Rheumatology International (2019) 39:743–750
https://doi.org/10.1007/s00296-019-04268-x

Rheumatology
INTERNATIONAL

CASE BASED REVIEW

Is it required to routinely check fibrinogen level in patients with rheumatic diseases on tocilizumab? Case-based review

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Received: 11 February 2019 / Accepted: 26 February 2019 / Published online: 14 March 2019

Abstract

Tocilizumab (TCZ) may rarely cause hematological side effects including neutropenia and thrombocytopenia. TCZ is essentially expected to lower the fibrinogen levels to stay within the normal range, but TCZ-induced hypofibrinogenemia has been rarely reported in literature. Although it may remain asymptomatic, hypofibrinogenemia has clinical significance owing to the tendency of the condition to result in bleeding. A 65-year-old female patient with known polymyositis was, approximately 20 years after the diagnosis was made, examined due to elevated acute phase reactants leading to the diagnosis of giant cell arteritis (GCA) and TCZ treatment was initiated as she had former steroid-induced osteoporotic fractures. 1 month after the initial dose of intravenous (IV) TCZ, she presented with ecchymosis and was detected to have hypofibrinogenemia. Following the administration of the second dose, hypofibrinogenemia was detected again. In this review, we have analyzed this patient in addition to the cases in six other articles of TCZ induced hypofibrinogenemia which we found out based on our search strategy. Our aim is to point out a rare side effect of TCZ, hypofibrinogenemia, thus to emphasize a possible bleeding disorder and discuss probable underlying mechanisms.

Keywords Tocilizumab · Hypofibrinogenemia · Fibrinogen level · Bleeding

Introduction

Tocilizumab (TCZ) is a humanized monoclonal anti-interleukin 6 receptor (IL-6R) antibody of the immunoglobulin (Ig) G1 class. It has been approved for the therapy of rheumatoid arthritis (RA), besides systemic juvenile idiopathic arthritis (JIA), and giant cell arteritis (GCA), particularly in adult patients. It has been also used for the treatment of treatment-resistant adult-onset Still's disease (AOSD) and Takayasu's arteritis. Subcutaneous (SC) or intravenous (IV) administration of TCZ either alone or as a combination therapy is generally well-tolerated. Most frequent side effects of TCZ, given either as a single or combined therapy have been listed as upper respiratory tract infections, elevated liver transaminases, and headache followed by hypertension, hypercholesterolemia, and injection site reactions. Its hematological influence or side effects may include recovery of anemia as a result of suppressed inflammation as well as neutropenia or thrombocytopenia which may arise during the course of treatment [1, 2]. Levels of acute phase reactants such as C-reactive protein (CRP) and fibrinogen are expected to decline in patients using TCZ. The extent of such a decline is most likely to keep fibrinogen within

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the normal range, but rarely may end up with a fibrinogen level below the lower limit of normal and manifest itself as hypofibrinogenemia [3–8]. Hypofibrinogenemia is a risk factor underpinning bleeding. While on TCZ, patients have experienced bleeding such as ecchymosis and gingival bleeding due to lower fibrinogen levels and low fibrinogen levels during the preoperative period has also been associated with perioperative bleeding risk and an increased need of transfusion [6].

Here, we presented a patient who had suffered ecchymosis subsequent to the first dose IV TCZ treatment and was detected to have hypofibrinogenemia and following the second dose experienced the same adverse effect. Our aim is to point out a rare side effect of TCZ, hypofibrinogenemia, and thus to emphasize a possible bleeding disorder.

Search strategy

The present case-based review followed the search strategy recommended for narrative reviews [9]. We searched, MEDLINE/PubMed; Web of Science and Scopus databases using MeSH terms "tocilizumab" [AND] "hypofibrinogenemia" or "fibrinogen" until February 20, 2019. Case reports and clinical studies covering rheumatic diseases treated with TCZ followed by decreased fibrinogen levels (hypofibrinogenemia) were included to this review [3–8]. Experimental studies, reviews, article with normal to high fibrinogen levels, studies with no data about fibrinogen level, articles on non-rheumatic conditions (hemophagocytic lymphohistiocytosis, carcinomas etc.), articles including drugs other than TCZ, and any other irrelevant articles reporting not about TCZ and fibrinogen were excluded from the review. The flowchart depicting the search strategy of our study is shown in Fig. 1.

Of the six articles with TCZ induced hypofibrinogenemia patients, one was case series, two were case reports, and three were original articles (one comparing the fibrinogen levels of seven patients using TCZ to 108 non-users for the perioperative risk of bleeding, the next one evaluating the factor XIII levels as a primary and fibrinogen levels as a secondary parameter in 36 patients receiving TCZ, and the last one investigating the criteria of response to TCZ in 65 RA patients). Altogether, six articles we have identified plus our case were analyzed in detail [3–8].

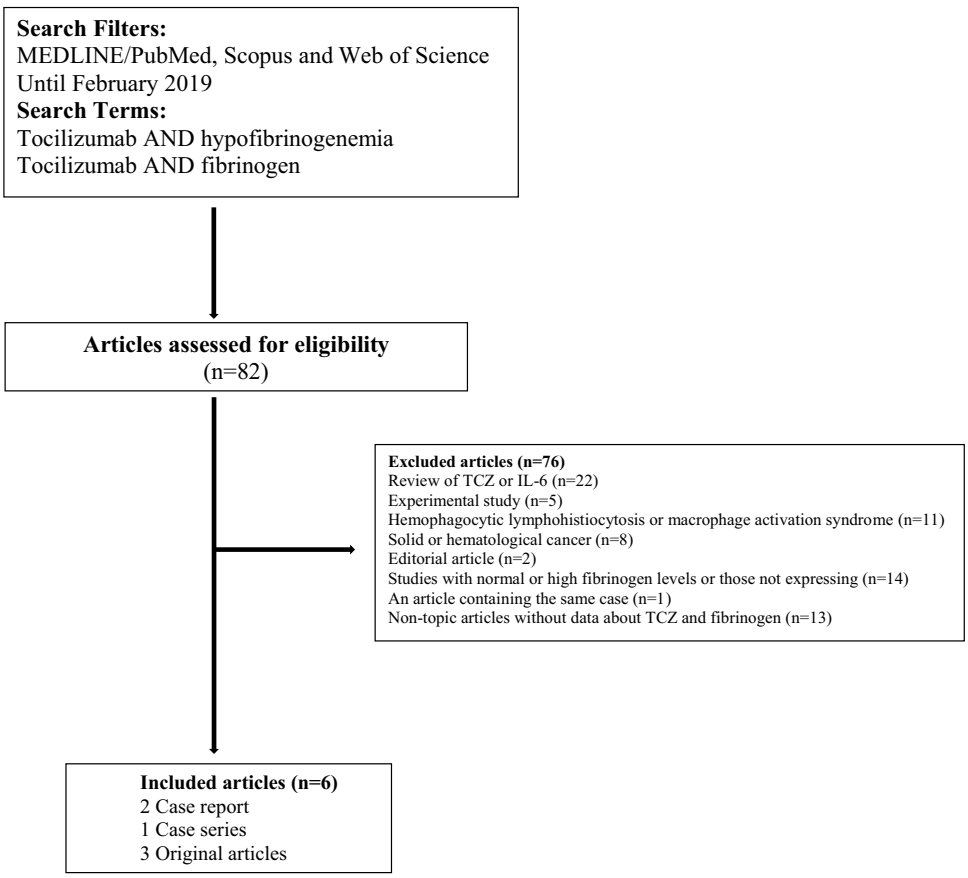

Fig. 1 Flowchart of the search strategy of the review

Case presentation

A 65-year-old female patient had been diagnosed with polymyositis in 1995 based on investigations [electroneuromyography (EMG), muscle biopsy, and elevated muscle enzymes] carried out for muscle weakness, fever and disseminated joint pain and thereupon started with methotrexate (MTX) and prednisolone. Her muscle enzymes occasionally elevated during the period of 1995–2008 when the patient was screened for malignancies three times, with no pathological results. In 2008 she had a vertebral fracture. Due to gastrointestinal intolerance, MTX (10–15 mg/week) was discontinued in 2013 [creatinine phosphokinase (CK) 781 IU/L, erythrocyte sedimentation rate (ESR): 30 mm/h, C-reactive protein (CRP): 2.34 mg/dL (normal range 0–0.5 mg/dL), muscle strength was comparable to the former assessment (3/5)]. From 2013 to December 2017 the patient's follow-up continued with no immunosuppressive agents (CK: 208 IU/L, ESR: 59 mm/h, CRP: 1.7 mg/dL). In February 2018, her results were ESR:97 mm/h, CRP: 5.4 mg/dl, CK: 173 IU/L, muscle strength: 3/5, EMG: normal, IgG: normal, IgA: 786 (52–453), and IgM: normal. Even it has been 20 years since the first diagnosis, and polymyositis was not active period; the patient's age, presence of B symptoms and elevated ESR what resulted in malignancy screening be deemed necessary. To this end, endoscopy, colonoscopy, abdominal and thoracic tomography, Positron emission tomography (PET-CT), gynecological examination and breast examination was conducted. Although immunofixation electrophoresis resulted as normal, the patient had anemia and elevated ESR; and non-secretory myeloma could not be ruled-out. To rule it and other hematological malignancies out, bone marrow biopsy was examined. But bone marrow biopsy revealed no pathology. The patient's ESR reached up to 117 mm/h. (Fibrinogen: 506 mg/dL). Neither a focus of infection nor any solid or hematological malignancy could be determined in our evaluations. As the patient had shoulder pain and slightly restricted motion, polymyalgia rheumatica (PMR) could not be ruled out and low-dose (12.5 mg/day) prednisolone was started. During her follow-up, symptoms of the patient have relieved by 70%, but ESR level raised up to 128 mm/h. She did not have jaw claudication or headache, but due to mild tenderness along her left temporal artery, a biopsy was obtained from her temporal artery which resulted in consistency with GCA. At the end of the first week of prednisolone treatment, ESR regressed down to 36 mm/h. As the patient had GCA and a positive history of vertebral fracture, based on the fact that she had experienced steroid-induced former osteoporotic fractures neither we deemed it medically appropriate nor the patient agreed with the use of a higher dose of steroids. The initial dose of IV TCZ (8 mg/kg–480 mg) was administered in May 2018. During her follow-ups, symptoms of the patient totally alleviated, with an ESR of 5 mm/h. 1 month later, the patient presented with multiple ecchymoses at the lateral side of her right foot and femoral region. Workup indicated platelet level: 258.000 /mm^3, and normal prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (PTT), and D-dimer. However, fibrinogen level was 184 mg/dL. Peripheral smear of the patient was examined, and appeared normal. Re-tested fibrinogen level was 180 mg/dL. The patient did not have any novice use of medication except for TCZ and prednisolone, her medical history was negative for infection and liver failure, her clinical picture was not suggesting disseminated intravascular coagulation or hemophagocytic lymphohistiocytosis. Consequently, TCZ was blamed for her hypofibrinogenemia. Our literature search has figured out TCZ might indeed cause hypofibrinogenemia, although rarely. Factor XIII test result was normal (> 155.8). Her ecchymoses disappeared spontaneously over 7 days. Fibrinogen level increased to 208 mg/dL 1 month after the first dose of the TCZ treatment. The value was 285 mg/dL 1.5 month later. During her follow-ups, prednisolone was continued at varying doses of 5–10 mg/day. She had headache and ESR: 45 mm/h (fibrinogen: 261 mg/dL) on her check-up 6 months later. Disease activation was suspected, leading us to consider the use of a higher steroid dose. However, the patient did not consent on steroid administration and upon her approval, she was given the second dose of IV TCZ. Following the administration of TCZ, fibrinogen level was checked 1 week and 2 weeks later, and was 234 mg/dL and 180 mg/dL, respectively. On the other hand, the patient had no symptoms of a bleeding which is a possible result of hypofibrinogenemia. Her fibrinogen level restored back to normal (220 mg/dL) at week 3. The patient's score based on Naranjo adverse drug reaction probability scale was 9 (definite), and thus existing condition of the patient was accepted as TCZ-induced hypofibrinogenemia [10] (Fibrinogen levels of the patient prior to and after TCZ treatments are depicted in Fig. 2).

Discussion

In our literature search, no data on the prevalence of TCZ-induced hypofibrinogenemia could be extracted. To be more precise, one of the original articles was authored by Imamura et al. where only seven patients had received TCZ (six with low and one with normal fibrinogen level) while the other original study by Souri et al. was encompassing 36 patients, just the average fibrinogen level of whom was mentioned with no data on how many of them has developed

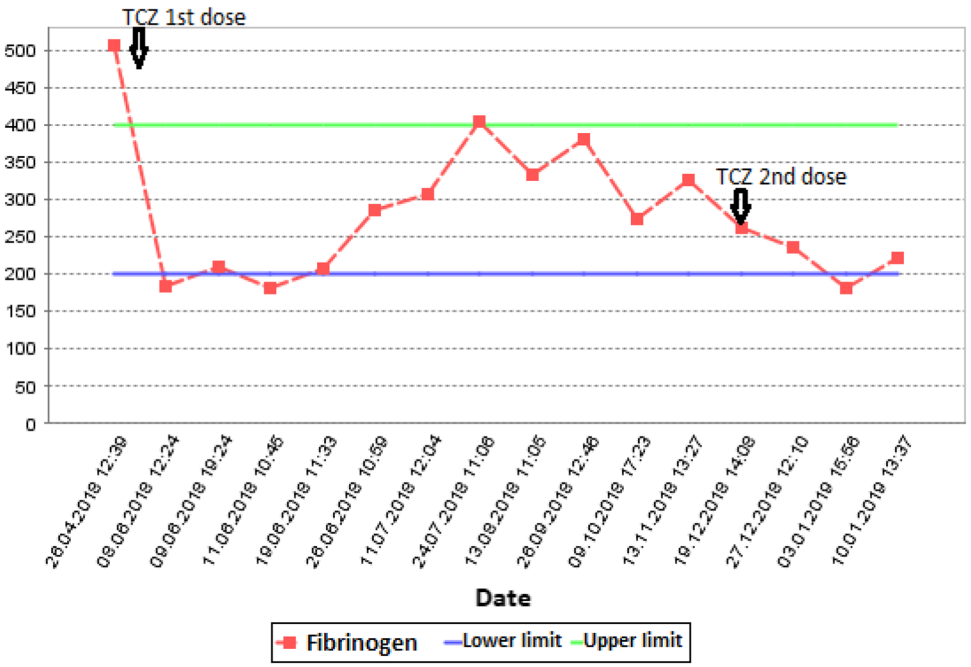

Fig. 2 Time courses of fibrinogen levels

hypofibrinogenemia [6, 7]. In the study by Okano et al., 29% of 65 RA patients who were administered TCZ were detected to have hypofibrinogenemia at the end of week 4 [8]. TCZ-induced hypofibrinogenemia has to be addressed by prospective observation studies with larger sample size to enable estimation of its frequency.

May any possible risk factors for this condition such as route of administration (SC or IV), dosage, or number of administration(s) of the drug or any patient-related factors?

When collectively analyzed, most of the patients in six articles had received TCZ due to RA, for which TCZ is indicated at the first place, but there are also patients who had been administered this drug due to GCA, AOSD, ankylosing spondylitis, and even aortitis and macular edema. Such a small but yet heterogeneous patient group makes it impossible to speculate that an underlying disease was a risk factor for hypofibrinogenemia. Age of the patients were varying at a range from 40 to 73 [3–8]. (The clinical and laboratory findings of the TCZ-induced hypofibrinogenemia cases in the literature are given in Table 1, corresponding comments of the authors were given in Table 2).

Most of the incidents had occurred following an IV administration, but this side effect has also been detected after a SC administration, as well. On top of that, the case report of Vitiello et al. mentions a case who developed hypofibrinogenemia 2 times after IV administrations, and once again following the SC administration [4]. Accordingly, the route of administration is not proven as a risk factor. A similar conclusion might also be drawn for drug dose. The reason is the fact that the majority of the patients were given IV TCZ which was weight-adjusted (8 mg/kg/month). It is also difficult to explain whether any other disease-modifying antirheumatic drugs (DMARDs) or steroids in combination with TCZ have exerted any additional risk. Merely 3 of the 7 patients reported by Martis et al. had received concomitant prednisone, but the others had not [3]. The studies by Matsuoka et al. and Imamura et al. do not mention about DMARDs [3–8].

When assessed for number of applications, the earliest incident, except for ours, had occurred after dose 3 and the latest case of hypofibrinogenemia had been following the administration of dose 48. Our case is first of its kind in literature to suffer TCZ-induced hypofibrinogenemia subsequent to the first dose. In all of the cases, pre-TCZ fibrinogen levels were normal to high. The lowest and highest measured levels of post-TCZ hypofibrinogenemia were 82 mg/dL and 197 mg/dL, respectively. When three original articles were excluded, almost 60% of TCZ-induced hypofibrinogenemia cases had no hypofibrinogenemia related symptoms, whereas other 4 cases had ecchymosis, gingival bleeding, and pelvic and inguinal hemorrhage [3–8]. In the study of Immamura et al., more bleeding was collected during total knee prosthesis surgery of patients who had used TCZ, compared to those who had not used. This was associated to the low level of fibrinogen [6]. Compared to the healthy individuals, TCZ users had a lower average level of fibrinogen which is at the lower edge of normal was recorded in the study conducted by Souri et al. who have not, on the other hand, identified any symptom of bleeding in such patients

Table 1 Demographic data and clinical findings of patients with TCZ induced hypofibrinogenemia in the literature

	Article type	Age/gender	Disease	TCZ dose and route of administration	Symptom of hypofibrinogenemia	Baseline fibrinogen level before TCZ	Lowest fibrinogen level	Lowest factor XIII activity	Hypofibrinogenemia after TCZ (number of infusions)	The other treatment MTX/PR
Our case	Case	65/F	Giant cell arteritis	8 mg/kg (480 mg), IV	Ecchymosis	506 mg/dL	180 mg/dL	155.8%	First infusion	−/+
Martis et al. [3]	Case series									
	Case 1	40/F	AS	8 mg/kg/IV	None	3.34 g/L	1.7 g/L	92%	37	−/−
	Case 2	53/F	RA	8 mg/kg/IV	None	3.78 g/L	1.14 g/L	53%	6	+/−
	Case 3	70/F	RA	8 mg/kg/IV	None	2.65 g/L	1.43 g/L	66%	8	+/−
	Case 4	73/F	RA	8 mg/kg/IV	Bleeding gums	2.28 g/L	0.82 g/L	63%	48	+/−
	Case 5	50/F	ME	8 mg/kg/IV	None	2.02 g/L	1.9 g/L	100%	15	−/+
	Case 6	60/F	AOSD	8 mg/kg/IV	None	N/A	1.6 g/L	102%	4	+/+
	Case 7	72/F	Aortitis	8 mg/kg/IV	None	5.5 g/L	1.97 g/L	139%	5	+/+
Vitiello et al. [4]	Case	75/–	Giant cell arteritis	8 mg/kg/IV	–	–	100 mg/dL	Unmeasured	3	+/+
Matsuoka et al. [5]	Case	48/M	RA	600 mg/month/ IV/ 18 months	Bleeding in the pelvis (spontaneous) and inguinal area (after open biopsy)	Normal range	179 mg/dL	52.4%	18	+/+
Imamura et al. [6]	Original article (seven patients)	US	RA	SC	The median volume of estimated blood loss was significantly larger in TCZ patients ($n=7$), (797.1 mL) than in non-TCZ patients ($n=108$), (511.4 mL, $p=0.0039$)	–	The median fibrinogen level was 190.0 mg/dL	–	–	–

Table 1 (continued)

	Article type	Age/gender	Disease	TCZ dose and route of administration	Symptom of hypofibrinogenemia	Baseline fibrinogen level before TCZ	Lowest fibrinogen level	Lowest factor XIII activity	Hypofibrinogenemia after TCZ (number of infusions)	The other treatment MTX/PR
Souri et al. [7]	Original article (comparison of fibrinogen and factor XIII levels of TCZ ($n=36$) and healthy groups ($n=29$) No hypofibrinogenemia was reported in the number of patients The fibrinogen mean level was given for all patients.)	US	RA	TCZ time and dose, route of administration not specified	None	US	The median level was 170 mg/dL in TCZ group vs 262 mg/dL in HC group	Factor XIII-A2–B2 antigen levels 0.76 mg/dL in TCZ group vs 0.94 mg/dL in HC group ($p>0.05$)	US	US
Okano T et al. [8]	Original article (19 patients) (hypofibrinogenemia was detected in 19 of 65 patients who were given TCZ)	60.5 years	RA	8 mg/kg/IV	US	US	The median level was < 200 mg/dL for 19 patients	US	After 4 weeks	+/+ (78.5%//50% of patients)

F female, *M* male, *RA* rheumatoid arthritis, *AS* ankylosing spondylitis, *AOSD* adult-onset Still's disease, *TCZ* tocilizumab, *MTX* methotrexate, *PR* prednisolone, *ME* (auto-immune) macular edema, IV intravenous, SC subcutaneous, *N/A* not available, *US* unspecified, *HC* healthy control

Table 2 Comments made by the authors within the literature presenting patients with TCZ-induced hypofibrinogenemia

	Article type	Comments by authors
Our case	Case report	The risk of hypofibrinogenemia faced by the TCZ-receiving patients should be recognized requiring fibrinogen level checks, even if not on a routine basis, to be conducted in case of ecchymosis, bleeding, or at preoperative setting
Martis et al. [3]	Case series (seven cases)	Unexpected hypofibrinogenemia in TCZ-treated patients, in our opinion, does not warrant further tests nor discontinuation of the biologic. Close attention should be given to patients with risks of haemorrhage or those who have to undergo surgery
Vitiello et al. [4]	Case report	This is the first report of combined hypofibrinogenemia and thrombocytopenia in a TCZ-treated patient. We are not aware about the factor XIII activity in this patient, but the drug was suspended in any case due to low platelet count-related haemorrhagic risk, furthermore enhanced by the presence of hypofibrinogenemia
Matsuoka et al. [5]	Case report	When recurrent bleeding is seen despite normal results for APTT and PT during administering of tocilizumab for treatment of RA, hemorrhagic-acquired factor XIII deficiency should be considered in a differential diagnosis
Imamura et al. [6]	Original article (seven patients)	TCZ treatment may significantly decrease preoperative fibrinogen levels and significantly increase the volume of hemorrhaging after total knee arthroplasty in patients with RA Surgeons should be made aware before surgery of the significant risk of postoperative bleeding complications in patients with low fibrinogen levels ($\leq$250 mg/dL)
Souri et al. [7]	Original article (Comparison of fibrinogen and factor XIII levels of TCZ group ($n=36$) and healthy group ($n=29$)	Physicians had better be aware that TCZ-treated patients are at an increased risk of hemorrhage, especially when they have concomitantly and/or significantly low platelet counts and fibrinogen, and factor XIII concentrations
Okano et al. [8]	Original article (19 patients) (Hypofibrinogenemia was detected in 19 of 65 patients who were given TCZ)	(No additional comments or suggestions regarding hypofibrinogenemia have been made)

TCZ tocilizumab, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *RA* rheumatoid arthritis

[7]. TCZ-induced hypofibrinogenemia patient may remain asymptomatic in terms of bleeding, but they may also be at risk of mucosal bleeding and bleeding during or after a surgery. The likelihood that patients are essentially asymptomatic and the obvious fact that fibrinogen is not a routine test in rheumatology practice may both contribute the underestimation of TCZ-induced hypofibrinogenemia.

Why does TCZ-induced hypofibrinogenemia develop?

The answer remains elusive, although several theories have been suggested. The first one is the reduced fibrinogen production. An inhibitor of IL-6 may, therefore, inhibit the expression of fibrinogen [5]. In this case, the next question comes to mind: whether this side effect arises from the cumulative influence of the TCZ. Although this adverse effect has occurred after an average of eight doses (4–48 doses) in the study of Martis et al., our patient has experienced the adverse effect as early as the initial dose [3]. Apparently, a cumulative dose might be speculated for some patients, but certain genetic traits might also be acting on the emergence of this drug side effect. The second theory involves TCZ-related factor XIII deficiency. The mechanism underlying the TCZ-related factor XIII deficiency is not clearly known. Possibly, TCZ down-regulates the factor XIII-A synthesis by hematopoietic cells. In their TCZ-treated RA patients, Souri et al. have found significantly lower plasma levels of both factor XIII-A and factor XIII-B (almost 25% of the normal levels). Factor XIII is a fibrin-stabilizing factor. In their study, factor XIII levels were found in a good correlation with plasma fibrinogen [7]. Not all but some patients who have experienced TCZ-associated bleeding have been reported to have impaired factor XIII activity along with decreased fibrinogen levels. In our review, not all of the cases had low factor XIII levels; more than half of the hypofibrinogenemia patients had normal factor XIII activity, some of whom had experienced bleeding symptoms [3–8]. Therefore, factor XIII deficiency on its own cannot be held responsible for TCZ-induced hypofibrinogenemia. Both TCZ-induced hypofibrinogenemia and impaired factor XIII activity have yet unclear mechanisms for which additional clinical studies are required to elaborate.

Is it required to discontinue the drug in case of TCZ-induced hypofibrinogenemia?

Martis et al. have advocated TCZ-induced hypofibrinogenemia does not necessitate discontinuation of the drug [3]. On contrary, we have not sustained TCZ treatment considering

the ecchymoses of the patient might be a predecessor of other possible hemorrhage. However, 6 months after the initial dose while the patient was on steroid treatment of 7.5 mg/day, she experienced the onset of headache and ESR of 45 mm/h and, therefore, given second dose of IV TCZ upon her approval. At the end of 5-week follow-up, there were no signs of bleeding. Re-administration or continuation of the drug does not seem reasonable following a remarkable bleeding arising from TCZ-induced hypofibrinogenemia, but we believe that TCZ might be continued taking the risk–benefit balance into account in asymptomatic hypofibrinogenemia patients where no alternative treatment option is available (as in our case who had steroid-induced multiple osteoporotic fractures).

How long after the discontinuation TCZ-induced hypofibrinogenemia restore back to normal?

In the study by Matsuoka et al., the patient's factor XIII activity reverted back 4 months after the discontinuation of TCZ (time to recovery of fibrinogen level was not mentioned). The patient had received TCZ for 18 months and had pelvic and inguinal hemorrhage. The authors assume such a long recovery time was needed due to long-term administration of TCZ [5]. Fibrinogen level of our patient was checked prior to the first dose of IV TCZ, which then was high, re-checked 3 weeks later due to ecchymosis and was low. In our retrospective analysis, ESR level was 5 mm/h 2 weeks after the first dose of TCZ, and probably, fibrinogen level was low during this period (we believe ESR might be detected very low due to decreased fibrinogen level). When we performed weekly fibrinogen, follow-up checks after the second dose of IV TCZ, fibrinogen level 1 week, 2 weeks, and 3 weeks after the administration of TCZ were normal, low, and again normal, respectively.

In conclusion, TCZ-induced hypofibrinogenemia and bleeding disorder is a rare adverse effect. Based on the entire analysis we have conducted, no possible prediction of hypofibrinogenemia could be suggested. However, as a management approach to rheumatoid patients, particularly in the event that quite low ESR levels are measured even if in the absence of a bleeding-related pathology during the course of treatment of asymptomatic patients on TCZ it should be kept in mind that their situation might be a result of low fibrinogen levels, not necessarily due to the disease taken under control. For patients on TCZ, routine fibrinogen checks are not deemed necessary, but must absolutely be carried out along with platelet count, PT, PTT, and factor XIII level testing, if necessary, in the event of suspicious TCZ-induced hypofibrinogenemia which should be considered in the presence of bleeding or ecchymosis.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from our patient included in the study.

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