	9 (27.2)
Low-dose aspirin and/or other antiplatelet drug	10 (30.3)
Diagnosis modalities, *n* (%)	
Ultrasonography-detected CPP deposition	26 (78.8)
Radiography-detected CPP deposition	27 (81.8)
Presence of CPP crystals in synovial fluid	28 (84.8)
Treatment received before anakinra, *n* (%)	
Colchicine	18 (54.5)
NSAIDs	7 (21.2)
Corticosteroids	12 (36.4)

NSAIDs non-steroidal anti-inflammatory drugs

[a] Swollen joint count at baseline ≥ 4

CRP level (116.1 ± 71.6 to 26.0 ± 23.1 mg/l, $p < 0.0001$). At day 4, among 12 patients receiving corticosteroids at baseline, 5 discontinued this treatment and the corticosteroid consumption decreased from 20.8 ± 8.2 to 7.0 ± 1.8 mg/day. Five patients had no or only partial response. For one patient, the final diagnosis was modified to polymyalgia rheumatic disease; another could decrease the consumption of corticosteroids (30 to 10 mg/day).

After a mean follow-up of 6.8 ± 5.9 months, relapse occurred in 9 (27.3%) patients. The mean time to relapse was 2.1 ± 1.8 months.

Anakinra was well tolerated, without skin complications. Only one patient had acute bacterial pneumonitis that resolved with an oral antibacterial agent. This case was described in the published pilot study [17].

Discussion

In this study, we reported 33 cases of acute CPPD arthritis treated with anakinra. A significant decrease of TJC, SJC, VAS, and CRP were confirmed with a good tolerance.

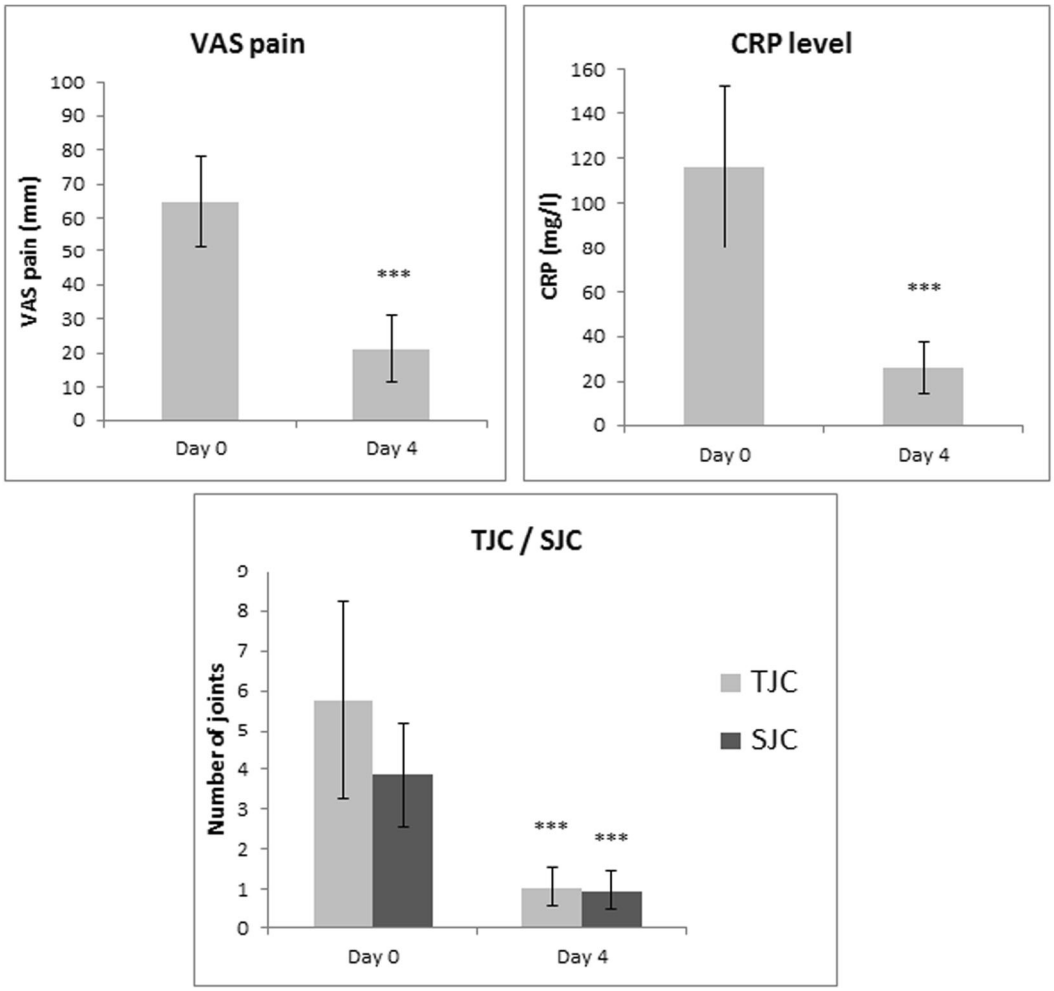
CPPD and gout are the main crystal-related diseases, and acute arthritis is one of the main clinical presentations. The mechanism of this crystal-related inflammation is now well known.

Monosodium urate and CCP crystals activate IL-1β production via the NLRP3 inflammasome [6, 7, 19]. This primordial role of IL-1β has led to considering anti-IL1 agents as an alternative to conventional therapeutics for treating gouty arthritis. Indeed, several studies suggested that anakinra and other anti-IL-1 agents such as canakinumab or rilonacept could be efficient, with a good safety profile, among patients with gouty arthritis with failure or contraindication to conventional therapies [8, 11, 18, 20–22]. Recent EULAR recommendations for gout allowed for use of these anti-IL-1 agents in these cases [4]. In CPPD, only a few reports with a few patients have described the same efficacy and safety profile [13–17] (Table 2).

In this study, we examined the use of anakinra for treating acute CPPD arthritis. To our knowledge, this is the largest reported series of patients receiving anakinra for the disease. We observed a high response rate and a rapid relief of inflammatory symptoms. Moreover, the safety was good, with only one benign infectious complication. These results agree with previously published data [17]. For acute CPP arthritis, only case reports [13–15, 17] suggested an efficacy of anakinra. In a multicenter study of 16 patients [17], we previously observed good efficacy, with relatively good tolerance, for treating CPP arthritis. In contrast to the treatment for gout, only anakinra has been evaluated for chronic CPP arthritis. In this form, a recent report of three patients suggested efficacy for only one patient [12]. Moreover, in our study, relapse occurred in 27.3% of patients, with a mean time to relapse of 2.2 ± 1.8 months. The lack of efficacy of anakinra in patients with chronic CPP arthritis [12] and the relapse rate could also be explained by the short half-life of anakinra. The presence of systemic inflammation probably also affects the response to anakinra, with a higher response for patients with inflammatory syndrome [23]. In our study, only one patient had a CRP level within the normal range, and the median CRP level was 110 mg/l, which could explain our high response rate.

Our findings suggest that anakinra may be an alternative treatment to conventional therapies for the acute form of CPPD. With its short half-life, it is relevant for acute CPP arthritis, leading to rapid relief of symptoms, particularly in an older-age population. Indeed, in this population, NSAIDs, colchicine and corticosteroids might be poorly tolerated or contraindicated because of renal impairment, history of gastrointestinal ulcer, diabetes mellitus, or drug interactions.

We observed relatively good tolerance of anakinra, with only one adverse event reported (bacterial pneumonitis) after



VAS: visual analog scale (0-100 mm), CRP: C-reactive protein, TJC: tender joint count, SJC swollen joint count

***p<0.0001 compared to day 0

Fig. 1 Efficacy of anakinra in acute calcium pyrophosphate arthritis

three injections. The infection resolved with oral antibacterial agents. Although anakinra is authorized for patients with clearance > 30 ml/min (European Medicines Agency, 2006), this treatment could be given to patients with kidney failure or on hemodialysis. In fact, NSAIDs and colchicine are contra-indicated for patients with clearance < 30 ml/min and the risk of infection could also limit steroids injections for patients on hemodialysis. In our study, three patients had severe renal impairment (clearance < 30 ml/min) and one was on hemodialysis. They received three injections of anakinra without any complications. Hung et al. showed a decrease in levels of biomarkers of inflammation in patients on hemodialysis with chronic inflammation (no history of crystal arthritis) who received anakinra three times a week for 4 weeks versus placebo, without serious adverse events [24]. Similar efficacy and safety were also reported in gouty patients with severe renal insufficiency and or on hemodialysis [25].

Our study has some limitations. First, the study was retrospective and analysis of efficacy was done according data collection in medical records limiting the exact assessment of efficacy. Moreover, we used different modalities of anakinra administrations and we in absence of comparison of anakinra with another treatment, we cannot speculate whether anakinra was superior to conventional therapies. However, this real-life observational study is the largest reported series and suggested, similar to gout, that anakinra might represent an interesting alternative to these conventional treatments for acute CPP arthritis. Future randomized trials are necessary to confirm our results and to validate the use of anakinra in CPP arthritis.

In conclusion, our results suggest that anakinra could be a relevant alternative for managing acute CPP arthritis, leading to rapid relief of inflammatory symptoms, with a good tolerance and a short period of immunosuppression.

Table 2 Previous studies evaluated anakinra for the management of CPPD arthritis

References	Study	Number of patients	Age (years)	Duration of anakinra treatment	Results	Tolerance
McGonagle et al [14]	Case report Chronic CPPD arthritis	1	63	100 mg/day for > 6 months	Clinical efficient in 14 days Normal CRP level in 3 months	No side effect
Diamantopoulos et al [16]	Case report Chronic CPPD arthritis	1	54	100 mg/day for 8 months	Good response after 1 week	No side effect
Moltó et al [13]	Retrospective study Acute CPPD arthritis	5	Mean: 71	100 mg/day for 3 days	Decrease of joint pain, 60 ± 17 reduced to 10 ± 10 mm Decrease of mean CRP level, 58 ± 43 to 4 ± 2 mg/L	Good tolerance One injection-site skin reaction without infection
Couderc et al [12]	Case series of chronic CPPD arthritis	3	68 49 68	100 mg/ day for 1 year for 1 patient 100 mg/day for 3 months for 2 patient	No efficient for 2 patients 1 patient: no flare and 3 swollen joints vs 7 swollen joints before treatment	No side effect
Ottaviani et al [17]	Retrospective study Acute CPPD arthritis	16	Mean: 80.2	12 patients: 100 mg/day for 3 days Others patients: 7, 8, 1 days and 6 months	Good response, 62.5% Partial response, 25% No response, 12.5%	Good tolerance One patient: uncomplicated acute bacterial pneumonitis
Aouba et al [15]	Case series Acute CPPD arthritis	2	65 84	100 mg/day for 9 days 100 mg/day for 11 days	Complete remission	No side effect

CPPD calcium pyrophosphate deposition

Acknowledgements We thank Laura Smales (BioMedEditing) for copyediting.

Compliance with ethical standards

The Institutional Review Board (No. 12-011) of Paris North Hospitals approved this study. Written informed consent was obtained from all participants in agreement with French bioethics laws.

Disclosures None.

References

1. Richette P, Bardin T, Doherty M (2009) An update on the epidemiology of calcium pyrophosphate dihydrate crystal deposition disease. Rheumatology (Oxford) 48:711–715
2. Neame RL, Carr AJ, Muir K, Doherty M (2003) UK community prevalence of knee chondrocalcinosis: evidence that correlation with osteoarthritis is through a shared association with osteophyte. Ann Rheum Dis 62:513–518
3. Zhang W, Doherty M, Bardin T, Barskova V, Guerne P-A, Jansen TL, Leeb BF, Perez-Ruiz F, Pimentao J, Punzi L, Richette P, Sivera F, Uhlig T, Watt I, Pascual E (2011) European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. Ann Rheum Dis 70:563–570
4. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castañeda-Sanabria J, Coyfish M, Guillo S, Jansen TL, Janssens H, Lioté F, Mallen C, Nuki G, Perez-Ruiz F, Pimentao J, Punzi L, Pywell T, So A, Tausche AK, Uhlig T, Zavada J, Zhang W, Tubach F, Bardin T (2017) 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 76:29–42
5. Terkeltaub RA (2009) Colchicine update: 2008. Semin Arthritis Rheum 38:411–419
6. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J (2006) Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 440:237–241
7. Mitroulis I, Skendros P, Ritis K (2010) Targeting IL-1beta in disease; the expanding role of NLRP3 inflammasome. Eur J Intern Med 21:157–163
8. Ottaviani S, Moltó A, Ea H-K, Neveu S, Gill G, Brunier L, Palazzo E, Meyer O, Richette P, Bardin T, Allanore Y, Lioté F, Dougados M, Dieudé P (2013) Efficacy of anakinra in gouty arthritis: a retrospective study of 40 cases. Arthritis Res Ther 15:R123
9. Pascart T, Richette P (2017) Current and future therapies for gout. Expert Opin Pharmacother 18:1201–1211
10. Sivera F, Wechalekar MD, Andrés M, Buchbinder R, Carmona L (2014) Interleukin-1 inhibitors for acute gout. Cochrane Database Syst Rev 9:CD009993
11. Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, Krammer G, Murphy V, Richard D, So AK (2012) Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis 71:1839–1848
12. Couderc M, Mathieu S, Glace B, Soubrier M (2012) Efficacy of anakinra in articular chondrocalcinosis: report of three cases. Joint Bone Spine 79:330–331
13. Moltó A, Ea H-K, Richette P, Bardin T, Lioté F (2012) Efficacy of anakinra for refractory acute calcium pyrophosphate crystal arthritis. Joint Bone Spine 79:621–623
14. McGonagle D, Tan AL, Madden J, Emery P, McDermott MF (2008) Successful treatment of resistant pseudogout with anakinra. Arthritis Rheum 58:631–633
15. Aouba A, Deshayes S, Frenzel L, Decottignies A, Pressiat C, Bienvenu B et al (2015) Efficacy of anakinra for various types of crystal-induced arthritis in complex hospitalized patients: a case series and review of the literature. Mediat Inflamm 2015:792173
16. Diamantopoulos AP, Brodin C, Hetland H, Haugeberg G (2012) Interleukin 1β blockade improves signs and symptoms of chronic calcium pyrophosphate crystal arthritis resistant to treatment. J Clin Rheumatol 18:310–311
17. Ottaviani S, Brunier L, Sibilia J, Maurier F, Ardizzone M, Wendling D, Gill G, Palazzo E, Meyer O, Dieudé P (2013) Efficacy of anakinra in calcium pyrophosphate crystal-induced arthritis: a report of 16 cases and review of the literature. Joint Bone Spine 80:178–182
18. So A, De Smedt T, Revaz S, Tschopp J (2007) A pilot study of IL-1 inhibition by anakinra in acute gout. Arthritis Res Ther 9:R28
19. Gross O, Yazdi AS, Thomas CJ, Masin M, Heinz LX, Guarda G et al (2012) Inflammasome activators induce interleukin-1α secretion via distinct pathways with differential requirement for the protease function of caspase-1. Immunity 36:388–400
20. Chen K, Fields T, Mancuso CA, Bass AR, Vasanth L (2010) Anakinra's efficacy is variable in refractory gout: report of ten cases. Semin Arthritis Rheum 40:210–214
21. Ghosh P, Cho M, Rawat G, Simkin PA, Gardner GC (2013) Treatment of acute gouty arthritis in complex hospitalized patients with anakinra. Arthritis Care Res 65:1381–1384
22. Terkeltaub R, Sundy JS, Schumacher HR, Murphy F, Bookbinder S, Biedermann S, Wu R, Mellis S, Radin A (2009) The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo-controlled, monosequence crossover, non-randomised, single-blind pilot study. Ann Rheum Dis 68:1613–1617
23. Verhoeven F, Prati C, Godfrin-Valnet M, Guillot X, Wendling D (2013) IL1 blockade in crystal-induced arthritis: impact of disease duration and the inflammatory syndrome. Comments on the article by Couderc M. et al. "Efficacy of anakinra in articular chondrocalcinosis". Joint Bone Spine 80:115–116
24. Hung AM, Ellis CD, Shintani A, Booker C, Ikizler TA (2011) IL-1β receptor antagonist reduces inflammation in hemodialysis patients. J Am Soc Nephrol 22:437–442
25. Thueringer JT, Doll NK, Gertner E (2015) Anakinra for the treatment of acute severe gout in critically ill patients. Semin Arthritis Rheum 45:81–85