



Tocilizumab-induced anaphylaxis in patients with adult-onset Still's disease and systemic juvenile idiopathic arthritis: a case-based review

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Abstract

The benefits afforded by tocilizumab (TCZ) in patients with adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA) have been described in previous studies. However, few reports have evaluated severe hypersensitivity reactions (HSRs) to TCZ in patients with AOSD or SJIA. We describe three instances of TCZ-induced anaphylactic reactions in AOSD/SJIA patients, and review relevant prior reports on patients with various rheumatic diseases. Two of our cases exhibited shock and cardiovascular collapse; TCZ was discontinued in all three cases. All events occurred within 20 min of TCZ infusion, after at least three prior infusions, indicating an IgE-mediated mechanism and previous sensitization to TCZ. In all three cases, mild HSRs had been observed about 1 month before the anaphylactic events, but pre-medication with antihistamines and corticosteroids failed to prevent anaphylaxis. All three cases had active AOSD or SJIA disease, and were refractory to other immunosuppressive agents. It is essential to be aware that severe anaphylaxis to TCZ can develop in patients with active refractory AOSD or SJIA, and to be cautious when medicating certain patients. Anaphylaxis is a serious condition that can be fatal; TCZ infusion should not be re-challenged via pre-medication in patients who exhibited mild HSRs before TCZ without desensitization.

Keywords Still's disease · Adult onset · Juvenile onset · Tocilizumab · Hypersensitivity · Anaphylaxis

Introduction

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disease of unknown etiology, characterized by a high spiking fever, evanescent maculopapular skin rash, arthritis, sore throat and neutrophilic leukocytosis [1]. Although initial acute manifestations are similar in patients with AOSD, the clinical course of AOSD may differ in three patterns: monocyclic, polycyclic, and chronic articular pattern [2]. AOSD is also known as an adult form of systemic juvenile idiopathic arthritis (SJIA). JIA is one of the most common chronic diseases of childhood, and characterized by persistent joints inflammation lasting longer than 6 weeks developing in younger patients [3]. There are six JIA subtypes: systemic, oligoarticular, polyarticular JIA, enthesitis-related JIA, juvenile psoriatic arthritis, and undifferentiated arthritis. SJIA and AOSD share common clinical features and the overexpression of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and IL-18 [4]. Recently, the potential efficacy of biologic agents in blocking proinflammatory cytokines, such as anti-IL-1, anti-IL-6, and anti-IL-18 agents, has been reported in AOSD and SJIA [5].

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Tocilizumab (TCZ), a recombinant humanized anti-human IL-6 receptor of the immunoglobulin G1 subclass monoclonal antibody that binds to circulating soluble and membrane-expressed IL-6R, is the first drug to block the IL-6 signal successfully [6]. It consists of light chain with 214 amino acids and heavy chain with 448 amino acids [3]. The four polypeptide chains are linked inter- and intramolecularly by disulfide bonds. TCZ was first approved by the Food and Drug Administration (FDA) in 2010 for a treatment for rheumatoid arthritis (RA). Since then, TCZ has been approved by FDA and the European Medicines Agency for the treatment of JIA and giant cell arteritis, and is also being used off the label for the treatment of several inflammatory diseases, such as lupus arthritis and Takayasu's arteritis [7]. TCZ is also effective for the treatment of severe or refractory AOSD and SJIA, alleviating inflammation and sparing corticosteroid use [8–10]. TCZ is administered as an intravenous infusion by 4 mg/kg or 8 mg/kg or as a subcutaneous injection with a prefilled syringe by 162 mg every other week, but increased to same dosage every week based on clinical response [7, 11]. The most common adverse reactions to TCZ are infections and gastrointestinal symptoms [12], but immediate and delayed hypersensitivity reactions (HSRs) have also been reported [13, 14].

Anaphylaxis is a serious type 1 hypersensitivity reaction with potentially life-threatening multisystem involvement caused by the sudden release of inflammatory mediators and cytokines from mast cells or basophils after exposure to allergens [15]. Among the mediators, histamine induces mainly vasodilation, increases vascular permeability, causes tachycardia, and decreases blood pressure [16]. Therefore, appropriate diagnosis and prompt treatment is critical. A few cases of anaphylaxis to TCZ have been described, mostly in patients with RA [17, 18]. Intradermal testing of TCZ has been suggested to serve as a simple and sensitive tool for diagnosis of IgE-mediated HSRs [13, 19]. However, there have been very few reports on severe anaphylactic reactions to TCZ in patients with AOSD or SJIA, and almost nothing is known about risk factors for such reactions in these patients. Herein, we describe the clinical characteristics of two cases exhibiting anaphylactic shock and one case evidencing anaphylaxis to TCZ in patients with AOSD or SJIA; we also review earlier relevant reports on patients with rheumatic diseases.

Case presentation

Patient 1

A 71-year-old woman was first diagnosed with AOSD 8 months previously, and her medical history included hypothyroidism. After being diagnosed with AOSD, she

was given steroid pulse therapy (1 g/day for 3 days) and underwent plasma exchange followed by oral prednisolone and cyclosporine (300 mg/day) to control the macrophage activation syndrome (MAS; confirmed by bone marrow biopsy) associated with AOSD. However, she had experienced frequent flares of AOSD causing fever, skin rash, and arthritis. As her AOSD was refractory to high-dose corticosteroids, cyclosporine, and mycophenolate mofetil (1 g/day), monthly infusions of TCZ (400 mg) had been initiated 4 months before presentation. The symptoms and laboratory data had improved, and prednisolone was tapered to 10 mg/day. 1 month before the anaphylactic event, the patient had an allergic reaction to TCZ, including mild skin rash and nausea. The symptoms resolved after the infusion of methylprednisolone and chlorpheniramine. Therefore, she was pre-medicated with an antihistamine and methylprednisolone before the fourth TCZ infusion.

Nevertheless, within 10 min of drug infusion, she complained of pruritus, followed by chest discomfort and nausea. The infusion was stopped but she collapsed when she tried to stand and was immediately referred to the emergency department for resuscitation. She was drowsy, had an urticarial rash over her entire body, and had pruritus, angioedema, nausea, and difficulty breathing. Her blood pressure (BP) had fallen to 76/43, and her pulse rate was 120/min. Her respiratory rate was 25/min, and the oxygen saturation level as revealed by pulse oximetry (SPO₂) was 98% in room air. Arterial blood gas analyses revealed mild respiratory alkalosis without hypoxemia. Laboratory data revealed leukocytosis [white blood cells (WBC) count, 23,360/mm³; 80% neutrophils and 13% lymphocytes], anemia [hemoglobin (Hb), 10.3 g/dL], elevated erythrocyte sedimentation rate (ESR; 85 mm/h), C-reactive protein (CRP; 10.91 mg/dL) and ferritin levels (1514.3 ng/mL), but normal liver function. The tryptase level was not measured. As anaphylaxis was apparent, she was promptly treated with intramuscular epinephrine and IV chlorpheniramine, corticosteroids, and ranitidine. As soon as epinephrine was injected, she regained consciousness. Her BP stabilized without additional vaso-pressors. 1 h later, the dyspnea, angioedema, and skin symptoms all improved. Given the severity of the event, the TCZ was discontinued and the prednisolone was increased to 20 mg/day.

Patient 2

A 28-year-old woman with a 1-year history of AOSD relapsed while on methotrexate (MTX) [subcutaneous (SC), 15 mg biweekly] and corticosteroids. She had received a single dose of TCZ (400 mg; 8 mg/kg) at the time of diagnosis to control severe inflammation associated with AOSD and exhibited a good response to both MTX and corticosteroids. On admission, she complained of fever (39.7 °C), sore

throat, myalgia, arthralgia, nausea, and a salmon-colored macular skin rash involving the face, extremities, and trunk. She lacked any comorbidities and had no history of allergy. The laboratory findings were: WBC count, 12,320/ μ L with a left shift (neutrophils 85.5%); Hb, 14.1 g/dL; platelets, 124,000/ μ L; ESR, 40 mm/h; CRP level, 6.04 mg/dL; aspartate aminotransferase level, 233 IU/L, alanine aminotransferase level, 80 IU/L; and ferritin, 1985 ng/mL. We initiated IV methylprednisolone at 100 mg/day and resumed TCZ infusion (400 mg). After TCZ infusion, she presented with mild itching and back urticaria, which resolved after prescription of an antihistamine. She was discharged after 7 days; she later received her third infusion of the drug at a lower dose (200 mg; 4 mg/kg) after pre-medication with antihistamine and hydrocortisone in the outpatient clinic. Approximately 20 min after the initiation of IV TCZ, she developed pruritic, erythematous, macular skin lesions over her entire body, dyspnea, abdominal pain, chills, fever (38.3 °C), and tachycardia (pulse rate 110/min), but no hypotension, angioedema, or stridor. Anaphylaxis was suspected and she was given an IV corticosteroid and an antihistamine. Volume expansion with isotonic crystalloid solutions was started with supplemental oxygen. Within 4 h, the cutaneous, respiratory, and gastrointestinal symptoms resolved. The TCZ was halted, and the patient was discharged with prescriptions for oral prednisolone (60 mg daily) and MTX (15 mg biweekly).

Patient 3

A 16-year-old girl was first diagnosed with SJIA at the age of 14 years, when she presented with an evanescent skin rash, fever, hepatosplenomegaly, and arthritis. She was refractory to high-dose corticosteroids, IV immunoglobulin, MTX, cyclosporine, and adalimumab; therefore, monthly infusions of TCZ (400 mg) had been initiated 9 months previously. This treatment appeared to be effective, but the patient was lost to follow-up. Three months later, she visited our emergency ward with a large pericardial effusion (LV post, 2.2 cm; RA side, 1.3 cm; RV free wall, 1.4 cm) and pulmonary hypertension associated with SJIA (TR $V_{\max}$, 4.4 m/s; RVSP, 84 mmHg). She received steroid pulse therapy followed by cyclosporine (150 mg/day), and the TCZ was restarted at 400 mg. During the infusion before the anaphylactic event, the patient exhibited an allergic reaction (mild skin rash, nausea, and abdominal pain), which was resolved with IV dexamethasone and chlorpheniramine. Therefore, she was pre-medicated with an antihistamine and dexamethasone before her sixth TCZ infusion; nevertheless, anaphylactic shock developed. Soon after the IV TCZ infusion, she developed pruritus, abdominal pain, and nausea, followed by dyspnea. The infusion was stopped, but she fainted while changing position. She was referred to our emergency ward

in critical condition; she required resuscitation. Her BP fell to 82/54, the pulse rate was 110/min, the respiratory rate 25/min, and the SPO₂ was 90% on room air. The laboratory data were as follows: WBC count, 21,000/mm³ (83.1% neutrophils and 10% lymphocytes); Hb, 10.1 g/dL; ESR, 26 mm/h; CRP, 13.40 mg/dL; and ferritin, 10,997.0 ng/mL. She was immediately given intramuscular epinephrine, IV chlorpheniramine, corticosteroids, and isotonic crystalloid solutions. Immediately after the epinephrine injection, she regained consciousness; her BP stabilized without additional vasopressors. The TCZ was discontinued and the prednisolone was increased to 60 mg/day. Subsequently, she was re-hospitalized to treat SJIA-associated MAS, confirmed by bone marrow biopsy. She is currently receiving monthly infusions of abatacept (400 mg), as well as MTX (15 mg/week) and prednisolone and cyclosporine (150 mg/day).

Search strategy

We searched the PubMed/MEDLINE and Scopus databases using the keywords “tocilizumab” AND “anaphylaxis” OR “hypersensitivity”; no time limit was imposed. Of the 68 retrieved articles published between May 2009 and May 2019, 22 articles reporting on HSRs other than anaphylaxis, such as erythroderma or drug eruption to TCZ, were excluded. We included original articles, letters to the editor, and case reports published in English. The remaining 46 articles were reviewed; 17 of these articles described anaphylaxis after TCZ infusion in patients with various rheumatic diseases. Information related to TCZ treatment, including patient age at the time of anaphylaxis, sex, disease duration before TCZ, TCZ dose and administration route, previous use of immunosuppressive agents, concomitant treatment, and clinical features of the anaphylactic reaction, was collected.

Results

Table 1 summarizes the clinical data and laboratory findings for our three cases. Table 2 summarizes previous reports of anaphylaxis after TCZ infusion in patients with various rheumatic diseases.

Discussion

We report three patients with AOSD or SJIA presenting with anaphylactic reactions after TCZ infusion, associated with mucocutaneous, respiratory, and gastrointestinal symptoms. Two cases showed shock and cardiovascular collapse (Grade III on the Ring and Messmer scale [31]). All events occurred

Table 1 Clinical and laboratory data for the three patients who developed anaphylaxis after treatment with tocilizumab

	Case 1	Case 2	Case 3
Age, years	71	28	16
Sex	F	F	F
Disease duration, months	4.1	15.0	26.0
Infusion with reaction	Fourth infusion	Third infusion	Sixth infusion
Time from first infusion to anaphylaxis, months	35.8	15.0	13.0
Clinical manifestations before tocilizumab			
Fever	+	+	+
Skin rash	+	+	+
Joint symptoms	–	+	+
Serositis	+	–	+
Organomegaly	+	–	+
Pouchot score	7	6	6
Anaphylaxis-associated symptoms/signs	Urticarial skin rash, pruritus, angioedema, nausea, difficulty breathing, chest discomfort, hypotension, tachycardia	Pruritic, erythematous macular skin lesions over the entire body, dyspnea; abdominal pain, chills and fever, tachycardia	Pruritus, nausea, abdominal pain, difficulty breathing, hypotension, tachycardia
Laboratory data			
WBC, / μ L	23,360	18,090	21,000
Platelets, / μ L	428,000	165,000	154,000
ESR, mm/h	85	34	26
CRP, mg/dL	10.91	12.29	13.40
Ferritin, ng/mL	1514.3	–	10,997.0
AST, IU/L	25	40	59
ALT, IU/L	22	32	92
LDH	–	–	441
Prior therapy	GC, cyclosporine, MMF	GC, MTX	GC, MTX, cyclosporine, IVIG, adalimumab
Concomitant treatment			
Corticosteroids ^a , mg/day	10	60	45
DMARDs	None	None	MTX

For calculation of the Pouchot score (0–12), 1 point is added for each of the following manifestations: fever, typical rash, pleuritis, pneumonia, pericarditis, hepatomegaly or abnormal liver function test results, splenomegaly, lymphadenopathy, leukocytosis $\geq 15,000/\text{mm}^3$, sore throat, myalgia, and abdominal pain [20]

WBC white blood cells, ESR erythrocyte sedimentation rate, CRP C-reactive protein, AST aspartate aminotransferase, ALT alanine aminotransferase, LDH lactate dehydrogenase, GC glucocorticoid, MTX methotrexate, MMF mycophenolate mofetil, IVIG intravenous immunoglobulin, DMARDs disease-modifying antirheumatic drugs

^aPrednisolone equivalent dose

within 20 min of TCZ infusion, after at least three prior infusions, suggesting an IgE-mediated mechanism and prior sensitization to TCZ. All patients had underlying active disease (Pouchot score 6 or 7) and had been refractory to treatment with corticosteroids and immunosuppressive agents, including MTX, cyclosporine, mycophenolate mofetil, and adalimumab.

Several adverse cutaneous events associated with TCZ therapy have been described, including urticaria, erythroderma, cutaneous vasculitis, purpuric eruption, and a psoriasisiform rash [13, 14, 19, 33–36]. Adverse cutaneous events due to TCZ were observed in 56 of 4009 RA patients (1.4%)

[37]. An analysis of national prospective registry data (the REGATE data) showed that serious infusion-related reactions (SIRRs) to TCZ developed in 29 of 1370 RA patients (1.9%; 1/100 patient-years) [17]. Of the 29 patients, 5 (17%) had a history of at least one IRR 1–3 months before the SIRR associated with TCZ infusion [17]. Similarly, in all three of our cases, mild allergic reactions were observed 1 month before the anaphylactic events (mild urticarial skin rash, $n=3$; nausea, $n=2$; and abdominal pain, $n=1$). Despite pre-medication with an antihistamine and a corticosteroid, subsequent TCZ infusion induced anaphylactic shock in two cases, and severe anaphylaxis in one.

Table 2 Previous reports of anaphylaxis after tocilizumab infusion in patients with rheumatic diseases

Author, year [Ref.]	Study design	Disease	Doses, routes of drug administration	Prior therapy	Concomitant therapy	Anaphylaxis; n (%) or incidence rate	Infusion triggering reaction	HSS grade
De Benedetti et al. 2012 [44]	Randomized clinical trial	JIA	A dose of 12 mg/kg (weight was < 30 kg) or 8 mg/kg (weight was ≥ 30 kg)	GCs, MTX, cyclosporine, sulfasalazine, thalidomide, Biologic agents (78%)	MTX (70%), GCs (84%)	0 (0%) with anaphylaxis, 1 with urticarial and angioedema	N.A.	N.A.
Ogata et al. 2014 [18]	Double-blinded, parallel-group, double-dummy phase III study	RA	TCZ-SC 162 mg q2w TCZ-IV 8 mg/kg q4w	MTX, SSZ, LEF, bucillamine, INF, ETA, ADA, TAC	None	TCZ-SC SIRs: 3.5% (6 of 173) TCZ-IV IRR: 6.9% (12 of 173) (1 anaphylaxis case)	2nd infusion (anaphylaxis)	N.A.
Sieper et al. 2014 [21]	Two-part, parallel-group phase II–III study	AS	TCZ-IV 8 mg/kg or 4 mg/kg q4w	NSAIDs, csDMARDs, anti-TNF agents	NSAIDs, MTX, SSZ, CQ, HCQ, GCs (≤ 10 mg/day)	4 anaphylaxis cases 1 serious IRR of 355 cases (2.4/100 person years)	1st infusion in one case 2nd–5th infusion for others	Serious
Justet et al. 2014 [22]	Case report	AOSD	TCZ-IV 8 mg/kg q4w	GC, MTX, anakinra	None	1 case	2nd infusion	Grade II ^a
Rocchi et al. 2014 [13]	Case report	RA AOSD	TCZ-IV	GCs, MTX, ETA, ADA, INF, plaque-nil, anakinra, CYC	N.A.	6.9% (5 of 72 cases) 4 with anaphylaxis 1 with pruritus	2nd–6th infusion	Mild to severe
Kostik et al. 2015 [23]	Retrospective study	sJIA	TCZ-IV 12 mg/kg (weight < 30 kg), 8 mg/kg (weight ≥ 30 kg) q2w vs. q4w	GCs, MTX, Cyclosporine A	N.A.	9% (3 of 33 cases) 3 with infusion reaction combined with hypotension	2nd and 3rd infusion	Severe
Yokota et al. 2016 [24]	Post marketing survey	sJIA	TCZ-IV 8 mg/kg q2w	GCs (88%), MTX (25.9%)	N.A.	7.2 (30 of 417 cases) of IRRs 3 with anaphylaxis	2nd–4th infusion	Mild to severe
Erdogan et al. 2018 [25]	Case report	AOSD	TCZ-IV 8 mg/kg	GCs, MTX, INF, canakinumab	N.A.	1 case	2nd infusion	Grade II
Yun et al. 2017 [26]	Retrospective cohort study using claims data	RA	TCZ-IV	GC, MTX, ETA, ADA, ABA, GOL, certolizumab pegol	MTX, GCs	0.3% (13 of 4566) [155.5 per 10 ⁶ person days (95% CI 90.3–267.8)]	Highest frequency of IRR after the 3rd infusion	Mild to severe
Tetu et al. 2018 [19]	Case report	RA AOSD	TCZ-IV TCZ-SC	MTX, ADA, ABA, anakinra, rituximab, anti-TNF agents	N.A.	3 cases	2nd infusion	Grade II–III ^b
Cansever et al. 2018 [27]	Case report	sJIA	TCZ-IV 600 mg q2w	GC, IVIG	N.A.	1 case	2nd infusion	Grade II ^c
Salmon et al. 2018 [17]	Nationwide prospective registry analysis	RA	TCZ-IV	MTX, LEF, other DMARDs, anti-TNF agents, GCs	N.A.	1.9% (29 of 1370) (1/100 patient-years)	Median 4th (2nd–9th) infusion	Grade II–IV ^d

Table 2 (continued)

Author, year [Ref.]	Study design	Disease	Doses, routes of drug administration	Prior therapy	Concomitant therapy	Anaphylaxis; n (%) or incidence rate	Infusion triggering reaction	HSS grade
Kokok et al. 2018 [28]	Retrospective study	SJIA	TCZ-IV 12 mg/kg (weight < 30 kg), 8 mg/kg (weight ≥ 30 kg) q2w	GCs, MTX, cyclosporine	GCs, MTX, cyclosporine	8.3% (4 of 48)	2nd–4th infusion	N.A.
Yasuoka et al. 2019 [29]	Retrospective cohort study	SJIA	TCZ-IV 8 mg/kg q7–15 days	GCs, cyclosporine, colchicine	GCs	5 of 40	3rd infusion	N.A.

Hypersensitivity was defined as a serious adverse event occurring within 24 h of injection or infusion, excluding injection site reactions, related to treatment

RA rheumatoid arthritis, TCZ tocilizumab, SC subcutaneous, IV intravenous, MTX methotrexate, SSZ sulfasalazine, LEF leflunomide, INF infliximab, ETA etanercept, ADA adalimumab, TAC tacrolimus, SIRS systemic reactions to SC injections (not at the site of SC injection), IRRs IV infusion-related reactions, N.A. not available, AS ankylosing spondylitis, NSAIDs non-steroidal anti-inflammatory drugs, DMARDs disease-modifying antirheumatic drugs, CQ chloroquine, HCQ hydroxychloroquine, GC glucocorticoid, AOSD adult-onset Still's disease, CYC cyclophosphamide, ABA abatacept, GOL golimumab, SJIA systemic juvenile idiopathic arthritis, IVIG immunoglobulin

^{a,c}Hypersensitivity grade of the World Allergy Organization grading system [30]

^bHypersensitivity grade of the Ring and Messmer clinical classification [31]

^dCommon Terminology Criteria for Adverse Events (CTCAE) [32]

Almost all anaphylactic reactions develop between the second and fifth TCZ infusions [13, 17–19, 22, 26, 27, 29], but may occur after the first infusion [21]. In a double-blinded, parallel-group phase III study (the MUSASHI study), the frequency of systemic reactions to TCZ-SC injections (162 mg/q2 weeks) was 3.5% (6 of 173 RA patients), and the incidence of IRRs to TCZ-IV infusions (8 mg/kg/q4 weeks) was 6.9% (12 of 173 RA patients) [18]. Anaphylactic events (including fatalities) have been reported after IV administration of TCZ [13, 17, 18, 21]. As in previous studies, our cases had received IV TCZ infusions. All three patients had earlier received TCZ at 8 mg/kg every 4 weeks, but one patient with relatively mild symptoms of anaphylaxis had received TCZ at 4 mg/kg after two infusions at 8 mg/kg.

Few studies have sought to identify risk factors for serious anaphylactic reactions to TCZ in patients with AOSD or SJIA. Only one study evaluated the risk factors for TCZ anaphylaxis in patients with SJIA, and it showed that patients who were younger, shorter, lighter, and with more disease activity may be at higher risk for anaphylactic reactions to TCZ [29]. However, the present study was retrospective in nature and had an extremely small sample size for the evaluation of risk factors for TCZ anaphylaxis. Nevertheless, we list the risk factors for anaphylaxis based on common features of the three cases and a literature review. First, our three cases had active severe disease refractory to various immunosuppressives before the anaphylactic reactions to TCZ. Similarly, a previous case report of TCZ-induced anaphylactic reaction in an AOSD patient also emphasized that the patient suffered from severe disease despite treatment with high-dose corticosteroids, MTX, and anakinra [22]. Second, leukocytosis and elevated cytokine levels may have affected the development of TCZ anaphylaxis in our patients. One previous report suggested that a high WBC count and elevated cytokine level are risk factors for rituximab-induced anaphylaxis in patients with hematological malignancies [38]. Furthermore, IL-18 acts with IL-3 to activate mast cells and basophils, to enhance the production of Th2 cytokines including IL-4 and IL-13, which in turn create an environment amenable to the development of an allergen/IgE-dependent response [39]. IL-18 is thought to be a useful biomarker for the diagnosis and evaluation of disease activity in patients with AOSD and those with SJIA [40, 41]. One study showed that the IL-18-dominant subset included more patients who developed MAS [41]. Although we did not measure IL-18 levels in our patients, these patients with active AOSD and SJIA may have expressed high levels of IL-18, facilitating a Th2-like response to TCZ. Furthermore, in the two cases of shock, associations with MAS developed before (or soon after) the anaphylactic events. Some reports have documented an association between MAS and anaphylactic shock induced by TCZ in patients with AOSD or SJIA

[24, 28, 42]. Third, although TCZ anti-drug antibodies were not measured in our three patients, previous reports suggest that anti-drug antibodies are associated with HSR, including anaphylaxis in patients with JIA [43]. Overall, TCZ anti-drug antibodies were detected in 68% (15/22) of patients with infusion reactions to TCZ [44]. Fourth, it was reported that the absence of concomitant synthetic disease-modifying antirheumatic drug (DMARD) treatment tended to increase the risk of anaphylactic reaction in patients with RA [17]. In the present study, one patient with SJIA underwent concomitant MTX therapy, but the two AOSD patients did not receive DMARDs.

Desensitization should be performed only when a biologic agent is needed as first-line therapy [25]. The standard protocol for desensitization to monoclonal antibodies has 12 steps and is based on 3 different solutions [45]. TCZ desensitization using the standard protocol was successful in cases of active AOSD or JIA after prior anaphylaxis or allergic reaction [11, 22]. Recently, one patient with AOSD for whom no acceptable therapeutic alternative was available was reported to have received TCZ treatment with slow desensitization after anaphylactic reaction [25]. In another report, the reintroduction of TCZ after switching to SC (to 162 mg daily) was successful; the authors suggested that TCZ-SC re-challenge should be considered before TCZ-IV desensitization in patients with negative skin test results [19]. All three of our patients had active disease; corticosteroids could not be discontinued, and skin tests could not be performed. Furthermore, anaphylaxis developed even after pre-medication with antihistamine and corticosteroid in patients with a history of prior mild allergic reaction. Therefore, TCZ should be discontinued immediately, and desensitization or switching to the SC route should be reconsidered in those who exhibit allergic reactions to TCZ infusion if there is no drug to replace TCZ; therapy should not be continued with pre-medication.

Our work had several limitations. First, we did not measure the levels of tryptase or total IgE, which would have facilitated evaluation of anaphylactic or allergic status. Nevertheless, in our cases, anaphylaxis was clearly induced by TCZ. Second, as mentioned above, we were unable to perform skin TCZ tests. Third, our sample size was very small, so we were unable to reliably define risk factors for anaphylactic reactions in patients with AOSD or SJIA.

In conclusion, TCZ infusion can trigger anaphylactic reactions in patients with active refractory AOSD or SJIA. Anaphylaxis can be developed even after pre-medication in patients with a history of prior mild allergic reaction and fatal, so physicians must be very cautious when prescribing TCZ for certain AOSD/SJIA patients. Further studies are required to define the risk factors after TCZ infusion, and patients should be educated regarding risk factors that can lead to increasingly severe anaphylactic reactions to TCZ.

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Compliance with ethical standards

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