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Adult-Onset Still's Disease. An Italian multicentre retrospective observational study of manifestations and treatments in 245 patients.

Paolo Sfriso¹, Roberta Priori², Guido Valesini², Silvia Rossi³, Carlo Maurizio Montecucco³, Anna D'Ascanio⁴, Linda Carli⁴, Stefano Bombardieri⁴, Gaetana LaSelva⁵, Florenzo Iannone⁵, Giovanni Lapadula⁵, Stefano Alivernini⁶, Gianfranco Ferraccioli⁶, Michele Colaci⁷, Clodoveo Ferri⁷, Daniela Iacono⁸, Gabriele Valentini⁸, Luisa Costa⁹, Raffaele Scarpa⁹, Andrea LoMonaco¹⁰, Valentina Bagnari¹⁰, Marcello Govoni¹⁰, Ilaria Piazza¹¹, Silvano Adami¹¹, Francesco Ciccia¹², Giovanni Triolo¹², Elisa Alessandri¹³, Maurizio Cutolo¹³, Luca Cantarini¹⁴, Mauro Galeazzi¹⁴, Piero Ruscitti¹⁵, Roberto Giacomelli¹⁵, Francesco Caso^{1,9}, Paola Galozzi¹, Leonardo Punzi¹

1 Rheumatology Unit, Department of Medicine – DIMED, University of Padova, Padova, Italy

2 Department of Internal Medicine and Medical Specialities – Rheumatology Unit, Sapienza University of Roma, Roma, Italy

3 Department of Rheumatology, IRCCS Policlinico San Matteo Foundation, University of Pavia, Pavia, Italy

4 Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

5 Rheumatology Unit, Interdisciplinary Department of Medicine, University of Bari, Bari, Italy

6 Division of Rheumatology, Catholic University of the Sacred Heart, University of Roma, Roma, Italy

7 Rheumatology Unit, Department of Medical and Surgical Science for Adults and Children, University of Modena e Reggio Emilia, Modena, Italy

8 Rheumatology Section, Department of Clinical and Experimental Internal Medicine, Second University of Napoli, Napoli, Italy

9 Rheumatology Unit, Department of Clinical Medicine and Surgery, University Federico II, Napoli, Italy

10 Rheumatology Unit, Department of Clinical and Experimental Medicine, Sant'Anna Hospital, University of Ferrara, Ferrara, Italy

11 Rheumatology Unit, Department of Medicine, University of Verona University of Verona, Verona Italy

12 Division of Rheumatology, Department of Internal Medicine, University of Palermo, Palermo, Italy

13 Research Laboratory and Division of Clinical Rheumatology, University of Genova, Genova, Italy

14 Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinic, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy

15 Division of Rheumatology, Department of Biotechnological and Applied Clinical Science, University of L'Aquila, L'Aquila, Italy.

Corresponding Author:

Sfriso Paolo, MD PhD

Rheumatology Unit, Department of Medicine – DIMED

via Giustiniani, 2 – 35128 Padova, Italy

email: paolo.sfriso@unipd.it

Running header:

AOSD in 245 Italian patients

ABSTRACT

Objective: Adult Onset Still's disease (AOSD) is a systemic inflammatory condition of unknown aetiology characterized by typical episodes of spiking fever, evanescent rash, arthralgia, leukocytosis and hyperferritinemia. Given the lack of data in Italian series, we promote a multicentric data collection to characterise the clinical phenotype of Italian patients with adult-onset Still's disease (AOSD).

Methods: Data from two hundred and forty-five subjects diagnosed with AOSD were collected by 15 centres between March and May 2013. The diagnosis was made following Yamaguchi's criteria. Data regarding clinical manifestations, laboratory features, disease course, and treatments were reported and compared with those presented in other published series of different ethnicity.

Results: The most frequent features were: arthritis (93%), pyrexia (92.6%), leukocytosis (89%), negative ANA (90.4%), and neutrophilia (82%). As compared to other North American, North European, Middle Eastern, and Far Eastern cohorts, Italian data show differences in clinical and laboratory findings. Regarding the treatments, in 21.9% of cases corticosteroids and traditional DMARDs have not been able to control the disease while biologics have been shown to be effective in 48 to 58 patients.

Conclusion: This retrospective work summarizes the largest Italian multicentre series of AOSD patients and present clinical and laboratory features that appear to be influenced by the ethnicity of the affected subjects.

Key words:

Adult-onset still's disease, retrospective study, clinical presentation, laboratory findings, biologic drugs.

INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare complex autoinflammatory disorder of unknown aetiology. First described in children by George Still in 1896 [1], same symptoms were reported in 1971 by Eric Bywaters in adult patients who did not fulfil criteria for classic rheumatoid arthritis [2]. Its incidence is approximately 0.16 per 100,000 persons in France [3], and it affects usually young adults (median age 36 years).

The pathogenesis of AOSD is unknown, but genetic factors and various infectious agents have been considered as predisposing factors [4]. Genetically predisposed individuals would develop autoinflammatory reactions to environmental triggers, leading to neutrophil and macrophage activation, a hallmark of AOSD.

Main features of AOSD include high spiking fever, arthralgia or arthritis, evanescent skin rash, sore throat, hepatosplenomegaly, leukocytosis with neutrophilia, elevated liver enzymes and ESR, and hyperferritinemia with decreased glycosylated ferritin (<20%). According to the clinical course of the disease, AOSD may be conventionally divided into three main patterns [5]: monocyclic pattern, characterized by systemic single episode completely resolving within months; intermittent or polycyclic pattern, associated with one or more disease flares and characterized by complete remissions lasting to a couple of years; chronic pattern, usually associated with polyarthritis.

Diagnosis is difficult, delayed and usually based on classification criteria set, such as Yamaguchi's and Fautrel's criteria [5-6]. Due to the heightened clinical heterogeneity in AOSD, exclusion of other entities including infectious, neoplastic and autoimmune disorders should be ruled out before any diagnosis.

The treatment of AOSD remains largely empirical, relying only on small retrospective case series [7]. Patients usually respond to nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids,

disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, and polyvalent intravenous immunoglobulins (IVIg). Biologic agents are considered for treatment of corticosteroids- and DMARDs-refractory cases and represent major therapeutic advances. IL-1 inhibition with Anakinra (IL-1 receptor antagonist), Canakinumab (anti-IL-1 monoclonal antibody) or Rilonacept (anti-IL-1 fusion protein) seem to be effective, well tolerated and steroid-sparing in systemic AOSD patients, whereas TNF- α blockers could be interesting in chronic polyarticular AOSD. Inhibition of IL-6 with tocilizumab is documented and seems effective in patients with active arthritis [8].

Most of the data on AOSD come from monocentric studies with limited number of cases.

The Italian Society of Rheumatology study group on autoinflammatory diseases promoted a multi-centric data collection of Italian AOSD cases aiming to develop a national registry. In this work we report the clinical manifestations, laboratory profile, patterns of disease course and therapy, collected by the different centres.

PATIENTS AND METHODS

Fifteen Italian University Hospital centres participated in this retrospective study and collected clinical and laboratory data together with disease and therapy information from AOSD patients.

Data is referred to a cohort of patients recorded between March and May 2013. Diagnosis of AOSD was based on Yamaguchi diagnostic criteria [6], and required the presence of 5 major, minor or exclusion findings, of whom 2 or more must be major. Major Yamaguchi criteria include the presence of intermittent high spiking fever ($\geq 39^{\circ}\text{C}$) lasting one week or longer, arthralgia lasting more than 2 weeks, characteristic rash and leukocytosis (white blood cell count $\geq 10,000/\mu\text{l}$ per mm^3) with $>80\%$ granulocytes; whereas minor criteria are sore throat, lymphadenopathy and/or

splenomegaly, abnormal liver function tests and negative rheumatoid factor and ANA titre. The presence of infections, malignancies and other rheumatic diseases are exclusion conditions. Each centre has recorded patients data by using a standardised form, created specifically for collecting AOSD cases. Together with clinical characteristics, laboratory features are reported including blood cell count, coagulation parameters, serum(SF) ferritin, ESR, C-reactive protein (CRP), liver enzymes, rheumatoid factor (RF), antinuclear autoantibody (ANA).

All treatments were listed with information about doses, durations and adverse events, along with the follow-up of different biologic treatments.

Concerning the disease course, the patients were stratified into four classes: polycyclic systemic, chronic articular polycyclic, monocyclic systemic, and chronic articular monocyclic.

The collected data were compared with those reported in five published series of different ethnic origin and with samples size more than 50 subjects [4, 5, 8-10]. Descriptive statistics are represented as mean \pm standard deviation (SD).

This retrospective study was approved by Padua Hospital Ethics Committee.

RESULTS

Clinical features

Two hundred and forty-five patients (116 females and 129 males) with AOSD diagnosis and Caucasian origin were collected. The median age at the onset of disease manifestations was 38.8 years (range, 16-78.6), and the median delay of diagnosis was 1.5 months (range, 0-232). The disease manifestations were reported and compared with other series [4, 5, 8-10] in Table 1. At the time of onset, principal manifestations consisted on arthralgia (93%), arthritis (75.8%), pyrexia

(92.6%) and leucocytosis (89%). Patients experiencing fever report high temperature ($39.1^{\circ}\text{C} \pm 0.7$) and one or two spikes per day in 27.3% and 51.9% of cases, respectively. The pattern of fever was intermittent, with an average duration of 10.3 days and an intercritical phase of 3.2 days. Other symptoms observed in AOSD patients were: typical rash (67.7%), sore throat or pharyngitis (61.8%) and lymphadenopathy (60.4%). Among patients with arthritis 23.7% had monoarthritis, 44.3% had oligoarthritis and 32.0% had polyarthritis.

Reactive hemophagocytic syndrome (RHS) was reported in 7 patients (2.85%).

The clinical course in our patients were polycyclic systemic in 40.8% of cases, chronic articular polycyclic in 30.7%, monocyclic systemic in 23.9% and chronic articular monocyclic in 4.6%.

Laboratory features

As presented in Table 2, leukocytosis (white blood cell count $\geq 10,000/\text{mm}^3$) occurs in 81% of patients (mean \pm SD, $16,200 \pm 7,850/\text{mm}^3$) and was composed of $\geq 80\%$ PMN in 70.3% (mean \pm SD, $13,483 \pm 7,341/\text{mm}^3$). CRP was increased in 93% of patients (mean \pm SD, 101.9 ± 88.6 mg/L) in a range 1-355mg/L. Platelet count was $378 \pm 176 \times 10^9/\text{L}$ (range, 20-922) and thrombocytosis ($>400 \times 10^9/\text{L}$) occurred in 46% of patients.

Elevation of hepatic enzymes was observed in 53.5% of patients and rheumatoid factor was positive only in 3.8%. Patients were tested for autoantibodies: 0.5% of patients was positive for anti-CCP, 9.6% for ANA and 3.7% for anti-ENA. Serum ferritin above the normal levels was observed in 56.4% of patients (mean \pm SD, $5,743 \pm 9,723$) within a range of 156-52,395).

Comorbidities

At the time of the last follow-up, almost 70% of patients presented comorbidities: cardiovascular diseases in 61 patients, pneumopathies in 17, nephritis in 12, hepatitis in 11, bowel diseases in

8, thyroiditis in 26, autoimmune diseases in 8, diabetes in 19, neoplasia in 6, and other diseases in 4 patients (Table 3).

Treatment

84.5% of patients received steroids and 3% steroids in bolus. 51% of those patients took DMARDs and about 35% concomitant drugs (FANS), such as indomethacin, ibuprofen, diclofenac. Among patients treated with DMARDs, 60% used methotrexate, 18.5% cyclosporin, 13.2% hydroxychloroquine, 3.4% salazopyrin, 2.4% azathiopyrin and 2.4% leflunomide.

As reported in Table 4, treatment with first line biologic agents was prescribed on 58 occasions (23.7%), 3.5 ± 4.3 years after the disease diagnosis and at 40.6 ± 15.3 years of age. Within them, 46.6% received TNF-blockers and 53.4% Anakinra. Second line biologic drugs were used 19 times (7.7%), of which TNF-blockers in 10 patients, Anakinra in 4 patients and others in 5 patients.

Moreover, third line biologic agents were used as treatment on 7 occasions (2.8%): 4 times TNF-blockers and 3 times others.

Forty-two patients are reported to continue with biologic treatments; in details, 30 patients use first line biologic agents (13 TNF-blockers and 17 Anakinra), 9 patients take second line agents (3 TNF-blockers, 4 Anakinra, and 2 others), and 3 patients receive third line biologics (2 TNF-blockers and 1 others). Sixteen up to 58 patients treated with biologic agents have definitively withdrawn this treatment, due to adverse events (8 times), loss or lack of efficacy (2 times), and remission (6 times).

Given the absence of consensus regarding a disease activity measures in AOSD, the therapeutic efficacy of the biologic agents was evaluated based on disappearance of all clinical symptoms and biological manifestations (complete response, partial response, no response). The therapeutic efficacy of Anakinra and TNF-blockers is reported in Table 5.

DISCUSSION

AOSD is a heterogeneous complex disorder with unknown pathogenesis and difficult diagnosis [7]. Due to the limited number of clinical cases, often referring to individual centers, the Italian Society of Rheumatology study group on autoinflammatory diseases promoted a multicentric collection of Italian AOSD patients data. The main aims of this registry are to define the clinical and laboratory pattern of AOSD and the therapeutic attitude towards the disease in Italy. Furthermore, as long-term purpose, the registry aims to identify prognostic factors of the disease. Up to date, AOSD data on the Italian population derive only from monocentric studies and are not a complete representation of the nation [11-14].

In this retrospective study, we reported 245 patients with AOSD diagnosis referring to 15 Italian Rheumatologic Centres, 6 from northern Italy, 5 from central Italy and 4 from the southern Italy. To the best of our knowledge, this registry collects the largest number of AOSD patient data in Italy. Table 1 and 2 present a wide variability in the frequencies of clinical and laboratory features in our Italian AOSD patients compared with data from different ethnicity. Italian and Japanese patients were generally older at disease onset than subjects from the other series. In our study, the mean age of the patients at the time of diagnosis was 40.5 ± 16.5 years, whereas in other European countries, Turkey and China the mean age is around 34 years. The delay to final diagnosis was highly variable from 0 to 232 months (median 1.5 months), which indicates possible diagnostic difficulties.

The tendency for AOSD to show female predominance has been already noticed [4, 5, 9, 10], but the reason is not clear. Curiously, in our population males and females are equally affected, this

may be due to an unexpected selection bias or may reflect a peculiar characteristic of the Italian population.

In the present study, arthralgia (93%) and fever (92.6%) were the most common clinical findings, the frequency of which were similar to the other reported cases. Symptoms such as pharyngitis and maculopapular rash appear to be less frequent in Italian and Turkish subjects, whereas lymphadenopathy is most experienced by Italian, Spanish and Chinese patients than other series. Spanish patients showed the lowest frequency of hepatomegaly and sore throat, while the French subjects had the highest frequency of pericarditis. Recently, in a single-center retrospective study on 39 AOSD patients F. Dall'Ara et al. looked for predictors of the use of biologic agents. They suggested that pericarditis may be a possible marker of severe AOSD associated with higher probability of a disease refractory to conventional DMARDs. They found pericarditis in 7 patients (38%) receiving biologic agents and in 1 patient (5%) of those receiving traditional DMARDs. Our data show a similar tendency since we found pericarditis in 20% of patients receiving biologic agents and in 12% of patients receiving traditional DMARDs, thus supporting the suggestion that pericarditis in AOSD patients should be considered a red flag for clinicians. [15]

In the Chinese cohort a higher prevalence of lymphadenopathy, hepatomegaly, maculopapular rash and pharyngitis was noted. In our series, rash, lymphadenopathy, and sore throat were sensitive (>60%) and specific (> 60%), suggesting that these 3 features are useful for establishing a diagnosis of AOSD in the Italian cohort.

Hemophagocytic syndrome is a rare life-threatening syndrome that can complicate the course of AOSD. It is suggested that prevalence of RHS in AOSD is underestimated due to underdiagnosis in several cases. In our cohort, we observed RHS only in 2.8% of patients. This number is low in comparison to other AOSD series however is consistent with the recently reported results of

Zhang Y. et al. who retrospectively identified 10 cases of RHS among 315 AOSD patients (3.2%) [16].

With regard to clinical course, monocyclic subset was reported most commonly [14, 17], whereas in our cohort, most frequent subsets were polycyclic systemic pattern (40.8%) and chronic articular polycyclic (30.7%).

Particular attention should be paid to the laboratory values, since it may be a very helpful diagnostic hint for AOSD. Among other laboratory features, the white blood cell count seems to be an interesting predictor of patient outcome. Increased white blood cell counts were associated with AOSD relapses, whereas other studies showed a significant association between elevated serum ESR or CRP and a poor prognosis or higher relapse rates [9,18].

Notably, the Italian cases experienced hyperferritinemia and showed a remarkably higher levels of serum ferritin respect to Turkey and Chinese series. Besides total ferritin level, the diagnostic interest of the glycosylated ferritin (GF) has been suggested [19]. Unfortunately GF determination was not available in Italian routine clinical practice at the time of the study enrollment.

The determination of RF and ANA is also recommended, since it can be effective in narrowing the differential diagnosis. The frequency of RF and ANA positivity, always at low titre in our patients, is comparable to other studies.

The treatment of AOSD remains largely empirical, based on few case studies but not on randomized trials. NSAIDs are traditionally recommended as initial treatment of AOSD, although they are rarely effective in controlling the disease with a response rate of 20-25% [20].

Corticosteroids are usually required to induce symptom remission and is indicated in case of life-threatening complications in AOSD [21,22]. To reduce the effects of the steroids, immunomodulatory agents as methotrexate (MTX) can be used as second-line treatment [23].

However, if conventional immunosuppressive therapy is not effective, biological agents targeting

IL-1, IL-6 and TNF- α represent major therapeutic advances. In our cases, corticosteroids and traditional DMARDs have not been able to control the disease in 21.9% of patients while biologics have been shown positive effects. The efficacy of infliximab (anti TNF- α) in corticosteroid- and MTX-resistant AOSD patients was demonstrated in several case series and case reports [24,25]. Infliximab is generally well tolerated; however, it has been associated with side effects including infusion reactions, skin rash, infections, fulminant hepatitis and exacerbation of heart failure. Switching from one TNF- α inhibitor to another may be useful. In fact, Etanercept (anti TNF- α) was used successfully for the treatment of AOSD patients with complications, whereas adalimumab was effective as second line biologic drug in Etanercept or Infliximab not responders [26]. Treatment with IL-1 inhibitor (Anakinra) resulted in rapid and complete resolution of both systemic and articular manifestations as well as normalization of inflammatory marker levels [27]. Three of our cases received anti-IL-6 receptor, which has been considered for treating AOSD. A recent review of 35 patients reported that 86% of tocilizumab-treated patients experienced prompt articular improvement, and 96% experienced a disappearance of systemic symptoms [28]. We conducted a nationwide survey of AOSD, which provides important information on the clinical, laboratory, and therapeutic features in the greatest cohort of Italian patients. Nevertheless, the present study has few limitations. First, the study was retrospective and had to contend with some degree of missing clinical and laboratory investigation data. Therefore, we await additional studies from other institutions in different countries to enrich and confirm the present results.

Conflict of interest: the authors declare they have no conflicts of interest

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	our data	Fautrel 2002	Cagatay 2009	Kong 2010	Gerfaud- Valentin 2014	Asanuma 2014	Average (731 patients)
Country	Italy	France	Turkey	China	Spain	Japan	
N.	245	72	84	104	57	169	
Female	47.30%	NR	70.20%	75%	53%	72%	55%
Male	52.70%	NR	29.80%	25%	47%	28%	35%
^a Ageat onset	38.8	NR	NR	NR	NR	46	42.4
^b Delay of diagnosis	1.5	NR	NR	NR	4	1.5	2.33
Arthralgia	93.00%	88.80%	96.40%	90%	95%	83.10%	90%
Fever	92.60%	85%	95.20%	100%	95%	91.60%	93%
Sore throat	62%	NR	65.50%	78%	53%	59.30%	57%
Maculo papular rash	67.70%	71%	59.50%	95%	77%	62.20%	70%
Hepatomegaly	41.7%	NR	38.10%	44%	21%	NR	26%
Lymphadenopathy/ Splenomegaly	60.40%	44.40%	33.30%	66%	60%	44.70%	53%
Pericarditis	17.3%	20.80%	11.90%	NR	19%	3.10%	11%

Table. 1: Clinical manifestations of 245 Italian AOSD patients compared to 5 previously published series. The final column lists the average percentages of all patient series.

NR= not reported. ^a = years (median). ^b = months (median)

	our data	Fautrel 2002	Cagatay 2009	Kong 2010	Gerfaud- Valentin 2014	Asanuma 2014	Average (731 patients)
CRP [mg/L]	101.9 ± 88.6	NR	115.9 ± 68.1	NR	183.4 ± 108.5	positive in 91.5%	134
elevated ESR (>20 mm/h)	87%	NR	94%	96%	96%	68.90%	77%
Leucocyte count [N./mm ³]	16,200 ± 7,854	NR	16,234 ± 7,785	NR	13,930 ± 7,050	NR	15,455
> 10.000/mm ³	81%	88.80%	84.15%	99%	72%	79.40%	84%
Neutrophil count (N./mm ³)	13,483 ± 7,341	NR	NR	>8,000 in 98%	11,980 ± 6,140	NR	12,732
PMN >80%	70.30%	69.80%	55.56%	NR	77%	71.50%	59%
Platelet count (10 ⁹ /L)	378 ± 176	NR	378 ± 158	> 300 in 77%	NR	<15 in 13.6%	
>40.000/mm ³	46%	NR	23.80%	26%	26%	NR	24%
Serum ferritin [ng/mL]	5,743 ± 9,723	NR	1,126 ± 1,474	NR	8,745 [84- 130,000]	NR	5,204
>N	56.40%	69.40%	NR	99%	NR	88.50%	60%
>3N	80.10%	*38.9%	*38%	83%	NR	60%	53%
Elevated liver enzymes	53.50%	73.60%	NR	62%	54%	73.90%	55%
Negative ANA	90.40%	91.70%	NR	100%	92%	74.20%	78%
Negative RF	96.20%	98.60%	NR	95%	100%	79.90%	82%

Table. 2: Laboratory features of 245 Italian AOSD patients compared to 5 previously published series. The final column lists the average values of all patient series.

* = serum ferritin >5N

Comorbidities	N.
Autoimmune diseases	
Anti-CCP positivity	1
Urticarial vasculitis	1
Behçet disease	1
Raynaud's syndrome	2
Systemic lupus erithematosus	1
Psoriasis	1
IBD	1
Neoplasia	
Prostatic carcinoma	2
Frontal meningioma	2
Chronic myeloproliferative disease	1
Astrocytome	1

Table. 3: Comorbidities in 245 Italian AOSD patients at the time of last follow-up.

Biologic Agents	N. beginners (%)	N. in progress (%)
1st line biologics		
Anakinra	31 (53.4%)	17 (56.7%)
TNF-blockers	27 (46.6%)	13 (43.3%)
-Adalimumab	4 (6.9%)	
-Etanercept	12 (20.7%)	
-Infliximab	5 (8.6%)	
Total	58 (23.7%)	30 (12.2%)
2nd line biologics		
Anakinra	4 (21.1%)	4 (44.4%)
TNF-blockers	10 (52.6%)	3 (33.3%)
-Adalimumab	5 (26.3%)	
-Etanercept	3 (15.8%)	
-Infliximab	2 (10.5%)	
Others	5 (26.3%)	2 (22.2%)
-Abatacept	1 (5.3%)	
-Rituximab	2 (10.5%)	
-Tocilizumab	2 (10.5%)	
Total	19 (7.7%)	9 (3.7%)
3rd line biologics		
Anakinra	0 (0%)	
TNF-blockers	4 (57.1%)	2 (66.7%)
-Etanercept	2 (28.6%)	
-Golimumab	1 (14.3%)	
-Infliximab	1 (14.3%)	
Others	3 (42.9%)	1 (33.3%)
-Abatacept	1 (14.3%)	
-Rituximab	1 (14.3%)	

-Tocilizumab	1 (14.3%)	
Total	7 (2.8%)	3 (1.2%)

Table. 4: First, second and third line of biologic treatments followed by Italian AOSD cohort.

	Anakinra	TNF-blockers
complete response	26	9
partial response	7	10
no response	1	22
Total treated	35*	41

Table 5: Therapeutic response to Anakinra and TNF-blockers in 76 treatment courses.

*A patient cannot be evaluated, due to the short period of treatment.