Pediatric Recurrent Pericarditis: Appropriateness of the Standard of Care and Response to IL-1 Blockade

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Objective To analyze, in a cohort of pediatric patients with recurrent pericarditis undergoing anti-interleukin (IL)-1 treatment: the agent and dosing used as first-line treatment, the long-term efficacy of IL-1 blockers, the percentage of patients achieving a drug-free remission, and the presence of variables associated with drug-free remission.

Study design Data were collected from patients' charts. The annualized relapse rate (ARR) was used for evaluation of treatment efficacy, and bivariate logistic regression analysis was used for variables associated with drug-free remission.

Results Fifty-eight patients, treated between 2008 and 2018, were included in the study (mean follow-up. 2.6 years). Of the 56 patients treated with first-line drugs, 14 not responsive patients were underdosed. Fifty-seven patients were treated with anakinra: the ARR before and during daily treatment was 3.05 and 0.28, respectively ($P < .0001$); an increase to 0.83 was observed after the reduction/withdrawal of treatment ($P < .0001$). The switch from anakinra to canakinumab (5 patients) was associated to an increase of the ARR (0.49 vs 1.46), but without statistical significance ($P = .215$). At last follow-up, only 9 of the 58 patients had withdrawn all treatments. With the limits of a retrospective study and the heterogeneity between the patients enrolled in the study, a shorter duration of treatment with anakinra was the only variable associated with drug-free remission.

Conclusions This study shows that most pediatric patients with recurrent pericarditis needing IL-1 blockade received an inadequate treatment with first-line agents. The effectiveness of anakinra is supported by this study, but few patients achieved drug-free remission. The different rate of response to anakinra and canakinumab may suggest a possible role of IL-1α in the pathogenesis of recurrent pericarditis. *(J Pediatr 2023;256:18-26)*.

Data from a multicenter study described clinical characteristics and response to treatment of pediatric patients with recurrent pericarditis, consistent with what is observed in the adult population; of note, a high rate of recurrence after steroidal treatment was reported in this study.[1] In 2015, the European Society of Cardiology (ESC) published new guidelines for

ARR	Annualized relapse rate
ESC	European Society of Cardiology
IL-1	Interleukin 1
NSAIDs	Nonsteroidal anti-inflammatory drugs

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the management of acute and recurrent pericarditis in the adult population; an adaptation to the pediatric age was proposed, even though data about the effectiveness of the different treatments are lacking in this population.[2] According to these guidelines, nonsteroidal anti-inflammatory drugs (NSAIDs) represent the first-line treatment for acute pericarditis, together with low doses of colchicine.[3,4] Steroids are not recommended as first-line treatment, increasing the risk of dependence and chronicity.[5] Guidelines suggest the use of low doses of steroids (≤0.5 mg/kg/day of prednisone), together with colchicine, in patients not responding to NSAIDs.[2] Various immunosuppressive drugs (high-doses immunoglobulins, azathioprine, biological) were suggested as third-line treatment in non-responding patients, even though evidence for their effectiveness was lacking.[2]

The clear effect of interleukin-1 (IL-1) inhibition with anakinra (the recombinant IL-1 receptor antagonist) has been described in children with recurrent pericarditis resistant to colchicine and steroid-dependent in different series of pediatric and adult patients.[1,6–9] We performed a multicenter national study that retrospectively analysed pediatric patients with recurrent pericarditis undergoing anti-IL-1 treatment and followed in centers with pediatric cardiology and rheumatology.

The aims of this study were to evaluate the appropriateness of the first-line treatments (NSAIDs, colchicine) before anti-IL-1 treatment, to evaluate the long-term efficacy of different IL-1 blockers and the modification of the schedule of administration during the follow-up period; to analyze the number of patients able to achieve complete control of the disease and discontinue all treatments; and to identify, with the limits of a retrospective study, possible variables associated with higher probability to discontinue treatment without disease flares.

Methods

In 2019, a national survey in referral Italian centers of pediatric cardiology and rheumatology collected all patients with recurrent idiopathic pericarditis treated with IL-1 blockers. Pericarditis was diagnosed according to the ESC guidelines, in the presence of at least 2 of the following criteria: (1) typical pericardial chest pain, (2) pericardial friction rub, (3) typical electrocardiographic changes (widespread ST-segment elevation or PR-segment depression), or (4) pericardial effusion at echocardiography.[2] Disease onset was considered the first 28 days from the beginning of the symptoms. A disease flare (relapse) was defined as recurrence of chest pain along with 1 or more of the following signs: fever, pericardial friction rub, electrocardiographic changes, echocardiographic evidence of new or worsening pericardial effusion, or elevation of acute phase reactants.[10]

Patients with both idiopathic and postoperative pericarditis were included in the study because, according to guidelines, the therapeutic approach is the same for both conditions; recurrent pericarditis developed in the context of a defined inflammatory systemic disease (such as systemic-onset juvenile idiopathic arthritis or monogenic autoinflammatory diseases) were excluded from the study. The demographics, clinical, laboratory and procedural data were retrospectively collected from patients' charts.

A complete response to treatment was defined as the disappearance of disease-related symptoms and the normalization of cardiac ultrasound examination and acute phase reactants, partial response as an amelioration of the clinical picture, radiologic and laboratory values but without a complete normalization. An inadequate response was defined as no significant changes occurring in the clinical picture with the treatment. Drug-free remission was defined as the complete control of the clinical picture and laboratory findings despite the discontinuation of all ongoing treatment for at least 6 months. Corticosteroid dependence was defined as the need of continuous treatment to prevent disease relapses or the occurence of relapse within 30 days from any attempt of steroids withdrawal.

Treatment appropriateness with first-line (NSAIDs and colchicine) and second-line (steroids) drugs was evaluated according to the ESC guidelines.[2] For NSAIDs, ibuprofen was considered adequate at the dosage of 30-50 mg/kg/day (maximum 2400 mg/day), indomethacin 1-2 mg/kg/day (maximum 150 mg/day), naproxen 10-15 mg/kg/day (maximum 1500 mg/day), and acetylsalicylic acid 30-50 mg/kg/day (maximum 3000 mg/day); colchicine was considered adequate at the dosage of 0.5 mg/day for children less than 5 years of age and 1-2 mg/day for children of 5 years of age and older. The correct dosage of steroids was considered 0.5 mg/kg/day or less of prednisone or equivalent.

Quantitative data are presented as medians (1st - 3rd quartile) or mean ± SD unless otherwise stated, and categorical data as absolute numbers and percentages.

Relapse was annualized as Poisson outcomes using the total number of relapses observed out of the total person-time of follow-up before IL-1 blockade, during full-dose treatment and after treatment tapering or discontinuation and was compared by a mixed effect negative binomial model accounting for the repeated measures analysis.

Comparisons of demographic and clinical characteristics between patients who withdrew all treatments and patients who did not were performed with Mann-Whitney *U* test for quantitative data and by means of the χ^2 test, or the Fisher's exact test, as appropriate, for categorical data. A bivariate logistic regression analysis was used to identify possible factors associated to an increased probability to withdraw the biological treatment. SAS 9.3 (Institute Inc., Cary, NC) was used for the computation.

Results

58 patients (37 male and 21 female) from 19 centers were included in the study. The demographic data and clinical characteristics of patients are reported in **Table I** (available at www.jpeds.com). Fifty-four patients (93%) had idiopathic and 4 patients (7%) postpericardiotomy recurrent pericarditis. A concomitant genetic non-inflammatory

disease was present in 6 patients (10%): Mhyre syndrome, Melas syndrome, Rett syndrome, arrhythmogenic dysplasia, deletion in 16p11.2 chromosome, and Sotos syndrome. None of the patients had a clinical picture suggestive of an autoinflammatory disease or positive family history; 30 patients were screened for mutations in genes responsible for hereditary periodic fever syndromes, owing to physician choice; none of them had a confirmatory genotype or satisfied the new classification criteria for recurrent fevers (Table I).[11]

The median age at disease onset was 12.6 years (range, 4.5-17.5 years), and the median age at the beginning of treatment with IL-1 blockers was 13.5 years (range, 6.0-25.4 years). The median duration of disease before anti-IL-1 treatment was 0.5 years, with a wide range (4 days to 12.3 years), whereas the median number of relapses before treatment with IL-1 blockers was 3 (range 1-10). The median duration of follow-up from disease onset in all patients included in the study was of 2.6 years (range, 1.2-5.2 years). In the first 28 days from disease onset, 25 patients (43%) received treatment with NSAIDs, 10 (17%) NSAIDs and colchicine, 2 (4%) steroids, 14 (24%) NSAIDs and steroids, and 7 (12%) NSAIDs, colchicine, and steroids (Figure 1, A).

At the beginning of treatment with IL-1 blockers, 4 patients (7%) received treatment with NSAIDs, 8 (14%) NSAIDs and colchicine, 7 (12%) steroids, 5 (9%) NSAIDs and steroids, 12 (21%) NSAIDs, colchicine and steroids, 13 (22%) colchicine and steroids, 5 (9%) colchicine, 2 (3%) steroids and methotrexate, and 2 (3%) were off therapy (Figure 1, A). Overall, NSAIDs were used in monotherapy or in combination with other drugs in 56 patients (Table II). Among the 25 patients who received NSAID as monotherapy, 10 of 18 patients (55%) without a complete response and 6 of 7 with a complete response (85%) were receiving an adequate dosage according to the 2015 ESC guidelines. Figure 2, A displays the response to treatment with ibuprofen, the drug more frequently used, according to the appropriateness of the dosage.

Of the 58 patients, 49 received treatment with colchicine during the disease course. The median dosage was 1 mg/day (range, 0.5-2.0 mg/day) and the median duration of treatment was of 5 months (range 5 days to 4 years)

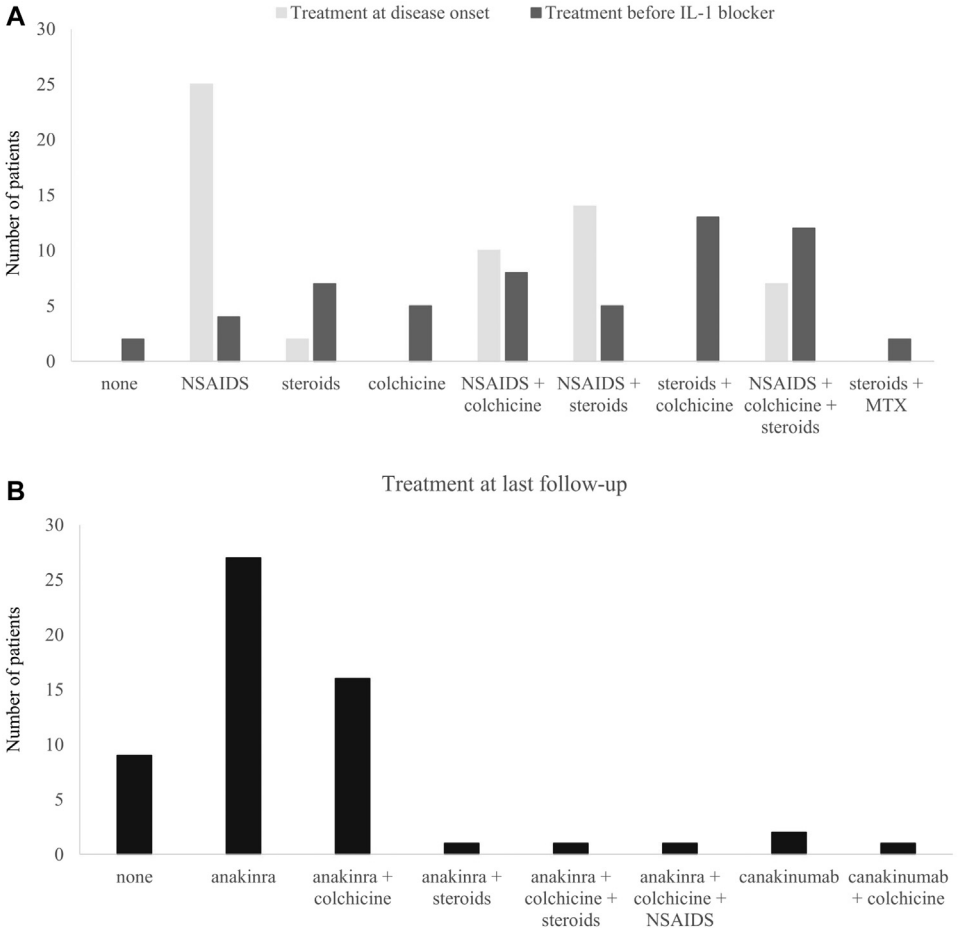


Figure 1. Treatment of the patients included in the study at disease onset (first 28 days from the beginning of symptoms), **A**, at the time of initiation of anti-IL-1 treatment and **B**, at last follow-up. *MTX*, methotrexate.

Table II. Conventional, second and third lines treatments used in the 58 patients included in the study

Patient	NSAID	Duration of treatment with NSAIDs (months)	Adequate dosage of NSAIDs	Initial response to treatment (NSAIDs)	Colchicine	Duration of treatment with colchicine (months)	Adequate dosage of colchicine	Initial response to treatment (colchicine)	Steroidal drug (mg/kg/day)	Duration of treatment with steroids (months)	Initial response to treatment (steroids)	Other treatment
1	Indomethacin	3	Y	Complete	Y	18	Y	Partial	PDN (0.3)	1	Complete	
2	Ibuprofen	NK	Y	Partial	N	–	–	–	PDN (2)	NK	Complete	Mycophenolate
3	Naproxen	3	Y	Abstent	Y	6	Y	Partial	PDN (1)	33	Complete	Immunoglobulins, methotrexate
4	Ibuprofen	5	N	Complete	Y	4	Y	Partial	PDN (2.5)	3	Complete	
5	ASA, ibuprofen	0.1	N	Absent	N	–	–	–	PDN (1.7)	4	Complete	
6	Ibuprofen, indomethacin	6	Y	Complete (ibuprofen) absent (indomethacin)	Y	6	Y	Complete	–	–	–	
7	ASA, ibuprofen	NK	NK	Absent	Y	2	Y	Partial	PDN (2)	18	Complete	Methotrexate
8	Ibuprofen	1	N	Absent	Y	4	N	Absent	MPN (2)	0.3	Partial	
9	–	–	–	–	Y	1	Y	Partial	PDN (1)	15	Complete	
10	Ibuprofen	1	N	Partial	N	–	–	–	PDN (0.6)	4	Complete	
11	Ibuprofen	2	Y	Absent	Y	4	Y	Absent	PDN (1)	2	Absent	
12	Ibuprofen	2	N	NK	Y	40	Y	Partial	PDN (0.65)	11	Complete	
13	NK, ibuprofen	2	Y	Partial	Y	2	Y	Partial	PDN (0.2)	0.75	Partial	
14	Naproxen	4	Y	Partial	Y	3	Y	Partial	PDN (1)	8	Partial	
15	Ibuprofen	1	Y	Partial	Y	6	Y	Partial	PDN (1)	4	Partial	
16	Ibuprofen	3	N	Partial	Y	9	Y	Partial	PDN (1.1)	6	Complete	
17	Ibuprofen, indomethacin	44	N	Partial	Y	9	Y	Partial	MPN (0.6)	20	Complete	
18	Naproxen	13	Y	Partial	Y	24	Y	Partial	PDN (2)	10	Complete	
19	Ibuprofen	2	Y	Partial	Y	7	Y	Complete	PDN (1)	4	Complete	
20	Ibuprofen, ASA, Indomethacin	4	Y	Complete	Y	10	Y	Complete	PDN (1)	5	Complete	
21	Ibuprofen	3.5	N	Partial	Y	14	Y	Partial	PDN (1.1)	14	Complete	
22	Ibuprofen	1	Y	Absent	Y	15	Y	Partial	MPN (2)	8	Complete	
23	Ibuprofen	3	N	Partial	Y	2	Y	Complete	PDN (1)	3	Partial	Immunoglobulins
24	Ibuprofen	24	Y	Absent	Y	41	Y	Complete	PDN (1)	1	Complete	
25	Ibuprofen	2.5	Y	Partial	Y	9	Y	Complete	PDN (1)	2	Complete	
26	Ibuprofen	0.5	Y	Partial	Y	0.5	N	Partial	–	–	–	
27	Indomethacin	10	Y	Absent	Y	12	Y	Complete	PDN (0.6)	8	Complete	
28	ASA	0.1	Y	Partial	Y	5	Y	Complete	PDN (0.66)	10	Complete	Hydroxychloroquine
29	ASA	0.3	Y	Complete	Y	12	Y	Partial	PDN (1)	15	Complete	
30	Ibuprofen, indomethacin	5	Y	Partial	Y	21	Y	Partial	PDN (1)	5	Partial	
31	ASA, indomethacin		Y	Complete	Y	48	Y	Complete	PDN	72	Complete	
32	Indomethacin	2	Y	Complete	Y	5	Y	Complete	PDN (0.5)	3	Complete	
33	Ibuprofen	4	N	Partial	Y	2	Y	Partial	–	–	–	
34	Ibuprofen	0.25	Y	Absent	Y	6	Y	Partial	–	–	–	
35	Ibuprofen, indomethacin, ibuprofen	2	Y	Complete	Y	2	Y	Partial	–	–	–	
36	–	–	–		N	–	–	–	PDN (1.1)	0.6	Partial	
37	ASA	1	NK	Absent	Y	18	Y	Partial	PDN (1.5)	4.3	Complete	
38	Ibuprofen	0.25	Y	Complete	N	–	–	–	MPN (1)	2	Complete	
39	Ibuprofen	0.16	N	Absent	N	–	–	–	–	–	–	
40	Indomethacin	5	Y	Partial	Y	3	Y	Absent	PDN (1)	8	Complete	

(*continued*)

Table II. Continued

Patient	NSAID	Duration of treatment with NSAIDs (months)	Adequate dosage of NSAIDs	Initial response to treatment (NSAIDs)	Colchicine	Duration of treatment with colchicine (months)	Adequate dosage of colchicine	Initial response to treatment (colchicine)	Steroidal drug (mg/kg/day)	Duration of treatment with steroids (months)	Initial response to treatment (steroids)	Other treatment
41	Ibuprofen, indomethacin	2	Y	Partial	Y	10	Y	Partial	–			
42	Ibuprofen	0.75	N	Partial	Y	1.5	Y	Partial	MPN (0.8)	2	Complete	
43	Ibuprofen	0.50	N	Partial	Y	8.25	Y	Partial	MPN (1.3)	8	Partial	
44	ASA, ibuprofen, indomethacin	5.50	N	Partial	Y	0.5	N	Complete	–	–	–	
45	Ibuprofen, indomethacin	0.25	Y	Complete	Y	0.01	N	Absent	MPN (bolus)	1	Complete	
46	Ibuprofen	0.25	Y	Complete	Y	1	Y	Complete	MPN (bolus)	4	Complete	
47	Indomethacin		N	Absent	Y	NK	N	Partial	MPN (bolus)		Partial	Hydroxychloroquine, Azathioprine
48	NK, ibuprofen		Y	Complete	N	–	–	–	–	–	–	
49	Ibuprofen	2.60	Y	Partial	Y	5	Y	Partial	MPN (1.7)	1	Partial	
50	Ibuprofen	9	N	Absent	N	–	–	–	MPN (bolus)	4	Complete	
51	Ibuprofen, naproxen	1	Y	Partial	Y	8	Y	Partial	MPN (1)	3.5	Partial	
52	NK	0.50	NK	Partial	Y	0.25	N	Absent	PDN (2)	3	Complete	
53	Ibuprofen	1.50	Y	Partial	Y	3	Y	Absent	–	–	–	
54	Ibuprofen	0.75	N	Partial	Y	2	Y	Partial	PDN (1)	5	Partial	
55	Ibuprofen	1	Y	Partial	Y	3	Y	Partial	PDN (0.5)	2.5	Partial	
56	Naproxen, indomethacin	6	Y	Partial	N	–	–	–	PDN (2)	7	Partial	Methotrexate
57	Ibuprofen, ASA, indomethacin	7	Y	Partial	Y	2	N	Absent	PDN (1.2)	2	Complete	
58	Ibuprofen, ketoprofen	3	Y	Absent	Y	5	Y	Absent	PDN (1)	NK	Absent	

ASA, acetylsalicylic acid; *MPN*, methylprednisolone; *PDN*, prednisone; *NK*, Not known.

(Table II). The addition of colchicine to the ongoing treatment allowed achieving an initial complete control of the disease in 11 patients (23%), improved the disease but without a complete response in 29 (59%), and in 9 patients (18%) did not change the disease course. Of note, 5 of the 9 non-responding patients (55%) were receiving an inadequate dosage of treatment, and this was the case for 1 of the 29 partial responders (3%) and 1 of the 11 complete responders (9%) (Figure 2, B).

Steroids were used in 48 of the 58 patients (Table II). The median interval of time between the disease onset (first episode) and the beginning of treatment was of 1 month (range, 1 day to 6.5 years). The median duration of treatment was 4 months (range, 10 days to 6 years). Twelve patients received intravenous steroidal treatment, followed by oral therapy: 4 patients received pulses (methylprednisolone 30 mg/kg/day for a maximum of 1 g for 3 days, then 2 mg/kg/day), whereas 8 patients received treatment with methylprednisolone 0.25-2 mg/kg/day in 1-2 doses. The other 36 patients received oral treatment with a median dosage of prednisone (or equivalent) of 1 mg/kg/day (range, 0.2-2.5 mg/kg/day). Four patients (2 complete and 2 partial responders) of the 48 patients received a low dosage (≤0.5 mg/kg/day of prednisone); the other 44 (92%) received a higher dosage that, of note, did not allow the complete control of the clinical picture (Figure 2, C). Steroid dependence was observed in 45 patients.

Seven patients were treated with third-line treatment before the beginning of therapy with IL-1 blockers, without a persistent control of the disease (Table II): methotrexate (3 patients), immunoglobulins (2 patients), hydroxychloroquine (2 patients), azathioprine (1 patient), and mycophenolate (1 patient). There were 57 patients who received anakinra and 1 patient who received canakinumab as the first anti-IL-1 drug. The median time between the disease onset and the beginning of IL-1 blockade was of 0.5 years (range, 0.3-1.1 years), with a cumulative number of disease flares of 203 in a cumulative time of 69.4 years (3 relapses/year).

At the last follow-up, 9 patients (15%) were in drug-free remission, and 49 were still receiving IL-1 blockade treatment: 27 patients (47%) anakinra, 19 (33%) anakinra with other first/second-line drugs, 2 (3%) canakinumab, and 1 (2%) canakinumab and colchicine (Figure 1, B). The mean dosage of anakinra at the beginning of the treatment was 1.69 ± 0.55 mg/kg/day and the median duration of treatment was 1.3 years (IQR, 0.5-2.3 years) (Table III, available at www.jpeds.com).

A complete response to treatment was achieved in 54 patients (95%) with complete control of clinical manifestations in a mean time of 2 ± 1.64 days and normalization of laboratory and echocardiographic variables in a median time of 7 days (IQR, 2-45 days). During daily treatment with anakinra the cumulative number of relapses was 2 within a cumulative duration of treatment of 36.9 years (0.01 relapse/year). Of the 54 patients with a complete response to treatment with anakinra, 35 patients (65%) attempted a reduction

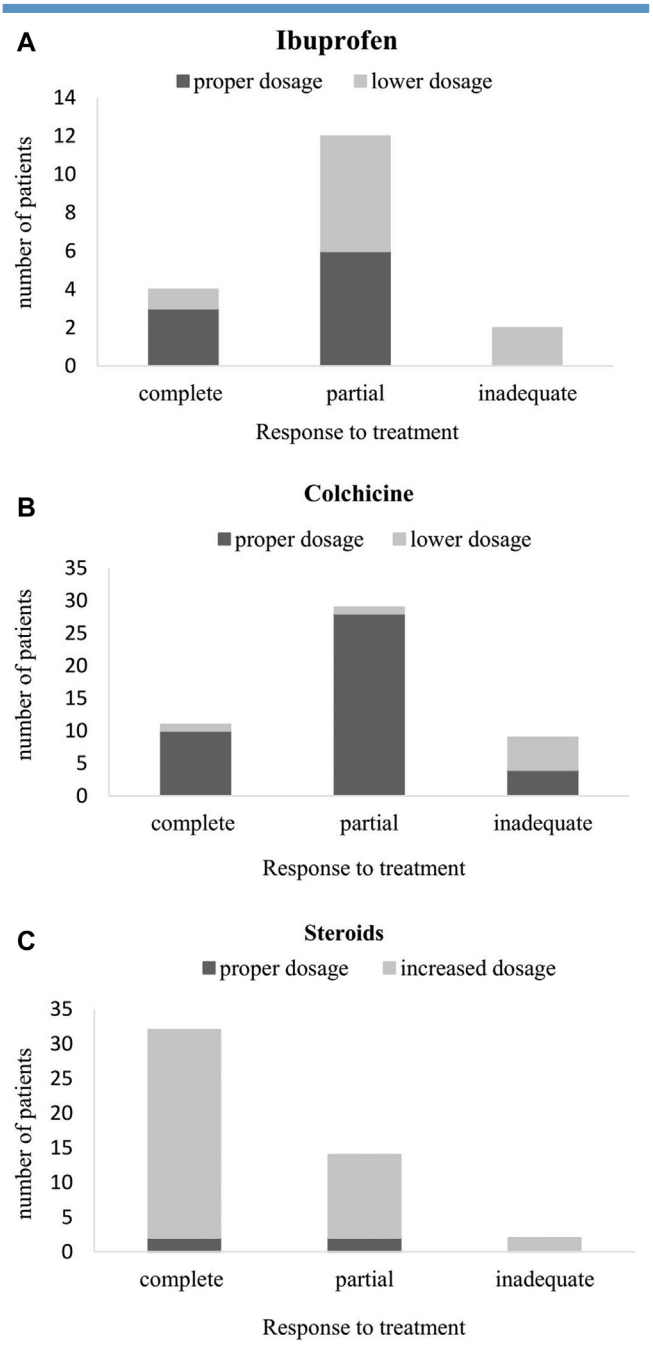


Figure 2. **A**, Appropriateness of dosage and response to treatment with NSAIDs, **B**, colchicine, and **C**, steroids. Treatment with first-line (NSAIDs and colchicine) and second-line (steroids) drugs was considered adequate according to the ESC guidelines.[2] Ibuprofen was considered adequate at a dosage of 30-50 mg/kg/day; colchicine was considered adequate at the dosage of 1-2 mg/day for children more than 5 years of age and 0.5 mg/day for children 5 years or age or less. The correct dosage of steroids was considered 0.5 mg/kg/day or less of prednisone or equivalent.

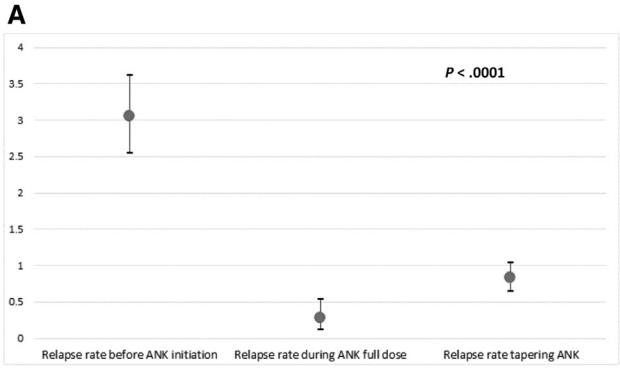
of treatment and 21 (60%) experienced a flare (Figure 3, available at www.jpeds.com). At first tapering attempt, 9 patients decreased progressively the number of injection

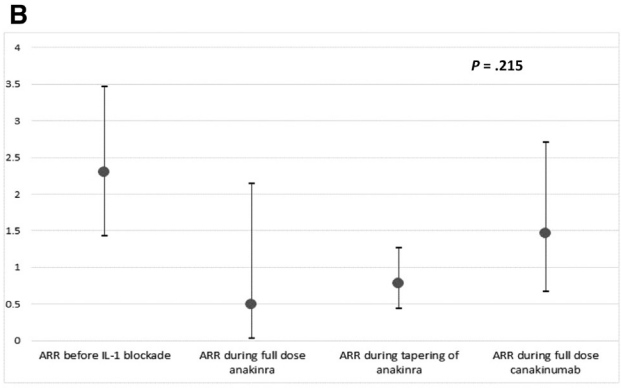
per week, 24 patients moved to an administration every other day. Two patients withdrew treatment without tapering. During the tapering or withdrawal period, the cumulative number of relapses was 65 with a cumulative time of 79.8 years (0.8 relapse/year). Daily treatment with anakinra was reintroduced in 17 of 21 patients with complete response; two patients were switched to canakinumab and two patients were treated with colchicine and short courses of steroids, with benefit.

The analysis of ARR showed that, concerning the pretreatment period (ARR, 3.05; 95% CI, 2.55-3.61), anakinra was effective in preventing the occurrence of relapses during continuous daily treatment (ARR, 0.28; 95% CI, 0.12-0.53; $P < .0001$). However, an increase in the number of relapses was then observed after the reduction or discontinuation of treatment (ARR, 0.83; 95% CI, 0.65-1.04; $P < .0001$) (**Figure 4**, A). During treatment with anakinra, 27 of 28 patients withdraw treatment with NSAIDs, 21 of 38 withdrew colchicine, and 36 of 38 withdrew steroids. Despite the complete control of the clinical manifestations in 16 of the 17 patients receiving colchicine together with anakinra, this treatment was maintained, owing to physician choice; moreover, in 2 patients colchicine was reintroduced during anakinra tapering. At last follow-up 46 patients were still in treatment with anakinra: 27 patients were in monotherapy and in 19 anakinra was associated with other drugs (**Figure 1**, B).

To evaluate the presence of predictive factors associated with the possibility to withdraw the treatment with anakinra without subsequent relapse, the 9 patients in drug-free remission at the last follow-up were compared with the 19 in which the withdrawal was not possible owing to flare during tapering or withdrawal. The 19 patients still receiving daily treatment, the 7 patients who were tapering the treatment without relapse and the 3 patients with a persistent partial response to treatment were excluded from the statistical analysis. The χ^2 test for the categorical variables and the Mann-Whitney test for the continuous variables identified that the only variable associated with a statistically significant difference between the two groups was the duration of treatment with anakinra, which was shorter in the group of patients in drug-free remission at last follow-up. The duration of follow-up from disease onset to anakinra withdrawal was also shorter in this group of patients (**Table IV**, available at www.jpeds.com). The bivariate logistic regression analysis identified that the shorter duration of treatment with anakinra was the only variable associated with the probability of withdrawing treatment with statistical significance (**Table V**, available at www.jpeds.com).

Six patients were treated with canakinumab. In one patient the drug was the first IL-1 blocker used, whereas the other 5 patients received canakinumab after a switch from anakinra (**Table VI**, available at www.jpeds.com). The mean dosage at the beginning of treatment with canakinumab was 2.6 ± 0.8 mg/kg every 4 weeks. At the last follow-up, 2 patients (33%) were still on treatment with canakinumab as monotherapy with complete response, whereas 1 patient (17%), with a previous partial response to anakinra, was on treatment with canakinumab and colchicine, without complete control of the disease (**Figure 1**, B). Three patients (50%) withdrew treatment with canakinumab for a lack of response. In all of them, the restoration of anakinra treatment led to complete disease control. The cumulative number of relapses during treatment with canakinumab was 9 with a cumulative time of 8.6 years (1 relapse/year). The ARR of the 6 patients treated with canakinumab was 1.46





	ARR	95% CI	
ARR before anakinra	3.05	2.55	3.61
ARR during full-dose anakinra	0.28	0.12	0.53
ARR during tapering/ discontinuation of anakinra	0.83	0.65	1.04

	ARR	95% CI	
ARR before IL-1 blockade (6 pts)	2.30	1.43	3.46
ARR during full dose anakinra (5 pts)	0.49	0.03	2.14
ARR during tapering of anakinra (5 pts)	0.78	0.44	1.26
ARR during full dose canakinumab (6pts)	1.46	0.67	2.71

Figure 4. **A**, Annualized relapse rate before treatment, during daily treatment and after tapering or discontinuation of the 35 patients treated with anakinra. **B**, Annualized relapse rate before treatment, during daily treatment with anakinra, during anakinra tapering or discontinuation and during full dose of canakinumab of the 6 patients treated with canakinumab.

(95% CI, 0.67-2.61) during continuous treatment. In the 5 patients who switched from anakinra to canakinumab, the ARR during daily anakinra was 0.49 (95% CI, 0.03-2.14) and 0.78 (95% CI, 0.44-1.26) during anakinra tapering. Both were lower than the ARR observed during canakinumab treatment; however, the difference was not statistically significant ($P = .215$) (**Figure 4**, B).

The safety profile of both anakinra and canakinumab was good. Of 57 patients, 11 (19%) treated with anakinra and none of the 6 patients treated with canakinumab displayed some adverse event during their follow-up. Seven patients treated with anakinra experienced a mild local reaction at the site of injection, not requiring the withdrawal of the drug; in 1 patient the reaction was severe and required the discontinuation of the treatment and subsequent desensitization, with success.[12] Two patients complained of an increased frequency of infections (none severe) and 1 of dizziness and nausea; none of these patients discontinued the treatment owing to the side effects. One patient showed a transient increase of transaminases and creatinine-kinase, requiring the withdrawal of the drug; owing to a flare of the disease, anakinra was subsequently restarted without side effects.

Discussion

In this study we have observed that most of pediatric patients with recurrent pericarditis treated with conventional treatment, before the use of IL-1 blockers, were undertreated. In particular, this phenomenon was observed for NSAIDs, especially ibuprofen, the most commonly used drug, and for colchicine, indicating the need to consider an adequate dosage of NSAIDs and colchicine in children, before judging the drugs as ineffective.

An opposite trend was observed for steroid treatment. Indeed, even high doses of steroids were not able to achieve a complete control of the flares of pericarditis in 33% of treated patients; moreover, 94% of the treated patients presented a steroid dependence. This observation supports the concept to reconsider the role of steroids in pediatric recurrent pericarditis. So far, data on IL-1 blockers were obtained in steroid-dependent and colchicine-resistant children. However, the early use of IL-1 blockers in patients resistant to adequate dosage of NSAIDs and colchicine, without a course of steroids, could lead to more rapid and effective control of the diseases, avoiding severe side effects. Indeed, this was the case for 10 patients enrolled in the present study, who showed a prompt response to IL-1 blockers without the previous use of steroids.

In line with previous studies, conducted in smaller series of patients, anakinra was confirmed as an effective treatment in controlling the disease flares with a daily administration.[6,8,9] Moreover, in most patients anakinra was able to maintain remission despite the withdrawal of steroids. Colchicine was maintained or introduced during anakinra tapering in 19 patients. However, it was not associated with a lower risk of relapse during the tapering of the drug or after discontinuation (data not shown). This outcome may be related to the small number of patients in the cohort and the prolonged treatment with first- and second-line drugs before the beginning of treatment with anakinra.

This study provides more evidence on the role of canakinumab as a possible alternative anti-IL-1 treatment in recurrent pericarditis. In pediatric patients, a case of a child with idiopathic recurrent pericarditis with an anaphylactic reaction to anakinra was recently described. In this case, high doses (5 mg/kg monthly) of canakinumab were able to maintain clinical remission in association with colchicine; however, in 2 other cases this drug was not able to control disease activity.[13,14]

Taken together, those data may support the relevance of IL-1α in the induction and maintenance of the inflammatory response at the tissue level in recurrent pericarditis.[15] In the first national survey,[7] a number of patients treated with anakinra displayed a flare of the disease during treatment tapering or withdrawal. These findings differ from what was observed in the registry of adult patients with recurrent pericarditis treated with anakinra, in which 60% of patients could withdraw treatment with anakinra after 6 months and 74% of them were free from recurrence after 18 months from discontinuation.[16] Of note, in our cohort of patients, the only variable associated with the probability of drug-free remission, identified through the multivariate analysis, was the shorter duration of treatment with anakinra. It is difficult to state if this observation could reflect a possible change in homeostasis or the pericardial membrane or it is only related to the variability of the cohort included in the study. Of note, the mean duration of treatment to achieve the drug-free remission in our cohort of patients was 1.82 years, which is much longer than what was observed in the adults.[16] Unfortunately, the multivariate analysis was not able to identify other predictive variables associated with the possibility to withdraw anakinra without a relapse in our cohort of patients. This is likely due to the limitations related to the study: wide variability of the cohort included in the present study in terms of age and year at presentation, disease duration, previous treatment, steroid usage, duration of daily anakinra administration, modality of its tapering, and concomitant treatment. This study is multicenter and retrospective; moreover many patients had their disease onset before the availability of proper guidelines for this disease. Only a proper longitudinal study performed in a homogeneous group of patients from disease onset, using a common approach to assess disease activity, could address the best possible strategy to decrease the frequency of disease flare at anakinra withdrawal.

Anakinra has been demonstrated as effective, by a randomized trial, in patients with colchicine-resistant and steroid-dependent recurrent pericarditis.[9] Only a randomized trial in pediatric patients with recurrent pericarditis not responsive to NSAIDS and colchicine, could demonstrate that anakinra is more effective than steroids. Longitudinal studies should provide evidence on the best possible approach to prevent disease relapses during anakinra tapering or withdrawal. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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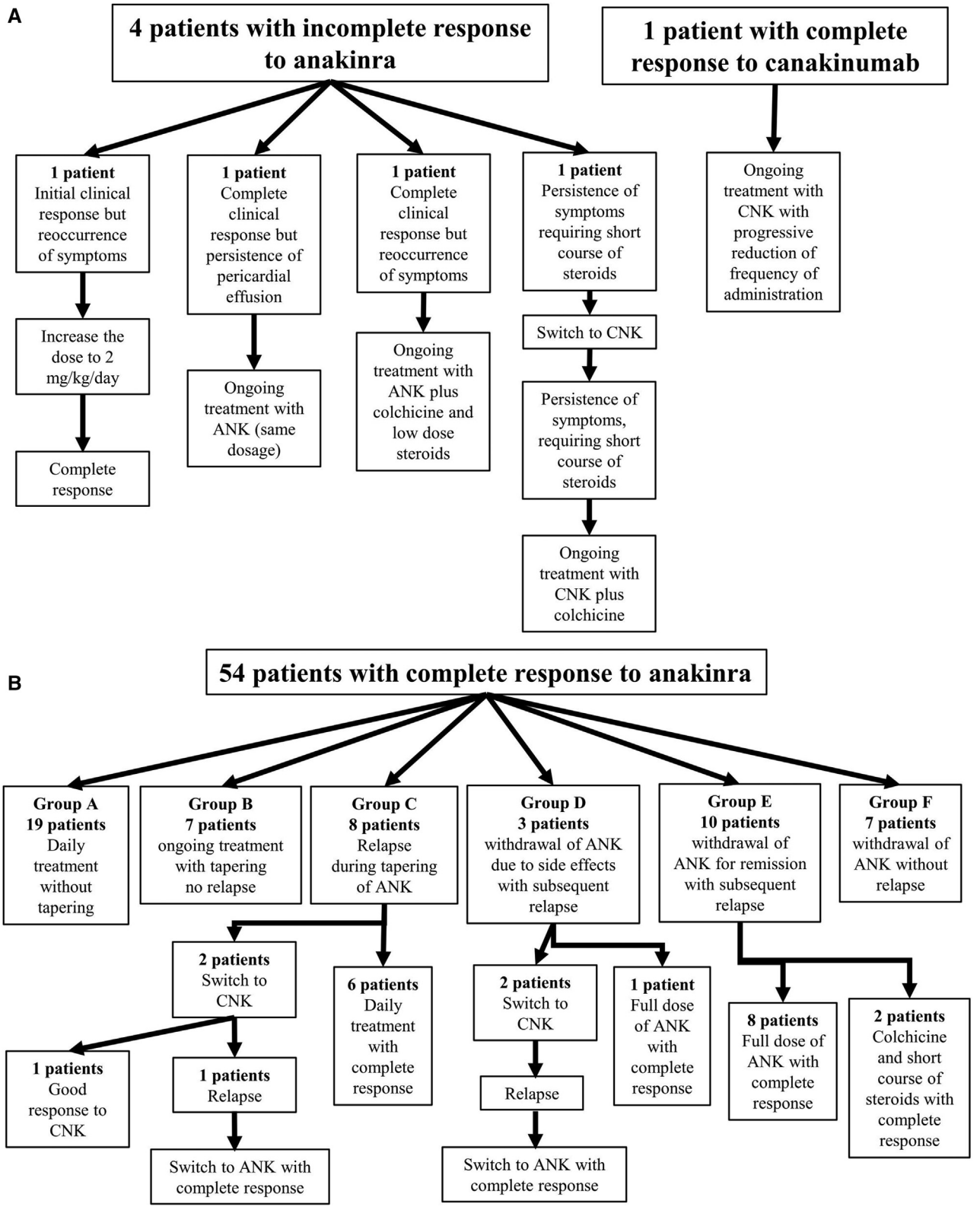

Figure 3. Outcome of the 58 patients included in the study. **A**, Outcome of patients without a complete response to anakinra (ANK) and of the patient treated with canakinumab (CNK) with complete response. **B**, Outcome of the 54 patients who displayed a complete response to anakinra.

Table I. Detailed demographic data and treatment with IL-1 blockers of the patients included in the study

Patient	Sex	Idiopathic/ postsurgery pericarditis	Concomitant disease	Genetic screening for AID (mutation possibly detected)	Age at disease onset (years)	No. of relapses/ year before first IL-1 blocker	Age at beginning of treatment with IL-1 blocker	IL-1 blocker	IL-1 blocker at last follow-up	Other drugs at last follow-up
1	Male	Idiopathic	–	*MEFV*	14.11	2.5	15.61	ANK	ANK 1.3 mg/kg/day	Colchicine
2	Male	Idiopathic	Mhyre syndrome	–	5.66	5	6.24	ANK	ANK 1 mg/kg 2 days a week	
3	Female	Idiopathic	–	*MEFV, TNFRSF1A*	13.45	3	16.75	ANK	ANK 1.8 mg/kg 2 days a week	
4	Male	Idiopathic	–	*MEFV, TNFRSF1A*	11.62	5	12.59	ANK	ANK 1.3 mg/kg 3 days a week	
5	Male	Idiopathic	–	–	9.48	1	9.56	ANK	none	
6	Male	Idiopathic	–	*TNFRSF1A*	6.32	0.75	10.40	ANK	ANK 2 mg/kg every other day	
7	Male	Idiopathic	–	–	12.20	3	12.62	ANK	None	
8	Female	Idiopathic	Melas syndrome	–	10.59	3	10.89	ANK	ANA 2.5 mg/kg 5 days a week	
9	Female	Idiopathic	–	*MEFV, TNFRSF1A*	13.88	2	14.55	ANK	None	
10	Male	Idiopathic	–	*MEFV, TNFRSF1A*	14.44	1	14.47	ANK	None	
11	Female	Idiopathic	–	–	13.06	2	13.35	ANK	ANK 2 mg/kg/day	
12	Male	Idiopathic	–	*TNFRSF1A*	15.37	3	16.23	ANK	ANK 1.3 mg/kg every other day	Colchicine
13	Male	Postsurgery	–	*MEFV, TNFRSF1A, MVK, NLRP3, NLRP12*	10.21	3	11.55	ANK	ANK 1.2 mg/kg/day	Colchicine
14	Male	Idiopathic	–	*MEFV*	13.90	3	14.23	ANK → CNK → ANK	ANK 1.2 mg/kg 2 days a week	
15	Male	Idiopathic	–	–	13.55	3	13.83	ANK	ANK 2 mg/kg/day	Colchicine
16	Female	Idiopathic	–	*MEFV, TNFRSF1A, MVK, NLRP3*	15.91	1	16.58	ANK	ANK 2.2 mg/kg/day	
17	Female	Postsurgery	–	*MEFV, TNFRSF1A, MVK, NLRP3*	6.18	3	6.88	ANK → CNK → ANK	ANK 1.7 mg/kg/day	
18	Male	Idiopathic	–	*MEFV*	10.16	2	12.15	ANK	ANK 1.7 mg/kg/day	Colchicine
19	Female	Idiopathic	–	*MEFV, TNFRSF1A*	13.86	3	14.32	ANK	ANK 1.8 mg/kg 6 days a week	Colchicine
20	Male	Idiopathic	–	*MEFV* (I591T), *TNFRSF1A*	8.73	1.7	9.06	ANK	ANK 2 mg/kg 3 days a week	
21	Male	Idiopathic	–	*MEFV, TNFRSF1A*	14.85	3	15.62	ANK	ANK 1.1 mg/kg/day	
22	Female	Idiopathic	–	*MEFV, TNFRSF1A, MVK, NLRP3*	12.02	4	12.97	ANK	ANK 1.5 mg/kg/day	Colchicine
23	Male	Idiopathic	–	*MEFV, TNFRSF1A*	13.49	5	13.86	ANK	ANK 1.25 mg/kg 3 days a week	Colchicine
24	Male	Idiopathic	–	*MEFV, TNFRSF1A, MVK,NLRP3*	7.72	0.75	11.38	ANK	ANK 1 mg/kg/day	
25	Male	Idiopathic	–	*MEFV, TNFRSF1A, MVK*	6.98	4	8.07	ANK	ANK 1.5 mg/kg every other day	Colchicine
26	Female	Idiopathic	–	–	9.45	1	9.56	ANK → CNK → ANK	ANK 1.7 mg/kg/day	
27	Male	Postsurgery	–	*MEFV, TNFRSF1A, MVK, NLRP3*	13.05	3	13.58	ANK	ANK 1.2 mg/kg/day	

(*continued*)

Table I. Continued

Patient	Sex	Idiopathic/ postsurgery pericarditis	Concomitant disease	Genetic screening for AID (mutation possibly detected)	Age at disease onset (years)	No. of relapses/ year before first IL-1 blocker	Age at beginning of treatment with IL-1 blocker	IL-1 blocker	IL-1 blocker at last follow-up	Other drugs at last follow-up
28	Male	Idiopathic	–	*MEFV* (E148Q), *TNFRSF1A*	15.87	2.17	18.28	ANK	ANK 2 mg/kg 5 days a week	
29	Male	Idiopathic	Rett syndrome	*TNFRSF1A*	12.80	3	13.64	ANK	None	
30	Male	Idiopathic	–	*MEFV, TNFRSF1A, MVK, NLRP3*	13.06	4	15.47	ANK	ANK 1.8 mg/kg 4 days a week	Colchicine
31	Male	Postsurgery	Arrhythmogenic dysplasia	–	13.11	0.35	25.44	ANK	ANK 1.3 mg/kg/day	Steroids and colchicine
32	Male	Idiopathic	–	*MEFV, TNFRSF1A, MVK, NLRP3, NLRP12*	16.64	8	17.44	ANK	ANK 1.67 mg/kg/day	Colchicine
33	Male	Idiopathic	Multiorgan syndrome (de novo deletion in 16p11.2)	–	12.06	3	12.22	ANK	ANK 1.6 mg/kg/day	
34	Female	Idiopathic	–	–	11.11	1	11.12	ANK	ANK 2.2 mg/kg/day	Colchicine
35	Female	Idiopathic	–	–	11.71	4	12.38	ANK	ANK 1.5 mg/kg/day	Colchicine
36	Male	Idiopathic	–	–	13.78	2	13.85	ANK	ANK 2 mg/kg/day	
37	Male	Idiopathic	Sotos syndrome	–	13.73	3	14.21	ANK	None	
38	Male	Idiopathic	–	–	8.75	3	8.81	ANK	ANK 2 mg/kg/day	
39	Male	Idiopathic	–	–	11.82	2	11.93	ANK	ANK 1.5 mg/kg/day	
40	Male	Idiopathic	–	–	16.00	4	16.65	ANK	None	
41	Male	Idiopathic	–	–	15.10	2	15.38	ANK	ANK 1.7 mg/kg/day	Colchicine
42	Male	Idiopathic	–	–	12.56	4	12.81	ANK	ANK 1.2 mg/kg/day	
43	Female	Idiopathic	–	–	17.95	3	24.03	ANK	None	
44	Female	Idiopathic	–	–	17.15	4	18.28	ANK	ANK 1.7 mg/kg/day	
45	Female	Idiopathic	–	–	12.38	2	12.42	ANK	ANK 2 mg/kg 2 days a week	
46	Male	Idiopathic	–	–	6.92	4	7.16	ANK	ANK 2.3 mg/kg/day	
47	Male	Idiopathic	–	*MEFV*	11.80	2	15.77	ANK	None	
48	Female	Idiopathic	–	–	11.55	0.5	16.98	ANK	ANK 1.4 mg/kg every other day	
49	Male	Idiopathic	–	–	5.80	2	6.00	ANK	ANK 2.8 mg/kg/day	Colchicine
50	Female	Idiopathic	–	–	12.42	2	12.69	ANK	ANK 1.2 mg/kg every other day	
51	Female	Idiopathic	–	–	13.48	3	13.72	ANK	ANK 2.3 mg/kg/day	Colchicine
52	Male	Idiopathic	–	–	12.58	3	12.88	ANK	ANK 1.5 mg/kg every other day	
53	Female	Idiopathic	–	*MEFV*	11.60	4	11.84	ANK	ANK 2 mg/kg/day	
54	Male	Idiopathic	–	*MEFV, TNFRSF1A, MVK, NLRP3, NLRP12*	13.99	4	14.21	ANK	ANK 2.2 mg/kg every other day	Steroids
55	Male	Idiopathic	–	*MEFV, TNFRSF1A, MVK*	12.50	3	12.79	ANK	ANK 2 mg/kg/day	NSAIDS and colchicine
56	Female	Idiopathic	–	*TNFRSF1A, MVK*	4.48	1	11.56	ANK → CNK	CNK 2.5 mg/kg every 10 weeks	
57	Female	Idiopathic	–	–	13.60	4	14.07	ANK → CNK	CNK 2.6 mg/kg every 4 weeks	Colchicine
58	Female	Idiopathic	–	*MEFV, TNFRSF1A* (R92Q), *MVK, NLRP3*	16.24	0.65	24.09	CNK	CNK 2.5 mg/kg every 8 weeks	

AID, autoinflammatory diseases; *ANK*, anakinra; *CNK*, canakinumab.

Table III. Clinical outcome, response to treatment, side effects, duration of treatment and attempts to reduce/withdraw treatment of the 47 patients treated with anakinra

Patient	Duration of steroidal treatment (months)	Time between disease onset and anti-IL-1 treatment (years)	No. of relapses before treatment with anakinra	Initial dosage (mg/kg/day)	Response to treatment	Side effects	Duration of daily treatment (years)	No. of attempts of tapering/ withdrawal	Relapses after tapering/ withdrawal	Total duration of treatment with anakinra (years)	Anakinra at last follow-up
1	18	1.50	4	1.3	Complete	None	1.03 (ongoing)	–	–	1.03	1.3 mg/kg/day
2	–	0.58	5	3.3	Complete	None	1.00	2	1	1.05	1 mg/kg 2 days a week
3	6	3.30	10	1.2	Complete	None	0.04	9	8	10.92	1.8 mg/kg 2 days a week
4	4	0.97	5	1.3	Complete	None	0.50	7	6	7.30	1.3 mg/kg 3 days a week
5	–	0.08	1	2	Complete	None	0.77	1	3	1.96	No
6	6	4.08	2	2	Complete	None	0.69	1	0	1.25	2 mg/kg every other day
7	2	0.42	3	1.2	Complete	None	0.30	3	2	2.46	No
8	4	0.30	3	2.5	Complete	None	0.13	1	0	0.14	2.5 mg/kg 5 days a week
9	1	0.67	3	1.3	Complete	None	0.02	2	1	2.66	No
10	–	0.03	1	1.6	Complete	None	0.59	1	0	1.42	No
11	4	0.29	2	2	Complete	None	0.22 (ongoing)	–	–	0.22	2 mg/kg/day
12	40	0.86	3	1	Complete	Mild local reaction	0.73	3	2	3.02	1.3 mg/kg every other day
13	2	1.34	4	1.5	Complete	None	0.30 (ongoing)	–	–	0.30	1.2 mg/kg/day
14	3	0.33	3	1.2	Complete	None	0.2	9	8	9.87	1.2 mg/kg 2 days a week
15	6	0.28	1	2	Complete	None	0.27 (ongoing)	–	–	0.27	2 mg/kg/day
16	9	0.66	2	2.2	Complete	Mild local reaction, upper airway infections	1.03 (ongoing)	–	–	1.03	2.2 mg/kg/day
17	9	0.70	3	1.4	Complete	Severe local reaction	0.05	1	1	0.91	1.7 mg/kg/day
18	24	1.99	4	2	Complete	None	0.13 (ongoing)	–	–	0.13	1.7 mg/kg/day
19	7	0.46	3	2	Complete	None	0.16	1	0	0.37	1.8 mg/kg 6 days a week
20	10	0.33	4	2	Complete	None	1.01	2	1	2.10	2 mg/kg 3 days a week
21	14	0.77	3	1.1	Complete	None	0.37	1	1	2.16	1.1 mg/kg/day
22	15	0.95	4	1.5	Complete	None	0.59 (ongoing)	–	–	0.59	1.5 mg/kg/day
23	2	0.37	5	1.4	Complete	Mild local reaction	1.06	3	2	4.20	1.2 mg/kg 3 days a week
24	41	3.66	3	1	Complete	None	0.53 (ongoing)	–	–	0.53	1 mg/kg/day
25	9	1.09	4	1.5	Complete	None	0.28	1	0	0.32	1.5 mg/kg every other day

(*continued*)

Table III. Continued

Patient	Duration of steroidal treatment (months)	Time between disease onset and anti-IL-1 treatment (years)	No. of relapses before treatment with anakinra	Initial dosage (mg/kg/day)	Response to treatment	Side effects	Duration of daily treatment (years)	No. of attempts of tapering/ withdrawal	Relapses after tapering/ withdrawal	Total duration of treatment with anakinra (years)	Anakinra at last follow-up
26	0.5	0.12	1	1	Complete	None	0.13	1	1	1.38	1.7 mg/kg/day
27	12	0.53	3	1.2	Complete	None	0.40 (ongoing)	–	–	0.40	1.2 mg/kg/day
28	5	2.41	5	1 → 2	Partial → complete	None	0.80	6	5	0.62	2 mg/kg 5 days a week
29	12	0.84	3	1	Complete	None	0.52	1	0	0.61	No
30	21	2.41	8	1.8	Complete	None	0.38	1	0	1.46	1.8 mg/kg 4 days a week
31	48	12.34	4	1.3	Partial	Airway infections	0.46 (ongoing)	–	–	0.46	1.3 mg/kg/day
32	5	0.80	8	1.7	Complete	None	0.32 (ongoing)	–	–	0.32	1.7 mg/kg/day
33	2	0.16	3	1.6	Partial	Mild local reaction	0.50 (ongoing)	–	–	0.50	1.6 mg/kg/day
34	6	0.01	1	2.2	Complete	None	0.50 (ongoing)	–	–	0.50	2.2 mg/kg/day
35	2	0.68	4	1.5	Complete	None	0.52 (ongoing)	–	–	0.52	1.5 mg/kg/day
36	–	0.07	2	2.3	Complete	None	1.29 (ongoing)	–	–	1.29	2 mg/kg/day
37	18	0.48	3	1	Complete	None	0.94	1	0	1.30	No
38	–	0.06	3	2.4	Complete	None	1.11	2	2	4.12	2 mg/kg/day
39	–	0.12	2	2.2	Complete	None	1.28 (ongoing)	–	–	1.28	1.5 mg/kg/day
40	3	0.65	4	1	Complete	None	0.99	1	3	1.79	No
41	10	0.28	2	1.7	Complete	None	0.79 (ongoing)	–	–	0.79	1.7 mg/kg/day
42	1.5	0.25	4	1.2	Complete	Increase of creatinine kinase and transaminase	1.18	2	2	3.36	1.2 mg/kg/day
43	8.25	1.08	3	1.7	Complete	None	1.01	1	0	1.81	No
44	0.5	1.13	4	1.4	Complete	None	1.88	1	1	3.49	1.7 mg/kg/day
45	0.01	0.04	2	2.1	Complete	None	1.26	3	2	5.20	2 mg/kg 2 days a week
46	1	0.24	4	3.1	Complete	None	0.35	1	1	2.25	2.3 mg/kg/day
47	NK	3.97	8	1.2	Complete	None	1.40	1	0	2.28	No
48	–	5.42	3	1.4	Complete	Mild local reaction. nausea. dizziness	1.29	1	0	1.68	1.4 mg/kg every other day
49	5	0.20	2	2.8	Complete	None	0.24 (ongoing)	–	–	0.24	2.8 mg/kg/day
50	–	0.28	2	1.4	Complete	None	1.36	3	2	5.84	1.2 mg/kg every other day
51	8	0.24	3	2.4	Complete	None	0.56 (ongoing)	–	–	0.56	2.3 mg/kg/day
52	0.25	0.30	3	1	Complete	None	1.33	7	6	9.72	1.5 mg/kg every other day
53	3	0.24	4	2	Complete	Mild local reaction	0.08 (ongoing)	–	–	0.08	2 mg/kg/day
54	2	0.22	4	2.2	Complete	Urticarial rash	0.15	1	0	0.43	2.2 mg/kg every other day

(*continued*)

Table III. Continued

Patient	Duration of steroidal treatment (months)	Time between disease onset and anti-IL-1 treatment (years)	No. of relapses before treatment with anakinra	Initial dosage (mg/kg/day)	Response to treatment	Side effects	Duration of daily treatment (years)	No. of attempts of tapering/ withdrawal	Relapses after tapering/ withdrawal	Total duration of treatment with anakinra (years)	Anakinra at last follow-up
55	3	0.30	3	2	Complete	None	0.18 (ongoing)	–	–	0.18	2 mg/kg/day
56	–	7.08	4	2	Complete	None	1.42	4	3	7.03	No
57	2	0.47	4	2.1	Partial	Mild local reaction	0.25	1	1	3.14	No

Table IV. Comparison between the 9 patients that had withdrawn all treatments with the 19 in which the withdrawal of treatment was not possible, owing to relapses of the disease

Characteristics	Patients in treatment with anakinra	Patients off therapy	*P* value
No. of patients	**19**	**9**	
Duration of steroidal treatment (months)	10.03 ± 8.54 (n = 16)	9.66 ± 5.54 (n = 8)	.667
No. of relapses before anakinra	3.84 ± 1.86	3.22 ± 2.05	.210
Distance between disease onset and initiation of anakinra (years)	0.37 (0.25-0.97)	0.48 (0.08-0.84)	.768
Duration of treatment with daily anakinra (years)	1.0 (0.62-1.26) (n = 18)	0.94 (0.59-0.99)	.328
Initial dosage (mg/kg/day)	1.40 (1.10-2.00)	1.20 (1.0-1.60)	.357
Duration of follow-up from disease onset to withdrawal of anakinra (years)	4.39 (2.49-8.28)	2.56 (1.78-2.89)	.039*
Duration of treatment with anakinra (years)	3.49 (2.10-7.02)	1.91 (1.42-2.28)	.027*
Duration (years) of follow-up (disease onset – last visit)	4.39 (3.02-8.28)	4.84 (2.65-6.13)	.922
C reactive protein at the beginning of treatment with anakinra	6.55 (4.80-14.90) (n = 18)	13.35 (10.14-26.90)	.105
Days to achieve complete response to treatment with anakinra	5.00 (3.00-7.00) (n = 17)	7.00 (5.00-8.00) (n = 7)	.405
Presence of disease related symptoms at the beginning of treatment with anakinra	16 (84.21)	7 (77.78)	1.00*
Presence of pericardial effusion at the beginning of treatment with anakinra	13/18 (72.22)	6/8 (75.00)	1.00*
Tapering modality			1.00*
Progressive reduction of number of injection	4 (21.05)	2 (22.22)	
Administration every other day	13 (68.42)	7 (77.78)	
Withdrawal without tapering	2 (10.53)	0 (0.00)	

Values are mean ± SD, median (IQR), or number (%).
The *t* test or Mann-Whitney test was used depending on the variables' distribution.
*Fisher exact test. In bold: statistically significant values.

Table V. Bivariate logistic regression analysis between the 9 patients that had withdrawn all treatments and the 19 in which the withdrawal of treatment was not possible owing to the occurrence of relapses

Characteristics	OR (95% CI)	*P* value
Duration of steroidal treatment (months)	0.82 (0.49-1.35)	.425
No. of relapses before anakinra	0.80 (0.45-1.45)	.470
Distance between disease onset and initiation of anakinra	0.90 (0.50-1.61)	.721
Duration of treatment with daily anakinra (years)	0.36 (0.05-2.56)	.310
Initial dosage (mg/kg/day)	0.38 (0.07-2.22)	.284
Duration of follow-up from disease onset to withdrawal of anakinra (years)	0.66 (0.4-1.08)	.101
Duration of treatment with anakinra (years)	0.53 (0.27-1.04)	.066*
Duration of follow-up (disease onset – last visit) (years)	0.98 (0.79-1.21)	.83
C reactive protein at the beginning of treatment with anakinra	1.10 (0.99-1.22)	.067
Days to achieve complete response to treatment with anakinra	0.99 (0.87-1.12)	.883
Presence of disease related symptoms at the beginning of treatment with anakinra	0.66 (0.09-4.84)	.679
Presence of pericardial effusion at the beginning of treatment with anakinra	1.15 (0.17-7.74)	.883

*Statistically significant values.

Table VI. Response to treatment, number of relapses in anakinra (ANK) and canakinumab (CNK) in the 6 patients treated with canakinumab

Patient	No. of relapses before treatment with IL-1 blockers	Response to treatment ANK	No. of relapses in daily ANK	No. of relapses after tapering/ withdrawal ANK	Duration of treatment ANK (years)	Side effects ANK	Reason of switch from ANK to CNK	Disease activity at the beginning of treatment with CNK	Initial dosage of CNK (mg/kg every 4 weeks)	Response to treatment CNK	No. of relapses at full dose CNK	No. of relapses after tapering/ withdrawal CNK	Duration of treatment CNK (years)	Side effects CNK	Treatment at last follow-up
14	3	Complete	0	8	9.5	None	Prolonged treatment with ANK	Active	1.8	Inadequate	2	–	0.1	None	ANK 1.2 mg/kg 2 days a week
17	3	Complete	0	1	0.04	Severe local reaction	Side effects	Active	2.1	Inadequate	4	–	1.6	None	ANK 1.7 mg/kg/ day
26	1	Complete	0	1	0.1	None	Poor compliance	Active	4.0	Inadequate	1	–	0.1	None	ANK 1.7 mg/kg/ day
56	4	Complete	0	3	7.0	None	Prolonged treatment with ANK	Inactive	2.5	Complete	0	0	2.2	None	CNK 2.5 mg/kg every 10 weeks
57	4	Partial	1	1	0.2	Mild local reaction	Partial response to ANK	Inactive	2.6	Partial	1	1	0.3	None	CNK 2.6 mg/kg every 4 weeks plus colchicine
58	5	–	–	–		–	–	Active	2.5	Complete	0	0	4.3	None	CNK 2.5 mg/kg every 8 weeks