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Original article

# Anakinra treatment of acute calcium deposits in hand and wrist

## *Traitement des dépôts aigus de calcium à la main et au poignet par anakinra*

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ABSTRACT

Acute calcium deposit (ACD) in the hand and wrist is a cause of acute pain due to crystal-induced soft-tissue inflammation. There are no standard management guidelines for this condition, which is frequently treated with non-steroidal anti-inflammatory drugs (NSAIDs), with variable efficacy, some patients presenting symptoms for several months. We retrospectively analyzed the results of all patients treated with anakinra for hand or wrist ACD in our department in 2020. We extracted data on treatment duration, pain, range of motion, skin erythema, hypervascularization, edema, and X-ray findings. Ten patients were treated for hand or wrist ACD with anakinra 100 mg per day for a mean 2.7 days. We observed rapid and significant improvement in pain, range of motion, local erythema and edema from day 2 and a decrease in skin temperature from day 3. Calcifications significantly decreased in size or disappeared in the majority of the patients. There were no adverse events or recurrences at 1 year's follow-up. Anakinra was associated with significant clinical improvement after only two days' treatment and may be considered to treat patients with hand or wrist ACD, especially in case of contraindications to NSAIDs or glucocorticoids. Further controlled studies are needed to confirm the present observations.


*Mots-clés:*
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RÉSUMÉ

Les dépôts aigus de calcium (ACD) dans la main et le poignet sont une cause de douleur aiguë due à l'inflammation des tissus mous induite par les cristaux. Il n'existe pas de prise en charge standard de cette affection, fréquemment traitée par des anti-inflammatoires non stéroïdiens (AINS) avec une efficacité variable, certains patients présentant des symptômes pendant plusieurs mois. Nous avons analysé rétrospectivement le résultat de tous les patients traités par anakinra pour ACD à la main ou au poignet dans notre service en 2020. Nous avons extrait les données sur la durée du traitement, la douleur, l'amplitude des mouvements, l'érythème cutané, l'hypervascularisation, l'œdème et les résultats radiologiques. Dix patients ont été traités pour ACD à la main ou au poignet par anakinra 100 mg par jour pendant une durée moyenne de 2,7 jours. Nous avons observé une amélioration rapide et significative de la douleur, de l'amplitude articulaire, de l'érythème local et de l'œdème à partir du 2ème jour et une diminution de la température cutanée à partir du 3ème jour. Les calcifications avaient diminué significativement de taille ou disparu chez la majorité des patients. Nous n'avons observé aucun événement indésirable ou récidive après un an de recul. L'anakinra a été associé à une amélioration clinique significative après seulement deux jours de traitement de l'ACD à la main ou au poignet et peut être envisagé pour traiter les patients atteints de cette affection, en particulier ceux présentant une contre-indication aux AINS ou aux glucocorticoïdes. D'autres études contrôlées sont nécessaires pour confirmer nos observations.


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## 1. Introduction

Calcific periarthritis and peritendinitis consist in acute deposit of basic calcium phosphate (hydroxyapatite) crystals (acute calcium deposits: ACD) in soft tissues adjacent to articulations [1]. The hand and wrist are affected in 2.4% of cases. This low prevalence is associated with frequent misdiagnosis, and only 46% of cases are correctly diagnosed at initial presentation [2]. Patients experience rapid onset of pain with hand swelling, erythema, tenderness and restricted range of motion. Standard radiography shows dense amorphous opacification without cortical or trabecular patterns, well-contoured, in proximity to an articulation or tendon. The actual mechanism of deposition of hydroxyapatite into psammoma-like bodies surrounded by inflammatory cells, mostly neutrophils [3] remains unknown, but the common feature of crystal-induced inflammation is NLRP3 inflammasome activation leading to interleukin-1β production [3].

The condition is benign and self-limiting, but pain is excruciating, often rated 8–10/10 on visual analog scales (VAS). Finger motion and grip strength are limited by pain. Non-steroidal anti-inflammatory drugs (NSAIDs) and rest are widely used in primary care, but steroid infiltration, barbotage and high-energy shock-wave therapy have also been proposed. Although some studies reported that symptoms disappeared in 2 weeks [4], patients treated with NSAIDs reported severe pain for up to 10 days and some residual pain even at 1 year. In the study by Kim et al., none of 10 patients was pain-free at 6 months [5]. Corticoid injection or barbotage might not be adapted to the hand due to the close proximity of important nerves, vessels and tendons as well as the superficial localization of the calcification that may lead to skin atrophy [6].

IL-1 blockade is effective in acute gouty arthritis and has been studied for calcium pyrophosphate deposition (CPPD) related arthritis [7,8]. Anakinra, an interleukin-1 receptor antagonist (Fig. 1), showed efficacy in calcific (hydroxyapatite) periarthritis of the shoulder [9]. It is also used in pediatric rheumatology to treat various auto-inflammatory conditions and has a good safety profile [10].

The present study reports our experience in terms of efficacy and safety using anakinra in the treatment of ACD in the hand and wrist.

## 2. Methods

### 2.1. Patient selection

We retrospectively analyzed all patients treated in our department from February 1, 2020, to December 31, 2020, with anakinra for calcific periarthritis and peritendinitis of the hand and wrist. We included only patients with acute pain of less than 7 days' progression and no history of trauma, who presented local inflammatory signs (pain, swelling, erythema and heat) and standard radiographs showing an amorphic homogenous calcification in the painful zone. We excluded patients receiving NSAIDs or corticosteroids in the previous two weeks and with pre-existing inflammatory rheumatic disease or arthritis. Anakinra 100 mg was administered subcutaneously once a day. Treatment duration was decided by the physician based on pain resolution. For patients treated with anakinra, no splinting or NSAIDs were associated. Approval was obtained from the local review board (CER-VD, BASEC-ID 2021-01811).

### 2.2. Outcomes

Patients were seen daily at the outpatient clinic until complete pain relief, and then usually again after one and three weeks. All consultations were performed by the same physician (AD). During consultation, pain was evaluated on a 0–10 VAS. Range of motion (RoM) was measured using a standard goniometer or Kapandji functional score when the trapeziometacarpal joint was involved [11]. Locoregional inflammation parameters were measured and compared between the affected and contralateral healthy hand. Local temperature was measured by a Visiofocus PRO® 06480 laser surface thermometer (Tecnimed™, Vedano Olona, Italy) and erythema was measured using Dermacatch® (Colorix™, Neu-

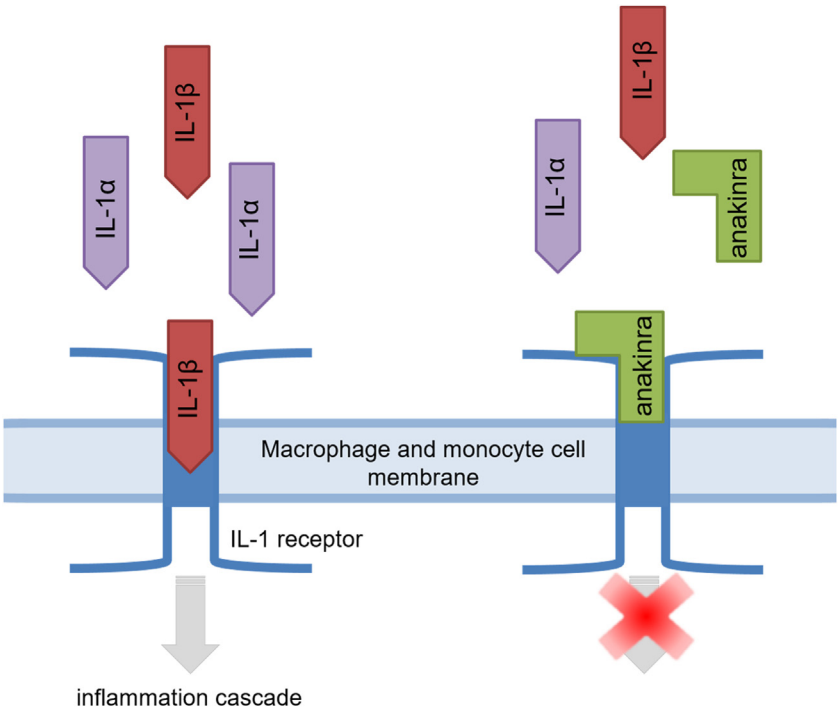


**Fig. 1.** Anakinra action mechanism.

chatel, Switzerland) [12]. The Aixplorer® ultrasound system (Supersonic Imagine™, Aix-en-Provence, France) was used to measure swelling, defined as the distance between bone and skin surface over the calcification in B-mode. Vascularization was evaluated in power-Doppler mode around the calcification and was rated on a semi-quantitative scale (0 = no Doppler signal; 1 = ≤20% of surface with positive Doppler signal; 2 = ≥20% of surface with Doppler signal). Radiographic evaluations of calcium deposit size before and at end of treatment were included when available. Complications of treatment and recurrence at 12 months were screened for by telephone.

### 2.3. Statistics

We used the non-parametric Wilcoxon signed-rank test to compare pre- and post-therapeutic outcomes. $p < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. Patient characteristics

Ten patients were treated with anakinra for ACD-related periarthritis and peritendinitis from February to December 2020 (Table 1): 8 females and 2 males; mean age, 45 ± 11 years (range, 29–58 years). The hand was involved in 6 patients and the wrist in 4. The mean interval between symptom onset and first consultation was 2.1 ± 1.4 days (range, 0–4 days). Mean anakinra treatment duration was 2.7 ± 1.1 days (range, 1–5 days).

### 3.2. Outcomes

At presentation, mean pain at rest was rated 5 ± 2.4 (range, 1.5–8) and mean pain in movement was 8 ± 1.7 (range, 6–10). At day 2, mean pain was 1.1 ± 1.3 (range, 0–4) at rest and 3.5 ± 3.1 (range, 1–7) in movement. There was a significant decrease in pain at rest (p = 0.01) after 2 days' treatment with anakinra (Fig. 2). Complete resolution of pain at rest was observed for all patients at 1–6 days, with a mean duration of 2.7 days (Fig. 2); all patients were free of pain in movement by day 7.

At presentation, mean differences between the pathologic and the healthy side were: 1.23 ± 1.2°C (range, 0.2–4.3°C) for temperature, 21.5 ± 7.65 (range, 14–33) for erythema, and 0.25 ± 0.16 cm (range, 0.05–0.54 cm) for swelling (Fig. 2a, b). There was a significant reduction in temperature (p = 0.03) between days 0 and 3, and non-significant reductions in erythema (p = 0.06) and swelling (p = 0.09) between days 0 and 2. Mean RoM in flexion/extension (excluding the trapeziometacarpal joint) was 51 ± 30° (range, 5°–90°) at presentation, increasing significantly to 93 ± 23° (range, 65°–115°) (p = 0.03) at day 2 (Fig. 2). Mean vascularization score was 1.6 ± 0.5 (range, 1–2) at presentation, significantly decreasing to 0.5 ± 0.8 (range, 0–2) at day 2 (p = 0.03) (Fig. 3c, d).

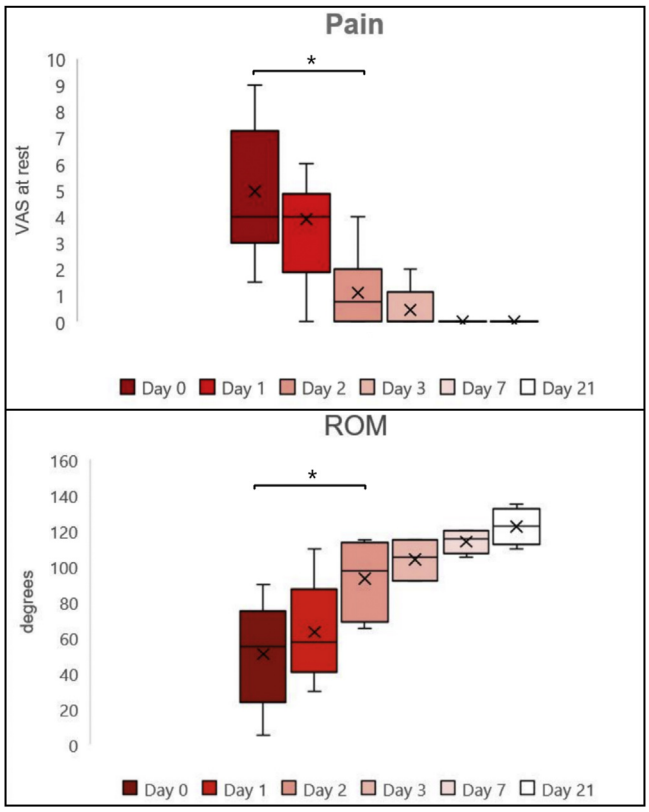


**Fig. 2.** Boxplot of pain at rest (0-10 VAS) and range of motion (RoM) at days 0, 1, 2, 3, 7 and 21 after treatment with anakinra 100 mg per day. Box (interquartile range (IQR); 75th–25th percentile), central line (median; 50th percentile), lower whisker (5th percentile), upper whisker (95th percentile).

The mean calcification size was 12.5 ± 7 $mm^2$ (range, 6.3–27.1 $mm^2$) at presentation, significantly decreasing to 2.5 ± 3 $mm^2$ (range 0–8.2 $mm^2$) (p = 0.03) after a mean 23.7 days. Calcification disappeared completely in 2 cases (Fig. 4).

Nine patients could be contacted 12 months after treatment. No recurrences were reported. One patient was diagnosed with hyperparathyroidism 3 months after ACD treatment. There were no adverse effects. Only 3 patients took additional analgesics (1–2 g paracetamol daily) during treatment.

## 4. Discussion

ACD of the hand and wrist is a self-limiting disorder with excellent prognosis, but resolution of pain varies from 3 weeks to

**Table 1**
Patient characteristics.

| Patient number | Age | Gender | Location of calcification | Dominant hand | Interval between symptom onset and start of treatment | Duration of anakinra treatment (days) |
|---|---|---|---|---|---|---|
| 1 | 55 | F | IP thumb | D | 4 days | 2 |
| 2 | 53 | F | MCP 4 | D | 0 | 3 |
| 3 | 31 | F | Radiocarpal | ND | 1 day | 1 |
| 4 | 58 | F | TM | D | 3 days | 3 |
| 5 | 31 | F | IP thumb | D | 2 days | 5 |
| 6 | 53 | M | Ulnocarpal | D | 2 days | 2 |
| 7 | 29 | F | IP thumb | D | 3 days | 2 |
| 8 | 46 | M | FCU | D | 1 day | 3 |
| 9 | 43 | F | MCP 3 | D | 4 days | 3 |
| 10 | 52 | F | Ulnocarpal | ND | 1 day | 3 |

*F*: female; *M*: male; *IP*: interphalangeal; *MCP*: metacarpophalangeal; *TM*: trapeziometacarpal; *FCU*: flexor carpi ulnaris; *D*: dominant; *ND*: non-dominant.

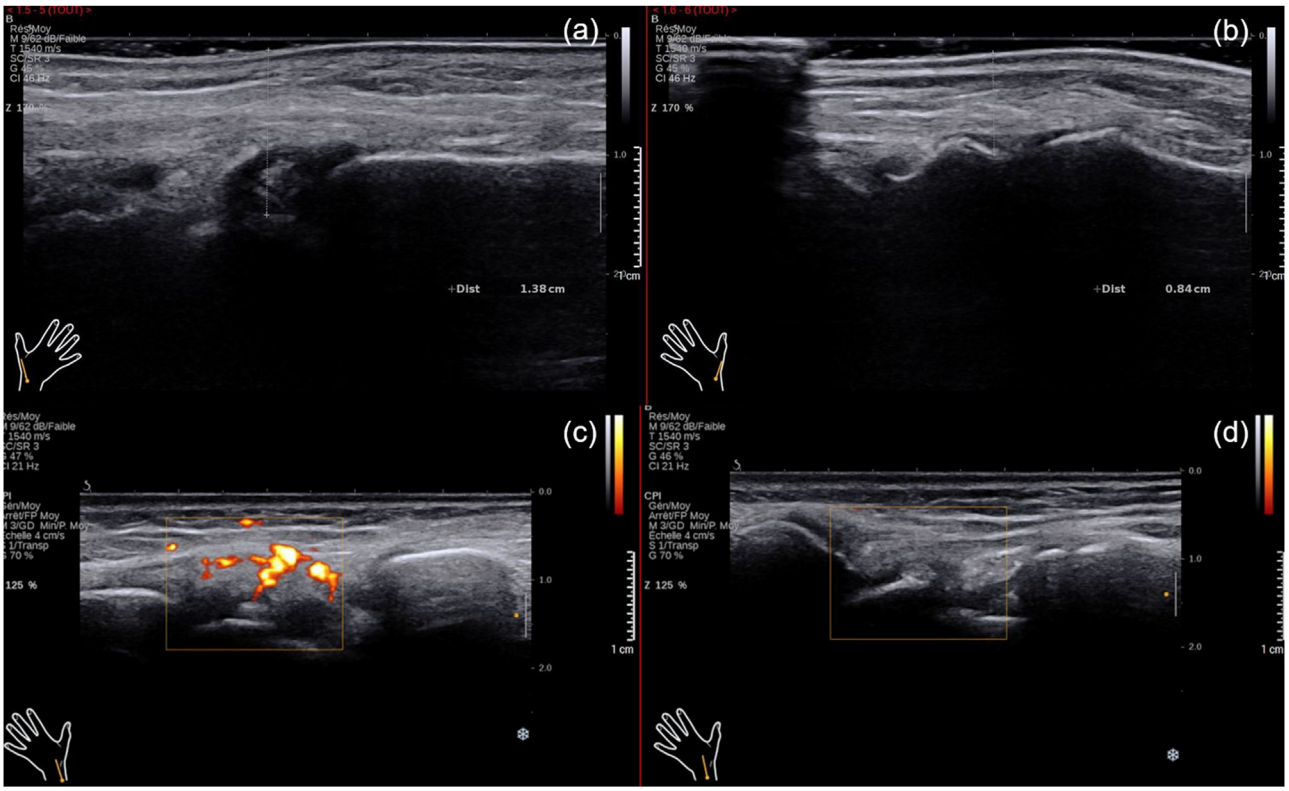


**Fig. 3.** B-mode ultrasonographic assessment of swelling, defined as distance between skin surface over the calcification and underlying bone in patient n°4, with trapeziometacarpal involvement at day 0 on calcification side (a) and healthy side (b). Power-Doppler images of patient n°3 with radiocarpal calcification, showing intense vascularization (score = 2) at day 0 (c) and no vascularization (score = 0) at day 1 (d).

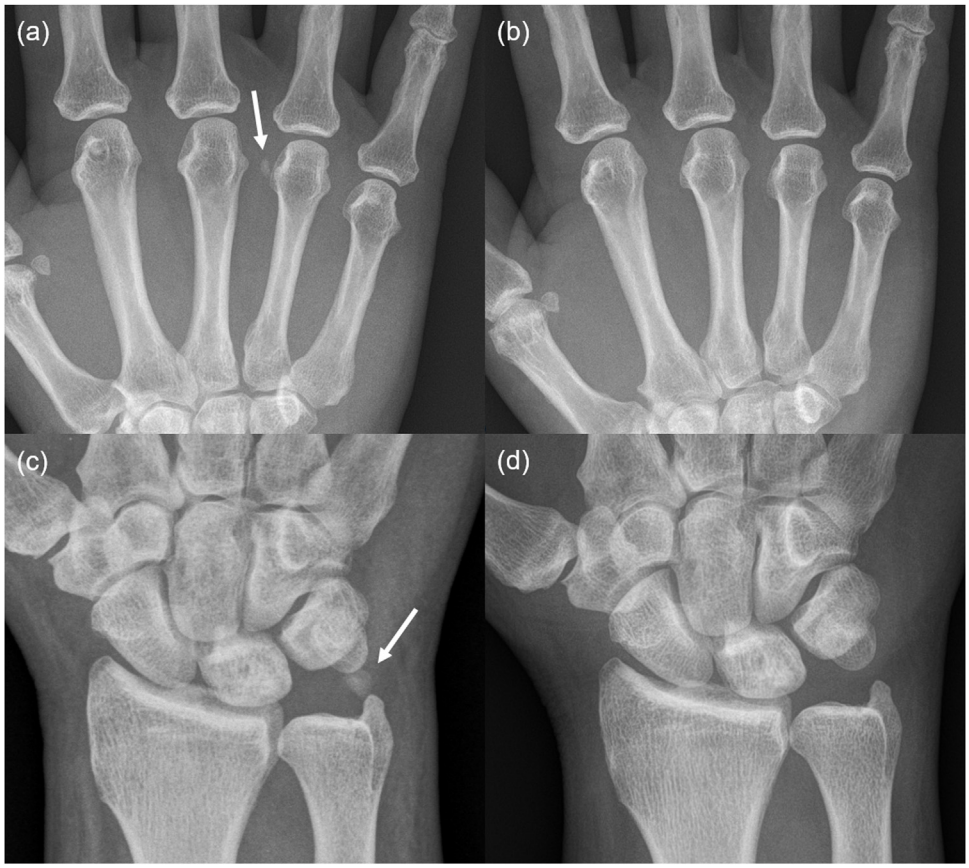


**Fig. 4.** Posteroanterior radiographs of the right hand of patient n°2 at day 0, showing the calcification in the third intermetacarpal space (*white arrow*) (a) and its disappearance at day 3 after 3 days' treatment with anakinra (b). Posteroanterior radiographs of the right hand of patient n°6 at day 0, showing ulnocarpal calcification (*white arrow*) (c) and its disappearance at day 5 after 2 days' treatment with anakinra (d).

18 months and recurrence has been reported, which is also in line with our experience [2,5,13–15]. The disease is rare, so management is not standardized, and current practices include high-dose NSAIDs, injection of local anesthetics or steroids, and surgical resection. A recent study of ACD in the hand demonstrated that the average VAS pain score at the initial consultation was 7, while at 3, 6, and 9 months it was 4.3, 3.3 and 2.9 respectively when treated with NSAIDs [5]. For steroid injection, studies postulate that the most important effect is due to the action of the needle, fragmenting calcification, leading to an increase in surface area and thus faster resorption of the deposits [2]. A recent systematic review [16] concluded that all treatment modalities that aimed to break up the crystals (barbotage, high-energy extracorporeal shockwave and arthroscopy) are well tolerated and effective in shoulder calcifications, but it is obvious that in some locations in the hand these modalities cannot be considered.

The efficacy of anakinra was good in a series of 10 patients with hand and wrist ACD without safety issues. In 2013, a study reported 5 cases of shoulder periarthritis treated by anakinra. All patients reported a rapid decrease in pain after only one dose, with VAS at rest decreasing from 9.6 to 0.5. Shoulder RoM improved rapidly, and no adverse events were reported [7]. A series of 23 cases of calcific periarthritis in different locations reported significant pain reduction at 3 days despite some residual pain lasting 2 years in 60% of patients [9]. Anakinra showed non-inferiority compared to usual care in acute gout arthritis in a randomized controlled study [17] and demonstrated effectiveness and good tolerance even in comorbid patients with recurrent and refractory crystal-related arthritis [18–22]. The safety profile of this drug is good also in polymorbid patients and children, even with prolonged treatment (78 weeks). The most common adverse effect is mild to moderate injection site irritation. Neutropenia and infection are found less frequently [21]. Recently, a double-blind randomized controlled study comparing the effectiveness of 100 mg anakinra vs. 30 mg oral prednisone for 3 days in CPPD-related acute arthritis showed that pain at 72 h was significantly lower in the anakinra group [8].

Anakinra was our alternative to high-dose NSAIDs and steroids. It was especially relevant during COVID-19 pandemic, since serious concerns were raised in Spring 2020 about NSAID and corticoid administration in patients with COVID-19 [23,24]. All patients were completely free of pain at rest at day 6 and no recurrence of pain was reported at 1 year. At day 2, half of the patients were free of pain, and at day 3 only 3 of the 10 patients reported residual pain. This significant decrease in pain occurred after only 2 injections of anakinra. The other local inflammation parameters and RoM also improved in 2–3 days. Calcification disappeared completely in only 2 patients, but the size of the calcification decreased significantly within a mean 23.7 days, consistently with other studies reporting correlation between pain relief and resolution of calcification [9]. Anakinra seems promising for pain relief and resorption of hand and wrist ACD.

There were no adverse effects in this study, in line with the good safety profile reported with IL-1 blockers [21,25]. Also, the treatment was relatively cheap, 1 dose of anakinra costing around €60 in Switzerland, and patients received a mean 2.7 injections. The rapid results also allowed earlier return to work. We are encouraged by these outcomes and plan to perform a prospective controlled study.

This feasibility study had several limitations: retrospective design, no control group, and a small number of patients. Due to the COVID-19 pandemic and restrictions on hospital activity in 2020, follow-up and complementary investigations such as X-ray were limited. Ultrasound measurement modalities for vascularization and swelling should be standardized to improve reliability.

**Conflict of interest**

There is no potential conflicts of interest.

**Funding**

The authors received no financial support.

## Ethics

This study has been performed in accordance with the ethical standards as laid down in the declaration of Helsinki. Ethical approval was provided by CER-VD Ethical Commitee of Vaud, Lausanne, Switzerland (No. 2021-01811).

## Informed consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

## Acknowledgements

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