Biologic treatments for adult-onset Still’s disease
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Abstract
Adult-onset Still’s disease (AOSD) is a systemic inflammatory disorder that is a diagnosis of exclusion. It is characterized by high spiking fevers, arthritis or arthralgia, and an evanescent salmon-coloured rash. Many other systemic manifestations and laboratory test abnormalities may occur. Biologic drugs, TNF-α inhibitors, and IL-1 and IL-6 blockers have been used for the treatment of patients with AOSD refractory to conventional treatment or those with life-threatening manifestations aiming for better disease control. Data on biologic treatments in AOSD are limited and consist mainly of case reports, small case series and retrospective studies. Using biologic agents (anti-TNF-α, anti-IL-1 and anti-IL-6) with traditional immuno-suppressive drugs resulted in significant improvement of disease outcomes. IL-1 and IL-6 inhibitors seem to be more efficient than TNF-α inhibitors.

Key words: adult-onset Still’s, TNF-α inhibitor, tocilizumab, anakinra, canakinumab, rituximab, abatacept.

Introduction
Adult-onset Still’s disease (AOSD) is a systemic inflammatory disorder that is a diagnosis of exclusion. It is characterized by high spiking fevers, arthritis or arthralgia, and an evanescent salmon-coloured rash. Many other systemic manifestations such as lymphadenopathy, serositis, pericarditis, endocarditis, myocarditis and organomegaly may occur, along with laboratory test abnormalities including leucocytosis, high serum ferritin levels and elevated liver enzymes. AOSD is a rare disease that affects younger people, the majority presenting between 16 and 35 years of age. The precise aetiology of AOSD is unknown. However, many hypotheses have been proposed in the pathogenesis of AOSD. Chen et al. [1] demonstrated a predominance of T helper cell (Th1) cytokines in patients with active untreated AOSD.

The Th1 immune response is characterized by increased production of IL-2, IFN-γ and TNF-α cytokines that activate macrophages and NK cells, and promote cell-mediated immunity [2]. Serum levels of IL-6, IL-8, IL-18 and TNF-α were elevated in both the sera and pathological tissues of patients with active AOSD [3]. Additionally, IL-1β and IL-6 may account for the distinctive features of AOSD. IL-1β activates the thermoregulatory centre, resulting in fever; activates IL-1 receptors on the endothelium, resulting in rashes; and also acts on the bone marrow to increase mobilization of granulocyte progenitors and mature neutrophils, resulting in peripheral neutrophilia. IL-1 also causes an increase in platelet production, which results in thrombocytosis, and decreases the response to erythropoietin, causing anaemia. IL-1 induces the production of IL-6. Circulating IL-6 stimulates the hepatocytes to synthesize several acute-phase proteins [4]. Hence dysregulated production of IL-1 may play a critical role in the pathogenesis of AOSD, justifying the use of IL-1 inhibitors as a therapeutic option.

Several classification criteria have been published and the most widely used is Yamaguchi’s criteria [5]; however, a French group has recently proposed a new set of criteria [6]. The treatment of patients with AOSD includes NSAIDs, corticosteroids, DMARDs and recently biologic agents.

Materials and methods
Medline, PubMed and SCOPUS were searched for published data from January 2000 to December 2012, using the search terms adult-onset Still’s disease and biologics, adult-onset Still’s disease and infliximab, etanercept, adalimumab, golimumab, abatacept, rituximab, tocilizumab, anakinra and canakinumab, for all available articles in the English language. The reference lists from review articles were also checked. Only published, peer-reviewed articles were included. Abstracts from annual scientific meetings were excluded.

Results
The literature search identified 78 articles. Six retrospective studies, 10 review articles, 13 small case series and 48
case reports were identified. Only one randomized study of anakinra was identified.

Biologic agents used in AOSD

TNF-α inhibitors

*Infliximab.* Infliximab is a chimeric monoclonal antibody that antagonizes TNF-α. It has been prescribed at a dose of 3–5 mg/kg of body weight given i.v. at weeks 0, 2 and 6 and every 6–8 weeks thereafter.

In a case series of six AOSD patients, infliximab was given and resulted in marked improvement in all six patients for both systemic and articular manifestations, as well as serological variables (CRP, ESR and hyperferritinemia) [7]. Infliximab was also effective in patients with active AOSD resistant to corticosteroids and MTX and has a corticosteroid-sparing effect. The efficacy of infliximab in corticosteroid- and MTX-resistant AOSD patients was demonstrated in several case series and case reports [8–14]. An observational study reported the outcomes of 20 AOSD patients (predominantly systemic in 5 patients and polyarticular in 15) who were resistant to conventional DMARD therapy treated with TNF-α inhibitors (infliximab and etanercept) with a mean disease duration of 8.5 years. Infliximab was used to treat 10 patients and etanercept was used for 5, while 5 received both drugs consecutively. After a mean (s.d.) follow-up of 13 (14) months, complete remission was seen in 5 patients (1 treated with etanercept and 4 treated with infliximab) and a partial response was observed in 16 cases (7 treated with etanercept and 9 treated with infliximab). Treatment failed in four cases (two with each anti-TNF-α) [15]. Aeberli et al. [16] reported that of three of four AOSD patients who responded well to TNF-α inhibitors (infliximab and etanercept), two patients were initially treated with infliximab but had to be switched to etanercept due to allergic reactions, and infliximab was given to one patient 4 months later after discontinuation of etanercept due to bacterial infection. A recent retrospective study of 16 AOSD patients reported the response to biologic agents where infliximab was used in 9 cases. However, five patients were non-responders or suffered relapses and were changed to another biologic agent [17].

Infliximab is generally well tolerated, however, it has been associated with side effects including infusion reactions [12], skin rash [10], infections [15], fulminant hepatitis in a patient with concomitant hepatitis B who then required a liver transplant [18] and exacerbation of heart failure [15].

*Etanercept.* Etanercept is a recombinant soluble form of human TNF-α receptors that is linked to the Fc portion of immunoglobulin G. A small, prospective, 6-month open-label trial evaluated etanercept in 12 AOSD patients who had active chronic polyarthritis with a mean disease duration of 10.7 years and were resistant to at least one DMARD. Etanercept was given in biweekly doses of 25 mg s.c. The ACR improvement criteria were used to evaluate the efficacy. Ten patients successfully completed the study: seven patients achieved an ACR-20, and among them four and two achieved an ACR-50 and an ACR-70, respectively. Three patients had concomitant systemic manifestations and only one of them improved; however, arthritis did not improve in any of these three patients. Two patients discontinued etanercept because of disease flare. The dosage of etanercept was increased in four patients to 25 mg three times per week [19]. Ten patients with refractory AOSD were treated with etanercept: only one achieved a complete response and seven achieved a partial response [15]. Etanercept was given as 25 mg twice a week to four AOSD patients: only one patient who had a chronic articular course achieved remission and the remaining three patients failed to show any response [17]. It was also given to two AOSD patients: one achieved a significant improvement but not a complete response, while the second patient failed to show any response [20]. Kumari et al. [21] reported a prolonged remission in a patient with AOSD treated with etanercept. Two AOSD patients who were treated with etanercept after they developed allergic reactions to infliximab achieved remission; however, it had to be discontinued in one patient due to systemic bacterial infection [16]. Etanercept 50 mg/week failed to show any improvement in one AOSD patient [22].

Etanercept was used successfully for the treatment of AOSD patients with complications that included myocarditis [23], heart failure [24], cardiac amyloidosis [25] and renal amyloidosis [26]. Etanercept was well tolerated and the side effects reported included injection site reactions, skin rash and infections [15, 19, 27].

*Adalimumab.* Adalimumab is a fully humanized monoclonal antibody that inhibits TNF-α. It has been used successfully in some patients with AOSD [28]. Adalimumab was effective in treating a patient who failed to respond to etanercept [20]. It was also prescribed after infliximab to a patient with AOSD to treat chronic arthritis without further outcome details [29]. However, it failed to demonstrate any improvement in two AOSD patients [22]. Macrophage activation syndrome secondary to disseminated histoplasmosis has been described in two patients with AOSD receiving adalimumab [30, 31]. No data were found about golimumab, a humanized monoclonal antibody that inhibits TNF-α that is given subcutaneously once a month, in the treatment of AOSD. Switching from one TNF-α inhibitor to another may be useful, as demonstrated in several cases [15, 32]. Aikawa et al. [32] reported six AOSD patients received infliximab, of whom five were switched to other anti-TNF-α agents (two were switched to etanercept and both were subsequently switched to adalimumab, three were switched to adalimumab and one had to stop all anti-TNF-α agents).

*IL-1 inhibitor*

Increased IL-1 levels have been observed in active untreated disease that significantly decreased following treatment with the IL-1 receptor inhibitor [33].

*Anakinra.* Anakinra is a recombinant inhibitor of the IL-1 receptor that blocks the action of IL-1. Kotter et al. [33] reported a small case series of four AOSD patients refractory to corticosteroids and DMARDs and one patient who was also refractory to etanercept and infliximab. One
patient had life-threatening symptoms (toxic megacolon, pneumonitis, disseminated intravascular coagulation) despite high-dose corticosteroids. Treatment with anakinra 100 mg/day s.c. resulted in a quick response. Two additional case series were reported of four AOSD patients refractory to corticosteroids, MTX and TNF-α inhibitor. Treatment with anakinra 100 mg/day resulted in rapid and complete resolution of both systemic and articular manifestations as well as normalization of inflammatory marker levels [34, 35]. A recent retrospective study reported 28 refractory AOSD patients, 50% of whom failed one or more biologic agents (11 with etanercept, 9 with infliximab, 3 with adalimumab, 2 with rituximab), who received anakinra 100 mg/day. Nineteen patients (68%) received anakinra with MTX, while six patients (21%) received anakinra as monotherapy. All the patients achieved a rapid and clinically significant response to anakinra (within a few hours or days). Sixteen patients (57%) continued anakinra (at the last follow-up with a mean duration of 23 months), 12 patients (42%) achieved complete remission and 4 (14%) achieved partial response with persistence of musculoskeletal symptoms. Twelve patients (43%) discontinued anakinra—two due to partial response considered unsatisfactory by clinicians, four due to AOSD flare after a period of complete remission (mean duration of remission 13.8 months), two due to side effects (severely itchy skin rash at the site of the injection despite a significant response of AOSD) and one due to a desire for pregnancy during a period of partial remission. Of note, three patients (11%) discontinued anakinra because they achieved complete remission. It has a steroid-sparing effect, which was also demonstrated in this study. Anakinra was well tolerated and the only observed adverse event was a rash at the site of injection, which was mild in all patients. No severe infection was observed [36].

Another study of 25 patients with active AOSD resistant to corticosteroids (n = 17), DMARDs (n = 4) or TNF-α inhibitors (n = 4) who received anakinra was reported. Sixteen patients received daily anakinra (100 mg/day) with a DMARD and nine patients received anakinra as monotherapy for a median time of 15 months. Twenty-one patients (84%) responded completely and the response was maintained until the last visit in all but one patient. Three patients (12%) had partial response and presented with arthralgia (n = 2) or arthritis and intermittent fever (n = 1) at the end of the follow-up. One patient (4%) with prominent articular disease failed anakinra. Three patients developed a severe urotelial reaction after the first few months of treatment (one patient at 1.5 months and two patients at 3 months) and discontinued therapy. Seven patients (28%) developed infections (one trachibronchitis, one H1N1 virus infection of the upper respiratory tract, one gastroenteritis with fever, one soft tissue abscess and three lower urinary tract infections), which led to a transient discontinuation of the immunosuppressive treatment. Five patients had a local hypersensitivity reaction at the site of injection. Anakinra was discontinued in three patients because of severe urticarial-like skin reactions and in one patient with severe trachibronchitis [37]. Fifteen AOSD patients treated with anakinra were reported by Lequerre et al. [38]. All patients received MTX and 10 patients (67%) had failed TNF-α inhibitors. Eleven patients achieved a rapid and at least 50% improvement, nine achieved a complete response and two achieved a partial response. The dose of corticosteroids was greatly reduced in eight patients and stopped in two. Four patients discontinued the anakinra (two because of a lack of efficacy and two due to a skin rash after 1 month and 3 months, respectively) [38]. A case series of eight patients with AOSD refractory to glucocorticoids, DMARDs and/or TNF-α inhibitors (six patients to etanercept, two patients to adalimumab and one patient to infliximab) reported rapid and long-lasting responses to anakinra. A steroid-sparing effect was also demonstrated in this study [39]. Several case reports have described a rapid response to anakinra in AOSD patients refractory to other DMARDs or biologic treatment [40-48]. A recent open, randomized, multicentre study demonstrated the efficacy of anakinra for inducing remission in refractory AOSD. Twenty-two AOSD patients refractory to corticosteroids (> 10 mg/day of prednisolone) with or without concomitant DMARD were randomized to anakinra (n = 12) or DMARD (n = 10) for 24 weeks. The primary endpoint was achievement of remission.

Efficacy was assessed at weeks 8, 12 and 24. Seven patients on anakinra and five patients on DMARDs were in remission at week 8, while six patients on anakinra and only two patients on DMARDs at week 24 were in remission. These differences did not reach statistical significance; however, more patients on anakinra than on DMARDs achieved remission. Three patients on anakinra but none on DMARDs were able to discontinue oral corticosteroids (P = 0.22). More patients on anakinra than on DMARDs achieved significant improvements in the physical health summary (P = 0.011). An open-Phase extension of 28 weeks was completed by 17 patients, 9 of whom originally received anakinra and 8 who received DMARDs. Half of the patients randomized to DMARDs had a disease flare that was treated with anakinra as monotherapy or combined with a DMARD, resulting in a total of 14 patients receiving anakinra, half of whom were in remission at week 52. Only three patients originally on DMARDs remained on the same medication at week 52. Although the differences between groups did not reach statistical significance, patients on anakinra showed more robust responses [49].

Of note, acute respiratory distress syndrome and severe systemic inflammatory response syndrome have been reported in a patient treated with anakinra [50]. Thrombocytopenia was also reported in one patient with AOSD who received anakinra [51].

Canakinumab. Anakinra has a short half-life of 4–6 h, demanding daily injections that are often inconvenient. This has resulted in the development of a new IL-1β antagonist. Canakinumab is a humanized monoclonal antibody against IL-1β with a half-life of 26 days. It has been approved for the treatment of cryopyrin-associated
autoinflammatory syndromes, but it could represent a new therapeutic option for AOSD. It has been used successfully in two AOSD patients who were resistant to corticosteroids, MTX and anakinra as 150 mg s.c. injections every 8 weeks. Canakinumab was well tolerated, with the exception of transient diarrhea. No increased incidence of infections or injection site reactions were noted [52].

**IL-6 inhibitor (tocilizumab)**

Elevated levels of IL-6 and other proinflammatory cytokines have been demonstrated in AOSD patients. It has been associated with systemic symptoms such as fever and skin rash and correlated with raised serum CRP, ferritin and leukocytosis levels, as well as with disease activity [3]. Hence IL-6 inhibitors can be used successfully in the management of AOSD patients. Tocilizumab is a humanized monoclonal antibody that antagonizes IL-6 receptors.

Suematsu et al. [17] reported retrospective data on 16 Japanese AOSD patients who had been treated with at least one biologic agent. Eleven patients were treated with tocilizumab: six patients were given tocilizumab as the first administered biologic agent and the remaining five patients were switched to tocilizumab from other biologics. Notably, all patients except one (observation period 1 month) responded well to tocilizumab, and in two of these patients the corticosteroid was withdrawn. In addition, one patient was in drug-free remission for >8 years after 18 months of treatment with tocilizumab. Serum CRP and ferritin levels almost normalized within 7.1 weeks (mean) and 5.8 weeks, respectively [17].

An observational, uncontrolled study of 14 patients with refractory AOSD treated in France was reported. All patients had chronic arthritis and failed anakinra and 12 patients failed at least one TNF-α inhibitor. The effectiveness of treatment was assessed using the DAS28 and the European League Against Rheumatism (EULAR) criteria and systemic improvement was defined as the resolution of systemic manifestations. Eleven patients successfully completed the 6-month study and the mean DAS28 decreased from 5.61 to 2.91, a EULAR remission (DAS <2.6) was achieved in 57% of the patients and resolution of systemic manifestations was observed in 86% of patients. Moreover, in this study tocilizumab had been observed to have a corticosteroid-sparing effect. Two patients withdrew due to side effects (one patient developed a necrotizing angiodermatitis and another had chest pain and chills at each tocilizumab infusion) and one withdrew due to systemic flare. The response to tocilizumab was rapid and sustained [53]. In another small case series of three AOSD patients refractory to many different medications, including TNF-α inhibitors and IL-1 inhibitor (anakinra), tocilizumab was rapidly effective [22].

Several other case reports have demonstrated a successful response to tocilizumab in AOSD patients [54-67]. A macrophage activation syndrome was reported in AOSD patients receiving tocilizumab [61, 68].

**Co-stimulatory inhibitor (abatacept)**

Abatacept is a selective co-stimulation modulator that inhibits T lymphocytes by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a co-stimulatory signal necessary for activation of T lymphocytes. Two patients have been treated successfully with abatacept after they failed corticosteroid, MTX and TNF-α inhibitors [69, 70]. However, it failed in two other patients [53, 71].

**B cell depleting agent (rituximab)**

Rituximab is a chimeric monoclonal anti-CD20 antibody. Two AOSD patients refractory to corticosteroids, DMARDs and TNF-α inhibitors were treated successfully with rituximab (375 mg/m² i.v. infusion given twice at 4-week intervals) [72]. In a case series of patients with AOSD, rituximab was used to treat one patient resistant to DMARDs and resulted in remarkable improvement; however, further details were not reported [73]. Bartoloni et al. [74] reported a patient with refractory AOSD who was treated successfully with rituximab. However, it failed in treating other patients with resistant AOSD [36, 38, 53].

## Conclusions

AOSD is a rare systemic inflammatory disorder, which might explain the absence of prospective, controlled treatment trials. Data on biologic treatments are essentially extrapolated from observational studies, case series or single case reports. Biologic agents are considered for treatment of AOSD patients who are refractory to corticosteroids and DMARDs and represent major therapeutic advances. Limited data are currently available about abatacept and rituximab in managing refractory AOSD, as a few patients have been reported with conflicting results. TNF-α, IL-1 and IL-6 inhibitors were effective in the treatment of refractory AOSD patients. However, IL-1 and IL-6 inhibitors seem to be more efficient than TNF-α inhibitors, although, because of the lack of randomized control trials, publication bias cannot be excluded.

## Rheumatology key messages

- Biologic agents are used to treat refractory AOSD patients.
- Switching from one TNF-α inhibitor to another may be useful for refractory AOSD patients.
- In refractory AOSD, IL-1 and IL-6 inhibitors seem to be more efficient than TNF-α inhibitors.

## Disclosure statement

The author has declared no conflicts of interest.

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