Anakinra for constrictive pericarditis associated with incessant or recurrent pericarditis

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ABSTRACT

Objective

Frequent flares of pericardial inflammation in recurrent or incessant pericarditis with corticosteroid dependence and colchicine resistance may represent a risk factor for constrictive pericarditis (CP). This study was aimed at the identification of CP in these patients, evaluating the efficacy and safety of anakinra, a third-line treatment based on interleukin-1 inhibition, to treat CP and prevent the need for pericardiectomy.

Methods

Consecutive patients with recurrent or incessant pericarditis with corticosteroid dependence and colchicine resistance were included in a prospective cohort study from 2015 to 2018. Enrolled patients received anakinra 100 mg once daily subcutaneously. The primary end point was the occurrence of CP. A clinical and echocardiographic follow-up was performed at 1, 3, 6 months and then every 6 months.

Results

Thirty-nine patients (mean age 42 years, 67% females) were assessed, with a baseline recurrence rate of 2.76 flares/patient-year and a median disease duration of 12 months (IQR 9–20). During follow-up, CP was diagnosed in 8/39 (20%) patients. After anakinra dose of 100 mg/day, 5 patients (63%) had a complete resolution of pericardial constriction within a median of 1.2 months (IQR 1–4). In other three patients (37%), CP became chronic, requiring pericardiectomy within a median of 2.8 months (IQR 2–5). CP occurred in 11 patients (28%) with incessant course, which was associated with an increased risk of CP over time (HR for CP 30.6, 95% CI 3.69 to 253.09).

Conclusions

In patients with recurrent or incessant pericarditis, anakinra may have a role in CP reversal. The risk of CP is associated with incessant rather than recurrent course.

INTRODUCTION

Constrictive pericarditis (CP) is the most feared complication of pericarditis.[1 2] Pericardiectomy is required in advanced stages and is associated with a >5% perioperative mortality.[3 4] However, with the help of multimodality imaging, surgery can be avoided in patients with subclinical evidence of pericardial inflammation. In these patients, a clinical improvement may be obtained with conventional anti-inflammatory drugs (non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids).[5–7]

Little is known about the occurrence and management of CP in the setting of recurrent or incessant pericarditis, that it is usually corticosteroid-dependent and colchicine-resistant. Indeed, the frequent flares of pericardial inflammation in these patients may represent a major risk factor for CP, while the refractoriness to conventional anti-inflammatory therapy would make surgery the unique option.

This study was aimed at the identification of CP in these patients, evaluating the efficacy and safety of third-line treatment based on interleukin-1 (IL-1) inhibitor anakinra to treat CP and prevent the need for pericardiectomy.

METHODS

Study design and population

Patients with recurrent or incessant pericarditis, with corticosteroid dependence and colchicine resistance were included in a prospective cohort study. Consecutive patients were recruited from 2015 to 2018 at the time of a pericarditis recurrence, according to the following inclusion criteria: adult patients (aged >18 years), providing oral and written informed consent, with corticosteroid-dependent and colchicine-resistant pericarditis defined as recurrent or incessant flares despite conventional therapy including corticosteroids, NSAIDs, corticosteroids and colchicine. Exclusion criteria were: hypersensitivity to anakinra or *Escherichia coli*-derived proteins, neutropenia (absolute neutrophil count $<1.5\times10^9$/L), active tuberculosis and active malignancy.

All enrolled patients were started on anakinra 100 mg once daily by subcutaneous injection. Anakinra was maintained for a minimum of 3 months and then continued, tapered or discontinued according to clinical evaluation. This treatment is well established in this setting.[8] According to international guidelines[8] and national legislative framework (ie, law no. 648/96), anakinra was prescribed through specific treatment plan document, dispensed by hospital pharmacy service and charged to National Health Service.

Concomitant treatment for pericarditis (colchicine, NSAIDs, corticosteroids) was discontinued according to clinical evaluation.

Clinical, laboratory testing, electrocardiographic and echocardiographic assessments were performed in all patients at the time of enrolment, according to local practice and in accordance with established guidelines.[8]

The primary end point was the occurrence of CP. As indicated in current international guidelines,[8] echocardiographic assessment of CP was done according to established criteria[9]: septal bounce, respiratory variations of mitral, tricuspidal and hepatic veins flow, lateral E'<septal E' on tissue Doppler imaging. A clinical and echocardiographic follow-up was performed at 1, 3, 6 months and then every 6 months.

According to 2015 European Society of Cardiology guidelines,[8] pericarditis was classified as recurrent in case of one or more relapses after a documented first episode, with a minimum symptom-free interval of 4–6 weeks. When symptoms persisted for >4–6 weeks without a symptom-free interval, pericarditis was defined as 'incessant'. This cohort study followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology statement.

Statistical analysis

Continuous variables, presented as means and SD or medians and IQR, were compared by non-parametric tests: Mann-Whitney U test was used for independent data. Categorical variables, presented as counts and percentages, were compared using the χ^2 test with Yates correction or Fisher's exact test as appropriate. The survival probability and the freedom from pericardial constriction (PC) were evaluated by the Kaplan-Meier curves, and compared by the Mantel-Cox test. Cox proportional hazard models were used to establish the risk of constriction. All analyses were performed using the SPSS V.18.0 (SPSS, Chicago, Illinois, USA) and a two-sided significance level of <0.05 was considered statistically significant.

Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.
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RESULTS

Thirty-nine patients (mean age 42 years, 67% females) were assessed. At baseline, median duration of pericardial disease was 12 months (IQR 9–20) with a median of 4 prior recurrences (3–5), 1 prior emergency department (ED) admission (1–3), 1 prior hospitalisation (0–2). Pericarditis recurrence rate was 2.76 flares-patient/year, that is, a mean of one new recurrence every 132 days. Demographic characteristics are described in table 1.
A diagnosis of CP was based on clinical, echocardiographic, CMR and CT data and was achieved in 8/39 patients (20%). Baseline features of patients with or without CP were similar, but with a more frequent presence of an incessant course of symptoms (88% vs 13%, p<0.001; table 2). Indeed, among the 11 (28%) patients with incessant course of symptoms, a markedly higher incidence of CP was observed (63% vs 4%, risk ratio=47, 95% CI 4.5 to 492, p<0.001). Incessant course was associated with an increased risk of CP over time (figure 1), according to Cox regression model analysis (HR for CP 30.6, 95% CI 3.69 to 253.09).
Recurrence rate before anti-IL-1 treatment initiation, despite being high in both groups, was not associated with an increased risk for CP (3.88 flares-patient/year in CP group vs 2.62 flares-patient/year in others, risk ratio=1.43, 95% CI 0.95 to 2.1, p=0.10). None of the eight patients had signs or symptoms of heart failure at the time of study enrolment. After anti-IL-1 treatment initiation in five patients out of eight (63%), a complete resolution of CP was obtained at follow-up (figure 2), within a median time of 1.2 months (IQR 1–4). In other three out of eight patients (37%), PC persisted and became chronic, later requiring pericardiectomy within a median time of 2.8 months (IQR, 2–5).
All patients were treated with full-dose anakinra for a median duration of 6 months (IQR 4–7), followed by a tapering period with a median duration of 3 months (IQR 0–6).
There were no differences in concomitant medications between patients with or without CP (table 3). Although all patients had been corticosteroid-dependent, at the time of enrolment 30 (77%) patients were still on steroids. During the treatment with anakinra, steroids were successfully tapered and discontinued in 37 (95%) patients. NSAIDs were discontinued in 38 (98%) patients, while colchicine was continued in 29 (74%) patients. AEs mostly consisted of mild, transient skin reactions (with erythema, pruritus and/or pain) at the injection site, as shown in table 3. One patient required drug discontinuation for intolerable arthralgias and myalgias, without evidence of creatine kinase elevation.

DISCUSSION

Chronic inflammation of the pericardium may lead to fibrotic scarring, calcifications and subsequent impairment of diastolic filling, namely CP.[10] However, CP may also be detected in patients with a first episode of acute pericarditis, especially if associated with a specific aetiology and may be transient with resolution after anti-inflammatory therapy.[11 12] Hancock[11 13] first described subacute fibroelastic CP which, as opposed to chronic 'rigid shell' CP, may be caused by a transiently thickened and stiff pericardium, due to inflammation with oedema and fibrin deposition.[11]
In the setting of acute pericarditis with CP, international guidelines[8] recommend anti-inflammatory treatments, including NSAIDs, colchicine and corticosteroids, which may successfully hamper the progression to chronic, non-reversible constriction. At this stage, surgical pericardiectomy is often required.[3 4] Chronic CP develops in about 1% of patients with idiopathic aetiology, while there is a higher risk in case of bacterial (especially tubercular) or postpericardiotomy aetiology.[14]
Relapse is the most frequent complication following acute pericarditis and a careful clinical management of the first episode is key to prevent it.[15] Indeed, recurrent pericarditis may occur in up to 30% patients, rising to 50% in those who have not been treated with colchicine, received corticosteroids or had multiple recurrences.[16 17] About 5%–10% patients with recurrent pericarditis will later develop corticosteroid-dependent and colchicine-resistant recurrent pericarditis.[18 19] In addition to the negative impact on their quality of life,[14 20] these patients have a challenging clinical management because of inadequate response to standard anti-inflammatory treatment, usually with multiple unsuccessful attempts to taper corticosteroids.[21] However, as we recently showed in the International Registry of Anakinra for Pericarditis (IRAP), anti-IL-1 agents such as anakinra are effective to obtain a marked reduction of recurrences, hospitalisations and ED admissions, extinguishing chronic pericardial inflammation.[22]

In patients with recurrent pericarditis, chronic inflammation may be sustained by autoinflammatory pathways, in which IL-1 plays a key role. Indeed, autoreactive processes are started after the first episode of acute pericarditis and then a chronic low-grade inflammation is sustained over time.[18] The persistent activation of inflammasomes such as NOD-like receptor pyrin domain-containing-3 causes a downstream release of IL-1, which amplifies the inflammatory response.[15 23–25] Anakinra is a recombinant IL-1 receptor antagonist which inhibits IL-1 action. Used for >15 years in the setting of rheumatoid arthritis and systemic autoinflammatory diseases,[8 9] the treatment of recurrent pericarditis has recently shown safety and efficacy in various case reports,[26 27] small case series,[28 29] a randomised controlled trial on 21 patients[30] and a large international registry previously published by our group.[22]

Pericarditis may be classified either as 'incessant' or 'intermittent', when discontinuation or attempts to wean from anti-inflammatory drugs lead to, respectively, a relapse within 4–6 weeks or later.[14] The occurrence and management of CP in the setting of incessant or recurrent pericarditis is currently unknown and was the focus of the present study. The incidence of CP in the present cohort of patients was 20%, markedly greater when compared with the clinical setting of acute pericarditis. This greater proportion might be due to the longer history of pericardial exposure to repeated episodes of inflammation. Furthermore, although an idiopathic aetiology was diagnosed in most patients, which is commonly associated with uncomplicated and benign course of disease, it is noteworthy to mention that the population of the study included only the subset of patients who later developed corticosteroid-dependent and colchicine-resistant recurrent pericarditis.

Since patients with corticosteroid dependence and colchicine resistance do not respond anymore to conventional drugs, the clinical management of CP is challenging in this setting. These patients should be strictly followed up and offered advanced therapeutic strategies as soon as possible. However, the use of anakinra was effective to revert CP in 63% patients. Indeed, the reversibility of CP is possible due to presence of active inflammation of the pericardium. A possible stepwise algorithm for the treatment of corticosteroid-dependent and colchicine-resistant pericarditis with CP, based on the opinion of the authors, is proposed in figure 3. An interesting finding of the present study is that CP occurred more frequently (HR=31) in patients with an 'incessant' course of pericarditis. This is in agreement with previous evidences in literature that incessant pericarditis may progress to constriction within a few weeks or months, while this progression is unusual for idiopathic recurrent pericarditis.[14] A limitation of the present study is that C reactive protein was not assessed during the follow-up. In conclusion, anakinra may have a role in CP reversal. The risk of PC is associated with incessant rather than simple recurrent course.

Key questions

What is already known on this subject?

- Constrictive pericarditis (CP) is a rare and serious complication following pericarditis.
- Anakinra, an anti-interleukin (IL)-1 agent, may be efficacious and safe for the treatment of refractory recurrent pericarditis.

What might this study add?

- The main finding of the study is that pericardial constriction may occur in about 20% patients with corticosteroid-dependent, colchicine-resistant pericarditis.
- Incessant course of symptoms is a main risk factor for CP in these patients.
- Anti-IL-1 agents such as anakinra may have a role in CP reversal.

How might this impact on clinical practice?

- Patients with incessant course of symptoms should be closely observed for pericardial constriction.
- In patients with pericardial constriction, the use of anti-IL-1 agents such as anakinra should be prescribed in the attempt to revert constriction.

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FOOTNOTES

- AA and MI contributed equally.
- **To be presented at ESC Congress 2020 under Young Investigation Award- Best Poster** To be presented at ESC Congress 2020 under Young Investigation Award- Best Poster
- **Contributors** AA: study design and conception, data collection, interpretation and analysis, article drafting, critical revision and approval of the final version, responsible for the overall content as guarantor. MMI: study design and conception, data collection, interpretation and analysis, article drafting, critical revision and approval of the final version, responsible for the overall content as guarantor. CG: critical revision and approval of the final version. AB: critical revision and approval of the final version. YA: critical revision and approval of the final version. GMDF: critical revision and approval of the final version.
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- **Patient consent for publication** Not required.

- **Ethics approval** The study was approved by the Ethics Committee and all patients provided written informed consent. Protocol data were collected in accordance with the institutional review board policies and complied with the Declaration of Helsinki.
- **Provenance and peer review** Not commissioned; externally peer reviewed.
- **Data availability statement** Data are available on reasonable request.

Table 1 Demographics at the time of enrolment

Variable	Population (n=39)
Age, years	42±12
Female gender	26 (67%)
Pericardial disease duration, months	12 (9–20)
Previous pericarditis recurrences	4 (3–5)
Previous recurrence rate, no. flares-patient/year	2.76
Previous ED admissions	1 (1–3)
Previous hospitalisations	1 (0–2)
Incessant course of symptoms	11 (28%)
Aetiology	
Idiopathic	29 (74%)
Postcardiac injury syndrome	5 (13%)
Autoimmune disease*	4 (10%)
Radiation	1 (3%)
CRP elevation	31 (79%)
Pericardial effusion	22 (56%)

Values are presented as no. (%) or mean±SD or median (IQR).
*Presumed in patients with a defined diagnosis of rheumatoid arthritis, Sjögren syndrome.
CRP, C reactive protein; ED, emergency department.

Table 2 Patients with evidence of pericardial constriction (PC)

Variable	PC+ (n=8)	PC− (n=31)	P value
Age, years	35±12	43±11	0.08
Female gender	5 (63%)	21 (68%)	0.99
Pericardial disease duration, months	9 (8–14)	12 (9–22)	0.32
Previous pericarditis recurrences	4 (2–5)	4 (3–5)	0.43
Recurrence rate before anti IL-1 treatment, no. flares-patient/year	3.88	2.62	0.10
Recurrence rate after anti IL-1 treatment, no. flares-patient/year	0.71*	0.72†	0.99
Previous ED admissions	1 (1–2)	1 (1–3)	0.25
Previous hospitalisations	2 (1–2)	1 (0–2)	0.10
Incessant course of symptoms	7 (88%)	4 (13%)	**<0.001**
Aetiology			
Idiopathic	6 (75%)	23 (74%)	0.99
Postcardiac injury syndrome	1 (13%)	4 (13%)	0.99
Autoimmune disease‡	1 (13%)	3 (10%)	0.99
Radiation	–	1 (3%)	0.99
CRP elevation	7 (88%)	24 (77%)	0.94
Pericardial effusion	6 (75%)	16 (52%)	0.44
Concomitant medications at the time of enrolment			
NSAIDs	5 (62%)	19 (61%)	0.99
Colchicine	8 (100%)	29 (94%)	0.99
Corticosteroids	7 (88%)	23 (74%)	0.65
Triple therapy (NSAIDs+colchicine+corticosteroids)	4 (50%)	15 (48%)	0.99
Follow-up, months	6±4	6±4	0.68

*P<0.001 for comparison before vs after anti-IL-1 treatment.
†P<0.001 for comparison before vs after anti-IL-1 treatment.
‡Presumed in patients with a defined diagnosis of rheumatoid arthritis, Sjögren syndrome.
CRP, C reactive protein; ED, emergency department; IL, interleukin; NSAIDs, non- steroidal anti-inflammatory drugs.

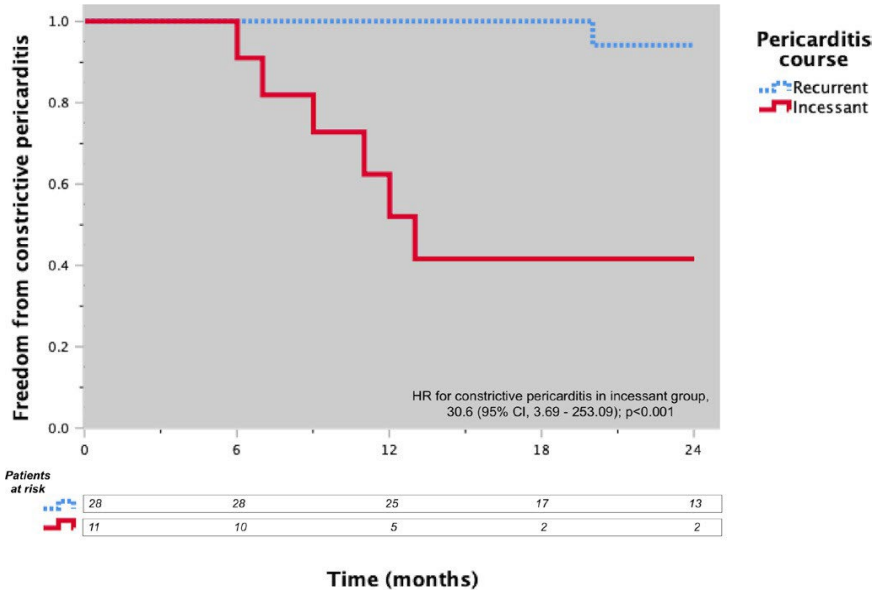

Figure 1 Freedom from constrictive pericarditis in patients with incessant course of symptoms, based on the time from the first episode of pericarditis (months).

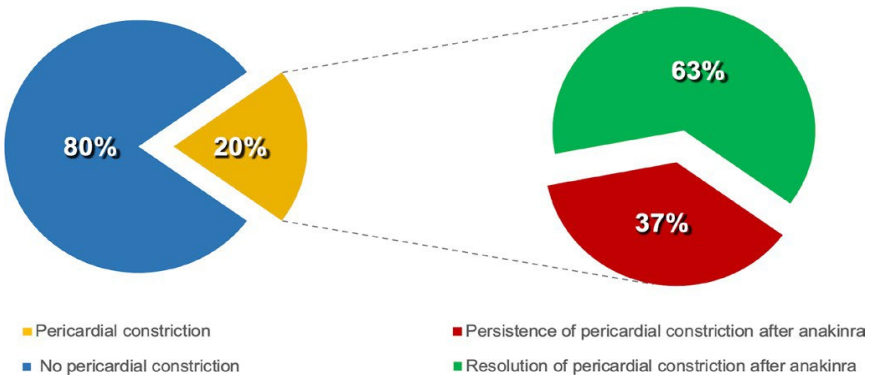

Figure 2 Pericardial constriction at baseline and after treatment with anakinra, in patients with corticosteroid-dependent and colchicine- resistant pericarditis.

Table 3 Adverse events (AEs)

Aes	Population (n=39)
Occurrence of one or more AEs	21 (54%)
Mild transient skin reactions at injection site	16 (41%)
Arthralgias and myalgias	3 (8%)
Transient neutropenia (<1.5×10⁹/L)	1
Infection (lymphocoele infection)	1
Hot flashes and sweating	1

Values are presented as no. (%).

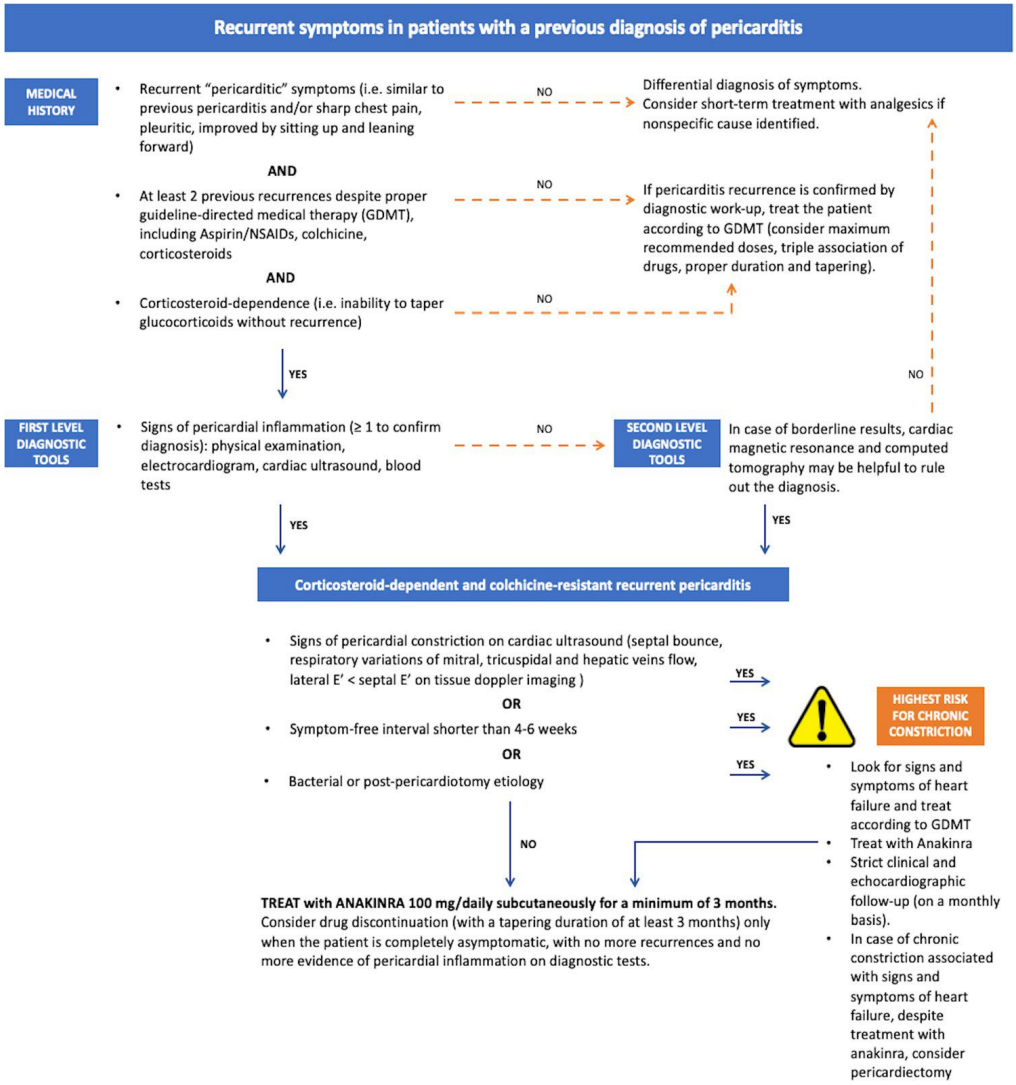

Figure 3 Algorithm for the treatment of corticosteroid-dependent and colchicine-resistant pericarditis with constrictive pericarditis (CP), proposed by the authors.