Biologics in the treatment of calcium pyrophosphate deposition disease: systematic literature review

E. Cipolletta[1], A. Di Matteo[1,2], A. Scanu[3], M. Isidori[1], J. Di Battista[1], L. Punzi[4], W. Grassi[1], E. Filippucci[1]

[1]*Rheumatology Unit, Department of Clinical and Molecular Sciences, Polytechnic University of Marche, Carlo Urbani Hospital, Jesi, Ancona, Italy;*
[2]*Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, United Kingdom;*
[3]*Rheumatology Unit, Department of Medicine-DIMED, University of Padua, Italy;*
[4]*Rheumatology Unit, Centre for Gout and Metabolic Bone and Joint Diseases, SS Giovanni e Paolo Hospital, Venice, Italy.*

Edoardo Cipolletta, MD
Andrea Di Matteo, MD
Anna Scanu, PhD
Martina Isidori, MD
Jacopo Di Battista, MD
Leonardo Punzi, MD, PhD
Walter Grassi, MD, PhD
Emilio Filippucci, MD, PhD

Please address correspondence to:
Edoardo Cipolletta,
Reumatologia, Dipartimento di Scienze Cliniche e Molecolari,
Università Politecnica delle Marche,
Ospedale Carlo Urbani,
Via Aldo Moro 25,
60035 Jesi (AN), Italy.
E-mail: edoardocipolletta@gmail.com

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ORCID ID:
E. Cipolletta: 0000-0002-6881-8197
A. Di Matteo: 0000-0003-0867-7051
E. Filippucci: 0000-0002-7251-7784

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ABSTRACT

The main aim of this systematic literature review (SLR) was to summarise the evidence in the use of biological therapies in calcium pyrophosphate deposition disease (CPPD). We performed a SLR using PubMed, Embase and Cochrane databases. Only studies reporting the efficacy of biologics in CPPD were selected. The search resulted in 83 articles; 11 were further evaluated in the SLR. Seventy-six patients were included: 2 received infliximab, whereas 74 anakinra. Anakinra was used in refractory disease (85.1%) or in patients with contraindications to standard treatments (23.0%). Clinical response to anakinra was observed in 80.6% of patients with acute and 42.9% of those with chronic CPPD. Short-term treatment was well tolerated and adverse events were reported in 4.1% of the cases. This review provides evidence in favour of the use of anakinra as a therapeutic option in patients with CPPD, especially in acute refractory CPPD or when standard treatments are contraindicated.

Introduction

Calcium pyrophosphate deposition disease (CPPD) is characterised by the deposition of calcium pyrophosphate (CPP) crystals at articular and periarticular level (1). Patients with CPPD may present with different clinical phenotypes ranging from asymptomatic chondrocalcinosis to acute monoarthritis (2) as in gout and chronic polyarthritis resembling rheumatoid arthritis (3).

Several treatment options are available for CPPD. However, the great majority of these therapies are "borrowed" from those used for other rheumatic diseases, such as gout and rheumatoid arthritis. In fact, only very few pharmacological randomised and controlled studies have been conducted in CPPD. As in gouty arthritis, colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids are the cornerstone of the treatment (4). However, CPPD mainly affect elderly and the use of these treatments may be greatly limited (5). In these patients, special care must be taken due to higher rates of comorbidities and contraindications and, therefore, to higher risk of side effects (6).

In the treatment of recurrent acute CPP-crystal or chronic CPP-crystal inflammatory arthritis other molecules have been tested such as hydroxychloroquine and methotrexate (7-10). However, since now, the efficacy of these therapies has limited evidence.

Biologics have been used in several cases refractory to conventional treatment. In the last decade, IL-1 inhibitors have shown their efficacy in the treatment of acute gout (11, 12). On the other hand, only few case reports and case series have analysed the efficacy of IL-1 inhibitors in the treatment of CPPD, reporting conflicting results. Additionally, even smaller experience is available with tumour necrosis factor α (TNF-α) blockers in CPPD. Therefore, in the 2011 European League Against Rheumatism recommendations for the management of CPPD the use of biologics was not considered.

We performed a systematic literature review to summarise the evidence on the use of biological therapies in CPPD and discuss how TNFα and IL-1 pathways can be implicated in the pathophysiology of the disease.

Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses for Individual Patient Data (PRISMA-IPD)

guidelines were used for this review (13).

Eligibility criteria

Published articles reporting the use of TNF-α and/or IL-1 inhibitors in the treatment of CPPD [probable or definite diagnosis according to Ryan and McCarty criteria (14)] were reviewed. For inclusion, the following information must be reported: clinical presentation (mono-, oligo-, polyarthritis), biological treatment strategy (molecule, duration and dose) and patient outcome.

Articles, in which the data were pooled without description of individual patient data, were excluded from the subsequent numerical analysis.

Search strategy

We evaluated the PubMed (*i.e.* including MEDLINE, National Library of Medicine, and PubMed Central), Embase and Cochrane databases, starting from January 1980 to 15th September 2019, and abstracts from the past two EULAR and ACR annual meetings using the strategies recommended by the Cochrane Handbook. The MeSH terms used were ((tumor necrosis factor alpha OR TNFα OR TNF alpha OR TNF-α OR infliximab OR adalimumab OR golimumab OR certolizumab OR etanercept) OR (rilonacept OR anakinra OR canakinumab OR gevokizumab OR IL-1 OR IL1) OR (IL-6 OR IL6 OR tocilizumab OR sarilumab) OR secukinumab OR ustekinumab OR ixekizumab OR abatacept) AND (chondrocalcinosis OR CPPD OR calcium pyrophosphate OR pseudogout). The search was restricted to studies on humans and in English or Italian languages. The references contained within the studies obtained were then examined to identify additional reports.

Titles and abstracts were screened by two reviewers (E.C. and M.I.). If an abstract was selected by a reviewer, the full-text article was retrieved and subsequently screened for eligibility criteria prior to selection for review. Any disagreement in the selection process was resolved by consensus with other two authors as adjudicators (E.F. and A.D.M.). The same reviewers extracted the data from the selected articles using a standardised template designed for this review. The following data were extracted: authors, publication year, diagnostic criteria of CPPD, patient age, sex and comorbidities, disease duration, clinical phenotype (acute CPP-crystal or chronic CPP-crystal inflammatory arthritis), number of involved joints (mono-, oligo- or polyarthritis), reasons for the use of biologics, treatment strategy (molecule, duration and dose), previous used drugs, tender joint count (TJC), swollen joint count (SJC), visual analogue scale (VAS) for pain, C-reactive protein (CRP), physician judgement about the efficacy of biologics, duration of follow-up period, adverse events and disease relapse during follow-up.

The final selection included studies on patients with probable or definite CPPD, independently of the clinical phenotype, in which biologics were used to treat CPPD. As there are no published data supporting use of biologics other than anakinra and infliximab in CPPD, we will focus our systematic literature review, mainly on anakinra.

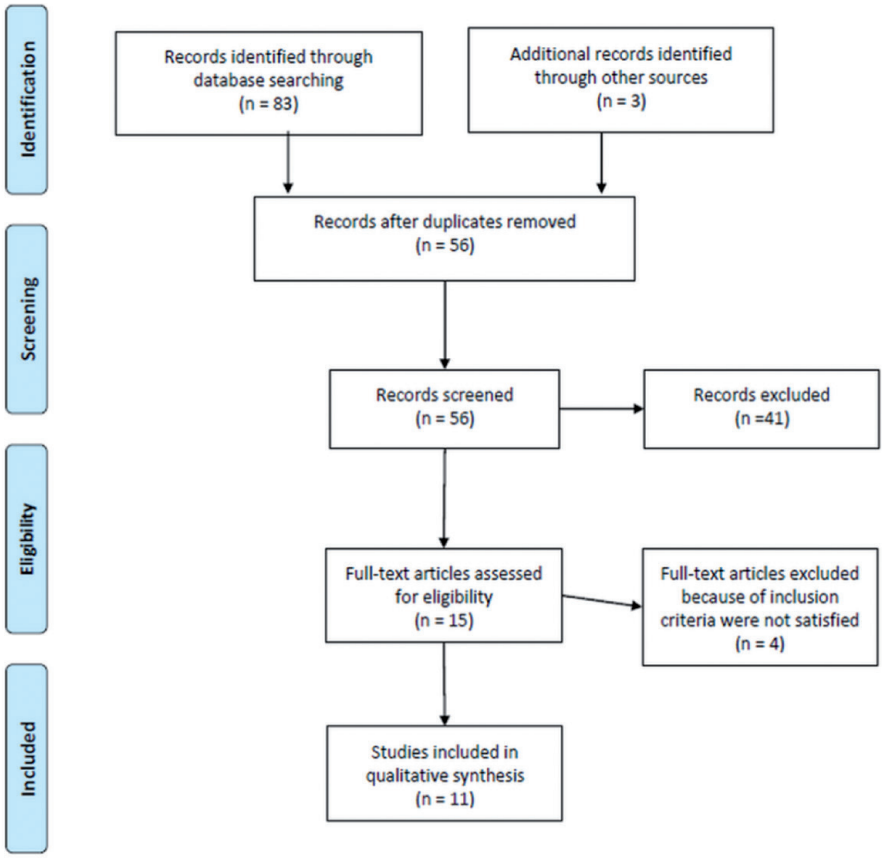

Fig. 1. Flow diagram of the review process.

Quality assessment

The quality of selected studies was assessed using the Newcastle Ottawa Scale. Quality assessment was performed by one reviewer (E.C.) and checked by the second one (M.I.). Any concern on quality scoring was decided by consensus. The Newcastle Ottawa Scale has a scoring scale under three sections namely; selection, comparability and outcome. The quality score is based on a "star" system (range 0–10 stars) with a higher score representing better methodological quality. Studies receiving more than 6 stars were considered to be at low risk of bias, those receiving 4 to 6 stars at intermediate risk of bias, and those receiving less than 4 stars at high risk of bias (15).

Statistical analysis

The results are reported as mean ± standard deviation (SD) for the quantitative variables and as absolute frequency and/or corresponding percentage for the qualitative variables. The Mann-Whitney test was used for quantitative variables which were not normally dis-

Table I. Studies evaluating biological therapies in patients with calcium pyrophosphate deposition disease.

Authors	Year of publication	Study design	Population of interest	Number of CPPD patients	Diagnostic criteria	Clinical presentation	Axial or peripheral involvement
McGonagle D. *et al*.	2008	Case report	CPPD	1	SFA	Chronic CPPD	Peripheral
Announ N. *et al*.	2009	Case report	CPPD	1	SFA	Acute CPPD	Peripheral
Couderc M. *et al*.	2012	Case series	CPPD	3	Imaging	Acute and chronic CPPD	Peripheral
Diamantopoulos A.P. *et al*.	2012	Case report	CPPD	1	SFA	Chronic CPPD	Peripheral
Moltó A. *et al*.	2012	Case series	CPPD	5	SFA	Acute and chronic CPPD	Peripheral
Ottaviani S. *et al*.	2013	Case series	CPPD	16	SFA and/or imaging	Acute CPPD	Peripheral
Verhoeven F. *et al*.	2013	Case series	G and CPPD	2	NR	Acute and chronic CPPD	Peripheral
Bruges-Armas J. *et al*.	2014	Case series	CPPD	2	NR	Chronic CPPD	Axial and peripheral
Aouba A. *et al*.	2015	Case series	G, CPPD and HADD	1	Imaging	Acute CPPD	Axial and peripheral
Desmarais J. *et al*.	2018	Case series	G, CPPD	11	SFA and/or imaging	Acute CPPD	Peripheral
Thomas M. *et al*.	2018	Case series	CPPD	32	SFA and/or imaging	Acute CPPD	Peripheral

CPPD: calcium pyrophosphate deposition disease; G: gout; HADD: hydroxyapatite deposition disease; NR: not reported; SFA: synovial fluid analysis.

tributed, Student's t-test for the quantitative variables which had a normal distribution and the Chi-square test for the qualitative variables. Correlation between duration of IL-1 inhibitor treatment and clinical parameters was tested. The Point-biserial correlation (Rbp) was used to evaluate the association between the treatment duration with IL-1 inhibitor and the qualitative variables [clinical phenotype (acute CPP-crystal or chronic CPP crystal inflammatory arthritis) and number of involved joint (mono-, oligo- and polyarticular)], whereas the Pearson's correlation (R) was used to correlate the treatment duration with biologics and the quantitative variables (disease duration, age). Predictors of clinical response to biological treatment were identified using logistic regression analysis. Data analysis was conducted using the Statistical Package for Social Sciences (SPSS), v. 24.0 for Windows.

Results

There are limited data in the Literature related to the use of biologics in CPPD. There are no randomised and controlled trials and all data derive from small case series and case reports.

Figure 1 reports the different phases of the selection process. The search strategy identified 83 articles. After the examination of titles and abstracts, 15 articles were included for the review and after the evaluation of the full-text articles, 4 articles were excluded from the subsequent analysis. Of the 4 excluded papers, 2 were literature reviews, in one data extraction was not possible, and one was written in German. Of the remaining 11 articles (15-25), 3 were single case-reports (19, 21, 24) and 8 were case-series (15, 16, 18, 20, 21, 23-25). Ten (90.9%) articles were focused on the use of anakinra (15-24), whereas one (9.1%) on the use of infliximab (25). Descriptive data of the studies are summarised in Table I.

Quality assessment

On the quality assessment scale, 8 articles were judged at intermediate risk of bias (16, 17, 19-24) and 3 at high risk of bias (23-25).

Table II reports a summary of the Newcastle Ottawa Scale for each article.

Baseline characteristics

Seventy-six patients were included in this systematic literature review. The clinical characteristics are summarised in Table III. The mean age was 74.5±12.1 years and 29 (38.2%) patients were male. In 57 (75.0%) patients one or more comorbidity was present. Hypertension was the most common underlying condition [42 (55.3%)], followed by coronary artery disease [37 (48.7%)], chronic kidney disease [36 (47.4%)], diabetes mellitus [22 (28.9%)] and peptic ulcer disease [3 (3.9%)]. In 39 (51.3%) patients more than one comorbidity was present [in 9 (11.8%) two, in 16 (21.0%) three and in 14 (18.4%) four].

Sixty-seven (88.2%) patients presented with an acute CPP-crystal arthritis (mean disease duration: 2.7±6.9 months; polyarticular involvement in 61.2%, oligoarticular in 31.3% and monoarticular in 7.5%), whereas 9 (11.8%) patients with a chronic CPP crystal inflammatory arthritis (mean disease duration: 130.1±133.6 months; polyarticular involvement in 66.7% and oligoarticular in 33.3%).

It should be noted that the definition of acute CPP-crystal arthritis is rather homogeneous among studies. Acute CPP-crystal arthritis was defined as an acute-onset, self-limiting, painful swelling of one or more joints usually associated with a variable increase of CRP levels, with or without skin erythema and fever. On the other hand, chronic CPP-crystal inflammatory arthritis is only poorly defined and it was described as a persistent synovitis in one or more joints with or without a variable increase of CRP levels even if a clear indication for its duration was not reported (usually several months and at least two months).

The diagnosis of CPPD was based on synovial fluid analysis in 46 (60.5%) patients, on characteristic findings at imaging evaluation in 10 (13.2%) patients, on synovial fluid analysis and/or imaging in 17 (22.4%) patients, whereas it was not reported in 3 (3.9%) patients.

Biologics efficacy was defined in different ways across studies as reported in Table IV.

Reasons for initiation of biologic treatment

All patients had a documented reason for starting treatment with anakinra or infliximab: inadequate response to conventional therapies in 65 patients (85.5%) [37 (48.7%) were refractory to oral and/

Table II. Newcastle Ottawa Scale for evaluating quality of case-report and case series.

Authors	Year of publication	Selection	Comparability	Outcome	Sum	Risk of bias
McGonagle D. *et al*.	2008	1	1	2	4	Intermediate
Announ N. *et al*.	2009	1	1	2	4	Intermediate
Coudrec M. *et al*.	2012	0	0	1	1	High
Diamantopoulos A.P. *et al*.	2012	1	1	2	4	Intermediate
Moltó A. *et al*.	2012	1	1	2	4	Intermediate
Ottaviani S. *et al*.	2013	1	1	2	4	Intermediate
Verhoeven F. *et al*.	2013	0	0	1	1	High
Bruges-Armas J. *et al*.	2014	0	1	1	2	High
Aouba A. *et al*.	2015	1	1	1	3	Intermediate
Desmarais J. *et al*.	2018	1	1	2	4	Intermediate
Thomas M. *et al*.	2018	1	1	2	4	Intermediate

Table III. Clinical and demographic data of calcium pyrophosphate deposition disease patients receiving biologics.

Female/Male	47/29
Age (years)	74.5±12.1
Disease duration (months)	17.3±59.3
Acute CPP arthritis	
Number of patients (%)	67 (88.2)
Disease duration (months)	2.7±6.9
Monoarthritis (%)	5 (7.5)
Oligoarthritis (%)	21 (31.3)
Polyarthritis (%)	41 (61.2)
Chronic CPP arthritis	
Number of patients (%)	9 (11.8)
Disease duration (months)	130.1±133.6
Monoarthritis (%)	0 (0)
Oligoarthritis (%)	3 (33.3)
Polyarthritis (%)	6 (66.7)
Previous therapies	
Colchicine (%)	36 (47.4)
Steroids (%)	37 (48.9)
NSAIDs (%)	29 (38.2)
Methotrexate (%)	3 (3.9)
Sulfasalazine (%)	1 (1.3)
Anti-TNF-α (%)	1 (1.3)
Comorbidities	
Coronary artery disease (%)	37 (48.7)
Chronic kidney disease (%)	36 (47.4)
Diabetes mellitus (%)	22 (28.9)
Hypertension (%)	42 (55.3)
Peptic ulcer disease (%)	3 (3.9)

CPP: calcium pyrophosphate; NSAIDs: non-steroidal anti-inflammatory drugs; TNF-α: tumour necrosis factor alpha.

or intra-articular steroids, 36 (47.4%) to colchicine, 29 (38.2%) to NSAIDs] and contraindications to standard treatments in 18 patients (23.7%) [contraindications to NSAIDs were reported in 16 (21.0%), to colchicine in 11 (14.5%) and to steroids in 11 (14.5%)]. Moreover, 3 patients (3.9%) were refractory to second-line therapies. Methotrexate was used in 3 patients (3.9%), sulfasalazine and adalimumab in 1 patient (1.3%).

Treatment scheme of anakinra

Seventy-four (97.3%) patients received anakinra subcutaneously at the dose of 100 mg/day. Various treatment regimens have been adopted. Fifty-one patients (68.9%) were treated for 1-3 days, in 16 patients (21.6%) anakinra was administered for 5–9 days and in 7 patients (9.5%) for 30–365 days.

Average duration of anakinra treatment was 19.3±58.1 days. In 67 patients with acute CPP-crystal arthritis the mean duration of anakinra treatment was 6.7±21.8 days, whereas in 7 patients with chronic CPP crystal inflammatory arthritis it was 139.0±131.8 days.

Duration of anakinra treatment prior to complete resolution of symptoms was associated with the clinical phenotype of chronic CPPD (Rpb: 0.67, $p<0.001$) and with disease duration (R: 0.49, $p<0.001$), but not with the number of involved joints ($p=0.85$).

Efficacy of anakinra

All the articles described physician-reported efficacy of anakinra. Moreover, in 54 patients (73.0%) CRP levels and in 52 patients (70.3%) VAS for pain, TJC and SJC were available before and after treatment.

According to clinical judgement, 57 patients (77.0%) were "complete responders", 4 (5.4%) were "partial responders" and 13 (17.6%) were "no responders".

In 47 out of 57 (82.5%) responders, complete resolution of symptoms was obtained within 4 days after the first injection of anakinra (average time: 4.0±1.9 days).

Table V reports the pooled efficacy of anakinra.

Long-term efficacy of anakinra and disease relapse

In 50 (67.6%) patients out of 74 patients treated with anakinra, information about the follow-up was available. Average duration of follow-up was 6.6±2.9 months. In 15 out of 45 responders (33.3%) a relapse after anakinra discontinuation occurred within 2.53±2.68 months.

Predictors of anakinra efficacy

Forty-one patients (55.4%) were eligible for this analysis. Neither clinical nor demographic characteristics at baseline were predictive of anakinra response. Table VI shows the results of the logistic regression analysis.

Efficacy of infliximab

Two (2.7%) patients were treated with intravenous infliximab 3 mg/kg each 8 weeks. The duration of anti-TNF-α treatment was 9 years. Resolution of symptoms was observed within 4 months in both patients.

Safety of biologics

Short-term treatment with anakinra was generally well tolerated. Only 3 patients (4.1%) reported adverse events with anakinra: local skin reaction at the injection site, skin rash on the back and bacterial pneumonia. Neither of the two patients treated with infliximab reported adverse events during the follow-up period of 9 years.

Discussion

The chronic and degenerative arthropathy (osteoarthritis with CPPD) accounts for approximately half of patients, whereas acute CPP-crystal arthritis (pseudogout) and chronic CPP-crystal inflammatory arthritis represent roughly 25% and 5% of the cases (1, 14, 27). Most patients of the studies assessed in this review had an acute CPP-crystal arthritis (90.5%) rather than chronic CPP-crystal inflammatory arthritis (9.5%). This finding can be explained by the fact that anakinra treatment was used only in a selected population (hospitalised patients or with contraindications to standard treatment or with refractory disease) not reflecting the entire spectrum of CPPD patients.

Table IV. Definition of clinical response to biological treatment.

Authors	Response	Definition of clinical response
Announ N. *et al*.	Complete	Normalisation of CRP level and complete resolution of joint symptoms.
Aouba A. *et al*.	Complete	Normalisation of CRP level and complete resolution of joint symptoms.
Bruges-Armas J. *et al*.	Complete	Absence of pain and a complete resolution of all tender and swollen joints.
Couderc M. *et al*.	NR	/
Desmarais J. *et al*.	Complete	Functional improvement such as ability to bear weight on affected limbs when unable to initially or a documented clinical response such as great improvement or VAS pain reduction >50%.
Diamantopulos A.P. *et al*.	Complete	Normalisation of CRP level and complete resolution of joint symptoms.
McGonagle D. *et al*.	Complete	Normalisation of CRP level and complete resolution of joint symptoms.
Moltò A. *et al*.	Complete	Normalisation of CRP level and complete resolution of joint symptoms.
Ottaviani S. *et al*.	Complete	Report of complete or near complete resolution of joint symptoms (TJC and SJC) or documentation in the medical chart of the word "good" response after treatment.
	Partial	Report of improvement in joint symptoms but not a complete resolution.
Thomas M. *et al*.	Complete	Physician evaluation or medical records stating "good clinical response" 4 days after the first anakinra injection considering SJC, TJC, VAS pain score and CRP level.
Verhoven F. *et al*.	NR	/

CRP: C-reactive protein; NR: not reported; SJC: swollen joint count; TJC: tender joint count; VAS: Visual Analogue Scale.

Table V. Efficacy of anakinra in the treatment of calcium pyrophosphate deposition disease.

	Acute CPPD (n=67)	Chronic CPPD (n=7)
Clinical efficacy (%)	54 (80.6)	3 (42.9)
Pre TJC	6.3 ± 2.4	3.8 ± 2.4
Post TJC	1.2 ± 0.6	1.3 ± 1.5
Mean reduction	*5.1 ± 2.3**	*2.5 ± 1.9 +*
Pre SJC	4.8 ± 2.2	3.8 ± 2.4
Post SJC	1.1 ± 0.6	1.3 ± 1.5
Mean reduction	*3.7 ± 2.2**	*2.5 ± 1.9 +*
Pre VAS pain (0-100 mm)	68.5 ± 9.5	/
Post VAS pain (0-100 mm)	24.2 ± 10.4	/
Mean reduction	*44.2 ± 10.9**	/
Pre CRP (mg/l)	40.9 ± 50.9	50.0 ± 66.5
Post CRP (mg/l)	22.2 ± 8.6	3.2 ± 2.5
Mean reduction	*18.6 ± 54.**	*46.7 ± 64.0 +*

CRP: C-reactive protein; CPPD: calcium pyrophosphate deposition disease; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale.
+ *p*-values were not calculated in chronic CPPD group because of a too small sample size.
* In acute CPPD group all *p*-values were <0.01.

Table VI. Baseline clinical and demographic predictors of clinical response to anakinra treatment.

Variables	Beta	Wald	*p*-value	OR
Age	-0.1	0.0	0.99	0.99
Gender	38.8	0.0	1.0	>300
Clincal phenotype	-178.8	0.0	1.0	0.0
Disease duration	68.8	0.0	0.99	>300
Articular involvement	244.5	0.0	1.0	>300
Refractory disease	19.9	0.0	1.0	>300
CRP level	-0.1	0.0	0.86	1.0

CRP: C-reactive protein; OR: odds ratio.
Dependent variable: complete clinical response. Independent variables: age, gender, disease duration, clinical phenotype (acute or chronic CPPD), articular involvement (poly-, oligo-, mono-articular), refractory disease (CPPD resistant to more than 1 conventional treatment), CRP level.

The treatment strategy in CPPD is currently tailored according to clinical features (asymptomatic CPPD, acute CPP-crystal arthritis, chronic CPP-crystal inflammatory arthritis or osteoarthritis with CPPD) and general risk factors such as comorbidities, age and previous therapies (4, 28).

In our review, 85.1% of patients were refractory to standard treatments (NSAIDs, glucocorticoids and colchicine) and 4.1% to second-line therapy (*i.e*. methotrexate) whereas 23.0% has one or more contraindications to standard treatments such as NSAIDs, glucocorticoids, colchicine, methotrexate and hydroxychloroquine.

Nowadays, CPPD is mostly considered as an autoinflammatory syndrome characterised by joint inflammation (29). During the last years a vast amount of evidence has been accumulating indicating that IL-1 is a master cytokine in CPPD (29, 30).

Recently, studies have suggested that blockade of the NACHT, LRR, and PYD domains-containing protein 3 (NALP3)-inflammasome IL-1β pathway may offer a new treatment strategy for crystal-related arthritis.

A two-step mechanism is required for the production of IL-1β: firstly the activation of the pattern-recognition receptors (*e.g*. Toll-like receptors) upregulates the expression of pro-IL-1β (31). Second, the activation of the inflammasome, mediated by crystals, leads to the cleavage of the pro-IL-1β into the mature cytokine (32-34). IL-1β orchestrates further inflammation by promoting the release of other cytokines and chemokines (such as TNF-α, IL-6 and IL-8), the endothelial cell activation and the neutrophils recruitment (30). Anakinra, the first IL-1 inhibitor that was approved, is an IL-1 receptor (IL-1R) antagonist that blocks the binding of IL-1α and IL-1β to the IL-1R (35). Due to its rapid effect (3–5 days),

anakinra is suitable for the treatment of acute crystal-related arthritis (11, 12). The data we have reviewed showed that symptoms resolution occurred within 4.0±1.9 days after the first injection of anakinra.

Of the 67 patients presenting with acute CPP-crystal arthritis, the 76.1% was treated for 1-3 days, whereas in 23.9% anakinra was administered for 5–9 days. As suggested by our data, longer treatment may be necessary in patients with a longer disease duration and in chronic CPP-crystal inflammatory arthritis. Moreover, as reported by Aouba, axial involvement (*e.g.* crowned dens syndrome) may require longer treatment than peripheral arthritis (20).

Despite various definitions of treatment efficacy were adopted, 77.0% of patients was classified as complete responders. Considering acute CPP-crystal arthritis, clinical response to anakinra was observed in 80.6% of patients. A significant reduction of TJC (mean reduction of 5.1±2.3), SJC (mean reduction of 3.7±2.2), VAS pain (mean reduction of 44.2±10.9) and CRP level (mean reduction of 18.6±54.1 mg/l) was observed. Although our results suggest that anakinra is effective in chronic CPP-crystal inflammatory arthritis too (response rate of 42.9%), the sample size (n=7) was too low to draw any definitive conclusions.

In contrast to the brief attacks of acute gouty arthritis that usually last for several days, acute CPP-crystal arthritis may last for weeks to months. As observed by different research groups, gout seems to have a better response to anakinra than CPPD (17, 26). In 2013, Verhoeven hypothesised that both the presence of systemic inflammation and a short duration of crystal-induced arthritis may predict a good response to treatments targeting IL-1 (26). However, the pooled analysis conducted in our review did not show any significant predictors of good response to IL-1 inhibitors in CPPD.

As previously reported in gout and in rheumatoid arthritis (36-39), our data support the safety of anakinra both in acute CPP-crystal and in chronic CPP-crystal inflammatory arthritis. Adverse events were reported in 4.1% of patients and among them, skin reactions and respiratory infections were the most common.

Anti-TNF-α agents have been used successfully in a broad range of rheumatic diseases. However, data related to the use of TNF-α blockers in CPPD are very limited. Nevertheless, a theoretical rationale in targeting this cytokine may be advocated. So far, there are only 3 patients with chronic CPP-crystal inflammatory arthritis treated with anti-TNF-α agents, reporting conflicting results. Efficacy of anti-TNF-α inhibitors was reported in 2 patients treated with infliximab, whereas no response was observed with adalimumab. Infliximab was maintained for 9 years without loss of efficacy and serious adverse events. In 2007, Josefina *et al*. reported a case of recurrent attacks of pseudogout in a patient with rheumatoid arthritis treated with etanercept (40). This finding supports the involvement of different inflammatory pathways in CPPD and in rheumatoid arthritis and, in particular, a minor role of TNF-α blockers and a more important role of IL-1 inhibitors in the pathogenesis of CPP-crystal arthritis.

The small sample size, in particular of patients with chronic CPP-crystal inflammatory arthritis, is the main drawback of this review. Other limitations are the absence of a generally-accepted definitions of acute and chronic CPP-crystal arthritis and of the response criteria; information on the follow-up, inflammatory markers, TJC and SJC was not available for all the patients.

Finally, the overall quality of the studies included in this review was moderate-to-low. All of them were case series or case reports and neither randomisation nor control group were adopted in any of these studies.

In conclusion, the results of the studies included in this review support the IL-1 inhibitors as a therapeutic option in patients with CPPD, especially in acute CPP-crystal inflammatory arthritis, in refractory disease or in subjects with relevant comorbidities, in whom standard treatments are contraindicated. Anakinra had a rapid anti-inflammatory effect and it was well-tolerated in short-term treatment strategy. However, more high-quality researches (*e.g.* randomised controlled clinical trials) are needed to confirm our results and to provide more robust evidence for the efficacy of IL-1 inhibitors in CPPD.

Competing interests

A. Di Matteo has received speaking fees from Grünenthal; W. Grassi has received speaking fees from AbbVie, Celgene, Grünenthal, Pfizer and Union Chimique Belge Pharma; E. Filippucci has received speaking fees from AbbVie, Bristol-Myers Squibb, Celgene, Novartis, Pfizer, Roche and Union Chimique Belge Pharma.

The other co-authors have declared no competing interests.

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