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Anakinra in idiopathic recurrent pericarditis refractory to immunosuppressive therapy; a preliminary experience in seven patients

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A B S T R A C T

Background: Approximately 5% of idiopathic recurrent pericarditis (IRP) patients are refractory or intolerant to NSAIDs, Colchicine and corticosteroids. The empiric treatment approach for these patients includes immunosuppression with Azathioprine (AZA) or immunomodulation with intravenous human immunoglobulin (IVIG). We assessed the efficacy and safety of long-term Anakinra treatment in refractory IRP patients after failure of prior immunosuppressive therapy and/or failure of IVIG.

Methods: Clinical data of seven IRP patients were retrospectively analyzed. Treatment efficacy was determined by decrease of IRP recurrence and by the ability to withdraw or taper corticosteroids without a relapse. Safety was assessed by the occurrence of adverse events.

Results: 7 IRP patients (4 male, median age 41) with a median disease duration of 4 years (range: 1.25–9 years) were treated with Anakinra (median treatment duration: 20 months). All patients were resistant or intolerant to NSAIDs, Prednisone, Colchicine and at least one immunosuppressive or immunomodulatory drug such as AZA, Methotrexate, Plaquenil, or IVIG. The median number of recurrences before Anakinra was 6 (range: 4–7) and all patients were corticosteroid-dependent and had steroid-related side effects. After initiation of Anakinra, none of the patients had IRP relapse. Prednisone was tapered down to 5 mg/day or less in all patients. Four patients discontinued prednisone altogether. No significant adverse effects have occurred as a result of Anakinra treatment and all patients continued treatment after the study period.

Conclusion: Long-term Anakinra is a rapid-acting, efficient and safe steroid sparing agent even for patients with IRP refractory to previous immunosuppressive and/or immunomodulatory agents.

1. Introduction

Recurrent pericarditis is one of the main complications of acute pericarditis that affects approximately 20–50% of all patients with acute pericarditis [1]. It usually occurs after the first episode of acute pericarditis with a symptom-free interval of 4–6 weeks. The specific etiology includes infectious, neoplastic, autoimmune, or autoinflammatory causes, but in 70% of the cases, the etiology remains unknown [2,3]. The pathogenesis of idiopathic recurrent pericarditis (IRP) is not fully understood. It may involve the autoinflammatory mechanisms of the innate immune system and the autoimmune mechanisms of the adaptive immune system, with an infectious cause as a trigger [4–9]. The autoimmune etiology of IRP is supported by the similarity between IRP and pericardial involvement in patients with autoimmune diseases [7]. Moreover, some patients with a diagnosis of IRP may be later diagnosed as having an autoimmune disease, especially Sjogren's syndrome or rheumatoid arthritis [8].

In addition, a subset of IRP patients exhibit antinuclear antibodies (ANA) and antibodies directed against specific cardiac antigens [10]. Furthermore, some IRP patients respond to glucocorticoids [4], immunosuppressive agents such as Azathioprine (AZA) [11], or immunomodulatory agents such as intravenous immunoglobulins (IVIG) [12]. However, the pathogenic role of autoantibodies in IRP has not been proven, and some patients have relapses despite immunosuppressive or immunomodulatory treatment. The role of the innate immune system in the pathogenesis of IRP may be supported by clinical and pathogenic similarity between IRP and FMF, a classical autoinflammatory disease [13–15]. Both diseases are characterized by acute recurrent episodes of sterile pericardial inflammation with elevated C-reactive protein (CRP) and erythrocyte sedimentation rate

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(ESR) that are often followed by symptom-free interval and complete normalization of inflammatory markers [14]. The therapeutic efficacy of Colchicine, an anti-inflammatory drug, for the treatment and prevention of pericarditis recurrence is similar to its efficacy in preventing attacks of FMF, and this provides further evidence for the autoinflammatory etiology of IRP [1,2,15]. Although Colchicine's main mechanism of action is blocking tubulin polymerization and disrupting tubulin fibers, it may also interfere with the NLRP3 inflammasome complex and modulate the innate immune system response by blocking Interleukin-1β (IL-1β) processing [16].

Anakinra, an IL-1 targeting agent, has been recently proposed as a valid treatment for autoinflammatory diseases such as FMF, cryopyrin-associated periodic syndrome (CAPS) and TNF-receptor associated periodic syndrome (TRAPS) [17–19]. Likewise, several studies, including a recent randomized controlled trial, showed that Anakinra is a potential therapeutic option for IRP [20–29]. In the present study we provide further evidence for the efficacy of long-term Anakinra in seven IRP patients who were corticosteroid-dependent and resistant to other therapies including Colchicine and different immunosuppressive agents.

2. Methods

In this retrospective study, we analyzed medical records of 7 patients with refractory IRP who received Anakinra after failure of previous treatment regimens. IRP was diagnosed based on a history of acute pericarditis (according to the currently accepted diagnostic criteria [1]) that was followed by recurrence of pericarditis despite appropriate treatment. The diagnosis of the first episode of pericarditis was based on the fulfillment of at least 2 of the following criteria: 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, or new or worsening pericardial effusion [1]. All patients underwent comprehensive evaluation, including microbiologic and immunologic tests, chest x-ray, electrocardiography, echocardiography, and whole body CT, in order to rule out infectious, autoimmune, paraneoplastic and metabolic reasons for pericarditis. Patients with secondary pericarditis were excluded.

All enrolled patients underwent cardiac magnetic resonance imaging (MRI) before administration of Anakinra or during the first month after its initiation. The level of CRP before initiation of Anakinra and at the last follow up were obtained from medical records. The previous failed treatment regimen in all patients included long-term corticosteroids, Colchicine and at least one immunosuppressive agent. While immunosuppressive drugs and IVIG were discontinued shortly before the commencement of Anakinra, corticosteroids and Colchicine were subsequently tapered in parallel with Anakinra treatment. All patients have signed an informed consent form prior to enrollment in the study.

3. Results

Our study included 7 patients (4 male, 3 female) with refractory IRP who received treatment with Anakinra in the Sheba medical center and in the Assuta Ashdod medical center during 2016–2018. Demographic and clinical characteristics are summarized in Table 1. The median age was 41 years (range 25–75 years). The median disease duration was 4 years (range: 1.5–9 years) and the median number of IRP relapses before Anakinra was 6 (range: 4–7).

None of the 7 patients exhibited positive ANA or had FMF mutations. All patients had pericardial effusion according to contrast chest CT and Echocardiography. Chest CT also revealed pericardial thickening in 2 patients and pleural effusion in 3 patients. Cardiac MRI revealed pericardial late gadolinium enhancement in 6 patients, and in the remaining patient, large pericardial effusion was observed. No constrictive pattern was seen in any of the patients.

Prior to treatment with Anakinra, all patients were unsuccessfully treated with NSAIDs, Colchicine, and Prednisone. Additional treatment consisted of immunosuppressive drugs, including AZA (6 patients, 86%), Methotrexate (2 patients, 29%) and Hydroxychloroquine (1 patient, 14%), as well as IVIG (2 patients, 29%). The two patients who didn't respond adequately to IVIG were also refractory to AZA, and one of them was also unsuccessfully treated with two additional immunosuppressive drugs. The median duration of the failed therapy was 18 months (range: 6–103 months). All patients were corticosteroid-dependent with a least 3 relapses after attempted drug tapering. The maximal dosage of Prednisone given before treatment with Anakinra varied from 20 mg to 80 mg per day (median: 60 mg per day). In addition, all of them had steroid-related side effects, including weight gain (7 patients, 100%), cushingoid appearance (3 patients, 43%), hirsutism (1 patients, 14%) change in behavior (3 patients, 43%), acne (1 patients, 14%) and gynecomastia (1 patients, 14%).

The median duration of Anakinra treatment was 20 months (range: 5–34 months) at the end of the follow-up period, and none of the patients had IRP recurrence. The initial dosage of Anakinra was 100 mg/day in all patients, and in one patient the dosage was successfully reduced to 100 mg/every other day. At the end of the follow up period, Anakinra was given as monotherapy in two patients. All patients had a rapid response to Anakinra treatment within a few days. In 4 patients, after starting treatment with Anakinra, Prednisone was gradually discontinued during the first year of treatment. In 2 other patients still receiving Prednisone, the dosage was gradually reduced to a low dose of < 5 mg/day. In one patient, Prednisone was continued at a dosage of 5 mg/day due to adrenal insufficiency, despite the gradual tapering of the drug.

Colchicine treatment was discontinued in 3 patients, while the other 4 patients continued being treated at dosages of 0.5–1 mg/day. Before treatment with Anakinra, CRP levels were significantly elevated in all patients (median: 10.5 mg/dL, range: 9–26.5 mg/dL, normal: < 0.5 mg/dL). Following this treatment, at the last visit of the follow-up period, CRP levels have normalized in 6 patients and significantly decreased by 91% from pre-treatment levels in the remaining patient. No significant adverse effects have occurred as a result of Anakinra treatment. In two patients, a local reaction at the injection site that disappeared after 1 month was observed. One patient developed shingles 18 months following the initiation of Anakinra (Figs. 1 and 2).

4. Discussion

We report a series of 7 patients with refractory steroid-dependent IRP which were successfully treated with Anakinra for approximately 20 months. Prior to Anakinra treatment, these patients were refractory to NSAIDs, Colchicine and at least one immunosuppressive agent, mainly AZA. In addition to immunosuppressive drugs, two patients were refractory to IVIG. Treatment with Anakinra was well tolerated and resulted in rapid clinical and laboratory response, with complete prevention of IRP recurrence in all enrolled patients, in contrast to a median of 6 episodes on the previous treatment regimen. This allowed to withdraw or taper Prednisone and Colchicine, as well as to avoid the use of additional immunosuppressive agents. In addition, this new treatment strategy resulted in a reduced economic burden that was associated with recurrent hospitalizations. To the best of our knowledge, this is a first case series of refractory IRP patients which were treated with Anakinra in our country.

According to the most recent guidelines from the European Society of Cardiology (ESC), Aspirin (ASA)/NSAIDs and Colchicine are recommended as the first line of IRP treatment, and corticosteroids and Colchicine may be used as the second line of treatment in patients who are resistant or intolerant to ASA/NSAIDs [1]. During the past two decades, substantial data has accumulated regarding the efficacy of Colchicine in the prevention of IRP recurrences [1,2,30–34]. The drug was first found to be safe and effective by several case series and

Table 1
Demographic and clinical characteristics of IRP patients treated with Anakinra.

	Disease duration (years)	Prior failed treatments[a]	Duration of Anakinra treatment (months)	Number of recurrences before and after Anakinra	Anakinra and background therapy	CRP before Anakinra treatment and at last visit (mg/dL)[c]
29 M	4	NSAIDs, Colchicine (2 mg/day), AZA[b], PRD (80 mg/day)	26	Before: 7 After: 0	Anakinra (100 mg/day), Colchicine (0.5 mg/day)	Before: 16 Last visit: Normal
35 F	1.5	NSAIDs, Colchicine (1.5 mg/day), AZA, PRD (40 mg/day)	12	Before: 4 After: 0	Anakinra (100 mg/day), Colchicine (0.5 mg/day)	Before: 9 Last visit: Normal
45 M	3	NSAIDs, Colchicine (2 mg/day), AZA, HCQ, MTX, IVIG, PRD (40 mg/day)	18	Before: 6 After: 0	Anakinra (100 mg/day), Colchicine (1 mg/day), PRD (1 mg every other day)	Before: 9 Last visit: 0.8
25 F	3.5	NSAIDs, Colchicine (2 mg/day), AZA, PRD (60 mg/day)	20	Before: 5 After: 0	Anakinra (100 mg/every other day)	Before: 16 Last visit: normal
43 M	4	NSAIDs, Colchicine (1.5 mg/day), MTX, PRD (60 mg/day)	34	Before: 5 After: 0	Anakinra (100 mg/day)	Before: 9.5 Last visit: normal
75 F	4	NSAIDs, Colchicine (1.5 mg/day), AZA, IVIG, PRD (40 mg/day)	32	Before: 6 After: 0	Anakinra (100 mg/day), PRD (5 mg/day)	Before: 26.5 Last visit: normal
41 M	9	NSAIDs, Colchicine (1.5 mg/day), AZA, PRD (60 mg/day)	5	Before: 7 After: 0	Anakinra (100 mg/day), Colchicine (1 mg/day), PRD (2.5 mg/day)	Before: 10.5 Last visit: normal

Abbreviations: NSAIDs - Nonsteroidal anti-inflammatory drugs, AZA - Azathioprine, PRD - Prednisone, HCQ - Hydroxychloroquine, MTX - Methotrexate, IVIG - Intravenous Immunoglobulin, CRP - C-reactive protein.
[a] With maximum dosage of Prednisone indicated.
[b] Azathioprine dosage was 2 mg/kg/day for all patients.
[c] Normal CRP level: < 0.5 mg/dL.

nonrandomized studies [30–32]. Thus, one of the early studies reported that Colchicine managed to prevent recurrences in 5 IRP patients and allowed to discontinue steroids within 2 to 6 months [31]. In 2004, based on this data and on experts' opinions, the ESC guidelines recommended the use of Colchicine for the treatment of IRP and for prevention of pericarditis recurrences [33]. More recently, several randomized and controlled clinical trials have demonstrated that the addition of Colchicine to conventional therapy with ASA or an NSAID might significantly decrease the recurrence rate in IRP [2,34].

Approximately 5% of IRP patients have refractory disease which is characterized by inability to achieve remission under the second line of treatment, the need for unacceptably high doses of corticosteroids or drug intolerance. Until the past decade, the empiric treatment options in refractory IRP were AZA, IVIG or other immunosuppressive drugs, but no optimal regimen for preventing recurrences has been established [11,12]. Thus, one retrospective single-center study investigating the efficacy of AZA in 46 IRP patients indicated that 59% of the study population achieved disease remission within 12 months, and 85% were able to discontinue corticosteroids within 4 to 12 months of AZA commencement. A different study that included 13 IRP patients

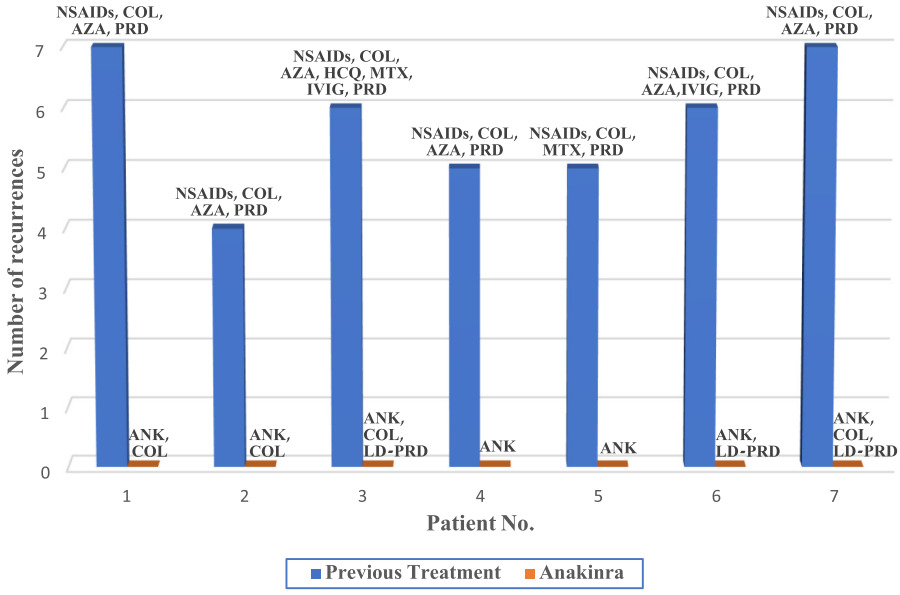

Fig. 1. Number of recurrences on different treatment regimens.
Abbreviations: NSAIDs - Nonsteroidal anti-inflammatory drugs, COL - Colchicine, AZA - Azathioprine, PRD - Prednisone, LD-PRD - Low dose Prednisone (< =5 mg/day), ANK - Anakinra, HCQ - Hydroxychloroquine, MTX – Methotrexate, IVIG - Intravenous Immunoglobulin.

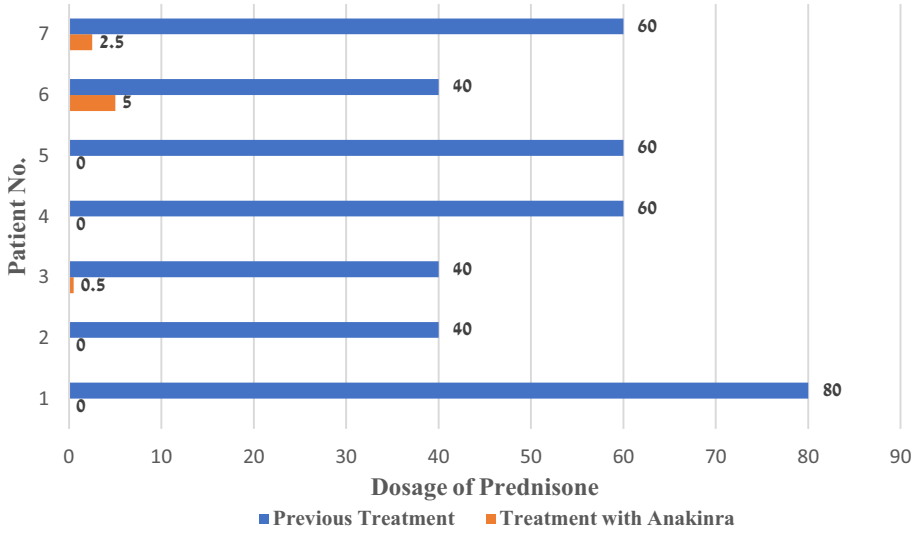

Fig. 2. Dosage of Prednisone on different treatment regimens.

reported that the frequency of pericarditis recurrences was significantly lower in patients treated with immunosuppressive agents (mainly AZA and Methotrexate), in comparison with patients treated with corticosteroids alone or treated with a combination of ASA/NSAIDs and colchicine [35]. This study also suggested that Methotrexate or Mycophenolate Mofetil could considered in patients with AZA contraindication or side effects. While AZA, Methotrexate or Mycophenolate Mofetil may serve as a steroid sparing agents, they are a slow-acting drug. In contrast, IVIG has a rapid onset of action and may be useful for acute episodes of IRP, in addition to its efficient steroid-sparing effect [11]. A systematic review that summarized 30 cases of IRP patients treated with IVIG indicated that 73% of them were recurrence-free after the initiation of treatment, and only 17% were still receiving corticosteroids at the end of the 33-month follow-up period [12].

The current ESC guidelines from 2015 state that Anakinra may be considered as an alternative therapeutic option to AZA or IVIG in patients with refractory IRP [1]. This recommendation was initially based on data derived from case reports and case series [20,24,25], but it was later supported by the first randomized, double-blind, placebo-controlled withdrawal trial of refractory IRP patients (AIRTRIP, 27). This study clearly demonstrated that Anakinra is a rapidly acting, steroid-sparing, and safe agent for refractory IRP patients with a clinical response at day 8 and corticosteroids discontinuation within 6 weeks.

Similarly to the AIRTRIP study, the majority of case series on refractory IRP patients had focused on patients which were successfully treated with Anakinra after failure of the second line of treatment (Colchicine and corticosteroids). To date, only a few case series included patients who had also failed immunosuppressive therapy, such as those included in the present report. For instance, one prospective study conducted on ten patients with refractory IRP included two AZA non-responders [24]. In a different case series, 7 out of 13 patients were resistant to previous treatments such as AZA, Hydroxychloroquine, Mycophenolate mofetil or Methotrexate [25]. In the present study, 6 patients had been ineffectively treated with Azathioprine and 2 patients were resistant to IVIG before receiving Anakinra therapy.

The efficacy of Anakinra in our IRP patients and in previous reports had raised the possibility that Anakinra could be considered as the first choice of treatment after failure of NSAIDs, Colchicine and corticosteroids in patients with severe IRP. In particular, this treatment may be appropriate in patients with clear inflammatory phenotype and significantly elevated CRP level as well as in patients with corticosteroid-related side effects. Anakinra may also be potentially used in patients who have contraindications to corticosteroids such as severe diabetes, osteoporotic fractures, recurrent infections, etc. [23].

In our study, all patients continued treatment with Anakinra without recurrence of pericarditis. Similarly, the AIRTRIP study reported recurrences in only 18% of the patients who were treated with Anakinra during a period of 8 months. In contrast, high rates of recurrences following the cessation of the drug were observed in the AIRTRIP study (90%) and in other case series [24,26,27]. In the majority of cases, these recurrences were successfully managed with Anakinra re-challenge but additional trials are required to determine the optimal protocol for treatment with Anakinra, including the required duration of treatment and the tapering of the drug. In addition, the role of Colchicine in the prevention of IRP recurrences following Anakinra discontinuation remains unknown and should be investigated.

In summary, our case series demonstrates that Anakinra is a rapid-acting, efficient and safe therapeutic option for corticosteroid-dependent patients with IRP refractory to conventional therapy and empiric immunosuppressive or immunomodulatory agents such as AZA and IVIG.

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