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SCIENTIFIC LETTERS

Efficacy of anakinra as a treatment for recurrent pericarditis☆

Eficacia de anakinra como tratamiento de la pericarditis recurrente

To the editor,

Recurrent pericarditis is defined as an episode of pericarditis following a previous episode of acute pericarditis separated by symptom-free interval of 4–6 weeks. Its clinical presentation consists of recurrent episodes of pain in the middle of the chest associated with electrocardiographic changes, pericardial effusion and elevation of C-reactive protein (CPR) and erythrocyte sedimentation rate (ESR).

There is growing evidence of the efficacy of the biopharmaceutical anakinra in the treatment of this disease, which we will summarise before presenting our experience in a tertiary hospital.

When it comes to the aetiology of the disease,[1] it has been hypothesised that pericarditis may result from infectious or paraneoplastic triggers or autoimmune disease. In recent years, different authors have reported cases of recurrent pericarditis in the context of the recently described autoinflammatory diseases, in which the immune dysfunction involves the primary or innate immune response as opposed to antibodies or the adaptive immune system. An autoinflammatory aetiology should be considered when infectious, autoimmune and paraneoplastic causes have been ruled out. In monogenic autoinflammatory diseases, defects in the regulation of the inflammasome (an intracellular multi-protein complex with a key role in innate immunity) lead to overproduction of pro-inflammatory cytokines such as IL-1β, triggering different inflammatory symptoms, such as fever, exanthema, elevation of acute phase reactants or serositis. Our knowledge of these diseases is growing exponentially, with new disorders described each year. However, some of them, like familial Mediterranean fever, were already known in classic medicine. Recurrent pericardial effusion is one of the common symptoms of this monogenic disorder. On the other hand, there are diseases known to have an autoinflammatory aetiology whose specific gene signature has yet to be identified, as is the case of systemic juvenile idiopathic arthritis (formerly known as Still disease), which may manifest with inflammatory pericarditis.

As for treatment, the options traditionally considered for management of recurrent pericarditis include non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin as first-line treatment, with use of systemic corticosteroids and colchicine if needed.[2,3] However, a certain percentage of patients develop corticosteroid dependence and resistance to colchicine. Recently, the European Society of Cardiology published clinical guidelines for the diagnosis and management of pericardial diseases,[4] which recommended contemplating the use of anakinra in patients refractory to ''classical'' treatment.

Anakinra is a recombinant IL-1β receptor antagonist and is possibly the most commonly used drug for treatment of autoinflammatory diseases, which explains its role in recurrent pericarditis of this aetiology. Several authors have reported its efficacy in the treatment of recurrent pericarditis, with patients exhibiting a rapid and sustained response. Imazio et al.[5] conducted a multicentre prospective cohort study in 110 paediatric patients with an 11-year follow up. Anakinra was used in 12 cases refractory to ''classical'' therapy and associated with a statistically significant decrease in the incidence of recurrence (4.29/year vs 0.14/year).

On the other hand, preliminary results were published a few months ago for the AIRTRIP randomised clinical trial,[6] the first to compare the efficacy of anakinra versus placebo in patients with recurrent idiopathic pericarditis and corticosteroid dependence. The trial has enrolled 21 patients (with a mean age of 45.4 years and 1 patient younger than 18 years), assigning 10 to the placebo arm and 11 to anakinra. Pericarditis recurred in 90% of patients receiving placebo compared to 18.2% of patients treated with anakinra, and all patients receiving the drug were able to discontinue corticosteroid treatment.

Our case series includes 4 patients whose characteristics are summarised in Table 1. They were 4 girls with recurrent pericarditis in who treatment with anakinra proved drastically effective, with resolution of cardiac and systemic manifestations in the absence of relevant adverse events. All patients underwent testing for monogenic inflammatory diseases, with such a disease identified in only 1 (familial Mediterranean fever).

Since autoinflammatory diseases have only been recently described, paediatricians and cardiologists still have little

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Table 1 Clinical characteristics of 4 girls with recurrent pericarditis and complete response to ANK.

	Patient 1	Patient 2	Patient 3	Patient 4
Age at onset (years)	9	11	3	12
No episodes before ANK	3	6	3	1
Time elapsed from onset to ANK	9 months	24 months	12 months	24 months
Treatments before ANK	Ibuprofen Colchicine Prednisone	Ibuprofen Dexamethasone Colchicine	Ibuprofen Prednisone Colchicine	Ibuprofen Prednisone Colchicine
Symptoms associated with pericarditis[a]	Fever, asthenia, pleurisy, peritonitis	Fever, asthenia, exanthema, pleurisy	Fever, abdominal pain	Pachypleuritis
CPR (mg/L)[a]	104	250	162	350
ESR (mm/h)[a]	118			
WBC and % N[a]	13 600, 80%	19 000, 82%	9300, 56%	17 100, 82%
Comorbidity	No	Probable sJIA, MAS	No	FMF
CPR (mg/L)[b]	0.54	0.8	1.63	0.59
ESR (mm/h)[b]	12	6	7	4
WBC and % N[b]	4330, 23%	5300, 59%	8170, 27.5%	9510, 82%
No episodes after initiation of ANK	0	1, 30 days after discontinuing ANK	0	1, 30 days after discontinuing ANK
Current treatment and its duration to date	None (received 18 months)	ANK 100 mg/day (1.6 mg/kg), 5 years	ANK 75 mg (4 mg/kg) every 72 h, 20 months	ANK 100 mg/day (2 mg/kg), 3 year

ANK, anakinra; CPR, C-reactive protein; ESR, erythrocyte sedimentation rate; FMF, familial Mediterranean fever; JIA, juvenile idiopathic arthritis; MAS, macrophage activation syndrome; N, neutrophils; sJIA, systemic juvenile idiopathic arthritis; WBC, white blood cells.
[a] Peak values in a typical episode.
[b] First test performed after initiation of ANK.

knowledge of them, so we believed that sharing our experience through this journal would be relevant. The growing evidence in this field underscores the need to consider the possibility of an autoinflammatory aetiology in children presenting with seemingly idiopathic recurrent pericarditis. As for its management, anakinra seems to be the most promising treatment option in cases with concomitant systemic involvement (elevation of acute phase reactants, fever). Further studies are needed to strengthen the evidence on the efficacy of this biopharmaceutical, determine whether it could be used as first-line treatment after recurrence, and analyse the incidence of recurrences after completion of treatment.

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