European Heart Journal Supplements (2021) **23** (Supplement E), E83–E86
The Heart of the Matter
doi:10.1093/eurheartj/suab097

ESC
European Society
of Cardiology

Recurrent pericarditis is less scary: the new therapeutic solutions

Rita Del Pinto[1,2] and Claudio Ferri[1,2]*

[1]*Department of Clinical Medicine, Public Health, Life and Environmental Sciences, University of L'Aquila, L'Aquila, Italy; and*
[2]*Unit of Internal Medicine and Nephrology, ESH Excellence Center for Hypertension and Cardiovascular Prevention, S. Salvatore Hospital, L'Aquila, Italy*

KEYWORDS
Pericarditis;
Interleukin-1;
Anakinra;
Rilonacept

Pericarditis is a common inflammatory disease affecting the pericardial sac, resulting from a variety of stimuli that trigger a stereotyped immune response. Generally self-limiting, this condition can be burdened by a significant risk of acute complications and relapses, with recurrence rates affecting up to 30% of patients, especially in the case of diagnostic and therapeutic delay. Therapeutic options in recurrent forms, initially based only on the use of traditional drugs such as colchicine, non-steroidal anti-inflammatory drugs, and corticosteroids, have recently been enriched with new molecules, such as interleukin 1 blockers anakinra and rilonacept, particularly indicated in refractory forms dependent on corticosteroids. Other medically relevant therapeutic possibilities in refractory disease include azathioprine, methotrexate, and intravenous immunoglobulins. This brief review aims to summarize the treatment strategies of recurrent pericarditis in light of the most up-to-date evidence and recommendations.

Recurrent pericarditis is defined as the reappearance, after a disease-free period of at least 4–6 weeks, of symptoms and signs typical of pericardial inflammation in individuals with a previous episode of acute disease.[1] It occurs in percentages ranging from 15 to 30% of cases following the first attack of acute pericarditis[1] and up to over half of cases not initially treated with colchicine,[2] especially if treated with corticosteroids, thus characterizing itself as one of the most frequent complications of acute disease.

In etiopathogenetic terms, recurrent pericarditis is believed to be an autoinflammatory phenomenon characterized by inappropriate activation of innate immunity,[3] with prominent role of the interleukin 1 (IL-1)[4] cytokine family, often attributable to inadequate treatment of the acute form. In support of this hypothesis, there are elements such as the time interval between the acute event and the recurrence, the evidence of non-specific autoantibodies, and the generally satisfactory response to corticosteroid therapy. Consistently with this, the female sex, more susceptible to pathologies underlying the immunological component, is more exposed to the risk of recurrence. Preformed IL-1α is released from damaged or inflamed pericardial cells and can help propagate inflammation by activating the NLRP3 inflammasome, responsible for cascading the inflammatory response by producing IL-1β.[5] The non-redundant roles of IL-1α and β in inflammation underline the importance of a treatment targeted to both cytokines. Additional factors associated with an increased risk of recurrence include previous use of corticosteroids and a history of recurrent episodes. A viral aetiology is reported in a variable percentage up to 20%.[1] Clinically indistinguishable from the acute episode, which can be discerned on an anamnestic basis, recurrent pericarditis is diagnosed on the basis of the same clinical, laboratory and instrumental criteria recommended by the guidelines, including physical examination, electrocardiogram, echocardiogram, chest X-ray, and serum markers of inflammation [C reactive protein (CRP)] and myocardial-cytonecrosis [creatine kinase and troponin (Tn)], with the possible addition of

*Corresponding author. Email: claudio.ferri@cc.univaq.it

computerized axial tomography and/or nuclear magnetic resonance which, in doubtful or atypical cases, may show oedema or increased uptake of the contrast medium by the inflamed pericardium.[1]

Given that therapy should be targeted to the cause, traditional medical therapy of recurrent pericarditis consists of the use of non-steroidal anti-inflammatory drugs (NSAIDs), usually to be gradually reduced over 2–4 weeks after symptoms resolve, in combination with at least 6 months of weight-adjusted colchicine treatment (0.5 mg once daily if body weight $<$70 kg; 0.5 mg twice daily if $\geq$70 kg) (Class IA recommendations according to guidelines).[1] Colchicine is a cornerstone of the therapy of pericarditis, both in acute forms and in recurrences, as it would be able to improve the response to anti-inflammatory drugs, increase remission rates, and reduce the incidence of recurrence up to 50%.[1] Triple therapy based on the addition of low-dose corticosteroids (e.g. prednisone 0.2–0.5 mg/kg/day) may be necessary in case of incomplete response to the NSAID/colchicine combination to achieve prompt symptom control in individuals in whom the infectious genesis of the pathology has been excluded, but the reduction of the dosage must take place with the measured speed in widely delayed times to avoid the recurrence of the disease or its chronicization.[1] Due to these risks, the use of corticosteroids a low dose should be limited to patients with specific indications (e.g. systemic inflammatory diseases, post-pericardiotomy syndromes, pregnancy, and pericarditis associated with the use of immune checkpoint inhibitors) or with true contraindications to the use of NSAIDs, while the use high-dose corticosteroids is contraindicated.[1,6]

However, it is possible that, in a minority of cases (5-10%), an adequate clinical response to the first two lines of treatment is not obtained, due to both resistance to therapy and the development of corticosteroid dependence.[7] Therapeutic options in these cases include immunosuppressive therapies (e.g. azathioprine, methotrexate),[8–10] intravenous immunoglobulins (IVIG)[7] and IL-1 antagonists (e.g. anakinra)[11] and have recently expanded with the latest evidence regarding the use of the IL-1 inhibitor rilonacept.[5,12]

Azathioprine, an immunosuppressive drug belonging to the purine analogue class, was shown to be effective in long-term use (13.6 $\pm$ 5.1 months) in 46 corticosteroid-dependent patients (age range 11–71 years; mean age 39.7 $\pm$ 17.1 years; 22 males; mean prednisone dosage 1.2 $\pm$ 0.4 mg/kg/day) with recurrent pericarditis (at least two relapses).[8] During azathioprine therapy at a dosage of 1.5–2.5 mg/kg/day, 84.7% were responsive to treatment and managed to gradually reduce the steroid to complete suspension after 4–12 months, with no relapses in 63% of patients, while 15.2% were resistant to treatment (more than 3 relapses). 58.6% of patients were able to discontinue azathioprine without relapse after an average of 14.6 $\pm$ 4.1 months of treatment. The drug was globally well tolerated, with mild and transient hepatotoxicity in 10.8% of cases, leukopenia in 6.5%, and gastrointestinal symptoms in 0.9%. Azathioprine is primarily a slow-acting corticosteroid-sparing agent, useful for controlling the disease for long-term follow-up, and preferable in the first instance over other third-line drugs, due to lower costs.[1]

The use of IVIGs in refractory forms of recurrent pericarditis (mean no. of three relapses) was examined in a recent meta-analysis of 17 reports, for a total of 30 patients (47% with idiopathic pericarditis, 43% associated with systemic inflammatory diseases, 10% with infectious forms).[7] The standard posology reported was 400–500 mg/kg/day for 5 consecutive days, with possible additional courses in relation to clinical response. After a mean follow-up of approximately 33 months, the percentage of patients who had not experienced relapses stood at 73.3%, while relapsing cases (26.6%) occurred after the first course of IVIG; 16.6% of patients were still on corticosteroid therapy at the end of follow-up. The treatment was not burdened by serious complications, and the most described undesirable effect was headache (3% of cases).[7]

Anakinra is a recombinant inhibitor of the IL-1 receptor produced in Escherichia coli cells by recombinant DNA technology, capable of antagonizing both the IL-1α released by pericardial cells and the IL-1β produced by inflammatory cells. After the first evidence from isolated series, a double-blind, placebo-controlled, randomized discontinuation clinical trial [Anakinra—Treatment of Recurrent Idiopathic Pericarditis trial (AIRTRIP)] was conducted on 21 patients with recurrent (at least three relapses) corticosteroid-dependent and colchicine-resistant form.[11] The drug was administered at a dose of 2 mg/kg/day subcutaneously (maximum 100 mg/day) for 2 months; Once the clinical picture was resolved, the patients were then randomized to continue anakinra (n. 11) or to receive a placebo (n. 10) for 6 months or until pericarditis recurrence. After a mean follow-up of 14 months, there was a clear difference in favour of anakinra in terms of the incidence rate of recurrent pericarditis [$-$1.95%; 95% confidence interval (CI): $-$3.3% to $-$0.6%]. In the placebo group, the median time to exacerbation was 72 days after randomization (interquartile range: 64–150), indicating that half of the patients assigned to placebo experienced exacerbations 72 days after randomization. Conversely, more than half of patients randomized to continue anakinra were still relapse-free at the end of the study at 180 days ($P < 0.001$). 95.2% of patients treated with anakinra experienced transient local skin reactions, 14.3% had an increase in serum transaminases levels, while 4.8% experienced herpes zoster requiring temporary drug withdrawal.

The efficacy and safety of the drug have been confirmed by data from the International Registry of Anakinra for Pericarditis (IRAP), in which 14 reference centres for pericardial diseases from 6 different countries have collaborated so far, for a total of 224 patients (46 $\pm$ 14 years, 63% women, 75% with idiopathic pericarditis).[9] After a median treatment time of 6 months (range 3–12), anakinra reduced the recurrence of pericarditis by six times (from 2.33 to 0.39 exacerbations per patient per year), the admissions to the Emergency Department by 11 times (from 1.08 to 0.10 accesses per patient per year), the hospitalizations rates by 7 times (from 0.99 to 0.13 admissions per patient per year), and significantly reduced dependence on corticosteroids (from 80% to 27%, $P < 0.001$). A duration of full-dose

treatment for more than 3 months, followed by a gradual reduction in dosage for a period of more than 3 months, was the therapeutic regimen associated with the lowest risk of relapse. Adverse events, however not serious, consisted mainly of transient skin reactions at the injection site (38%), artho-myalgia (6%), elevated transaminases (3%), skin and respiratory infections (3%), and neutropenia (1%)). Further evidence supports the efficacy of anakinra in patients resistant or intolerant to NSAIDs, prednisone, colchicine, and at least one immunosuppressive or immunomodulatory drug such as azathioprine, methotrexate, plaquenil, or IVIG.[13] Anakinra is currently prescribed in Italy for forms of corticosteroid-dependent and colchicine-resistant recurrent pericarditis at a dosage of 2 mg/kg/day (maximum 100 mg/day) subcutaneously, also in association with colchicine, and treatment should be continued for at least 3–6 months, followed by a gradual reduction of the dosage. Symptom control occurs quickly after the first-second administration, allowing concomitant corticosteroid therapy to be safely reduced and then discontinued. It is important to remember that anakinra should be avoided in immunocompromised patients and in patients with an active infection.[14]

The major novelty in the treatment of recurrent pericarditis is represented by rilonacept.[5,12] It is a long-acting dimeric fusion protein produced with 'cytokine trap' technology and has a high affinity for both IL-1β and IL-1α. The results of a recent open-label, single-arm, active phase II pivotal study showed that rilonacept provides rapid and long-lasting clinical and laboratory benefit in adult patients with recurrent ($\geq$2 relapses) idiopathic or post-cardiotomy, or corticosteroid dependent, pericarditis.[12] Study participants (n. 25, mean age 42.8 $\pm$ 10.5 years, 60% female) were treated with rilonacept at a loading dose of 320 mg subcutaneously, followed by a weekly maintenance dosage of 160 mg subcutaneously, for a period of 6 weeks; this period was followed by an optional 18-week treatment extension period aimed at weaning from pre-existing therapy. The results showed an average pain reduction of 4 points on a numerical scale of 11 (baseline and final score: 4.5 and 0.7, respectively) and a sustained decrease in CRP (from 4.62 mg/dL at baseline to 0.38 mg/dL at the end of treatment). In parallel, a decrease in annual relapses of pericarditis was observed. Prednisone was successfully discontinued in 84.6% of patients receiving it at baseline and was at least tapered in all dependent patients. The study recorded a single serious adverse event of an infectious nature leading to discontinuation of rilonacept.

The results of the randomized, double-blind phase 3 discontinuation study Rilonacept Inhibition of Interleukin-1 Alpha and Beta for Recurrent Pericarditis: a Pivotal Symptomatology and Outcomes Study (RHAPSODY) then confirmed the efficacy of rilonacept in the rapid resolution of recurrent episodes of pericarditis and in the significant reduction in the risk of relapse compared to placebo.[5] The study, conducted on a total of 86 patients with acute symptoms of recurrent pericarditis, recorded on a numerical scale (0–10, with pain increasing with increasing score) and with signs of systemic inflammation (elevated CRP) during standard therapy (NSAIDs, colchicine, prednisone), included a first phase of 12 weeks in which rilonacept replaced basic therapy, and a second phase in which individuals responsive to therapy (n. 61) were randomized in a 1:1 ratio to continue rilonacept 160 mg (n. 30) or receive placebo (n. 31), both in single weekly administration in the absence of other therapy, for a total median duration of 9 months (range: 3–14 months).

Median time to pain response was 5 days (95% CI 4–6 days), and PCR normalization time was 7 days (95% CI 5–8 days), with complete weaning from corticosteroids with rilonacept. The risk of relapsing pericarditis in the second phase was significantly lower in individuals randomized to rilonacept (7%) than in those assigned to placebo (74%) (hazard ratio 0.04, 95% CI 0.01–0.18; $P < 0.001$ at log-rank test). The observed benefit with rilonacept was independent of prior therapy. Injection site adverse reactions (34% of patients) and upper respiratory tract infections (23% of patients) were the most common adverse reactions to rilonacept; overall, there were five serious adverse events in the two treatment arms, none of which were fatal.

On the basis of these evidences, it can be stated that the armamentarium against colchicine-resistant, corticosteroid-dependent non-infectious recurrent pericarditis has been enriched with new and effective options aimed at the pathogenetic mechanisms of the disease, the use of which must however be considered, in addition to and on the evaluation of costs, also—and above all—on the estimation of risks, if necessary through the consultation of multidisciplinary experts, without neglecting the active involvement of the patient and his caregivers during treatment.

Conflict of interest: none declared.

References

1. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, Brucato A, Gueret P, Klingel K, Lionis C, Maisch B, Mayosi B, Pavie A, Ristic AD, Sabaté Tenas M, Seferovic P, Swedberg K, Tomkowski W; ESC Scientific Document Group. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2015;**36**:2921–2964.
2. Imazio M, Belli R, Brucato A, Cemin R, Ferrua S, Beqaraj F, Demarie D, Ferro S, Forno D, Maestroni S, Cumetti D, Varbella F, Trinchero R, Spodick DH, Adler Y. Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial. *Lancet* 2014;**383**:2232–2237.
3. Caforio ALP, Brucato A, Doria A, Brambilla G, Angelini A, Ghirardello A, Bottaro S, Tona F, Betterle C, Daliento L, Thiene G, Iliceto S. Anti-heart and anti-intercalated disk autoantibodies: evidence for autoimmunity in idiopathic recurrent acute pericarditis. *Heart* 2010;**96**:779–784.
4. Dinarello CA, Simon A, van der Meer JWM. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nat Rev Drug Discov* 2012;**11**:633–652.
5. Klein AL, Imazio M, Cremer P, Brucato A, Abbate A, Fang F, Insalaco A, LeWinter M, Lewis BS, Lin D, Luis SA, Nicholls SJ, Pano A, Wheeler A, Paolini JF. Phase 3 trial of interleukin-1 trap rilonacept in recurrent pericarditis. *N Engl J Med* 2021;**384**:31–41.
6. Chiabrando JG, Bonaventura A, Vecchié A, Wohlford GF, Mauro AG, Jordan JH, Grizzard JD, Montecucco F, Berrocal DH, Brucato A, Imazio M, Abbate A. Management of acute and recurrent pericarditis: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**75**:76–92.
7. Imazio M, Lazaros G, Picardi E, Vasileiou P, Carraro M, Tousoulis D, Belli R, Gaita F. Intravenous human immunoglobulins for refractory

recurrent pericarditis: a systematic review of all published cases. *J Cardiovasc Med* 2016;**17**:263–269.
8. Vianello F, Cinetto F, Cavraro M, Battisti A, Castelli M, Imbergamo S, Marcolongo R. Azathioprine in isolated recurrent pericarditis: a single centre experience. *Int J Cardiol* 2011;**147**:477–478.
9. Imazio M, Andreis A, De Ferrari GM, Cremer PC, Mardigyan V, Maestroni S, Luis SA, Lopalco G, Emmi G, Lotan D, Marcolongo R, Lazaros G, De Biasio M, Cantarini L, Dagna L, Cercek AC, Pivetta E, Varma B, Berkson L, Tombetti E, Iannone F, Prisco D, Caforio ALP, Vassilopoulos D, Tousoulis D, De Luca G, Giustetto C, Rinaldi M, Oh JK, Klein AL, Brucato A, Adler Y. Anakinra for corticosteroid-dependent and colchicine-resistant pericarditis: the IRAP (International Registry of Anakinra for Pericarditis) study. *Eur J Prev Cardiol* 2020;**27**:956–964.
10. Peiffer-Smadja N, Domont F, Saadoun D, Cacoub P. Corticosteroids and immunosuppressive agents for idiopathic recurrent pericarditis. *Autoimmun Rev* 2019;**18**:621–626.
11. Brucato A, Imazio M, Gattorno M, Lazaros G, Maestroni S, Carraro M, Finetti M, Cumetti D, Carobbio A, Ruperto N, Marcolongo R, Lorini M, Rimini A, Valenti A, Erre GL, Sormani MP, Belli R, Gaita F, Martini A. Effect of anakinra on recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence: the AIRTRIP randomized clinical trial. *JAMA* 2016;**316**:1906–1912.
12. Klein AL, Lin D, Cremer PC, et al. Efficacy and safety of rilonacept for recurrent pericarditis: results from a phase II clinical trial. *Heart* 2020; doi: 10.1136/heartjnl-2020-317928.
13. Dagan A, Langevitz P, Shoenfeld Y, Shovman O. Anakinra in idiopathic recurrent pericarditis refractory to immunosuppressive therapy; a preliminary experience in seven patients. *Autoimmun Rev* 2019;**18**:627–631.
14. Correia Et de O, Dos Santos Barbetta LM, de Almeida JPCL, Mesquita ET. Anakinra in recurrent pericarditis: current evidence on clinical use, effectiveness, and safety. *J Cardiovasc Pharmacol* 2020;**76**:42–49.