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Graz, am 02.02.2018 *Johanna Leonie Ruff eh*

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Zusammenfassung

Adult-onset Still's disease ist eine seltene autoinflammatorische Erkrankung unbekannter Genese des Erwachsenenalters.
Der adulte Morbus Still ist ein heterogenes Krankheitsbild, welches meistens charakterisiert ist durch ein typisches, lachsfarbenes Exanthem, hohes Fieber und Gelenksbeschwerden. Das klinische Bild kann sich vielseitig präsentieren, Organmanifestationen wie Hepato-/Splenomegalie, Lymphadenopathie und Serositis treten häufig auf. Im Labor zeigen sich deutlich erhöhte Ferritin - und Entzündungswerte, vor allem glykosyliertes Ferritin scheint betroffen und kann als als Marker für die Krankheitsaktivität nützlich sein. Neue Erkenntnisse führen zu der Annahme, dass zwei unterschiedliche Verlaufsformen mit verschiedenen Zytokinprofilen und Symptomen existieren. So gibt es einen systemischen Verlauf, welcher sich durch erhöhte Werte von IL-18,IL-6 und IL-1β, INF-γ, Organbeteiligung, hohes Fieber und einen ausgeprägten Anstieg von Ferritin im Serumäußert. Dem gegenüber steht ein Verlauf, bei welchem Gelenksbeschwerden und erhöhte Werte von IL-8, IL-17, IL-6, IL-23 und TNF-α im Vordergrund stehen. Es existieren bis dato keine allgemeingültigen Diagnosekriterien, in der Regel werden die sogenannten „Yamaguchi-Kriterien" zur Diagnosefindung angewandt. Auch Guidelines zur Therapie und Management der PatientInnen fehlen. Mittel der Wahl sind in vielen Fällen Glukokortikoide, oft mit erheblichen Nebenwirkungen wie Steroidabhängigkeit. Neue Biologicals zeigen in der „off-label" Anwendung bereits gute Ergebnisse, dies konnte bisher jedoch nur in retrospektiven Analysen und Fallberichten analysiert werden. Bei PatientInnen mit systemischem Verlauf erscheint vor allem der frühe Einsatz von Interleukin-1 Hemmern sinnvoll. Zudem wird die Herausgabe eines vielversprechenden Interleukin-18 Hemmers erwartet. PatientInnen mit vorwiegend Gelenksbeschwerden profitieren vor allem von TNF- α Blockierung und dem frühen Einsatz von Methotrexat. Therapeutikum erster Wahl bleiben zunächst Gluokokortikoide. Es gilt in Zukunft, die neuen Medikamente anhand großer kontrollierter Studien zu evaluieren, mehr über Zytokin- und genetische Profile von AOSD PatientInnen herauszufinden und allgemeingültige Guidelines zu erstellen.

Abstract

Adult-onset Still's disease is a rare autoinflammatory syndrome of unknown etiology, which affects mostly young adults.

Its clinical presentation is heterogenous, but usually characterized by a typical salmon-pink rash, high spiking fever and arthritis. Organ involvement such as hepato-/splenomegaly, lymphadenopathy and serositis occur frequently. High levels of ferritin and inflammatory markers are often present, especially glycosylated ferritin seems to be affected and may serve as a marker for disease activity. Currently, new findings concerning the patients' cytokine profiles lead to the assumption that there exist two subtypes of AOSD with different clinical manifestation and immunologic profile: A systemic course with high levels of IL-18,IL-6 und IL-1β, INF-γ, high fever, organ involvement and exaggerate levels of ferritin, with a greater risk of severe complications such as Macrophage Activation Syndrome; and an articular course with arthritis as the predominating symptom and high levels of IL-8, IL-17,IL-6,IL-23 und TNF-α. This course is more likely to become chronical.

Until now there are no general diagnostic criteria available, but Yamaguchi criteria are the most widely used ones. There exist no general guidelines concerning therapeutic strategies, either. Most physicians choose steroids as first line therapy, which often results in steroid dependence as a severe side effect. New biologic DMARD already showed good results in off-label use, but their efficacy could only be evaluated by retrospective data analyses and case reports. Patients with systemic disease course seem to benefit particularly from Interleukin-1 inhibitors and a promising interleukin-18 inhibitor will be provided soon. For articular manifestations TNF-α inhibitors and the early use of methotrexat show good results. Steroids still remain first-line therapy, but therapeutic strategies must be adapted to disease course and cytokine profile of the patients to successfully treat refractory AOSD. Large cohort controlled randomized trials are indispensable to further elucidate the efficacy of biologicals in AOSD. A focus should also lie on the development of general guidelines for the management of AOSD patients and further research concerning cytokine – and genetic profiles.

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Abbreviations

ALF Acute Liver Failure
ALT Alanine Aminotransferase
AOSD Adult Onset Still's Disease
BP Binding Protein
CAPS Cryopyrin-Associated Periodic Syndromes
CD Cluster of differentiation
CMV Cytomegalovirus
COX Cyclooxygenase
CRP C-reactive protein
CYP Cytochrome P
DHFR Dihydrofolate Reductase
DHODH Dihydroorotate Dehydrogenase
DIC Disseminated Intravascular Coagulopathy, Siehe
DMARDs Disease-modifying Antirheumatic Drugs
EBV Epstein-Barr Virus
EMA European Medicines Agency
ESR Erythrocyte Sedimentation Rate
FUO Fever of unknown origin
GF Glycosylated Ferritin
HLA Human Leukocyte Antigen
HLH Haemophagozytic Lymphohistiocytosis
IFN Interferon
IgG Immunglobulin G
IL Interleukin
MAS Macrophage Activation Syndrome
MEFV Mediterranesn Fever
MTX Methotrexate
NF Nuclear Factor
NSAID Nonsteroidal Anti-Inflammatory Drugs
NYHA New York Heart Association
PAH Pulmonary Arterial Hypertension
PCR Polymerase Chain Reaction
SJIA Systemic Juvenile Idiopathic Arthritis
TH T helper cell
TNF Tumor necrosis factor

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1 Introduction

Adult-onset Still's disease is a rare autoinflammatory syndrom that was first described by Eric Bywaters. It is named after George Frederic Still, who in 1899 observed a combination of symptoms in children similar to rheumatoid arthritis complicated by systemic manifestations -– the so-called Still's disease or systemic juvenile idiopathic arthritis (SJIA). In 1971 Bywaters found similar symptoms in adults, assuming it could be the same disease and naming it Adult-onset Still's disease. Characteristics of this disorder include – similar to its pediatric counterpart - (poly-)arthritis, high spiking fever and a characteristic salmon-pink rash, but clinical presentation can be heterogeneous, which makes it difficult to find the right diagnoses. Diagnostic criteria have been proposed but no general guidelines exist. The delay in finding the right diagnosis and establishing the right treatment often results in poor outcome, chronification of the disease with joint destruction or even severe complications that may lead to death.
Recent findings concerning the patients' cytokine profile might help to develop new strategies for diagnostic and treatment and help to better understand pathogenic pathways. In the last two decades, the development and administration of new (biologic) drugs have allowed new prospects for successful and more individualized treatment. Until this point, steroid therapy was seen as first line therapy, which often comes with steroid dependence and other side effects. The aim of this work is to summarize recent perceptions about AOSD and new treatment options.

2 Adult-onset Still's disease

2.1 Epidemiology

AOSD is a very uncommon disease and there are still no precise data available on its incidence. In Europe the annual incidence is described to be 0.1 to 0.4 per 100.000 inhabitants(1), prevalence rate in Asia and Europe is estimated to range from 1 to 10 patients per million(2). These data are very uncertain owing to the heterogeneous manifestations of AOSD and the lack of guidelines and distinct diagnostic criteria. The majority (three quarters) of patients that have been reported worldwide are between 16 and 35 at the time of disease onset. Women seem to be affected somewhat more frequently than men, with an incidence rate of 0.34 versus 0.22 per 100.000 in Japanese patients. (1,2).

2.2 AOSD and SJIA

AOSD is seen as the adult counterpart of Systemic Juvenile Idiopathic Arthritis (SJIA). Both maladies share similarities in symptoms, etiopathology, and response to treatment. They even seem to have similar cytokine - and gene-expression profiles (3). In spite of this, evolution of symptoms, clinical manifestation and epidemiology do show some differences and it is not yet entirely proven that it is really one and the same disease(4). For this reason this review will exclusively analyse data provided for - or at least in correlation with AOSD, without considering information only valid for SJIA.

2.3 Pathogenesis

2.3.1 Immunologic pathways

There is not yet much known about the exact immunologic pathways of AOSD. What researchers have found out so far is that there seems to be a mismatch of cytokines produced by TH1 cells and those produced by TH2 cells in favour of TH1(5) and that the cytokine profile of patients with chronic arthritis and those with systemic manifestation of AOSD seem to be different. In detail, patients with systemic subset tend to have elevated levels of IL-1ß, IL-18,IL-4, IFN-α/β, an increase in INF-γ and hyperferritinemia. In contrast, those patients that develop chronic arthritis have high IL-17, IL-23, IL-6 and TNF - α levels, while IFN - γ and ferritin levels remain low(6,7). Therefore, certain cytokines seem to correlate with certain disease manifestations.

Inoue et al. proposed to divide AOSD patients in two subgroups due to their serum cytokine profile: Those with predominant elevations in IL-6 and those with highly elevated IL-18. They analysed the cytokine profile of 27 Japanese AOSD patients all diagnosed according to Yamaguchi criteria (8). Patients belonging to the IL-18 subgroup showed remarkably higher levels of serum ferritin compared to IL-6 subgroup. In the IL-6 subgroup arthritis appeared significantly more often than in IL-18 subgroup (9).
Ichida et al. confirmed in a retrospective data analysis of 71 Japanese patients that there seem to be two subtypes of AOSD, one with high levels of IL-18 and systemic features and another with low IL-18 levels and arthritis (10).
Girard et al. showed similar results in European patients (7). It remains controversial whether a classification in IL-6/IL-18 subgroups might be reasonable and needs to be further investigated, but a correlation between arthritis in AOSD and IL-6 serum levels seems quite evident, just as between IL-18 levels and systemic course of AOSD (6, 9).

2.3.1.1 IL -1

IL -1 belongs to the Interleukin 1 family and takes great part in immunologic processes. This family contains several agonistic and antagonistic ligands whereof IL -1β is the one having the highest relevance for AOSD. A number of cells are able to produce IL -1β precursor, including macrophages, dendritic cells and monocytes. IL -1β precursor has to be activated by cleavage through caspase-1 before the release of its active form into the extracellular space. In turn caspase-1 is in need of inflammasome and its component cryopyrin to attain its active form. Gain of function mutations in cryopyrin can lead to an excessive secretion of IL -1β (11). These mutations are highly associated with a number of (auto-) inflammatory diseases and IL -1β is found to be elevated in AOSD as well(11,12).The effects of IL -1β include the activation of several cytokines and acute phase proteins of the innate immune response leading to clinical manifestations like fever, leucocytosis, thrombocytosis, articular damage through cartilage erosions and arthritis, weight loss and liver damage – typical clinical features of AOSD(12).
IL-1 receptor antagonists are already used off-label to treat AOSD and seem to be highly effective, underlining the assumption of IL-1 playing a role in AOSD pathogenesis (6, 12).

2.3.1.2 IL-6

IL-6 has an influence on the production of ferritin in the liver and may thus contribute to hyperferritinemia and hepatomegaly as common features of AOSD. An increase in IL-6 levels is associated with disease activity - elevated levels are found during fever spikes and correlate with high CRP. IL-6 was also found in skin biopsies taken from lesions of the typical salmon-coloured rash in AOSD patients and could thus be a possible predictor of skin manifestations (6,13). It seems to play a role in the development of the typical, salmon pink skin rash, as well as hepatomegaly, hyperferritinaemia and elevation of CRP and liver enzymes (6,14).

2.3.1.3 IL-8

IL-8 is a proinflammatory cytokine that was found to be elevated in patients suffering from AOSD. Its aim is to stimulate and degranulate neutrophils in inflammatory reactions (6). It does not seem to correlate with disease activity. Interestingly, IL-8 tends to be higher in patients suffering from the chronic articular form of AOSD, which makes it a promising marker to differentiate between the systemic and the chronic course of the disease. It was also found in skin lesion biopsies together with IL-6 and IL-18 (13).

2.3.1.4 IL-17

IL-17 was found elevated in numerous autoimmune diseases and likewise in AOSD (6,15,16). This proinflammatory cytokine is produced by T helper 17 (TH17) cells. TH17 cell differentiation from naïve T cells is induced by IL-6 and IL-13 and its role is among others to impede the invasion of bacterial and fungal germs by strengthening mucosal barrier surfaces (16). The secretion of IL-17 leads to the release of proinflammatory cytokines and chemokines, as well as matrix metalloproteases (15). Its role in AOSD pathogenesis is not yet proven but the levels of IL-17 and circulating TH17 cells are found elevated in AOSD. They seem to correlate with disease activity and the levels of IL-18, IL-6, IL-1ß, IL-21, and IL-23 and tend to decrease after successful therapy. A dysregulation of TH17 cells and an excessive release of IL-17 may thus play a role in the evolution of the disease or at least should be regarded in the development of targeted therapies that for example inhibit TH17 proliferation (15,16).

2.3.1.5 IL-18

IL-18 is a cytokine of the IL-1 family that has great bearing in innate and adaptive immunity. It is produced by various cell types, mainly macrophages and dendritic cells. Its functions in the inflammatory process are manifold, like the induction of IFN-γ production in natural killer cells in collaboration with IL-12 and in TH1 cells by the determination of Th1 maturation, as well as the activation of nuclear-factor kappa B (NF-κB), a transcription factor that plays an important role in immune response. Furthermore, it stimulates the release of chemokines and

metalloproteases and can activate cell-mediated cytotoxicity thus causing tissue damage (5,17). It is controlled by IL-18 binding protein (IL-18BP), especially the IL-18BPa isoform. This isoform has a high affinity to IL-18, its binding impedes receptor interaction of the cytokine necessary for the activation of NF-κB and the production of IFN-γ, and thus prevents exceeding inflammatory reactions (17). High levels of IL-18 are found in a number of inflammatory diseases, but in AOSD its elevation seems to be remarkably high, up to a 100-1000 fold of what was reported from other diseases(5). A cut-off of 148.9pg/ml was proposed by Priori et al. to differentiate between active AOSD and sepsis (18). It is not only found elevated in the sera of AOSD patients, but also in synovial biopsies (5). There is a strong association of high IL-18 levels and liver damage, which may result from the fact that IL-18 is produced by Kupffer cells in the liver where it can activate NK cells and CD8. This may also contribute to the erased levels of IL-18 found in MAS, a severe complication of AOSD (5,14,19). Indeed, patients with high IL-18 levels seem to have a greater risk to develop MAS and a systemic course of disease, while low levels where associated with chronic articular forms of the disease (17). The serum level of IL-18 strongly correlates with disease activity and high blood levels of ferritin, Alanine Aminotransferase (ALT), C-reactive protein (CRP) and leukocytes (5,6,14). Girard et al. found that this also applies for free IL-18 levels, i.e. IL-18 is not bound to IL-18BP. It even seems to have a higher sensitivity for disease activity compared to total IL-18. Apparently, there is not only an overproduction of IL-18 but also a deficiency in IL-BPa, resulting in a mismatch of Il-18:IL-BPa ratio. Interestingly, Girard et al. also noticed that in their cohort of 37 AOSD patients from Germany and Switzerland IFN-γ levels remained low or undetectable, as well as IL-12 levels. This led them to the conclusion that, in the absence of IL-12, IL-18 is not capable of producing IFN-γ, which in turn stimulates the production of IL-18BP. They propose the use of free IL-18 as a marker for disease activity and underline the need for further investigation of IL-18BPa and its potential use in AOSD therapy (17).

(Free) IL-18 may thus serve as a marker for disease severity, liver involvement and systemic manifestation of AOSD and seems to play an important role in its pathogenesis. Its use in the management of AOSD is very promising and needs to be further investigated (5,6,14,17,19,20).

2.3.1.6 IFN-γ

The role of Interferone (IFN)-γ in AOSD is discussed controversially. Some authors claim that high IFN- γ levels and disease activity do not correlate, whereas others assert that there is at least a connection between IFN- γ induced chemokines like C-X-C motif chemokine 10 (CXCL10 or IP-10) - and disease activity(21). IFN-γ contributes to growth and differentiation of macrophages, whose activation is exaggerated in AOSD as well as in MAS, a severe complication of AOSD (14).

2.3.1.7 TNF-α

TNF-α is a pyrogenic cytokine originally named “cachexin “since it causes cachexia. It plays an important role in acute phase reaction processes, as well as osteoclastosis and synoviocyte proliferation (19). The excessive activation of TNF receptors can provoke a severe inflammatory response with cell proliferation or apoptosis (22). It was found to be elevated in AOSD and systemic juvenile idiopathic arthritis in tissue and sera (9,19), although its levels were lower compared to rheumatoid arthritis. It does not seem to correlate with disease activity but with CRP levels. There was no difference between TNF-α levels of patients with systemic or chronic articular pattern (23). It does not appear to be elevated specifically in AOSD and thus it does not serve as a marker for the disease, but its inhibition showed good results in numerous case reports, which is further described below.

2.3.2 Predisposing genetic background

Several studies have suggested a connection between the course of AOSD and HLA antigens, namely HLA class I types B35 , DR2, DR5 and HLA class II types DRB1*15 and DRB1*12(1). B35 was more likely to be associated with self-limited course (24) while in a Japanese study DR2 and DR5 led to a chronic disease course (1).

MEFV exon 10 (M694I, G632S) mutations were found more frequently in AOSD patients compared to a healthy control group in Japanese population, which suggests low-frequency variants of MEFV gene as a predisposing factor(25).
The role of IL-18 in pathogenesis of AOSD has recently come under intense scrutiny since it usually is highly elevated and thus the presence of polymorphisms in human IL-18 gene seems plausible. Indeed, there seems to be an association of the diplotype configuration of S01/01 as a susceptibility factor (26).
Nevertheless a genetic contribution to AOSD pathogenesis is not yet sufficiently explored and further research needs to be done in the future(1).

2.3.3 Environmental factors

Not only genetic but also environmental factors seem to affect AOSD pathogenesis. Several germs have been identified as possible triggering agents in disease onset. Especially viruses frequently correlate with disease onset like rubella virus, parvovirus B19, echovirus 7, cytomegalovirus, also coxsackievirus B4, Epstein-Barr virus, mumps, parainfluenza virus, human herpes virus 6, hepatitis a and b virus, adenovirus and others (1,2,27).
Also bacterial germs such as Mycoplasma pneumoniae, Yersinia enterocolitica, Campylobacter jejuni, Borrelia burgdorferia, Brucella abortus and Chlamydia trachomatus / - pneumonia have been described in conjunction with onset in several case reports (1,2,28).

2.4 Clinical expression

2.4.1 Symptoms

Clinical presentation of AOSD is heterogeneous and unspecific. Nevertheless, some symptoms show certain characteristics that seem to appear in the majority of the patients naming a salmon-coloured rash, uncommonly high spiking, quotidian fever towards the evening, and arthritis. Although AOSD is a diagnosis

of exclusion, the occurrence of the following symptoms can help to identify patients suffering from AOSD.

2.4.1.1 Pharingytis

A nonsuppurative, severe pharyngitis with negative bacteria culture or sore throat frequently appears at the beginning of the disease or during recurrence (1). In an Italian multicentre retrospective study of 245 cases, around 62% of the patients suffered either from sore throat or pharyngitis (29). Other studies from Asia showed frequencies between 50% and 80% (30,31).

2.4.1.2 Fever

A quotidian, intermittent, high spiking fever over 39°C is one of the most frequent symptoms in AOSD (32). It usually lasts less than 4 hours and reaches its highest temperature in the early evening (33). The high temperature often comes along with shivers and is accompanied by the typical salmon-pink rash. Therefore, fever of unknown origin (FUO) should be considered as a potential manifestation of AOSD (34).

2.4.1.3 Skin

One of the few typical symptoms for AOSD is an evanescent, non-pruritic, maculopapular salmon-pink rash that usually occurs during fever spikes. It mainly affects trunk and proximal limbs, but may also appear in the face, palms, and soles of the feet. The rash happens to be confused with drug allergy due to NSAID or antibiotics previously given to treat joint pain and rule out infection. Koebner phenomenon can sometimes be seen. The skin efflorescence usually heals up completely without resulting in scars (33,35). Skin biopsy should only be done to rule out differential diagnoses since the histopathology is nonspecific, showing slight inflammatory infiltrates in the upper dermis (1).

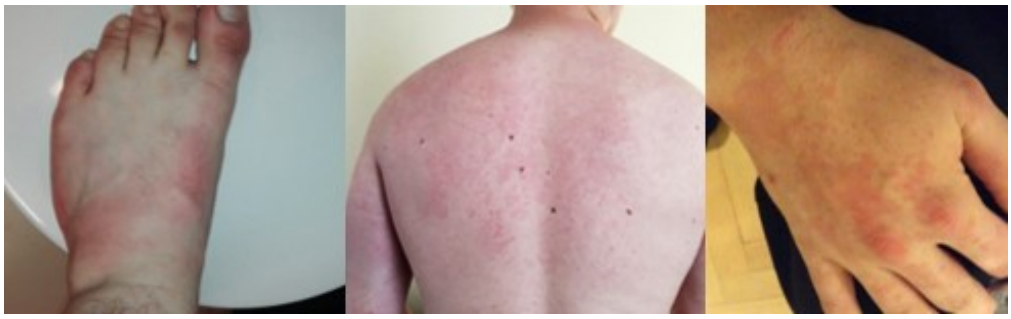

Figure 1 *Salmon-pink rash of a 23-year-old male AOSD patient (Dr. Liesel Ruff,Bonn)*

2.4.1.4 Joint involvement: Arthralgia or Arthritis

Most patients suffer from arthralgia (80% to 100%) or arthritis (18-100%) (1). At disease onset, arthritis might be mild and oligoarticular but become more severe, polyarticular and destructive after weeks or months. Joint pain usually worsens during fever spikes. Any joint can be affected but symptoms most frequently appear in knees, ankles and wrists.
Synovial fluid usually shows unspecific signs of inflammation; radiographic findings are nonspecific as well. Approximately, one third of the patients develop chronic and erosive arthritis, of which bilateral ankylosing carpal arthritis is predominant (2). The presence of ankylosis is even proposed to be used as a major diagnostic criteria by John Cush (37).

2.4.1.5 Lymphadenopathy

Lymphadenopathy usually affects the cervical chain with symmetrically swollen lymph nodes but may also appear diffuse and systemic. It is seen in up to 60% of the patients (1,29,38). Suspicious-looking, enlarged, non-symmetric lymph nodes should always be clarified by biopsy to exclude malignant lymphoma.
Histopathology differs clearly from the features found in rheumatoid arthritis, Sjögren's syndrome or systemic lupus erythematosus presenting as benign reactive hyperplasia consisting of plasma cells, neutrophils and B - and T - lymphocytes. Splenomegaly (20% to 60%) and hepatomegaly (20% to 40%) are commonly associated with lymphadenopathy (1,29,38,39).

2.4.1.6 Liver

Hepatomegaly occurs in about 20% to 40% whereas elevated liver enzymes are reported to appear in 50% to 70% (29). Liver failure can be associated with macrophage activation symptom. Acute liver failure (ALF) may appear in some patients and can lead to liver transplantation or even death. Liver function tests should be provided regularly. Valluru et al. reviewed characteristics of case reports on acute liver failure in patients with AOSD, suggesting methylprednisolone mega-dose pulse therapy to handle AOSD related ALF(40).

2.4.1.7 Others

Constitutional features have been described by a majority of the patients, including fatigue, nausea and rapid weight loss of up to 20 kg within the first month after disease onset (37). Also gastrointestinal symptoms have been described, which can be associated with acute pancreatitis or aseptic peritonitis (2). Serositis in general is a common symptom often appearing as pericarditis or pleuritic (41). Less frequent manifestations were described in single case reports including kidney involvement such as glomerulonephritis and acute kidney failure; neurologic symptoms like aseptic meningitis, encephalitis and ischemic stroke; ophthalmologic manifestations such as uveitis, conjunctivitis and retinopathy; thrombosis and angioedema (2,42)

2.4.2 Laboratory Features

The majority of the patients suffering from AOSD shows certain laboratory findings that are mostly to be seen as a result of the occurring systemic inflammation. Still they might help to rule out some differential diagnoses, even more since some parameters that are typical for other rheumatologic disorders like antinuclear antibodies and rheumatoid factor remain negative. Some biological features, above all serum ferritin and glycosylated ferritin (GF) are promising markers for disease activity and may help to establish the diagnosis. (1)

2.4.2.1 White blood cell count

An increase in white blood cell count can be seen in up to 98% of the patients. Leukocyte count usually exceeds 10.000-15.000 cells/mm^3 and even reaches 50.000 cell/mm^3 (2). The percentage of neutrophils usually represents more than 80%(43).

Leukopenia may occur as well and is mostly seen in patients with macrophage activation syndrome (MAS) (2).

2.4.2.2 Liver enzyme abnormalities

Elevated liver enzymes can be found in 50% to 75%. They are more common in patients with hepatomegaly and might be either due to hepatotoxic medical treatment such as NSAID or simply part of the inflammatory process (1,2). Hepatic insufficiency, fulminant hepatitis and necrosis have been described.

2.4.2.3 Inflammation

In almost all patients C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are highly elevated. They are highly unspecific parameters and can be found elevated in most differential diagnoses as well. Nevertheless, some authors see a correlation between increased CRP and serum ESR and a poor prognosis (29,30).

2.4.2.4 Ferritin

An elevation of serum ferritin is seen in up to 70% of the patients and is described to have a sensitivity of 80% and a specificity of 46%. It seems to increase dependent on disease activity and is thus proposed to be used to control the efficiency of treatment (1).

Since the 1970‘s serum ferritin is used as a diagnostic marker for many different diseases. Its reference range differs depending on the laboratory but usually rates between 30 to 300ng/ml for men and 10 to 200 ng/ml for women are described as normal(44)

A highly elevated serum ferritin is seen in infections (e.g. HIV), malignant diseases (e.g. melanoma, lymphoma), hemochromatosis and other disorders and thus can hardly be used to get any specific diagnostic information. Nevertheless, an extraordinary increase of serum ferritin namely more than 5 times the upper limit of normal has been described in AOSD and proposed as a diagnostic marker (45) Fautrel et al. reviewed the diagnostic meaning of serum ferritin and glycosylated ferritin (GF). They suggested that the combination of elevated serum ferritin and a GF rate < 20% should be seen as important diagnostic tools for AOSD if they appear together with typical clinical manifestation. Limiting factors are the lack of laboratories providing tests for GF as well as the fact that GF seems to remain decreased in non-active AOSD and thus is independent of disease activity.

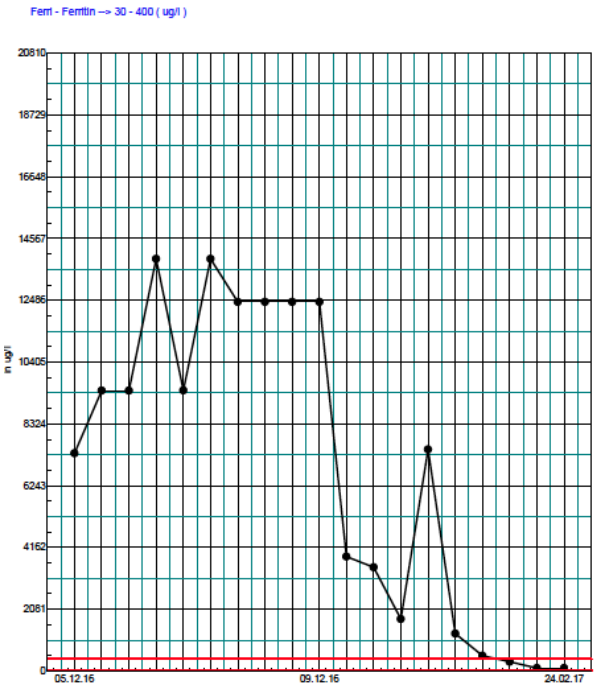

Figure 2 *Ferritin level of a 23-year-old male AOSD patient before and after prednisolone therapy (09.12.16) (Dr. Liesel Ruff,Bonn)*

2.4.2.5 Immunologic studies

In 90% of the patients, ANA and RF are found to be negative (1). The most promising immunologic parameter seems to be Interleukin (IL)-18. An elevation of this pro – inflammatory cytokine apparently correlates with disease activity, particularly free IL-18 serum levels (5,17). Elevated levels of IL-6, tumor necrosis factor (TNF) – α and interferon- γ are also very common and seem to play an important role in the pathogenesis of AOSD (2). Patients suffering from systemic AOSD seem to have a different immunological profile compared to those with chronic arthritis as the prominent symptom: elevated levels of IL-1β, IL-18, IL-4, INFα/β, an increase in INF γ and a hyperferritinemia are more common in patients with systemic subset, while high IL-17, IL-23, IL-6 and TNF – α level and low INF-γ and ferritin are more commonly seen in patients with arthritis as the predominant feature (6,14). However, cytokine tests are not yet used in clinical routine and their potential role as diagnostic parameters still needs to be investigated. So far they might be helpful to exclude other (auto-) inflammatory disorders.

2.5 Classification criteria

2.5.1 Yamaguchi

The most widely used classification criteria were published in 1992 by Yamaguchi et al.(8), as demonstrated in table 1. They describe 5 major and 2 minor criteria whereof at least 5 clinical expressions should be seen in the patient, including 2 of the major criteria. Furthermore differential diagnoses should be ruled out: The absence of infection - above all sepsis and Epstein-Barr virus- , malignant diseases like lymphoma and inflammatory diseases like polyarteriitis nodosa must be demonstrated.

Yamaguchi criteria have a sensitivity of 96.2% and a specificity of 92.1%(2).

Major criteria	Minor criteria
Fever ≥ 39 °C for 1 week	Lymphadenopathy or splenomegaly
Arthralgia > 2 weeks	Pharyngitis/ sore throat
Leukocytes ≥ 10,000/mm^3	Abnormal aminotransferases
Maculopapular non pruritic, salmon-pink rash	Negative rheumatoid factor or antinuclear antibodies
Neutrophils ≥ 80%	

Exclusion criteria
Absence of infection
Absence of malignant diseases
Absence of inflammatory diseases

At least 5 criteria, including 2 major, no exclusion criteria

Table 1 *Yamaguchi criteria*

2.5.2 Fautrel

In 2002 Bruno Fautrel at al. published a new type of classification criteria (Table 2) (35) based on their retrospective multicentre study „*Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease"*(45), which shows the importance of glycosylated ferritin in the diagnostics of AOSD.

Six major and 2 minor criteria are proposed including high spiking fever, arthralgia, transient erythema, pharyngitis, glycosylated ferritin, neutrophil count, maculopapular rash and leukocytes count. On patients showing either 4 major criteria or 3 major – and 2 minor criteria AOSD can be presumed.

The specificity and sensitivity are reported to be 98.5% and 80.6%. The main disadvantage of Fautrel criteria remains the lack in laboratories able to measure glycosylated ferritin.

Major criteria	Minor criteria
Fever ≥ 39 °C for 1 week	Lymphadenopathy or splenomegaly
Arthralgia > 2 weeks	Pharyngitis/ sore throat
Leukocytes ≥ 10,000/mm^3	Abnormal aminotransferases
Maculopapular non pruritic, salmon-pink rash	Negative rheumatoid factor or antinuclear antibodies
Neutrophils ≥ 80%	

Exclusion criteria
Absence of infection
Absence of malignant diseases
Absence of inflammatory diseases

At least 5 criteria, including 2 major, no exclusion criteria

Table 2 *Fautrel criteria*

2.5.3 Cush Criteria

The Texan rheumatologist Dr. John Cush published in 1984 diagnostic criteria (Table 3) with a sensitivity of 80% and a specificity of >92%. Similar to his colleagues he determines major (each with a value of 2 points) and minor criteria (1 point each)(33). They differ slightly from the ones chosen by Fautrel and Yamaguchi: For example he does not consider ferritin but includes some other symptoms such as ankylosis and serositis. Then - in contrast to Fautrel and Yamaguchi - the time of observation plays a central role in this diagnostic tool to differentiate between definite AOSD and probable AOSD.

Major criteria (2 p.)	Minor criteria (1 p.)
Quotidian fever ≥ 39 °C	Onset age < 35
Still's rash	Arthritis
Carpal Ankylosis	Sore throat
White blood cells >12500/mm^3 and Erythrocyte sedimentation rate >40mm/hr	Reticuloendothelial system involvement or abnormal Liver function tests
Negative rheumatoid factor and antinuclear antibodies	Serositits
	Cervical/tarsal Ankylosis

Definite AOSD: 10 Points + 6 months of observation
Probable AOSD: 10 Points + 6 weeks of observation

Table 3 *Cush criteria*

2.6 Differential Diagnosis

Since clinical features are mostly unspecific there are many differential diagnoses to be considered before making the diagnoses of AOSD.
It is extremely important to rule out the most severe differential diagnoses such as infection or malignancies, since AOSD therapy like steroids may impair the course of infections and – the reverse - treatment for other suspected diseases with NSAIDs or antibiotics can lead to complications such as MAS in AOSD.

2.6.1 Infection

Due to the high fever, sore throat, joint pain, rash and unspecific constitutional features AOSD is often being misdiagnosed and mistreated as an infection at disease onset. It is highly important to exclude bacterial or viral germs as a cause of the symptoms since treatment e.g. with antibiotics might lead to severe complications.

Depending on the medical history patients should be tested on viral infections like HIV, viral hepatitis, Parvovirus B19, Zika Virus, Dengue Virus, Chikungunya, rubeola and rubella, as well as bacterial infections such as lyme disease, yersiniosis, tuberculosis, brucellosis, mycoplasma pneumoniae and syphilis. Even parasitological infections should be considered as a potential differential diagnoses, e.g. toxoplasmosis. PCR, blood cultures and serology should be used to rule out potential infections.(43)

2.6.2 Malignant diseases

The most likely malignant differential diagnosis might be malignant Hodgkin or non-Hodgkin lymphoma. Lymphadenopathy is a common symptom of AOSD and the presence of suspicious-looking, non-symmetrical, enlarged lymph nodes should always result in biopsy.
Other malignancies might be masked by AOSD as well, including paraneoplastic syndromes, Castleman's disease, solid cancers of colon, kidney or lung, angio-immunoblastic lymphadenopathy and others (2,43,46).

2.6.3 Autoimmune/autoinflammatory diseases

Certain autoimmune diseases can mimic AOSD, overall those whose clinical manifestation often appear as rash and joint – or muscle pain. Especially polyarteriitis and poly-/dermatomyositis might be confused with AOSD. In patients mostly suffering from arthritis, seronegative rheumatoid arthritis should always be considered.
Also autoinflammatory diseases may show similar symptoms as AOSD, for example hyperimmunoglobulin D syndrome, familial Mediterranean fever and TNF-receptor-associated periodic syndrome, even though they usually already show symptoms during childhood. They can be ruled out by genetic testing (2).

2.6.3.1 Schnitzlers Syndrome

Schnitzlers syndrome is a rare disease of unknown origin and pathogenesis, considered to be of autoinflammatory origin. Common symptoms include lymphadenopathy, fever, joint pain, splenomegaly or hepatomegaly and an urticarial rash, thus very similar to Still's disease. Just as AOSD it is a diagnosis of exclusion, which makes it even more difficult to differentiate between these two very rare syndromes (47).

2.6.3.2 Sweet Syndrome

Acute febrile neutrophilic dermatosis or Sweet's syndrome is usually characterised by distinctive skin alterations with painful red nodules or papules in the papiallry dermis. But it may also show extracutanous manifestations that resemble AOSD, such as arthritis, myalgia, fever, leukocytosis with neutrophilia and elevated erythrocyte sedimentation rate. Biopsy of the skin lesions and cytokine profile can help to establish the right diagnosis (48).

Other systemic disorders may be confused with AOSD like sarcoidosis, systemic lupus erythematosus, Whipple disease, Kikuchis disease and more.

2.7 Natural history

2.7.1 Evolution of Symptoms

Most authors describe three natural courses of the disease, based on the progress of clinical symptoms.

A **monocyclic pattern** is defined as a systemic, self-limiting single episode of the disease that will lead to complete remission and thus to the total absence of clinical symptoms usually within 9 – 12 months(2,42,49)It is characterised by mostly systemic symptoms at disease onset such as high fever and abnormal liver function tests while joint involvement is seen less frequently(38)20-50% of the

patients suffering from AOSD will undergo a monocyclic course of the disease, exact data vary in different studies, but the early onset of treatment and short diagnostic delays seem to have a positive influence on fast and absolute remission(2,38,42,49,50).

The **polycyclic** or intermitted course is characterized by multiple symptomatic episodes with complete remission between the single flares. Remission periods may last from weeks to even many years while flares can manifest with both systemic and/or articular symptoms, which usually last for about 12 months. A polycyclic evolution is seen in 10-40% of the patients.

In some cases, it may merge into a persisting **chronic articular** disease course with polyarthritis as its dominating symptom. Systemic features may occur as well but are seen less frequently in the chronic disease pattern. Chronic articular evolution has been described in up to 67% of the patients (2) but most authors presume that about 40% of the patients will develop a chronic form of the disease. (42) About one-third of these patients will suffer from erosive arthritis possibly leading to disability that may strongly influence their daily life (2,38,42).

2.7.2 Subtypes

Recently it is assumed that there exist two subtypes of AOSD, one with predominantly systemic and one with articular manifestation. Cytokine profile, clinical symptoms, laboratory features and response to treatment seem to be different, although a distinct categorization is not always possible.
The **systemic** subtype is characterized by organ involvement like hepatitis, hyperferritinemia, macrophage activation, an excessive inflammation process with especially high levels of IL18, IL6, IL1β. They probably are at a greater risk to develop MAS or other severe systemic complications.
Patients belonging to the **arthritis** subgroup suffer from chronic polyarthritis that may lead to join destruction over the time. Their cytokine profile is dominated by high levels of IL-6, IL-8, IL-17, IL-23, TNF-α and IFN- γ(19,51).

2.8 Prognosis

2.8.1 Puchot systemic score

In 1991 Puchot et al. (52) published a score, which should facilitate to differentiate between active and non-active AOSD and thus give an idea about the prognosis of the disease condition.

This systemic score determines 12 common disease manifestations:

1. Fever
2. Typical rash
3. Pneumonia
4. Pleuritis
5. Pericarditis
6. Hepatomegaly or abnormal liver function tests
7. Splenomegaly
8. Lymphadenopathy
9. Leucocytosis ≥ 15.000/mm^3
10. Sore throat
11. Myalgia
12. Abdominal pain

Each manifestation is scored as 1 point and a total of ≥ 4 points is considered to be a sign of an active disease. Sensitivity is described to be 92% with a specifity of 93%.

In 2016 Ruscitti et al. (53) published a retrospective analysis where they investigated the use of Pouchot systemic score as a prognostic factor. Therefore, they analysed 100 cases from three centres regarding disease manifestation at time of diagnosis, outcome and systemic score.
Based on their results they proposed a cut-off value of a systemic score ≥7 as a prognostic factor and to identify patients with a higher risk of AOSD - related death.

Thus it might be used to assess disease activity and to detect those patients having a higher risk to die of AOSD.

2.8.2 Prognostic factors

Prognosis also depends on the course of disease, as well as on the subtype. In a retrospective data analyses of 7 patients from France Gerfaud-Valentin et al. investigated predictive factors for either favourable (monocyclic) or non-favourable (polycyclic, chronic articular, complications) outcome. They found out that in their patients' cohort the occurrence of arthritis and joint erosions at the time of diagnoses were predictive factors for an unfavourable outcome, namly a chronic articular course of disease. High fever in contrast seems to be predictive for a systemic, monocyclic course. The early testing for glycosylated ferritin led to early diagnosis, which itself was described as predictive for a good prognosis and monocyclic disease course. A delay in diagnosis of over 2 months redounded to a poorer prognoses. Also high levels of leukocyte count, erythrocyte sedimentation rate and CRP seem to lead to higher relapse rates and poor prognoses (38). These findings need to be confirmed by prospective studies with larger patient cohorts from different countries and under consideration of the received treatments, but they can at least be indicators to detect patients with a higher risk for poor prognosis and the development of severe complications.

2.9 Complications

2.9.1 MAS

Macrophage activation syndrome is a disorder similar to haemophagozytic lymphohistiocytosis (HLH) that mainly appears in juvenile systemic rheumatoid arthritis and adult onset still's disease but may also be associated with other rheumatic diseases. It comes along with an overwhelming inflammation caused by activated T-lymphocytes and hemophagocytic macrophages. MAS is often

triggered by infections, such as EBV, CMV (54) and others or flares of the primary disease.

There are some case reports describing an association between MAS activation and certain drugs.

MAS is potentially fatal with mortality rates between 20-30%. This is often in consequence of a delay in diagnostic and appropriate treatment. Main symptoms are cytopenias, liver dysfunction and coagulopathy resembling disseminated intravascular coagulations. Persistent fever, decreased erythrocyte sedimentation rate, and elevated liver enzymes are commonly seen. Macrophages mostly infiltrate bone marrow and lymph nodes, but can be found in every other organ as well. The incidence of MAS in AOSD is about 7-15% and it seems to be slightly more frequent in women compared to men (55,56)

Pathophysiology is not yet fully understood but the main factor seems to be a cytokine storm, induced by an exceeding activation of macrophages and cytotoxic CD8+T cells (57). Villanueva et al. suggested that there might be a correlation between natural killercell (NK) dysfunction and MAS and that NK dysfunction may also contribute to the onset of MAS in SJIA (58).

There exist no specific diagnostic criteria for MAS in AOSD but several authors proposed diagnostic criteria for MAS in its counterpart SJIA (59).

Also it is proposed to use the well established diagnostic criteria for HLH, published by the International Histiocyte society. Some authors even propose to classify MAS among histiocytic disorders instead of seeing them as a separate entity (56)

Bone marrow aspirate is very helpful for diagnostics and seems to be more sensitive than bone marrow biopsy (55).

Bone marrow biopsy usually shows haemophagocytosis and can be used as a diagnostic criterion (57). Also remarkably high levels of Ferritin seem to be quite characteristic for MAS and can help to differentiate between MAS and for instance sepsis (60). However, diagnosis is difficult since symptoms are very unspecific and can easily be confused with sepsis or a flare of actual AOSD.

There are no guidelines concerning the therapy of MAS in AOSD but the usual treatment consists of methylprednisolone pulse therapy, e.g. 30mg/kg daily for three days and 2-3mg/day subsequently (57) or 500-100mg/day for 6 days (61).

MAS has also been treated successfully with tocilizumab (62), cyclosporine A (63,64) and anakinra(65).

2.9.2 Disseminated intravascular coagulopathy (DIC)

DIC is a syndrome resulting from a disturbance in the coagulation system. It never occurs isolated but is always associated with a given underlying disease such as malignancy, sepsis, trauma or others. They all share the ability to activate coagulopathy either by cytokine activation or by the release of procoagulopathic substances. This can lead to microvascuar thrombosis resulting in organ failure and to excessive bleeding due to a deficiency of coagulation factor and platelets. (66-68). The aim of the treatment will always be to medicate the underlying condition, since in most cases DIC will spontaneously resolve if the primary disorder is being controlled. Nevertheless, in some cases blood component therapy is indicated to control severe bleeding and avoid further complications and aggravation (67,68). It is a life-threatening disorder that has also been described in association with AOSD (66). Several case reports have been published assuming that DIC might be triggered by MAS (66,69), a flare of AOSD itself(70) or be iatrogenic due to AOSD treatment(71). This makes an early diagnose of DIC even more difficult. Clinicians should be sensitized to symptoms like purpura and petechia, as well as non-remitting fever – symptoms that usually do not occur in AOSD. Also an abrupt fall of erythrocyte sedimentation rate and an increase in serum-soluble adhesion molecules and soluble thrombomodulin can help to identify DIC (72).
Therapy of DIC in AOSD includes established treatment options for AOSD such as methotrexate, corticosteroids (71,72), anakinra(73) or IL-6 inhibitors(74) and – in severe cases – the administration of heparin(71).

3 Therapeutic agents

3.1 Traditional

3.1.1 NSAID:

Non steroidal anti inflammatory drugs have an analgetic, antipyretic and antiphlogistic effect by inhibiting the biosynthesis of prostaglandins. This happens through blocking cyclooxygenases (COX) 1 and 2. COX-1 is involved in the physiological production of prostaglandins, while COX-2 mainly gets induced by inflammatory processes (75)

Adverse effects:
Adverse effects are mainly induced by COX-1 inhibition. They include gastrointestinal symptoms such as ulcers, nausea, dyspepsia and diarrhea, kidney disfunction with edema and hypertension, allergic skin reactions, inhibition of thrombocyte aggregation, anemia and cardiovascular disorders such as myocardial infarction (75).

Use in AOSD:
High spiking fever, muscle- and joint pain are beyond the first symptoms of AOSD. NSAID are especially useful in the beginning of the disease since they reduce the inflammation process, help to control the fever and reduce the pain. Most authors describe their use as symptomatically adjuvant and less in a therapeutic way, others claim that 15-20% respond to NSAID as an initial treatment (76). They are usually given in combination with glucocorticoids. In this case, the administration of proton-pump inhibitors for protection of the gastrointestinal mucosa is very important.

3.1.2 Glucocorticoids

Glucocorticoids belong to the class of steroid hormones and are physiologically produced by the adrenal cortex.

Mechanism of action:
They have an anti-inflammatory and immunosuppressive effect and hence are commonly used to treat autoimmune diseases. Their mode of action is complex but among others they work by inhibiting interleukin 1,3,4,5,6,8, TNF- α, interferon and the synthesis of cytokine receptors. Furthermore, they stimulate the synthesis of lipocortin-1 which itself inhibits phospholipase A2 and thus the release of arachidonic acid. These mechanisms play an important role in controlling acute and chronic inflammatory processes in the human body. The use of glucocorticoids in autoimmune/- inflammatory diseases is very common (77).

Adverse effects:
They are mostly seen in long term use of glucocorticoids and rarely seen in single dose treatment. Due to their immunosuppressive effects patients have an increased risk to contract infections, impaired wound healing, and osteoporosis. Also arterial hypertension and steroid myopathy are commonly seen (78)
Cushing`s syndrome is a result of corticosteroid overdose. Most common symptoms include upper body obesity, round face, slender arms and legs, fatigue, muscle weakness, hypertension, metabolic disorders such as diabetes and others.

Contraindications:
Absolute: Acute viral infection, especially hepatitis A, B and C, Varicella attenuated vaccines should not be given during glucocorticoid therapy;
Relative: History of osteoporosis, gastrointestinal ulcera, active tuberculosis

Use in AOSD:
The use of glucocorticoids (mainly prednisolone) in AOSD is reasonable due to their immunosuppressive and anti-inflammatory effects. They are used as first-line therapy in many cases and seem to be more effective in the systemic course than

in patients with articular manifestations. Around 60% of the patients respond to steroid therapy (79). Steroid dependence remains a serious problem, it occurs in around 45% of the patients and often requires the addition of steroid sparing agents (80)The dosage administered varies and depends on disease activity, but the initial dose usually is around 0.5 - 1.0mg/kg. In severe cases high-dose intravenous pulse therapy with methylprednisolone can be beneficial. The duration of the treatment depends strongly on disease activity, down tapering should be carried out slowly due to the risk of relapse but should be done within 6 months to avoid steroid dependence (33).

3.1.3 Tacrolimus

Tacrolimus or FK-506 is a macrolide immunosuppressive agent isolated from the fermentation broth of *Streptomyces tsukubaensis*. It was developed in the 1990s to prevent and treat organ rejection in transplantation. It has a mean disposition half-life of about twelve hours and is administered orally or as IV injection. Tacrolimus is metabolized by CYP3A4/5 in the liver, its bioavailability is approximately 15% in healthy persons. The fat content of alimentation and gene polymorphisms of CYP3A5 influence its blood concentration. It strongly binds to the cytosolic FK506 binding protein (FKBP) thus prevent its activation. This inhibits the release and transcription of cytokines such as IL-2 and thus results in immunosuppression. Its mode of action is very similar to cyclosporine (81).

Adverse effects:

The most common adverse effects as reported by the U.S. Food&Drug Administration include infections, mainly of the respiratory tract, diarrhea, nausea, constipation, peripheral edema, tremor and anemia. Patients treated with Tacrolimus are under a greater risk to develop lymphoma or other malignancies and have an increased risk to develop infections (82).

Use in AOSD:

The use of tacrolimus in AOSD is still off-label and only very few case reports have been published. The usual dosage administered in AOSD was 2-4mg/day orally,

partially in combination with steroids. In 8 case reports of refractory AOSD 7 patients received at least partial remission or reduction of steroids (83-85). Adverse effects were seen in one patient who developed an increase in serum creatinine and potassium levels (85). Interestingly, tacrolimus could reduce the levels of IL-18(83,84) and it could be shown that in vitro tacrolimus and cyclosporine A inhibited the production of IL-18 in peripheral blood mononuclear cells(86). Its usage in refractory AOSD with high levels of IL-18 seems promising and demands further investigation.

3.1.4 Cyclosporine

Cyclosporine is a lipophilic cyclic endecapeptide, which is obtained from the fungi *Trychoderma polysporum* and *Cynlindrocarpum lucidum.* It has an immunosuppressive effect and was primarily developed and used for transplant medicine (87).

Mechanisms of action:
Cyclosporine inhibits the synthesis of lymphokines, especially interleukin-2. It binds to cyclophilin, a cytosolic protein, building a complex that has the ability to block calcineurin. By blocking calcineurin they inhibit transcription factors such as NFAT or NF-κB, which are important for the synthesis of cytokines in T-lymphocytes, especially IL-2. As a result, cellular immune reactions are being suppressed (87)It also shows an antiphlogistic effect(75).

Adverse effects:
Hepatotoxicity, kidney failure, tremor, hypertrichosis, and gingival enlargement. Long-term adverse effects include hypertension, diabetes mellitus, adiposity and hyperlipidaemia.

CAVE: Cyclosporine is metabolized by CYP3A4 and inhibits CYP3A4 and P-glycoprotein at the same time. This may lead to drug interactions with inhibitors or inductors of CYP3A4, which might increase or decrease the level of cyclosporine (75).

Use in AOSD:

Cyclosporine has already been used off-label in numerous cases of refractory AOSD. A case series from 2010 published by Franchini et al. analysed the efficacy of cyclosporine (250mg/day) in 12 patients with chronic articular or systemic disease course and reported an efficacy of 75%. It was also efficient in treating one patient who developed hemophagocytosis with multi-organ failure in combination with steroid pulse therapy and a dosage of 300mg/day.(88)
Another retrospective study from Japan published by Mitamura in 2009 reports the efficacy of cyclosporine combined with corticosteroids in 6 patients.(89)
The case of a 19-year-old male patient in Israel published by Bishara et al. in 2016 showed good results of cyclosporine in AOSD complicated by severe hepatitis concurrent with hyperferritinemia.(90)
A 40-year-old female patient from Korea developed pulmonary arterial hypertension (PAH) after a flare of AOSD. The flare was treated with steroids and anakinra, but the treatment did not lead to total remission and the disease was complicated by PAH. The initial treatment was thus discontinued and replaced by a combination of furosemide, bonsentan, prednisone and cyclosporine (150mg). Bonsentan had to be discontinued due to a drug interaction with cyclosporine, but the treatment combination administered lead to remission of AOSD and improvement of PAH symptoms. After a few months the patient could continue with only sildenafil 75mg and cyclosporine 100mg/day (91).

Cyclosporine seems to be effective in refractory AOSD, especially in combination with steroids, even in the case of severe complications.

3.1.5 Gold salt

Gold salt is commonly used in other rheumatic diseases. A retrospective study shows that there might be an association between gold salt and the onset of macrophage activation syndrome. The authors propose gold salt to be contraindicated in AOSD, also because their efficacy is not proven (55).

3.2 DMARD

Disease-modifying antirheumatic drugs is a group of therapeutic agents with different pharmacological characteristics that are used to treat rheumatic diseases with the aim of receiving remission or at least retardation. They have an immunosuppressive effect which makes them very useful in all kind of rheumatoid or autoinfammatory diseases. Since they do not show any analgesic effect, DMARDs are often combined with NSAID. They are classified as synthetic or biological DMARDS.
What is common in all synthetic DMARDs is the delayed onset of action, which lies between 1-6 months (75).

3.2.1 Methotrexate (MTX):

MTX is a commonly used antirheumatic drug, as well as in oncological patients.

Mechanisms of action:
MTX acts as an antifolate. By inhibiting dihydrofolate reductase (DHFR) it impedes the reduction from dihydrofolic acid to tetrahydrofolic acid. Tetrahydrofolic acid is an important cofactor in the formation of purine and thymidine. T-Lymphocyte proliferation gets inhibited, and B- Lymphocytes seem to react even more sensitive to MTX (87).
The synthesis of cytokines, mainly IL -1 (92) and IL-6, is hindered (93). MTX directly interferes in DNA/RNA synthesis and leads to the loss of function of a cell or even cell death.

Adverse effects:
They include anemia, gastrintestinal bleeding, hepatotoxicity, kidney failure, pneumonitis, pulmonary fibrosis and neurotoxicity. It should not be given during pregnancy due to its teratogenic effect (92).

Use in AOSD:
Methotrexate is commonly used in AOSD patients, especially in those who suffer from arthritis due to reported positive effects in rheumatoid arthritis. The usual dosage administered is 5-25mg/week. It has a good steroid sparing effect and can thus be used in systemic and articular disease manifestations, but it seems to be more effective in articular disease. It was shown to be effective in approximately 70%(51).

3.2.2 Leflunomide

Leflunomide is a DMARD that is commonly used in the treatment of RA and psoriasis arthritis.

Mechanism of action:
It inhibits pyrimidine synthesis by blocking Dihydroorotate Dehydrogenase (DHODH). After its transformation to its active metabolite A771726 in liver and intestinal wall, Leflunomide impedes the de-novo biosynthesis of Pyrimidine by inhibiting DHODH. Pyrimidine is indispensable for the formation of T-lymphocytes, leflunomide does thus prevent their excessive synthesis. Furthermore, it has an antiproliferative effect that is used in the treatment of rheumatoid arthritis and psoriatic arthritis to protect the joints.(94) Its half-life time is about fifteen days.

Adverse effects:
Adverse effects include nausea, vomiting, diarrhea, alopecia, hypertension, leukopenia, an increased risk of infection and liver damage (92)Liver function tests should be done regularly. It should not be administered at the same time as MTX or other hepatotoxic DMARDs.

The usual dosage administered in rheumatoid arthritis is 100mg/day orally for three days as an initial dose to reach a steady-state- level followed by 10-20mg/day and usually shows to be effective after four to six weeks. Leflunomide requires a washout procedure, which is also induced if severe side effects appear or if a switch to another medication is scheduled. It implies the administration of 8g

cholestyramine 3 times daily or 50g of activated powdered charcoal 4 times a day for approximately eleven days (94).

Use in AOSD:

Although leflunomide is a well-established drug in the therapy of RA and psoriasis arthritis, case reports about its usage in AOSD a rare and hard to find.
In 2002 Pirildar et al. published two cases of patients who were successfully treated with a combination of leflunomide and chloroquine (95).
In 2005 Cefle et al. published the case of a 24-year-old female with AOSD refractory to indomethacin, steroids, hydrochloroquine, MTX, azathioprine and cyclophosphamide. She eventually achieved remission under treatment with a combination of azathioprine and leflunomide and did not undergo any flares or exhibit any adverse events within one year of follow-up (96)-

3.2.3 Sulfasalazine

Sulfasalazine is a DMARD, commonly used in rheumathoid arthritis (97). It is mentioned because its common use in rheumatoid arthritis might suggest its administration in AOSD and SJIA as well, but actually it was associated with severe side effects and even the onset of MAS (98). Jung et al. claimed that sulfasalazine can provoke severe side effects in patients with AOSD, SJIA and RA with systemic symptoms (99), other authors reported similar effects(100).It is thus not recommended to be administered in AOSD or should at least be used very carefully.

3.3 Biological DMARD

So called “Biologicals” are therapeutic agents that are produced by using biological sources, and can be proteins, sugars, monoclonal antibodies or others. In the case of immunosuppressive drugs mainly TNF-α and IL-receptor antagonists are used.

3.3.1 IL-1 Inhibition

IL-1 seems to play an important role in AOSD pathogenesis, IL-1 levels are found elevated in almost all patients and are correlated with certain clinical manifestations. The blockade of IL-1 is already well established in its juvenile counterpart SJIA and seems to be very effective in AOSD as well. Recently, several therapeutic agents intervening in IL-1 pathways are available, but their use in AOSD is still off-label.

3.3.1.1 Anakinra

Anakinra is a recombinant, non-glycosylated analogon of the endogenous cytokine IL-1 receptor antagonist and was the first available IL-1 inhibitor. By selectively binding to IL1-R1 it impedes the interaction of Il-1R1 and Il-1-alpha/beta. Anakinra has a very short half-life and has to be injected subcutaneously every day. The usual dosage administered is 100mg/day and rapid improvements of clinical features within hours or days have been described (12,101). It is accredited for rheumatoid arthritis in combination with MTX, and in cryopyrin-associated periodic syndromes (CAPS).

Adverse effects:

A slight to modest skin reaction in injection site appears in up to 70% of the patients but were reported as mild to moderate in 95%. Headache, neutropenia and allergic reactions were described as well. As it effect is immunosuppressive, the danger on infection raises, especially when combined with TNF- α inhibitors due to the great risk of developing severe neutropenia.

Contraindications are hypersensitivity to ingredients of the product, renal impairment and severe neutropenia.

Cytochrome P450 might be suppressed by cytokines such as Il-1. The administration of an IL-1 antagonist may thus have an influence on P450 levels, which has to be taken into consideration when administering substrates metabolized through CYP450.

Use in AOSD:

In October 2017 Junge et al. provided an elaborate review on literature analysing the efficacy of IL-1-inhibitors in AOSD (101). They therefore reviewed all available articles from English language journals that report treatment outcome of AOSD patients who received IL-1 inhibitors. This is the largest and most current review on this topic. It summarizes case reports of about 130 patients from numerous single case reports, case series and a randomized case trial, and collected data from 5 national surveys.

Anakinra was described to be particularly effective in patients who suffered from a predominantly systemic course, while those with arthritis as the predominant symptom responded more slowly and showed lower response rates. Joint symptoms sometimes persisted for longer than systemic symptoms.

Of 134 published cases, 98 (73%) of the patients went into remission and 24 (18%) achieved partial remission. Similar data were provided by the national surveys, where full remission was reported for 56-60% of the patients and partial remission for 13-35%.

A steroid sparing effect could be achieved in most cases. Of 111 patients from different articles, steroid administration could be stopped in 32 (29%) cases and in 43 (39%) patients steroid dosage could be reduced.

However, efficacy was lost in numerous patients over time, which Junge et al. consider to be a result of the short half-life of anakinra. The most common adverse events were rather mild and include injection site reactions, infections and elevated liver enzymes. Severe adverse events like MAS or severe infections were described occasionally as well.

Junge et al. compared data from canakinumab and rilonacept to anakinra and found that there was less tolerability for anakinra, especially compared to canakinumab, due to the frequent occurrence of injection site reactions. They suggest further investigation on canakinumab, since it seems to be as efficient as anakinra with less unwanted events.

As a conclusion they propose the early use of IL-1 inhibitors to avoid long-term complications, especially in patients with a systemic course of AOSD.

In June 2017 Colafrancesco et al. published data of 140 patients from 18 Italian centres who were treated with anakinra. 74.2% of the patients suffered from a

systemic disease course and 25.4% from a chronic-articular course. There was no difference in observed responses, but Colafrancesco et al. discuss these findings as controversial due to conflicting results published by other authors.
The dosage administered in most of the patients was 100mg per day, with a mean duration of treatment of 36 months. Those patients who received less (i.e. 50mg per day or 100mg every other day) needed an up-titration later on. Most patients responded to the treatment within three months. Anakinra was found to be primarily inefficient in 10.7% and secondarily inefficient in 7.8% of the patients. Adverse events occurred in 47 (33.5%) of the patients, 40/47 patients showed skin reactions (at injection side or diffuse allergic reactions) and 7/47 had infections. Colafrancesco et al. conclude that anakinra is an efficient, safe drug to be used in the treatment of AOSD. The frequent occurrence of injection site reactions is seen as the major problem. Canakinumab should be considered as a good alternative due to similar efficacy and less side events. (102).

Anakinra seems to be a very efficient drug in refractory AOSD treatment, especially as a steroid-sparing regimen. However, some severe side effects have been reported, most notably hepatotoxicity (103,104). Injection site reactions occur frequently and may be a restrain especially for young patients (105). Although a great number of case reports exist, comparison is difficult due to a lack of clear criteria regarding diagnosis, remission and follow up.

3.3.1.2 Rilonacept

Rilonacept is a dimeric fusion protein consisting of the FC portion of human IgG linked to IL-1R and IL-1R accessory protein (12). It binds to IL-1 alpha as well as IL-1 beta and its main field of application is in the treatment of CAPS(106)Its half-life is longer compared to anakinra permitting a subcutaneous administration once a week(12).The dosage used in CAPS constitutes of 320mg loading dose, followed by 160mg weekly in adult patients.

Adverse effects:
Adverse effects (as published by the producer Regeneron®) include injection site reactions, gastrointestinal bleedings and colitis, upper respiratory infections and

rarely hypersensitivity reactions. Patients are under a higher risk to be hit by infections, a combination with TNF- α inhibitors or other IL-1 blocking agents is not recommended (107).
There are no contraindications described (107).

Use in AOSD:
Rilonacept is a relatively new drug and experience in its therapeutic use is rare, apart from CAPS. Due to its longer half-life compared to anakinra it seems like a promising alternative to treat refractory AOSD, but so far there exist only very few case reports about its application in Still's disease.

Petryna et al. published 3 cases of successful use of rilonacept (220mg loading dose, 160mg maintenance dose) in AOSD in year 2012.
The first patient, a 41-year-old female, suffered from both articular and systemic symptoms. She was treated with MTX, high-dose steroids, azathioprine, leflunomide and anakinra without achieving complete remission. Anakinra was then replaced by rilonacept and the patient's conditions improved within one month. Complete remission was attained within 18 months and MTX and prednisone could be discontinued.
The second patient presented with mostly articular affliction and hyperferritinemia. The 36-year-old woman received MTX and steroids without success and responded only partially to the administration of anakinra. A treatment with rilonacept led to remission within one month and lasted for 26 months of follow up, interrupted by only two less intense flares.
Patient number three, a 44-year-old woman, had a long history (4 years) of arthritis as a predominant symptom, accompanied by fever and erythema. She was refractory to MTX, steroids, abatacept and anakinra but achieved remission and tapering down of prednisolone for a follow up of 16 months. (108)

According to Junge et al.(101) Goldbach-Mansky et al. published 2 case reports of patients with refractory AOSD who benefited from 100mg 3x/day rilonacept maintenance dose, followed by 100-320 as-needed doses. One patient presented with mostly systemic symptoms and required a dosage of only 100mg/week to improve his clinical condition, the other patient suffered from articular

manifestation that improved after 360mg/week rilonacept therapy, while the systemic symptoms remained almost the same.

In a case presented by Kontzias et al. a 36-year-old Hispanic woman presented with mostly systemic disease course. She showed a good response to prednisone 60mg/day but it was impossible to taper down the steroid dosage without evoking another flare, although anakinra was added. Rilonacept therapy was initiated with 160mg/week and led to remission for 18 months. After this period, she developed a chronic articular course of disease, which could not be successfully controlled with rilonacept and finally medication had to be switched to canakinumab with good results in both articular and systemic features.(109)

3.3.1.3 Canakinumab

Canakinumab is a human monoclonal antibody, which is highly specific for IL-1 beta. It impedes its binding to IL-1R complex and thus directly prevents excessive IL-1 beta release to result in exceeding inflammatory response. Furthermore it seems to act as a positive feedback to IL-1 beta itself, reducing its production and release, which implicates an effect that lasts longer than the actual half-life of the agent (12).
Canakinumab is the IL-1 inhibitor with the longest half-life so far. It has to be administered subcutaneously every 4 weeks as recommended by the producer, with a dosage of 4mg/kg body weight. This dosage was recommended for patients suffering from SJIA (110). Canakinumab has the approval to be used in Cryopyrin – associated periodic syndrome and has recently received the approval to be administered in AOSD in Europe (111). Currently, there is a phase 2 clinical trial investigating the efficacy of canakinumab in AOSD, result can be expected soon (112). The usual dosage administered in AOSD so far varied in different studies from 150-180mg/4-8 weeks (101).

<u>Adverse effects:</u>
Adverse effects reported in SJIA and published by the producer include upper respiratory tract infections, abdominal pain and injection site reactions. As other IL-

1 blockers, it should not be administered simultaneously with TNF- α inhibitors (110).

Use in AOSD:

In 2012 the first two case reports of AOSD successfully treated with canakinumab was published by Kontzias et al.

Their first patient, a 38-year-old Hispanic woman, was diagnosed with AOSD complicated by MAS. She first showed a good response to methylprednisolone pulse therapy follow by prednisolone 1mg/kg but experienced a flare 4 months after discharge. MTX and anakinra were added to the treatment but the patient relapsed again three times within one year of follow up. A treatment with 150mg subcutaneous canakinumab every 8 weeks was initiated and complete remission could be achieved without relapse for a follow up of 12 months. No adverse effects appeared and steroid dosage could be tapered down successfully.

The second patient, a 36-year-old Hispanic woman, presented a systemic course of AOSD. She was initially treated with steroids with a good response, but tapering down of the steroid dosage was impossible without provoking another flare. Anakinra was added and subsequently replaced by rilonacept due to a longer half-life. Systemic symptoms improved but a shift to a chronic articular disease course occurred. MTX was added, without showing the expected results and eventually canakinumab 150mg every 8 weeks was administered instead of rilonacept. The new treatment led to complete remission of both systemic and articular features lasting at least for a follow up of 6 months (113).

In 2013 Banse et al. published the first case report about a patient who developed MAS after canakinumab treatment. The 49-year-old woman had a history of 6 years of AOSD, complicated by pulmonary sarcoidosis, chronic sinusitis and psoriasis. She was refractory to steroids, MTX, and infliximab. Eventually she was successfully treated with anakinra for one year, until escape phenomenon arose. She then received four injections of tocilizumab, whereupon cutaneous melanoma occurred. After the administration of two injections of canakinumab, the patient developed MAS with bone marrow biopsy showing phagocytosis. It could successfully be treated with glucocorticoids 1,5mg/kg/day and intravenous polyvalent immunoglobulins 0,5g/kg/day (114).

In 2014 Barsotti et al. published the case of a 20-year-old woman who was hospitalized in 2002 with the clinical image of AOSD, refractory to numerous therapeutic agents. She was initially treated with 6-methylprednisolone 40mg/day and MTX 7,5mg/week and responded well to the medication. After three months she relapsed and 6-methylprednisolone pulse therapy combined with MTX and hydrochloroquine was initiated. It was not possible to taper down the steroid dosage without provoking another flare and over the next years the patient developed a chronic articular disease course. In 2009 etanercept therapy was started without any success, it was thus replaced by adalimumab which had to be discontinued due to a skin reaction after the first injection. The administration of anakinra finally led to remission for the next two years but had to be replaced by tocilizumab in 2011 due to a relapse. This change in medication provoked an anaphylactic reaction to tocilizumab, which thus had to be discontinued. Eventually canakinumab 150mg every two weeks was administered subcutaneously and the patient's conditions improved within two months and she finally achieved complete remission of both articular and systemic features. Remission was stable under a combination therapy of canakinumab, MTX and 6-methylprednisolone for a follow up of 18 months (115).

In 2014 another case report was published by Lo Gullo et al., describing the case of a 40-year-old woman who was diagnosed with AOSD in 2006. The initial treatment with MTX and methylprednisolone showed good results but steroids could not be tapered down within the following four years without having the initial symptoms rising up again. Leflunomide, hydroxychloroquine, ciclosporin failed as steroid sparing agents and therapeutic strategies with anakinra, tocilizumab and infliximab resulted in allergic reactions or were inefficient. She finally was treated successfully with a combination of canakinumab 150mg every 8 weeks, methylprednisolone 24mg/day and MTX15mg/week. Apart from a flare presenting with arthritis two months after the new treatment was initiated, the patient responded very well to this combination therapy and remission was achieved within ten months. Steroid dose could slowly be reduced and the patient stayed in remission for a follow up of 14 months (116).

In 2015 Rossi-Semerano et al. investigated differences in efficacy and safety between anakinra and canakinumab in 189 patients suffering from autoinflammatory diseases. Two patients with AOSD received canakinumab 150mg, one of them every four weeks for a period of 148 days without being effective, the other patient in intervals of 8 weeks. He responded well to the treatment. In 52% of the patients who received canakinumab (not only AOSD) adverse effects occurred, mostly mild infections of the respiratory system (17%), liver toxicity (9%) and injection site reactions (4%). However, 13% developed severe adverse events and one patient died of staphylococcal pneumonia (117).

In 2017 Colafrancesco et al. published a retrospective data analysis to evaluate the efficacy of ilnterleukin-1 inhibitors in Italian patients. The majority of the patients received anakinra, but four patients were presented who received canakinumab after being refractory to anakinra. Three of them were even also refractory to other bDMARD.
Two of the patients received canakinumab as monotherapy, the other two where treated with a combination therapy of canakinumab and other DMARDs.
All patients received canakinumab at a dosage of 150mg every 8 weeks. They all experienced an improvement in their clinical conditions but in one patient, who suffered from chronic articular disease course, treatment was discontinued after nine months since he kept being afflicted with arthritis, fever and lymphadenopathy. The other patients suffered from a systemic course of AOSD. One patient developed MAS after 6 months of treatment, but canakinumab was continued after recovery. In one patient, canakinumab therapy led to complete remission. Adverse effects were not reported in any of the four patients (102).

3.3.2 IL-6 inhibition

3.3.2.1 Tocilizumab

Tocilizumab is a humanized monoclonal IgG1 antibody against the alpha subunit CD126 of IL-6 receptor that inhibits the impact of IL-6 by binding on both the

soluble and the membrane bound receptors for IL-6. It is approved to be used in rheumatoid arthritis, giant cell arteritis and SJIA (118).

Adverse effects:

The most common adverse effects in patients suffering from SJIA treated with tocilizumab described by the producer are upper respiratory tract infections, headache, nasopharyngitis and diarrhea. Anaphylaxis and infusion reactions were seen rarely. Cases of patients developing MAS under treatment with tocilizumab were described, although it is not verified whether MAS resulted from the treatment. As it works immunosuppressive, tocilizumab should not be administered if serious infections such as hepatitis or tuberculosis were diagnosed in a patient. Also the development of serious infections have been reported in patients treated with Tocilizumab.

The dosage suggested by the producer to be administered in SJIA is 8mg/kg intravenous every two weeks (118).

Use in AOSD:

Tocilizumab has already been used to treat AOSD in numerous cases all over the world and the majority of case reports showed good efficacy. The usual baseline dosage administered was 8mg/kg every 4 weeks, often in combination with MTX and prednisolone. Steroid dosage could usually be tapered down during treatment with tocilizumab (76,119-127). Few case reports even describe successful tocilizumab monotherapy avoiding the administration of steroids (76,128). Most patients had already received treatment with DMARD, steroids, MTX or other biologicals.

In almost all cases, tocilizumab therapy achieved very good results with a decrease in systemic and articular features, inflammatory markers and a general improvement of the patient's condition. It was even effective in cases of AOSD complicated by MAS (120), sarcoidosis, pulmonary arterial hypertension (129), systemic inflammatory response syndrome (130) and chronic hepatitis and amyloidosis (131).

Reported adverse effects occurred rarely with mostly mild characteristics including infections of the upper respiratory or urinary tract, leuko-/neutropenia (76) and injection site reactions (119). Some severe infections were reported (76) and one

patient developed internal bleedings. Although it might be helpful to treat MAS, in some case reports MAS onset or acute severe liver injury was associated with tocilizumab treatment (132,133). A possible association was thereupon re-evaluated by Deroux et al. who eventually negated a correlation of MAS and tocilizumab treatment (134).

3.3.3 IL-18 inhibition

3.3.3.1 Tadekinig alfa

Tadekinig alfa is a promising product consisting of recombinant IL-18 binding protein (IL18-BP). It was particularly designed for the purpose of treating autoinflammatory diseases with an imbalance in IL-18:IL-18BP ratio. It has an orphan drug status for the treatment of Hemophagocytic lymphohistiocytosis and the producers are currently running phase II studies for its use in the treatment of MAS associated with mutations in $NLRC_4$ gene and AOSD.
In the phase II study for its therapeutic use in AOSD, patients received either 80mg s.c. or 160mg s.c. for twelve weeks, with a follow up of four more weeks (135). Results are not yet officially published, but due to the great significance of IL-18 in pathogenesis of AOSD this new therapeutic agent looks really promising. So far one case has report been presented in 2015 dealing with a 3 months old girl that suffered from a mutation in Nod –like receptor C4 gene, which comes along with very high levels of IL-18 resulting in an intense systemic inflammation. The child was treated with IL-18BP thanks to a successful compassionate use investigational drug application sent to the US Food and Drug Administration by her treating physician. Due to the producers website the girl received full remission and is still being treated with IL-18BP (135).
Its actual use and safety in the treatment of AOSD remains to be seen.

3.3.4 TNF- α blockade

TNF-α inhibitors are biologic agents that have been successfully used in rheumatoid arthritis. They seem to be effective in AOSD as well, albeit TNF-α levels are lower compared to those found in rheumatoid arthritis. There are few differences in the structure and mechanism of action of different agents used for TNF inhibition in AOSD and thus slightly different treatment results (22).

3.3.4.1 Infliximab

Infliximab is a chimeric IgG1 monoclonal antibody used for the treatment of numerous rheumatological and autoinflammatory diseases. It is able to form stable complexes to monomer and trimer soluble TNF-α, as well as the transmembrane form (tmTNF) of it. It inhibits the activation of endothelial cells by TNF-α (22). Infliximab in administered as an infusion intravenously.

Adverse effects:

Very common adverse effects as described by the European Medicines Agency (EMA) for the product Remicade® as an example for infliximab-based agents include a higher risk for infections, especially of the upper respiratory tract, abdominal pain and nausea, headache and infusion-related reactions. The administration of infliximab is contraindicated in patients suffering from severe acute infections such as tuberculosis, sepsis or abscesses, or heart failure respective NYHA class III/IV. The concurrent administration of infliximab and other biologicals is not recommended (136).

Use in AOSD:

In 2001 Kraetsch et al. published data of a cohort of 6 patients successfully treated with infliximab. All patients were diagnosed with AOSD according to Yamaguchi criteria and had already received high dose steroid therapy or other immunosuppressive therapy without achieving remission. They all suffered from severe disease with systemic and articular manifestation. The patients received 3-5mg/kg infliximab infusions on weeks 0,2,6, followed by further administration every 6-8 weeks according to disease activity. Clinical and serological features

improved in all six patients. During a follow up of 5-28 months only one patient developed moderate infusion reactions, no other adverse effects were reported and all patients benefited from the treatment with infliximab (137).

In 2001 an other study with a cohort of three patients refractory to steroid therapy was published by Cavagna et al.. All patients suffered from active disease and did not respond to prednisone and MTX. Thus infliximab was added with a dosage of 3mg/kg at weeks 0, 2 and 6, followed by intervals of 8 weeks. MTX remained administered with 15mg/week in all three patients while steroids were adapted to disease activity. During a follow up of 50 weeks all patients experienced improvement in disease activity. One patient developed an urticarioid rash after the administration of the fifth infusion, treatment with Infliximab was therefore stopped. The other patients did not develop any adverse effects and benefited from the treatment. They relapsed after drug discontinuation but symptoms could be controlled successfully after administering infliximab again and reducing the interval for administration from 8 to 4 weeks (138).

A prospective, non-comparative case series of four male patients was published in 2004 by Kokkinos et al. Three patients presented with a relapse of already diagnosed AOSD while one patient experienced his first flare of disease. All of them had already received high-dose steroids and three of them had already been treated with MTX as well. Infliximab was administered at a dosage of 3-5mg/kg to all patients on week 0, followed by recurrent administration after 4-12 weeks, depending on disease activity. A clinical response was observed in all four patients within two weeks leading to complete remission within 16 weeks. In a follow up period of 5-18 months no adverse reactions occurred and all patients stayed in remission (139).

In 2010 an interesting case report was published by Babacan et al. presenting the history of a 38-year-old male patient who developed membranous glomerulonephritis as a rare complication of AOSD. The patient was refractory to high-dose steroids, MTX and hydrochloroquine with arthritis and proteinuria being the predominating symptoms. A therapy with infliximab 3mg/kg bodyweight was

initiated and after 10 weeks of treatment articular symptoms disappeared and proteinuria decreased (140).
Infliximab seems to achieve good results in the treatment of refractory AOSD and reported adverse effects are rare and mild. The usual dosage administered in the case reports described above was 3-5mg/kg at week 0, 2 and 6 followed by different intervals (usually 8 weeks), which is equal to the dosage recommended for the treatment of rheumatoid arthritis(136). Further investigation is needed with larger cohorts to assess the rate of adverse effects, optimize the duration of treatment intervals and investigate the potential use of infliximab in early treatment of AOSD and its role as a steroid-sparing agent.

3.3.4.2 Etanercept

Etanercept is a fusion protein containing the extracellular ligand binding domain of human tumor necrosis factor receptor -2/p75 bound to the Fc domain of human IGg1.
Etanercept only binds to the trimer form of soluble TNF. The accruing complex is rather unstable – bioactive TNF can easily dissociate. It may also bind to the transmembrane form of TNF but again forms less stable complexes compared to infliximab. It might thus be less efficient in the inhibition of TNF-α mediated inflammatory responses than infliximab (22).

Adverse effects:
Very common adverse effects as described by the European Medicines Agency (EMA) for the products Benepali® and Enbrel® as examples for Etanercept-based agents include a higher risk for infection and injection site reactions. Allergic reactions, fever and pruritus are commonly seen. As it is immunosuppressive, contraindications include severe active infections and sepsis and of course known hypersensitivity to the product. Patients should not receive anakinra, abatacebt or sulfasalazine concurrently with etanercept (141,142).

Use in AOSD:

The use of etanercept in AOSD has to be discussed controversially. Very few case reports about its administration in AOSD exist, it should thus not yet be considered as a standard therapy until further investigation is done.

In 2008 Yang et al. published the case of a 24-year-old woman in Taiwan, who was diagnosed having AOSD in 2006. The patient developed myocarditis while having a flare of AOSD. She initially received NSAID, low dose prednisolone and cyclosporine to treat the disease flare, and antibiotics to treat a urinary infection with E.coli, but her clinical condition worsened. She developed high fever and 80mg intravenous methylprednisolone had to be added to the treatment, without achieving an improvement of the patient's condition. She then developed myocarditis as a complication of the AOSD flare presenting with high fever, elevated cardiac enzymes, pleural effusion, leukocytosis and hyperferritinemia. She received dobutamine and diuretics for the congestive heart failure and administration of methylprednisolone was continued for three days. She additionally received 25mg etanercept subcutaneously twice a week and her conditions improved rapidly. The patient could leave the hospital 26 days after initiating etanercept therapy without having any relapse in symptoms for a follow up of 3 months under the continuation of etanercept therapy combined with NSAID, low-dose glucocorticoid and cyclosporine (143).

In 2014 Kiyonaga et al. described the potentially beneficial effect of etanercept as a steroid-sparing agent in a case report of an 84-year-old Japanese man. The patient was diagnosed due to Yamaguchi criteria and suffered mainly from arthralgia, fever and leucocytosis. He responded well to prednisolone 30mg/day but developed severe steroid adverse effects, i.e. hyperglycemia, hypogammaglobulinemia and steroid-induced myopathy. The administration of cyclosporine A did not improve the patient's condition. CRP levels increased and MTX was administered to taper down prednisolone, but the attempt failed and CRP kept rising. Finally, cyclosporine A was discontinued and a combination of etanercept 50mg/week and methylprednisolone 125mg/day was initiated. Steroids could successfully be tapered down and the patient went into remission, which lasted for a follow up of two years, without any adverse effects occurring. He

underwent only one relapse due to the discontinuation of etanercept, but its readministration led to total remission again.(144)

These case reports may lead to the conclusion that etanercept could be used in combination with methylprednisolone and other agents to treat refractory AOSD and to benefit from its steroid-sparing effect. Nevertheless, it should be used with caution.

Stern et al published in 2001 the case of a young woman who developed MAS triggered by EBV during an AOSD flare. After receiving etanercept her condition did not improve. Etanercept was discontinued and a treatment with corticosteroids and cyclosporine A was initiated, which led to an improvement of the patients conditions. Therefore, Stern et al. suggest to use etanercept carefully in patients with AOSD associated with MAS. (145).

This was in line with other case reports that suspected a role of etanrecept in triggering the evolution of MAS, with a dramatic increase of TNF-alfa in serum (151) (152-154) .

3.3.4.3 Adalimumab

Adalimumab is another IgG1 monoclonal antibody which binds directly to TNF and prevents an interaction of the cytokine with its cell surface receptors p55 and p75. It leads to a dwindling of CRP, ESR and Il-6 level and has an influence on the level of adhesion proteins that are involved in the migration of leucocytes.

Adverse effects:

Very common side effects as reported by EMA include infections of the respiratory tract, leukopenia, increased lipids, headache, abdominal pain, nausea and vomiting, elevated liver enzymes, rash, musculoskeletal pain and injection site reactions. Severe common side effects include skin cancer, systemic infections, metabolic disorders and others (150).

Use in AOSD:

Only very few care reports give an account of the successful use of adalimumab in AOSD.

In 2003 Benucci et al. published the case of a 48-year-old man with AOSD refractory to steroids and MTX. After being treated with adalimumab 40mg/2 weeks the patient achieved remission (151).

In 2014 Cavalli et al. retrospectively evaluated 20 patients suffering from AOSD. Among their cohort one patient with complicated chronic articular disease received adalimumab for 48 months with very good results (152).

In 2014 Souabni et al. presented a case of a 26-year-old female patient who developed MAS after a treatment with Adalimumab. It is possible that the TNF inhibitor triggered MAS (153).

Data about the efficacy of Adalimumab in the treatment of AOSD are very rare and it might even trigger MAS. It can thus not yet be recommended for the treatment of AOSD until further data is available.

3.3.5 Abatacept

Abatacept is a homodimeric fusion protein consisting of the Fc portion of human IgG1 merged with the extracellular domain of cytotoxic T-lymphocyte associated antigen 4 (CD152/CTLA4). CTLA4 is a protein receptor expressed by activated T-cells whose function is the downregulation of the immune response by activated T-cells to prevent an overreaction. One pathway of the activation of T-cells happens through a co-stimulation of CD80 and CD86 antigen presenting cell (APC) membrane glykoproteins. Abatacept supports the function of CTLA4 by binding to CD80/CD86 receptors and thus inhibits T-cell activation (154,155). Abatacept is approved for rheumatoid arthritis, psoriatic arthritis and polyarticular juvenile idiopathic arthritis.

Adverse effects:

Adverse effects as described by the European Medicines Agency (EMA) for the product Orencia® as an example for abatacept-based agents, infections - especially of the upper respiratory tract - are seen very commonly, while common adverse reactions include infections in general, headache, dizziness, hypertension, cough, rash, fatigue, asthenia, abnormal liver function tests and gastrointestinal symptoms such as abdominal pain, nausea, diarrhea and dyspepsia.

It is not recommended to combine abatacebt with TNF- α inhibitors due to an increased susceptibility to infection (154).

Use in AOSD:

There are few case reports showing the efficacy of abatacept in AOSD. There were no case reports published depicting the failure of abatacept in the treatment of AOSD or describing severe adverse effects.

Quartuccio et al. reported the case of a 57 year old patient who was diagnosed with AOSD according to Yamaguchi and Fautrel criteria. His first flare was successfully treated with high-dose steroids and MTX but he underwent a relapse after 9 month with fever and arthritis as the predominating symptoms. Over a period of many months he received adalimumab, MTX, prednisone, anakinra, infliximab, etanercept, and leflunomide without achieving remission and being accompanied by severe adverse reactions of the treatment. Finally, abatacept 10mg/kg as an intravenous infusion on day 1,15,30 followed by every 4 weeks administration was added to the current treatment consisting of MTX 15mg/week, leflunomide 10mg/day and prednisone 20mg/day. This combination was highly effective, an antipyretic effect occurred after the first infusion and fever did not return during a follow up of 9 month. Arthritis disappeared after the third month of treatment and a relapse two months later could be treated successfully with intraarticular steroid injections. Adverse reaction did not appear and prednisone dose could be gradually tapered down (156).

In 2011 Ostrowski et al. published the case of a 31-year-old Hispanic man suffering from refractory AOSD according to Yamaguchi criteria. He had initially

received prednisolone MTX and hydroxychloroquine and etanercept without success. Etanercept administration had to be stopped since the patient developed bacterial pneumonia. After a period of remission for four years under MTX and prednisone, the weaning off of prednisone led to a relapse of the symptoms, particularly rash, arthralgia and fever. Abatacept was administrated in a dose of 750mg intravenously at day 0,14 and then every 4 weeks, which led to remission within one month. Prednisone could successfully be tapered down and the patient stayed in remission during a follow up of 35 month with maintenance dosages of MTX 7.5mg/week, hydrochloroquine 400mg/day and abatacept without showing any adverse effects of the treatment (157).

Abatacept seems to be a promising agent to treat refractory AOSD although there is a lot more data needed to prove its efficacy.

3.3.6 Rituximab

Rituximab is a monoclonal human-murine antibody approved for the treatment of rheumatoid arthritis, non-Hodgkin lymphoma, chronic lymphocytic leukaemia and granulomatosis with polyangiitis. It selectively binds to CD20, a non-glycosylated surface protein of normal and malignant B-cells. It then induces B-cell depletion via cell-lysis, antibody dependent cellular cytotoxicity, complement-dependent cytotoxicity or apoptosis. CD20 is highly expressed on B-cell lymphomas, which explains the use of rituximab in this malignant condition. B-cells also play a role in inflammatory reactions, their suspension by blocking CD20 may thus be beneficial in autoimmune/-inflammatory diseases and explain the efficacy of blocking it in rheumatoid arthritis (155,158).

Adverse effects:
Very common adverse reactions as described by the European Medicines Agency (EMA) for the product MabThera® as an example for rituximab-based agents are infections of the upper respiratory tract and the urinary tract, headache, a decrease in IgM levels and infusion-related reactions(158).

Use in AOSD:

In 2006 Ahmadi-Simab et al. reported two cases of patients successfully treated with rituximab. Both patients presented with articular and systemic symptoms and were refractory to prednisolone, MTX, cyclosporine, leflunomide, cyclophosphamide, intravenous immunoglobulin and TNF-α inhibitors. They were finally treated successfully with two infusions of rituximab at a dosage of 375mg/m^2 supplemented by a single dose of 100mg prednisolone IV every four weeks. The patients received remission and the oral dosage of steroids could be decreased to 5mg/day in combination with MTX and cyclosporine (159).

In 2011 R. Mohammed published the case of a 30-year-old male patient who presented with a severe flare of AOSD. He was first diagnosed having AOSD 3 years before and was then treated with prednisolone, MTX, leflunomide and NSAID. This treatment led to an improvement of his symptoms but he could not achieve complete remission. He then underwent another severe flare of disease with both systemic and articular symptoms, which was not to be controlled with DMARDS and steroid injections. For being refractory to the treatment initiated, the patient eventually received a combination therapy of rituximab 375mg/m^2 (2 doses of 1g infusion every two weeks), prednisolone 20mg/day and selective COX-2 inhibitors. The patient's clinical condition improved significantly and he finally received remission of clinical symptoms and laboratory features(160).

In 2013 an interesting case report was published by Padilla et al. reporting the successful treatment of a patient with AOSD complicated with pulmonary arterial hypertension with rituximab. A 43-year-old woman was diagnosed with AOSD due to Yamaguchi criteria, with polyarthritis as the dominating symptom. She received a treatment with sulfasalazine, prednisone and NSAID but could not get rid of articular affliction. She additionally developed dyspnoea and was diagnosed with PAH associated to the AOSD flare. A treatment with sildenafil, cyclophosphamide and methylprednisolone pulse therapy did not lead to an improvement of her conditions and a treatment with 2g rituximab (1g every 2 weeks) was initiated. This was repeated three times; meanwhile the clinical condition of the patient improvement and she finally achieved remission. The patient stayed asymptomatic for a follow-up of 30 month(161)

In 2016 Belfeki et al. published the case of a 38-year-old female patient who was diagnosed with AOSD due to Yamaguchi and Fautrel criteria. She exhibited both systemic and articular symptoms and was refractory to treatment consisting of prednisone 60mg/day (tapered down to 15mg/day within 12 month) plus MTX 20mg/week. Since her condition did not improve, the patient received infusions of 1g rituximab in two administrations every two weeks. She recovered from both systemic and articular symptoms and remained in remission during 12 months of follow up after the last dose of rituximab. Oral steroids could be tapered down to 5mg/day and MTX dose remained unchanged (162).
One case report published by Schäfer et al. describes the successful application of rituximab in a patient suffering from AOSD complicated by MAS. The 25-year-old man underwent a disease flare after 5 years of AOSD history treated with 100mg/day anakinra and 5mg/day prednisolone. He then developed MAS, which was treated according to HLH-49 protocol with etoposide and dexamethasone, without convalescing. Epstein-Barr-virus infection was detected as a possible trigger of MAS. The patient received rituximab 375mg/m^2 once a week, which lead to virus suppression after three cycles. His conditions improved, even more after the addition of anakinra and cyclosporine (163).

3.3.7 Intravenous Immunoglobulines

Intravenous immunoglobulines (IVIG) are collected and prepared human immunoglobulines (mostly IgG and sometimes small amounts or fractures of IgA or IgM) from pools of donated plasma from at least 1000 persons. The half-life of IgG *in vivo* is about 3 weeks. IVIG are commonly used in autoimmune diseases since they contribute to the regulation and decrease of inflammation by inhibiting the release of cytokines, chemokines and metalloproteases. Furthermore they suppress macrophage activation by blocking macrophage FC receptors. Their mode of action and role in autoimmune disorders is complex but their use is yet well established and shows good effectiveness (164).

Use in AOSD

IVIG have been used in AOSD with good results, although only few data is available. Most patients who received IVIG experienced an improvement in clinical conditions, some even went into remission and adverse events were rarely seen. Still IVIG cannot be seen as a first line-therapy due to its high costs and the lack in data available.

In 1998 Vignes et al. performed an uncontrolled, unblinded open-label study with seven patients receiving IVIG. They were all diagnosed with AOSD due to Yamaguchi criteria. Three patients achieved remission; one was responding very well to the treatment and disease could finally be controlled by only giving NSAID. One other patient relapsed and two patients did not respond at all to the treatment (165).

Permal et al. published an open trial with seven patients who received between one and eight infusions of IVIG in a dose of 1mg/kg/day for two days. All of them responded well to the treatment, four of them achieved full remission, three patients relapsed (166).

In a retrospective observational study Gerfaud-Valentin et al. analysed data from fifty-seven patients in Lyon, France. In only four patients a control of disease could be achieved. Acute renal failure occurred in one patient after IVIG was administered. Those patients refractory to IVIG had a poorer prognosis compared to those who responded well (38).

In 2011 Kim et al. investigated the efficacy of IVIG in a retrospective study of fifty-four Korean patients. 23 of the patients had received IVIG, receiving 2mg/kg intravenously for 2-5 days. 7 of them were refractory to the treatment and 9 went into remission (167).

4 Therapeutic strategies

So far no randomized controlled trials have been published that evaluate the efficacy of different treatment strategies in AOSD. Several authors have proposed treatment algorithms. The most detailed one was published in May 2017 in the Journal “Expert Review of Clinical Immunology” by Dae Hyun (51).
He suggests to differentiate between patients with - or without life threatening complications:
Those with life threatening complications should be treated with a megadose of systemic steroids (e.g. 30mg/kg/day of intravenous methylprednisolone), optionally added by calcineurin inhibitors. Biologic DMARDs should be added according to the clinical presentation, whereat IL-1 inhibition should be preferred to IL-6 inhibition. In case of the occurrence of infection related MAS, IVIG should be considered.
Patients with active AOSD but without life threatening complications should be treated as followed:
They should receive steroids at a dose of about 0,5mg/kg, complemented by MTX or cyclosporine if necessary, therapy should be maintained if successful. In case of refractory AOSD it should be differentiated between systemic-dominant and arthritis-dominant course of disease.
Patients with arthritis-dominant disease course should be treated with TNF-α inhibitors. If the patient develops systemic symptoms, IL-6 inhibitors should be added.
In the case of systemic manifestations patients without arthritis should be treated with IL-1 inhibitors superior to IL-6 inhibitors.
Another algorithm was published by Jamilloux in 2015(80). He suggests to adapt the treatment to the subtype of disease if refractory to steroids, thus to treat patients with systemic manifestations differently than those with articular disease. Jamilloux proposes to start corticosteroid therapy as soon as possible with 0,5-1mg/kg/day dosages and make further treatment decisions depending on response to steroids and clinical manifestations. High dose methylprednisolone pulse therapy is suggested in cases with severe organ involvement. Tapering of steroids should be started within 4-6 weeks if the patient shows a good response.

In case of steroid dependence, he proposes to add MTX at a dosage of 7,5-20mg/week as a steroid-sparing agent. He recommends controlling blood count, renal and liver functions every 1-2 months.
If refractory to steroids, patients should be treated with biologicals according to their subtype of disease as second-line treatment.
He suggests anakinra for patients with systemic subtype refractory to steroids at a dosage of 100mg/day. In case of treatment failure with IL-1 antagonists he suggests to use tocilizumab at a dosage of 5-8mg/kg body-weight in intervals of 4-8 weeks, especially in patients who also suffer from articular symptoms.
The articular subtype refractory to steroids should be treated with TNF-α inhibitors, particularly infliximab at a dosage of 3-5mg/kg at week 0,2,6 followed by intervals of 8 weeks. If the patient is refractory to TNF- α inhibitors, tocilizumab and anakinra should be tried (80).

Another treatment algorithm was published by Efthimiou et al. in 2005. They suggest MTX plus low dose steroids as first-line treatment, followed by biologic agents if necessary. In particular, they recommend IL-1 inhibitors or TNF-alpha inhibitors, infliximab preferential to etanercept. A second-line treatment is not further specified; it may include leflunomide, azathioprine, IVIg, thalidomide, IM gold, cyclophosphamide, ciclosporin and IL-6 inhibitors (33).

This strategy does not differentiate between articular and systemic disease and does not yet fully consider the latest approaches and development in treatment options. The administration of gold salt for example can not be recommended anymore.

4.1 Conclusion

All treatment algorithms share the initial treatment with corticosteroids as first-line therapy. Response is usually good and whether the patient responds to steroids or not may already help to assess the prognosis. If steroids can be reduced after 4-6 weeks without provoking a relapse, steroid dependence and other adverse events are rare. Steroids can be administered orally, which is a great advantage

compared to intravenous or subcutaneous. Furthermore, glucocorticoids are much more affordable compared to biologic drugs. Thus I consider glucocorticoids as a reasonable first-line treatment.
The treatment algorithm of Jamilloux et al. and the one of Dae Hyun are addressing the different subtypes of AOSD. Recent findings strongly suggest that a systemic and an articular subtype do exist, or at least that different cytokine profiles lead to certain clinical manifestations. It would thus make sense to appropriately adapt the treatment algorithms to these subtypes. The decision which biologic drug might be used best should depend on the individual cytokine profile of the patient and the predominant symptoms. More directed therapies depending on the individual cytokine profile are expensive, but may help to avoid ineffective treatment and frequent, unnecessary change of medication.
Jamilloux et al. and Dae Hyu propose to treat systemic subtypes with IL-1 inhibitors, primarily Anakinra. This seems very reasonable since IL-1 is predominantly high in the systemic course of disease. It may even make sense to directly add IL-1 inhibitors to steroid therapy in case of steroid dependence instead of MTX. MTX is more effective in patients with articular symptoms and an early addition of anakinra could help to quickly control systemic symptoms and even prevent the development of MAS. The decision to treat patients according to the course of disease should probably done directly if they do not respond to steroids.
Anakinra is the IL-1 inhibitor most frequently used to treat AOSD with the most data available. Still I suggest to try canakinumab or even rilonacept due to their longer half-life, especially in patients with skin reactions to the injection.
Infliximab should be preferred to etanercept since it seems to have to better binding properties.

Considering the given results and contemplations I suggest the following algorithm as potentially useful in the management of AOSD patients. It is of course limited by the lack of experience with new therapeutics, randomized studies and definite and comparable results, but could possibly help to ease decision making.

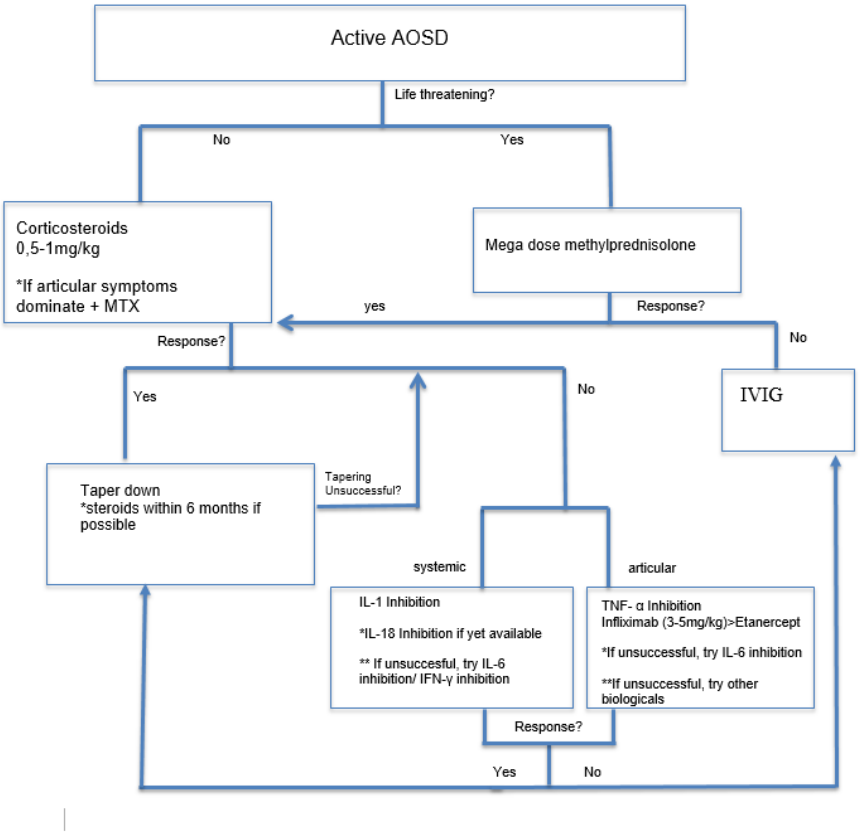

Figure 3 *Treatment algorithm AOSD*

5 Future perspectives and challenges

Future challenges include the development of guidelines for the appropriate management of AOSD and its most dreaded complication MAS. This includes instructions about how to monitor these patients, which parameters should be controlled and at which intervals. Also the question of vaccination plans for AOSD patients has to be discussed. AOSD flares and MAS are commonly triggered by infections. Furthermore most therapeutic agents induce immunosuppression, what makes them more susceptible for infections. This raises the question which vaccinations should be recommended for AOSD patients, especially those who had already undergone MAS. And it needs to be investigated whether vaccinations themselves could trigger MAS or AOSD flares.

Pathogenesis of AOSD and MAS have to be further investigated. Only if we understand the pathways behind the disease will we be able to manage it. This

includes clear guidelines concerning laboratory parameters, especially cytokine profiles, to speed up diagnostic processes and to get an evidence on features that are really characteristic for AOSD. Standardized diagnostic parameters should be established to make case reports better comparable. Additionally the patients' origin should always be mentioned due to its impact on outcome and disease course.
Current and newly developed therapeutic agents need to be tested in large cohort randomized, controlled, prospective trials. The development of IL-18 inhibitors seems to be very promising, especially for the treatment of systemic subtypes and MAS. A personal treatment plan adapted to individual cytokine profiles and symptoms may be expensive but important to prevent unnecessary and time-consuming changes in treatment and assure the best outcome for our patients.
A focus should also be laid on further studies on the patients' genetic profiles. This may help to better understand the pathways of AOSD and will probably open new ways to innovative treatment options in the future.
A fundamental aspect is the spread of knowledge concerning AOSD to medical practitioners. An unfavorable outcome of the disease is often associated with a delay in diagnosis. Many patients are initially misdiagnosed due to the heterogenous presentation of AOSD and its rarity. Usually general practitioners are the first to see the patients, they need to get sensitized to AOSD as a possible differential diagnosis of high spiking fever and instructed how to manage it.

There are still many challenges that have to be overcome in the future, but with the rising popularity and recognition of AOSD and new prospects in diagnostics, treatment and understanding of the pathogenesis of this rare disease, we are on a good way to improve the outcome of the treatment and optimize patient care.

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