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Adult-Onset Still's Disease

Pathogenesis, Clinical Manifestations and Therapeutic Advances

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Contents

Abstract

Adult-onset Still's disease (AOSD) is a rare, systemic inflammatory disease of unknown aetiology, characterized by daily high spiking fevers, evanescent rash and arthritis. Our objective was to review the most recent medical literature regarding advances in the understanding of disease pathogenesis, diagnosis and treatment. There is no single diagnostic test for AOSD, and diagnosis is based on

clinical criteria and usually necessitates the exclusion of infectious, neoplastic and autoimmune diseases. Laboratory tests are nonspecific and reflect heightened immunological activity with leukocytosis, elevated acute phase reactants and, in particular, extremely elevated serum ferritin levels. Abnormal serum liver function tests are common, while rheumatoid factor and antinuclear antibodies are usually absent. Recent studies of the pathogenesis of the disease have suggested an important role for cytokines. Interleukin (IL)-1, IL-6 and IL-18, macrophage colony-stimulating factor, interferon-γ and tumour necrosis factor (TNF)-α are all elevated in patients with AOSD. Prognosis depends on the course of the disease and tends to be more favourable when systemic symptoms predominate.

Treatment includes the use of corticosteroids, often in combination with immunosuppressants (e.g. methotrexate, gold, azathioprine, leflunomide, tacrolimus, ciclosporin and cyclophosphamide) and intravenous immunoglobulin. Biological agents (e.g. anti-TNFα, anti-IL-1 and anti-IL-6) have been successfully used in refractory cases. Further progress has been hampered by the rarity and heterogeneity of the disease, which has not permitted the execution of randomized controlled studies.

Adult-onset Still's disease (AOSD) is a rare, systemic inflammatory disorder, the cause of which is still under investigation. Classically, it presents with evanescent rash, fever and articular involvement, although not all three presentations have to be present at the same time.[1] Bywaters[2] was the first to describe AOSD as a distinct clinical syndrome in 1971. According to data extrapolated from a small retrospective French study, the yearly incidence has been estimated to be 0.16 per 100 000 population.[3] It usually occurs in young people, aged between 16 and 35 years.[4] However, in a Japanese epidemiological study, the estimated mean age of disease onset was 38.1 years.[5] Women are affected equally[3] or slightly more frequently than men (female-to-male ratio = 60 : 40),[6] although men may be more likely to present at younger ages.[6] Interestingly, physically or emotionally stressful conditions during the year preceding the onset of AOSD have been associated with the disease.[7]

Our objective was to review the most recent advances in the understanding of the pathogenesis, diagnosis and treatment of AOSD. PubMed and the Cochrane Database of Systematic Reviews were searched for articles published from 1971 to 2007 using the terms: 'Adult-onset Still's disease', 'Adult-Onset Still's Disease' and 'Still's disease'. Full-text articles relating to human disease were selected for relevance. The following co-indexing terms were used: 'pathogenesis', 'etiology' and 'treatment'. Additionally, a few selected articles pertaining to the pathophysiology of systemic-onset juvenile idiopathic arthritis (JIA) or paediatric Still's disease were retrieved.

1. Pathogenesis, Clinical Manifestations and Diagnosis of Adult-Onset Still's Disease (AOSD)

1.1 Pathogenetic Concepts

An interplay among several factors contributing to the mechanism of the disease has been speculated. Genetic factors in combination with environmental factors, such as infection in the setting of immune disarray, may lead to the phenotypic expression of the disease

1.1.1 Genetic Component

Although several aetiological parameters have been investigated in an effort to identify possible disease mechanisms, there is still a long way to go in determining the pathophysiology of AOSD. It has been inferred that a genetic component is a predisposing factor required for the disease to be pheno-

typically expressed; however, studies conferring genetic associations with the disease and disease patterns are inconclusive. Human leukocyte antigen (HLA)-B17, HLA-B18, HLA-B35 and HLA-DR2 were associated with AOSD in a retrospective study of 62 patients.[8] Another study found HLA-DR1 to be negatively associated with AOSD.[9] HLA-Bw35 and HLA-DR7 alleles have been reported to be present in increased frequency among AOSD patients.[10] However, another study found a negative association between the disease and HLA-Bw35 and a positive association with HLA-DR4.[9] A Korean study demonstrated that the alleles HLA-DRB1*15 and HLA-DRB1*12 were more frequent in AOSD patients, whereas HLA-DRB1*04 alleles were less frequent than in the controls.[11] In the same study, the DRB1*14 allele correlated with the monocyclic systemic type of the disease.[11] By contrast, in a Japanese cohort study, DRB1*1501 (DR2) and DRB1*1201 (DR5) alleles were more frequently found in the chronic articular form than in the systemic form, whereas DQB1*12 was equally frequent in both types.[12] In general, the low prevalence of the disease, its erratic clinical expression and the varying genetic background of the patients, in combination with technical limitations in HLA typing, may, to some extent, explain the variability of these genetic associations. Moreover, geographical variability in phenotypical expression of the disease depicts the potential importance of environmental and genetic factors in its pathogenesis (table I).

Table I. Comparative prevalence of clinical manifestations and laboratory findings across the largest series of adult-onset Still's disease

Parameter	Japan (Ohta et al.[6])	Taiwan (Chen et al.[13])	Canada (Pouchot et al.[8])	France (Masson et al.[14])	(Andres et al.[15])	Netherlands (van de Putte and Wouters[16])	Turkey (Pay et al.[17])	(Mert et al.[18])	India (Bambery et al.[19])	(Singh et al.[20])	Greece (Akritidis and Sakkas[21])	Norway (Evensen and Nossent[22])
No. of patients	90	82	62	65	17	45	95	20	18	14	16	13
Age range (y)	16–45	16–35	16–45	16–45	17–54	16–35	16–82	16–65	16–50	16–59	18–57	15–77
Women (no.)	74	59	28	34	12	NR	50	12	10	5	8	3
Fever (%)	100	100	100	94	82	100	99	100	100	100	100	100
Arthritis (%)	72	100	94	69	47	98	85	90	100	100	94	69
Rash (%)	87	87	87	85	77	82	82	85	50	57	100	77
Sore throat (%)	70	84	92	68	35	42	66	75	NR	36	44	62
Hepatomegaly (%)	48	NR	44	9	47	NR	45	40	83	57	0	23
Splenomegaly (%)	65	NR	55	22	35	36	42	25	56	57	38	23
Lymphadenopathy (%)	69	NR	74	48	35	71	37	15	67	71	NR	62
Anaemia (%)	59	NR	68	50	NR	69	75	65	NR	50	31	NR
Raised ESR (%)	96	90	100	95	94	100	94	100	100	100	88	100
Raised LFT (%)	85	NR	76	51	76	84	64	65	33	43	44	62

ESR = erythrocyte sedimentation rate; **LFT** = liver function test; **NR** = not reported.

1.1.2 Infectious Component

It has been suggested that an infectious agent has a triggering effect on the pathogenetic sequence of the disease, primarily due to temporal relationships between disease onset and viral syndromes, and also, the fact that many viral syndromes closely resemble the clinical presentation of AOSD (high spiking fever, lymphadenopathy and splenomegaly).[8] Viruses that have been reported to interact with the genetic background of the host include parvovirus B19,[23,24] rubella virus, echovirus 7,[25] human herpes virus 6, parainfluenza virus, Epstein-Barr virus, cytomegalovirus, coxsackievirus B4,

mumps and adenovirus.[26] Bacterial infections with *Chlamydia pneumoniae*,[27] *Yersinia enterocolitica*, *Brucella abortus* and *Borrelia burgdorferi* have also been associated with AOSD,[26] a finding that has prompted empirical treatment schemes containing clarithromycin.[28]

Overall, the loose associations between infectious agents, HLA alleles and AOSD have led investigators in the past to look further into the immunological pathways of the disease that seem to be highly affected.

1.1.3 Immune Dysregulation

Currently, it is believed that the immune response is dysregulated in AOSD patients. Although the exact mechanism underlying this is still unclear, it has been demonstrated that the proinflammatory cytokines derived from type 1 T helper cells (T_h1) [interleukin (IL)-2, interferon (IFN)-γ and tumour necrosis factor (TNF)-α] predominate in favour of those derived from type 2 T helper cells (T_h2) [IL-4, IL-5, IL-6 and IL-10].[29] In line with this evidence, TNFα, IL-6, IL-8 and IL-18 were found at significantly higher levels in sera and pathological tissues of AOSD patients than in healthy controls.[30] Studies have demonstrated significant correlations of IL-6 and IL-8 levels with clinical activity score and serological markers of inflammation, such as C-reactive protein (CRP) levels.[31] Additionally, cytokines such as IL-6, IFNγ and IL-1β may account for biochemical abnormalities, such as the extreme serum levels of ferritin, commonly seen in AOSD.[31]

Among other cytokines, IL-18 is thought to play a pivotal role in the inflammatory cascade by orchestrating the T_h1 response and inducing other cytokines such as IL-1β, IL-8, TNFα and IFNγ. Notably, Japanese patients with a specific genetic polymorphism of the IL-18 gene (S01/S01 diplotype) were prone to increased disease severity.[32] Moreover, IL-18 has been inferred to mediate the hepatotoxic manifestations of the disease.[33] Serum intracellular adhesion molecule-1, which may depict inflammatory cytokine activity, was found at significantly elevated levels in active, untreated AOSD patients, and correlated well with both clinical activity score and biochemical markers.[34]

1.2 Clinical Manifestations

Typical presentation of AOSD consists of a triad of symptoms which include a high spiking fever, an evanescent rash, and arthritis or arthralgia. Not all three symptoms need to be present at disease onset, and atypical presentations may occur (figure 1). Several sets of validated diagnostic criteria have been developed over the years, with those of Yamaguchi et al.[35] being the most widely used (table II). Furthermore, the natural history of the disease may follow clinically distinct patterns.[36] In general, three patterns of the disease have been identified (table III).

1.2.1 Fever

AOSD is frequently the indolent cause of fever of unknown origin.[38] Awareness of its pattern can be a valuable clue to the recognition of the disease. Typically, fever is high (>39°C) and spiking, usually daily and occasionally twice daily.[39] The spike is usually observed late in the afternoon or early evening and resolves spontaneously.[40] Fever is considered to be a prerequisite for the diagnosis, as its overall incidence in five of the largest retrospective studies was estimated to be 95.7%.[1] Symptoms that occasionally precede the fever or rash and that should raise suspicion about the underlying cause include sore throat, seen in more than 70% of patients, as well as constitutional symptoms such as anorexia, myalgia or arthralgia, fatigue, nausea and weight loss. Wasting, evidenced by metabolic markers, such as low albumin levels, tends to follow the inflammatory activity of the disease.[41]

1.2.2 Still's Rash

The rash, which is often named 'Still's rash', after the disease, is characterized by evanescence, salmon-pink colour and morbilliform maculopapular eruptions. It commonly involves the proximal limbs and the trunk, while rarely affecting the face and distal limbs. It presents typically during the febrile attacks, can be mildly pruritic, and is frequently mistaken for a pharmacogenic rash.[39,40] The appearance of new skin lesions in areas previously traumatized, known in the literature as 'Koebner's phenomenon', has been reported. Skin

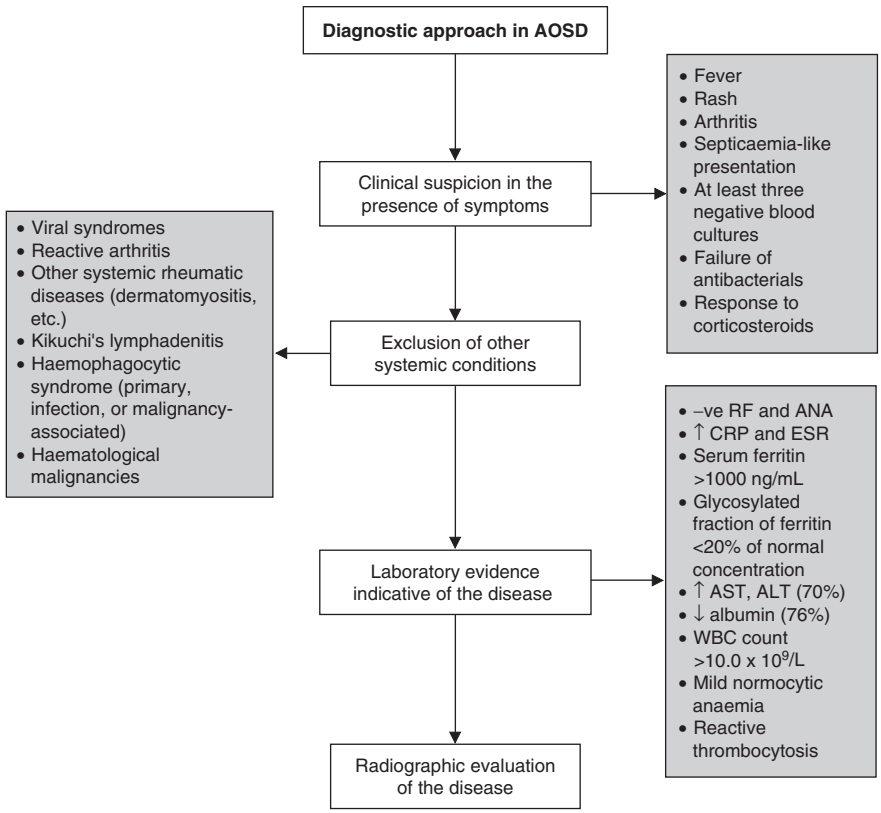

Fig. 1. Diagnostic approach to adult-onset Still's disease (AOSD). **ANA** = antinuclear antibodies; **CRP** = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **RF** = rheumatoid factor; **WBC** = white blood cell; ↑ indicates increased; ↓ indicates decreased; **–ve** = negative.

biopsy of the affected areas reveals a picture of chronic inflammation with a perivascular mononuclear preponderance, vascular dilation and dermal oedema.[14] The mean incidence of Still's rash has been estimated to be as high as 72.7% in a retrospective analysis of large series of AOSD patients.[1]

1.2.3 Arthritis

Clinically, AOSD closely resembles its paediatric sibling, sudden-onset JIA. Arthritis is a prominent feature of the disease with an overall estimated prevalence ranging from 64% to 100%.[1] Arthritis may initially present as oligoarthritis (i.e. involving fewer than four joints, and then develop into polyarthritis, affecting both large and small joints).[41] Although joint involvement does not follow a specific pattern, it seems that knees, wrists and ankles are the most commonly affected. Other sites involved include elbows, shoulders, proximal and distal interphalangeal joints, metacarpophalangeal (and metatarsophalangeal) joints, temporomandibular joints and hip joints. Ankylosing carpal arthritis seems to be a consistent feature of late (1–3 years after onset) AOSD, preceded by gradual, selective, carpometacarpal and intercarpal non-erosive joint space narrowing.[42] Notably, this pericapitate pattern of arthritic involvement has been suggested to be a differential diagnostic characteristic between AOSD and rheumatoid arthritis (RA).[43] Severe involvement of the hip joint, leading to bilateral hip destruction in nine patients in less than 4 years has been reported from a French group, although the finding has not been supported by other series.[44]

Table II. The most commonly used diagnostic criteria for adult-onset Still's disease (AOSD)

Reference	Major criteria	Minor criteria	Diagnosis
Yamaguchi et al.[35] (sensitivity 96.2%; specificity 92.1%)	1. Fever ≥39°C, lasting ≥1 week 2. Arthralgia lasting ≥2 weeks 3. Typical rash 4. Leukocytosis (≥10 000/mm^3) including ≥80% of granulocytes	1. Sore throat 2. Lymphadenopathy and/or splenomegaly 3. Liver dysfunction 4. Negative RF and negative ANA	*Exclusions:* 1. Infections (especially sepsis and infectious mononucleosis) 2. Malignancies (especially malignant lymphoma) 3. Rheumatic diseases (especially polyarteritis nodosa and rheumatoid vasculitis with extra-articular features) *Classification of AOSD requires*: 5 or more criteria including 2 or more major criteria
Cush et al.[36] (sensitivity 84%)	(2 points) 1. Quotidian fever >39°C 2. Still's (evanescent) rash 3. WBC count >12 000/mm^3 + ESR >40 mm/h 4. Negative RF and ANA 5. Carpal ankylosis	(1 point) 1. Onset <35 years 2. Arthritis 3. Prodromal sore throat 4. RES involvement or abnormal LFTs 5. Serositis 6. Cervical or tarsal ankylosis	*Probable AOSD*: 10 points with 12 weeks' observation *Definite AOSD*: 10 points with 6 months' observation
Fautrel et al.[37] (sensitivity 80.6%; specificity 98.5%)	1. Spiking fever ≥39°C 2. Arthralgia 3. Transient erythema 4. Pharyngitis 5. PMN ≥80% 6. Glycosylated ferritin ≥20%	1. Maculopapular rash 2. Leukocytes ≥10 000/mm^3	*Classification of AOSD requires*: 4 or more major criteria or 3 major criteria + 2 minor criteria

ANA = antinuclear antibodies; **ESR** = erythrocyte sedimentation rate; **LFT** = liver function test; **PMN** = polymorphonuclear leukocytes; **RES** = reticuloendothelial system; **RF** = rheumatoid factor; **WBC** = white blood cell.

1.2.4 Liver Abnormalities

Liver pathology, as indicated by hepatomegaly on physical examination, and elevated aminotransferases in laboratory tests, is seen in approximately 50–75% of patients.[6,8,14] Abnormal liver function is thought to be part of the inflammatory process of the disease itself, yet concomitant use of potentially hepatotoxic treatments often complicates the causative mechanisms of the biochemical picture.[15,39] Fulminant hepatic failure requiring liver transplantation is extremely rare.[45,46]

1.2.5 Other Less Common Manifestations

AOSD can affect all organ systems with great variability. Serositis, in the form of pleuritis and pericarditis, can be encountered in the clinical picture of AOSD, although this is rare. Splenomegaly has been reported in 43.9% of cases.[1] Pulmonary manifestations extend from fibrosis and pleural effusions to adult respiratory distress syndrome in very rare cases.[47-49] Cardiac tamponade and myocarditis leading to fibrinoid necrosis have also been infrequently reported.[50] Renal involvement can take place in the form of interstitial nephritis, subacute glomerulitis, renal amyloidosis or collapsing glomerulopathy.[51-54] Reactive haemophagocytic syndrome (RHS), characterized by unrestrained T-cell and macrophage proliferation with cytokine overproduction, although rare, may be life-threatening and may have a higher incidence in AOSD than in those with other inflammatory diseases.[55] Thrombocytopenia or absence of hyperleukocytosis, lymphopenia, coagulopathy and high triglyceride levels are prominent features of this complication.[55] Finally, AOSD can be complicated by thrombotic thrombocytopenic purpura, pure red aplasia or can present with neurological complications such as cranial neural palsies, seizures or aseptic meningoencephalitis.[6,8,56,57]

1.3 Laboratory and Radiographic Abnormalities

Although the diagnosis of AOSD remains clinical, certain laboratory abnormalities may play a role in helping clinicians establish a diagnosis.

Immune dysregulation of AOSD is generally not reflected by positive titres of rheumatoid factor or antinuclear antibodies as in other rheumatic diseases, and the absence of positive titres of these markers has been used as a classification criterion.[1,35]

1.3.1 Acute Phase Reactants

The erythrocyte sedimentation rate (ESR) is invariably elevated in AOSD patients,[8,39] as is generally the case with CRP,[21] serum amyloid A,[19] haptoglobin and serum complement.[6] A characteristic laboratory abnormality, although not necessarily diagnostic, is the often extreme, elevated serum level of ferritin, a known acute phase protein. The underlying mechanism of high ferritin levels seems to be irrelevant to its role in iron metabolism. It is probably the by-product of the uninhibited action of cytokines, such as IL-1β, IL-18, TNFα and IL-6, which 'whip' the reticuloendothelial system into producing and releasing massive amounts of ferritin.[26] Elevated serum ferritin levels (approximately 1000 ng/mL), higher than five times the upper limits of normal (40–200 ng/mL) may suggest the presence of the disease with an 80% sensitivity and 46% specificity.[58,59] Much higher ferritin levels, ranging up to 30 000 ng/mL, are not infrequent.[41]

Ferritin has been proposed to be a very useful marker of disease activity, as its levels correlate with clinical scores and tend to predict clinical response to treatment.[60-62] Its low specificity reflects the fact that high ferritin levels can also be found in several other conditions such as liver disease (e.g. haemochromatosis, Gaucher's disease), infections (e.g. sepsis, HIV), malignancies (e.g. leukaemia, lymphoma) and RHS.[41,55,59] The glycosylated fraction of ferritin, which tends to drop in inflammatory diseases, is consistently found below 20% in AOSD, making it a more specific marker of the disease.[37,58,59] Fautrel et al.[58] combined the 5-fold increase of serum ferritin with its characteristically low glycosylated fraction increasing the specificity (93%) but lowering the sensitivity (43%) of this diagnostic tool. Unfortunately, except from a few designated centres, it is not a widely available biochemical test, so its use is not meaningful in everyday clinical practice.

Another novel candidate acute phase marker of AOSD, which can also be useful in the differential diagnosis of diseases characterized by high ferritin levels, is haem oxygenase 1 (HO-1). HO-1 has anti-inflammatory properties that are mediated by haem's degradation products. HO-1 levels were significantly higher in patients with active haemophagocytic syndrome and AOSD than in other rheumatic diseases and its levels correlated well with serum ferritin. Additionally, serum levels of both ferritin and HO-1 returned to normal after treatment. Of interest, hyperferritinaemia caused by liver diseases or frequent transfusions due to haematological diseases is not associated with increased HO-1 levels.[63]

1.3.2 Haematological Abnormalities

The most commonly associated laboratory finding in AOSD is, without doubt, the leukocytosis (predominantly neutrophilic) resulting from bone marrow granulocyte hyperplasia.[64] Peripheral blood leukocyte counts $>15 \times 10^9$/L were found in 50% of 62 patients, while counts $>20 \times 10^9$/L were encountered in 37% of cases in the same series.[8] Anaemia of chronic disease is frequently seen during flares, in contrast to periods of remission when haemoglobin values tend to normalize. Reactive thrombocytosis is common. Importantly, if the opposite (i.e. thrombocytopenia) is present, then

Table III. Patterns of adult-onset Still's disease and prognostic features

Patterns	Features	Prognosis
Self limiting/monocyclic	Systemic symptoms such as fever, rash, serositis, organomegaly	Majority of patients achieve remission within 1 year of initial episode. Favourable prognosis
Intermittent/polycyclic systemic	Recurrent flares with or without articular symptoms	Complete remission between episodes that tend to be far apart and milder than initial episode
Chronic articular	Predominance of articular symptoms	Joint destruction may occur, necessitating surgical intervention. Unfavourable prognosis

RHS, a life-threatening complication of AOSD requiring immediate immunosuppressive treatment, should be strongly suspected.[55,64] Coagulation abnormalities are infrequent and reflected by prolonged times of prothrombin and partial thromboplastin. Rarely, disseminated intravascular coagulation has been reported.[8]

1.3.3 Radiographic Imaging Techniques

Initially, as expected, radiographs do not provide any specific diagnostic information except for possible tissue swelling, joint effusion, mild periarticular demineralization or even normal anatomy.[8] Years later, if the disease follows the chronic articular form, a distinctive radiographic pattern of intercarpal, pericapitate ankylosis may become apparent. Additionally, intertarsal and cervical zygapophyseal ankylosis has been noted to occur in 19% and 12% of patients with AOSD, respectively.[41] Also, in the chronic articular form, Fujii et al.[65] have proposed the 'carpo-metacarpal ratio' as a radiographic quantitative index of carpal joint involvement.

2. Conventional Treatment of AOSD

Until very recently, AOSD was treated with NSAIDs, systemic corticosteroids and traditional immunosupressants, with methotrexate being the most common immunosupressants.

2.1 NSAIDs

Since the initial description of AOSD in 1971, our understanding of its underlying inflammatory mechanisms has evolved alongside the development of anti-inflammatory drugs. At the time of the initial description of the disease, the most widely used anti-inflammatory drugs were NSAIDs and corticosteroids. Therefore, it is understandable why NSAIDs were initially investigated as treatment for the disease, in an effort to oppose the overt inflammatory response. NSAIDs work through inhibition of the cyclo-oxygenase enzyme, thus impairing the transformation of arachidonic acid to prostaglandins, prostacyclin and thromboxanes.[66] Early studies were disappointing, as they demonstrated minimal efficacy of NSAIDs as monotherapy in only 7–15% of patients.[6,8] A subsequent larger, multicentre, randomized French study confirmed the previous results, providing a comparative description of the most prevalent treatment options at that time (i.e. aspirin, NSAIDs and corticosteroids).[67] This study made it clear that aspirin was ineffective, suggested a modest, adjunct role for NSAIDs, such as naproxen or indomethacin, and clearly showed that 88% of the patients studied eventually required corticosteroids for symptomatic control.[39]

2.2 Corticosteroids

When NSAIDs were proven ineffective, the use of corticosteroids came to the therapeutic forefront owing to their potent anti-inflammatory actions. These actions include inhibition of the production of proinflammatory cytokines such as TNFα and IL-1 by macrophages and lymphocytes,[68] modulation of the signalling pathway of IFNγ,[69] induction of lymphocyte apoptosis,[70] inhibition of lymphocyte proliferation[71] and inhibition of phospholipase A2, thereby blocking the production of prostaglandin and leukotrienes.[72] Most studies support the need for corticosteroids in the majority of patients at some point in the course of the disease.[26] Prednisone proved to be a reliable anti-inflammatory agent in a study of 45 patients where 76% of them experienced improvement of their symptoms.[9] The initial dose of prednisone is usually 0.5–1.0 mg/kg/day administered orally. In refractory cases, intravenous pulse methylprednisolone and dexamethasone have been used successfully.[73,74] Despite their success in suppressing both systemic and articular symptoms, they appear to be ineffective in modifying the progressive anatomical, and radiographically evident, joint destruction in the chronic articular form of the disease.[16]

Long-term corticosteroid use is marred by clinically significant adverse events. Thinning of the skin, cataracts, hypertension, hyperlipidaemia and osteoporosis are among the common ones. Management of cardiovascular risk factors and preventive administration of calcium, vitamin D and bisphosphonates are all indicated for patients taking corticosteroids for long periods of time. Other adverse

effects include gastritis, infection, diabetes mellitus and mood changes.[75]

2.3 Disease-Modifying Antirheumatic Drugs

The use of a disease-modifying antirheumatic drug (DMARD) during the course of AOSD treatment often becomes a necessity in refractory cases where corticosteroids have been given at therapeutic doses without signs of remission, or as corticosteroid-sparing agents.[1] Additionally, given the fact that a portion of symptom-free patients develop destructive arthritis despite treatment with corticosteroids,[4,9,67] it has become common practice to add a DMARD early in the course of the disease, especially in patients with the prolonged febrile, polycyclic, or chronic articular disease patterns.[19] Apart from methotrexate, other DMARDs used to treat AOSD with variable efficacy are ciclosporin,[76] hydroxychloroquine, gold, penicillamine, azathioprine, leflunomide,[39,77] cyclophosphamide[78] and tacrolimus.[79]

2.3.1 Methotrexate

The efficacy of methotrexate in AOSD can probably be attributed to its pharmacological mechanism, which is characterized by increased adenosine release and activity. This results from inhibition of the enzyme aminoimidazolecarboxamidoadenosineribonucleotide transformylase, which, in turn, leads to inhibition of adenosine-degrading enzymes such as adenosine deaminase and adenosine monophosphate deaminase.[80] Adenosine interferes with neutrophil function and the synthesis of proinflammatory cytokines, such as TNFα and IL-6, that seem to play an important role in AOSD pathogenesis.[81,82] Similar to its use in RA, methotrexate is administered orally, once a week, in doses up to 30 mg/week.[1]

Bearing in mind the recurrent nature of the disease, its low prevalence and the different clinical courses it may manifest, the execution of double-blind, randomized trials using different therapeutic protocols is difficult. As a result, treatment of refractory cases of AOSD with methotrexate was initially empirical, based on extrapolated data from its effective use in treating RA and systemic-onset JIA.

In a study of 26 patients who did not respond to corticosteroids or who developed potentially serious adverse effects, 18 (69%) achieved complete remission and 11 (42%) were able to remain symptom free without taking corticosteroids when a low dose (7.5–17.5 mg) of methotrexate was administered.[83] Another retrospective study of 13 Japanese patients not only confirms methotrexate's efficacy in controlling disease activity but also suggests methotrexate be used in patients who have not previously been treated with conventional agents such as corticosteroids.[84] In another smaller corroborating study, a weekly 10-mg dose of methotrexate proved to be useful in reducing acute symptoms in four of six patients, although the risk of flare recurrence was not reduced. In addition, it was suggested that a 6-month treatment should be considered to allow the methotrexate treatment to take effect.[85] An 85% reduction in corticosteroid dosage in a French study of 13 patients adds to the undoubted value of methotrexate in treating patients not tolerating corticosteroid adverse effects.[67] Methotrexate has been used both alone and in combination with biological agents, which are starting to gain popularity in AOSD treatment because of their promising results.[86-99] Because the treatment regimen in AOSD patients is established in a stepwise manner depending on its efficacy and tolerability, comparative prospective trials investigating methotrexate monotherapy and methotrexate in combination with a biological agent are rare.

Methotrexate was first indicated for RA in the early 1980s and, therefore, it has a long-studied safety profile. In general, long-term experience shows that methotrexate is relatively safe provided that monthly full blood counts and liver function tests are performed. Most of its adverse reactions are caused by its antifolate activity. While in RA folate coadministration has proved to be beneficial, especially regarding its oral and gastrointestinal adverse effects,[100] in AOSD, randomized, controlled trials are yet to be carried out. Additionally, there is much scepticism about the fact that folate supplementation undermines methotrexate efficacy via a competitive affinity of folinic acid and methotrexate for the same

cellular transport molecules.[101,102] This explains the lack of consensus concerning folate supplementation in the treatment scheme of either RA or AOSD patients.

Adverse reactions in AOSD patients treated with methotrexate include gastrointestinal symptoms such as vomiting and nausea, mouth ulcers, headache, acute interstitial pneumonia, liver toxicity, blood test abnormalities, such as neutropenia[83,84] or pancytopenia,[103] and opportunistic infections.[104] Although most of these adverse effects have a relatively strong causal relationship with methotrexate, the cause of the liver toxicity remains to be elucidated. AOSD is well known to cause a large spectrum of liver abnormalities, from abnormal laboratory tests, such as elevated transaminases, to a rare form of cytolytic hepatitis and liver failure,[14,15,105,106] although most of the time patients remain asymptomatic. In a European single-centre study of 17 patients, 76% demonstrated abnormal biochemical liver indices and 47% had hepatomegaly at clinical examination.[15] Thus, it is hard for clinicians to interpret liver abnormalities in that many available treatment modalities, even the more 'innocent' ones such as NSAIDs, have the potential to cause liver toxicity. However, recommended NSAID doses for AOSD, far from being able to induce drug-related hepatitis, usually lead to a complete clinical and biological recovery in 3 weeks, even in cases of severe hepatitis.[15,67] Liver toxicity, in the form of elevated liver function tests, even due to low-dose methotrexate has been reported in patients with RA, especially in the initial treatment stages, [107,108] as well as in AOSD patients.[84] Nevertheless, in cases of life-threatening hepatitis, treatment options should be chosen cautiously, as fulminant hepatic failure has been reported in AOSD patients.[45,109]

Methotrexate, used to treat other rheumatological disorders, has been known to cause opportunistic infections, particularly of the upper respiratory tract,[110] such as histoplasmosis in a child with JIA.[111] In addition, patients with RA or JIA treated with methotrexate seem to be prone to haematological malignancies such as lymphoma, especially Epstein-Barr virus-associated lymphoma.[112,113]

2.3.2 Intravenous Immunoglobulins

Intravenous immunoglobulin (IVIG) constitutes a mixture of pooled polyspecific IgG derived from the blood of healthy human donors.[114] They have long been used as immunomodulating agents in the treatment of several autoimmune and inflammatory diseases such as Kawasaki's disease[115] and JIA.[116] Bearing in mind that IVIG possesses potent anti-inflammatory activity, as evidenced by its beneficial effects on inflammatory diseases, it seemed logical that it would act similarly in AOSD. The body of evidence pointing to the efficacy of IVIG in NSAID-refractory cases of AOSD is not vast and data collected mostly originate from small, uncontrolled, nonblinded studies and case reports.[117-120] In such a study, four of seven patients treated early with IVIG achieved remission, suggesting that use of IVIG prior to corticosteroids can lead to early control of the disease.[118] IVIG in combination with mycophenolate mofetil in an African man with refractory AOSD proved to be beneficial at a dose of 0.4 g/kg daily for 5 days.[51] The favourable effect of IVIG in AOSD could be explained by its multifactorial mechanisms of action. Among them, modulation of the distorted cytokine network,[114] which in AOSD is skewed in favour of T_h1 cytokines, can be inferred to be the prevalent mechanism.[29] Of interest, published data suggest that IVIG plays a significant role in restoring the existing imbalance of T_h1 and T_h2 in various autoimmune diseases.[114] In view of the plausible efficacious IVIG treatment of patients with AOSD, clinical trials to document its results are imperative.

Most of the adverse effects of IVIG are mild and transient, and include headache, flushing, fever, chills, nausea, fatigue, myalgia, arthralgia, back pain and, especially in patients at risk for hypertension, elevated blood pressure.[114] Elderly patients who are not well hydrated are prone to develop oliguric acute renal failure, which is transient and preventable with sufficient hydration and a slow infusion rate. Thromboembolic complications are an additional issue particularly in high-risk patients such as in those who are immobilized for prolonged periods or those with diabetes.[114,121] Aseptic meningitis is a rare adverse effect, which resolves spontaneously

and can be prevented with administration of NSAIDs.[122] Rarely, anaphylactic reactions have been reported in patients who were IgA deficient, but careful screening and administration of IgA-depleted immunoglobulin to these patients is the proper course of action.[114,123] Anaphylaxis in patients with IgA deficiency treated with IVIG is correlated with the presence of anti-IgA antibodies of the IgG and IgE isotypes in the patients' serum.[124]

2.3.3 Ciclosporin, Chloroquine, Gold, Penicillamine, Azathioprine, Cyclophosphamide and Tacrolimus

The use of combinations of DMARDs became prevalent in non-remissive AOSD patients in an effort to explore other potential therapeutic strategies or to minimize adverse effects of the existing regimens. Considering the diverse immunogenetic background, which might play a role in the therapeutic response in AOSD patients, investigators attempted to override mechanisms of resistance by administering a series of immunosuppressive agents. Nevertheless, their efficacy remains equivocal. Wouters and van de Putte[39] demonstrated a mere 44% (8 of 18 trials) clinical improvement with one or several of the following: chloroquine (0 of 3 responded), gold (6 of 8), penicillamine (4 of 6) and azathioprine (0 of 1). In a more recent study of 65 patients who received corticosteroids in combination with either methotrexate or chloroquine as first-line treatment, it was demonstrated that 21 of 28 (75%) responded to a corticosteroid/chloroquine regimen and 30 of 36 (83%) responded to the corticosteroid/ methotrexate scheme.[17] In the same study, two patients treated initially with corticosteroids and azathioprine clinically improved, whereas a patient treated with a combination of corticosteroids and sulfasalazine failed to achieve remission.[17] Several case reports with diverse success have emerged in the literature, using agents such as ciclosporin,[76] tacrolimus,[79] combined leflunomide and azathioprine,[77] and cyclophosphamide.[47,125]

3. New Treatments for AOSD: Biological Response Modifiers

In light of the growing body of evidence on pathogenetic concepts of the disease and given the fact that many AOSD patients do not respond to the broadly accepted first-line treatment (methotrexate, prednisone ± NSAIDs), novel treatment modalities were sought (figure 2; table IV). These agents, well known for their efficacy in other inflammatory diseases, such as RA, target biological molecules, which seem to play a pivotal role in the mechanism of the disease. Consequently, inhibiting the action of proinflammatory cytokines, such as TNFα, IL-1 and IL-6, was a decisive step forward in the treatment of refractory AOSD patients.

One of the first TNFα inhibitors put to the test in AOSD was etanercept. Etanercept is a fully humanized fusion protein constructed of two recombinant p75 soluble TNFα receptors (CD120b) linked to the Fc portion of human IgG1.[140] Additionally, etanercept binds TNFβ and, as opposed to infliximab, it does not lyse cells expressing transmembrane TNFα in the presence or absence of complement.[141] Of note, both etanercept and infliximab, apart from their TNFα-inhibiting effect, have proved to

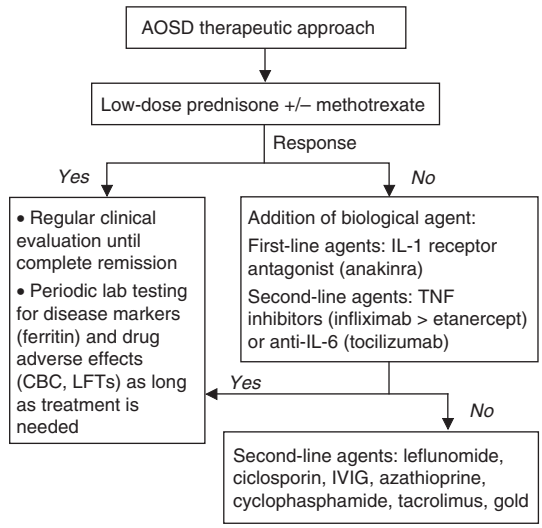

Fig. 2. Therapeutic algorithm for adult-onset Still's disease (AOSD). **CBC** = complete blood count; **IL** = interleukin; **IVIG** = intravenous immunoglobulin; **lab** = laboratory; **LFT** = liver function test; **TNF** = tumour necrosis factor; **>** indicates greater efficacy.

Table IV. Retrospective overall outcome analysis of studies utilizing biological response modifiers in adult-onset Still's disease

Studies	No. of patients/cases	Total patients	Usual treatment scheme	Remission
Infliximab				
Kraetsch et al.[126]	6	44	Infliximab + DMARDs + corticosteroid	91% (40/44)
Dechant et al.[127]	8			
Fautrel et al.[94]	15			
Kokkinos et al.[89]	4			
Cavagna et al.[88]	3			
Huffstutter and Sienknecht[90]	2			
Caramaschi et al.[92]	1			
Bonilla Hernan et al.[91]	2			
Dilhuydy et al.[93]	1			
Michel et al.[128]	1			
Olivieri et al.[129]	1			
Etanercept				
Husni et al.[87]	12	25	Etanercept + methotrexate + corticosteroid	72% (18/25)
Fautrel et al.[94]	10			
Serratrice et al.[130]	1			
Kumari and Uppal[131]	1			
Asherson and Pascoe[132]	1			
Adalimumab				
Benucci et al.[95]	1	1	Adalimumab + methotrexate + corticosteroid	100% (1/1)
Anakinra				
Haraoui et al.[133]	4	23	Anakinra + methotrexate + corticosteroid	91% (21/23)
Fitzgerald et al.[99]	4			
Kotter et al.[134]	4			
Kalliolias et al.[135]	4			
Vasques Godinho et al.[136]	1			
Rudinskaya and Trock[137]	1			
Quartuccio and De Vita[138]	1			
Chu et al.[139]	4			
Tocilizumab				
Iwamoto et al.[96]	1	1	Tocilizumab + methotrexate + corticosteroid	100% (1/1)

DMARDs = disease-modifying antirheumatic drugs.

downregulate the T-cell production of IFNγ and granulocyte-macrophage colony-stimulating factor,[142] which are inferred to participate in the inflammatory process of the disease.[12,29,31] Etanercept is administered subcutaneously twice weekly at a dose of 25 mg. As with RA, etanercept is frequently coadministered with methotrexate, even if it is approved as monotherapy,[141] and has been similarly used in AOSD.

In a 6-month, open-label pilot study in which 12 patients participated, 66.7% experienced amelioration of their symptoms after etanercept treatment. Nine of the patients received prednisone concomitantly and methotrexate was added to the treatment scheme of five patients during the study.[87] Several other case reports contribute to the usefulness of etanercept in refractory AOSD patients,[120,130,131] though larger double-blind cohort studies are required in order to validate its potential beneficial effects.

Larger-scale etanercept studies may be executed taking into consideration several safety issues de-

rived from the long-term experience of its use in RA and JIA. A common adverse effect is injection site reaction, such as redness, pain, swelling and itching, particularly in the first month of treatment. Other frequent adverse effects that need to be addressed are mild upper respiratory tract infections, pharyngitis, respiratory disorders, dyspepsia, abdominal discomfort and rashes.[143] In a 4-year study of 34 patients with JIA who received etanercept, the rate of serious adverse effects was 0.13 per patient-year and the rate of serious infections was 0.04 per patient-year in a total etanercept exposure of 225 patient-years.[144] Nevertheless, blocking the activity of TNFα leads to a limited and defective protection against pathogenic organisms, especially opportunistic ones such as *Mycobacterium tuberculosis*, atypical species of *Mycobacterium*, *Candida*, *Histoplasma*, *Cryptococcus* and *Listeria* spp.[141,145,146]

Infliximab is a genetically engineered chimeric monoclonal antibody, 75% human and 25% mouse in origin, which binds to soluble and transmembrane TNFα but not to TNFβ. The human portion accounts for its activity, whereas the mouse portion contains a variable region binding site. Infliximab has been shown *in vitro* to lyse cells expressing TNFα on their surface via complement and antibody-dependent cell-mediated cytotoxicity.[141] Infliximab is administered intravenously and after an initial infusion, it is administered at 2, 6 and then every 8 weeks thereafter.[147] This treatment scheme applies to RA, although AOSD patients have been treated similarly.

Infliximab has been used successfully in refractory cases of AOSD. One of the first reports to demonstrate its efficacy was that of Cavagna et al.,[88] who administered infliximab (together with methotrexate and prednisone) in three patients at a dose of 3 mg/kg at weeks 0, 2, 6 and once every 8 weeks for 50 weeks. The overall scheme yielded very favourable results in terms of both clinical response (fever control) and inflammatory activity reflected by biochemical markers (ESR, CRP and serum ferritin).[88] A consequent corroborating small cohort study of six patients demonstrated very promising results as all patients achieved clinical remission early in the course of the disease, suggesting that early administration of TNFα inhibitors might have more beneficial results.[126] The latter is inferred in a case of early (1 month) AOSD where methotrexate was thought to be contraindicated because of hepatitis B virus (HBV) infection with persistent low titres of HBV DNA.[129] Ten AOSD patients unresponsive to methotrexate and corticosteroids achieved remission only after infliximab infusion in several open-label studies.[89-93] Although it is difficult to ascribe the clinical improvement of each patient to appropriate treatment because of the recurrent nature of the disease, it is postulated that anti-TNFα therapy may have a lasting beneficial effect, as five of eight patients treated with infliximab remained in remission in a 5-year follow-up period even after termination of treatment.[127] Infliximab and etanercept were investigated in a European, multicentre, observational study of 20 patients who were previously treated with high doses of methotrexate and corticosteroids without success. Clinical response was noted in patients with a systemic form of the disease as well as in patients with the polyarticular form. Most patients (16 of 25) responded partially to the treatment with either one of the agents (7 of 10 on etanercept and 9 of 15 on infliximab), while 5 of 20 achieved complete remission (four on infliximab and one on etanercept). Of interest, switching between TNFα antagonists does not seem to be as effective as it is in RA.[94]

Adalimumab is a fully humanized monoclonal antibody, which binds both soluble and membrane TNFα, blocking the interaction with the p55 and p75 receptors. It has been shown to lyse cells expressing TNFα on their surface in the presence of complement.[141] Currently, it is indicated for clinical use in RA, psoriatic arthritis, ankylosing spondylitis and Crohn's disease.[148] It is administered subcutaneously every week or every other week at a dose of 40 mg.[147] In AOSD, there is a single case report referring to clinical improvement in disease refractory to methotrexate and corticosteroids.[95] Overall, the experience with this agent is limited in AOSD, as it was the most recently approved by the US FDA anti-TNFα agent, and probably also be-

cause of the recent shift in attention to IL-1 inhibition, discussed in more detail in the next paragraph. The most common adverse effects associated with adalimumab, derived from experience with its use in RA, include injection site reactions, upper respiratory tract infections, headache, rash, urinary tract infections and hypertension.[147]

Bearing in mind the shared pathogenetic components of JIA and AOSD, and the fact that proinflammatory cytokines play a significant role in AOSD, some investigators have used IL-1-receptor antagonists in cases refractory to conventional agents and TNFα inhibitors.[149] The purified recombinant human IL-1-receptor antagonist exerts its effects via the competitive inhibition of binding of IL-1α and IL-1β to the IL-1 receptor, thereby blunting the activity of this proinflammatory cytokine.[150]

In one of the first case reports showing the favourable response to the IL-1 receptor antagonist anakinra, a patient with a 4-year history of AOSD had frequent flares despite being treated with high doses of corticosteroids (up to 1 mg/day), several DMARDs and, later on, infliximab. As soon as anakinra was administered at a dose of 100 mg/day subcutaneously in addition to methotrexate, prednisolone and naproxen, the patient experienced a rapid amelioration of her systemic and joint symptoms.[97] A consequent paper corroborating the therapeutic benefits of anakinra demonstrated rapid haematological, biochemical and cytokine defervescence in four non-remitting AOSD patients. Of note, when anakinra was withheld on two occasions, patients relapsed, only to improve after reintroduction of the agent. Additionally, it was postulated that the beneficial effects of TNFα inhibition are exerted through reduced production of IL-1 given that TNFα is known to induce IL-1.[99] Although well established prospective studies comparing anakinra with other biological agents are still needed to solidify any potential therapeutic advantage, emerging evidence supports its use in terms of efficacy, rapidity of action, corticosteroid-sparing effects and tolerability.

Anakinra was very well tolerated in all of the patients in the aforementioned study.[99] Data extrapolated from large series of patients with RA treated with anakinra for an extended period of time (up to 36 months)[151,152] demonstrate that it is well tolerated and worth considering for resistant cases of AOSD. The most frequent adverse effects reported include injection site reactions, upper respiratory tract infections, headaches, arthralgia, sinusitis, nausea and diarrhoea. Concomitant corticosteroid use (which is common in AOSD) is thought to increase the risk of serious adverse effects such as pneumonia and cellulitis.[152] Thus, careful monitoring of patients with additional risk factors for infections is mandatory and justifies the fact that anakinra is contraindicated in patients with active infections.[152] The recent death of an AOSD patient treated with anakinra due to cardiac complications[153] and another case of reversible thrombocytopenia associated with the use of anakinra in AOSD[138] pose questions for possible causal relationships but, as yet, any inferred association remains speculative.

IL-6, a proinflammatory cytokine, is considered to play a reinforcing role in the development of the inflammatory process in AOSD. Studies have shown that serum IL-6 levels are higher in AOSD patients (with both systemic and articular disease) than in patients with inactive disease or healthy controls. Furthermore, its levels correlate with clinical activity and biochemical markers of the disease, making IL-6 a candidate biomarker.[30,31] These data, in addition to the clinical benefit of IL-6 blockade demonstrated in one particularly refractory AOSD case in Japan[96] and in related sudden-onset JIA,[154,155] support the rationale of administering IL-6 receptor antagonists in AOSD. Tocilizumab, formerly known as MRA, is a humanized anti-IL-6 receptor monoclonal antibody of κIgG1 subclass that has been shown to compete for both the membrane-bound and soluble forms of the human IL-6 receptor, thus diminishing the proinflammatory activity of IL-6.[156]

In patients with sudden-onset JIA, safety signals associated with intravenous infusions of tocilizumab

at doses of up to 8 mg/kg were infections, such as herpes simplex mouth ulcers, and a mild elevation of total cholesterol levels.[154,155] In a European study where tocilizumab was used to treat RA patients unresponsive to methotrexate, there was a dose-related increase in the mean serum transaminase level (accentuated by concomitant use of methotrexate), with no evidence of clinical hepatitis. Moreover, abnormal serum lipid levels, as evidenced by elevated total cholesterol levels, triglycerides and high density lipoproteins, occurred during tocilizumab treatment.[157] Tocilizumab is in the late stages of development for the treatment of RA.

4. Conclusion

AOSD is a rare, multi-system, inflammatory disease of unknown aetiology and with considerable phenotypic variability. Since all available evidence comes from case reports and case series, the quality of the available evidence is limited. The rarity of the disease, combined with the lack of a funded, international collaborative research initiative, makes the execution of rigorous clinical trials wishful thinking. The only encouraging news comes from the relatively newly formed National Institutes of Health Rare Diseases Clinical Research Network, which could be instrumental in coordinating such an effort for AOSD and other rare diseases. Until such an effect occurs, a rational therapeutic approach could be to capitalize on the findings of basic science, such as cytokine biology, and the identification of specific therapeutic targets. Although first-line agents such as methotrexate and prednisone have proved to be effective in a majority of patients with the disease, there are still groups of patients with refractory disease who can benefit from the use of the biological agents more recently incorporated into clinical practice. For example, the discovery of the significance of IL-1 led to use of the currently available IL-1 receptor antagonist (anakinra), with far better success in AOSD than in RA, the indication for which it was originally approved. Currently existing agents (e.g. anti-TNFα) or those in the late stages of development (e.g. anti-IL-6) may offer therapeutic alternatives. These results obviously need to be validated in larger studies, and while convincing the pharmaceutical industry to design new drugs for rare diseases may be extremely difficult, asking them to provide currently available drugs for new indications may be a more pragmatic approach.

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