Joint Bone Spine 86 (2019) 83–88

Available online at ScienceDirect www.sciencedirect.com

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Original article

Efficacy of anakinra in acute hydroxyapatite calcification-induced joint pain: A retrospective study of 23 cases

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ARTICLE INFO

Article history:
Accepted 14 May 2018
Available online 5 June 2018

Keywords:
Hydroxyapatite
Calcification
Anakinra
Ultrasonography
Follow-up

ABSTRACT

Objective: Hydroxyapatite (HA) crystal calcifications in or around the joint can induce acute flares with severe pain. A previous pilot study suggested that the interleukin-1β (IL-1β) inhibitor anakinra was effective. The goal of this observational study was to confirm these results in a larger set of patients and to report on the long-term follow-up.
Methods: Flare was defined as acute pain for < 10 days. Calcification in or around a joint (rotator cuff: 15/23 patients) was confirmed by conventional radiography and/or ultrasonography (US). Anakinra 100 mg daily was administered subcutaneously for 1 to 3 consecutive days. Clinical data collected before the injection and on days 3 and 21 included pain score on a visual analog scale (VAS, 0–10 cm) and C-reactive protein (CRP) level. When available, US baseline and follow-up findings were compared. Long-term follow-up data were collected from patient charts and/or after a phone call.
Results: 23 patients (15 males, mean [SD] age 58 [11] years) were included. Baseline mean (SD) VAS pain was 7.7 (1) cm and CRP level was elevated in half of the patients. After therapy, mean (SD) VAS pain score decreased rapidly in the first 3 days to 1.6 (1.4) cm ($P < 0.001$) and remained stable for 3 weeks at 1.8 (2.1) cm. US assessment revealed decreased Doppler intensity but no significant change in size of calcifications. No significant side effects were noted. After long-term follow-up (median duration 24 months), half of the patients still had some chronic pain, but only 4 experienced acute relapse.
Conclusion: This study suggests that IL-1β inhibition may be an efficient therapeutic approach for acute HA flare, with a good safety profile.

1. Introduction

Hydroxyapatite (HA)-related calcification in or around a joint is a common condition. These calcifications can be asymptomatic but can also be associated with chronic or acute inflammatory pain. These acute flares are mainly linked to the dissolution of HA crystals and can occur in tendons, bursae or even joints, notably in the shoulder [1]. The flares are usually self-limiting but can last up to 2 or 3 weeks, with intense pain and limitation of function. Non-steroidal anti-inflammatory drugs (NSAIDs) and steroid infiltrations can be insufficient to control the symptoms, but in some patients, these therapies can be contraindicated [2], so alternative therapies are required.

The mechanism leading to the sudden dissolution of the calcific material remains largely unexplained [3]. The liberation of small carbonate calcium crystals seems to induce, like for gout, an activation of macrophages leading to a vascular invasion of the tendon, and a massive local migration of neutrophils [3–5] responsible for the inflammation.

In other crystal diseases such as gout and calcium pyrophosphate disease (CPPD), interleukin-1 (IL-1) appears to be the main pro-inflammatory cytokine implicated in the inflammatory process. Similarly, for these crystal diseases, studies in animal models have confirmed that IL-1 inhibition was able to block the inflammation induced by carbonate calcium material [4], which suggests that anti-IL-1 agents could be effective in treating HA flares. In gout, the concept that IL-1 inhibition may be clinically effective has been demonstrated with three different inhibitors [6–8]. In CPPD,

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https://doi.org/10.1016/j.jbspin.2018.05.008
1297-319X/

anakinra was effective for acute arthritis, with a good safety profile [9]. In a previous pilot study of five patients with acute HA hyperalgic shoulders, anakinra showed rapid relief of pain within 1 day and recovery of mobility after 3 days [10].

In this study, we aimed to confirm the results of the pilot study in a larger set of patients and to extend the observation to other localizations, with a long-term follow-up.

2. Methods

2.1. Patient selection

We retrospectively analyzed data for all consecutive patients who received anakinra for an acute flare secondary to HA calcification inflammation in two different hospital rheumatology departments (Lausanne and Paris) between March 2011 and July 2017. To be included in the study, patients had to have acute pain at rest for < 10 days, evidence of calcification in or around the painful joint (ultrasonography [US] and/or conventional radiography), and failure of a short (at least 3 days) course of full-dose NSAIDs. Exclusion criteria were steroids therapy in the previous 2 weeks, current infection, and a concomitant diagnosis of CPPD, gout or another rheumatologic disease that could explain the symptoms. When patients had chronic symptoms, anakinra was prescribed only when those patients reported an acute exacerbation of the symptoms at rest and not only mechanical pain.

Because this was an investigator-driven study, no participation from the pharmaceutical company was requested, and medication was delivered on the basis of compassionate use.

2.2. Evaluation

At inclusion, disease data collected were symptom duration, involved joints, previous medications and comorbidities. Before anakinra administration (day 0), patients underwent clinical examination, evaluation of pain by a visual analog scale (VAS, 0–10 cm) [11] and laboratory tests including C-reactive protein (CRP) level (mg/L). Clinical evaluation was limited to the acute phase (short-term follow-up). From the results of a pilot study [6], clinical and VAS pain evaluations were repeated on days 3 and 21. CRP level was again tested on day 3.

2.3. Imaging assessment

US and/or radiography were performed before the treatment in 22 and 20 patients, respectively, and in most patients at least once again after the treatment. US evaluation was performed by trained rheumatologists who used an Esaote MyLab70 machine (Bichat hospital, Lausanne hospital) or GE logic 90 machine (Lausanne hospital). Calcification was defined as a hyperechoic lesion with or without an acoustic shadow according to the density of the calcification. The size and US features of the calcifications, when available, were compared before and after treatment. The intensity of power Doppler findings, when available, was estimated semi-quantitatively on US charts (0: no; + = low; ++ = moderate; +++ = intense Doppler activity). The local radiologist performed radiography of calcifications before anakinra treatment for all patients and when needed during the short-term follow-up (21 days).

2.4. Modality of anakinra treatment

Because anakinra is not yet an accepted compound for this indication, consent was requested and given after the expected results, and potential side effects were explained to all patients. The regimen for anakinra injection was derived from that used for acute gout [12] and in the pilot study. It was limited to a maximum of 3 subcutaneous injections. The study was approved by the local Swiss ethics committee (CRV: 2017-00270).

2.5. Long-term follow-up

Late onset regarding the persistence of chronic pain and the occurrence of new flares was obtained from the patient's medical chart and by phone calls. The same VAS was used to evaluate residual local pain at the time of the phone call.

2.6. Statistical analysis

We used Fisher's exact test, chi^2 test, paired t test and Mann-Whitney test as appropriate for data analysis. $P \leq 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

We examined data for 23 patients (15 [65%] males, mean [SD] age 58 [11] years); 17 (including the five from the pilot study) [10] were recruited from Lausanne and 6 from Paris. The clinical and demographic characteristics of these patients are detailed in Table 1. The main location of HA joint pain was the shoulder ($n = 15$) followed by the hand or wrist ($n = 3$), foot ($n = 4$) and acromioclavicular joint ($n = 1$). Twelve patients reported chronic pain in the affected joint and 8 (36%) had a previous acute HA joint flare. At baseline, the mean (SD) VAS pain score was 7.6 (1.9) cm.

Sixteen patients received the full regimen of 3 injections, but some felt so well after the first or second injection that they or their doctors decided on no further injections.

For the 17 patients with a detailed clinical assessment, the active and passive motion of the affected joint was severely restricted in most (Appendix A, file S1; See the supplementary material associated with this article online). X-rays confirmed US calcifications (Fig. 1) when both procedures were available (19 patients). CRP level was elevated in half of the patients tested (9/19), with a mean (SD) baseline level of 29 (52) mg/L (normally < 10 mg/mL) (Table 2).

US was performed at baseline for 22/23 patients. A detailed description of the calcification was available for 17. The mean (SD) size of calcifications was 11 (6) mm. Only 2 (12.5%) patients showed an arc-shaped aspect with shadowing suggesting a highly calcified and solid concretion. The others had a nodular (Fig. 1) or fragmented calcification with rounded borders and no shadowing, which suggested non-solid calcification according to the US classification of Chiou [13]. This latter aspect also suggests a calcification ready for or in the process of dissolution [11]. When the calcifications were located in the rotator cuff, different tendons could be implicated: the infra scapularis ($n = 5$), supra spinatus ($n = 4$), infraspinatus ($n = 1$) and biceps ($n = 1$). In the other locations, the calcification was located in the capsule of the joint in the soft tissue or in the tendon sheath. Doppler signals were present for all 17 patients evaluated and were very or moderately intense around the calcification in 15. Overall, 12/17 patients (70%) showed effusion in the bursa, joint or tendon sheath.

Table 2 compares CRP level, VAS pain and US signs of inflammation around the calcification (Doppler and or effusion). CRP level was elevated mostly when the calcification was localized at the shoulder, where the amount of local inflammation was probably sufficient to induce systemic inflammation.

Table 1
Characteristics of the patients at baseline and at the end of follow-up.

Patients	Age(Years)	GenderF/M	Location of calcification	Chronic symptoms or previous flares (yes/no)	New flares, *n*	Time to flare (months)
1	71	F	Shoulder	No	0	
2	68	F	Shoulder	No	0	
3	57	M	Shoulder	Yes	1	2
4	57	F	Shoulder	No		
5	50	M	Shoulder	No	0	
6	40	F	Shoulder	No	0	
7	53	F	Shoulder	Yes	0	
8	56	M	Shoulder	No	0	
9	66	F	Shoulder	No	0	
10	53	F	Shoulder	Yes	3	60
11	60	m	Shoulder	No	0	
12	50	F	Shoulder	No	0	
13	64	M	Hand	No	0	
14	28	M	Feet	No	0	
15	52	F	Acromio-clavicular	Yes	0	
16	36	F	Shoulder	Yes	1	3
17	43	F	Hand	Yes	1	0.5
18	61	F	Feet	Yes	0	
19	87	F	Feet	Yes	0	
20	93	F	Shoulder	No	0	
21	66	M	Wrist	Yes	0	
22	49	F	Feet	Yes	2	2
23	65	F	Shoulder	Yes	0	
Total	*57*	*15/7*		*11/23*	*8*	

Characters in italics: numbers / total evaluated.

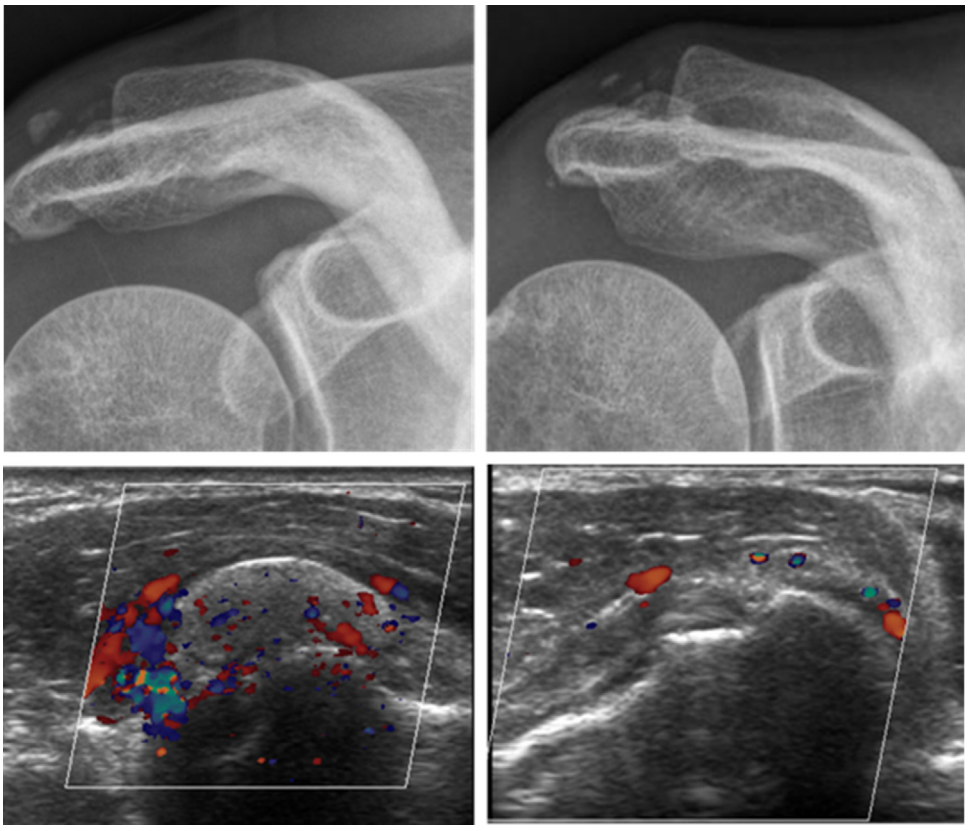

Fig. 1. Top: X-ray fragmentation and reduction in size of an acromio-clavicular calcification 3 weeks after subcutaneous anakinra injection. Bottom: reduced Doppler activity for a subscapularis calcification 3 days after subcutaneous anakinra injection.

3.2. Immediate and short-term follow-up

Twelve patients received the complete regimen of three anakinra injections, 8 had two injections and 3 a single injection. After 3 days of treatment, the mean (SD) VAS pain score significantly decreased from 7.6 (2) to 1.6 (1.4) ($P < 0.0001$) (Fig. 2). Except for 2 patients, all showed normalized CRP level. After 3 weeks, mean (SD) VAS evaluation was available for 15 patients and scores remained stable at 1.9 (2.1) cm. Two patients who received a single injection of anakinra reported a new flare that was treated by one additional injection, with efficacy (Table 1). Recovery of motion at the shoulder was almost complete for the 10 patients tested at baseline and

Table 2
Comparison between baseline CRP (*normal* < 10 mg/mL), VAS pain (0–10) at and US inflammation according to the localization of the calcification.

CRP	VAS	Doppler	Effusion	Localisation
216	5			Shoulder
108	9	+++	n	Shoulder
41	10	+++	y	Shoulder
28	10			Shoulder
28	7	+++	y	Shoulder
21	6	+++	y	Feet
19	5			Feet
18	10	+++	y	Shoulder
17	10	+++	y	Shoulder
9	5			Feet
7	8	++	y	Shoulder
6	7			Feet
5	10			Wrist
4	8	+++		Shoulder
4	8	++	y	Shoulder
3	8	+++	y	Shoulder
3	7			Shoulder
2	3			Hand
1	6	++	y	Hand
	10	+++	y	Shoulder
	9	+++	y	Acromio-clavicular
	8	+++	y	Shoulder
	8	+++	n	Shoulder

Doppler scores: 0 = no; + = low; ++ = moderate; +++ = intense activity; y: yes; n: no.

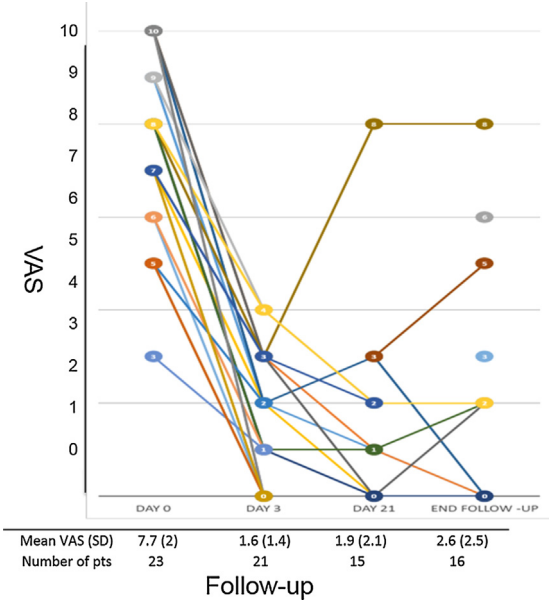

Fig. 2. Mean (SD) visual analog scale (VAS) pain score at baseline and during follow-up.

after 3 weeks (Appendix A, file S1). No side effect related to the drug was reported during or in the weeks after the treatment.

US follow-up data were available for 13 patients; for 8, the first follow-up US was performed at the end of treatment. The remaining 10 patients underwent a second US or the first US within 4 weeks after treatment. At day 3, effusions in the bursa or the joints present at baseline had disappeared, but residual Doppler signals were still present (Fig. 1). At the second US control, only 2 patients presented residual Doppler activity (Table 3).

Fragmentations of the calcification were observed in most patients on radiography (Fig. 1) and on US. Although some patients showed reduced calcification size, the calcification did not disappear in any patients and the mean size remained unchanged: 10 (5) mm at baseline to 11 (6) mm after 3 weeks (Table 3).

3.3. Long-term follow-up

Long-term follow-up data were available for all 23 patients. The median (Q1–Q3) follow-up duration was 7 months (3–76). Nine patients had more than 1 year of follow-up. Only 4/22 patients experienced acute relapse, mainly (75%) during the first 6 months. These flares were treated once again with anakinra, with efficacy. Some residual chronic pain was still present in 14 patients, mainly linked to associated lesions of the affected joints. Among the 16 patients with available data, the mean (SD) VAS pain score was 2.6 (2.5) (Fig. 2).

4. Discussion

This retrospective study confirmed the results of a previous pilot study (anakinra appeared to be a fast-acting and effective drug in reducing pain secondary to HA-related joint inflammation [10]). Most of the patients showed a marked decrease in pain within a few hours after the first injection. At day 3, after one or two supplementary injections, the relief of pain (VAS score ≤ 2) was almost complete for two-thirds of the patients. The clinical effect of anakinra on pain and joint mobility appears to be related to reduced inflammation, as confirmed by the decreased CRP level and Doppler intensity around the calcification [3].

Long-term follow-up showed that even if some chronic pain was present in half of our patients, acute relapses were uncommon (4/23). The rarity of new flares during follow-up is encouraging as compared with other treatments. Indeed, up to one third of patients receiving aspiration or lavage, for instance, can experience a temporary recurrence [2].

The persistence or reappearance of mechanical pain in some patients after a few weeks could reflect the lack of dissolution of the calcification itself but could also be due to the presence of associated lesions, particularly with calcifications located in the rotator cuff.

This study also confirmed that the calcifications can be well evaluated by US. Indeed, the procedure allows for precise measurements of the diameter of the calcification, a good description of the type of calcification mostly suggesting ongoing dissolution in acute flares, an evaluation of importance of surrounding inflammation [14] and finally the demonstration of associated lesions

Table 3
Baseline and short-term evolution of ultrasonography imaging.

Patient	D0				D3				D21			
	Clacification				Clacification				Clacification			
	Size, (mm)	Aspect	Effusion	Doppler	Size, (mm)	Aspect	Effusion	Doppler	Size, (mm)	Aspect	Effusion	Doppler
1	11	Fragmented	N	+++	8	Fragmented	N	+	6	Fragmented	N	0
2	26	Fragmented	Y	+++	14	Fragmented	N	++	17	Fragmented	N	+
3	20	Nodular	Y	+++	20	Nodular	N	+	20	nodular	N	0
4	30	Fragmented	Y	+++	20	Fragmented	N	+	5	Fragmented	N	0
5	15	Fragmented	Y	+++	14	Fragmented	N	+	11	Fragmented		
6		Nodular	Y	+++	3	Fragmented	N	+				
7	20	Nodular		+++					2	Fragmented	Y	0
8	20	Nodular		+++					17	Fragmented	N	0
9									8	Fragmented	N	0
10	11	Arc shaped	N	++					11	Arc shaped	N	++
11	16	Fragmented	Y	++					10	Fragmented	N	+
12	5	Fragmented	N	++	4	Fragmented	N	0				
13	5	Fragmented	Y	++	4	Fragmented	N	1				
N/Mean (SD)	22 (8)		*7/10*	+++	11 (6)		0/8	+	11 (5)		*1/8*	0/+

D: say; N: no; Y: yes. Doppler scores: 0 = no; + = low; ++ = moderate; +++ = intense activity. Size: maximum diameter. Characters in italics: numbers / total evaluated.

that could explain some residual chronic pain before and after the acute flare. The effect of the treatment on the calcification itself remains less clear. Although the calcifications became fragmented and diminished in size in some patients, they had not disappeared in any patient after 3 weeks of follow-up. This finding is not surprising, because anakinra, like steroids, is a potent anti-inflammatory agent and not a resorptive drug. The medication could even limit the dissolution of the calcific material. The effect of anakinra on calcifications in the long-term could not be evaluated because for most patients, US or radiography was not performed late during follow-up. Little is known about the long-term persistence of calcification [3]. A radiography study demonstrated the prevalence of both asymptomatic and symptomatic calcifications in the shoulder increasing with age, up to > 7% in patients older than 60 years [15]. Two studies [1,16] suggested that a long follow-up may be necessary to observe the total dissolution of the concretion after an acute flare [17].

Although the number of patients receiving treatment was small, a clinically pertinent point as compared with other therapeutic modalities is the absence of reported local and systemic side effects. Because calcific tendinopathies can relapse in the long-term, the re-use of a biologic treatment could lead to some allergic problems [18], although a fusion protein such as anakinra is much less immunogenic than monoclonal antibodies. Four of our patients received treatment again during follow-up without any problems.

The strength of the study is the well-documented short evaluation of the patients in the short-term but also the long-term follow-up in many patients. However, our study has some important limitations due to the retrospective observational design and the missing data for some of the evaluated parameters. A randomized controlled trial is needed to show that IL-1 inhibition is definitively effective in acute HA flare. Moreover, the drug has been tested in only very acute inflamed conditions, which does not prove that it can be useful in chronic or subacute pain syndromes associated with a calcific tendinopathy, with or without Doppler activity. Finally, the potential future indication of anakinra as compared with other available treatment modalities needs to be better evaluated, including the cost-effectiveness. Of note, the cost of this drug delivered for only 2 or 3 days is not much more than that for other treatments such as steroids or the cost for the rest, especially if future studies confirm that anakinra can shorten the duration of acute invalidating pain and loss of function.

In conclusion, this study suggests that IL-1β inhibition may be a therapeutic possibility for acute HA flare. The IL-1 inhibitor we tested, anakinra, seems an interesting compound because it can be administered subcutaneously with no need for local infiltration, acts rapidly, is short-lived (thereby limiting the risk of infection [19]) and does not seem to be followed by rebound flares. Randomized controlled trials are needed to better determine the place of this treatment in HA flare management.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgement

We thank Laura Smales (BioMedEditing) for copyediting.

Appendix A. Supplementary data

Supplementary data (File S1) associated with this article can be found, in the online version, at: https://doi.org/10.1016/j.jbspin.2018.05.008.

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