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Efficacy of colchicine in addition to anakinra in patients with recurrent pericarditis

Valentino Collini,[1] Alessandro Andreis ,[2] Marzia De Biasio,[1] Maria De Martino,[3] Miriam Isola,[3] Nicole Croatto,[3] Veronica Lepre,[4] Luca Cantarini,[5] Marco Merlo,[4,6] Gianfranco Sinagra,[4,6] Antonio Abbate,[7] George Lazaros,[8] Antonio Brucato,[9] Allan L Klein,[10] Massimo Imazio [1,3]

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For numbered affiliations see end of article.

Correspondence to
Dr Massimo Imazio; massimo.imazio@uniud.it

ABSTRACT

Aim Anakinra, an anti IL-1 agent targeting IL-1 alfa and beta, is available for the treatment of recurrent pericarditis in cases with corticosteroid dependence and colchicine resistance after failure of conventional therapies. However, it is unclear if the combination with colchicine, a non-specific inhibitor of the inflammasome targeting the same inflammatory pathway of IL-1, could provide additional benefit to prevent further recurrences. The aim of the present observational study is to assess whether the addition of colchicine on top of anakinra could prolong the time to first recurrence and prevent recurrences better than anakinra alone.

Methods International, all-comers, multicentre, retrospective observational cohort study analysing all consecutive patients treated with anakinra for corticosteroid-dependent and colchicine-resistant recurrent pericarditis. The efficacy endpoint was recurrence rate and the time to the first recurrence.

Results A total of 256 patients (mean age 45.0±15.4 years, 65.6% females, 80.9% with idiopathic/viral aetiology) were included. 64 (25.0%) were treated with anakinra as monotherapy while 192 (75.0%) with both anakinra and colchicine. After a follow-up of 12 months, 56 (21.9%) patients had recurrences. Patients treated with colchicine added to anakinra had a lower incidence of recurrences (respectively, 18.8% vs 31.3%; p=0.036) and a longer event-free survival (p=0.025). In multivariable analysis, colchicine use prevented recurrences (HR 0.52, 95% CI 0.29 to 0.91; p=0.021).

Conclusions The addition of colchicine on top of anakinra treatment could be helpful to reduce recurrences and prolong the recurrence-free survival.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Anakinra, an anti IL-1 agent targeting both IL-1 alfa and beta, is safe and efficacious to treat corticosteroid-dependent and colchicine-resistant cases of recurrent pericarditis. Colchicine is a well-known drug that could halve the recurrence rate acting also as a non-specific inhibitor of the inflammasome, the cytosolic complex that generates IL-1 after its activation.

WHAT THIS STUDY ADDS

⇒ Colchicine added on top of anakinra can be helpful to further reduce the subsequent rate (HR 0.52, 95% CI 0.29 to 0.91; p=0.021).

⇒ A possible explanation is that the sequential block of the inflammatory pathway generating IL-1 by two drugs (colchicine and anakinra) could be more efficacious than anakinra alone.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This observational study suggests to combine anakinra with colchicine for the treatment and prevention of recurrent pericarditis and may be the basis for a specifically designed trial to test this combined treatment versus single use of anakinra.

INTRODUCTION

Anakinra is the recombinant form of the natural inhibitor of interleukin (IL)-1[1] and has been proved to be safe and efficacious to treat and prevent recurrences of pericarditis in patients with corticosteroid-dependent and colchicine-resistant cases with elevated C reactive protein (CRP) at presentation.[2–4]

In clinical practice, clinicians often use monotherapy with anakinra to treat these patients and this has been also suggested by the proven efficacy of rilonacept, an IL-1 trap, as monotherapy in the RHAPSODY trial.[5]

Colchicine is a non-specific inhibitor of the inflammasome due to its capability to interfere with microtubules polymerisation, a function that is essential for the assembly of the inflammasome and the subsequent generation of activated IL-1.[6 7] In patients with pericarditis, the anti-inflammatory efficacy of anakinra is related to its blocking effect either on IL-1 alfa or beta thus reducing their proinflammatory levels.[1]

However, it is unknown if the combination of colchicine and anakinra could provide an

additional advantage over the use of anakinra alone in order to prevent further recurrences.

The aim of the present observational study is to assess whether the addition of colchicine on top of anakinra could prolong the time to first recurrence and prevent recurrences better than anakinra alone.

METHODS

Population and study design

This multicentre, observational, retrospective, cohort study included all patients who started receiving anakinra for corticosteroid-dependent and colchicine-resistant recurrent pericarditis (RP) at eight tertiary university centres for pericardial diseases across Europe and North America from January 2013 to December 2022.

Inclusion criteria

Only adult patients (>18 years) with a follow-up of 12 months were included in the study. According to the 2015 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of pericardial diseases, RP was diagnosed with a documented first episode of acute pericarditis, a symptom-free interval of 4–6 weeks or longer and evidence of subsequent recurrence despite guideline-based medical treatment (non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and/or corticosteroids). All patients had corticosteroid dependence defined as unability to taper or withdraw corticosteroids without a relapse.

Exclusion criteria

We excluded patients with a follow-up of less than 12 months, allergic reactions to anakinra leading to discontinuation and incessant pericarditis since the aim of the study was specifically to evaluate only patients with recurrences (see figure 1).

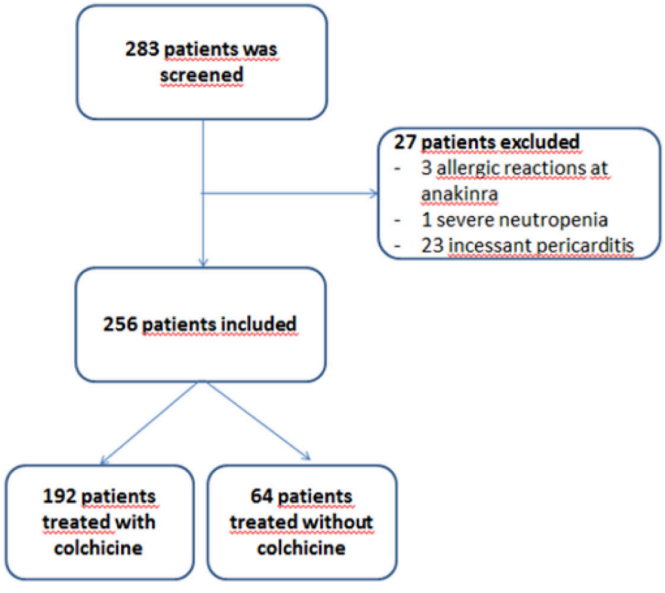

Figure 1 Flow diagram of study population. No patients were lost during follow-up.

Study procedures

History (including the duration of pericardial disease and the number of recurrences), clinical examination, laboratory tests, ECG and multimodal imaging assessments were routinely performed at the start of anakinra in all patients, according to local practice and with established guidelines. Colchicine administration after initiating anakinra was based on the clinical judgement of the individual physician. As recommended by the 2015 ESC pericarditis guidelines, colchicine was administered at weight-adjusted doses to all patients (0.5 mg once daily if patient weight is <70 kg, 0.5 mg two times per day if the patient weight is >70 kg). All patients received anakinra 100 mg once daily by subcutaneous injection for 6 months and then tapered. Corticosteroids was administered at low to moderate doses (ie, prednisone 0.2–0.5 mg/kg/day) and slowly tapered in all cases. Both anakinra and concomitant medical treatment for pericarditis (NSAIDs, colchicine, corticosteroids) were maintained, tapered or discontinued based on the clinical judgement of the individual physician.

Endpoints

The primary efficacy endpoint was the time to the first recurrence, diagnosed when chest pain recurred along with one or more of the following signs: fever, pericardial friction rub, ECG changes or echocardiographic evidence of new or worsening pericardial effusion. We also evaluated the recurrence rate with or without colchicine on top of anakinra. The occurrence of any adverse event was evaluated as safety endpoint.

Statistical analysis

Continuous variables were expressed as mean±SD or median and IQR, according to the data distribution. The data were analysed using the Shapiro-Wilk test to verify the normal distribution. Categorical variables were presented as absolute numbers and percentages. The Student's t-test or the Mann-Whitney U test was used to compare continuous variables between groups, as appropriate. Comparison of categorical variables was performed by χ^2 analysis or the Fisher's exact test, as appropriate. Event-free survival was defined as freedom from recurrence and was determined using the Kaplan-Meier approach for colchicine and no-colchicine groups. Comparisons between survival distributions were performed using the log-rank test. Univariable and multivariable Cox regression analyses were performed to determine the effect of each variable on survival, with estimation of the HR, after the proportional hazards assumption had been verified. Multivariable regression included all the significant variables with a p<0.10 in the univariable analysis, adjusting for possible cofounders. Results are presented as HRs and 95% CIs. The proportional hazard assumption was tested using the Schoenfeld residual test. Analyses were performed by using Stata V.18.0 (Stata).

Table 1 Baseline features of the studied population according to the use of colchicine

	Colchicine (–) (n=64)	Colchicine (+) (n=192)	P value
Gender, n (%)			0.76
Female	41 (64.1)	127 (66.1)	
Male	23 (35.9)	65 (33.9)	
Age, mean (SD)	45.4 (16.0)	44.9 (15.2)	0.81
Idiopathic/viral aetiology, n (%)	56 (87.5)	151 (78.6)	0.12
Fever, n (%)	19 (29.7)	58 (30.2)	0.94
Cardiovascular risk factors, n (%)	37 (57.8)	114 (59.4)	0.83
Pericardial effusion, n (%)	32 (50.0)	82 (42.7)	0.31
Pericardial disease duration, months, median (IQR)	24 (10.9–51)	25 (10.6–46.1)	0.88
Previous pericarditis recurrences, median (IQR)	3 (2.5–4.5)	3 (3–5)	0.51
CRP>5, n (%)	41 (64.1)	111 (57.8)	0.38
NSAIDs, n (%)	28 (43.8)	100 (52.1)	0.25
Corticosteroids, n (%)	43 (67.2)	154 (80.2)	**0.032**
12 months-follow up	64 (100)	192 (100)	–

Bold type p values of data considered for multivariable analysis.
CRP, C reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs.

RESULTS

Baseline data

Among the initial 283 patients, 27 were excluded because they had incessant pericarditis (n=23) or because of side effects that necessitated discontinuation of anakinra soon after initiation of therapy (n=4) (figure 1). Baseline characteristics are presented in table 1. A total of 256 patients were included (figure 1). Patients had a mean age of 45.0±15.4 years, 168 (65.6%) were females and 207 (80.9%) had an idiopathic aetiology. A specific aetiology was detected in 49 cases out of 256 patients (19.1%) and was, respectively: a systemic inflammatory disease (26 cases, 10.1%), postvaccination (5 cases, 2.0%), postcardiac injury syndrome (18 cases, 7.0%). Transthoracic echocardiography was performed in all patients. At baseline, the median duration of disease was 24 months (IQR 11–48) with a median of 3 prior recurrences (IQR 3–5). 64 (25.0%) patients were treated with colchicine, while 192 (75.0%) were treated without colchicine. Pericardial effusion was present in 114 cases (44.5%) and was mild in 83 of 114 cases (72.3%), and severe in 8 cases (4.9%). Although all patients had been corticosteroid-dependent, at the time of enrolment 197 patients (77.0%) were still on active treatment with glucocorticoids (the median dose of prednisone dose was 14.5 mg/day), while 128 patients (50%) continued active treatment with NSAIDs. As reported in table 1, baseline characteristics were similar between the two groups, except for a higher frequency of prednisone use in patients receiving colchicine.

Follow-up data

During a follow-up of 12 months, 56 (21.9%) patients had recurrences. Among them, 9 patients experienced recurrences with full-dose anakinra, while 36 patients had recurrences during tapering of anakinra and 11 after anakinra discontinuation. A lower incidence of recurrence was observed among patients receiving colchicine with a longer event-free survival (figure 2, p=0.025). Anakinra was continued in all cases for 6 months at a dosage of 100 mg/day, then tapered at the discretion of the individual investigator (there were two main tapering regimens: (1) use of anakinra every other day with a full dose, 100 mg/day, for 3 months and then half dose, 50 mg/day, every other day for additional 3 months in 140/256 cases (54.6%), and (2) tapering of one daily dose per week every month in 116/256 cases (45.4%). Colchicine was maintained on top of anakinra for 6 months and continued in 75/192 (39%) patients throughout the entire follow-up of 12 months.

In multivariable Cox regression analysis (table 2), colchicine use prevented recurrences (HR 0.52, 95% CI 0.29 to 0.91; p=0.021).

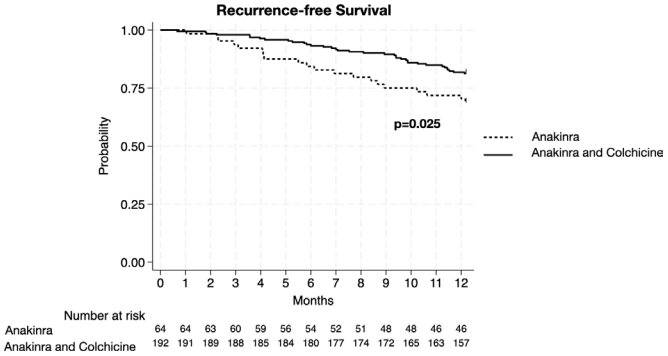

Figure 2 Event-free survival according to colchicine use in the two cohorts.

Table 2 Univariable and multivariable Cox regression analysis to assess risk factors for time to recurrence in the studied population

	Univariable analysis		
	HR	95% CI	P value
Age	0.99	0.97,1.01	0.252
Female gender	1.09	0.62,1.92	0.753
Idiopathic/viral aetiology	2.14	0.92, 5.00	0.077
CRP>5	1.71	0.97,3.03	**0.064**
Pericardial disease duration	1.00	0.99,1.00	0.090
Number of recurrences	1.04	0.98,1.10	0.233
Pericardial effusion	1.79	1.06,3.05	**0.030**
Colchicine	0.54	0.31,0.93	**0.027**
NSAIDs	1.16	0.69,1.97	0.570
Corticosteroids	1.65	0.81,3.36	0.171
	Multivariable analysis		
	HR	**95% CI**	**P value**
Idiopathic/viral aetiology	2.07	0.88,4.88	0.097
CRP>5	1.37	0.76,2.47	0.293
Pericardial effusion	1.54	0.90,2.66	0.116
Colchicine	0.52	0.29,0.91	**0.021**
Corticosteroids	1.69	0.81,3.55	0.164

Bold type features that were considered in multivariable analysis for p values.
.CRP, C reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs.

Anakinra-associated side effects were recorded in 85 (33%) patients, mostly were skin reactions at injection site 60 (23%), while arthralgias and myalgias were recorded in 11 (4%) cases, transaminase elevation in 7 (3%) patients, infections in 6 (2%) cases and neutropenia in 2 (1%) patients. Colchicine was relatively well tolerated: one patient discontinued the drug for a skin reaction, while six patients presented mild gastrointestinal side effects. Previous use of corticosteroids was associated with severe side effects in about 25% of patients before the beginning of anakinra. No additional side effects were reported with concomitant use of anakinra with corticosteroids.

DISCUSSION

To the best of our knowledge, this observational study is the first and largest study evaluating the efficacy of colchicine added to anakinra to prevent further recurrences of pericarditis. In this study, colchicine on top of anakinra provided a significant reduction of the subsequent recurrences within 12 months (HR 0.52, 95% CI 0.29 to 0.91; p=0.021) and prolonged the event-free survival from recurrences.

It is now well recognised that anakinra, an anti IL-1 agent targeting both IL-1 alfa and beta, is safe and efficacious to treat corticosteroid-dependent and colchicine-resistant cases of RP. In the AIRTRIP trial, a double-blind, placebo-controlled, randomised withdrawal trial conducted among 21 consecutive patients with corticosteroid-dependent and colchicine-resistant RP and elevation of CRP, anakinra was administered at 2 mg/kg per day, up to 100 mg, up to 6 months or until a pericarditis recurrence. RP occurred in 9 of 10 patients (90%; incidence rate, 2.06% of patients per year) assigned to placebo and 2 of 11 patients (18.2%; incidence rate, 0.11% of patients per year) assigned to anakinra, for an incidence rate difference of −1.95% (95% CI −3.3% to −0.6%).[2] However, this study did not have the power to compare monotherapy with anakinra versus combined therapy with anakinra plus colchicine according to physician prescription.

In a subsequent real-world, international registry, the IRAP (International registry of anakinra for pericarditis) registry, among 224 patients with refractory recurrent pericarditis (46±14 years, 63% women, 75% idiopathic)[3] anakinra reduced pericarditis recurrences by 6-fold (2.33–0.39 per patient per year), emergency department admissions by 11-fold (1.08–0.10 per patient per year) and hospitalisations by 7-fold (0.99–0.13 per patient per year) after a median treatment of 6 months. Corticosteroid use was decreased by anakinra (respectively, from 80% to 27%; p<0.001). In this study, the majority (88%) of patients continued colchicine, after initiation of anakinra but the efficacy of dual inflammasome inhibition in preventing recurrence was not analysed.

Such impressive results led to the common off-label use of anakinra for patients with RP refractory to NSAIDs, colchicine and corticosteroids in several European countries. In some European countries, such as Italy, the drug use has been authorised and reimbursed by the National Healthcare System for corticosteroid-dependent and colchicine-resistant RP with elevated CRP at presentation. In the USA, rilonacept has been registered for RP based on the results of the RHAPSODY trial[5] leading also to monotherapy in such patients.

Colchicine is a well-known drug, that could halve the recurrence rate, acting also as a non-specific inhibitor of the inflammasome, the cytosolic complex that generates IL-1 after activation.[8] Based on several spontaneous clinical trials the efficacy and safety of colchicine has been well documented either in acute or RP[9–12] leading to a strong recommendation of class I, level of evidence A to use colchicine on top of standard anti-inflammatory therapy in patients with acute and RP to prevent recurrences.[13]

Colchicine interferes with the generation of IL-1 by inhibiting the activation of the inflammasome, that triggers IL-1 activation. On this basis, colchicine and anakinra could act together to achieve a sequential block of the inflammatory pathway leading to the generation of IL-1, providing a valuable aid to reduce subsequent recurrences on anakinra, during its tapering and later after discontinuation of the drug.

In this study, colchicine added on top of anakinra was helpful to further reduce the subsequent rate (HR 0.52,

95% CI 0.29 to 0.91; p=0.021), providing evidence, for the first time, that the sequential block of the inflammatory pathway leading to the generation of IL-1 is more efficacious than a single agent.

Study limitations

This study has potential limitations. First of all, this a retrospective observational study where treatment assignments were made according to the clinician judgement. Nevertheless, the study population with or without colchicine was relatively well balanced but the use of corticosteroids. However, despite this imbalance, that could increase the recurrence rate in the colchicine-treated patients, colchicine maintained a significant effect on the reduction of recurrences. Another study limitation is the limited sample size that prevented to use a propensity score matching.

Nevertheless, the finding that the combined use of colchicine could further reduce the recurrences and prolong the recurrence-free survival is an important working hypothesis, that can now be tested formally in a randomised trial.

Conclusion

In conclusion, this observational study suggests to combine colchicine with anakinra for the treatment and prevention of RP and may be the basis for a specifically designed trial to test this combined treatment versus single use of anakinra. This observational study may be helpful to guide specific recommendations on the combined use of anakinra and colchicine in RP in the setting of ongoing European guidelines on pericarditis.

Author affiliations
[1]Cardiothoracic Department, University Hospital "Santa Maria della Misericordia", Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Udine, Italy
[2]Division of Cardiology, Department of Medical Sciences, Azienda Ospedaliero Universitaria Citta della Salute e della Scienza di Torino, University of Torino, Torino, Italy
[3]Department of Medicine (DMED), University of Udine, Udine, Italy
[4]Cardiology Specialty School, University of Trieste, Trieste, Italy
[5]University of Siena, Siena, Italy
[6]Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), Trieste, Italy
[7]Virginia Commonwealth University, Richmond, Virginia, USA
[8]Department of Cardiology, University of Athens Medical School, Hippokration Hospital, Athens, Greece
[9]Department of Biomedical and Clinical Sciences "Sacco", University of Milano, Milano, Italy
[10]Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio, USA

Twitter Massimo Imazio @ImazioMassimo

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Patient consent for publication Consent obtained directly from patient(s).

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Data availability statement Data are available on reasonable request.

ORCID iDs
Alessandro Andreis http://orcid.org/0000-0002-1203-000X
Massimo Imazio http://orcid.org/0000-0002-5722-0245

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