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CASE BASED REVIEW

Tocilizumab-induced psoriasis-like eruption resolved by shortening the dose interval in a patient with rheumatoid arthritis: a case-based review

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Abstract
Tocilizumab (TCZ) is a humanized antihuman interleukin-6 (IL-6) receptor antibody used for the treatment of inflammatory diseases such as rheumatoid arthritis (RA). While TCZ could act as a therapeutic agent, it has a potential for inducing adverse drug events including psoriasis-like eruption. Seven cases with specific reference to TCZ-induced psoriasis eruption have been reported worldwide so far. In these cases, treatments with the same dosage of TCZ were either maintained or discontinued. Herein, we report a case involving a 74-year-old man diagnosed with rheumatoid factor-positive and anti-citrullinated protein antibody-positive RA with comorbidity of atopic dermatitis. TCZ was administered intravenously with oral methotrexate. After the third infusion, the patient developed TCZ-induced psoriasis-like eruptions, which were resolved by shortening the dose interval. Eruption recurrence was not observed after frequent TCZ subcutaneous injection. Our case may help physicians manage TCZ-induced psoriasis-like eruption.

Keywords Rheumatoid arthritis · Tocilizumab · Psoriasis · Interleukin-6 receptors · Adverse drug reaction · Atopic dermatitis

Introduction

Tocilizumab (TCZ) has been approved by the Japanese health insurance system for the treatment of rheumatoid arthritis (RA), Castleman's disease, juvenile idiopathic arthritis, Takayasu's arteritis, and giant-cell arteritis. In addition, some case reports have shown that TCZ was effective in the treatment of psoriatic lesion [1, 2].

Tocilizumab could act as a therapeutic agent; it has a potential for inducing adverse drug events including psoriasis-like eruption. A wide spectrum of adverse events is reported in the course of TCZ therapy. TCZ-induced psoriasis-like eruption was reported as an adverse event in 2 of 9792 patients (0.02%) according to a post-marketing surveillance [3]. Here, we discuss a case in which shortening the dose interval made the eruption disappear and no recurrence was reported.

Case report

A 74-year-old man had been diagnosed with rheumatoid factor (RF)-positive and anti-citrullinated protein antibody (ACPA)-positive RA 2 years ago. At the time of RA diagnosis, he complained of constant swelling and pain in his hands, wrists, elbows, and knees for about 2 years. Serum levels of RF (normal value < 15 IU/mL) and ACPA (normal value < 4.5 U/mL) were 293.1 IU/mL and 429 U/mL, respectively; C-reactive protein levels (normal value < 0.14 mg/dL) were 10.8 mg/dL. Clinical Disease Activity Index score was 56.9. Erosions were seen in some proximal interphalangeal joints and the wrists on radiographs. He reported his pain as 7.6/10 (0 = no pain; 10 = greatest pain ever) using a visual analog scale. He had been using loxoprofen sodium hydrate gel and celecoxib 400 mg/day. The patient did not respond

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well to the pain relief medications. At the first visit, he was 1.77 m tall, and weighed 61 kg. His past medical history included atopic dermatitis (AD) and pulmonary emphysema. His pulmonary function tests presented vital capacity (VC) of 4.26 L (percentage predicted VC(%VC), 121.7%), a forced vital capacity (FVC) of 4.22 L, forced expiratory volume in 1 s (FEV_1) of 2.83 L (percentage predicted FEV_1(%FEV_1), 67.06%), a FEV1/FVC ratio of 0.67, total lung capacity of 2.52 L, and a residual volume of 2.21 L. Chest computed tomography showed traction bronchiectasis and honeycombing in the lower lobes. He had no history of psoriasis or tuberculosis. There were no lesions in his sacroiliac joints, distal interphalangeal joints, or nails. He had smoked 30 cigarettes a day for 50 years and rarely drank alcoholic beverage.

In February 2016, treatment for RA began with the administration of 12 mg/w of oral methotrexate (MTX), together with 15 mg/d of oral prednisolone (PSL). In May 2016, additional intravenous administration of abatacept (ABT), 750 mg every 4 weeks, was initiated because of worsening polyarthritis. In September 2017, ABT treatment was discontinued because of the secondary failure; instead, TCZ 8 mg/kg every 4 weeks was started intravenously with 12 mg/w of oral MTX. At this timing, he weighed 57 kg. After the third infusion, in mid-November 2017, the patient developed itchy red patches covered with white scales on both legs when polyarthralgia had worsened. At this point, no malignant findings were observed in the whole-body positron-emission tomography–computed tomography, but an exacerbation of interstitial pneumonia was noted. On December 12, 2017, we switched the route of administration to TCZ subcutaneous injection of 162 mg every 2 weeks. From December 26, 2017, we shortened the dosing interval to once every week with the aim of not only controlling RA inflammation but resolving psoriasis-like eruption which had appeared as a side effect. The reason for switching intravenous drip infusion (IV) to subcutaneous injection is that higher doses of TCZ can be administered by subcutaneous injection than by intravenous injection according to the approved dosage and administration of TCZ in Japan. Specifically, while we can only administer TCZ up to 8 mg/kg intravenously, we can administer 162 mg/body/2 weeks; in addition, the dosing interval of subcutaneous injection can be shortened to a minimum of 1 week when sufficient response is not obtained. In our case, considering his body weight, we could only administer 456 mg/4 weeks by IV, but 648 mg/4 weeks in total by 1-week-interval subcutaneous injection. On the same day, the eruption was diagnosed as psoriasis-like eruption by a skilled dermatologist (Fig. 1), and topical corticosteroid was prescribed. By December 29, 2017, the patient noticed that the eruption started to turn to pigmentation. He stopped applying the topical corticosteroid 2 weeks after the prescription. On February 21, 2018, MTX was discontinued because of worsening interstitial pneumonia and clinical remission of RA. TCZ and PSL have been maintained at the same dose without any eruption relapse or RA flare-up. The clinical course is shown in Fig. 2. Written informed consent was obtained from the patient for publication of the report.

Discussion

IL-6 is the main cytokine involved in the induction of acute phase response. It forms a complex with membrane-expressed IL-6 receptor (mIL-6R) and synthesizes C-reactive protein in the liver. Therefore, it has been suggested that IL-6 is a marker of activity of the original disease [4]. It has been known that IL-6 has a variety of effects, and its excessive or sustained production is involved in the onset and development of various inflammatory diseases. TCZ is a competitive inhibitor that prevents IL-6 from interacting with both mIL-6R and soluble IL-6 receptor (sIL-6R).

Several reports have shown that TCZ has a therapeutic effect on psoriasis [1, 2, 5, 6]. TCZ treatments for psoriatic skin lesion are reported in two cases [1, 2]. By shortening the TCZ dose interval, we tried not only to control RA inflammation but to resolve psoriasis-like eruption which had appeared as a side effect. To the best of our knowledge,

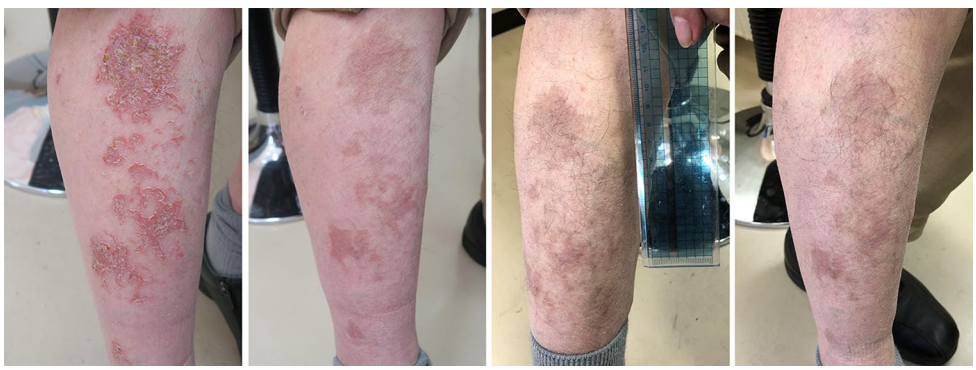

Fig. 1 Clinical photographs of the patient's right lower leg before and after TCZ therapy (2017/12/26, 2018/1/23, 2018/2/20, 2018/3/20 from the left)

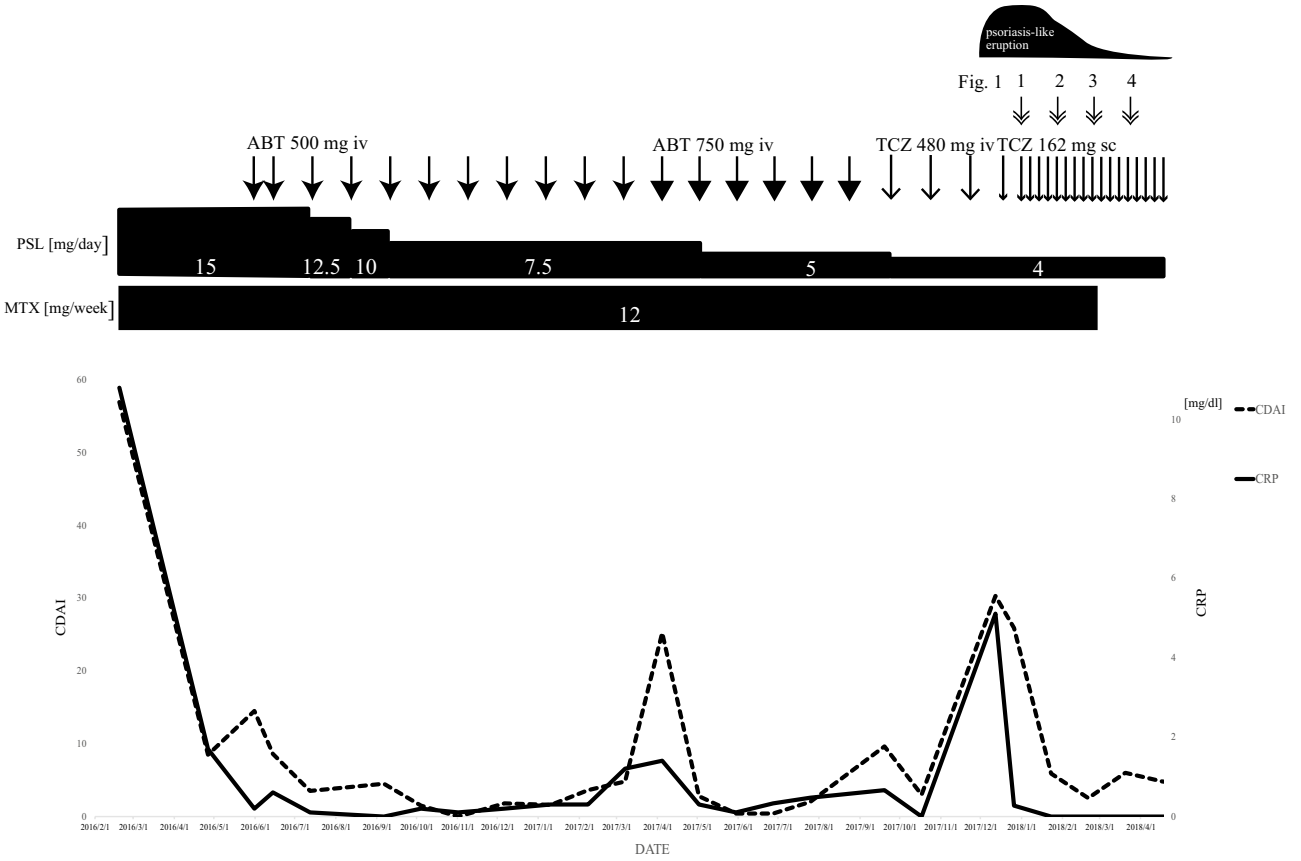

Fig. 2 Clinical course of the presented case

this treatment plan for TCZ-induced psoriasis-like eruption is the first of such attempt made worldwide.

A literature search in the databases of PubMed and ICHUSHI (Japanese medical database) was conducted. The search strategy was built using the combination of the following two search terms: "psoriasis" and "tocilizumab". Inclusion criterion for relevant articles was diagnosis of "psoriasis-like eruption" which newly appeared or worsened in patients treated with TCZ. The process of systematic literature review was presented by flow diagram (Fig. 3). Exclusion criteria were as follows: not case reports; not treated with TCZ.

A literature search has revealed seven cases of psoriatic lesion induced by TCZ. While TCZ was discontinued in four cases, TCZ was continued with the same dose after the eruption developed in the other three cases. Details are given in Table 1 [7–12]. Age, sex, and underlying diseases varied. It took 10 days at the shortest and 84 weeks at the longest, from the administration of TCZ to the appearance of eruption. Psoriasis-like eruptions were observed even when underlying diseases were active or not active.

In our case, no pathologic examination was done for skin eruption because we could not obtain permission from the patient, and it was diagnosed as psoriasis-like eruption based on the clinical findings by a skilled dermatologist. The skin eruption was diagnosed not as psoriatic arthritis because it did not satisfy the CASPAR criteria [13]. The development of psoriasis-like eruption and RA exacerbation occurred simultaneously in our case. However, there is no definite consensus on the relationship between the TCZ-induced eruption and RA activity based on the literature search, as with the fact that the skin symptom and severity of arthritis do not correlate in parallel in patients with psoriatic arthritis [14]. Accumulation of further cases is required to investigate the detail.

Some case reports have indicated that TCZ increased circulating blood IL-6 levels, but others did not show the increase [15, 16]. Moreover, there have been several reports that sIL-6R levels increased as an effect of TCZ [15, 16]. In our case, intravenous TCZ 8 mg/kg may have been unable to block the IL-6-IL-6R pathway sufficiently because the dosage was not sufficient for elevated sIL-6R. Skin irritation may have appeared because of external irritation typified by internal stimulation such as cytokine disturbance. The failure of IL-6 to bind topically to mIL-6R might be explained by the observation that shedding of mIL-6R from the cellular

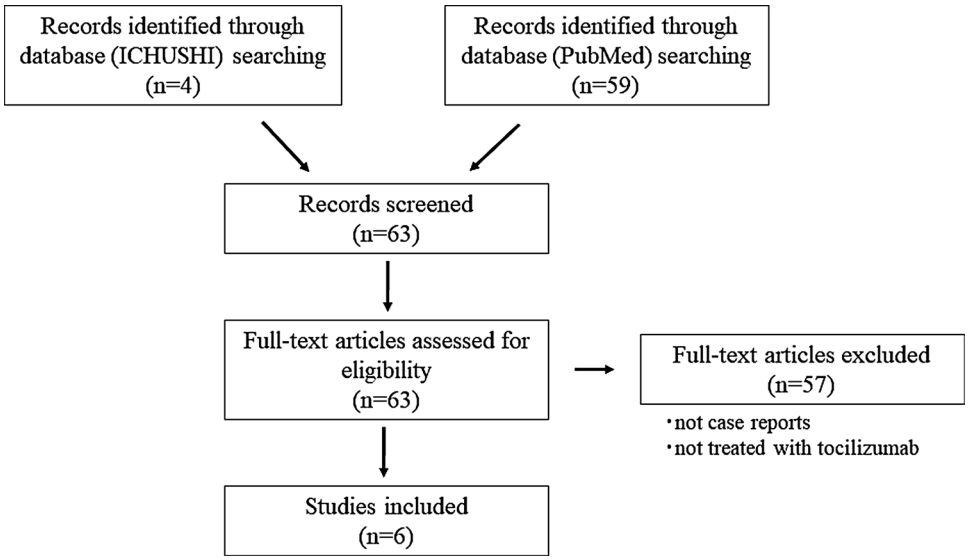

Fig. 3 Flow diagram for systematic literature review on psoriasis-like eruption after treatment with TCZ

surface has been identified as a major source of sIL-6R [17, 18]. In future studies, investigation of receptor expression in the cellular membrane in patients using TCZ may be of help in considering this hypothesis concerning sIL-6R levels.

In addition, the elevation of IL-6 promotes the differentiation of $CD4^+$ T cells into Th17 cells [19]. Th17 cells are known to produce IL-17A, IL-17F, IL-22 [20]. These ILs are exacerbating factors for psoriasis [21]. In other words, the elevation of IL-6 leads to the differentiation of naive T cells to Th-17, and as a result, may possibly enhance the production of IL-17A, IL-17F, and IL-22, which exacerbates psoriasis.

For a more specific discussion, the patient has underlying disease of AD. It is known that AD patients showed elevated IL-22 both in peripheral blood and in active skin lesions [22]. Especially in AD patients with high circulating IL-22 levels, by activation of IL-6 pathway, further production of IL-22 may promote keratinocyte proliferation and epidermal hyperplasia. This possible mechanism may be conducive to the appearance of TCZ-induced psoriasis-like eruption because a part of the keratinization mechanism of the epidermis is common to psoriasis and AD. It may be necessary to carefully observe the skin in AD patients under treatment with TCZ like our case, although every hypothesis remains a matter of speculation because we could not measure the levels of molecules (e.g. sIL-6R, IL-6, IL-17 and IL-22) or perform skin biopsy.

We achieved the resolution of psoriasis-like eruption in the patient when the TCZ dose interval was shortened and a 2-week steroid topical therapy was undertaken on the discretion of a dermatologist. In the opinion of a well-experienced dermatologist, it was rare to observe psoriasis improvement in a few days simply with steroid topical application. Although the eruption was thought to be side effect of TCZ, 1-week-interval subcutaneous TCZ injection was maintained in our patient without any eruption relapse without using topical steroid. Based on the above-mentioned hypothesis, it can be inferred that the eruption improved as the TCZ concentration became sufficient for neutralizing the elevated sIL-6R by increasing the total dose.

The appearance of psoriatic eruption has been reported in connection with various biological drugs, particularly anti-tumor necrosis factor-α inhibitors, but the cause has not been elucidated. The appearance or disappearance of eruption by the administration of TCZ suggests that there may be a relationship between IL-6 and the onset of psoriasis. Previous studies have reported that the plasma concentration of sIL-6R before treatment with TCZ was related to activity of RA after the start of the TCZ treatment. In the TCZ treatment, the lower the plasma concentration of sIL-6R was at the start of treatment, the higher the remission rate of RA was. In other words, it can be said that the therapeutic effect of TCZ depends on the plasma concentration of sIL-6R [23]. There is a possibility that the suggested hypothesis can be verified by monitoring the blood concentration of TCZ and sIL-6R in patients with psoriasis-like eruption.

When TCZ will be increasingly used worldwide because of expanding indications, psoriatic eruption as an adverse event may occur more frequently. In such cases, shortening the TCZ dose interval may have ameliorating effects on TCZ-induced psoriasis-like eruption instead of stopping it as the present case showed. Our case may help physicians manage TCZ-induced psoriasis-like eruption.

Table 1 Literature summary of TCZ-induced psoriasis-like eruption

	Author	Publication year	Age/sex	History of psoriasis	Initial diagnosis	TCZ dosage	Combination therapy	Activity of the underlying disease	From TCZ initiation to eruption development	Continued or stopped TCZ	Therapy for the eruption
1	Laurent et al.	2010	37/W	+	ASD	8 mg/kg/4 weeks	PSL 30 mg/day	First therapy: N/D Second therapy: inactive	First therapy: 10 days Second therapy: 1 week	First therapy: stopped Second therapy: continued	Steroid topical therapy
2	Laurent et al.	2010	52/W	+	PsA	8 mg/kg/4 weeks	None	Active	15 days	Stopped	N/D
3	Wendling et al.	2012	57/W	−	RA	8 mg/kg/4 weeks	PSL 5 mg/day	Active	9 weeks	Continued	N/D
4	Suzuki et al.	2012	41/M	−	CD	7.3 mg/kg/2 weeks	PSL 5 mg/day	Inactive	12 weeks	Continued	Steroid topical therapy
5	Grasland et al.	2013	41/W	−	RA	8 mg/kg/4 weeks	None	Inactive	84 weeks, 96 weeks	Continued	Steroid topical therapy
6	Palmou-Fontana et al.	2013	79/W	−	RA	8 mg/kg duration was not described	PSL 10 mg/day	Inactive	21 weeks	Stopped	Steroid topical therapy
7	Sparsa et al.	2014	47/W	−	PsA	8 mg/kg/4weeks	None	Active	6 weeks	Stopped	Abatacept
8	Hayakawa et al.	2018	76/M	−	RA	8 mg/kg/4 weeks	PSL 4 mg/day + MTX 12 mg/w	Active	9 weeks	Continued	Shortening TCZ dosing interval

ASD adult Still's disease, *CD* Castleman's disease, *N/D* no data, *PsA* psoriatic arthritis, *PSL* prednisolone, *RA* rheumatoid arthritis, *TCZ* tocilizumab

Authors' contributions MH designed the study, and wrote the initial draft of the manuscript. KI contributed to the design of the study, the collection and interpretation of data, and the assistance of the preparation of the manuscript. All other authors contributed to the data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from the patient described in the case report. The patient has also agreed on publishing the pictures included in this manuscript.

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