Clin Rheumatol (2014) 33:49–55
DOI 10.1007/s10067-013-2381-5

ORIGINAL ARTICLE

Tocilizumab for the treatment of adult-onset Still's disease: results from a case series

Paola Cipriani · Piero Ruscitti · Francesco Carubbi · Ilenia Pantano · Vasiliki Liakouli · Onorina Berardicurti · Roberto Giacomelli

Received: 24 April 2013 / Revised: 5 July 2013 / Accepted: 21 August 2013 / Published online: 5 September 2013

Abstract Adult-onset Still's disease (AOSD) is a chronic inflammatory disease of unknown etiology which commonly affects young adults. Treatment of AOSD patients includes nonsteroidal anti-inflammatory drugs, corticosteroids, and DMARDs. Interleukin (IL)-6 blockade is an attractive therapeutic option for AOSD because this cytokine contributes to the pathogenesis of major AOSD symptoms. Tocilizumab (TCZ) is a humanized anti-IL-6 receptor antibody that blocks the effects of IL-6. Preliminary results of TCZ in AOSD have been promising. Here, we reported our experience evaluating both the safety and the efficacy of 12 months therapy with TCZ in 11 patients with AOSD refractory to corticosteroids and MTX therapy, followed for 18 months, including the first 12 months of active treatment and the last 6 months to evaluate the activity of the disease when the treatment was discontinued. The main outcome measures were the European League Against Rheumatism (EULAR) improvement criteria and improvement of systemic symptoms at the 3, 6, 12, and 18-months follow-up periods. Our patients rapidly responded and experienced a sustained clinical remission over time during active treatment. Disease Activity Score 28 decreased from 5.62 (3.75–8.28) [median (range)] at baseline to 1.61(0.49–3.5) at month 12. EULAR remission was achieved in 81.82 % at 12 months. Tender joint and swollen joint counts displayed a progressive reduction during active therapy study period. During treatment, we observed a resolution of fever in our AOSD patient. In conclusion, TCZ might represent a suitable option for the therapy of refractory AOSD patients.

P. Cipriani (✉) · P. Ruscitti · F. Carubbi · I. Pantano · V. Liakouli · O. Berardicurti · R. Giacomelli
Department of Biotechnological and Applied Clinical Science, Rheumatology Unit, School of Medicine, University of L'Aquila, Delta 6 Building, Via dell'Ospedale, 67100 L'Aquila, Italy
e-mail: paola.cipriani@cc.univaq.it

Keywords Adult-onset Still's disease · First line therapy · Interleukin-6 · Tocilizumab

Introduction

Adult-onset Still's disease (AOSD) is an inflammatory disease of unknown etiology which commonly affects young adults [1]. AOSD is a rare condition, interesting at all ages, and its expression and progression are highly variable [2]. Usually, it is characterized by high spiking fever, arthritis, and an evanescent, macular, and salmon-colored rash, appearing on the trunk and the extremities. Although some patients have a unique flare without any recurrence, most of the patients experience several episodes which progress to a chronic form [3, 4].

Two chronic forms are described in literature: a systemic form with fever, asthenia, and other general symptoms, and an arthritic form with polyarthritis which could be erosive in up to 50 % of patients [1–4].

AOSD pathogenesis is still poorly understood and controversial.

The immunological signature represents a key feature in AOSD pathogenesis. High levels of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-18, tumor necrosis factor-α (TNF-α), and interferon-γ were found to be significantly increased in patients with active AOSD when compared to normal subjects [5]. It might be the result of a global reactive syndrome with activation of macrophage, natural killer cells, and B lymphocytes leading to a predominant cell-mediated immune response [5]. A predominance of Th1 cytokines was described in the peripheral blood and tissues of patients with active untreated AOSD.

To date, no specific laboratory tests are available for AOSD. Clinical diagnosis could be performed excluding

important mimickers such as infections, malignancies, and others systemic autoimmune disorders.

The most widely accepted diagnostic criteria have been presented by Yamaguchi and colleagues including major and minor criteria [6]. More recently, Fautrel and colleagues proposed classification criteria that include diagnostic markers such as serum ferritin and glycosylated ferritin [7].

Treatment of AOSD patients is largely empiric and based on the results of case reports or small case series due to rarity of this disease. It includes nonsteroidal anti-inflammatory drugs, corticosteroids, and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) for severe and potentially disabling manifestations [8].

In this setting, commercially available biologic agents for rheumatoid arthritis (RA) have been employed in AOSD with variable success [9]. Recently, small series and retrospective studies have shown improvement in some patients with AOSD following biologic therapy with TNF-α antagonists [10, 11] or anakinra, an antagonist of IL-1 [12, 13]. Nevertheless, efficacy of these biologic agents is inconstant and severe side effects have also been reported [9–13].

IL-6 blockade might be an attractive therapeutic option for AOSD because this cytokine contributes to the pathogenesis of major AOSD symptoms including fever, leukocytosis, acute-phase protein production and bone resorption [14]. Tocilizumab (TCZ) is a humanized anti-IL-6 receptor antibody that recognizes both the membrane-bound and the soluble form of IL-6 receptor and specifically blocks IL-6 mediated pathways. The results obtained in short series with limited follow-up have been already published [14–19].

Furthermore, growing evidences described the efficacy and safety of TCZ in children with systemic juvenile idiopathic arthritis (SJIA), which is considered to share many common pathogenetic pathways with AOSD. SJIA is characterized by chronic arthritis and systemic manifestations such as spiking fever, rash, hepatosplenomegaly, lymphadenopathy, serositis, and elevated inflammatory markers [20]. IL-6 levels are particularly higher in this juvenile disorder correlating with disease activity. Thus, IL-6 is a rational target for the treatment of SJIA and TCZ is approved since 2008 in Japan and 2011 by the US Food and Drug Administration and European Medicine Agency for kids with SJIA [21, 22].

In this work, we reported our experience concerning both the safety and the efficacy of the therapy with TCZ in patients with AOSD refractory to corticosteroids and MTX.

Patients and methods

Eleven consecutive patients with AOSD referring to the Rheumatology Clinic at University of L'Aquila between January 2009 and January 2012 were treated with TCZ. The treatment was approved by the local ethics committee, and written informed consent was obtained from all patients according to the Declaration of Helsinki. All patients fulfilled the criteria proposed by Yamaguchi for AOSD [14]. All patients underwent chest X-ray and serological analyses to exclude B and C viral hepatitis, latent TBC, and/or other severe infectious diseases prior the biological treatment.

Patients showing more than six tender and/or swollen joints and/or systemic involvement such as fever and/or loss of body weight more than 10 % in the last 3 months and/or inflammatory anemia not responding to conventional therapies for 3 months or evidence of drug toxicity received TCZ (8 mg/kg every 4 weeks) for 12 months and successively underwent to 6 months of follow-up after discontinuation of the treatment. Due to the lack of validated measures for joint involvement in AOSD, we assessed the joint involvement of our patients by Disease Activity Score 28 and EULAR improvement criteria [23], as reported in other series [10, 11, 19]. Pain was evaluated using a 100-mm visual analogue scale. The number of active joints was defined by the presence of swelling or restriction of motion accompanied by pain or tenderness or both. Clinical records were collected at the baseline and at 3, 6, and 12 months of active treatment and at 18 months [26].

The improvement of systemic symptoms was considered the primary outcome in our cohort. In this regard, the presence or absence of fever and patient global health using a 100-mm visual analogue scale (VAS) were evaluated.

Furthermore, routine laboratory tests including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin serum levels, and hemoglobin were reported. These values were used as surrogate markers of IL-6 function to assess the response to the treatment. Adverse events were recorded in a specific form.

After 12 months of active treatment, patients discontinued biologic treatment and they were followed up to the next 6 months to evaluate the activity of the disease.

Statistical analysis was performed with GraphPad 5.0 software. Our results are expressed as median (range). One way repeated measures ANOVA and Bonferroni multiple comparison post hoc test were calculated. P values less than 0.05 were considered significant.

Results

Patients' clinical characteristics are summarized in Table 1. All enrolled patients assumed prednisone and eight out of 11 patients assumed MTX. At radiological examination, seven patients (four in combination therapy and three with prednisone alone) showed joint erosions.

In all patients, TCZ was administrated at 8 mg/kg every 4 weeks. Eight patients were treated in combination with MTX plus prednisone, and three patients received TCZ plus prednisone without MTX. These later discontinued MTX

Table 1 Clinical characteristics of the 11patients with adult-onset Still's disease treated with tocilizumab

Women (Man)	6 (5)
Age, mean (range) years	46.45 (28; 73)
Disease, duration, mean(range) years	6.1 (1; 12)
Chronic arthritis (%)	11 (100)
Radiologic damage (%)	7 (63.64)
Fever (%)	11 (100)
Recurrent systemic flare (%)	8 (72.72)
Lymphadenopathy (%)	7 (63.64)
Sore throat (%)	6 (54.54)
Hepatosplenomegaly (%)	6 (54.54)
Serositis (%)	3 (27.27)
NSAIDS ever used (%)	11 (100)
Methotrexate ever used (%)	11 (100)
Methotrexate ongoing (%)	8 (72.72)
Long-term corticosteroid therapy	11 (100)

because of severe hypertransaminasemia and megaloblastic anemia. The median dosage of MTX remains stable during all period study 15 (0–25). Patients' therapies are reported in Table 2. All patients successfully completed the treatment and the follow-up period until the 18 months.

Median Disease Activity Score in 28 joints (DAS28) decreased from 5.62 (3.75–8.28) at baseline to 2.31 (1.25–6.28) at month 3, 1.88 (0.63–3.57) at month 6, and 1.61 (0.49–3.5) at month 12 (Fig. 1). EULAR remission (DAS28 <2.6) was achieved in 45.45 % (five out of 11) at 3 months. EULAR remission was reached in 63.63 % (seven out of 11) at 6 months and 81.82 % (9 out of 11) at 12 months. A good EULAR response (DAS28 <3.2) was achieved by other patient during 12 months of active treatment.

Tender joint and swollen joint count displayed a progressive reduction during active therapy study period (Fig. 1). A statistically significant improvement of joint assessment was observed after 6 and 12 months of treatment when compared to baseline ($p < 0.05$ for any comparison).

Eight patients had fever at the beginning of biologic treatments. Remission of fever and improvement of systemic symptoms including skin involvement were observed in all patients during the study period. Furthermore, the results of median patient VAS global health were 75 (80–50)mm at baseline, 35 (0–70)mm at 3 months, 20 (10–60)mm at 6 months, and finally, 0 (0–30)mm at 12 months. The improvement in patient VAS global health values was statistically significant ($p < 0.005$) for any comparison between baseline and each time point during active treatment (Fig. 1).

Prednisone dosage was progressively tapered according to clinician judgment during scheduled visits. The median dosage was 50 (25–100)mg/day at baseline, 12.5 (12.5–25)mg/day at month 3, 6.25 (5–12.5)mg/day at month 6, and 0 (0–12.5)mg/day at month 12 (Table 2) showing an higher corticosteroid-sparing activity of TCZ; in fact, after 12 months, eight out of 11 patients (72.72 %) discontinued corticosteroid therapy.

The ESR, CRP, ferritin, and hemoglobin values of patients in our cohort are summarized in Table 3.

Concerning TCZ safety profile in AOSD, no severe adverse events including death was observed. Only minor adverse events were observed. Specifically, one patient developed upper respiratory tract infection needing antibiotic therapy and two patients reported injection-site reaction after one infusion of TCZ. In addition, no significant cytopenias were observed throughout the study.

The analysis of clinical conditions after discontinuation of biological therapy at month 18 showed that eight out of 11

Table 2 Methotrexate and corticosteroid therapies of the 11patients with adult-onset Still's disease treated with tocilizumab

	Methotrexate, mg/weekly		Systematic corticosteroids, mg/daily					
	Months of therapy before TCZ	Dosage	Months of therapy before TCZ	t0	t1	t2	t3	t4
Patient 1	4	0[a]	12	75	12.5	12.5	6.25	25
Patient 2	6	25	8	100	12.5	6.25	0	0
Patient 3	9	15	12	25	12.5	5	0	0
Patient 4	5	0[a]	24	50	25	12.5	12.5	50
Patient 5	6	12.5	36	25	12.5	5	0	0
Patient 6	12	20	8	25	12.5	5	0	0
Patient 7	8	20	11	50	12.5	5	0	0
Patient 8	8	0[a]	18	25	25	12.5	5	37.5
Patient 9	16	17.5	15	50	12.5	6.25	0	0
Patient 10	12	10	18	25	12.5	6.25	0	0
Patient 11	12	17.5	20	50	12.5	6.25	0	0

[a] Untreated patients due to history of methorexate related adverse event

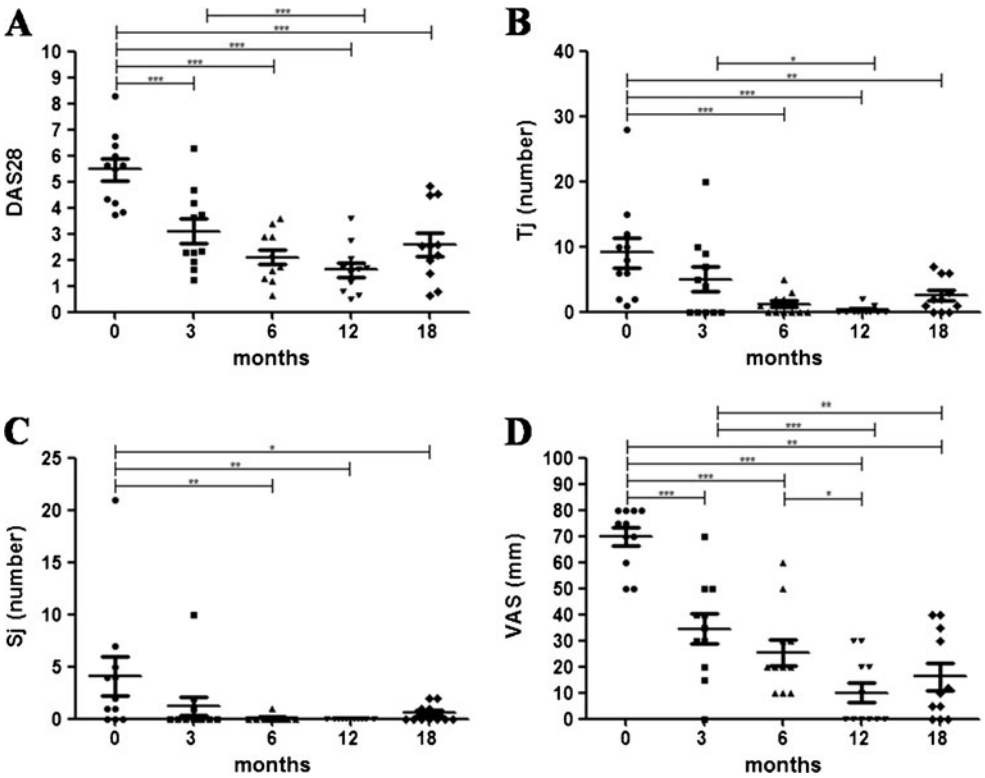

Fig. 1 Clinical activity scores at baseline, at 3, 6, 12 months of treatment with tocilizumab therapy, and after 6 months of follow-up (18 months) in adult Still's disease patients. **a** Disease Activity Score in 28 joints (DAS28), **b** tender joints (Tj) number, **c** swollen joints (Sj) number, **d** visual analogue scale (VAS) of patient global health expressed as millimeters (mm). *$p<0.05$; **$p<0.01$; ***$p<0.001$

patients (72.72 %) were still maintaining clinical remission, and all these patients were still receiving only MTX. The three patients that experienced a flare, showing both systemic and joints symptoms, needed an increasing dose of corticosteroids, and interestingly, they were not assuming MTX for previous intolerance. These patients reported an increase number of tender and swollen joint, the onset of systemic symptoms, and a worsening of patient VAS global health. Furthermore, laboratory tests showed higher serum concentrations of ESR, CRP, and ferritin.

Discussion

Growing evidences on the role of IL-6 in AOSD pathogenesis provide the basis for TCZ therapy in this disease.

Table 3 Laboratory parameters of 11 patients with adult-onset Still's disease treated with tocilizumab

	ESR					CRP					Ferritin					Hemoglobin				
	t0	t1	t2	t3	t4	t0	t1	t2	t3	t4	t0	t1	t2	t3	t4	t0	t1	t2	t3	t4
Patient1	9	2	2	2	32	12.2	1.25	2.1	0.9	17.9	335	120	25	36	736	15	14.5	15.4	15	10.2
Patient2	16	5	2	2	8	12.4	0.5	1.16	0.2	0.2	1500	168	10	40	42	12.2	14.7	13.5	16.1	15.8
Patient3	30	13	2	10	10	1.9	1.56	2.12	1.2	1.2	1200	230	69	50	48	10.8	13.4	13.3	14	13.9
Patient4	83	36	20	36	26	10	3.87	35	5.8	25.8	400	52	87	31	831	9.3	14.2	14.4	14.6	10.6
Patient5	51	12	8	3	3	32.5	0.8	1.8	0.56	0.56	500	89	50	87	52	8.7	13.8	15.6	13.9	14.1
Patient6	52	18	16	11	10	25	3	19.7	2.34	2.12	500	100	40	64	74	12.4	14.7	13.8	12.8	13.2
Patient7	58	6	5	8	5	47.7	0.65	1.2	1.3	1.1	664	23	25	25	15	8.9	13.1	12.9	14.2	12.9
Patient8	64	23	10	15	35	27.9	7.8	3.56	2.9	22.9	300	145	90	12	512	9.7	12.9	13.8	12.5	13.2
Patient9	42	20	15	10	2	15.9	4.25	4.8	3.54	2.5	854	65	30	50	20	11.3	13.3	14.8	14	14.6
Patient10	36	11	10	11	9	12.5	2.98	2.8	2.12	1.12	756	50	25	36	46	10.3	15.2	14.8	15.5	15.8
Patient11	45	14	12	5	2	10.2	5	0.9	0.51	0.1	400	215	68	43	25	12.5	16.8	16	13.6	15

Laboratory tests at baseline (t0), 3 (t1), 6 (t2), and 12 (t3) months of treatment with tocilizumab therapy and after 6 months (t4) of follow-up. Erythrocyte sedimentation rate (ESR) is expressed as millimeter/hour (mm/h); C-reactive protein serum levels is expressed as milligram/liter (mg/1); ferritin serum levels is expressed as nanogram/milliliter (ng/ml); and hemoglobin is expressed as gram/deciliter (g/dl)

In agreement with previous data [14–19], we observed a dramatic improvement of all disease-related clinical and serological findings after TCZ therapy in the totality of AOSD patients which were refractory to combination therapy with MTX and prednisone.

In particular, we observed a decrease of swollen and tender joint counts as well as of DAS28 after TCZ treatment. Furthermore, such improvement was rapid and sustained until 12 months. In addition, disease remission according to EULAR criteria was achieved in 81.82 % of our patients.

Of note, our work was planned to evaluate the TCZ as first line therapy in patients resistant at conventional combination therapy with corticosteroid plus MTX. In fact, several studies has been recently published exploring the possibility to treat AOSD by biologics after the failure of TNF-α blockers or anakinra and employing TCZ as rescue therapy [19, 24]. The different selection of patients among published papers could explain the differences in the results obtained in our study when compared to other published trials. Probably, our patients could be considered less severe than patients enrolled after many biologic therapies, but, in our opinion, this is not a limit of our study but an important tool because of the large amount of patients reaching remission Achieving and maintaining remission are presently considered the most important goal in many rheumatic diseases, and as we showed in this short but homogeneous population, this target may be reached in a large percentage of patients when electively treated by TCZ.

Interestingly, our data are in agreement with results raised from clinical trials performed in patients with RA [25]. In addition, a randomized placebo-controlled trial demonstrated the efficacy and safety of TCZ in children with SJIA. In this study, children with SJIA refractory to conventional treatment were treated with TCZ achieving and maintaining clinical and laboratory remission [21] as observed in our patients.

Taking into account the lack of validated radiological scores for AOSD joint involvement, we did not perform any radiological examination during the study period. However, we could speculate as reported in clinical trial for RA or SJIA that TCZ therapy in AOSD might inhibit progression of joint radiological damage [25, 26].

Furthermore, we observed a reduction of patient VAS global health that might be related in our experimental group to the resolution of systemic symptoms, including fever and skin eruption which was sustained during the entire study period and probably leading to a significant improvement of health-related quality of life. Our results concerning systemic involvement are in agreement with previous studies involving TCZ-treated RA patients [27]. TCZ [34], ESR, CRP, and ferritin values were reduced by TCZ treatment at month 3 and such decrease remained stable during the study period. The decrease of the inflammatory markers paralleled to clinical improvement. It is well known that anemia due to chronic inflammation, neutrophilic leukocytosis, and reactive thrombocytosis are commonly observed during active AOSD [4]. These abnormalities were also documented in our cohort of patients, and TCZ treatment led to a progressive normalization of all parameters. Serum ferritin level correlates with AOSD disease activity, and disease remission is associated to its normalization [28–30]. In our cohort of AOSD patients, we found a strong correlation between ferritin serum values and activity of the disease with a progressive and sustained reduction of these levels until normalization. Furthermore, we observed a significant improvement of hemoglobin levels in our patients. It is well known that the effect of TCZ in increasing the hemoglobin in patients with higher levels of inflammatory cytokines, mainly IL-6, via the inhibition of hepcidin pathway, and this increase could be related with the improvement is some systemic symptom such as fatigue and adynamia [31].

Corticosteroid long-term therapy is a cornerstone in AOSD treatment [4]. However, it is well known that corticosteroids are weighted by several deleterious side effects such as hyperglycemia, glaucoma, and systemic hypertension. To note, the higher the initial dose, the higher the risk to develop such effects [32]. We found a statistically significant reduction of corticosteroid daily intake from baseline to 12 months, confirming that TCZ displays a strong and very effective corticosteroid-sparing effect. It must be pointed out that at month 12 72.72 % of our patients discontinued corticosteroid therapy, maintaining a good clinical response. This result mirrors what observed in previous studies reporting that corticosteroid treatment was successfully tapered and discontinued in AOSD patients treated with TCZ [33, 35].

Our study suggests that TCZ might be considered as a helpful therapeutic option in those patients needing a long-term therapy with corticosteroid in order to reach a good clinical response.

In a recent study enrolling 112 children aged 2 to 17 years, with active and persistent SJIA, TCZ was reported to be effective in reducing signs and symptoms of disease. At week 52, a large percentage of the patients who received TCZ had no fever and no joints with active arthritis and had discontinued oral glucocorticoids [36]. As far as RA patients receiving a combination therapy of TCZ and DMARDs are concerned, it has been demonstrated that TCZ monotherapy displays a similar efficacy profile [37].

Concerning the safety issue in our study, no severe side events including death were observed during the study period. Only few minor adverse events, one episode of upper respiratory tract infection and infusion site reaction, were reported during our study period. Such findings mirror the results arising from clinical trials involving RA patients in which a generally good safety profile of TCZ has been demonstrated [31]. However, the follow-up duration of the present study do not allow any speculation on long-term safety profile in AOSD patients. Again, the different therapeutic background

of our patients could explain the better safety profile of our study.

The analysis of clinical conditions at 6 months after discontinuation of biological therapy showed that 72.72 % were still maintaining the clinical remission. These data in our patients mirror those observed in SJIA patients treated with TCZ in which after the discontinuation of therapy only a small percentage of children experimented a flare of the disease [21].

It remains unclear how long TCZ should be administered. The lack of published guidelines concerning treatment with biologics for AOSD [38] and how long to treat patients in other rheumatic diseases such as RA and spondyloarthropathies lead us to discontinued therapy after reaching a persistent remission. AOSD is a chronic disease with long course and late relapses, and on this basis, we have chosen to avoid the risk of a long period of exposition to a strong immunosuppressive therapy in our patients. In this setting, some authors suggest that the decrease of serum IL-6 during TCZ treatment might indicate disease remission and might be a guide for discontinuation [14]. In this regard, ESR, CRP, and ferritin serum levels could be measured to assess the disease response as a surrogate marker of IL-6 function.

In conclusion, our study demonstrated that blocking IL-6 with TCZ could be a therapeutic option for AOSD patients in which overproduction of IL-6 plays a pathological role. Although we cannot draw certain conclusions due to the limited number of cases, our results demonstrated the potential therapeutic effect of this treatment. Future clinical studies investigating the safety and the efficacy will elucidate the clinical benefits of IL-6 blockade for AOSD patients.

Acknowledgments The authors thank Mrs. Federica Sensini for her technical assistance.

Disclosures None.

References

1. Bywaters EG (1971) Still's disease in the adult. Ann Rheum Dis 30: 121–133
2. Cabane J, Michon A, Ziza JM, Bourgeois P, Bletry O, Godeau P, Kahn MF (1990) Comparison of long-term evolution of adult onset and juvenile onset Still's disease, both followed up for more than10 years. Ann Rheum Dis 49:283–285
3. Kong XD, Xu D, Zhang W, Zhao Y, Zeng X, Zhang F (2010) Clinical features and prognosis in adult-onset Still's disease: a study of 104 cases. Clin Rheumatol 29:1015–1019
4. Efthimiou P, Paik PK, Bielory L (2006) Diagnosis and management of adult onset Still's disease. Ann Rheum Dis 65(5):564–572
5. Choi JH, Suh CH, Lee YM, Kim SS, Nahm DH, Park HS (2003) Serum cytokine profiles in patients with adult onset Still's disease. J Rheumatol 30:2422–2427
6. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H et al (1992) Preliminary criteria for classification of adult Still's disease. J Rheumatol 19:424–430
7. Fautrel B, Zing E, Golmard JL, Le Moel G, Bissery A, Rioux C, Rozenberg S, Piette JC, Bourgeois (2002) Proposal for a new set of classification criteria for adult-onset still disease. Med (Baltimore) 8: 194–200
8. Fautrel B (2008) Adult-onset Still disease. Best Pract Res 22(5):773–792
9. Pouchot J, Arlet JB (2012) Biological treatment in adult-onset Still's disease. Best Pract Res Clin Rheumatol 26:477–487. doi:10.1016/j.berh.2012.07.002
10. Husni ME, Maier AL, Mease PJ, Overman SS, Fraser P, Gravallese EM, Weinblatt ME (2002) Etanercept in the treatment of adult patients with Still's disease. Arthritis Rheum 46:1171–1176
11. Fautrel B, Sibilia J, Mariette X, Combe B, the Club Rheumatisms et Inflammation (2005) Tumour necrosis factor _ blocking agents in refractory adult Still's disease: an observational study of 20 cases. Ann Rheum Dis 64:262–266
12. Fitzgerald AA, Leclercq SA, Yan A, Homik JE, Dinarello CA (2005) Rapid responses to anakinra in patients with refractory adult onset Still's disease. Arthritis Rheum 52:1794–1803
13. Lequerre T, Quartier P, Rosellini D, Alaoui F, De Bandt M, Mejjad O, Kone-Paut I, Michel M, Dernis E, Khellaf M, Limal N, Job-Deslandre C, Fautrel B, Le Loët X, Sibilia J, Société Francophone pour la Rhumatologie et les Maladies Inflammatoires en Pédiatrie (SOFREMIP), Club Rhumatismes et Inflammation (CRI) (2008) Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still's disease: preliminary experience in France. Ann Rheum Dis 67:302–308
14. de Boysson H, Février J, Nicolle A, Auzary C, Geffray L (2013) Tocilizumab in the treatment of the adult-onset Still's disease: current clinical evidence. Clin Rheumatol 32:141–147. doi:10.1007/s10067-012-2105-2, Epub 2012 Oct 30
15. Nakahara H, Mima T, Yoshio-Hoshino N, Matsushita M, Hashimoto J, Nishimoto N (2009) A case report of a patient with refractory adult-onset Still's disease who was successfully treated with tocilizumab over 6 years. Mod Rheumatol 19:69–72
16. Matsumoto K, Nagashima T, Takatori S, Kawahara Y, Yagi M, Iwamoto M, Okazaki H, Minota S (2009) Glucocorticoid and cyclosporine refractory adult onset Still's disease successfully treated with tocilizumab. Clin Rheumatol 28:485–487
17. Sumida K, Ubara Y, Hoshino J, Suwabe T, Hiramatsu R, Hasegawa E, Hayami N, Yamanouchi M, Sawa N, Takemoto F, Takaichi K (2010) Etanercept-refractory adult-onset Still's disease with thrombotic thrombocytopenic purpura successfully treated with tocilizumab. Clin Rheumatol 29:1191–1194
18. Sabnis GR, Gokhale YA, Kulkarni UP (2011) Tocilizumab in refractory adult-onset Still's disease with aseptic meningitis-efficacy of interleukin-6 blockade and review of the literature. Semin Arthritis Rheum 40:365–368
19. Puéchal X, DeBandt M, Berthelot JM, Breban M, Dubost JJ, Fain O, Kahn JE, Lequen L, Longy-Boursier M, Perdriger A, Schaeverbeke T, Toussirot E, Sibilia J, Club Rhumatismes Et Inflammation (2011) Tocilizumab in refractory adult Still's disease. Arthritis Care Res (Hoboken) 63:155–159
20. Prakken B, Albani S, Martini A (2011) Juvenile idiopathic arthritis. Lancet 377:2138–2149
21. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, Iwata N, Umebayashi H, Murata T, Miyoshi M, Tomiita M, Nishimoto N, Kishimoto T (2008) Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomized, double-blind, placebo-controlled, withdrawal phase III trial. Lancet 371:998–1006
22. De Benedetti F, Brunner H, Ruperto N, Calvo N, Cuttica I, Malattia R et al (2010) Tocilizumab in patients with systemic juvenile idiopathic

arthritis: efficacy data from the placebo controlled 12-week part of the phase 3 TENDER trial. Arthritis Rheum 62(suppl 10):1434
23. Van Gestel AM, Haagsma CJ, van Riel PL (1998) Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 41:1845–1850
24. Suematsu R, Ohta A, Matsuura E, Takahashi H, Fujii T, Horiuchi T, Minota S, Ishigatsubo Y, Ota T, Takei S, Soejima S, Inoue H, Koarada S, Tada Y, Nagasawa K (2012) Therapeutic response of patients with adult Still's disease to biologic agents: multicenter results in Japan. Mod Rheumatol 22:712–719. doi:10.1007/s10165-011-0569-6
25. Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Murata N, van der Heijde D, Kishimoto T (2007) Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x-ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis 66:1162–1167
26. Inaba Y, Ozawa R, Imagawa T, Mori M, Hara Y, Miyamae T, Aoki C, Saito T, Yokota S (2011) Radiographic improvement of damaged large joints in children with systemic juvenile idiopathic arthritis following tocilizumab treatment. Ann Rheum Dis 70:1693–1695
27. Strand V, Burmester GR, Ogale S, Devenport J, John A, Emery P (2012) Improvements in health-related quality of life after treatment with tocilizumabin patients with rheumatoid arthritis refractory to tumour necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study. Rheumatol (Oxford) 51(10):1860–1869
28. Fautrel B, Le Moel G, Saint-Marcoux B, Taupin P, Vignes S, Rozenberg S, Koeger AC, Meyer O, Guillevin L, Piette JC, Bourgeois P (2001) Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease. J Rheumatol 28:322–329
29. Van Reeth C, Le Moel G, Lasne Y, Revenant MC, Agneray J, Kahn MF, Bourgeois P (1994) Serum ferritin and isoferritins are tools for diagnosis of active adult Still's disease. J Rheumatol 21:890–895
30. Akritidis N, Giannakakis I, Giouglis T (1996) Ferritin levels and response to treatment in patients with adult Still's disease. J Rheumatol 23:201–202
31. Garnero P, Thompson E, Woodworth T, Smolen JS (2010) Rapid and sustained improvement in bone and cartilage turnover markers with the anti-interleukin-6 receptor inhibitor tocilizumab plus methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate: results from a substudy of the multicenter double-blind, placebo-controlled trial of tocilizumab in inadequate responders to methotrexate alone. Arthritis Rheumatol 62:33–43
32. Udoetuk JD, Dai Y, Ying GS, Daniel E, Gangaputra S, Rosenbaum JT, Suhler EB, Thorne JE, Foster CS, Jabs DA, Levy-Clarke GA, Nussenblatt RB, Kempen JH (2012) Risk of corticosteroid-induced hyperglycemia requiring medical therapy among patients with inflammatory eye diseases. Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study Research Group. Ophthalmology 119(8): 1569–1574
33. Rech J, Ronneberger M, Englbrecht M, Finzel S, Katzenbeisser J, Manger K, Manger B, Schett G (2011) Successful treatment of adult-onset Still's disease refractory to TNF and IL-1 blockade by IL-6 receptor blockade. Ann Rheum Dis 70:390–392
34. Naniwa T, Ito R, Watanabe M, Hayami Y, Maeda S, Sasaki K, Iwagaitsu S (2010) Case report: successful use of short-term add-on tocilizumab for multirefractory systemic flare of adult-onset Still's disease. Clin Rheumatol. doi:10.1007/s10067-010-1562-8
35. Sakai R, Nagasawa H, Nishi E, Okuyama A, Takei H, Kurasawa T, Kondo T, Nishimura K, Shirai Y, Ito T, Kameda H, Takeuchi T, Amano K (2012) Successful treatment of adult-onset Still's disease with tocilizumab monotherapy: two case reports and literature review. Clin Rheumatol 31:569–574
36. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, Cuttica R, Ravelli A, Schneider R, Woo P, Wouters C, Xavier R, Zemel L, Baildam E, Burgos-Vargas R, Dolezalova P, Garay SM, Merino R, Joos R, Grom A, Wulffraat N, Zuber Z, Zulian F, Lovell D, Martini A, PRINTO, PRCSG (2012) Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med 20(367):2385–2395
37. Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM, Schett G, Amital H, Navarro-Sarabia F, Hou A, Bernasconi C, Huizinga TW (2013) Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis 72:43–50
38. Mavragani CP, Spyridakis EG, Koutsilieris M (2012) Adult-onset Still's disease: from pathophysiology to targeted therapies. Int J Inflamm 2012:879020. doi:10.1155/2012/879020