JAMA | Preliminary Communication

Effect of Anakinra on Recurrent Pericarditis Among Patients With Colchicine Resistance and Corticosteroid Dependence
The AIRTRIP Randomized Clinical Trial

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IMPORTANCE Anakinra, an interleukin 1β recombinant receptor antagonist, may have potential to treat colchicine-resistant and corticosteroid-dependent recurrent pericarditis.

OBJECTIVE To determine the efficacy of anakinra for colchicine-resistant and corticosteroid-dependent recurrent pericarditis.

DESIGN, SETTING, AND PARTICIPANTS The Anakinra—Treatment of Recurrent Idiopathic Pericarditis (AIRTRIP) double-blind, placebo-controlled, randomized withdrawal trial (open label with anakinra followed by a double-blind withdrawal step with anakinra or placebo until recurrent pericarditis occurred) conducted among 21 consecutive patients enrolled at 3 Italian referral centers between June and November 2014 (end of follow-up, October 2015). Included patients had recurrent pericarditis (with ≥3 previous recurrences), elevation of C-reactive protein, colchicine resistance, and corticosteroid dependence.

INTERVENTIONS Anakinra was administered at 2 mg/kg per day, up to 100 mg, for 2 months, then patients who responded with resolution of pericarditis were randomized to continue anakinra (n = 11) or switch to placebo (n = 10) for 6 months or until a pericarditis recurrence.

MAIN OUTCOMES AND MEASURES The primary outcomes were recurrent pericarditis and time to recurrence after randomization.

RESULTS Eleven patients (7 female) randomized to anakinra had a mean age of 46.5 (SD, 16.3) years; 10 patients (7 female) randomized to placebo had a mean age of 44 (SD, 12.5) years. All patients were followed up for 12 months. Median follow-up was 14 (range, 12-17) months. Recurrent pericarditis 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%). Median flare-free survival (time to flare) was 72 (interquartile range, 64-150) days after randomization in the placebo group and was not reached in the anakinra group (P <.001). During anakinra treatment, 20 of 21 patients (95.2%) experienced transient local skin reactions: 1 (4.8%) herpes zoster, 3 (14.3%) transaminase elevation, and 1 (4.8%) ischemic optic neuropathy. No patient permanently discontinued the active drug. No adverse events occurred during placebo treatment.

CONCLUSION AND RELEVANCE In this preliminary study of patients with recurrent pericarditis with colchicine resistance and corticosteroid dependence, the use of anakinra compared with placebo reduced the risk of recurrence over a median of 14 months. Larger studies are needed to replicate these findings as well as to assess safety and longer-term efficacy.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT02219828

JAMA. 2016;316(18):1906-1912. doi:10.1001/jama.2016.15826

Supplemental content

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Recurrent pericarditis is a difficult clinical problem[1,2] that affects up to 30% of patients after a first episode of acute pericarditis[3] and up to 50% of those with a first recurrence, if not treated with colchicine.[4,5] The optimal regimen for avoiding recurrences has not been clearly established. Treatment modes in recurrent pericarditis include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, colchicine, immunosuppressive agents, and pericardiectomy.[1,2] Quality of life may be severely affected in frequently relapsing cases, and patients with frequent recurrences can develop corticosteroid dependence.

Anakinra is an interleukin (IL) 1β recombinant receptor antagonist that has been proposed as a potential treatment for recurrent pericarditis. Anakinra was used first in pediatric patients,[6] then evaluated in adults.[7] Anakinra administered daily subcutaneously for several months showed a rapid response with corticosteroid withdrawal in both children and adults.[7,8] Current evidence for anakinra is based entirely on case reports and retrospective series[9]; to our knowledge, no randomized clinical trials have been conducted.

The aim of this randomized clinical trial was to evaluate the efficacy and tolerability of anakinra in adults and children with recurrent idiopathic pericarditis that was corticosteroid dependent and colchicine resistant.

Key Points

Question Is anakinra, an interleukin 1β recombinant receptor antagonist, effective in the treatment of recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence?

Findings In this double-blind, placebo-controlled, randomized withdrawal trial of 21 patients, recurrent pericarditis occurred in 9 of 10 patients assigned to placebo and 2 of 11 patients assigned to anakinra, a significant difference.

Meaning In patients with recurrent pericarditis with colchicine resistance and corticosteroid dependence, anakinra compared with placebo reduced the risk of recurrence over a median of 14 months. Larger-scale trials are needed for confirmation of these findings.

Methods

Study Design

The Anakinra—Treatment of Recurrent Idiopathic Pericarditis (AIRTRIP) study was an investigator-initiated, 8-month, multicenter, randomized, double-blind, placebo-controlled, medication withdrawal study to evaluate the efficacy and tolerability of anakinra in adults and children with idiopathic recurrent pericarditis. The study was approved by the ethics committees at each participating center. All adult patients or the parents of pediatric patients provided written informed consent. The trial was registered at EudraCT on May 9, 2013, and was subsequently also registered at ClinicalTrials.gov. It consisted of 2 parts: (1) an open-label treatment period in which anakinra was administered daily for 60 days, followed by (2) a double-blind withdrawal period in which patients who had a sustained complete response in part 1 were randomized to receive anakinra or placebo daily for up to 6 months. The end of the study was the end of part 2 (8 months after enrollment) or the time of relapse, whichever occurred first. Patients who had another pericarditis recurrence could have the option to be retreated with anakinra. All patients were then followed up for another 4 months to assess safety (**Figure 1**).

The trial protocol and statistical analysis plan are available in Supplement 1.

Patients

Between June and November 2014, all consecutive corticosteroid-dependent patients with recurrent pericarditis (with ≥3 previous recurrences) were enrolled at the time of a recurrence of pericarditis until a population of at least 21 patients was achieved.

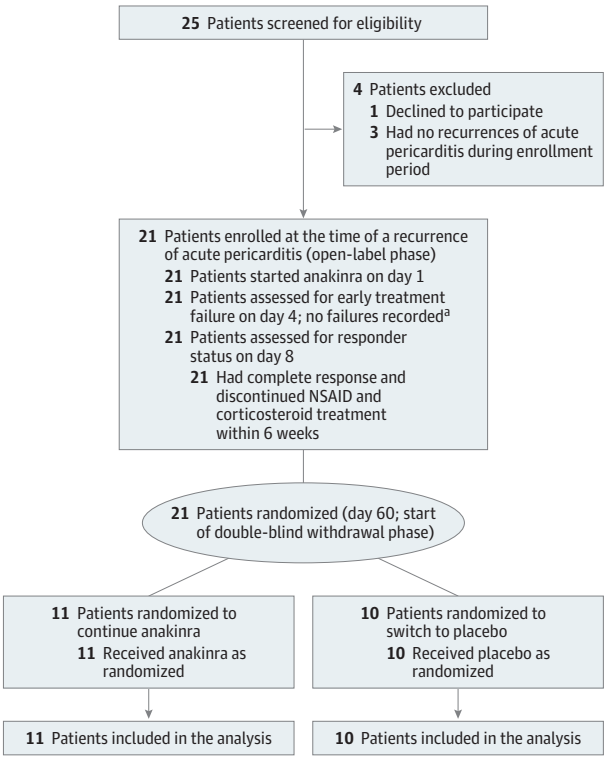
Inclusion Criteria

All patients eligible for inclusion in this study had recurrent idiopathic pericarditis, defined as a first episode of acute pericarditis followed by recurrences (with ≥3 previous recurrences), and were older than 2 years and younger than 70 years at the screening visit. The first episode of pericarditis was diagnosed when at least 2 of the following criteria were present[3-5]: pericarditic-typical chest pain (sharp and pleuritic, improved by sitting up and leaning forward), pericardial friction rubs, widespread ST-segment elevation or PR depressions not previously reported, and new or worsening pericardial effusion. Recurrence was diagnosed when chest pain reoccurred along with 1 or more of the following signs: fever, pericardial friction rub, electrocardiographic changes, or echocardiographic evidence of new or worsening pericardial effusion.[3-5] To be enrolled in this study, increased concentration of C-reactive protein (CRP) was mandatory both in the first attack and in the following recurrences, with a value greater than 1 mg/dL (normal range considered 0-0.5 mg/dL), as well as treatment with corticosteroids. All patients had corticosteroid dependence (drug tapering or withdrawal invariably followed by a new relapse). Pericarditis that was secondary to specific etiologies were excluded, including tuberculous, neoplastic, or purulent etiologies, postcardiac injury syndromes, and systemic diseases including rheumatic autoimmune diseases.

Exclusion Criteria

Patients were not eligible for enrollment if they were pregnant or lactating; had a history of immunodepression, including a positive human immunodeficiency virus test result; had a positive QuantiFERON (QFT-TB G In-Tube) test result or positive purified protein derivative test result (≥5-mm induration) after the first attack of pericarditis (patients with a positive purified protein derivative test result [≥5-mm induration] at screening could be enrolled only if they had either a negative chest x-ray result or a negative QuantiFERON test result); had any live vaccinations within 3 months prior to the start of the trial; had a history of malignancy of any organ system, treated or untreated, within the past 5 years; had a history of significant other medical conditions that in the investigator's opinion would exclude a patient from participating in this trial;

Figure 1. Participant Flow in the AIRTRIP Randomized Clinical Trial



NSAID indicates nonsteroidal anti-inflammatory drug.

[a] To allow early rescue therapy in case of failure of anakinra.

or had a history of recurrent and/or evidence of active bacterial, fungal, or viral infection(s).

Study Drug Administration and Randomization

Patients fulfilling study entry criteria received open-label treatment with anakinra (adults: 100 mg/d; children: 2 mg/kg per day up to 100 mg) subcutaneously. A clinical, laboratory, electrocardiographic, and echocardiographic assessment was performed at study day 1 (baseline), day 4 (after 72 h of treatment), and day 8. On day 4, patients were divided into 2 categories. Those with a reduction of 30% or more from baseline pericardial pain on a 21-circle visual analog scale (VAS) (a VAS from 0-10 cm in which the values are increased by 0.25 at every circle),[10] a 30% or greater decrease in CRP concentration, and no increase in pericardial effusion on echocardiogram continued the study. Patients who eventually did not meet these criteria were considered to have "early treatment failures," and the protocol allowed rescue therapy as per physician decision and withdrawal from the study and follow-up for safety (Figure 1 and Supplement 1). Responder status was again assessed at day 8. At day 8, responders withdrew from NSAIDs and corticosteroids (see section on co-medications below). Treatment with anakinra was continued until day 60, when all 21 patients were randomized in a double-blind fashion to continue anakinra (n=11) or to switch to placebo (n=10) for another 6 months. Placebo was delivered by a syringe with identical appearance to the study drug.

Participants were randomly assigned in a 1:1 ratio to treatment groups by a computer-based automated sequence, and patients and physicians were blinded.

Co-medications

Patients could enter the study while taking whatever medications they were using to treat their pericarditis except for other IL-1 blockers. All enrolled patients were being treated with long-term corticosteroid therapy, with the dose of corticosteroids not increased in the 3 days preceding enrollment. All were also being treated with colchicine at enrollment or previously (colchicine was previously withdrawn in 1 patient for lack of efficacy and in 2 for poor tolerability [**Table 1**]). Co-medications had to remain unchanged in responders until day 8. In responders at day 8, medications were tapered: NSAIDs were tapered and withdrawn within 15 days; corticosteroid therapy was progressively tapered and stopped within 6 weeks from response. Prednisone (or equivalent) tapering was 5 mg every week in adults and 0.2 mg/kg every week in children. Colchicine discontinuation was optional.

Follow-up and Outcomes

Patients underwent clinical and laboratory evaluations at months 1, 2, 4, 6, and 8 or at time of relapse, whichever occurred first; outcomes assessment was blinded to study treatment assignment. If a patient assigned to placebo had a recurrence of pericarditis, open-label treatment with anakinra was restarted. In case of relapse, as defined below, during the first 2 months of open-label therapy the patient was considered to have treatment failure. For ethical reasons, if a relapse occurred during the withdrawal phase, the patient was unblinded, and patients who received placebo were retreated with anakinra, while patients who had been receiving anakinra were treated as per physician decision and considered to have late treatment failure.

The primary end points were pericarditis recurrence rate at 8 months and time to recurrent pericarditis after randomization. Secondary end points were responder status, time to response in the open-label phase (time frame, 60 days), and percentage of patients with corticosteroid withdrawal at 6 weeks. To assess responder status in the open-label phase, at days 8 and 60 the following 3 criteria all had to be met: no or mild pericardial pain (a score ≤2.5 on a 21-circle VAS), normal CRP concentration (C≤0.5 mg/dL), and absent or mild (≤10-mm) echocardiographic effusion. The study ended with the completion of the last follow-up at 8 months.

Statistical Analysis

This trial followed the recommendation of the CONSORT statement, with results reported by the intention to-treat principle in the double-blind withdrawal phase. Sample size was estimated to be 20 patients. We estimated that 10 patients per group would be sufficient to detect a difference in recurrence rate from 80% in the placebo group to 10% in anakinra patients with a power of 90% at a confidence level of 95%. The study hypothesis was that anakinra could reduce the expected recurrence rate from 80% to 10%.[6-9,11-15] Event-free survival was estimated by the Kaplan-Meier method. A 2-sided

Table 1. Participant Characteristics at Enrollment and Randomization

Characteristics	At Enrollment			At Randomization	
	All Patients (n=21)	Anakinra (n=11)	Placebo (n=10)	Anakinra (n=11)	Placebo (n=10)
Sex, No. (%)					
Male	7 (33.3)	4 (36.4)	3 (30.0)		
Female	14 (66.6)	7 (63.6)	7 (70.0)		
Age, y					
Mean (SD)	45.4 (14.3)	46.5 (16.3)	44 (12.5)		
Range	15-69	15-69	26-66		
Time with pericarditis, mean (SD), mo	27.8 (25.3)	29.2 (28.8)	26.0 (22.2)		
Pain VAS score, mean (SD)[a]	7.7 (1.7)	7.1 (1.8)	8.3 (1.3)	0.3 (0.5)	0.5 (1.1)
CRP level, mean (SD), mg/dL	4.2 (3.9)	3.7 (2.2)	4.8 (5.3)	0.2 (0.2)	0.3 (0.2)
Pericardial effusion, No. (%)	18 (85.7)	9 (81.8)	9 (90.0)	0	0
Previous recurrences of pericarditis, No.					
Mean (SD)	6.8 (3.6)	6.9 (2.9)	6.7 (4.3)		
Range	3-16	3-12	3-16		
Therapy, No. (%)					
Corticosteroids	21 (100)	11 (100)	10 (100)	0	0
NSAIDs	15 (71.4)	8 (72.7)	7 (70.0)	0	0
Colchicine	18 (85.7)	10 (90.9)	8 (80.0)	6 (54.5)	6 (60.0)

Abbreviations: CRP, C-reactive protein; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a] Higher pain visual analog scale (VAS) scores indicate higher pain on a 0- to 10-point scale.

log-rank test was used to compare the time to flare between randomization and the end of month 8 in the 2 treatment groups. The Fisher exact test was used to evaluate rate of recurrence in the withdrawal phase. Incidence rates of recurrence in the anakinra and placebo groups were estimated with their 95% confidence intervals, as well as the incidence rate difference and incidence rate ratio between the 2 groups. All tests were 2-tailed, and a $P<.05$ was considered statistically significant. Analyses were performed using STATA software, release 13.

Results

Patients

A total of 25 patients were screened for entry in the study from 3 centers in Italy, and 21 were enrolled. Study enrollment, randomization, and retention are shown in Figure 1. Demographic and baseline characteristics were similar in the 2 groups (Table 1).

Mean age was 45.4 years (range, 15-69 years; 14 were female). One patient was in the pediatric age range (15 years old) and the remaining 20 patients were adults (aged >18 years). Mean number of recurrences before the study was 6.8 (range, 3-16), with a clinical history of recurrent pericarditis lasting 27.8 months on average (range, 4-100 months). Median duration of follow-up was 14 (range, 12-17) months.

Open-Label Phase

At the time of study enrollment, all 21 patients were experiencing a recurrence of pericarditis with a mean VAS pain score of 7.7 (range, 3.5-10); the mean CRP level was 4.2 (range, 1-16.1) mg/dL. Eighteen patients had evidence of pericardial effusion, which was mild in all cases (<10 mm) (eTable in Supplement 2).

All patients had a complete response to open-label anakinra treatment at day 8 (according to the protocol definition) that was maintained until randomization (day 60).

C-reactive protein was normalized in all patients at day 8 and remained at normal levels at day 60. Pain VAS scores quickly decreased; and the mean score was 0.4 at day 60 (range, 0-2). Also, patients' or parents' global assessment of overall well-being on a 21-circle VAS greatly improved over time; mean scores were 5.8 at day 0 and 1.6 at day 60 (10 indicates the worst quality).

All patients successfully discontinued corticosteroids within 6 weeks and proceeded to the double-blind withdrawal phase. At randomization (day 60), CRP levels were normal in all 21 patients, mean pain VAS score was 0.4, and none of the 21 patients were taking corticosteroids or NSAIDs.

Double-Blind Withdrawal Phase

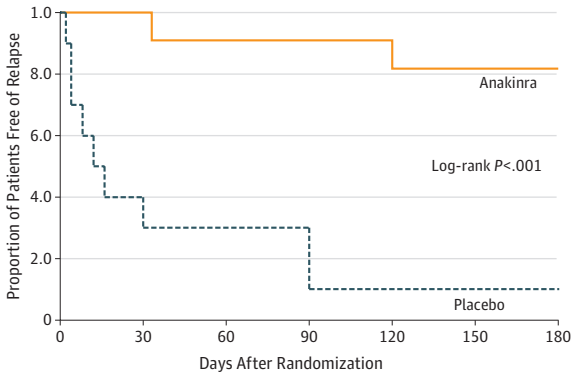
During the double-blind treatment phase, recurrence of pericarditis occurred in 9 (90%) of the 10 patients randomized to placebo (incidence rate, 2.06% of patients per year; 95% CI, 1.07%-3.97%) and in 2 (18.2%) of the 11 patients randomized to anakinra (33 and 120 days after randomization) (incidence rate, 0.11% of patients per year; 95% CI, 0.03%-0.45%). The incidence rate difference was −1.95% (95% CI, −3.3% to −0.6%) and the incidence rate ratio was 0.055 (95% CI, 0.006-0.264; **Table 2**). Median flare-free survival (time to flare) was 72 (interquartile range, 64-150) days after randomization in the placebo group; it could not be calculated in the anakinra group ($P<.001$). Half the patients

Table 2. Primary End Points: Pericarditis Recurrence Rate and Time to Flare After Randomization

End Points	Placebo (n=10)	Anakinra (n=11)	Difference (95% CI)	*P* Value
Risk of recurrence, No. (%)	9 (90)	2 (18)	−0.718 (−1.01 to −0.42)	.001[a]
Incidence rate, % patients/y (95% CI)	2.06 (1.07-3.97)	0.11 (0.03-0.45)	−1.95 (−3.3 to −0.6)	
Incidence rate ratio (95% CI)	1 [Reference]	0.055 (0.006-0.264)		<.001[b]
Time to flare				
Flare-free survival, median (interquartile range), d	72 (64-150)	Not calculable		<.001[c]
Days to flare, mean (range)[d]	28.4 (2-90)	76.5 (33-120)	−48.1 (−118.1 to 21.9)	<.001[e]

[a] By Fisher exact test.
[b] By χ^2 test.
[c] By log-rank test.
[d] Calculated for patients with recurrences.
[e] By Wilcoxon rank-sum test.

Figure 2. Kaplan-Meier Analysis of Patients With Recurrent Pericarditis Free of Relapse in the Double-Blind Withdrawal Phase, From Day 0 to Day 180 After Randomization (Intention-to-Treat Analysis)



No. at risk

Placebo	10	4	3	3	1	1
Anakinra	11	11	10	10	10	9

No. of treatment failures

Placebo	6	1	0	2	0
Anakinra	0	1	0	0	1

assigned to placebo were free of flare 72 days after randomization, while more than half of patients assigned to anakinra were still free of recurrence at the end of the study (*P*<.001; **Figure 2**). In patients with recurrences, the mean time to flare was 28.4 (range, 2-90) days vs 76.5 (range, 33-120) days in the placebo and anakinra groups, respectively, resulting in an absolute mean difference of −48.1 (95% CI, −118.1 to 21.9) days.

Nine patients (4 randomized to placebo and 5 randomized to anakinra) discontinued colchicine and 12 patients (6 randomized to placebo and 6 randomized to anakinra) maintained colchicine therapy (according to physician and patient decisions). During the double-blind treatment, concurrent treatment with colchicine did not significantly affect recurrence rate (7/12 [58.3%] with colchicine and 4/9 [44.4%] without colchicine), and time to flare (median flare-free survival, 90 days with colchicine; could not be calculated in the noncolchicine group; log-rank *P* = .77), but the study did not have the power to compare monotherapy with anakinra vs combined therapy with anakinra plus colchicine. In patients with recurrences, the mean time to flare was 52.7 (range, 2-120) days in the colchicine group vs 10 (range, 4-16) days in the noncolchicine group, respectively, resulting in an absolute mean difference of −42.7 (95% CI, −97.1 to 11.7) days.

Adverse Events

The most common adverse effect in anakinra-treated patients was a local reaction at the injection site, observed in 20 of 21 patients (95%) during the initial open-label phase; generally, reactions disappeared over 1 month; 3 patients temporarily discontinued anakinra in the open-label phase but resumed it after topical treatment and systemic antihistamines, and no patient discontinued the study for this adverse effect (**Table 3**). Herpes zoster occurred in 1 patient treated with anakinra during the open-label phase of the study, leading to temporary discontinuation of anakinra.

A 69-year-old hypertensive and hypercholesterolemic patient in the anakinra group developed ischemic optic neuropathy at day 210 (in the double-blind withdrawal phase) that did not appear to be related to the experimental treatment.

Three patients (14.3%) showed an elevation of transaminases (<2 times normal values) in the open-label phase, reversible after temporary discontinuation or dose reduction of anakinra.

No adverse effects were recorded during treatment with placebo.

Discussion

To our knowledge, this is the first randomized clinical trial to assess the efficacy of anakinra for refractory idiopathic recurrent pericarditis with corticosteroid dependence and after failure of colchicine therapy. In this study, we observed that anakinra allowed corticosteroid withdrawal in all patients. Moreover, flares of pericarditis were markedly reduced, occurring in 9 of 10 patients (90%) randomized to placebo and 2 of 11 patients (18%) randomized to anakinra during the double-blind treatment.

Refractory recurrent pericarditis is a major clinical management issue because it is corticosteroid dependent and does not respond to colchicine; thus, patients are unable to withdraw corticosteroids without a relapse. Corticosteroids impair growth in children, and Picco et al[6] described the first 3 patients, all children, successfully treated with anakinra; at present, 10 reports describing 46 patients (adults and children) have been published.[6-8,11-17] The 2015 guidelines of the European Society of Cardiology[18] stated that anakinra, azathioprine, and high-dose intravenous immunoglobulins may

Table 3. Adverse Events in Anakinra-Treated Patients

Adverse Events	No. of Patients (%)		
	Open-Label Phase (n=21)	Double-Blind Withdrawal Phase (n=11)	Entire Study Period (n=21)
Overall adverse events	20 (95.2)	1 (9.1)	20 (95.2)
Infections[a]	1 (4.8)	0	1 (4.8)
Transaminase elevation	3 (14.3)	0	3 (14.3)
Local skin reactions	20 (95.2)	0	20 (95.2)
Ischemic optic neuropathy	0	1 (9.1)	1 (4.8)
Permanent drug discontinuation	0	0	0

[a] The infection adverse event was a case of herpes zoster.

be considered in corticosteroid-dependent recurrent pericarditis that is resistant or intolerant to colchicine, but the level of evidence was low (C, based on case series and expert opinion). This study is the first randomized, placebo-controlled trial of anakinra for idiopathic recurrent pericarditis showing that anakinra is a potential option for this subset of patients. These findings also provide evidence that IL-1 plays an important role in the pathogenesis of idiopathic recurrent pericarditis.[6,19]

Anakinra use is associated with an increased risk of adverse effects, especially related to injection site reactions. These generally occurred early after drug delivery, were relatively transient (generally a few weeks), and can be treated with oral antihistamines and topical corticosteroids.[20] Warming the syringe to room temperature before use is advisable, along with application of a cold pack to the injection site approximately 2 to 3 minutes before and immediately after the injection. Patients should be informed in advance about the potential for such reactions to prevent unjustified drug discontinuation. Additional potential adverse effects include transaminase elevation that was observed in 3 (14.3%) of 21 patients and was limited and transient. The most important potential adverse effect is an increased risk of infections; in our study, 1 patient (4.7%) developed herpes zoster and required temporary discontinuation of the study drug.

The first use of anakinra dates to 1996[21]; serious infections are rare, and in a review of 5 clinical trials, they appeared in 1.7% of patients in the active treatment group compared with 0.7% in the placebo group.[22] Neutropenia has been reported in approximately 5% of cases but without evidence of association with clinical events.[22-24]

Anakinra has both advantages and disadvantages to consider in treating patients similar to those in this study. The main advantages of the drug are a rapid onset of effect and the capability to allow a quick withdrawal of corticosteroids. The potential disadvantages include a long duration of therapy as well as high costs. Strict selection of patients is important: only patients with a clear inflammatory pattern are candidates for this therapy. Such patients usually have a history of high fever, strikingly elevated levels of CRP, and pleural effusion, particularly in the pediatric age range; these clinical signs are likely associated with a pivotal pathogenic role of IL-1. Conversely, patients with mild or doubtful symptoms and/or normal or near normal levels of CRP are not good candidates for anti–IL-1 therapy.[25]

The main limitation of this study is its small sample size. However, given the large treatment effect, the current study had the statistical power to verify the initial study hypothesis. The sample size was inadequate to assess true frequency of adverse events. We acknowledge the extremely wide confidence intervals and, hence, imprecision around the primary outcome. An additional limitation is the median follow-up time of 14 months, which may have limited the observations of additional recurrences during follow-up; however, the main aim of the study was to assess the efficacy of the drug to control the disease and allow corticosteroid withdrawal. Larger and longer-term studies will be important in the future to confirm the findings of the present study. In addition, the study population was limited to patients with idiopathic recurrent pericarditis; thus, additional research is needed to assess the efficacy of anakinra in specific settings such as recurrent pericarditis related to autoimmune diseases. Moreover, future studies are needed to determine whether IL antagonists should be considered the standard therapy for a first recurrence, instead of corticosteroids.

Conclusions

In this preliminary study of patients with recurrent pericarditis with colchicine resistance and corticosteroid dependence, the use of anakinra compared with placebo reduced the risk of recurrence over a median of 14 months. Larger studies are needed to replicate these findings as well as to assess safety and longer-term efficacy.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Brucato reports receipt of a research grant from Acarpia. Dr Gattorno reports receipt of grants, speakers bureau fees, and consulting fees from Novartis and SOBI. Dr Ruperto reports speakers bureau and consulting fees from AbbVie, Amgen, Biogenidec, Alter, AstraZeneca, Baxalta Biosimilars, Biogenidec, Boehringer, Bristol-Myers Squibb, Celgene, CrescendoBio, EMD Serono, Hoffman La Roche, Italfarmaco, Janssen, MedImmune, Medac, Novartis, Novo Nordisk, Pfizer, Sanofi Aventis, Servier, Takeda, and UCB Biosciences. Dr Rimini reports receipt of personal fees from Abbott and Nutricia. Dr Martini reports receipt of personal fees from Abbvie, Boehringer, Celgene, CrescendoBio, Janssen, MedImmune, Novartis, Novo Nordisk, Pfizer, Sanofi Aventis, Vertex, and Servier. No other disclosures were reported.

Funding/Support: SOBI (Sweden) provided anakinra and placebo as part of unrestricted institutional grant.

Role of the Funder/Sponsor: The study funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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