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How I treat patients with Adult Onset Still's Disease in clinical practice

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Abstract

*Adult onset Still's disease (*AOSD) is a rare systemic inflammatory disease of unknown etiology characterized by four cardinal signs which are almost always present in patients: high spiking fever, arthralgia (with or without synovitis), maculo-papular salmon-pink evanescent skin rash, striking leukocytosis with neutrophilia. Here, we review the clinical features of AOSD and describe the best practice approaches for its management, reviewing available guidelines and recommendations and providing experts' insights.

In 1971, EG Bywaters (1) described a cohort of 14 adults presenting the same symptoms as the pediatric disease described in 1897 by Sir GF Still (2), so he proposed calling it *adult onset Still's disease (*AOSD). Juvenile onset Still's disease, now preferably called Systemic-onset Juvenile Idiopathic Arthritis (SoJIA) is considered one of the subsets of juvenile idiopathic arthritis, although there is a great deal of epidemiological, pathophysiological and therapeutic evidence that suggests it can be distinguished from this spectrum of disease. Another controversial issue is whether AOSD and SoJIA are the same disease. The overlapping of epidemiological, genetic and clinical data that is present in the two diseases seems to be sufficient to hypothesize that they represent the expression of the same disease but at different ages: some differences were observed, particularly regarding a higher seasonality rate in the pediatric form and a greater presence of sore throat in adults. (3).

AOSD is a rare systemic inflammatory disease of unknown etiology characterized by four cardinal signs which are almost always present in patients: high spiking fever, arthralgia (with or without synovitis), maculo-papular salmon-pink evanescent skin rash, striking leukocytosis with neutrophilia. The annual incidence has been estimated between 0.16 and 0.62 per 100,000 people (4-7). An annual incidence of 0.26 per 100,000 inhabitants was observed in 2013 in Piedmont, Italy, thanks to the rare diseases registry (unpublished data). The prevalence has been estimated as ranging from 1 to 6.77 per 100,000 inhabitants (6-8). The disease more frequently affects the young adult: the median age at diagnosis ranges from 26 to 39 years (9-12) although onset has been reported up to 88 years (11). When considering rheumatologic surveys, AOSD is more frequent in women, but to a lesser degree in internal medicine surveys (3, 13); in more up-to-date rheumatologic surveys the sex ratio is more or less the same (11,12).

Clinical picture

One of the main symptoms of the disease is fever that is present in 85-100% of patients (Table 1). It appears with daily or twice-daily spikes over 39 C°, habitually in the afternoon. It usually represents the first symptom, preceding other clinic manifestations. On the basis of some evaluations, AOSD represents from 3-20% of the causes of fevers of unknown origin in Europe (13). Arthralgia with or without synovitis is present at variable rates (72-95%) depending on whether patients have been examined in internal medicine departments or in rheumatology departments. Arthritis can be moderate and transient, it usually affects the wrists, knees and ankles, but it can evolve to a more severe form of chronic destructive symmetrical polyarthritis with a classical trend to develop carpal ankylosis. A characteristic macular or maculo-papular salmon-pink evanescent skin rash occurring during fever spikes and mainly located close to the limbs and the trunk may be observed in 62-77% of patients. A sore throat is frequently present in AOSD and may appear prior to, or at the same time as, the other symptoms occurring in the first month of disease flares.

Many other clinical manifestations may be observed n the course of the disease: myalgia, lymphadenopathy, hepatosplenomegaly, serositis, abdominal pain, elevated acute phase reactants (APRs) and hyperferritinemia (Tab. 1). Furthermore, in the literature other rare clinical manifestations have been reported (Tab. 2).

To date, no specific laboratory tests are available to diagnose the disease. In most patients, a considerable increase is observed in the rate of acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well as in leukocytosis with neutrophilia and often anemia and thrombocytosis. An increase in the ferritin rate is often noticed and it is usually related to disease activity. Hyperferritinemia can be associated with a considerable reduction in the glycosylated fraction of ferritin, and such a combination would prove to be very specific for the diagnosis (17), but unfortunately the glycosylated ferritin dosage is not a routine lab test. In one-third of patients there is an increase in serum liver enzyme levels, especially alanine and

aspartate aminotransferase. Antinuclear antibodies, rheumatoid factor and anti-citrullinated protein autoantibodies are present in only a small percentage of patients and mostly at low titers.

Tab 1 Clinical features and laboratory findings in AOSD (% of reported cases) (8, 10-15)

Fever	85-100	WBC > 104/mm3	72-91
Rash	62-77	PMN> 80%	69-78
Arthralgia/arthritis	72-95	Anemia	53-65
Sore throat/pharyngitis	37-63	C-reactive protein ↑	96-98
Myalgia	13-53	ESR ↑	96-98
Lymphadenopathy	4-60	Seum ferritin (>500 μg/L)	69-97
Splenomegaly	25-30	Glycosylated ferritin ≤ 20%	72-76
Lymphadenopathy +splenomegaly	45-60	Elevated liver enzymes	53-75
Hepatomegaly	21-44	Negative rheumatoid factor	95-99
Pleurisy	8-24	Negative ANA	90-92
Pericarditis	3-21		
Abdominal pain	18-48		

Tab 2 Uncommon manifestations in AOSD (13, 16,)

pulmonary hypertension,

myocarditis,

cardiactamponade

aseptic meningitis/encephalitis, ischemic stroke

pure red cell aplasia

intestinal pseudo- obstruction

pseudo-angiocholitis

membranous glomerulonephritis, necrotizing crescentic glomerulonephritis,

tubulo-interstitialnephritis

inappropriate ADH secretion

inflammatory orbital pseudotumor, uveitis, retinopathy, conjunctivitis

portal veinthrombosis

neuro-sensorial deafness

reversible posterior leuko-encephalopathy syndrome

amyloidosis

Sjögren'ssyndrome

Necrotizing granulomatous lymphadenopathy

angioedema

Classification criteria and diagnosis

Several sets of criteria have been proposed for the diagnosis of AOSD. The most frequently used criteria in clinical practice are those suggested by Yamaguchi M et al (18) in 1992, which includes four major criteria (fever, arthralgia/arthritis, typical skin rash and leukocytosis [≥10,000/mm3 with ≥80% polymorphonuclear cells]) and five minor criteria (sore throat, lymphadenopathy, hepatomegaly or splenomegaly, abnormal liver function tests and negative test for antinuclear antibodies and rheumatoid factor). Exclusion criteria are also well-establishe , i.e., infections, malignancies and other systemic disorders. Diagnosis is possible in the presence of at least five criteria, including at least two major ones and the presence of exclusion criteria.

In 2002, evidence that a large number of patients show hyperferritinemia together with a considerable reduction in glycosylated ferritin led Fautrel B et al (14) to propose a new set of criteria, including six major ones (fever, arthralgia/arthritis, typical skin rash, pharyngitis, polymorphonuclear cells ≥80% and glycosylated ferritin ≤20%) and two minor ones (macular papular rash and leukocytosis >10,000/mm3). For the diagnosis, ≥4 major criteria or 3 major +2 minor criteria are required. Yamamuchi's criteria have a 79.2% sensitivity and a 93.8% specificity (accuracy of 88.6%), while Fautrel's criteria have an 80.6% sensitivity and a 98.5% specificity (accuracy 92.1%) (16). Hyperferritinemia with low glycosylated fraction may appear later in the diseasecourse and patients may not meet Fautrel's criteria at the time of disease onset (19).

Diagnosis is often difficult due to the necessity to extend the differential diagnosis to infections, autoimmune disorders, systemic vasculitides, autoinflammatory diseases, drug reactions and other diseases (Tab. 3)

Tab 3. Differential diagnosis of AOSD. (13, 16, 20, 21)

Infections	**Autoimmune disorders**
systemic viral infections	lupus erythematosus,
HIV, Parvovirus B19, herpes virus,	rheumatoid arthritis,
viral hepatitis, measles, rubella	idiopathic inflammatory myositis
infective endocarditis and sepsis	
mycoplasma pneumonia	**Autoinflammatory diseases**
yersiniosis, brucellosis, borreliosis	familial Mediterranean fever
syphilis	hyper-IgD syndrome
toxoplasmosis	mevalonate-kinase deficiency
	TNF-receptor-associated periodic syndrome

Malignancies

malignant lymphomas,

angioimmunoblastic T-cell lymphoma

multicentric Castleman's disease

myeloproliferative disorders

leukemia

solid cancers (breast, lung

kidney, colon, melanoma)

sarcoidosis

systemic vasculitides

drug reactions/ DRESS

Other

reactive arthritis

Schnitzler's syndrome

Kikuchi-Fujimoto disease

Sweet's syndrome

Whipple disease

Furthermore, a delay in diagnosis related to disease complexity could occur and this delay may last up to 312 months (10). The delay in diagnosis is usually higher in the chronic form (11).

The disease course presents three main clinical patterns: a monocyclic or self-limiting pattern of variable duration that evolves towards complete remission, which however usually lasts more than 2 months and less than a year; a polycyclic or intermittent pattern in which two or more systemic disease episodes follow one another between a symptom-free period of at least 2 months; a chronic articular pattern with severe joint involvement that can cause joint destruction and long-term disability. Reported percentages of the various patterns differ depending on the surveys (9, 10, 11, 15). Both the self-limiting and the intermittent patterns are present in 30% of cases each, while the chronic pattern is found in about 40% of the observed cases (16).

During the course of AOSD, 15-20% of patients develop life-threatening complications (16) including reactive hemophagocytic lymphohistiocytosis (reHLH), also called macrophage activation syndrome (MAS) in the context of rheumatic diseases, fulminant hepatitis/acute hepatic

failure, disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, diffuse alveolar hemorrhage, acute respiratory distress syndrome, pulmonary arterial hypertension and multiple organ failure. Furthermore, severe iatrogenic complications, such as infections and septic shock, may also occur. The most common causes of death reported in the literature are infections, acute respiratory distress syndrome, multiple organ failure, reHLH/MAS, thrombotic microangiopathy, and central nervous system involvement(16).

Only a few studies have analyzed prognostic factors in AOSD. However, it seems that female gender, proximal arthritis at disease onset and steroid dependence may predict the chronic articular form of AOSD, whereas high fever (> 39 °C) and high levels of liver enzymes or CRP may be associated with the systemic form of the disease (19).

In 1991, Pouchot J et al (22) suggested an AOSD scoring system that has never been validated. The authors selected 12 clinical features of the disease (fever, typical rash, pleuritis, pneumonia, pericarditis, hepatomegaly or abnormal liver function tests, splenomegaly, lymphadenopathy, sore throat, myalgia, abdominal pain and leukocytosis > 15,000/mm3) and assigned a score of one to each feature, with a maximum score of 12. A recent study (23) which used this score on 100 patients highlighted that a higher systemic score and the presence of AOSD-related complications at the time of diagnosis were significantly associated with greater mortality. The authors pointed out that a systemic score equal to, or above seven represents a relevant prognostic factor for identifying patients at higher risk of AOSD-related death. In the above-mentioned work, the highest number of deaths was observed in 13 patients presenting reHLH/MAS (a very worrisome complication that may be observed in various series, such as this one, in 12-15% of the patients) (13). The PRINTO diagnostic criteria (which were recently suggested for SoJIA) can also be used for the diagnosis of this very serious complication (24). Accordingly, diagnosis is possible in a patient with (suspected) SoJIA with fever and serum ferritin > 684 ng/ml and two of the following: platelet count ≤181,000 /L, aspartate aminotransferase >48 U/L, triglycerides > 156 mg/dl and fibrinogen ≤360 mg/dl.

It was recently suggested that a distinction should be made between two AOSD subsets (as is already the case in juvenile idiopathic arthritis (25)) with regard to the predominant clinical expression. The first subset is marked by prevalent systemic manifestations, with extremely high levels of ESR, CRP and ferritin, possible multi-organ involvement and reHLH/ MAS. The second subset is marked predominantly by chronic polyarthritis with limited inflammatory manifestations that may resemble rheumatoid arthritis (19).

Etiology and pathogenesis

The disease etiology is still unknown and even the pathogenesis is still debated. At present, AOSD is considered a heterogeneous syndrome between autoinflammatory syndromes and autoimmune diseases, in which innate immunity seems to play an essential role. It has been hypothesized that various external factors, such as infectious agents, malignancies and other environmental factors in patients with a genetic predisposition can activate innate immune cells thanks to Toll-like receptor (TLR) engagement, thus producing an abnormal response in both innate and adaptive immunity with consequent cytokine overproduction (16).

Since the clinical manifestations are similar to those of an infective process, we may assume that infectious agents play a relevant role in the pathogenesis of the disease; moreover, the sore throat along with the seasonality that is observed in SoJIA could represent further elements to this hypothesis. Many viruses and bacteria are involved, but their role has never been clearly defined. The role of an infectious agent could fit very well into the different disease forms: the monocyclic form could be secondary to a single infection; the polycyclic form, in which recurrent clinical episodes occur, may suggest the presence of infection/reinfection of different pathogens, while the chronic form could depend on the impossibility of the host to eliminate an antigen that acts as a chronic trigger (3).

It is assumed that infective factors, as well as environmental factors and malignancies (solid cancer and some hematologic disorders) can also be trigger factors of an abnormal immune response in subjects with a genetic predisposition. An association between AOSD and HLA alleles (B-17, B18, Bw35, DR2, DR4, DR5, DQ1,DRB1*12 and –DRB1*15) has been observed in various populations, as has a negative correlation with the HLA-DR1 and HLA DRQ1*04 alleles (22, 26-29). Furthermore, polymorphisms have been described in genes encoding IL-18 and macrophage inhibitory factors (30, 31), two cytokines that are strongly involved in innate immunity. However, it must be stressed that a familial aggregation has not been observed and the characteristic mutations in the genes (NLRP3, NOD2, MEFV, or PSTPIP1) that are observed in typical monogenic autoinflammatory diseases have not been found in AOSD.

Many pathogenetic hypotheses have been put forward: the hemophagocytic lymphohistiocytosis (HLH) hypothesis, the hyperferritinemic syndrome hypothesis, the defective immunoregulation hypothesis and the autoinflammatory hypothesis (3).

The HLH hypothesis is supported by the clinical and biological features that are shared by HLH and AOSD which include high fever, lymphadenopathy, hepatosplenomegaly, skin rash (less common in HLH), liver dysfunction, hyperferritinemia, coagulopathy, NK cell dysfunction and high serum levels of active IL-18. Furthermore, up to 15% of patients with AOSD develop reHLH/MAS during the course of the disease and it has been observed that many patients affected by AOSD present elements indicating occult reHLH/MAS, thus leading to hypothesize that the two diseases may represent a continuum of severity (32).

It has recently been hypothesized that the high ferritin levels that are observed in AOSD may not only reflect an acute phase response, but may play a critical role in driving inflammation. Furthermore, it has been suggested that the term “hyperferritinemic syndrome” could include four uncommon immune-mediated conditions (MAS, AOSD, catastrophic antiphospholipid syndrome and septic shock) presenting high ferritin levels, similar clinical and laboratory presentations and

similar treatments, in which hyperferritinemia may be involved as a shared pathogenic mechanism (33).

The defective immunoregulation hypothesis is supported by the evidence that AOSD pathophysiology may not only be the result of unchained activation of proinflammatory mechanisms but also of defects in immunoregulation (3)

The clinical analogies of AOSD (including recurrent fever and multisystem inflammation with skin rash, serositis and arthritis) with classic autoinflammatory diseases such as cryopyrin (NLRP3)-associated periodic syndrome, TNF receptor-associated periodic syndromes and familial Mediterranean fever, as well as the dramatic response to IL-1 inhibitors, are all elements supporting the autoinflammatory hypothesis. According to this hypothesis, environmental signals(pathogen-associated molecular patterns or danger associated molecular patterns) in genetically predisposed subjects can activate the receptors of innate immunity (Toll-like receptors or Nod-like receptors) located on the dendritic cells and on macrophages, thereby triggering the activation and consequent secretion of cytokines. After that, increased TH1 and TH17 adaptive responses would be activated. The various cytokines would then be responsible for the different clinical features of AOSD: arthritis, skin rash, fever, neutrophilia, splenomegaly, coagulopathy, hepatitis, weight loss, increment of APRs and hyperferritinemia. In AOSD, natural killer cells (NK) present deficient cytotoxic functions (34). The NK stimulated by IL-18 produce interferon gamma (IFN-γ), that in turn has been shown to be one of the main drivers of the activation of macrophages (35) and is related to reHLH/MAS (3, 13).

Although this testing cannot be routine in clinical practice, the possible associations between the single cytokines and AOSD features have been analyzed. It has been pointed out that IL-1β, soluble interleukin-2 receptor, IL-18, IL-6 and IL-17 can be markers of disease activity, although tumor necrosis factor-α(TNF-α) and IFN-γ do not seem to be. IL-1β, IL-17 and IL-18 can be useful for monitoring the efficacy of treatment. IL-6 is related to elevated CRP levels, hyperferritinemia, salmon-colored rash, and hepatosplenomegaly; IL-18 is related to elevated CRP levels,

hyperferritinemia, neutrophilia, AOSD-related hepatitis, and reHLH/MAS, and furthermore, IL-8 is predictive of persistent arthritis (36).

The varying cytokine profiles observed in AOSD patients seem to confirm the presence of two disease subsets with different clinical features, as stated above. In the systemic subset, which sometimes can be similar to MAS, there are high IL-1β, IL-18, IL-4, INFα/β levels, with a pronounced INF γ increase and hyperferritinemia. This subset, that presents NK/CD8 cell dysfunction, fits well with an autoinflammatory disease that benefits from IL-1 inhibitors and could probably benefit from IL-18 and INF γ inhibitors. In the second arthritic subset there are high IL-17, IL- 23, IL-6 and TNFα levels, and low INFγ and ferritin levels. This second subset does not resemble an autoinflammatory disease, but rather it resembles rheumatoid arthritis, with which it could share the efficacy of IL-6 and TNFα inhibitors and could benefit from the use of IL-17 inhibitors as well (3, 19).

How I treat AOSD: Overview on available evidence and the experts' opinion

One of the main issues in the treatment of AOSD is that up-to-date recommendations and guidelines are lacking; therefore the therapeutic approach remains substantially empirical and still relies on the clinician's own experience. In order to identify the most appropriate individualized therapeutic strategy for AOSD patients, we take into consideration the following factors;

- the disease phase (onset, maintenance, flares)
- the ongoing predominant clinical features (systemic or articular)
- the presence/absence of complications

Although it may seem like a trivial consideration, at onset the clinician should be confident of the correct diagnosis. Initially, AOSD, especially in its systemic presentation, can be mistaken for

some febrile diseases including infections, systemic autoimmune diseases, hematologic conditions and malignancies. Therefore it is quite common to spend a considerable amount of time on a careful and extensive work-up to exclude an alternative diagnosis. In the meantime, nonsteroidal anti-inflammatory drugs (NSAIDs) can be useful to alleviate the patient's symptoms. Some authors feel that prompt response to NSAIDs could be considered a good prognostic sign indicating a more self-limiting disease (37). Conversely, some others suggest that NSAIDs should not be the first-line treatment and should only be used as adjunctive therapy to steroids and disease-modifying antirheumatic drugs (DMARDs) (13) . Overall, good response is observed in up to 20% of patients (37-39), but NSAIDs are rarely sufficient to control disease symptoms, and hepatotoxicity can arise. Indomethacin has been indicated as the preferred drug, but in our personal experience, other NSAIDs such as, parenterally-administered ketoprofen work just as well .

Once a diagnosis has been made, the next step consists of checking for the predominant clinical feature of the disease: systemic, articular or both. This evaluation can be helpful in planning a more patient-tailored therapeutic strategy since distinct patterns of presentation can be driven by complex pathophysiological pathways having a different propensity to respond to targeted therapies.

The main goal at disease onset is to induce complete clinical and biologic (i.e., laboratory) remission as quickly as possible. This is particularly true in cases of systemic presentation. In subjects presenting with a more indolent articular course, prevention of joint damage progression should be pursued. Although AOSD is considered a benign condition with a good prognosis, it may also suddenly turn into a very severe disease in which life-threatening complications (reHLH; disseminated intravascular coagulation (DIC); myocarditis, acute respiratory distress syndrome, fulminant hepatitis) may occur at any time. In these cases, it is mandatory to promptly check and intensively treat these complications which often require intensive care unit support.

In general, we use NSAIDs as bridging therapy only in the initial phases of the disease, but as soon as the diagnosis appears clear, glucocorticosteroids (GCs) are our first choice. Low-dose GCs (7.5 –

10 mg/day) usually suffice to control joint pain when there is no evidence of synovitis or effusion (i.e., arthralgias). In subjects with systemic onset, the GC dose should be more generous - up to 0.5-1 mg/Kg/day per os, or even i.v.0.8 mg/Kg/day prednisone equivalent (40). High-dose GCs are mandatory in life-threatening complications such as myocarditis, pericarditis, DIC, reHLH, acute hepatitis and acute respiratory distress syndrome, moreover, intravenous pulse GC therapy can also be used in these circumstances. In our experience, timing of administration has proven to be crucial and BID or TID schedules are usually required to avoid symptom exacerbation. For some refractory atypical skin rashes, betamethasone (usually up to 4-8 mg/daily) can be more effective than prednisone. The response to GCs should be obtained within hours or days, and good results are observed in 65 to 89% of cases (22, 38, 39). A relevant issue is that about 40-45% of patients develop GC dependence (10, 41) with an increased risk of GC-induced long-term side effects.

At this point, a timely evaluation of clinical response is advisable. If the target (remission) is reached, we continue administering GCs for at least 4-6 weeks, followed by slow tapering (max 5 mg/day every week). If the target is not reached or steroid-dependence occurs, starting a DMARD is usually our preferred choice.

When and which DMARD do I use in AOSD?

Patients presenting or developing arthritis represent the most common situations in which DMARDs can be useful as first line therapy in addition to GCs. Various DMARDs have been used in AOSD, but our preferred option is methotrexate (up to 15 -20 mg/week) or cyclosporin A (up to 3 mg/Kg/day). In milder cases, we also take hydroxychloroquine into consideration(6 mg/Kg/daily). Adding a DMARD can yield a steroid-sparing effect. Forty-four to 88% of patients usually respond to DMARDs. This approach corresponds to what has been reported in a large Italian multicenter retrospective observational study including 245 AOSD patients (12) In this study, 51% of patients

received a DMARD, mainly methotrexate (60%), cyclosporin A (18.5%) and hydroxychloroquine (13.2%).

Overall, due to the lack of randomized clinical trials, the available evidence supporting the use of methotrexate in AOSD is represented by small case series or case reports. Published data account for a total of about 60 patients treated with this drug (3,10,13,38, 42-45). Methotrexate has a similar effect on both systemic and arthritic AOSD (45, 46) with a reported rate of good clinical response or a steroid-sparing effect in up to 70% of subjects. Among the different and multiple mechanisms of action of methotrexate, an inhibitory effect against IL-1 has also been reported and this effect could be particularly useful in AOSD (47-49).

Maintenance. As mentioned above, when the onset storm is under control, cautious treatment tapering can be attempted along with a careful 'wait and watch' strategy. The rationale for this attitude lies in the unpredictable disease course over time, i.e., monocyclic, recurrent polycyclic or arthritic progressive.

Firstly, we try GC tapering, and if the patient remains in stable remission for at least 6 months, gradual tapering of the DMARD can be started. In the monocyclic course this strategy prevents overtreatingpatients who will probably not flare up again. In our experience, patients with polyarthritis persisting over 6 months are the ones at greater risk of having chronic persistent disease (15) ; in these cases the therapeutic approach, which is aimed at controlling disease activity and preventing joint damage progression, is similar to what is adopted in rheumatoid arthritis.

Flares.

It is not unusual for patients to flare up after having achieved remission . This eventuality is more frequent in patients who have discontinued therapy, but the occurrence of flares is unpredictable.

We usually resume GC administration and, if necessary, depending on the current or previous response, our first choice is to add or resume administering a DMARD (usually MTX). However, sometimes this may not be enough and a biologic DMARD should be considered. In general, when the addition of a DMARD (i.e., MTX or CYA) to a GC fails to achieve good and quick control of the disease (either at onset or in the event of flares) we discontinue the DMARD combination and switch to, or add a biologic DMARD (see below).

Life-threatening Complications.

One of the most challenging and dangerous complications which can occur in AOSD is the MAS, also known as reHLH, corresponding to an uncontrollable activation of the reticuloendothelial system leading to phagocytosis of hematopoietic cells by activated tissue macrophages. This dramatic condition may occur at any time during the disease and can be triggered by intercurrent infection, tissue damage (i.e., related to surgical procedures), trauma etc. Rapidly rising serum ferritin levels, appearance of cytopenia, and liver function test abnormalities are, in our experience, the most frequent heralding clues that should make us suspect there is an ongoing MAS. The prompt start of high-dose GCs (even administered as close as 2-3 sequential i.v. 500-1000 mg methylprednisolone pulses) is our first line treatment choice. I add high-dose intravenous immunoglobulins (400 mg/Kg/day for 5 consecutive days) if the patient is already on GC treatment or if no clinical or laboratory response is observed within 24-48 hours following high-dose GC administration Concomitantly with this emergency treatment we usually start oral cyclosporin, up to 3 mg/Kg/day. The effectiveness of biologics is controversial. Case reports have shown good response with both IL-1 inhibitors or anti-IL 6 (50-53-), while anti-TNF have proven to be ineffective or even harmful (54-56) since drug-induced reHLH has been reported with these drugs, as it has after anakinra (57,58) and tocilizumab administration (55,56). Myocarditis is another important and dangerous complication which can occur in AOSD. Successful response to anakinra

has been reported in some cases (59-61), and I think of IL-1 inhibition in the event of such complications.

In the pre-biologic era, we achieved successful response with an autologous CD34 stem cell transplantation in one young patient with refractory AOSD who failed to respond to a number of DMARDs and achieved complete and prolonged remission after this rescue treatment (62).

When and which biologic I use. There are no prospective, double-blind, randomized clinical trials that confirm the efficacy of the biologic agents in the management of AOSD. However, bDMARDs with different mechanisms of action have been increasingly and successfully used in the last fifteen years. Available evidence consist of single case reports and small case series. The rationale to use bDMARDs, usually showing an anti-cytokine effect, lies in our knowledge about the pathophysiology of the disease. To date there is enough consensus about the existence of important and predominant activation of the innate immune arm, in which the monocyte/macrophage system plays a pivotal role along with the secretion of a great deal of pro-inflammatory cytokines (TNF□, IL-1, IL-6, IL-18, IFN-□). The observation that in the juvenile counterpart of AOSD, i.e. SoJIA, some patients treated with anakinra, an inhibitor of IL-1 beta, quickly respond whilst others fail to respond at all (25), has suggested the hypothesis that there are at least two different subsets of the disease in which alternative inflammatory and immune activation pathways play a role. Given the substantial genetic, immunologic and clinical similarities betweenSoJIA and AOSD (3, 63) this different pattern of response to IL-1 inhibition appears applicable to AOSD as well. Current evidence supports the idea that in systemic onset with MAS-like features, inhibition of IL-1 beta could be the preferable first-line option with a reported response rate above 85%, while targeting IL-6 could be useful in the predominant arthritis pattern with a similar rate of response (64-66).Since anti-TNF (Infliximab, Etanercept and Adalimumab) were the first available biologic drugs, they were used at the beginning, however they seem to work to a lesser extent (25% of

responders); they have mostly been used in arthritis subsets, though with conflicting results : good (67-69) or poor response (70-72) with limited efficacy over time. No data are available for Golimumab and Certolizumabpegol.

In agreement with the current therapeutic algorithm, in our experience, Anakinra, a recombinant human IL-1 receptor antagonist, represents the first choice when dealing with a refractory systemic subset of AOSD. Its short half-life (4-6 hours) makes this drug particularly useful in testing therapeutic response in the early phases of the disease, even when the diagnosis is strongly suspected but not yet definitively reached and the clinical conditions of the patient or incoming complications require a more aggressive intervention. Once diagnosis is ascertained, IL-1 inhibition can be pursued with a long lasting drug such as Canakinumab, a fully human monoclonal anti-IL-1□ antibody, which has the not negligible advantage of more refracted administration and greater patient compliance(73-75). Another option could be Rilonacept, a fusion protein of the extracellular domains of IL-1R1 and IL-1RAP coupled to the Fc region of human IgG (76). IL-1 inhibitors can work very well both in monotherapy and in combination with methotrexate.

In the arthritis subsets, Tocilizumab, a humanized anti-IL-6 receptor antibody that recognizes both membrane-bound and soluble free forms of the IL-6 receptor, represents a suitable alternative to IL-1 inhibition, or perhaps even the preferred option; this drug is administered both in combination with methotrexate or as monotherapy. In case of failure with Tocilizumab, we try an anti-TNF, preferably in combination with methotrexate. There are no defined criteria for choosing which anti-TNF should be preferred; the patient's expectations or needs, comorbidities and local organizational assets should be evaluated when choosing the anti-TNF.

To date, at our center, we have treated 20 AOSD patients (mainly with articular presentation) with biologics: 9 with an anti-TNF (3 Infliximab, 4 etanercept, 2 adalimumab); 8 with anakinra and 3 with tocilizumab. Overall, good response has been observed in 4/9 patients treated with anti-TNF, 5/8 with anakinra and 3/3 with tocilizumab.

In AOSD, the use of biologic DMARDs in mono (switch from methotrexate, cyclosporin or other DMARDs) or as combi (add-on to the ongoing DMARD) has not been extensively evaluated nor clearly encoded. Clinicians can refer to the registered indication of the biologic, as in rheumatoid arthritis. Tolerability of conventional DMARDs, evaluation of previous response (primary failure or loss of efficacy of methotrexate or other DMARDs) and the patient's compliance should be considered.

There are no guidelines to drive decision-making about how long to continue biologic (or even, conventional) therapy once clinical remission is achieved. The pattern of clinical presentation, systemic or chronic arthritis and disease course should be evaluated.

In patients with systemic onset, response to IL-1 inhibitors must be expected within hours or days; in the arthritis subset the response (even with anti IL-6 or anti-TNF) may require more time, but the target of remission or low disease activity should be achieved within no more than 3 months. If clinical remission, rather than low disease activity, is maintained for at least 6-12 months, a cautious attempt to taper the biologic could be pursued. It is my personal opinion that persistent clinical remission in AOSD should be certified only after having gradually and slowly discontinued GCs with no evidence of disease flare. In these cases, the ongoing combination of the biologic and methotrexate can more safely allow an attempt at spacing the biologic DMARD until its complete withdrawal while continuing methotrexate. Obviously, this strategy can expose the patient to the risk of a flare up, but as stated above, the course of the disease is usually unpredictable and continuing biologic therapy when the patient persistently feels good may not be fully justified considering the possibility that the course of the disease could have been monocyclic.

However, a number of patients with chronic polyarticular disease need prolonged treatment, as is the case in rheumatoid arthritis, and in these cases tapering or discontinuing DMARD therapy is rarely successful or advisable.

Although I have no personal experience, in case of failure of IL-1, IL-6 or TNF inhibition, there are reports of the successful use of abatacept (77 78) and rituximab (79-83). This latter biologic has been employed in patients with pulmonary arterial hypertension (79-83) and HLH (83). Nonetheless, non responders have also been reported with both abatacept and rituximab.

In general, the safety profile of biologics in AOSD appears to be good and is substantially similar to what is observed in rheumatoid arthritis. However, it should be taken into account that sporadic case reports of severe complications of AOSD, such as acute hepatotoxicity or MAS, can be "paradoxically" induced by biologics themselves(56-58 , 84-88).

Conclusion

The best therapy for AOSD has not yet been defined by recommendations or guidelines, and still relies on the personal clinical experience of the attending physician. Once the diagnosis is confidently reached the first goal should be to quickly achieve clinical remission, especially in the systemic subset of the disease. GCs still remain the first line therapy, with the addition of cDMARDs (usually methotrexate or Cyclosporin) when non optimal response is observed within a short period of time, or if there is a real risk of GC dependence. Biologic DMARDs (anti-IL1, anti-IL6 and anti-TNF) have proven to be useful and can allow us to obtain complete control of the disease when GCs and cDMARDs have failed. Careful evaluation of the disease phase and of the predominant clinical pattern (systemic or articular), as well as the prompt treatment of complications and flares represent the cornerstones of a personalized approach to patients affected by AOSD.

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