

## PRACTITIONERS' SECTION

### ADULT-ONSET STILL'S DISEASE: A REVIEW

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#### ABSTRACT

**OBJECTIVE:** This article is an attempt to review recent literature regarding pathogenesis and clinical and laboratory findings in adult-onset Still's disease (AOSD). **MATERIALS AND METHODS:** A search was conducted in PubMed and Ovid for English language publications, using individual or linked search terms "adult-onset Still's disease," "adult Still's disease," "Still's disease," "AOSD," and other related terms, from 1996 to 2009, and the clinically relevant articles were subsequently selected. **RESULTS:** More than 1000 titles were reviewed by the authors, and the most important concepts were selected from 143 full-text articles. **CONCLUSION:** Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology and pathogenesis, usually presenting with high spiking fever accompanied by systemic manifestations. The disease is an entity with heterogeneous pathology; and diverse suggested etiologies, clinical manifestations and prognoses. There is no single diagnostic test for AOSD; rather, the diagnosis is based on a set of criteria, the most important of which are indeed clinical, but they also include paraclinical ones. Treatment aims at both minimizing inflammation and halting disease progression. For the former, nonsteroidal anti-inflammatory drugs have limited efficacy; so glucocorticoids in conjunction with disease-modifying antirheumatic drugs are also used. Novel therapeutic approaches such as anti-tumor necrosis factor blockade and monoclonal antibodies are promising.

**Key words:** Adult-onset Still's disease, adult Still's disease, Still's disease

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#### INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare inflammatory disorder of unknown

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etiology. Its main features are high spiking fever; evanescent rash; polyarthralgia; lymphadenopathy; hepatosplenomegaly; leukocytosis; and elevated liver enzymes, erythrocyte sedimentation rate (ESR) and ferritin.<sup>[1]</sup> The first description of an adult patient with signs and symptoms of AOSD (erroneously labeled rheumatoid arthritis) was published in 1896.<sup>[2]</sup> In 1971, Eric Bywaters described 14 adults with presentation similar to that of pediatric Still's disease; hence he used the term AOSD.<sup>[3, 4]</sup>

## MATERIALS AND METHODS

We searched in the PubMed and Ovid from 1996 to 2009, using keywords “adult-onset Still’s disease,” “adult Still’s disease,” “Still’s disease” and “AOSD” in combination with “fever of unknown origin.” We found more than 1000 titles. From among these titles, 143 published full-text English-language articles were identified for inclusion in this review. These articles, which included important case reports, original articles and review articles, were extensively reviewed by the authors. No randomized controlled trial was found, which may be due to the rarity of this disease. Major textbooks on rheumatology were also reviewed for background information.

## EPIDEMIOLOGY

Prevalence of AOSD is estimated to be 1.5 cases per 100,000-1000,000 people. It occurs worldwide and has been reported from France,<sup>[5,6]</sup> Norway,<sup>[7]</sup> Japan,<sup>[8,9]</sup> Greece,<sup>[10]</sup> USA,<sup>[11]</sup> Taiwan,<sup>[12,13]</sup> Spain,<sup>[14]</sup> Korea,<sup>[15,16]</sup> China,<sup>[17,18]</sup> Turkey,<sup>[19,20]</sup> India<sup>[21,22]</sup> and Iran.<sup>[23]</sup> The disease affects young people and has a bimodal age distribution with two peaks — at 15-25 and 36-46 years of age.<sup>[24]</sup> It is generally considered a disorder of youth,<sup>[25]</sup> but there are several reports of new cases of AOSD in older people.<sup>[24,26]</sup> The disease affects a slightly larger number of women as compared to men.<sup>[19,23]</sup> On the other hand, in some case series, male-to-female ratio was seen to be high.<sup>[4,6,21]</sup>

## PATHOGENESIS

The etiology of the disease is not fully

understood. Observations supporting the role of genetic, infectious and environmental factors have been published. In a review of 62 patients, HLAB17, B18, B35 and DR2 were associated with AOSD.<sup>[6]</sup> The existence of relationship of DRB1\*12, DRB1\*15 and HLA-DRB1\*04 with AOSD was reported in Korean patients.<sup>[27]</sup> In another study on Japanese patients, DRB1\*1501 (DR2) and DRB1\*1201 (DR5) alleles were more frequent in chronic articular than in polycyclic systemic AOSD; whereas DQB1\*0602 (DQ1) was observed in all types of AOSD.<sup>[28]</sup> Polymorphism in IL-1 and IL-18 genes was proposed by a few authors as a possible mechanism in pathogenesis of AOSD, but the former was not found to be associated with AOSD. Also, possession of the diplotype configuration of S01/S01 was found to be a major genetic risk factor for susceptibility to AOSD.<sup>[29-31]</sup>

Several reports have indicated the role of infectious factors but have not proved anything decisively. Viruses like rubella,<sup>[32]</sup> Epstein–Barr virus,<sup>[33]</sup> human herpes virus (HHV6),<sup>[34]</sup> hepatitis B and C,<sup>[35,36]</sup> parvovirus B19,<sup>[37]</sup> cytomegalovirus,<sup>[38]</sup> human immunodeficiency virus (HIV),<sup>[39,40]</sup> and bacteria like *Mycoplasma pneumonia*, *Chlamydia pneumonia*, *Chlamydia trachomatis* are considered to be risk factors.<sup>[41-43]</sup>

Several cytokines have been described in the pathogenesis of AOSD, including interleukin (IL)-1, IL-6, tumor necrosis factor–alpha (TNF- $\alpha$ ) and IL-18. Serum levels of these cytokines are highly elevated in active AOSD.<sup>[44]</sup> Higher levels of IL-18, IFN- $\gamma$ , sIL-2R and IL-8 were shown in patients with AOSD as compared to healthy controls. There is

a positive correlation between serum IL-18, sIL-2R and the level of serum ferritin in active AOSD.<sup>[45]</sup> Chen demonstrated that the mean percentage of Th1 cells was significantly higher in active AOSD, correlating with clinical activity score and serum IL-18, which plays a critical role in AOSD.<sup>[46]</sup> In several studies, it has been shown that high levels of IL-18 correlate with disease activity, and this is a predictor of liver dysfunction.<sup>[47,48]</sup> It has been also demonstrated for the first time that in biopsy specimens from skin lesions and synovium of patients with AOSD, Th1/Th2 cytokine mRNA expression is significantly higher than that in the specimens from healthy controls.<sup>[46]</sup>

Intercellular adhesion molecule 1 (ICAM-1) has been shown to be significantly higher in AOSD patients as compared with rheumatoid arthritis (RA) patients or healthy controls. Serum ICAM-1 levels correlate well with the clinical activity score, serum levels of ferritin, and aminotransferase in patients with AOSD.<sup>[49]</sup>

## CLINICAL MANIFESTATIONS

Fever, rash, sore throat and arthralgia are the most typical clinical features of AOSD.<sup>[4]</sup> Over 99% of patients manifest a fever  $\geq 39^{\circ}\text{C}$ . Fever is the most commonly quotidian or double quotidian manifestation. The highest temperatures are seen in late afternoon or early evening.<sup>[50]</sup> In the differential diagnosis of a patient with FUO (fever of unknown origin), AOSD should be considered; and maculopapular rashes, arthralgia and sore throat should raise the suspicion of AOSD.<sup>[51-54]</sup> Low-grade and atypical pattern of fever is sometimes seen in older patients.<sup>[19]</sup> Febrile spikes are often

accompanied by exacerbation of the other symptoms like rash, fatigue and arthralgia.<sup>[55]</sup>

The classic rash is an evanescent, salmon-pink, maculopapular eruption, which frequently appears during febrile attacks and is predominantly found on the proximal limbs and trunk with rare involvement of the face and distal limbs.<sup>[4,56,57]</sup> The rash can be mildly pruritic or may be associated with burning. In general, the Still rash lasts for hours and changes daily; although in some patients, the duration of the rash correlates well with the degree of systemic activity, and the rash may last for days without change.<sup>[50]</sup> It can be induced by a minor trauma (Köbner phenomenon).<sup>[58]</sup> Urticaria,<sup>[59,60]</sup> dermal plaque,<sup>[61-63]</sup> vesicles and pustules<sup>[64]</sup> are also described. Several atypical rashes have been reported.<sup>[65,66]</sup> Skin biopsy shows nonspecific inflammation and mild perivascular inflammation. Immunofluorescence of the skin biopsy may show some slight deposition of C3 at blood vessel wall.<sup>[67]</sup> Dermatographism is a frequently encountered phenomenon in patients with AOSD.<sup>[23]</sup>

The onset of the disease is usually heralded by a sore throat and constitutional manifestations. Sore throat is known as a cardinal sign of AOSD and may be associated with odynophagia.<sup>[68]</sup> Despite the presence of marked sore throat in most cases, physical examinations fail to show any significant findings. Throat cultures are negative, and viral serological tests are nondiagnostic in all AOSD patients. Antibiotic therapy is ineffective. Magnetic resonance imaging (MRI) of the larynx in 6 active AOSD patients has demonstrated cricothyroid perichondritis.<sup>[68, 69]</sup>

Arthralgia and arthritis occur in about 64% to 100% of the patients, and flare-up of joint symptoms occurs during the febrile spikes.<sup>[6,70,71]</sup> Presence of arthritis before constitutional and extra-articular manifestations is rare.<sup>[19]</sup> The most common joints involved are the knees, wrists, ankles and elbows. Sacroiliac involvement is uncommon but has been reported.<sup>[21,72]</sup> Narrowing of the carpometacarpal and intercarpal joint spaces is said to be specific for AOSD (as compared to more frequent radiocarpal joint involvement in RA).<sup>[73,74]</sup> Destructive arthritis is found in 25% of patients, and carpal joints are the most affected joints.<sup>[4,74]</sup> Destructive arthritis of the hips occurs in 5% to 33% of patients.<sup>[6,25]</sup> Joint fluid aspirate often discloses marked leukocytosis, with a neutrophilic predominance.<sup>[50]</sup> Generalized myalgia is seen in many patients and can be severe and coincide with fever spikes.<sup>[6,9]</sup>

Lymphadenopathy develops in approximately 44% to 90% of patients with AOSD<sup>[25,55,75]</sup> and may raise suspicion of lymphoma initially.<sup>[76-79]</sup> AOSD lymphadenopathy represents a wide spectrum of histopathological features: normal or nondiagnostic reactive hyperplasia, atypical paracortical hyperplasia, burnt-out histiocytic reaction, immunoblastic reaction and follicular hyperplasia. Occasionally, lymph node histology in AOSD may mimic malignant lymphoma.<sup>[16]</sup> Hepatosplenomegaly is common in early disease and reflects tissue infiltration by inflammatory cells.<sup>[19,23,80]</sup> Macrophage activation syndrome (MAS) is a life-threatening condition, which is characterized by uncontrolled activation and proliferation of T lymphocytes and macrophages in bone

marrow, reticuloendothelial system and central nervous system.<sup>[81]</sup> MAS is a dreaded complication of rheumatic diseases, especially systemic-onset juvenile rheumatoid arthritis (JRA).<sup>[82]</sup> It has also been reported in AOSD and should be considered in patients with AOSD when it presents with acute febrile illness; hepatosplenomegaly; lymphadenopathy; pancytopenia; increased serum liver enzymes; coagulopathy; central nervous system, pulmonary or renal involvement.<sup>[11,81]</sup> Hemophagocytosis which is seen in bone marrow aspiration and biopsy establishes the diagnosis, even though hemophagocytosis could be seen more frequently in biopsies from liver, lymph node and spleen.<sup>[82]</sup>

The reactive hemophagocytic syndrome (RHS) is a term describing a condition similar to MAS from the clinical and also the laboratory standpoint in patients with AOSD. It is characterized by fever, hepatosplenomegaly, lymphadenopathy, pancytopenia and increased serum liver enzymes, ferritin and triglycerides, which have been also described in MAS.<sup>[83]</sup> Despite similar immunologic abnormalities in MAS and RHS, there are significant heterogenic mechanisms leading to abnormal cytotoxicity in RHS and MAS;<sup>[84]</sup> although in recent studies, it is seen that authors believe that MAS is the primary type of hemophagocytic syndrome.<sup>[82]</sup> RHS is not so rare in AOSD, even though it could be underdiagnosed in clinical practice.<sup>[83]</sup>

Disseminated intravascular coagulopathy (DIC) is a critical condition secondary to pathological activation of coagulation system that occurs in the setting of several conditions, notably AOSD.

This entity has been reported by some authors in AOSD.<sup>[85-88]</sup>

inflammatory type with a predominance of neutrophils.<sup>[50]</sup>

There are several case reports about AOSD emerging first in pregnancy.<sup>[89-91]</sup> AOSD could be seen clinically in 3 forms: a self-limited or monocyclic pattern, an intermittent or polycyclic systemic pattern, and a chronic articular pattern.<sup>[19]</sup>

High levels of ferritin seem to be characteristic of AOSD.<sup>[3,19,68]</sup> Nearly 70% of patients have hyper-ferritinemia.<sup>[68]</sup> Cagatay reported very high levels of ferritin (>2000) in 38% of patients. High levels of ferritin can be seen in other diseases such as liver disease, infections and malignancies and especially in the hemophagocytic syndrome. Ferritin levels in AOSD are usually higher than those found in other autoimmune or inflammatory diseases.<sup>[3,68]</sup> Hyper-ferritinemia in AOSD is not related to iron metabolism and is likely to be a consequence of cytokine secretion induced by the reticuloendothelial system or hepatic damage;<sup>[3,19,94]</sup> but in most cases, ferritin levels are increased in the absence of overt liver damage.<sup>[3]</sup> Several cytokines — mainly, IL1 $\beta$ , IL-18, TNF- $\alpha$  and IL6 — seem to have some role in increasing the production of ferritin. A more specific diagnostic marker may be drop in glycosylated ferritin. In AOSD, decreased glycosylated ferritin, an isoform of ferritin, was noted in comparison with other inflammatory diseases. In 50% to 80% of healthy individuals,

In Table 1, clinical manifestations of AOSD that have been reported in various case series are shown.

### LABORATORY INVESTIGATIONS

An elevated ESR and leukocytosis more than 15000/ $\mu$ L are present in most of the patients. The findings of liver function tests may be elevated in up to three fourths of patients.<sup>[25,92]</sup> Anemia of chronic disease is common. Pancytopenia has been described in AOSD associated with hemophagocytic syndrome (HS).<sup>[93]</sup> Rheumatoid factor and antinuclear antibody tests are generally negative and, if positive, these are of low titers.<sup>[6]</sup> Synovial and serosal fluids are

**Table 1: Clinical manifestations of adult onset Still's disease**

Clinical features (Number of patients)	Cagatay <i>et al.</i> <sup>[84]</sup>	Chen <i>et al.</i> <sup>[82]</sup>	Pouchot <i>et al.</i> <sup>[62]</sup>	Mert <i>et al.</i> <sup>[20]</sup>	Bambery <i>et al.</i> <sup>[18]</sup>	Singh <i>et al.</i> <sup>[14]</sup>	Mehrpoor <i>et al.</i> <sup>[28]</sup>	Mitamura <i>et al.</i> (34)
F/M	59/25	59/23	28/34	12/8	10/8	5/9	21/7	22/12
Mean age (years)	33.33 $\pm$ 13.64	-	-	34	29	29.58	24.88 $\pm$ 11.64	40.6
Fever	95.2%	100%	100%	100%	100%	100%	100%	94%
Arthralgia	96.4%	100%	100%	90%	100%	100%	92%	91%
Arthritis	69%	100%	94%	65%	-	100%	60%	41%
Sore throat	65.5%	84%	92%	75%	-	35%	83%	85%
Rash	59.5%	87%	87%	85%	50%	57%	85%	91%
Dermatographism	26.2%	59%	-	-	-	-	92%	-
Lymphadenopathy	33.3%	-	74%	15%	67%	-	57%	58%
Splenomegaly	28.6%	-	55%	40%	56%	-	32%	64%
Pericarditis	11.9%	-	37%	-	0.05%	-	21%	9%

ferritin is glycosylated; while in inflammatory diseases, it drops to 20%-50%; and in AOSD, less than 20%.<sup>[3,95]</sup> Recently, in some studies, it was shown that hyper-ferritinemia, which is correlated to histiocyte hyperactivity, can lead to an association of AOSD with MAS.<sup>[19]</sup> Hyper-ferritinemia with a value between 4000 and 30000 mg/dL has been reported in association with onset and disease activity.<sup>[96]</sup>

The validity of the diagnostic test for hyper-ferritinemia has been evaluated in a retrospective study, where a fivefold increase in serum ferritin has 41% specificity and 80% sensitivity.<sup>[97]</sup> Furthermore, serum ferritin levels correlate with disease activity; and after remission, they get normalized. Glycosylated ferritin cannot be used to monitor disease activity or response to treatment, because it remains low for many months after the disease goes into remission.<sup>[98,99]</sup> Normal levels of total serum ferritin are not a criterion for exclusion of a diagnosis of AOSD.<sup>[100]</sup> Liver dysfunction in AOSD is frequent, and hepatic involvement can range from mildly elevated transaminases to severe hepatic failure unresponsive to treatment.<sup>[25,101-103]</sup>

The results of radiography are normal in the early phase of disease and may be helpful in the late stages and chronic phase, with

emerging erosions, joint space narrowing or frank ankylosis.<sup>[73,104]</sup>

## DIFFERENTIAL DIAGNOSIS

Before considering AOSD, many other diagnoses should be ruled out. Acute or chronic infections such as brucellosis, tuberculosis and bacterial endocarditic infections; malignant diseases, especially lymphoma; and autoimmune disorders like systemic lupus erythematosus and systemic vasculitides are among the most important differential diagnoses.

## DIAGNOSTIC CRITERIA

Despite the constellation of characteristic clinical manifestations, the diagnosis of AOSD is difficult in some instances, due to absence of specific serological and pathological findings. The Yamaguchi's criteria are the most widely cited criteria and were shown to be the most sensitive ones (93.5%).<sup>[105,106]</sup> In 2002, a new set of criteria were proposed by Fautrel *et al.*, which contained 2 new markers: serum ferritin and its glycosylated fraction. It does not have any exclusion criterion.<sup>[71]</sup> The sensitivity and specificity of Fautrel criteria were 80.6% and 98.5%, respectively. In Table 2, the two diagnostic criteria are shown.

**Table 2: Diagnostic criteria for adult onset Still's disease**

<i>Yamaguchi</i>	<i>Fautrel (new set of criteria)</i>
<i>Major</i>	<i>Major</i>
Arthralgia >2 weeks	Spiking fever $\geq 39^{\circ}\text{C}$
Fever >39 intermittent $\geq 1$ week	Arthralgia
Typical rash	Transient erythema
WBC >10000 (>80% granulocyte)	Pharyngitis
Minor	Neutrophil polymorphonuclear count $\geq 80\%$
Sore throat	Glycosylated ferritin fraction $\leq 20\%$
Lymphadenopathy and/or splenomegaly	Minor
Abnormal LFT	Typical rash
RF and ANA: Neg	Leucocytosis $\geq 10000/\text{mm}^3$

ANA: antinuclear antibody, RF: rheumatoid factor, LFT: liver function test, Neg: negative, RES: reticuloendothelial system.

## TREATMENT

Aspirin or NSAIDs are recommended as the initial treatment in AOSD, but the response rate is reported to be as low as 20% to 25%.<sup>[107]</sup> Liver enzymes should be closely monitored in patients in whom NSAIDs are used.<sup>[75,108]</sup> Since response to NSAID monotherapy is not enough, most patients are treated with corticosteroids in the course of their disease, with an efficacy of up to 95%. Prednisolone should be used for the patient who does not respond to NSAIDs and also for patients suffering from persistent anemia, pericarditis, serositis and marked elevation of liver enzymes.<sup>[50,109]</sup>

In a small number of case reports where the disease persisted despite administration of prednisolone, dexamethasone was used successfully.<sup>[110]</sup> Similarly, another case report demonstrated the efficacy of high-dose intravenous pulse methylprednisolone in treating disease refractory to prednisolone.<sup>[111]</sup> Intra-articular steroid injection is an important option in the treatment of AOSD patients with severe and chronic joint disease.<sup>[112]</sup>

Disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX), azathioprine, cyclosporine, cyclophosphamide have been used for maintenance therapy and control of disease.<sup>[113]</sup> Sulfasalazine appears to have severe adverse reactions in AOSD, as in systemic-onset JRA, and should be avoided in AOSD.<sup>[21,114]</sup> MTX is used in the treatment of AOSD due to its steroid-sparing effect. In many cases, arthritis and joint destruction are particularly found to respond to MTX administration.<sup>[24,115]</sup> Cyclosporine is a

valuable option in the treatment of AOSD and MAS.<sup>[81]</sup> In one case report, cyclosporine was used for treatment of AOSD with disseminated intravascular coagulation and multiple organ dysfunctions.<sup>[85]</sup>

Given the role of proinflammatory cytokines such as IL1 $\alpha$ , IL6 and TNF- $\alpha$  in the pathogenesis of AOSD, biologic agents have been used by some clinicians. Biological therapies can be administered to patients that do not respond to conventional medications such as corticosteroids and DMARDs.<sup>[116-119]</sup>

In various trials, use of infliximab, the monoclonal chimeric anti-TNF- $\alpha$  antibody, has also been reported to be effective in AOSD. In a study of 3 patients with chronic AOSD unresponsive to conventional treatment with prednisone and MTX, addition of infliximab (3 mg/kg in weeks 0, 2, 6, and every 8 weeks thereafter) led to improvements in both clinical and laboratory parameters.<sup>[119]</sup> In a Greek case series, 4 patients refractory to high doses of corticosteroids and MTX responded favorably to treatment with infliximab 3 mg/kg.<sup>[120]</sup> Infliximab at a dose of 5 mg/kg was found to be effective in a patient with early AOSD who was steroid resistant and ineligible for MTX treatment.<sup>[121]</sup> In another study, after administering infliximab to a patient of AOSD with persistent proteinuria and arthritis, proteinuria was decreased and arthritis was improved.<sup>[122]</sup> Adalimumab, which is an injectable protein that blocks the inflammatory effects of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), was also used in an AOSD patient.<sup>[123]</sup>

TNF-blocking agents (etanercept) have been employed in some studies.<sup>[124,125]</sup>

Etanercept in conjunction with MTX and corticosteroids was used successfully by Asherson and Pascoe in a single patient when multiple immunosuppressive drugs and plasmapheresis had failed.<sup>[126]</sup> Furthermore, etanercept was used in a patient with Still's disease and nephrotic syndrome due to renal AA amyloidosis, resulting in amelioration of proteinuria.<sup>[127]</sup> Deng-Ho Yang described a patient with flared-up AOSD and congestive heart failure due to left ventricular dysfunction. The patient showed no improvement with glucocorticoid therapy, but dramatic response was seen in the imaging and laboratory studies after therapy with etanercept.<sup>[128]</sup>

Administration of tacrolimus may be effective for patients with AOSD, even when TNF inhibitors and cyclosporine are not effective.<sup>[129]</sup>

Most recently, IL1 blockade (anakinra) has been used as a possible new therapeutic option. It was first used in a patient with refractory AOSD in the year 2005. After administration of anakinra, the patient achieved a prolonged remission.<sup>[130,131]</sup> Another study also showed the efficacy of anakinra in the treatment of 4 patients with AOSD that were refractory to treatment with corticosteroids and MTX. In all the 4 cases, the patients responded quickly to anakinra; symptoms resolved within days and laboratory values (WBC count, ferritin, C- Reactive Protein) were normalized.<sup>[132]</sup>

Due to the central role of IL-1R $\alpha$  in fulminant hepatic failure, anakinra was administered to a patient with AOSD complicated with acute hepatitis; the patient dramatically improved.<sup>[133]</sup> Plasma exchange<sup>[134,135]</sup> and

intravenous immunoglobulin<sup>[136-138]</sup> are the other treatments which were used in AOSD. These options were used in the treatment of patients with refractory AOSD with high serum levels of interleukin-10 and -18 (hypercytokinemia). Plasmapheresis [40 units of fresh frozen plasma six times totally (twice a week  $\times$  3 weeks)] resulted in rapid reduction in the elevated cytokine levels in the peripheral blood. The use of Intra Venous Immuno Globulin (IVIg) in AOSD has also been described in the treatment of flares at doses ranging from 0.4 to 2 g/kg/day for 2 to 5 days. Also in AOSD associated with pregnancy, IVIg 1 g/kg/day resulted in complete remission in one study.

Rituximab (monoclonal antibody, antiCD20) is a new option in treatment; there are some case reports about its usefulness in AOSD.<sup>[123,139]</sup>

Leflunomide, an immunomodulating agent, is used as a disease-modifying drug in rheumatoid arthritis. Inhibition of dihydro-orotate reductase by the A771726, the active metabolite of leflunomide, results in decreased lymphocyte proliferation. In addition, it seems that production of tumor necrosis factor- $\alpha$ , interleukin-1, nitric oxide and matrix metalloproteinase-3 by human synovial cells is inhibited by the A771726. In a few case reports, the efficacy of leflunomide was shown in the treatment of AOSD.<sup>[140-142]</sup>

As noted above, one of the cytokines that play an important role in AOSD is IL-6. It is suggested that systemic manifestations of AOSD, such as fever, leukocytosis and elevated ESR, are mediated by overproduction of IL-6. Tocilizumab, a humanized anti-IL-6 receptor (IL-6R) monoclonal antibody of the



IgG1 subclass, has been addressed in 2 case reports as being effective for AOSD.<sup>[143]</sup>

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