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Original article

Efficacy of anakinra in calcium pyrophosphate crystal-induced arthritis: A report of 16 cases and review of the literature

Sébastien Ottaviani[a], Lauren Brunier[a], Jean Sibilia[c], François Maurier[d], Marc Ardizzone[e], Daniel Wendling[f], Ghislaine Gill[a], Elisabeth Palazzo[a], Olivier Meyer[a], Philippe Dieudé[a,b,*]

[a] *Service de rhumatologie, hôpital Bichat, université Paris-Diderot, AP–HP, 46, rue Henri-Huchard, 75018 Paris, France*
[b] *Inserm U699, université Paris-Diderot, Paris, France*
[c] *Service de rhumatologie, CHU de Strasbourg-Hautepierre, Strasbourg, France*
[d] *Service de médecine interne, CH de Metz, Metz France*
[e] *Service de rhumatologie, CH de Mulhouse, Mulhouse, France*
[f] *Service de rhumatologie, CHU de Besançon, Besançon, France*

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ABSTRACT

Objectives: Calcium pyrophosphate (CPP) crystal-induced arthritis occurs particularly in elderly people. This population has frequently associated comorbidities and treatments, which could limit the use of conventional therapies (colchicine, non-steroidal anti-inflammatory drugs and corticosteroids). The aim of the study was to evaluate the efficacy and tolerance of anakinra in patients with CPP crystal-induced arthritis.
Methods: We performed a multicentric retrospective chart review of patients who received anakinra for CPP crystal-induced arthritis. Demographic information, comorbidities, co-prescription, short-term treatment outcomes, adverse event, complication and subsequent flares were reviewed.
Results: A total of 16 patients (12 females, mean age: 80.2 ± 11.1 years) received anakinra (100 mg subcutaneously per day). The mean number of anakinra injection was 15.5 ± 42.9 per patient (median: 3). All patients had contraindication and/or failure to conventional therapies. The majority (14 [87.5%]) of patients with CPP crystal-induced arthritis demonstrated a beneficial response to anakinra therapy: 10 good responses and four partial responses. A relapse occurred in six (37.5%) patients (mean time to relapse: 3.4 ± 4.9 months). One patient had an acute bacterial pneumonitis.
Conclusion: Our results suggest that anakinra is relatively well tolerated and could be a good option in the treatment of CPP crystal-induced arthritis, illustrating that IL-1β blockade may be helpful to control flares in patients having CPP crystal-induced arthritis for which conventional therapies are ineffective or contra-indicated.

1. Introduction

Calcium pyrophosphate deposition (CPPD) may present diverse clinical phenotypes, from asymptomatic chondrocalcinosis to acute calcium pyrophosphate (CPP) crystal-induced arthritis and osteoarthritis with CPPD, which may be associated with chronic symptoms and functional impairment of variable severity. CPP crystal-induced arthritis is the third most common inflammatory arthritis [1]. CPPD can be identified by X-rays, ultrasonography or by histological examination [2–4]. Acute CPP crystal arthritis may be associated with high inflammatory symptoms. Thus, one of the goals of the management will be rapid relief of inflammation. The rationale to support the use of oral non-steroidal anti-inflammatory drugs (NSAIDs), steroids or oral colchicine in acute CPP crystal-induced arthritis is extrapolated from evidence relating to the management of acute attacks of gout [5]. In contrast to gout, CPPD predominates in the older patient. Thus, care must be taken when advising drug treatments as there is abundant evidence about side effects from the use of colchicine (e.g., diarrhea) [6] and NSAIDs (e.g., gastrointestinal bleeding, cardiovascular events, renal impairment) [7,8]. These side effects greatly limit the use of these treatments, particularly in older people who often have comorbidities that increases the likelihood of toxicity or drug interaction.

Recent advances have stimulated new interest in the area of crystal arthritis, as crystals, including monosodium urate (MSU) and CPP, can be considered to be endogenous "danger signals" and are potent stimulators of immune as well as non-immune cells. Recent findings suggest that biological crystals are generally pro-inflammatory through their interactions with the NLRP3

* Corresponding author.
E-mail address: philippe.dieude@bch.aphp.fr (P. Dieudé).

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inflammasome complex, leading to NLRP3 activation, proteolytic cleavage and maturation of pro-interleukin-1β (pro-IL-1β) and secretion of mature IL-1β [9,10]. More recently, a role of IL-1α in gout inflammation was emerging, independently of caspase-1 activation [11]. Anti-IL1 agents, such as anakinra, which can inhibit both IL-1α and IL-1β [11], have been evaluated in gout, either in treatment of the acute attack or in the prevention of an attack while initiating urate-lowering therapy [12–15]. Overall, IL-1 inhibitors appear to be highly effective in reducing pain and signs of inflammation validating the concept that IL-1β and Il-1α are key cytokines in gout inflammation. IL-1 production by activation of NLRP3 inflammasome is considered as a common feature of crystal-induced inflammation. Consequently, targeting IL-1 may also be relevant in crystal-induced arthritis, notably in CPP crystal-induced arthritis patients, particularly those who had contraindications or intolerance to conventional drugs (i.e. NSAIDs, colchicine). Nonetheless, very few studies have reported the use IL-1β in CPP crystal-induced arthritis, to illustrate this concept: five case reports suggested that anakinra could be useful in both prevention and treatment of acute attacks of CPPD [16–18]. The purpose of this study was to analyze the use of anakinra for acute CPP crystal-induced arthritis in our country, focusing on the indications for treatment, the drug's efficacy and safety.

2. Methods

2.1. Patients

This is a retrospective chart review of patients who received anakinra for CPP crystal-induced arthritis. We performed a multicentric retrospective study; patients were identified through recall by the treating rheumatologists and by searching electronic medical records if available with the keyword "anakinra" or "Kineret," and data were collected through chart review. Patients receiving anakinra who were identified to have autoimmune diseases were excluded. Inclusion criteria comprised a diagnosis of CPP crystal-induced arthritis and at least one documented visit after the acute event requiring anakinra. As recommended, definitive CCP crystal-induced arthritis diagnosis was allowed by identification of CPP crystals in synovial fluid (SF) when available or presence of typical radiologic features evocating CPP deposition [2]. All patients provided informed written consent to receive anakinra.

2.2. Evaluation

The response was retrospectively assessed including at baseline and at the first documented visit after the flare the following items, if available: swollen (SJC) and tender joint count (TJC), patient's evaluation of pain by using visual analogic pain (VAS pain) scale (mm) and C-reactive protein (CRP) levels (mg/l). The outcome of anakinra treatment was categorized as a good response, partial response, or no response. A good response was defined as a report of complete or near complete resolution of joint symptoms (TJC and SJC) or documentation in the chart of the word "good" response after anakinra treatment. A partial response was defined as a report of improvement in joint symptoms but not a "good" response or complete resolution. No response was defined as the absence of relieve.

3. Results

3.1. Baseline characteristics

A total of 16 patients (12 females) who received anakinra for CPP crystal-induced arthritis were included. The clinical characteristics of the 16 patients are summarized in Table 1. Mean age was 80.2 ± 11.1 years and mean duration of flare was 10.7 ± 6.6 days. Mean VAS pain was 77.4 ± 11.9. Mean TJC and SJC was 6.5 ± 2.6 and 5.9 ± 2.1, respectively. The mean level of CRP was 97.2 ± 57.4 mg/l.

Presence of CPP crystal was documented by SF analysis in 13/16 patients (81%). Typical radiologic features evocating CPP deposition were found in 15/16 patients (94%).

Ultrasonography (US) power-Doppler was performed in 14 patients and showed effusion and/or hypervascularisation of all symptomatic joints. US features of CPP deposition such as calcifications of menisci and/or carpal triangular ligament were present in 13/16 patients (81%).

Corticosteroids were previously administered in 11 patients, NSAIDs and/or colchicine in seven patients. Among the 11 patients receiving oral corticosteroids, the mean level of prednisone dose was 22.8 ± 7.5 mg/day. All the patients had no significant response and/or contraindication to conventional therapy for CPP arthritis.

Associated comorbid conditions were arterial hypertension (HT) ($n = 9$), coronary artery disease (CAD) ($n = 9$), previous stomach ulcer ($n = 1$), diabetes mellitus (DM) ($n = 4$), renal impairment (RI) ([$n = 12$], mean clearance MDRD: 74.1 ± 16.6 ml/min/1,73m^2). Concomitant medications with potential interaction with conventional therapies were oral anticoagulants (OA) ($n = 5$), low-dose of aspirin as an antiplatelet drug (LDA) ($n = 4$).

Among the 16 patients, 12 were treated following the protocol proposed by So et al. [13]: anakinra was administered subcutaneously (SC) daily at a dose of 100 mg for 3 days. Regarding four patients, anakinra (100 mg/day SC) was administered for 7 days, 8 days, 1 and 6 months, respectively. The mean number of anakinra injection was 15.5 ± 42.9 per patient. On starting anakinra, the NSAID or colchicine therapy was discontinued for all patients. Patients who were already on oral corticosteroids continued their treatment at the same dose.

3.2. Effects of anakinra on calcium pyrophosphate arthritis

Among the 12 patients who were treated following the protocol suggested by So et al., all had a documented visit at day 4. The number of patients with good, partial and no response was eight (67%), three (25%) and one (8%), respectively. In these patients, IL-1β blockade led to a strong decrease of VAS pain (78.7 ± 11.6 to 28.8 ± 6.2 mm), mean TJC (6.9 ± 2.5 to 2.0 ± 0.6), SJC (6.3 ± 1.9 to 1.9 ± 0.7) and CRP level (109.8 ± 55.5 to 21.1 ± 10.3 mg/l) (Table 2). At day 4, none discontinued corticosteroid. Interestingly, the corticosteroid consummation between baseline and day 4 was decreased from 24.4 ± 6.2 to 4.6 ± 4.1 mg/day. Ultrasonography power-Doppler of baseline symptomatic joint was available at day 4 for 12 patients. Eleven patients (91.7%) had showed a decrease or complete resolution of synovial hypervascularisation US signal Fig. 1.

In the four remaining patients treated by other protocols of anakinra previously mentioned, a good ($n = 2$), partial ($n = 1$) and no response ($n = 1$) was noted (Table 2).

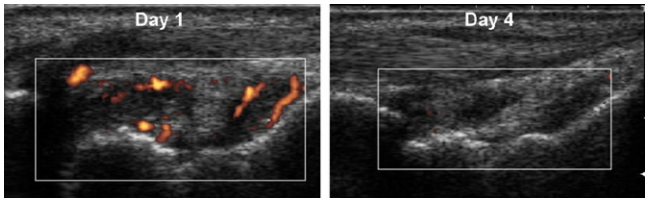

Fig. 1. Ultrasonography with power-Doppler of the right wrist (Patient nº 1). At day 1, mode B ultrasound revealed synovial hypertrophy with hypervascularisation in power-Doppler. After 3 days of anakinra, ultrasonography showed a decrease of the synovial hypertrophy and no vascularisation in power-Doppler.