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Tocilizumab for the treatment of adult-onset Still's disease

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Abstract

Introduction: Adult-onset Still´s disease (AOSD) is a systemic inflammatory condition that affects mainly young people. The clinical course consists of two distinctive patterns: one with a predominance of systemic symptoms and another manifested by progressive chronic polyarthritis. Glucocorticoids remain the mainstay in the treatment of AOSD. However, biologic therapies are often required to achieve clinical remission and allow glucocorticoid discontinuation.

Areas covered: The review summarizes the main retrospective and prospective studies, and case series on the use of the anti-interleukin (IL)-6 receptor tocilizumab in AOSD.

Expert opinion: Since IL-6 serum levels are highly increased in both active systemic and polyarticular phenotypes, IL-6 blockade was considered to be a plausible therapeutic option for the management of AOSD. Tocilizumab, the only anti-IL-6-receptor antagonist currently available for AOSD, has proved to be effective for the management of refractory AOSD patients, including those with life-threatening complications. Nevertheless, there are some reports describing patients who are refractory to any therapy. Future research should focus on the identification of prognostic biomarkers that help us to tailor an individualized treatment for each type of

patient and in the search of new disease activity indices that help us to monitor the response to the therapy more closely.

Keywords: adult-onset Still disease, anakinra, anti-IL6-receptor tocilizumab, anti-TNF-α drugs, biologics, glucocorticoids.

1. Introduction

Adult-onset Still´s disease (AOSD) is a systemic inflammatory disease of unknown origin affecting mainly young people with an estimated annual incidence between 0.16 and 0.4/100,000 persons worldwide **[1-3]**. It is slightly more common in women **[4,5]**, and there is a bimodal age distribution, with a peak between 15 and 25 years and another around 35-40 years **[1]**.

AOSD is included within the clinical spectrum of autoinflammatory disorders **[6,7]**. It shares many clinical and laboratory features as well as a gene profile activation with systemic onset juvenile idiopathic arthritis (sJIA) **[8-10]**. Because of that, AOSD and sJIA are currently considered two variants of the same disease **[3]**. In addition, extrapolation of the use of biologic therapies in AOSD was partially inferred from the good results obtained in sJIA.

Infectious and other environmental factors may trigger a systemic autoinflammatory response in genetically predisposed individuals leading to a dysregulation of the "inflammasome complex" with the overproduction of numerous pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-18, interferon (IFN)-γ and tumor necrosis factor (TNF)-α **[10,11]**.

AOSD is clinically characterized by daily high spiking fever, evanescent salmon-colored maculopapular rash, arthritis, musculoskeletal symptoms and neutrophilic leukocytosis. Other common manifestations include: sore throat, lymphadenopathy,

pulmonary infiltrates, pleuritis, pericarditis, abdominal pain and hepatosplenomegaly **[3,12,13]**. As the result of a systemic inflammatory response, patients with AOSD present elevation of acute-phase reactants (APR), such as the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP), marked leukocytosis with neutrophilia, anemia and thrombocytosis. Serum ferritin levels are particularly increased (classically more than 5 times above the upper limit of normal) and it may be a good biomarker of disease activity **[3,13]**. AOSD is also associated with a reduction in the glycosylated ferritin fraction, so that the combination of serum ferritin levels higher than 1000 μg/L with a glycosylated fraction <20% has been found to have a high specificity for a diagnosis of the disease **[14,15]**.

The presentation and course of AOSD may result into two well differentiated clinical phenotypes: a systemic and highly symptomatic pattern (systemic pattern, SP) and another consisting of a chronic articular disease (CAD), showing features of persistent polyarthritis with progressive joint destruction, and eventually more disabling than the SP **[10,16]**. Sometimes, we are not able to categorize chronic AOSD into two dominant forms, because there are mixed forms of the disease. Indeed, systemic form of disease may transit to arthritis dominant form and vice versa, which manifests once again the heterogeneity of this multifaceted disease. Interestingly, arthritis of the CAD can be erosive in up to 50% of patients **[17,18]**. Around 15-20% of patients with AOSD develop some life-threatening complications such as the macrophage activation syndrome (MAS), disseminated intravascular coagulation (DIC), severe myocarditis, endocarditis or pulmonary arterial hypertension (PAH) **[19,20]**. In particular, MAS is the most severe complication of AOSD, and it is associated with a high mortality rate occurring early during the course of the disease **[21,22]**. IL-6 has been proposed as one

of the most important mediators implicated in the pathogenesis of that complication **[23]**.

Due to the low incidence of the disease, the treatment of AOSD remains largely empirical, mainly based on case reports and small retrospective case series, and not on controlled studies. Non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GC) represent the first line therapy, particularly for musculoskeletal manifestations and fever, with response rates between 20% and 60% **[3,12,24]**. However, around 40-45% of patients with AOSD develop glucocorticoid-dependence and/or mild or severe long-term toxicity **[25]**. Therefore, disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX), cyclosporin A (CsA), azathioprine (AZA) or leflunomide (LEF) are often required as second line therapy **[24-26]**. In cases refractory to GC and DMARDs, biologic drugs, particularly anti-interleukin (IL)-1 and anti-IL-6 receptor (R) agents, have proved to be effective to control disease activity and its main complications **[27-29]**. In patients who are refractory to these therapies or in those with life-threatening complications other therapies such as: intravenous (IV) immunoglobulins, calcineurin inhibitors, cyclophosphamide or plasma exchanges may be used **[3,12,19]**.

Tocilizumab (TCZ), a humanized anti-IL-6R antibody that binds to both the membrane-bound and soluble form of IL-6R, is an effective biologic agent for the treatment of AOSD. Data from retrospective studies and case series demonstrate the efficacy of TCZ in monotherapy or combined to DMARDs for refractory AOSD, both in patients with the CAD and the SP patterns and for some life-threatening complications of the disease **[30-33]**. In the present review, we have focused on the use of TCZ for the treatment of AOSD. Data on the efficacy and safety of TCZ for AOSD therapy are discussed.

2. Areas covered

Glucocorticoids are the cornerstone of treatment of AOSD. However, they are effective in only 60% of patients with AOSD **[3,13]**. They have been reported to be more effective in patients with SP than in those with CAD **[24]**. Conventional immunosuppressive agents, mainly MTX, have been used as GC-sparing agents to reduce the frequency of relapses. However, results in terms of efficacy have not been well established. Large observational studies showed that 17-32% of AOSD patients are refractory to GC and conventional DMARDs and require biologic DMARDs therapy **[34-37]**. Among them, anti-IL1 and anti-IL6 agents are those that have shown better results.

Anti-IL1 agents, especially anakinra (ANK) and canakinumab, are especially useful in the SP of the disease. ANK has recently been approved by the European Medical Agency (EMA) for their use in AOSD **[38]**. Although the anti-IL-6R TCZ has not approved for the use of in AOSD therapy yet, it is commonly use in AOSD as *off-label* treatment. In this regard, the daily clinical practice supports the use of TCZ in patients with AOSD. Tumor necrosis factor (TNF) blocking drugs are currently considered as a second line of biologic therapy in patients with the CAD pattern **[3,28,38]**.

3. Unmet needs of currently available therapies in AOSD management

The diagnosis of AOSD is usually made by the exclusion of other systemic diseases. Most clinicians use the criteria proposed by Yamaguchi et al. **[39]** and Fautrel et al. **[40]** **(Table 1)**. However, there are limitations to determine disease activity, clinical course and prognosis. Biomarkers such as ferritin and its glycosylated fraction, procalcitonin, serum amyloid A or calprotectin have been used to monitor the disease. However, further investigation is needed to establish their applicability in the daily clinical

practice **[29]**. Although the use of biologic agents have been effective to induce remission in patients with disease refractory to conventional therapies, no biologic therapy is effective in all the patients. Early treatment in essential to modify the clinical course of the disease, preventing chronicity and severe complications **[3,32,41]**.

At present we cannot identify what patients will be refractory to conventional therapies and require a biologic agent. In this regard, a third of the patients only have a transient monocyclic pattern. On the other hand, there are new biologic agents that it is possible that may be more effective than those currently used for the management of refractory AOSD. It is the case of sarilumab, a new anti-IL-6 agent that blocks the receptor more efficiently than TCZ. Also, other biologic agents, such as the IL-18 and INF-ϒ antagonists, may replace the anti-IL-1 and anti-IL-6R antagonists in the near future **[29]**.

4. Tocilizumab in the treatment of AOSD

4.1 Introduction to the compound

IL-6 is a pleiotropic pro-inflammatory cytokine produced by a number of cells including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in different physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of hemopoiesis. This cytokine has been implicated in the pathogenesis of a broad spectrum of diseases including inflammatory diseases, osteoporosis and neoplasia. IL-6 is also a pivotal cytokine involved in the pathogenesis of AOSD, reason why it was considered as an important target for the treatment of this disease. Moreover, IL-6 serum levels are markedly increased in both the active SP as well as in the active CAD phenotype **[16,42]**. Therefore, IL-6 blockade can be considered to successfully manage, in most cases, both arthritis and systemic disease manifestations.

Inhibition of IL-6 signaling is possible by several different approaches: direct neutralization of the cytokine or blockade of the corresponding receptor, as well as by cytoplasmic signaling blockade through Janus kinase (JAK) inhibitors. There are two different IL-6R antagonists (TCZ and sarilumab) currently available for treating rheumatic diseases. However, only case series using TCZ for AOSD have been reported **[30,41,43]**.

TCZ is a humanized anti-IL-6R antibody that binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), inhibiting sIL-6R and mIL-6R-mediated signaling. TCZ is available for intravenous (IV) infusion and subcutaneous (SC) injections. Due to the extensive experience with TCZ in rheumatoid arthritis (RA), many of the pharmacological data that we will present in the following paragraphs are based on studies in patients with RA.

4.2 Clinical indications

The excellent data in terms of clinical efficacy and safety of TCZ in the treatment of RA and other rheumatic diseases supported the use of TCZ in AOSD patients who were refractory to GC, conventional DMARDs, and other biologic agents including anti-TNF-α agents and IL-1 blocking agents **[44]**. Its use was also supported by results from randomized placebo-controlled trials that showed the efficacy of TCZ in children with sJIA **[45,46]**.

TCZ alone or in combination with MTX is indicated for the treatment of severe, active and progressive RA in adults not previously treated with MTX or in patients intolerant or not responders to previous therapy with one or more conventional DMARDs or TNF-α antagonists. TCZ is also indicated for the treatment of active sJIA and juvenile idiopathic polyarthritis (pJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic GC **[47]**. Finally,

subcutaneous TCZ is recently approved for the treatment of giant cell arteritis (GCA) and intravenous TCZ for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and pediatric patients 2 years of age and older **[47]**. Nevertheless, the use of TCZ in AOSD is out of the technical brochure due to the absence of randomized clinical trials supporting its use for this specific indication. The posology of TCZ in the different clinical scenarios ranges between 4 mg/kg and 8 mg/kg body weight every 2-4 weeks for the IV administration and 162 mg weekly or every other week (eow) for the SC administration **[47]**. **Table 2** shows the main approved and off-label indications for the use of TCZ nowadays.

4.3 Pharmacodynamics

TCZ interferes not only with the pathological effects of IL-6, but also with its physiological effects at multiple levels. Rapid decreases in CRP, ESR and serum amyloid A (SAA) were observed in RA patients undergoing TCZ therapy. Decreases in the levels of CRP to within normal ranges are seen as early as week 2, with decreases maintained during the treatment **[47]**.

Consistent with the effect on ARP, TCZ administration was associated with reduction in platelet count within the normal range. TCZ also decreases the IL-6 driven effect on hepcidin production, leading to an increase of hemoglobin levels due to improvement of iron availability.

The absolute neutrophil count decreased to their lowest levels 3 to 5 days after starting the administration in healthy subjects who received TCZ at doses between 2 and 28 mg/kg. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. RA patients showed a similar pattern of absolute neutrophil counts following TCZ administration **[47]**.

4.4 Pharmacokinetics and metabolism

The pharmacokinetics (PK) of TCZ was determined using a population PK analysis on a database composed of 3552 RA patients treated with a one-hour IV infusion of 4 or 8 mg/kg TCZ every 4 weeks for 24 weeks or with 162 mg TCZ given subcutaneously either once a week or eow for 24 weeks **[47]**. The dose-response curve for TCZ flattens at higher exposures, resulting in smaller efficacy gains for each incremental increase in TCZ concentration. Clinically meaningful increases in efficacy were not demonstrated in adult patients treated with >800 mg of TCZ. Therefore, TCZ doses exceeding 800 mg per infusion are not recommended **[47]**.

TCZ undergoes a biphasic removal from the circulation after its IV administration. The total clearance of TCZ was concentration-dependent and is the sum of the linear and non-linear clearances. The t1/2 of TCZ was concentration-dependent. At steady-state following a dose of 8 mg/kg every 4 weeks, the effective t1/2 decreased with decreasing concentrations within a dosing interval from 18 days to 6 days.

There are no formal studies on the effect of renal or liver impairment on the PK of TCZ. Most patients in the population PK analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance <80 mL/min and ≥50 mL/min) did not influence the PK of TCZ. Finally, population PK analyses in RA patients showed that age, gender and ethnic origin did not affect the PK of TCZ **[47]**.

PK analyses in patients with RA did not show any effect of MTX, NSAIDs or GC on TCZ clearance. Concomitant administration of a single IV dose of 10 mg/kg TCZ with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure.

In vitro studies showed that TCZ has the potential to affect expression of multiple CYP enzymes including cytochrome P450 (CYP)1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 **[47,48]**.

In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of TCZ, respectively **[47-49]**. The effect of TCZ on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index (e.g., warfarin, cyclosporine or theophylline). Special attention should be paid when TCZ is coadministered along with CYP3A4 substrate drugs in which a reduction in their effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of TCZ on CYP450 enzyme activity may persist for several weeks after discontinuation of the therapy **[47-49]**.

4.5 Clinical efficacy of IL-6 pathway inhibition

Overall, the anti-inflammatory efficacy of TCZ in AOSD is good, rapid and sustained for most patients. Systemic manifestations improve more rapidly than joint manifestations **[50]**.

Data on the efficacy of TCZ in AOSD are based on several small prospective studies, retrospective studies and case series performed mainly in patients with AOSD refractory to GC, anti-TNF-α drugs and anti-IL-1 agents **[30,31,41,43,50-53]**. A recent meta-analysis of 10 original studies (147 subjects) on the efficacy of TCZ in AOSD showed overall high partial and complete remission rates of 85% and 77%, respectively. TCZ prevented new flares, it was well tolerated and allowed substantially to reduce the need for GC **[31,33]**. Recently, it has been published the first double-blind, randomized, placebo-controlled phase III clinical study with TCZ vs. placebo in 27 patients with AOSD refractory to glucocorticoids and systemic manifestations, with promising results **[54]**.

4.5.1 Prospective studies

In a small cohort study, Puéchal et al. assessed the efficacy and safety of TCZ in 14 patients with refractory AOSD **[30]**. Prior to the introduction of TCZ, all patients had joint symptoms (mean baseline DAS28: 5.61), and half of the patients also had systemic manifestations. All patients received 5-8 mg/kg of intravenous TCZ every 2-4 weeks (8 mg/kg/month IV in 9 cases) during 6-months. Overall, 64% (9/14) of patients experienced a good EULAR arthritis response at 3 months, and 57% (8/14) had a mean DAS28 of 2.92 at 6 months. Systemic symptoms resolved in 86% of patients, and GC dose was decreased from 23.3 to 10.3 mg/day. Three patients withdrew from the study due to necrotizing angiodermatitis, chest pain/chills during infusion, and systemic flare, respectively **[30] (Table 3)**.

Kim et al. reported 8 patients with AOSD treated with TCZ (8 mg/kg IV every 4 weeks) who had been refractory to DMARDs and/or etanercept **[55]**. Four patients achieved complete and 3 partial response after an average of 6.3 doses (range 2-13 doses), Improvement of clinical symptoms was observed after a mean of 4 weeks. The ESR, CRP, serum ferritin, IL-18, and IL-6 levels improved within 6.3 weeks, 6.3 weeks, 9.3 weeks, 12.5 weeks, and 9.3 weeks, respectively. Three patients discontinued the study, one each due to severe headache and chest discomfort, neutropenia, and hepatotoxicity. Other adverse events (AEs) including mild dizziness, hair loss, weight gain, and transient leukopenia were also reported **[55]**.

Kondo et al. conducted a prospective, single-arm study to assess the efficacy and safety of single-agent TCZ as induction therapy for AOSD **[56]**. Eight patients (2 men and 6 women) received TCZ 8 mg/kg every 2 weeks for 5 doses and then monthly for 5 months. At month 6, white blood cell (WBC) count declined from $14.075 \pm 4.732/mm^3$ to $7.042 \pm 2.939/mm^3$ ($p<0.01$), CRP decreased from 12.2 ± 7.4 mg/dL to 0.32 ± 0.62

mg/dL ($p<0.01$), and ferritin dropped from 9.176 ± 8.077 ng/mL to 3.380 ± 5.616 ng/mL ($p<0.01$). Fever, arthralgia, and rash improved in eight, six, and five patients, respectively. Two patients required prednisolone therapy. Three patients stopped treatment due to lack of efficacy (n=2) and an AE (n=1) **[56]**.

Li et al. described the efficacy and safety of TCZ in 8 women with refractory AOSD. They defined refractory disease in case of no response/dependence on GC, no response/intolerance to immunosuppressants or acute phase disease complicated by hepatic dysfunction or MAS **[57]**. TCZ was dosed at 4-8 mg/kg every 4 weeks. At 3 months, fever and rashes remitted in 7 of 8 patients and arthritis in all of them. WBC count, ESR, CRP, and ferritin levels significantly decreased ($p<0.01$) and the average prednisone dose was lowered from 51.3 ± 31.9 to 12.9 ± 7 mg/day ($p<0.01$) **[57]**.

Muraviev et al. conducted a small study including 6 women and 1 man with AOSD (average age 34.2 ± 10.7 years) refractory to NSAIDs, prednisolone, and MTX **[58]**. All patients had fever, typical rash, arthritis, leukocytosis (>10 x 10^9/L; n=5), throat pain (n=4), hepatic disturbances and lymphadenopathy, and received TCZ 8 mg/kg IV every 4 weeks. After the first dose of TCZ, fever resolved in 6 patients within 24 hours and in 1 patient within 48 hours. Arthritis symptoms resolved in 2 patients and were significantly improved in 5; CRP levels decreased in all patients. Six patients were maintained on TCZ, 1 patient achieved remission, and 5 showed improvement **[58]**. Summary of main prospective and retrospective studies published up to date are shown in **table 3**.

4.5.2 Retrospective Studies

Ortiz-Sanjuan et al. conducted a retrospective, open-label study that included 34 Spanish patients with AOSD who underwent TCZ. Twenty-two received 8 mg/kg IV every 4 weeks, 10 were treated with 8 mg/kg IV every 2 weeks and 2 with 4 mg/kg IV

every 4 weeks, with maintenance doses ranging from 4-8 mg/kg IV every 2 or 4 weeks **[50]**. All patients had experienced an inadequate response to GC and at least to one synthetic DMARD, and 50% had also failed a previous biologic agent. After 1 year of therapy, improvement from baseline was observed in joint manifestations (97.1% at baseline to 32.4%), cutaneous manifestations (58.8% to 5.9%), fever (58.8% to 5.9%), lymphadenopathy (29.4% to 0%), splenomegaly/hepatomegaly (11.8% to 0%), and pleuritis/pericarditis (8.8% to 0%). The following laboratory parameters also showed reduction at month 12 when compared with baseline results: abnormal CRP (82.4% at baseline to 23.5%) at month 12, elevated ESR (from 79.4% to 2.9%), leukocytosis (from 55.9% to 17.6%), anemia (from 44.1% to 2.9%), and elevated serum ferritin levels (from 47.1% to 2.9%). Additionally, the median dose [IQR] of prednisone decreased from 13.8 [5-45] mg/day at baseline to 2.5 [0-30] mg/day at 12 months. Infections were the most common AEs (n=10) after a median follow-up of 19 months, that led to discontinuation of therapy in 2 patients. Other AEs included leukopenia or neutropenia (n=4), hepatic enzyme elevations (n=4), hypercholesterolemia (n=1), and headache associated with TCZ infusion (n=1) **[50] (Table 3)**.

Song et al. performed a multicenter, retrospective study evaluating the efficacy of TCZ in 24 patients with AOSD [**51**]. The mean disease duration was 48.4 ± 43.7 months before TCZ onset with 12 patients exhibiting CAD, 11 patients with polycyclic SP, and 1 patient unclassified. Before TCZ therapy most patients had been treated with MTX (n=17) and various other conventional and biologic DMARDs. Eleven patients were evaluated at 12 months. Patients received a mean TCZ dose of 6.9 mg/kg (4-8 mg/kg) every 4 weeks for 8.4 ± 6.8 months. Response to TCZ was measured as a decrease in modified Pouchot's score ≥2 points from baseline for 2 consecutive months. The endpoint was not found to be statistically significant as the modified Pouchot's had a

mean decrease from 3.0 ± 1.9 at baseline to 1.1 ± 0.7 at 12 months. The mean CRP and ESR were significantly lower at 12 months when compared to baseline. The mean prednisolone dose decreased from 15.4 mg/day at baseline to 7.8 mg/day at 12 months. AEs occurred in 25% of patients including infusion reactions (n=2), gastrointestinal issues (n=2), leukopenia (n=1), and tuberculosis (n=1). Four patients relapsed after TCZ was discontinued for 5.0 ± 3.6 months [**51**] **(Table 3)**.

Suematsu et al. described the therapeutic response in 16 patients with AOSD who were treated with at least 1 biological agent **[52]**. All patients were refractory to high-dose GC and/or at least 1 immunosuppressant. The study included 4 men and 12 women with a mean duration of disease of 8.9 years (range 0.2-16.8 years). Eleven patients received TCZ 8 mg/kg/month IV. Six of these them received TCZ as the first biologic agent whereas 5 patients were switched from another biologic. TCZ achieved remission in 10 of the 11 patients. Ferritin and CRP levels approached normalization within a mean of 5.8 and 7.1 weeks, respectively. Resolution of fever and arthralgia occurred within 3.6 weeks and 5 weeks, respectively. After a median treatment duration of 11.6 months, patients who received TCZ had a mean reduction in glucocorticoid dose of 16.8 ± 17.2 mg. AEs included urinary tract infection, liver dysfunction, and stomatitis [**52**].

Elkayam et al. described 15 patients with AOSD who were treated with TCZ 8 mg/kg IV every month (n=12) or 8 mg/kg IV twice a month (n=3) **[43]**. Ten patients previously failed to at least one anti-TNF agent and all patients had arthralgia/arthritis at baseline. After 6 months, swollen and tender joint counts decreased from 8.6 ± 5.4 and 11.6 ± 6.8 to 1.09 ± 1.6 and 2 ± 1.8, respectively ($p<0.05$ for both). CRP and ESR levels decreased from 11.6 ± 15 mg/dL and 60 ± 28 mm/h at baseline to 0.5 ± 0.1 mg/dL and 3.9 ± 1.4 mm/h, respectively ($p<0.05$ for both comparisons). The mean prednisone dose decreased from 27.6 ± 26.3 mg/day at baseline to 4.9 ± 4 mg/day. By the end of the

mean 15.7 month follow-up, 9 patients had discontinued prednisone, none reported systemic symptoms, and 2 only had mild arthralgia. One patient who developed MAS after 11 months of treatment responded to an increased dose of prednisone and was switched to another biologic agent **[43]**.

Kim et al. retrospectively evaluated 37 patients with AOSD refractory to conventional therapy who were treated with biologic agents including TCZ IV (n=13) at doses similar to those used for RA **[59]**. Significantly more patients responded to TCZ (84.6%) than anti-TNF agents (45.9%) or ANK (50%; $p<0.05$). All but one of the 6 patients who were switched from an anti-TNF agent to TCZ responded. AEs were reported in 46.2% of TCZ-treated patients **[59]**.

Cipriani et al. described 11 patients (age range, 28-73 years) with AOSD refractory to conventional therapy who were treated with TCZ 8 mg/kg IV every 4 weeks for 12 months and followed up for another additional 6 months **[41]**. The median DAS28 decreased from 5.62 at baseline to 2.31 at 3 months, 1.88 at 6 months and 1.61 at 12 months. Nine patients (81.82%) achieved DAS28<2.6 at 12 months. All patients experienced a remission of fever (8 patients presented with fever at baseline) and an improvement in systemic symptoms. Tender joint and swollen joint count decreased significantly after 6 and 12 months of therapy ($p<0.05$). At 12 months, the median prednisone dose decreased from 50 (25-100) mg/day at baseline to 0 (0-12.5) mg/day and 8 of 11 patients were able to discontinue prednisone. At 18 months, 8 patients (72.72%) maintained clinical remission while on MTX only. No serious AEs or deaths were reported **[41]**.

Additional studies with ≤ 10 cases per study are shown in **table 4 [60,61]**.

4.5.3 Case series

The first experimental and successful trial of TCZ for a refractory case of AOSD was reported by Iwamoto el at in 2002 **[62]**. Since then, multiple case series describing the use of TCZ for the treatment of AOSD have been published **[63-71]**. Many of the patients had refractory disease following treatment with standard therapies such as GC, MTX, conventional DMARDs, and anti-TNF agents. The patients´ age ranged from 17 to 73 years old. Efficacy and safety outcomes varied, but generally, clinical and laboratory markers improved significantly following therapy with TCZ. Some of the safety outcomes reported included rash, psoriasis, MAS, systemic flares, and 1 death from a respiratory infection **[63-71]**.

A recent systematic review of case reports or case series showed that 35 patients received TCZ for the treatment of AOSD (8 mg/kg/ month in 22 patients) until 2013 **[69]**. The main clinical manifestations were arthritis in all patients and systemic symptoms such as fever or skin rash in 28 (80%). Thirty-three (94%) patients had been treated with other immune modulators such as MTX, TNF-α blockers or ANK without efficacy. Most patients achieved clinical response to TCZ; prompt joint improvement in 30/35 (86%) patients and a resolution of systemic features in 27/28 (96%). Twenty-eight (80%) patients were able to reduce glucocorticoid dosage, and 7 patients discontinued glucocorticoid therapy **[69]**.

Finally, some case reports have indicated that the IL-6 blockade is effective for the treatment of AOSD-related systemic complications including PAH, or MAS induced by other treatments **[72-74]**.

4.5.4 Clinical trials

The only randomized, double-blind, placebo-controlled study with TCZ vs. placebo in AOSD available up to date has recently been conducted by Kaneko et al in 27 patients with AOSD with systemic manifestations who were refractory to glucocorticoids **[54]**.

In this study, patients were randomized to TCZ (8 mg/kg) intravenously administered or placebo every 2 weeks during 12-weeks. Later, all patients received TCZ for 40 weeks in an open-label continuation study. The primary outcome was the American College of Rheumatology (ACR) 50 response at week 4. The secondary outcomes included ACR 20/50/70, systemic feature score, glucocorticoid dose and adverse events at each point **[54]**.

In the full analysis set, ACR50 response at week 4 was achieved in 61.5% of patients from the TCZ group and 30.8% of the patients from the placebo group (p=0.24). The change in systemic feature score at week 12 was -4.1 in the TCZ group and -2.3 in the placebo group (p=0.003). The dose of glucocorticoids at week 12 decreased by 46.2% in the TCZ group and 21.0% in the placebo group (p=0.017). At week 52, the rates of ACR20, ACR50 and ACR70 were 84.6%, 84.6% and 61.5%, respectively. Serious adverse events in all participants who received at least one dose of TCZ were infections, aseptic necrosis in the hips, exacerbation of the disease, drug eruption and anaphylactic shock. The study suggests that TCZ is effective in AOSD, although solid conclusions were not drawn due to the small sample size **[54]**.

4.5.5 Safety profile and tolerability

The most commonly reported AEs (occurring in ≥5% of patients treated with TCZ in monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension, neutropenia and increased hepatic alanine aminotransferase (ALT). The most serious AEs were serious infections, complications of diverticulitis, and hypersensitivity reactions. Once again, the most extensive information on AEs comes from that observed in patients with RA, where much more experience is available. **Table 5** shows the main AEs detected in people with RA treated with TCZ in clinical trials.

Special mention requires the occurrence of lipid alterations in these patients. Elevations in lipid parameters including total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in clinical trials in patients treated with TCZ. During the 6-month controlled trials performed in RA patients treated with TCZ, 24% of patients receiving TCZ experienced sustained elevations in TC ≥ 6.2 mmol/L, with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L. However, in the majority of patients, there was no increase in the atherogenic indices, and elevations in TC responded well to treatment with lipid lowering agents **[47]**. Furthermore, in patients with RA, TCZ is able to reduce the levels of lipoprotein(a), a molecule closely associated with increased cardiovascular risk **[75]**.

Regarding immunogenicity, a total of 2876 patients have been tested for anti-TCZ antibodies in the 6-month controlled clinical trials with IV TCZ in patients with RA. Of the 46 patients (1.6%) who developed anti-TCZ antibodies, 6 had an associated medically significant hypersensitivity reaction, of which 5 led to permanent discontinuation of treatment. Only thirty patients (1.1%) developed neutralizing antibodies **[47]**.

A higher frequency of injection site reactions (ISRs) was observed in patients treated with TCZ subcutaneously when compared with those treated IV. The frequency of ISRs was 10.1% and 2.4% for the subcutaneous TCZ and the subcutaneous placebo (IV group) weekly injections, respectively. These ISRs (including erythema, pruritus, pain and hematoma) were mild to moderate in severity. The majority resolved without requiring drug discontinuation **[47]**.

Overall, the safety profile of TCZ in AOSD seems to be similar to that reported in RA patients and other autoimmune diseases. However, while receiving TCZ, some patients with AOSD developed MAS **[76,77]**.

TCZ should be given in refractory AOSD, because it induces remission allowing reduction in the glucocorticoid dose **[41,43,50,51,69,78]**. Nevertheless, it is important to keep in mind that anti-IL-6 agents directly suppress APR production, even in the presence of a serious infections leading to septic condition **[60]**. In addition, TCZ can mask the clinical and laboratory features of MAS, and that TCZ itself may also cause MAS when it is administered after insufficient additional immunosuppressive therapy **[79]**. In this line, we must be alert to any symptom or sign of MAS in these patients, such as high non-remitting fever, central nervous system dysfunction, pancytopenia, abnormal coagulation tests, abnormally increased triglycerides or hyperferritinemia (generally >5000 mg/L) especially at the beginning of treatment, to avoid the development of more serious and irreversible complications. In fact, adequate immunosuppression followed by combination of TCZ could be safer than the initial administration of TCZ alone in these patients **[73,79,80]**.

Therefore, it is important to remark that the beneficial role of TCZ in MAS has shown conflicting results **[81-83]**. However, TCZ seems to be truly effective in CRS after CART-therapy, a syndrome close resembling MAS **[84,85]**.

4.5.6 Special warnings and precautions for use

Since TCZ generally increases the risk of infections, treatment with TCZ should not be initiated in patients with active infections. TCZ administration should be discontinued if a patient develops a serious infection until the infection is controlled. Healthcare professionals should exercise caution when considering the use of TCZ in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes and interstitial lung disease) which may predispose patients to infections. Furthermore, the effects of TCZ on CRP, neutrophils and signs of infection should be kept in mind when evaluating a patient for a potential infection as signs and

symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reaction **[47]**.

As recommended for other biological therapies, patients should be screened for latent tuberculosis (TB) infection prior to starting TCZ. Moreover, patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting /weight loss, low grade fever) suggestive of a TB infection occur during or after TCZ treatment.

TCZ should be used with caution in patients with previous history of intestinal ulceration or diverticulitis because diverticular perforation has been reported in RA patients undergoing TCZ therapy as a complication of diverticulitis.

Caution should be exercised when considering initiation of TCZ treatment in patients with elevated ALT or aspartate aminotransferase (AST) > 1.5 times over the upper limit of normality (ULN). In patients with baseline ALT or AST > 5 x ULN, treatment with TCZ is not recommended. As well, caution should be exercised when considering initiation of TCZ in patients with a platelet count < 100 x 10^3/μL. TCZ should be discontinued in patients who develop an absolute neutrophil count (ANC) < 0.5 x 10^9/L or a platelet count < 50 x 10^3/μ **[47]**. Nevertheless, although severe neutropenia may be associated with an increased risk of serious infections, there was no clear association between decreases in neutrophils and the occurrence of serious infections in clinical trials with TCZ to date. **Table 6** shows some general recommendations that we must follow in case of detecting laboratory alterations.

There are no adequate data from the use of TCZ in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-fetal death at a high dose. Thus, TCZ should not be recommended during pregnancy unless clearly necessary.

Furthermore, women of childbearing potential must use effective contraception during and up to 3 months after treatment **[47]**.

Finally, live and live attenuated vaccines should not be given concurrently with TCZ as clinical safety has not been established.

4.5.7 Regulatory affairs

Currently, TCZ is only approved for the treatment of RA, sJIA, pJIA, GCA and chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and pediatric patients 2 years of age and older **(Table 1**). However, its indication is not approved for AOSD yet, so its use in this entity must be done as off-label medication with prior information to the patient and signature of an informed consent previously to start the treatment.

4.5.8 Conclusions

Overall, and despite not being approved yet by the regulatory authorities, based on the data shown in the different studies mentioned in this review, we conclude that TCZ is an effective drug for the overall management of AOSD, both for systemic and joint manifestations, as well as for some severe complications of the disease.

5. Expert opinion

AOSD is a rare multisystem inflammatory disease of unknown origin that is included within the clinical spectrum of autoinflammatory disorders **[6,7]**. Two main clinical phenotypes have been recognized in AOSD: a systemic pattern and a CAD **[10,19,86-88]**. The systemic pattern may yield more severe and life-threatening complications in a short-term but the CAD is more devastating and disabling in the long-term **[20]**. Approximately 60-70% of patients may develop a chronic polyphasic form or CAD. MAS is the most important complication of the disease and it may present as the first

symptom or during the follow-up period associated with infections, drugs, and disease flare ups. Other life-threatening manifestations include disseminated intravascular coagulation, pulmonary hypertension, diffuse alveolar hemorrhage, liver failure, myocarditis and non-infective thrombotic endocarditis **[20,29,89]**.

Since AOSD is an uncommon disease its treatment is not based on controlled clinical trials but rather on case reports, case series, non-controlled prospective or retrospective studies and extrapolation from experiences in patients with sJIA and auto-inflammatory diseases **[45,46,90-92]**. Conventional treatment consists of NSAIDs, GC, and conventional DMARDs. Among them, GC are the keystone of treatment leading to remission in around 60% of patients, while the most common DMARDs are MTX and cyclosporine. Recent progress in our knowledge of the immunopathogenesis of AOSD has enabled us to introduce some specific biologic DMARDs for the treatment of AOSD. In this line, the use of anti-TNF, anti-IL-1, and anti-IL-6 agents represents a major therapeutic advance in patients with AOSD refractory to conventional therapy (**Figure 1**).

IL-1 inhibitors may be more efficient for systemic manifestations and IL-6 inhibitor for both joint involvement and systemic manifestations, while anti-TNF agents must be reserved for patients with typical CAD. An initial application of biological therapy is not recommended because around one-third of AOSD patients have a self-limited monocyclic pattern. In addition, inadequate use of biologics in the absence of general immune suppression may enhance the development of severe life-threatening complications such as MAS, so it is recommended to maintain a DMARD associated with the biologic to these patients whenever possible.

It is very important to measure disease activity accurately during the long-term follow-up of AOSD patients. However, currently available biomarkers have limited value for

the therapy and the detection of manifestations of disease. Thus, the development of composite biomarkers to detect disease activity including APR, serum ferritin and its glycosylated fraction, procalcitonin, calprotectin and serum levels of several ILs (IL-6 and IL-18) could improve our rational decision-making in the treatment of AOSD **[29]**.

Among the different biologics available today, TCZ is an effective drug for the global treatment of AOSD, both for systemic and articular manifestations, as well as for some severe complications of the disease. In this line, TCZ would be indicated in the second line after anti-IL-1 agents for systemic manifestations of the disease **[3,29,93]**. Similarly, TCZ could be positioned in the second line of biologic treatment for CAD, especially since the appearance of biosimilars of anti-TNFs, given that anti-TNF agents are effective in around 30-40% of these patients, which will make these drugs more cost-effective, reserving TCZ for a later line of therapy after GC, DMARDs and anti-TNFα biosimilars failure.

In order to identify all the available data concerning the effectiveness of biologic drugs in AOSD, a systematic review of the literature has been recently performed including nineteen observational studies, six of them using TCZ. The pooled analysis under a random-effects model showed an overall rate of satisfactory clinical response of 0.85 ($p<0.0001$) and an overall rate of complete remission of 0.66 ($p=0.01$), although the heterogeneity across studies was high ($Q=59.8$ with $df=19.0$, I^2: 68.2%) **[94]**.

Taken together, the main limitation to the use of TCZ in AOSD is that this biologic agent has not already been approved for this indication. Therefore, its use should be *off label* after failure to GCs, DMARDs and IL-1 or TNF antagonists according to the clinical phenotype. In addition, there are some concerns on TCZ use in patients with MAS.

In a near future, new biological agents against IL-18 or small molecules against Jak-1/Jak-2 may provide additional therapeutic options for AOSD. Other biologic agents that in inhibit IL-6 are currently under investigation. Among them, sirukumab, a human monoclonal antibody against IL-6, and sarilumab, an antagonist of IL-6R, are those that are in a more advanced phase of development, especially in patients with RA. Both molecules are administered subcutaneously every 2-4 weeks and have greater affinity for IL-6 than showed by TCZ. However, none of them have proved efficacy in AOSD. Furthermore, since levels of sIL-6 increase significantly higher fold compared to baseline in active disease, but the fold increase of sIL-6R is much lower than sIL-6, a biologic agent blocking sIL-6R such as TCZ would require rather smaller amount of antibody to achieve our goal than others blocking sIL-6.

Figure 1 shows a general therapeutic strategy for patients with active AOSD.

6. Five-year view

In the following years, a better definition of the AOSD phenotypes will be achieved. This fact will allow the clinicians to better identity those patients who would benefit of specific biologic agents. New biomarkers on molecules that seem to play a role in the pathogenesis of AOSD will help us to better monitor the disease allowing the clinicians to improve the evaluation of the risk of relapses **[29,95,96]**. The development of composite outcome measures will be very useful for establishing a rational therapeutic strategy in the treatment of patients with AOSD.

Further treatment options including sarilumab, a new anti-IL-6- agent with greater affinity for the IL-6 R than TCZ, inhibitors of intracellular signaling against Jak-1/Jak-2 and antagonists of IL-18 and IFN-γ need to be tested in patients with refractory AOSD. In this line, an open-label, multicentre, dose-escalating phase II clinical trial on the

safety and efficacy of tadekinig alpha, a recombinant human IL-18-binding protein (IL-18BP), in AOSD has been recently published with promising results, although the number of patients included was low [**97,98**].

7. Article Highlights

- AOSD is a heterogeneous disorder at the crossroads between autoinflammatory and autoimmune diseases.
- Glucocorticoids constitute the first line of treatment for AOSD.
- Conventional DMARDs, especially MTX, are often considered in refractory cases or as GC-sparing agents.
- Biologic agents must be considered in the management of AOSD refractory to GC and conventional DMARDs, since the ultimate goal in the management of AOSD is to achieve sustained remission and reduce the risk of relapses and life-threatening complications.
- The development of composite indices based on multiple biomarkers to detect disease activity definitely could support rational decision making in the treatment of AOSD.
- TCZ, a humanized anti-IL-6 receptor antagonist, is an effective drug for the global treatment of AOSD, both for systemic and joint manifestations, as well as for some severe life-threatening manifestations of the disease.
- Overall, the benefit/risk ratio and safety profile of TCZ is favorable and similar to that described in RA and other rheumatic diseases. However, some cases of MAS have been described after the start of treatment with TCZ as well as with other biological agents.
- Besides the currently available therapeutic options, new biologic agents against IL-18 or small molecules against Jak-1/Jak-2 may be additional therapeutic options in AOSD.

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Drug summary box

Drug name: tocilizumab (TCZ).
Phase: phase III clinical trial with tocilizumab in patients with AOSD [ref 54].
Indications currently approved: rheumatoid arthritis (RA)[1], systemic and polyarticular JIA[2], giant cell arteritis[3], severe or life-threatening cytokine release syndrome[3].
Pharmacology description/mechanism of action: humanized anti-IL-6R antibody that binds to both the membrane-bound and soluble form of IL-6R (sIL-6R and mIL-6R), inhibiting sIL-6R and mIL-6R-mediated signaling.
Chemical structure: TCZ is a recombinant, humanized, anti-human interleukin 6 (IL-6) receptor monoclonal antibody that achieves a significant therapeutic response rate. The light chain is made up of 214 amino acids (aa). The heavy chain is made up of 448 aa.
Pivotal trials: only one phase III clinical trial with TCZ in patients with AOSD up to date [ref 54].

AOSD: adult-onset Still´s disease; IL: interleukin; JIA: juvenile idiopathic arthritis; R: receptor; TCZ: tocilizumab.

[1] TCZ alone or in combination with methotrexate is indicated for the treatment of severe, active and progressive RA in adults not previously treated with methotrexate or in patients intolerant or not responders to previous therapy with one or more conventional disease-modifying anti-rheumatic drugs or tumor necrosis factor-α antagonists.
[2] In patients 2 years of age and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs and systemic glucocorticoids.
[3] Finally, subcutaneous TCZ is recently approved for the treatment of giant cell arteritis and intravenous TCZ for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients 2 years of age and older.

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FIGURE LEGENDS

Figure 1. Schematic view of the authors for a stepped treatment of AOSD. **Abbreviations**: DMARDs: disease-modifying anti-rheumatic drugs; GC: glucocorticoids; Igs: immunoglobulins; inh: inhibitors; IL: interleukin; INF-g: interferon-gamma; JAK/STAT: Janus kinase/signal transducers and activators of transcription; NSAIDs: non-steroidal anti-inflammatory drugs; OP: osteoporosis; TNF-α: tumor necrosis factor alfa.

Table 1. Useful classification criteria for the diagnosis of adult-onset Still´s disease proposed by Yamaguchi [39] and Fautrel [40].

Yamaguchi´s classification criteria for diagnosis of AOSD (1992)
Major criteria: 1. Fever ≥ 39ºC lasting ≥ 1 week 2. Arthralgia or arthritis lasting ≥ 2 weeks 3. Typical nonpruritic salmon-pink skin rash 4. Leukocytosis ≥ 10,000/mm^3 with granulocytes ≥ 80% Minor criteria: 1. Sore throat 2. Lymph node enlargement 3. Hepatomegaly or splenomegaly 4. Abnormal liver function tests 5. Negative ANA and RF tests Exclusion criteria: 1. Infections 2. Malignancy (mainly malignant lymphoma) 3. Other systemic disorders (mainly vasculitis) (≥ 5 criteria are required with at least 2 being major criteria AND no exclusion criteria)

Fautrel´s classification criteria for diagnosis of AOSD (2002)
Major criteria: 1. Spiking fever ≥ 39ºC 2. Arthralgias 3. Transient erythema 4. Pharyngitis 5. Polymorphonuclear cells ≥ 80% 6. Glycosylated ferritin ≤ 20%
Minor criteria: 1. Maculopapular rash 2. Leukocytosis > 10,000/mm^3 (≥ 4 major criteria or 3 major + 2 minors are required)

Abbreviations: AOSD: adult-onset Still´s disease; ANA: antinuclear antibodies; RF: rheumatoid factor.

Table 2. Main indications approved and off-label for the use of tocilizumab today.

Indications approved and off label for the use of TCZ*
Approved:
- Rheumatoid arthritis - Systemic juvenile idiopathic arthritis (sJIA) - Polyarticular juvenile idiopathic arthritis (pJIA) - CAR T cell-induced cytokine release syndrome (CRS) - Giant cell arteritis (only subcutaneous administration)
Off-label:
- Adult-onset Still´s disease (AOSD) - Autoinflammatory syndromes - Other inflammatory arthropaties

Abbreviations: CAR: chimeric antigen receptor; TCZ: tocilizumab.

*In all described scenarios, especially for patients refractory to conventional therapies.

Table 3. Efficacy of tocilizumab in AOSD: summary of data of the first clinical trial with tocilizumab and main prospective and retrospective studies published up to date[#].

Author (Country) [Ref. number]	Number of patients (Sex)	Previous treatment (n)	Dose (n) Duration of treatment	Overall response % (n)	Glucocorticoid before and after treatment (mg/day)*	Reasons for withdrawal (n)
Ortiz-Sanjuán (Spain) [50]	34 (26W, 8M)	MTX (31), LEF (5), CsA (2), a-TNF (18) RTX (6), ABT (2)	8 mg/kg/2 wks (10) 8 mg/kg/4 wks (22) 4 mg/kg/4 wks (2) TCZ monother (15) 12 months duration	Arthritis from 97.1% to 32.4%; skin rash and fever from 58.8% to 5.9% equally	13.8; 2.5 [§]	Infection, severe (2): pyelonephritis (1), bacterial spondylodiscitis (1)
Kaneko et al. (Japan) [54]	27 (20W, 7M)	NS; use of concomitant DMARDs or IS was prohibited during the study	8 mg/kg vs. placebo during 12 wks; open-label TCZ for 40 weeks subsequently	Systemic feature score was -4.1 in the TCZ group and -2.3 in the placebo group (p=0.003) at week 12th	Decreased by 46.2% in TCZ and 21.0% in the pbo group after 12 weeks	Anaphylactic shock to TCZ in 1 patient. Infusion reactions occurred in 5, of whom 4 received TCZ and 1 placebo. AEs led to TCZ cessation in 2 patients
Song et al. (Korea) [51]	22 (NS)	MTX (20), LEF (12), AZA (9), CsA (8), a-TNF (18), ANK (1), ABT (2)	8 mg/kg/4 wks (18) 6 mg/kg/4 wks (2) 4 mg/kg/4 wks (2) 7.5 months duration	Good response: 50% at 6 m; 64.3% at 12 m. Partial response: 31.8% at 6 months; 14.3% at 12 months	11.5 before; 7.5 after 6 m; 6.3 after 12 m	Hypertension and face swelling (1)
Elkayam et al. (Israel) [43]	15 (9M, 6W)	DMARDs (15) Anti-TNF (10)	8 mg/kg/2 wks (3) 8 mg/kg/4 wks (12) 6 months duration	Responders 86.7% (13/15)	27.6; 3.8	MAS (1)

Puéchal et al. (France) [30]	14 (9W, 5M)	MTX (14), ANK (14), a-TNF (12), ABT/RTX (7)	8 mg/kg/2 wks (4) 8 mg/kg/4 wks (9) 5 mg/kg/4 wks (1) 6 months duration	EULAR remission 54% (8/14). Systemic symptom resolved in 86% (7/8) at 6 months	23.3; 10.3	Necrotizing angiodermatitis (1) Chest pain (1) Systemic flare (1)
Suematsu et al. (Japan) [52]	11 (9W, 2M)	TCZ first bio line in 6; switching from another bio in 5	8 mg/kg/4 wks (11) 11.6 months duration	Remission in 10/11	Decrease in GC dose of 16.8 mg/day	Stomatitis (1), UTI (1), liver dysfunction (1) [¶]
Cipriani et al. (Italy) [41]	11 (6W, 5M)	MTX (8)	8 mg/kg/4 wks (11) 12 months duration	EULAR remission 81.8% (9/11) at 12 months	50; 0 at 12 mo [§] 8/11 discontinued	Non reported

Abbreviations in alphabetic order: ABT: abatacept; AEs: adverse events; ANK: anakinra; anti(a)-TNF: anti-tumor necrosis factor; AOSD: adult-onset Still´s disease; AZA: azathioprine; bio: biologic therapy; CsA: cyclosporin A; (b)DMARDs: (biological) disease-modifying antirheumatic drug; EULAR: European League against Rheumatism; IS: immunosuppressive agents; LEF: leflunomide; M: male: m (mo): months; MAS: macrophage activation syndrome; MTX: methotrexate; monother: monotherapy; n: number; NS: non specified; pbo: placebo; RTX: rituximab; TCZ: tocilizumab; UTI: urinary tract infection; W: women; wks: weeks.

*Values are expressed as mean, unless otherwise expressed; [§] Values in these 2 series are expressed as median.

[¶] In no case it forced the suspension of the drug.

[#] Based on data of ref. [32]

Table 4. Efficacy of tocilizumab in adult-onset Still´s disease: additional studies with n ≤ 10 cases per study.

Author (Country) [Ref. number]	Number of patients (Sex)	Previous treatment (n)	Dose (n) Duration of treatment	Overall response % (n)	Glucocorticoid before and after treatment (mg/day)*	Safety of the drug and AEs (n)
Nishina et al. (Japan) [31]	10 (6W, 4M)	MTX (6), TCR (2), CsA (1)	8 mg/kg/2 wks (6) 8 mg/kg/4 wks (4) 6-12 months duration	No relapses during TCZ therapy vs 11 before therapy; 4 pts discontinued therapy due to sustained remission; although 2/4 pts relapsed 6 and 14 mo later withdrawal	20; 11[§]	4 pts were hospitalized a total of 9 times due to infection (1 case), orthopedic surgery (4 cases in 2 pts), malignancy (2 cases in 1 pt) and others (2 cases in 2 pts). No discontinuation due to AEs
Takakuwa et al. (Japan) [53]	9 (8W, 1M)	DMARDs (NS) anti-TNF (7)	Non specified	TCZ induced higher clinical remission than a-TNF agents (5/7 vs 2/10, p=0.05); 4/5 pts who switched from a-TNF to TCZ achieved clinical remission	Non reported	During treatment with a-TNF, severe AEs were observed in 4 pts, which included ovarian cancer, severe hepatitis, CMV infection, and infusion reaction; no AEs were observed during TCZ therapy
Li et al. (China) [57]	8 (8W)	DMARDs (7), bDMARDs (NS)	4-8 mg/kg/4 weeks (8) ≥ 3 months follow-up	Complete remission 87.5% (7/8) at 3 months	51.7; 12.9	Infusion reactions (2), infections (3, two with UTI), MAS (1) [¶]
Bannai et al. (Japan) [60]	7 (4W, 3M)	MTX (3), CsA (2) IFX (1), ETA (1), TCR (1), BUC (1)	8 mg/kg/2 wks (6) 8 mg/kg/4 wks (1)	Good response in all (7) without any flares	Decrease in GC dose of 26.1 mg/d 1/7 discontinued	AEs occurred in 3 pts: MAS, CMV (2 episodes) and clostr. difficile in 1 pt, CMV and MAS in other pt [¥]; Suicide (1) [¶¶]

Cavalli et al. (Italy) [61]	4 (3W, 1M)	MTX (3), CsA (1), ANK (3), ETA (2)	Non reported	Complete response (2), Partial response (1), Failure (1)	Decrease in GC, 1/4 discontinued	HVZ (1)

Abbreviations in alphabetic order: ABT: abatacept; AEs: adverse events; ANK: anakinra; anti(a)-TNF: anti-tumor necrosis factor; AZA: azathioprine; BUC: bucillamine; clostr.: clostridium; CMV: cytomegalovirus infection; CsA: cyclosporin A; (b)DMARDs: (biological) disease-modifying antirheumatic drug; ETA: etanercept; EULAR: European League against Rheumatism; GC: glucocorticoids; IFX: infliximab; LEF: leflunomide; M: male: MAS: macrophage activation syndrome; MTX: methotrexate; mo: months; n: number; NS: non specified; pt(s): patient(s); RTX: rituximab; TCR: tacrolimus; TCZ: tocilizumab; UTI: urinary tract infection; VZV: varicella-zoster virus reactivation; W: women; wks: weeks.

[¥]The MAS was treated and resolved in both patients.

[¶] In no case it forced the suspension of the drug.

[¶¶] A case of suicide due to schizophrenia despite that AOSD was stabilized after introducing TCZ.

Table 5. Main adverse effects of TCZ according to the MedDRA Organ System Classification[#].

MedDRA Organ System Classification	Frequency categories with preferred terms*		
	Very common	**Common**	**Uncommon**
Infections and infestations	Upper respiratory tract infections	Cellulitis, pneumonia, oral herpes simplex, herpes zoster	Diverticulitis
Skin and subcutaneous tissue disorders		Rash, pruritus, urticaria	
Gastrointestinal complications		Abdominal pain, mouth ulcers, gastritis, diarrhea	Stomatitis, gastric ulcer
Nervous system manifestations		Headache, dizziness	
Laboratory abnormalities		Hepatic transaminases increased, total bilirubin increased[¶]	
Blood and lymphatic disorders		Leukopenia, neutropenia	
Metabolism and nutrition disorders	Hypercholesterolemia[¶]	Weight increased, hypertension	Hypertriglyceridemia
General disorders and administration site reactions	Injection site reactions (ISR)[§]	Peripheral edema, hypersensitivity reactions	
Respiratory, thoracic & mediastinal manifestations		Cough, dyspnea	
Renal diseases			Nephrolithiasis
Endocrine disorders			Hypothyroidism
Eye disorders		Conjunctivitis	

Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities.
Adverse reactions are listed according to MedDRA system organ class and frequency.
*Frequency categories are defined using the following criteria: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). ISR: Injection site reactions; TCZ: tocilizumab.

[¶] Includes elevations disclosed as part of the routine laboratory monitoring.
[§] Mainly following subcutaneous administration.
Most results shown in the table are obtained from double-blind controlled studies performed in patients with rheumatoid arthritis receiving tocilizumab as monotherapy or in combination with disease-modifying anti-rheumatic drugs (DMARDs).
[#] Modified from ref. [47].

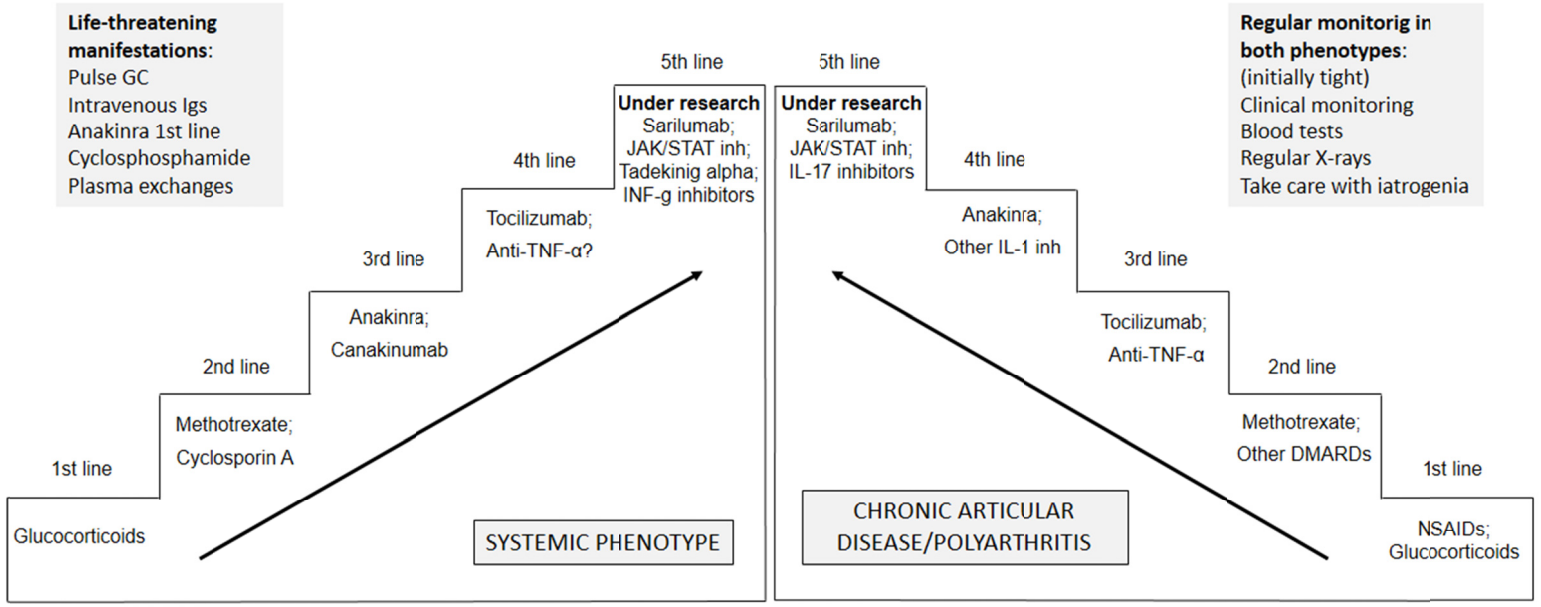
Table 6. Management of main laboratory abnormalities detected in adults with RA receiving treatment with TCZ in monotherapy or in combination with disease-modifying anti-rheumatic drugs (DMARDs)[#].

Laboratory abnormalities	**TCZ intravenous** **"ACTION TO TAKE"**	**TCZ subcutaneous** **"ACTION TO TAKE"**
Absolute neutrophil count (ANC)[*] (cells x 10^9/L)		
ANC > 1	Maintain dose	Maintain dose
ANC ≥ 0.5 and ≤ 1	Interrupt TCZ dosing	Interrupt TCZ dosing
	When ANC increases > 1 x 10^9/L restart TCZ at 4 mg/kg and increase to 8 mg/kg, as clinically appropriate	When ANC increases > 1 x 10^9/L restart TCZ dosing every other week and increase to every week injection, as clinically appropriate
ANC < 0.5	Discontinue TCZ	Discontinue TCZ
Low platelet count (cells x 10^3/μL)		
50 to 100	Interrupt TCZ dosing	Interrupt TCZ dosing
	When platelet count > 100 x 10^3/μL restart TCZ at 4 mg/kg and increase to 8 mg/kg as clinically appropriate	When platelet count > 100 x 10^3/μL restart TCZ dosing every other week and increase to every week injection, as clinically appropriate
< 50	Discontinue TCZ	Discontinue TCZ
Liver enzyme abnormalities		
> 1 to 3 x Upper Limit of Normal (ULN)	Modify the dose of the concomitant MTX if appropriate	Modify dose of MTX or DMARDs, or of the immunomodulatory agents (in case of GCA), if appropriate

	For persistent increases in this range, reduce TCZ dose to 4 mg/kg or interrupt TCZ until ALT or AST have normalized Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate	For persistent increases in this range, reduce TCZ dose frequency to every other week injection or interrupt TCZ until ALT or AST have normalized Restart with weekly or every other week injection, as clinically appropriate
> 3 to 5 x ULN (confirmed by repeating testing)	Interrupt TCZ dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN. For persistent increases > 3 x ULN, discontinue TCZ	Interrupt TCZ dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN For persistent increases > 3 x ULN (confirmed by repeat testing), discontinue TCZ
> 5 x ULN	Discontinue TCZ	Discontinue TCZ

Abbreviations: ALT: alanine aminotransferase; ANC: absolute neutrophil count; AOSD: adult-onset Still´s disease; AST: aspartate aminotransferase; DMARDs: disease-modifying anti-rheumatic drugs; GCA: giant cell arteritis; MTX: methotrexate; RA: rheumatoid arthritis; TCZ: tocilizumab; ULN: upper limit of normality. * In patients not previously treated with TCZ, initiation is not recommended in patients with an ANC < 2 x 10^9/L.
Data of toxicity in laboratory parameters in patients with AOSD are less studied.
Modified from ref. [47]

Keep in mind: prevention of OP & other complications: calcium, vitamin D, bisphosphonates[1]; chemoprophylaxis of tuberculosis[2]; vaccination[3]



[1] In case of osteoporosis or high risk fracture; [2] If positive contact history, positive Mantoux or chest X-ray suggestive of past tuberculosis; [3] Before biologic therapy

Figure 1