Tocilizumab in Adult-onset Still's Disease: the Israeli Experience

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ABSTRACT. ***Objective.*** To describe the Israeli experience of treating adult-onset Still's disease (AOSD) with tocilizumab (TCZ).

Methods. Israeli rheumatologists who treated AOSD with TCZ filled in questionnaires on symptoms, number of tender and swollen joints, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and dosage of prednisone at initial TCZ administration, after 6 months, and at the end of followup.

Results. Nine male and 6 female patients, aged 33 ± 12 years, mean disease duration 9 years (range: 1–25) were identified. They had used a mean of 3.6 disease-modifying drugs, including 10 patients with tumor necrosis factor blockers. Intravenous TCZ 8 mg/kg was administered every 4 weeks (12 patients) or every 2 weeks (3 patients). All patients completed at least 6 months of treatment. The mean followup period was 15.7 ± 9 months. At the onset of therapy, despite the use of prednisone (27.6 ± 26.3 mg/d), all patients reported joint pain. Fever was reported in 9 patients, rash in 7, pleuritis in 3, and hepatitis in 2 before TCZ use, with mean ESR and CRP levels of 60 ± 28 mm/h and 11.6 ± 15 mg/dl, respectively. After 6 months of treatment and at the end of followup, the number of tender and swollen joints, the ESR and CRP levels, and the prednisone dosage decreased significantly. Only 2 patients still complained of mild arthralgias, and none reported systemic symptoms at the end of followup.

Conclusion. TCZ 8 mg/kg was extremely efficacious in treating adult patients with refractory Still's disease. Both TCZ and interleukin 1 blockade should be considered in the treatment algorithm of AOSD. Randomized controlled studies are needed to validate these findings. (First Release Jan 15 2014; J Rheumatol 2014;41:244–7; doi:10.3899/jrheum.130881)

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Adult-onset Still's disease (AOSD) was first reported by Bywaters, who described a disease similar to the systemic type of juvenile idiopathic arthritis (JIA) in 14 adults[1]. The disease is characterized by sore throat, spiking fevers, arthritis, myalgias, rash, and serositis. The hallmark of the disease is an extremely increased acute-phase response, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and ferritin levels[2]. The prominent acute-phase response reflects the presence of cytokines with high levels of proinflammatory cytokines such as interleukin 1 (IL)-1, IL-6 [which is under the control of IL-1 (mainly IL-1β[3])], tumor necrosis factor (TNF)-α, and others. The first line of therapy is based on high doses of corticosteroids, such as prednisone, often requiring dosages around 1 mg/kg. The response to this treatment is not always optimal and is often accompanied by serious side effects. Further, the pattern of the disease is often that of relapses, thus requiring longterm treatment[2]. Improved understanding of the pathogenesis of systemic-onset JIA along with the development of biologic agents have led to a number of promising reports. Anakinra, an IL-1 receptor antagonist, has been shown to produce rapid reduction in systemic and local inflammation in patients with JIA and in those with refractory AOSD[4]. Likewise, multicenter trials have shown

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a beneficial effect of tocilizumab (TCZ) in this setting[5,6]. Several case reports and small series have suggested a similar effect of TCZ on AOSD[7,8].

TCZ was introduced into Israel in 2009, designated for the treatment of rheumatoid arthritis. The aim of our study was to report the accumulated experience of Israeli rheumatologists in the off-label use of TCZ for the treatment of patients diagnosed as having AOSD.

MATERIALS AND METHODS

Israeli rheumatologists who had ever treated a patient diagnosed with AOSD with a course of TCZ were asked to review their files and detail their experience by a questionnaire. These patients were located through an electronic message sent to all the rheumatologists registered in the Israeli Society of Rheumatology, requesting data on patients with AOSD who have been ever treated with TCZ. All of the patients who fulfilled the Yamaguchi criteria for AOSD[9] and were at least 18 years of age were included in our study (patients had to be at least 18 years of age at inclusion, but disease onset might have been during childhood). The retrieved data were those recorded at the initiation of TCZ administration, after 6 months of treatment, and at the end of followup. They included the patient's age, sex, disease duration, previous treatment for AOSD, symptoms that were present when starting the patient on TCZ (e.g., fever, rash, sore throat, arthralgias, serositis), signs (fever, number of tender and swollen joints), laboratory findings (ESR, CRP, and levels of transaminases), and dosage of corticosteroids and other disease-modifying antirheumatic drugs (DMARD).

Statistical analysis. The statistical analyses were performed with SPSS software using Student's t test and the chi-square test. Statistical significance was defined as $p < 0.05$.

RESULTS

Fifteen patients with AOSD (mean age 33 ± 12 years, 9 males) were identified by 12 rheumatologists throughout the country and they comprised the study group. Table 1 summarizes their demographic and clinical characteristics when they were started taking TCZ. The mean disease duration for the study group was 9 ± 11 years. The mean number of DMARD was 3.6 (range 1–7) before TCZ was initiated, with 10 patients previously treated with at least 1 TNF-α blocker. All of the patients had arthralgias/arthritis at inclusion, 9 had fever, 7 had rash, 3 had pleuritis, and 3 had recurring sore throats. The mean number of tender and swollen joints was 11.6 ± 6.8 and 8.6 ± 5.4, respectively, while the mean ESR and CRP levels were 60 ± 28 mm/h and 11.6 ± 15 mg/dl, respectively. All patients but one were receiving corticosteroids (mean dosage 27.6 ± 26.3 mg/d). Twelve of the patients were treated with intravenous TCZ at a dosage of 8 mg/kg/month and the other 3 received 8 mg/kg twice a month.

Table 1. Demographic and clinical characteristics of the 15 study patients with adult-onset Still's disease treated with tocilizumab.

Characteristic	n (%) or Mean ± SD
Men	9 (60)
Age, yrs	33 ± 12
Disease duration, yrs	9 ± 11
Arthralgias	15 (100)
Fever	9 (60)
Rash	7 (46)
Sore throat	3 (20)
Pleuritis	3 (20)
Mean prednisone dosage, mg/d	27.6 ± 26.3
DMARD, n (mean)	3.6 (range 1–7)
Previous treatment with ≥ 1 TNF-α blocker	10 (66)

DMARD: disease-modifying antirheumatic drug; TNF: tumor necrosis factor.

After 6 months of treatment, there was a significant decrease in the number of swollen and tender joints, as well as the ESR and CRP levels and the dosage of prednisone, as detailed in Table 2. This improvement was maintained at the end of the followup period (mean 15.7 ± 9 mos) when only 2 patients complained of mild arthralgias and none reported systemic symptoms. Prednisone had been discontinued in 9 of the 15 patients. One of the patients who had longstanding AOSD and secondary amyloidosis, primarily manifested as proteinuria up to 2 g/24 h, demonstrated significant clinical and laboratory improvement along with complete resolution of the proteinuria after 6 months of treatment with TCZ 8 mg/kg every 2 weeks. Another patient developed the clinical picture of macrophage activation syndrome (MAS) after 11 months of treatment; this patient had demonstrated a good response to TCZ in terms of fever, arthritis, acute-phase response, and prednisone dosage, which was decreased from 60 mg/d to 15 mg/d over a period of 12 months. However, at this stage, the patient presented with high fever, cytopenias, increased transaminases, and prolonged prothrombin time and partial thromboplastin time. A bone marrow aspiration was performed and interpreted as being normal, without signs of hemophagocytosis. The diagnosis of probable MAS was established based on clinical and laboratory findings. That patient responded to an increase in the dosage of prednisone up to 60 mg/d and was subsequently switched to canakinumab with complete resolution of symptoms and normalization of the acute-phase response.

The safety profile of TCZ was good. No infections were reported, and although TCZ has been found to induce liver toxicities, none were reported in this series.

DISCUSSION

This series of 15 Israeli patients with AOSD demonstrates the major therapeutic benefit of TCZ in this entity. All study patients had previously been treated with a wide variety of DMARD: most received TNF-α blockers and were on high-dose prednisone when they started treatment with TCZ. All had a very good response to treatment, with a great majority becoming asymptomatic without prednisone at the end of followup. Our results are consistent with previous reports in other countries. Puéchal, *et al*[7] described the first series of patients with AOSD who were treated with TCZ.

Table 2. Effect of tocilizumab (TCZ) on clinical and laboratory measures of Still's disease activity after 6 months of treatment and at the end of followup. Values are mean ± SD.

	Before TCZ	After 6 Months TCZ	End of Followup
Tender joints, n	11.6 ± 6.8	2 ± 1.8*	1.4 ± 2.1*
Swollen joints, n	8.6 ± 5.4	1.09 ± 1.6*	0.7 ± 1.5*
Fever, n	9	0*	0*
Prednisone dosage, mg/d	27.6 ± 26.3	4.9 ± 4*	3.8 ± 4.9*
ESR, mm/h	60 ± 28	3.9 ± 1.4*	4.5 ± 1.9*
CRP, mg/dl	11.6 ± 15	0.5 ± 0.1*	0.5 ± 0.5*

* Statistically significant, $p < 0.05$. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Those authors reported a good European League Against Rheumatology (EULAR) response in 64% of 14 patients at 3 months and the achievement of EULAR remission in 57% of those patients after 6 months. Systemic symptoms resolved in 86% of their patients, and the corticosteroid dosage was reduced by 56%. A recent review[10] summarized the 35 cases of AOSD treated by TCZ that have been published in the English literature to date. Most of the cases reported demonstrated a good response to the drug, with a decrease in the number of involved painful and tender joints and in the prednisone dosage.

These results are in line with randomized controlled clinical trials on the effect of TCZ in systemic JIA. These latter showed improvement in more than 85% of patients in the American College of Rheumatology core set of JIA[5,6].

One of our patients developed MAS while treated with TCZ. Shimizu, *et al* reported the clinical courses of 5 cases of MAS during TCZ treatment for JIA. Their patients' clinical symptoms, as well as serum levels of CRP, were relatively mild in comparison to the expected levels in MAS, suggesting a masking of the syndrome by TCZ[11]. Others have similarly suggested that patients with JIA and a history of MAS may be prone to develop a recurrence[12]. It is not clear whether TCZ itself can induce MAS or whether it is not sufficiently efficacious to prevent this disorder. The occurrence of this syndrome in our series mandates vigilance before widespread adaptation of this treatment modality. This case also raises the question of the optimal treatment for MAS. IL-1 blockade has been shown to successfully treat MAS[13] and it might be more appropriate in such cases. Further, IL-1 blockade seems to be an excellent treatment for AOSD, and the question of which modality should be used, i.e., IL-6 or IL-1 blockade, requires further investigation.

One of our patients had amyloidosis secondary to longstanding Still's disease. Under treatment with TCZ, there was normalization of the acute-phase response, which was accompanied by a resolution of the proteinuria, suggesting a regression of the amyloidosis. Successful treatment of amyloidosis with TCZ has been described in the case of another patient with Still's disease and amyloidosis, with associated hepatitis B, with a dramatic resolution of the symptoms and signs of amyloidosis[14]. Likewise, Okuda, *et al*[15] compared the clinical utility of TCZ and TNF-α blockers in cases of amyloidosis secondary to rheumatic diseases and demonstrated a 90% 5-year retention rate of TCZ and a dramatic decrease in serum amyloid A, suggesting that TCZ may be superior to TNF-α blockers in the treatment of amyloidosis.

Our study has several limitations including the relatively small sample of patients and the retrospective design. Our series is, however, the largest reported to date (15 patients compared to 14 patients reported by Puéchal, *et al*[7]), and its findings provide strong support to previous reports on the efficacy of TCZ in the treatment of AOSD.

Corticosteroids have long been the first-line treatment for AOSD. Steroid-sparing treatments, such as methotrexate and TNF-α blockers, have been used with limited success in patients with inadequate response or with a relapsing course[16]. The results of our current series along with those of previous reports suggest that TCZ seems to be a good option in the treatment of patients with refractory AOSD. Further studies are needed to establish whether a change in the treatment algorithm of AOSD including TCZ and IL-1 blockade at earlier stages of treatment is needed.

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