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Efficacy of Anakinra in Refractory Adult-Onset Still's Disease

Multicenter Study of 41 Patients and Literature Review

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Abstract: Adult-onset Still's disease (AOSD) is often refractory to standard therapy. Anakinra (ANK), an interleukin-1 receptor antagonist, has demonstrated efficacy in single cases and small series of AOSD. We assessed the efficacy of ANK in a series of AOSD patients.

Multicenter retrospective open-label study. ANK was used due to lack of efficacy to standard synthetic immunosuppressive drugs and in some cases also to at least 1 biologic agent.

Forty-one patients (26 women/15 men) were recruited. They had a mean age of 34.4 ± 14 years and a median [interquartile range (IQR)] AOSD duration of 3.5 [2–6] years before ANK onset. At that time the most common clinical features were joint manifestations 87.8%, fever 78%, and cutaneous rash 58.5%. ANK yielded rapid and maintained clinical and laboratory improvement. After 1 year of therapy, the frequency of joint and cutaneous manifestations had decreased to 41.5% and to 7.3% respectively, fever from 78% to 14.6%, anemia from 56.1% to 9.8%, and lymphadenopathy from 26.8% to 4.9%. A dramatic improvement of laboratory parameters was also achieved. The median [IQR] prednisone dose was also reduced from 20 [11.3–47.5] mg/day at ANK onset to 5 [0–10] at 12 months. After a median [IQR] follow-up of 16 [5–50] months, the most important side effects were cutaneous manifestations (n = 8), mild leukopenia (n = 3), myopathy (n = 1), and infections (n = 5).

ANK is associated with rapid and maintained clinical and laboratory improvement, even in nonresponders to other biologic agents. However, joint manifestations are more refractory than the systemic manifestations.

(*Medicine* 94(39):e1554)

Abbreviations: ACR = American College of Rheumatology, ANK = anakinra, AOSD = adult-onset still disease, CRP = c-reactive protein, DMARD = disease-modifying antirheumatic drugs, ESR = erythrocyte sedimentation rate, FDA = Food and Drug Administration, IFN-γ = interferon-γ, IL-1 = interleukin 1, IL-6 = interleukin-6, IL-18 = interleukin 18, IQR = interquartile range, NSAIDS = non-steroidal anti-inflammatory drugs, SD = standard deviation, TNF-α = tumor necrosis factor-α.

Adult-Onset Still's Disease (AOSD) is a systemic inflammatory disease of unknown origin characterized by daily high-spiking fevers, evanescent maculopapular rash, sore throat, arthritis and/or arthralgia, myalgia, serositis, lymphadenopathy, and hepatosplenomegaly. Laboratory evaluation typically demonstrates elevated acute-phase reactants, leukocytosis with neutrophil predominance, elevated levels of liver enzymes, and high levels of serum ferritin.[1,2]

Editor: Worawit Louthrenoo.
Received: July 8, 2015; revised: August 14, 2015; accepted: August 15, 2015.
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Presented (poster presentation) in part at the 2014 ACR/ARHP Annual Meeting in Boston, MA.
Dr MAG-G received grants/research supports from Abbott, MSD, and Roche, and had consultation fees/participation in company sponsored speaker?s bureau from Abbott, Pfizer, Roche, Janssen, Lilly, Bristol-Meiers, and MSD.
Dr RB received grants/research supports from Abbott, MSD, and Roche, and had consultation fees/participation in company sponsored speaker?s bureau from Abbott, Pfizer, Roche, Bristol-Meiers, Janssen, and MSD.
Dr FO-S received grants/research supports from Abbvie.
The remaining authors do not declare any financial disclosure.
This work was also partially supported by RETICS Programs, RD08/0075 (RIER), and RD12/0009/0013 from "Instituto de Salud Carlos III" (ISCIII) (Spain).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001554

AOSD is considered a complex autoinflammatory syndrome in which various environmental factors trigger an autoinflammatory systemic response in genetically predisposed individuals. Interleukin-1 (IL-1) appears to be implicated in AOSD pathogenesis as increased levels of this cytokine have been found in these patients compared to healthy controls.[3,4] Cytokine profile in AOSD sera is also characterized by the presence of interleukin-6 (IL-6), IL-18, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ).[5,6] Moreover, one of the major events in the pathogenesis of this syndrome seems to be a dysregulation of inflammasome complex and a related overproduction of active IL-1β promoted by IL-18.[7]

The central role of the inflammasome complex may explain the intermittent course of the disease and the clinical and laboratory features that are found in genetically predisposed autoinflammatory syndromes.

First-line treatment in AOSD has been classically based on nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. In an attempt to use the lowest possible dose of corticosteroids, other therapies, such as methotrexate, azathioprine, leflunomide, intravenous immunoglobulin, anti-TNF-α drugs, rituximab, or abatacept, are often given to achieve adequate control of the disease. However, the efficacy of these drugs is variable and they are not exempt from potential severe side effects.

Anakinra (ANK) is a recombinant, nonglycosylated form of human IL-1 receptor that acts as a pure receptor antagonist binding tightly to the IL-1 receptor and preventing activation of this receptor by either IL-1β or IL-1α. Approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis in 2001, its use in AOSD is supported by the pivotal role of IL-1β in this disease. In fact, ANK has been used for the treatment of AOSD with satisfactory results. However, in most cases information related to this issue was based on isolated cases reports or AOSD small series.[3,4,8–11]

Nevertheless, in an open, randomized, multicenter study that included 22 patients with AOSD taking prednisolone ≥10 mg/day, ANK induced more beneficial responses than disease-modifying antirheumatic drugs (DMARD).[12]

Taking into account these considerations, our aim was to evaluate the efficacy of ANK in a large series of Spanish patients with AOSD refractory to other therapies.

METHODS

Patients and Study Protocol

We conducted a retrospective, open-label, multicenter study that included 41 patients with AOSD. All patients had previously received standard synthetic immunosuppressive drugs and in some case other biologic agents. ANK was given due to lack of efficacy and/or adverse events to these drugs. AOSD was diagnosed at the Rheumatology units of 19 Spanish referral centers according to Yamaguchi's criteria.[13]

Before ANK onset, infections including hepatitis B or hepatitis C infections were excluded. In all patients latent tuberculosis was also ruled out by a tuberculin skin testing (PPD) and/or quantiferon and chest radiograph. Analysis of results was performed based on the information registered by each investigator following a protocol agreed beforehand that included the collection of the relevant clinical and laboratory data of the patients. This was an observational study of ANK therapy in patients with refractory AOSD. In studies such as this, ethics committee approval is not mandatory according to Spanish national regulation. However, written informed consent is mandatory and was obtained from all patients.

Clinical Definitions

The medical records were reviewed according to a previously established protocol. According to that, fever was defined if the temperature was ≥38°C in the week before the assessment period. Joint symptoms included arthralgia and/or arthritis. Cutaneous rash was considered to be present if patients had a salmon-pink, macular, or maculopapular rash predominantly on trunk and extremities. Hepatomegaly and splenomegaly if enlargement of liver or spleen was confirmed by ultrasound or computed tomography. Lymphadenopathy was defined as the enlargement of lymph nodes in at least 2 different sites. A diagnosis of pericarditis was made if the patient presented with chest pain and had pericardial rub or an effusion documented by echocardiogram. Pleuritis was identified by the presence of pleuritic pain and pleural effusion. Improvement of the clinical manifestations was considered to be present if resolution of the clinical manifestations occurred during the follow-up period.

Laboratory Data

According to the study protocol, information on routine laboratory markers of disease activity, including full blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin serum levels, liver enzymes, creatinine serum level, proteinuria, and hematuria was collected.

Anemia was defined as a hemoglobin level ≤11 g/dL. Leukocytosis as a white blood cell count ≥11,000/mm^3. The ESR was considered to be increased when it was higher than 20 or 25 mm/1st hour for men or women, respectively. CRP was defined as elevated when it was higher than 0.5 mg/dL. High ferritin serum level was defined as a serum ferritin ≥200 ng/mL.

Data Collection and Statistical Analysis

Data were first reviewed and then analyzed in an attempt to assess the following information: clinical and laboratory data, therapies used in the management of AOSD, including those given to the patients before the onset of ANK, response to this biologic therapy and adverse events. This information was extracted from the patients? clinical records, reviewed for confirmation of the diagnosis, and stored in a computerized file according to a protocol established beforehand and agreed upon by researchers. To minimize entry error all the data were double-checked.

Statistical analysis was performed using the software STATISTICA (StatSoft Inc. Tulsa, OK). Results were expressed as mean ± SD for variables with a normal distribution or as median and [25th–75th interquartile range (IQR)] when they were not normally distributed. The comparison of continuous variables was performed using the Wilcoxon test.

The effect of ANK on clinical features and other variables such as leukocyte count and hemoglobin level, ESR, CRP, ferritin, and daily prednisone dose was reviewed. Comparisons of these variables were made between baseline and 1st month, 3rd month, 6th month, and 1st year. In addition, clinical and laboratory data observed at last visit were also assessed.

RESULTS

Data from 41 patients (26 women/15 men) with AOSD that received ANK therapy were assessed. The mean age of the patients at the onset of ANK was 34.4 ± 14 years and the median [IQR]) duration of AOSD before ANK onset was 3.5 [2–6] years. Besides corticosteroids and before the onset of ANK all the patients had received traditional synthetic

immunosuppressive drugs and 20 (48.8%) of them other biologic therapies (Table 1).

ANK was prescribed as monotherapy (n = 12) or combined with other traditional synthetic immunosuppressive drugs (n = 29), usually with methotrexate (Table 1). The initial ANK dose was 100 mg/sc. every day (Table 1).

At ANK onset the most frequent clinical features were joint manifestations (n = 36), fever (n = 32), cutaneous rash (n = 24), lymphadenopathy (n = 11), hepatomegaly (n = 11), splenomegaly (n = 11), pericarditis (n = 8), and pleuritis (n = 6). Most patients also had abnormality of laboratory parameters including increase of ESR (n = 32) or CRP (n = 37), anemia (n = 23), and leukocytosis (n = 27) (Table 2). Nevertheless, most of them experienced improvement of clinical manifestations and laboratory abnormalities following ANK therapy. This improvement was clinically evident at month 1. The good response to ANK was maintained over time (Table 2 and Figure 1).

After 1 year of ANK therapy, the frequency of joint manifestations decreased from 87.8% at baseline to 41.5% of the patients, the cutaneous manifestations from 58.5% to 7.3%, fever from 78% to 14.6%, and lymphadenopathy from 26.8% to 4.9%. Also, the frequency of abnormal elevation of CRP and ESR decreased from 90.2% at the onset of ANK therapy to 46.3% and from 78% to 22% of the patients, respectively. It was also the case for the frequency of leukocytosis that decreased from 65.9% to 14.6%, anemia from 56.1% to 9.8%, and high ferritin serum levels from 63.4% to 36.6% of the patients (Table 2). Interestingly, after 1 year of ANK therapy the median [IQR] dose of prednisone had been reduced from 20 [11.3–47.5] mg/day at the onset of ANK to 5 [0–10] mg/day at 12 months. There was also a significant corticosteroid sparing effect when basal dose of prednisone was compared with those taken at 1 month ($P < 0.01$), at 3 months ($P < 0.01$), at 6 months ($P < 0.01$), and at 12 months ($P < 0.01$), respectively (Figure 1).

After 1 year from the onset of ANK therapy, 14 patients (34%) had discontinued this biologic agent because of remission (n = 1), side effects (n = 5), lack of efficacy (n = 7) and desire to become pregnant (n = 1).

After a median [IQR] follow-up of 16 [5–50] months, cutaneous reactions were the most common complications related to ANK therapy (n = 8; 19.5%). Nevertheless, in only 2 of these 8 patients the therapy had to be permanently discontinued due to a severe cutaneous rash. Clinical improvement of the cutaneous rash occurred in both patients following ANK discontinuation. The remaining 6 patients experienced mild local cutaneous reactions in the site of ANK injection (n = 6; 14.6%). In terms of infections, this therapy had to be permanently discontinued because of severe infections in only 2 patients. One of them had phalanx osteomyelitis and the other a respiratory tract infection by *Pseudomonas Aeruginosa* and an abscess in the gluteal muscle. Full recovery following antibiotic therapy was achieved in both cases. Other infections attributed to ANK were urinary tract infection (n = 2) and herpes zoster (n = 1). Other side effects observed were mild leukopenia (n = 3) and myopathy with elevation of muscle enzymes in 1 patient who had to discontinue ANK therapy for this reason.

Finally, with regard to the combination of ANK with conventional immunosuppressive drugs, we observed that improvement of systemic symptoms and joint manifestations was more commonly observed in those patients who received combined therapy with methotrexate when compared with those patients taking ANK alone. However, the difference was not statistically significant (data not shown).

TABLE 1. Main Features of 41 Patients With Refractory Adult-Onset Still's Disease Treated With Anakinra (ANK)

Mean age ± SD, yr	34.4 ± 14 (range: 16–66)
Sex, men/women	15/26
Disease duration before ANK, median [IQR], yr	3.5 [2–6]
Immunosuppressive treatment before ANK, n (%)	
[0,1-2]Nonbiologic agents	
MTX	32 (78.0)
LFN	7 (17.1)
CsA	4 (9.8)
CPM	2 (4.9)
SZP	1 (2.4)
MMF	1 (2.4)
[0,1-2]Biologic agents	
ETN	10 (24.4)
ADA	6 (14.6)
IFX	9 (21.9)
TCZ	1 (2.4)
Concomitant treatment with ANK at baseline, n (%)	
Corticosteroids	40 (97.6)
MTX	24 (58.5)
HCQ	1 (2.4)

ANK Dose and Interval of Administration

	at Baseline, n (%)	After 1 Yr, n (%)
100 mg/day	41 (100)	22 (53.7)
100 mg/48h	0 (0)	3 (7.3)
100 mg/72 h	0 (0)	1 (2.4)
100 mg/2 w	0 (0)	1 (2.4)

ADA = adalimumab; ANK = anakinra; CPM = cyclophosphamide; CsA = cyclosporine A; ETN = etanercept; HCQ = hydroxychloroquine; IFX = infliximab; IQR = interquartile range; LFN = leflunomide; MMF = mycophenolate mophetil; MTX = methotrexate; SD = standard deviation; SZP = salazopyrin; TCZ = tocilizumab; h = hours; w = week.

DISCUSSION

In this multicenter observational study, we have observed that ANK yielded a rapid and maintained clinical and laboratory improvement, even in patients with AOSD refractory to other biologic agents.

AOSD is considered an IL-1, IL-6, and IL-18-driven disease. Recently, the therapeutic paradigm of this disease has shifted to include more specific biologic response modifiers, especially in patients corticosteroid-dependent and/or refractory to traditional immunosuppressors. In this sense, our group has recently reported promising results by the use of the IL-6 inhibitor-tocilizumab in patients with refractory AOSD.[14]

The rationale for the use of the anti-IL-1 receptor antagonist ANK in AOSD is based on our understanding of the pivotal role of IL-1 in this disease.[1–7] Regarding the cytokine cascade in AOSD, IL-18 promotes TNF-α, and IL-1 production via the nuclear factor-κB pathway and induces IFN-γ production by Th1 lymphocytes. TNF-α also induces IL-1. Overproduction of IL-1β can explain the main symptoms of AOSD, inducing fever, leukocytosis, thrombocytosis, acute-phase reactant production, and bone resorption.

TABLE 2. Improvement of Clinical Manifestations and Laboratory Parameters Following Anakinra Therapy in 41 Adult-Onset Still's Disease Patients Refractory to Previous Immunosuppressive Drugs

Clinical Manifestations, %	Basal N = 41	Month 1 N = 41	Month 3 N = 37	Month 6 N = 32	Month 12 N = 27
Joint manifestations	87.8	48.7	41.5	39	41.5
Fever	78	17.1	12.2	10	14.6
Cutaneous manifestations	58.5	9.8	10	4.9	7.3
Lymphadenopathy	26.8	7.3	4.9	4.9	4.9
Splenomegaly and/or hepatomegaly	31.7	19.5	14.6	12.2	5.6
Pleuritis and/or pericarditis	19.5	7.3	2.4	2.4	2.4
Laboratory parameters					
Hemoglobin mean ± SD, g/dL	10.9 ± 2.1	12.1 ± 2.2	12.7 ± 2.2	12.9 ± 2	13 ± 2
Anemia (%)	(56.1)	(26.8)	(17.1)	(12.2)	(9.8)
Leukocytes/mm^3, mean ± SD	15120.7 ± 7752.3	8606.6 ± 4515.1	8679.3 ± 4122.8	8246.1 ± 3602.8	8300 ± 3853.4
Leukocytosis (%)	(65.9)	(19.5)	(22)	(14.6)	(14.6)
CRP median [IQR], mg/dL	8.9 [4.4–14.9]	1.1 [0.2–4.3]	0.7 [0.1–1.9]	0.5 [0.1–1.8]	0.5 [0.1–3]
High CRP (%)	(90.2)	(51.2)	(53.7)	(51.2)	(46.3)
ESR median [IQR], mm/1st h	60.5 [39–87]	18 [10–44]	15.5 [7–31]	9.5 [5.5–25]	10.5 [4.5–22]
High ESR (%)	(78)	(29.3)	(26.8)	(19.5)	(22)
Ferritin median [IQR], ng/mL	998 [196–4212]	471.5 [76–980]	138 [54.7–498]	159.5 [47–347]	108.5 [47–264]
High ferritin serum levels (%)	(63.4)	(39)	(39)	(36.6)	(36.6)

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IQR = interquartile range; SD = standard deviation.

Anakinra, a recombinant form of human IL-1 receptor that binds to the IL-1 receptor, has demonstrated efficacy in patients with rheumatoid arthritis.[15] Additionally, randomized placebo-controlled trials disclosed efficacy of ANK in systemic juvenile idiopathic arthritis, an entity that shows some similarities with AOSD.[16]

ANK has been used in isolated cases and small case series of refractory AOSD with promising results[1,1,3,4,8–12,17–21]

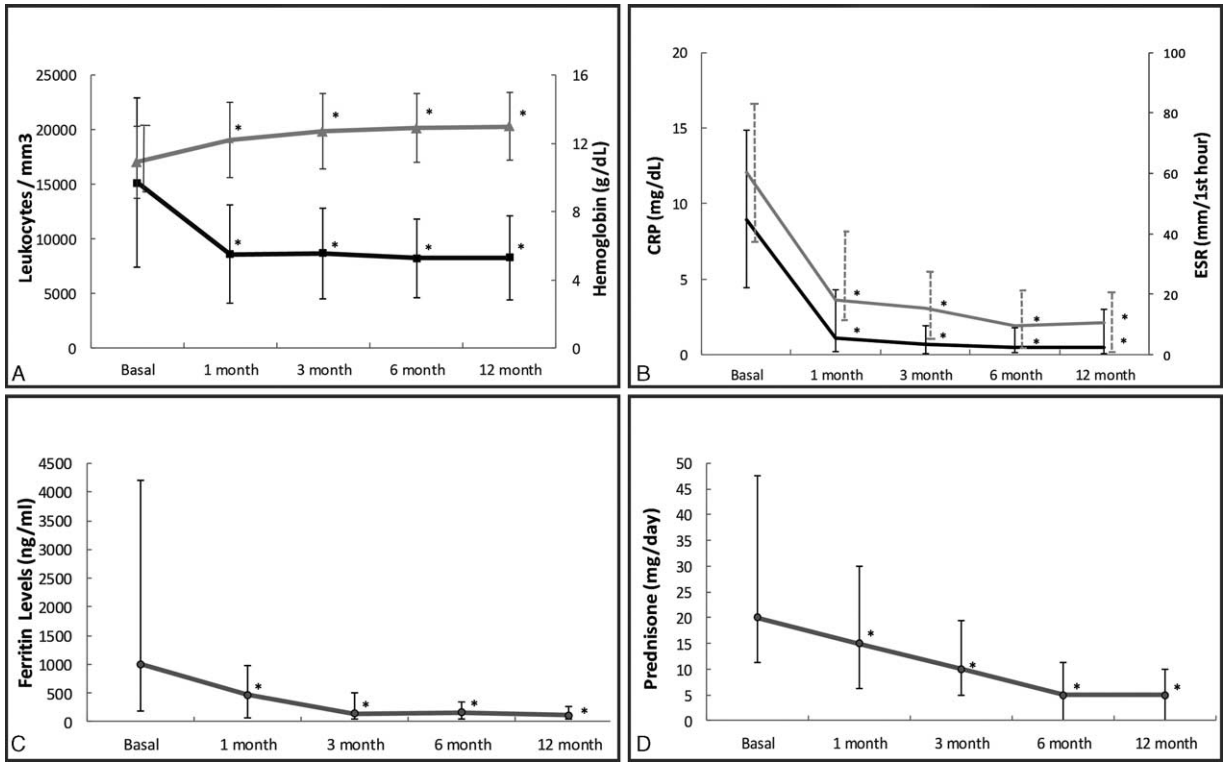

FIGURE 1. Rapid and maintained improvement following anakinra therapy (data expressed as mean and standard deviation [leukocyte count and hemoglobin] or median and interquartile range [all other variables] compared with basal results). A, Leukocyte count (black line) and hemoglobin value (grey line). B, C-reactive protein (CRP) (black line), and erythrocyte sedimentation rate (ESR) (grey line) levels. C, Ferritin level. D, Sparing corticosteroid dose effect following anakinra therapy. $^*P < 0.05$.

TABLE 3. Efficacy of ANK in AOSD in Published Series

Author	Number of Patients	Previous Treatment (n)	Treatment (n)	Overall Response (%)	Reason for Withdrawal	Side effects
Fitzgerald[3]	4	MTX (3), ETN (2)	ANK 100 mg/day monotherapy (3), adjunctive therapy (1)	100%	Pulmonary artery hypertension (1)	Viral pneumonia (1), Flu like illness (1)
Kotter[4]	4	Prednisone (4), MTX (4), ETN (1), IFX (1)	ANK 100 mg/day	100%		
Kalliolias[17]	4	Corticosteroids (4), MTX (1), ETN (1)	No data	100%		Injection site reaction (4)
Lequerré[8]	15	MTX (5), TNFi (10) + [ETN (7), IFX (7), and ADA (2)], Thalidomide (2), IVIG (5), Other DMARDs (6)	ANK 100 mg/day	11 (73%) of 15 patients had complete or partial response; complete response 9 (60%) of 15 (no systemic symptoms and at least 50% improvement of ACR score) and partial response in 2 (13%) of 15 (no systemic symptoms and 20 to 49% improvement of ACR score)	Inefficacy (2) Side effects (2)	Bronchitis (1), varicella (1), cutaneous infection (1), hepatitis A (1), osteonecrosis (1)
Naumann[9]	8	DMARDs (8), TNFi + (6) [ETN (6), ADA (2), and IFX (1)]	ANK 100 mg/day monotherapy (6), adjunctive therapy (2)*	100 %		None
Laskari[10]	25	DMARDs (4), TNFi (4)	ANK 100 mg/day monotherapy (9), adjunctive therapy (16)	21 (84%) of 25 had complete clinical response, 3 (12%) of 25 patients experienced partial clinical response (2 of them persisted with arthralgia or arthritis), and 1 (4%) no response (a patient with prominent articular disease)	Inefficacy (1) Relapsing disease (1) Skin reactions (3)	Infection (7)
Riera[1]	5	DMARDs (5), TNFi (2)	ANK 100 mg/day	100%		
Nordstrom[12]	12		ANK 100 mg/day	6 (50%) of 12 at week 4, 7 (58%) of 12 at week 8, and 6 (50%) of 12 at week 24		

Author	Number of Patients	Previous Treatment (n)	Treatment (n)	Overall Response (%)	Reason for Withdrawal	Side effects
Giampietro[11]	28	MTX (25), Other non-biologic DMARDs (5), IVIG (8), CPM (2), TNFi (23) [ETN (11), IFX (9), and ADA (3)], RTX (2)	ANK monotherapy (6) adjunctive therapy (22)	100% improvement at 1 month	2 insufficient response	
				At 23 months, 16 (57%) of 28 patients were still on treatment (12 patients had achieved complete remission [7 with predominant SYD and 5 predominant CAD] and 4 patients had experienced partial remission [3 with predominant SYD and 1 with predominant CAD])	4 flare	
					2 side effects 1 desire for pregnancy 3 for complete remission	
Iliou[20]	10	Corticosteroids, DMARDs (no more data is available)	Monotherapy 100 mg/day	100%		None
Gerfaud-Valentin[21]	6	No data available	No data	5 (83%) of 6	1 inefficacy	None
Cavalli[18]	20	Prednisone (18), MTX (15), HCQ (1), CsA (8), Colchicine (2), AZA (1), ETN (4), TCZ (1)	Monotherapy and adjunctive therapy	16 (80%) of 20 patients had complete or partial response; complete response in 14 (70%) of 20 (SYD: 11, CAD: 3) and partial response in 2 (10%) of 20 patients (both cases with CAD). 4 (20%) of 20 patients were non-responders (SYD:1 and CAD:3)	2 complete remission	2 reactivation herpes zoster
					4 inefficacy	2 injection site reaction
Present study	41	DMARDs (41): MTX (32), LFN (7), CSA (4), CPM (2), SZP (1), MMF (1), other biologic therapies (20)$^{+}$: ETN (10), ADA (6), IFX (9), TCZ (1)	ANK monotherapy (12), adjunctive therapy (29)		1 remission	2 cutaneous rash

Author	Number of Patients	Previous Treatment (n)	Treatment (n)	Overall Response (%)	Reason for Withdrawal	Side effects
Ortiz-Sanjuán					5 side effects	1 osteomyelitis
					7 lack of efficacy	1 respiratory infection
					1 desire of pregnancy	1 muscle abscess

ACR = American College of Erheumatology; ADA = adalimumab; ANK = anakinra; CAD = chronic articular disease; CPM = cyclophosphamide; CsA = cyclosporine A; DMARD = disease-modifying antirheumatic drugs; ETN = etanercept; HCQ = hydroxychloroquine; IFX = infliximab; IVIG = intravenous immunoglobulin; LFN = leflunomide; MMF = mycophenolate mophetil; MTX = methotrexate; RTX = rituximab; SYD = systemic disease; SZP = salazopyrin; TCZ = tocilizumab; TNFi = TNF inhibitors.

*In 2 patients from this series ANK was started in combination with disease modifying antirheumatic drugs (DMARDs) (both patients were on treatment with conventional DMARDs before the onset of ANK). In another 2 patients, ANK was initially used as monotherapy and conventional DMARD therapy was added in the follow-up because of persistence of symptoms.

+Some patients received more than 1 TNF inhibitor.

(Table 3). To the best of our knowledge, the largest series of patients treated with ANK because of refractory AOSD were reported by Laskari et al (n = 25) and Giampietro et al (n = 28).[10,11] In our study, we describe information on 41 AOSD patients followed for a median of 16 months. In keeping with former reports,[10,11] all the patients from our series had received synthetic immunosuppressive agents (Table 1). Moreover, many of them had also been refractory to biologic drugs, mainly anti-TNF-α agents (Table 1).

Improvement of laboratory parameters was found in most patients from our series at the time of the first available assessment of data (at month 1) after the onset of ANK therapy. Of note, improvement compared with basal results was also observed at 3, 6, and 12 months. In this regard, the significant reduction of CRP and ESR was especially remarkable compared with basal data prior to ANK onset. This finding was in agreement with former reports that also have described decrease of these acute phase reactants since the first month after the onset of ANK treatment.[10]

Rapid improvement of systemic symptoms, such fever and cutaneous manifestations, was also observed in our series. Laskari et al[10] also reported clinical and laboratory improvement in 18 of 25 patients (72%) after 1 year of treatment with ANK. Similar results were shown by Giampietro et al.[11] However, it is well known that joint manifestations in patients with AOSD may be more refractory than systemic manifestations. In this regard, Cavalli et al[11] found a complete response in 37% of patients with chronic articular disease treated with ANK and partial response in 25% (18). It was also the case in our series as 41.5% of patients had persistence of joint involvement after 1 year of ANK therapy. Similar results were described by Giampietro et al.[11] Taken together, our data along with those from previous reports indicate that joint manifestations have less response to anti-IL1 blockade when compared with other clinical manifestations of AOSD. Likewise, partial improvement of joint manifestations was observed in refractory AOSD treated with anti-IL-6.[14] Nevertheless, Laskari et al[10] reported improvement of joint manifestations (evaluated by ACR50 and ACR70 response) in 93% and 87% of their patients respectively.

Taken together, the reasons why articular symptoms show less response to anti-IL-1 therapy when compared with other organs are unknown. A plausible explanation is that proinflammatory cytokines may play a major role in the development of systemic manifestations of AOSD. According to that, either anti-IL-1 or anti-IL6 blockade would be more effective to improve active forms of systemic manifestations of AOSD. In contrast, joint involvement could be due to a different pathogenic mechanism, similar to that observed in chronic inflammatory arthritis, which would explain the partial response to the biologic agents targeting proinflammatory cytokines.

First-line therapy in AOSD is based on corticosteroids, often requiring high dose and for a long time with subsequent risk of side effects. In our series, ANK allowed a significant corticosteroid sparing effect. Prednisone dose was reduced significantly following ANK therapy (Figure 1). This is of particular relevance in patients with chronic course of AOSD, and in those who are refractory to conventional drugs since these patients receive an inappropriately high cumulative dose of corticosteroids leading to a high risk of side effects. This steroid-sparing effect is also another argument in favor of recommending ANK, given as a subcutaneous daily injection.

ANK was relatively safe in our series. Only 5 patients had to discontinue the treatment due to severe cutaneous reactions, severe infections and myopathy as described above. Another

minor side effect was mild leukopenia that was transient not requiring ANK discontinuation. These data were consistent with previously published series.[10,11,19]

As described in our study (Table 1), reduction of ANK dose because of clinical improvement was also performed in some patients reported by Laskari et al[10] and Giampietro et al.[11] However, a question still unanswered is the optimal duration of treatment with ANK in AOSD. In our series, two-thirds of the patients completed almost 1 year of ANK therapy. Twenty-two of 41 patients were still receiving a dose of 100 mg/day at 1 year. This biologic therapy had been discontinued in 1 patient because of clinical remission and a reduction in the number of doses was achieved in 5 patients in the first year from the onset of this drug (Table 1). None of these 6 patients experienced relapses during the extended follow-up. These results were consistent with those from previous series.[10,11] According to these findings, dose reduction may be considered when remission is achieved, increasing compliance and drug adherence and highlighting the potential cost-effectiveness of ANK.

We previously reported good results following anti-IL-6 tocilizumab therapy in AOSD patients refractory to conventional immunosuppressive drugs.[14] Therefore, comparison between ANK and tocilizumab should be conducted.

In conclusion, in the present report, we describe the largest series of AOSD ANK-treated patients refractory to conventional immunosuppressive drugs and in some cases to other biologic therapies. ANK yielded rapid and maintained clinical and laboratory improvement in these patients. Although ANK showed global efficacy, joint manifestations were found to be more refractory than systemic manifestations. However, the retrospective and open-label nature of the study constitutes a potential limitation. Hence, these promising results support the need for randomized clinical trials on the effectiveness of IL-1 receptor blockade in AOSD.

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