Long-Term Efficacy of Interleukin-1 Receptor Antagonist (Anakinra) in Corticosteroid-Dependent and Colchicine-Resistant Recurrent Pericarditis

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Objective To evaluate the long-term response and safety of interleukin-1 receptor antagonist (anakinra) in recurrent pericarditis.

Study design Fifteen patients (12 children, 3 adults) were enrolled in a multicenter retrospective study. All the patients were corticosteroid-dependent and 14 had received colchicine. Anakinra was given at 1-2 mg/kg/d. The primary outcome of the study was a reduction of at least 70% of disease flares after anakinra treatment compared with the pretreatment period. Secondary outcomes were: (1) number of complete or partial responders to anakinra and time for complete response; (2) number of patients who discontinued other ongoing treatments (non-steroidal anti-inflammatory drugs, corticosteroid, colchicine) and time needed for discontinuation; (3) number of relapses during continuous anakinra treatment; and (4) number of relapses during anakinra tapering or discontinuation.

Results All patients treated had a complete response within a few days and were able to rapidly withdraw concomitant treatments, including corticosteroids. During daily treatment, no patient had a relapse of the disease; 14 patients started tapering and 6 of them experienced a relapse, with a prompt response after anakinra reintroduction. Overall, after a median follow-up of 39 months (range 6-57), a 95 % reduction of flares was observed compared with pretreatment period.

Conclusion The long-term use of anakinra in monotherapy is associated with persistent control of recurrent pericarditis. *(J Pediatr 2014;164:1425-31)*.

Acute pericarditis is a frequent cause of chest pain in the emergency department.[1] The etiology of the initial attack is post-viral or remains unknown, thus labeling the pericarditis as "idiopathic." One or more recurrences arise in 15%-30% of patients after the initial episode of acute pericarditis.[2] Recurrent pericarditis also can be a clinical manifestation of various conditions, including rheumatic diseases, monogenic autoinflammatory diseases, and other genetic disorders.[3]

The typical clinical presentation of acute pericarditis as well as of its recurrences is severe precordial pain associated with fever and elevation of acute phase reactants. Pericardial friction rub can be detected at physical examination. Electrocardiographic and echocardiographic abnormalities are pivotal tools for the initial diagnosis.[3] The number of recurrences and the duration of disease-free intervals vary among patients. The long-term prognosis of recurrent pericarditis generally is good. However, quality of life can be severely affected in patients affected by frequent relapses, and side effects of corticosteroid treatment may be a concern.

The therapeutic approach during recurrences consists of administration of non-steroidal anti-inflammatory drugs (NSAID) associated with colchicine in patients experiencing frequent recurrent flares.[2,4,5] A considerable number of patients require corticosteroid treatment to control disease flares and prevent relapses.[5] Other therapeutic strategies have been attempted with alternative immunosuppressant agents without a clear benefit.[5] Interleukin-1 (IL-1) inhibition with anakinra (IL-1 receptor antagonist) has been described anecdotally as effective in the control of the disease in patients who are corticosteroid-dependent and colchicine-resistant.[6-9] Despite the dramatic effect described in the cases reported, no information is available on the long-term efficacy and safety of this therapeutic strategy. Moreover, there are no data on the rate of relapse after suspension of IL-1 blocking agents.

Thus, we performed a national multicenter study to retrospectively evaluate the long-term experience of the use of anakinra for recurrent pericarditis.

ECG	Electrocardiogram
IL-1	Interleukin-1
NSAID	Non-steroidal anti-inflammatory drug
SoJIA	Systemic onset juvenile idiopathic arthritis

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Methods

On April 2012, a survey among 15 pediatric rheumatology centers and 3 referral centers for autoinflammatory diseases in adults was performed. The aim of the survey was to identify the centers managing patients with recurrent pericarditis treated with one of the IL-1 blocking agents available in Europe (anakinra or canakinumab). Six centers (5 pediatric rheumatology and 1 adult center) were managing at least 1 patient. Fifteen consecutive corticosteroid-dependent patients (M:F = 11:4; 12 children and 3 adults; median age 18 years, range 8-60 years) were treated with anakinra from October 2007-January 2013. In the same time range the 6 centers were managing a total of 97 patients (62 adults, 35 children) with recurrent idiopathic pericarditis. Patients with systemic onset juvenile idiopathic arthritis (SoJIA), adult onset Still disease, systemic lupus erythematosus, and monogenic periodic fevers were excluded.

Pericarditis was diagnosed on the basis of the presence of at least 2 of the following criteria: (1) typical pericardial chest pain; (2) pericardial chest pain, pericardial friction rub; (3) widespread ST-segment elevation or PR-segment depression that was not previously reported; and (4) new or worsening pericardial effusion at echocardiography.[3] Other causes of recurrent pericarditis (infectious, neoplastic, metabolic, traumatic, or drug-related) represented exclusion criteria.[3]

Disease relapse (or flare) was defined by the presence of typical chest pain plus one or more of the following findings: fever, pericardial frictions rub, electrocardiogram (ECG) changes, echocardiographic evidence of a new or worsening pericardial effusion, elevation of acute phase reactants, and elevated leukocyte count.[10]

Corticosteroid-dependence was defined by the need of a continuous use in order to prevent disease relapses with a past experience of a disease flare in at least 2 attempts of corticosteroid tapering.

The off-label use of anakinra and the informed consent signed by patients or legal tutors were approved by the ethical board of each institute/hospital of participating centers. Clinical, laboratory, and instrumental variables were collected retrospectively from patients' charts and patients/parents interview using a common questionnaire. The following information was requested: disease onset, number of relapses according to the aforementioned definition, drug history (compound, dosage, and time of exposure) during the disease course and at baseline, clinical manifestations, and laboratory and instrumental examinations at baseline and at the last follow-up. Response to anakinra was evaluated as complete(normalization of clinical manifestations, laboratory and ECG and/or echocardiographic examinations) or partial (lack of normalization of at least 1 of the previous manifestations/findings). In case of complete response, the number of days occurring between baseline and normalization of clinical manifestations, and laboratory and instrumental examination were requested. The modification/withdrawal of other drugs (NSAID, corticosteroid, colchicine) during anakinra treatment also was recorded. Finally, the number of disease relapses during anakinra treatment and tapering, or after anakinra discontinuation also were evaluated.

The primary outcome of this retrospective study was to evaluate a reduction of at least 70% of disease flares after anakinra treatment compared with pretreatment period. Secondary outcomes were: (1) number of complete or partial responders to anakinra and time for complete response; (2) number of patients who discontinued other ongoing treatments (NSAID, corticosteroid, colchicine) and time until discontinuation; (3) number of relapses during continuous anakinra treatment; and (4) number of relapses during anakinra tapering or after discontinuation.

Results

The clinical characteristics of patients (11 males, 4 females; 12 children and 3 adults) are shown in **Table I**. Thirteen patients were considered affected by recurrent idiopathic pericarditis. None had a past history of recurrent or periodic fevers or other clinical manifestations compatible with autoinflammatory diseases. Genetic screening for monogenic periodic fevers was performed in 12 of 13 patients diagnosed with idiopathic pericarditis. Four of them were investigated for mutations in 3 genes associated with periodic fevers (*MVK*, *TNFSRF1A*, and *MEFV*), 3 patients were analyzed for 2 genes (*TNFRSF1A* and *MEFV*), and 5 patients for a single gene (2 for *TNFRSF1A* and 3 for *MEFV*).

Two patients displayed a concomitant genetic disorder. Patient no. 14, previously described by Picco et al, suffered from Mhyre syndrome and carried the c.1499 T > C mutation of SMAD4 gene.[11] Patient no. 15 was affected by Sotos syndrome and carried a deletion of chromosome 5.

The median age at disease onset (first episode of pericarditis) was 13 years (range 5-49). The age at baseline (start of anakinra treatment) was 14 years (range 6-56), with the median duration of the disease of 12 months (range 3-137). The mean number of disease flares before anakinra treatment was 9.8 (±9.7 SDS) (**Table I**). Each patient's drug history before anakinra treatment is reported in **Table II** (available at www.jpeds.com). NSAID were used in 13 of 15 patients. Fourteen out of 15 patients were treated with colchicine for a median period of 9 months (range 1-48) (**Table II**). According to the centers, these patients were considered as "colchicine-resistant" attributable to the occurrence of at least 1 disease flare despite colchicine use at standardized dosage (**Table II**).[4,12] Other treatments (methotrexate, azathioprine, chloroquine, mycophenolate mofetil, intravenous immunoglobulin) also were used without relevant efficacy according to the judgment of the referral centers (**Table II**). At baseline, the whole cohort was receiving corticosteroids with variable dosages (**Table II**). Most of the patients displayed early signs of hypercorticism.

The clinical characteristic of patients at baseline is reported in **Table III**. Thirteen patients started anakinra treatment