Off-label use of tocilizumab in psoriatic arthritis: case series and review of the literature

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ABSTRACT

Objective: To evaluate the efficacy of tocilizumab (TCZ) on three patients with psoriatic arthritis (PsA) and review the literature for other cases of PsA treated with TCZ.

Clinical Cases: The first patient started TCZ treatment after the failure of adalimumab (ADA), and etanercept (ETA) (Disease Activity Score, DAS28: 6.66). After 12 months, her DAS28 decreased to 3.26, and at present (24 months), she has achieved disease remission. The second patient started TCZ treatment after the failure of ADA. After 12 months, the DAS28 decreased from 4.90 to 3.99. After 48 months of treatment, the patient had a DAS28 of 3.76. The third case was treated with TCZ after the failure of both infliximab and rituximab therapy. After 12 months, the DAS28 dropped from 8.65 to 5.49. At present, after 37 months of treatment, the patient has a DAS28 of 4.67. In the literature, there are six cases of PsA, which have been treated with TCZ: in two of the cases, the patient showed a great improvement. Two cases failed to achieve disease remission, despite a moderate response to the treatment, and the other two cases showed no improvement.

Conclusion: It can be concluded that TCZ cannot be generally recommended as an alternative treatment for PsA with predominant peripheral involvement.

Keywords: Psoriatic arthritis; Tocilizumab; IL-6

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory joint disease associated with psoriasis. It is classified along with seronegative spondyloarthritis (SpA), and can be divided into 5 classic subtypes: symmetric polyarthritis, asymmetric oligo- or monoarthritis, distal interphalangeal joint arthritis, predominant axial disease, and arthritis mutilans.

PsA etiology remains a matter of intense research; however, the serum levels of interleukin-6 (IL-6) are significantly increased in these patients[1], and the serum IL-6 levels correlate with disease severity[2]. Other studies also show that transgenic mice with overexpression of IL-6, exhibit a phenotype of psoriasis[3]. This data suggests a potential pathogenic role for IL-6 in PsA[4].

Tocilizumab (TCZ), an antibody against the IL-6 receptor, is an established effective treatment for rheumatoid arthritis (RA)[5]. However, its efficacy on axial spondylarthritis (SpA) has been disappointing[6].

We report the medical cases of three patients with severe PsA with symmetric polyarthritis, treated with TCZ after an inadequate response to at least one anti-tumor necrosis factor (TNF).

CASE 1

A 37-year-old woman presented with a 16-year history of PsA, with exclusive peripheral joint involvement [hands; including metacarpophalangeal (MCP), proximal interphalangeal (PIP), and distal interphalangeal (DIP); wrists; shoulders; and knees]. There was no history of axial or extra-articular involvement. The patient was sequentially treated with sulfasalazine (SLZ) (3 g/day), methotrexate P.O. (MTX) (25 mg/week), and leflunomide (20 mg/day), all of which proved ineffective at improving arthritis and skin lesions. With a DAS28 of 6.99, the patient started adalimumab (ADA) 40 mg, every other week, on monotherapy. Despite an early improvement (Figure 1), after 12 months of treatment the skin lesions resolved but the patient retained several tender and swollen joints. At this point, the interval of ADA administration was shortened to once a week. Despite a failure to induce remission, the patient insisted in continuing ADA treatment, because she felt subjectively bet-

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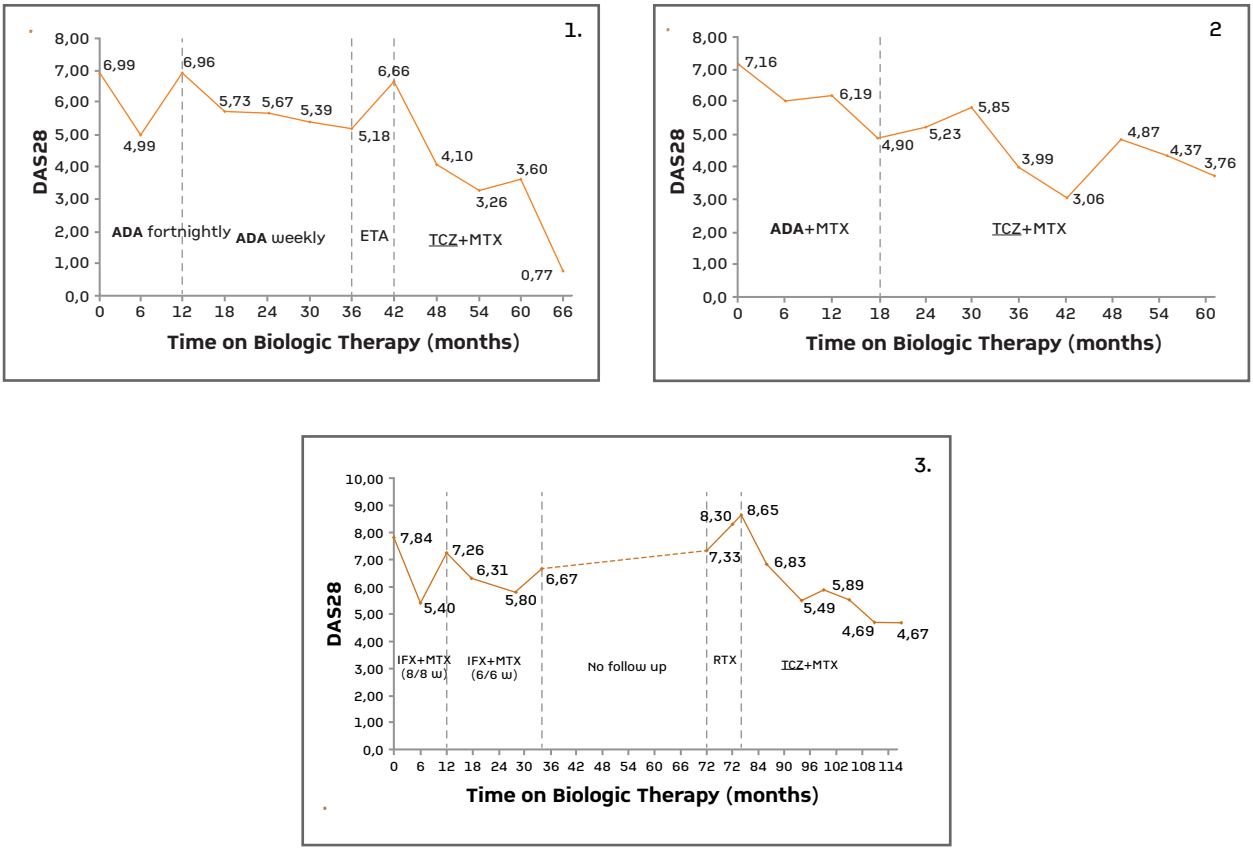

FIGURE 1, 2, 3. DAS28 variation since the first biologic treatment.

ter. After 30 months of treatment, the patient started etanercept (ETA) therapy, which also proved ineffective at improving articular disease activity after 6 months of treatment (DAS28: 6.66; Tender Joint Count (TJC): 13; Swollen Joint Count (SJC): 5).

After ETA failure, the patient started TCZ (8 mg/kg every 4 weeks), and MTX p.o. After 12 months of treatment, she achieved a DAS28 of 3.26 (TJC: 5; SJC: 2); C-reactive protein (CRP) decreased from 46.1 to 0.7 mg/L, and the erythrocyte sedimentation rate (ESR) from 42 to 3 mm. The Psoriasis Area and Severity Index (PASI), was 0 at 12 months. At present, after 24 months of treatment with TCZ combined with MTX p.o. (25 mg/week) and additional treatment with prednisolone at 5 mg/day, the patient's symptoms significantly improved, and disease remission was achieved (DAS28: 0.77; TJC: 0; SJC: 0) (Figure 1).

CASE 2

A 45-years-old woman presented with an 8-year history of PsA, with exclusive peripheral joint involvement. After being treated with cyclosporine for the skin disease, MTX subcutaneous (sc) (20 mg/week) treatment was started for the arthritis; however, the articular disease activity did not improve significantly (DAS28: 7.16).

ADA (40 mg every other week) was added to MTX *sc* (20 mg/week), and 18 months later, despite a significant improvement, the patient retained evidence of moderate disease activity (DAS28: 4.90; TJC: 5; SJC: 3). Treatment with TCZ (8 mg/kg every 4 weeks) combined with MTX *sc* (20 mg/week) was started, and after 12 months of treatment, the DAS28 decreased to 3.99 (TJC: 8; SJC: 7). At 12 months, the CRP decreased from 19.2 to 3.5 mg/L and the ESR from 44 to 21 mm with a PASI of 12.2. Currently, after 48 months of treatment, the patient maintains a moderate disease activity (DAS28: 3.76; TJC: 4; SJC: 3) but with substantial improvement of the joint pain and the functional disability (HAQ reduced from 1.75 to 0.63) as compared to the baseline values (Figure 2). During the treatment with TCZ, the patient was also taking 5 mg/day of prednisolone.

CASE 3

A 70-year-old woman presented with a 39-year history of PsA. The patient was initially treated with MTX p.o. (20 mg/week), to which was added SLZ (3g/day), without any significant clinical improvement. In 2004, treatment was started with infliximab (IFX) (3 mg/kg, every 8 weeks) combined with MTX p.o. (20 mg/week) due to the activity of the disease (baseline DAS28: 7.84). The IFX administration was shortened to 6 weeks, but the patient maintained a high disease activity (DAS28: 7.26). It should be noted that the patient frequently missed the scheduled treatments and medical appointments, and therefore, was never considered a candidate for a subcutaneous anti-TNF agent. The patient abandoned our clinic for five years, until being referred once again by her general practitioner (GP). At this stage, she had high disease activity and was now bedridden and rendered incapable of performing her daily tasks (HAQ: 3). It was decided to commence off-label rituximab (RTX) combined with SLZ (DAS28: 7.33), but 6 months later, due to no improvement, treatment was switched to TCZ (DAS28: 8.65; TJC: 28; SJC: 15) on monotherapy. After 12 months, the DAS28 decreased to 5.49 (TJC: 17; SJC: 1). At 12 months, the CRP decreased from 33.6 to 0.9 mg/L, and the ESR from 97 to 12 mm, with the PASI at 0.

At present, the patient has been treated with TCZ for 37 months, and despite maintaining a DAS28 score compatible with moderate disease activity (DAS28: 4.67; TJC: 19; SJC: 5), has experienced a significant clinical improvement. She now has a greatly improved functional status being able to walk with crutches and is able to perform basic daily activities autonomously (despite this subjective improvement, HAQ only decreased to 2.88) (Figure 3). The patient was unable to decrease the dose of prednisolone below 10 mg/day, which was additionally taken during treatment with TCZ.

DISCUSSION

The authors have presented three case reports that highlight the potential efficacy of off-label use of TCZ in the treatment of PsA. All the cases had a personal history of psoriasis, and exclusive peripheral joint involvement by PsA. None of the patients had other signs of SpA (namely axial involvement, enthesitis, or dactylitis). All patients tested negative for both rheumatoid factor and Anti-citrullinated protein antibody (ACPA) antibodies.

In all of the cases in this study, informed consent and authorization from the ethics committee to the off-label treatment was obtained. Our results show that there was an improvement of the articular disease activity, inflammatory markers, and functional disability, without deterioration of the cutaneous disease with TCZ treatment. All patients showed a significant reduction of DAS28 after one year, and the disease activity kept improving after that period, with the exception of one patient (Case 2) that maintained a similar disease activity, after the initial improvement. Despite failure to induce remission in two of our patients, we observed a clinical improvement in the three treated with TCZ. No adverse effects were identified in all the cases studied.

Although DAS28 have not been validated in PsA, the authors decided to use this score to assess disease activity, because it is largely used in the literature to determine both disease activity and treatment response in PsA patients, and in particular, to assess peripheral joint involvement[7-9]. Nevertheless, the authors recognize there are some limitations of this score in assessing disease activity in patients treated with TCZ, because the drug inhibits the formation of inflammation markers that are used in DAS28 calculation. This limitation can be observed in Case 2, in which the improvement in DAS28 is mainly due to the reduction of inflammation markers, because the joint count was practically unchanged. The use of other response criteria, such as ACR Response Criteria, was not possible due to lack of baseline information. A Medline search for the terms "psoriatic arthritis" and "tocilizumab" was performed, and six case reports of patients with PsA treated with TCZ were found, with conflicting results (Table I)[2,10-12]. In our literature review, we were unable to find any reported adverse effects of TCZ in patients with PsA. Hughes reported the case of a patient with peripheral PsA refractory to several DMARDs, including ETA and RXT, who was treated with TCZ (8 mg/kg every 4 weeks) combined with MTX (15 mg/week). After 4 infusions, the patient had an excellent response with no tender or swollen joints, and a significant reduction of inflammatory biomarkers[10]. Ogata *et al*., reported two cases of peripheral PsA refractory to several DMARDs[2]. In the first case, the patient was unresponsive to IFX, and started TCZ (8 mg/kg) every 4 weeks, which was later reduced to every 2 weeks without achieving disease remission, despite a significant reduction of the inflammatory markers. The patient was then treated with ADA, which was effective in controlling the disease activity. In the second case reported, the patient

TABLE I. MOST RELEVANT INFORMATION FROM THE IDENTIFIED CASES IN THE LITERATURE REVIEW

Ref.	Nº	Age	Disease duration (years)	Previous biologics	TCZ dose	Treatment duration	Initial DAS28	Final DAS28	Initial CRP (mg/L)	Final CRP (mg/L)	Initial TJC/STC	Final TJC/STC
Ogata, et al. 2012 (2)	1	41	4	Yes (IFX)	8 mg/kg	7 months (monthly infusion); 4 months (every 2 week infusion)	6.44	4.85	72.0	0	NA	NA
	2	47	6	Yes (Ustekinumab)	8 mg/kg	9 months	5.33	3.48	50.8	0	NA	NA
Lepka, et al. 2012 (9)	3	NA	10	Yes (Anti-TNF, not specified)	8 mg/kg	3 months	5.23	5.1	40	50	7/4	6/3
	4	NA	20	Yes (Anti-TNF, not specified)	8 mg/kg	3 months	4.92	4.70	10	10	12/7	11/6
Hughes, et al. 2013 (7)	5	57	8	Yes (ETA and RTX)	8 mg/kg	15 months	5.86	1.89	1.2	0.5	9/8	0/0
Costa, et al. 2014 (8)	6	43	6	Yes (ETA, ADA and IFX)	8 mg/kg	11 months	6.00	NA (TJC 2; SJC 0)	15.4	NA	15/4	2/0
Madureira et al.	7	37	16	Yes (ADA and ETA)	8 mg/kg	24 months	6.66	0.77	46.1	0.5	13/5	0/0
	8	45	7	Yes (ADA)	8 mg/kg	48 months	4.90	3.76	19.2	23.5	5/3	4/3
	9	70	39	Yes (IFX and RTX)	8 mg/kg	37 months	8.65	4.67	33.6	0.2	28/15	19/5

CRP: C Reactive Protein; ADA: Adalimumab; ETA: Etanercept; IFX: Infliximab; RTX: Rituximab; SJC: swollen joint count; TCZ: Tocilizumab; TJC: tender joint count

was also refractory to several DMARDs, and was then started on ADA. Despite the complete resolution of the psoriasis, ADA was unable to control the articular disease; further treatment with ustekinumab (UST) was also ineffective, with only a transitory response. One year later, treatment was switched to TCZ (8 mg/kg every 4 weeks), which also failed to achieve disease remission, despite a moderate response to the treatment. Costa *et al.*, reported a case of a female patient suffering with axial and peripheral PsA for 6 years. The patient was initially treated with MTX, which was suspended due to hepatic toxicity. Further sequential treatment with ETA (6 months), ADA (10 months), and IFX (6 months), were all ineffective in controlling disease activity. Before treatment with TCZ, her DAS28 was 6.00, and after 11 months no significant improvement was reported (insufficient data to calculate DAS28; TJC was 4, STJ was 0, and the patient VAS was 20 mm). Lekpa *et al.*, reported on retrospective data from 21 patients with axial (n = 13) or peripheral (n = 8) SpA treated with TCZ, collected through a questionnaire supplied to French rheumatologists or internal-medicine doctors. Two of these patients had peripheral PsA, and were treated for at least 3 months with TCZ, without efficacy, although both patients had a slight decrease in DAS28, the acute phase reactants remained very high (Table I)[12].

All nine cases describe severe forms of peripheral PsA, with previous failure of several synthetic and biological DMARDs, which could explain why TCZ failed to induce disease remission in most of these patients. Despite some degree of improvement in most of the patients, only two of the patients were able to achieve disease remission, and most of the cases maintained moderate or high disease activity after treatment with TCZ.

Despite the important role that IL-6 plays on RA and PsA, its blockade by TCZ appears not to have the same effect on both diseases. Ogata *et al.*, describe an interesting approach to this variance, concluding that it may be due to different roles played by IL-6 in RA and in PsA[4]. They state that in RA, IL-6 seems to have a pathogenic effect mainly on the priming phase of synovitis, by stimulating the differentiation of Th17 cells from naïve CD4+ T cells, and the activation of B and Th1 cells. In PsA it appears that IL-23 is mainly responsible for the differentiation of Th17 cells, which activate CD8+ cytotoxic cells and macrophages that are fundamental in synovitis development. The synovial membrane itself produces TNF that contributes to the effector phase of arthritis in both RA and PsA[4]. These different mechanisms may explain why TCZ is not as effective in treating PsA, compared to RA, and also why both diseases respond well to anti-TNF agents.

There is still a lack of effective treatment for PsA after the failure of synthetic DMARDs and anti-TNF drug therapy. Based on the data in our study, TCZ cannot be recommended as an alternative treatment for PsA with predominant peripheral involvement. Nevertheless, further studies are necessary to validate these observations.

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