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Original Article

Tocilizumab-induced Thrombocytopenia in Patients with Rheumatoid Arthritis

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Objective. Interlukin-6 (IL-6) increases platelet count during inflammation and may act in a manner similar to thrombopoietin. Tocilizumab is a monoclonal antibody of the IL-6 receptor and widely used in the treatment of rheumatoid arthritis (RA). Here, we evaluated the incidence of tocilizumab-induced thrombocytopenia and clinical factors associated with the development of thrombocytopenia. **Methods.** Patients with RA, who were treated with tocilizumab and had exposed to other biologics previously in a tertiary hospital between January 2014 and December 2017, were retrospectively evaluated. We compared occurrence of thrombocytopenia between tocilizumab and previous biologics. Furthermore, the factors associated with thrombocytopenia were analyzed using logistic regression analysis. **Results.** In total, 114 patients with RA were treated with tocilizumab for mean 90.5 weeks (interquartile range, 30.9～174.9). Thrombocytopenia was reported in 14 patients (12.3%) and it was higher rate compared with previous biologics. Most cases were grade 1 thrombocytopenia. Multivariate analysis showed that patient age (odds ratio [OR], 2.170; 95% confidence interval [CI], 1.118～4.211; p=0.022) and platelet count prior to treatment with tocilizumab (OR, 0.972; 95% CI, 0.954～0.990; p=0.002) were significantly associated with the development of thrombocytopenia. **Conclusion.** Old age is risk factor for developing tocilizumab-induced thrombocytopenia and higher platelet count prior to treatment is associated with lowering risk of development of thrombocytopenia. However, thrombocytopenia was tolerable. **(J Rheum Dis 2019;26:186-190)**

Key Words. Rheumatoid arthritis, Interleukin-6, antibodies, Thrombocytopenia

INTRODUCTION

Interleukin 6 (IL-6) plays a key role in rheumatoid arthritis (RA) by stimulating the proliferation of T cell or B cells, and promoting joint inflammation and erosion [1]. Previous studies showed that elevated serum IL-6 levels are correlated with reactive thrombocytosis during inflammation and thrombocytosis is correlated with RA activity [2,3]. Indeed, administration of recombinant IL-6 induces an increase in platelet count and thrombopoietin-like activity in the bone marrow [4].

Tocilizumab is a monoclonal antibody of the IL-6 receptor and widely used for the treatment of refractory RA [5]. In a previous clinical trial, the prevalence of thrombocytopenia in patients treated with tocilizumab was 8%–9% [6]. Currently, there are limited data regarding the risk of thrombocytopenia in patients receiving long-term treatment with tocilizumab and clinical factors associated with thrombocytopenia in clinical practice.

The aim of the present study was to evaluate the incidence and risk factors of thrombocytopenia in Korean population treated with tocilizumab.

MATERIALS AND METHODS

Study population

In this retrospective cohort, we reviewed the electronic medical records of patients with RA treated with tocilizu-

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mab between January 2013 and December 2017 and had exposed to other biologics including tumor necrosis factor (TNF) inhibitors or abatacept previously at a tertiary referral hospital in Seoul, South Korea. The study protocol was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea (no. 2018-0777). The requirement for informed consent was waived because of the retrospective study design.

The following data were collected from medical records: demographic information, including age and sex; duration of RA; comorbid medical conditions, such as hypertension, diabetes mellitus, and renal insufficiency; co-medication of conventional synthetic disease-modifying antirheumatic drugs, including methotrexate (MTX), sulfasalazine, leflunomide, and hydroxychloroquine; previous treatment with biologics, including TNF inhibitors, and abatacept; disease activity score 28 (DAS 28) with erythrocyte sedimentation rate (ESR) [7] and laboratory data, including, C-reactive protein (CRP), platelet, rheumatoid factor, and anti-citrullinated protein antibody.

Diagnosis of RA was made according to the criteria established by the American College of Rheumatology/European League Against Rheumatism collaborative initiative criteria [8]. Thrombocytopenia was defined as follows: 1) platelet count $<150,000/\mu L$ in at least two consecutive measurements in patients with a baseline platelet count $>150,000/\mu L$; or 2) >30% reduction from baseline at least two consecutive measurements in patients with a baseline platelet count $<150,000/\mu L$ [9]. The grade of thrombocytopenia was defined [10] as follows: Grade 1, $\geq 75,000 \sim < 150,000/\mu L$; Grade 2, $\geq 50,000 \sim < 75,000/\mu L$; Grade 3, $\geq 25,000 \sim < 50,000/\mu L$; Grade 4, $<25,000/\mu L$.

Statistical analysis

We used the McNemar's test to compare occurrence of thrombocytopenia between tocilizumab and previous biologics. Logistic regression analysis using the backward elimination method was performed to identify clinical factors associated with the development of thrombocytopenia, reporting the odds ratios (OR) and 95% confidence intervals (CI). Variables with a $p<0.2$ in a univariate analysis were selected for multivariate analysis. A $p<0.05$ otherwise denoted statistical significance in all analyses. We used IBM SPSS version 20.0 (IBM, Armonk, NY, USA) for all statistical analyses.

RESULTS

Baseline characteristics of patients with RA treated with tocilizumab

In total, 114 patients who had exposed TNF inhibitors or abatacept were treated with tocilizumab. The median duration of treatment was 90.5 weeks (interquartile range [IQR], 30.9~174.9). As shown in Table 1, the mean age was 58.4±1.2 years and the median duration of disease was 7.7 years (IQR, 3.7~14.2). The majority of patients were female and >95% patients were seropositive. MTX was co-administered in 71.9% patients. Among 114 patients, 80 patients (70.2%) initiated intravenous tocilizumab and 34 patients (29.8%) initiated subcutaneous tocilizumab. Before tocilizumab treatment, TNF inhibitors were used the most commonly (88.6%) and followed by abatacept (11.4%). At baseline, the mean DAS 28 with ESR was 4.4±1.0, CRP was 1.2 mg/dL (IQR, 0.3~2.5), and the mean platelet count was 281,500/μL (IQR, 230,800~351,300).

Table 1. Baseline characteristics

Characteristics	n=114
Age, yr	58.4±1.2
Female	93 (81.6)
Duration of RA, yr	7.7 (3.7~14.2)
Diabetes mellitus	8 (7.0)
Hypertension	18 (15.8)
Chronic kidney disease	3 (2.6)
RF positive	95 (83.3)
ACPA positive	81 (71.1)
Co-administration of medications	
Methotrexate	82 (71.9)
Sulfasalazine	5 (4.4)
Leflunomide	3 (2.6)
Hydroxychloroquine	3 (2.6)
Administration route	
Intravenous	80 (70.2)
Subcutaneous	34 (29.8)
Previous biologics	
TNF inhibitors	101 (88.6)
Abatacept	13 (11.4)
DAS 28 with ESR	4.4±1.0
CRP, mg/dL	1.2 (0.3~2.5)
Platelet count, /μL	281,500 (230,800~351,300)

Values are presented as mean±standard deviation, number (%), or median (interquartile range). RA: rheumatoid arthritis, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibody, TNF: tumor necrosis factor, DAS: disease activity score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

Thrombocytopenia developed in 14 patients (12.3%) who were treated with tocilizumab (Table 2). Time to development of thrombocytopenia was 27.1±28.6 weeks after exposure to tocilizumab. It was higher rate compared with occurrence in previous biologics although exposure to MTX was higher in previous biologics and baseline platelet count was not different. The severity of thrombocytopenia in all patients treated with tocilizumab was grade 1 and none of the patients suffered from bleeding. However, one patient discontinued treatment with tocilizumab because of the gradual deterioration of thrombocytopenia.

Clinical factors associated with thrombocytopenia in patients treated with tocilizumab

Logistic regression analysis was performed to evaluate the clinical factors associated with the development of thrombocytopenia (Table 3). Univariate analysis indicated that old age, presence of diabetes mellitus and low platelet count prior to treatment with tocilizumab were significantly associated with the development of thrombocytopenia. In addition, multivariate analysis showed that age (OR, 2.170; 95% CI, 1.118～4.211; p=0.022) and platelet count prior to treatment (OR, 0.972; 95% CI, 0.954～0.990; p=0.002) were significantly associated with the development of thrombocytopenia.

DISCUSSION

In the present study, we analyzed the incidence of thrombocytopenia in 114 patients treated with tocilizumab, switched from other biologics such as TNF inhibitors or abatacept. The rate of development of thrombocytopenia was 12.3%, it was higher than previous biologics, but the grade of thrombocytopenia was 1 in all patients.

IL-6 increases the number of circulating platelets during inflammation [11]. Further, IL-6 may play like thrombo-

Table 2. Thrombocytopenia in tocilizumab compared with previous biologics

Variable	Previous biologics	Tocilizumab	p-value
Thrombocytopenia	6 (5.3)	14 (12.3)	0.039*
Grade 1	5	14	
Grade 2	1	0	
Use of methotrexate	91 (79.8)	82 (71.9)	0.022*
Baseline platelet count, /1,000 μL	285 (232.8～354.0)	281.5 (230.8～351.3)	0.928†

Values are presented as number (%) or median (interquartile range). *McNemar's test. †Mann–Whitney U-test.

Table 3. Factors associated with tocilizumab-induced thrombocytopenia

Variable	Univariate analysis			Multivariate analysis		
	OR	CI	p-value	OR	CI	p-value
Age, /10 yr	2.773	1.515～5.077	0.001	2.170	1.118～4.211	0.022
Female	1.552	0.429～5.617	0.503			
Weight	1.001	0.948～1.056	0.984			
Duration of RA	1.032	0.962～1.108	0.381			
Diabetes mellitus	5.182	1.087～24.698	0.039	2.244	0.206～24.433	0.507
Hypertension	1.545	0.385～6.202	0.539			
CKD	3.769	0.319～44.525	0.292			
Use of methotrexate	0.468	0.148～1.478	0.196			
Prednisolone dose	0.946	0.799～1.121	0.522			
Administration route	0.354	0.075～1.677	0.191			
DAS 28 with ESR	0.523	0.270～1.013	0.055			
CRP	1.045	0.895～1.219	0.577			
Baseline platelet count, /1,000 μL	0.969	0.952～0.986	<0.001	0.972	0.954～0.990	0.002

OR: odd ratio, CI: confidence interval, RA: rheumatoid arthritis, CKD: chronic kidney disease, DAS: disease activity score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein. P-values were determined by logistic regression analysis.

poietin and physiologic regulator of megakaryocyte [12]. Tocilizumab, a monoclonal antibody of the IL-6 receptor, is effective against RA or giant cell arteritis. However, there are currently limited data regarding the effect of tocilizumab on platelet count. In a previous study investigating the long-term safety of tocilizumab, 11.3% patients experienced grade 1 thrombocytopenia, whereas 0.5% patients experienced grade 3 thrombocytopenia [13]. In another clinical study, the grade 3 thrombocytopenia induced by tocilizumab was reported in 0.3% of patients (similar to placebo) [14]. However, tocilizumab induced thrombocytopenia more frequently than adalimumab [6]. In the present study, the rate of development of tocilizumab-induced thrombocytopenia was 12.3% and it was higher compared with previous biologics but the severity of all cases of thrombocytopenia was grade 1 throughout the study. In addition, bleeding was not reported in any of the patients. Based on these findings, tocilizumab-induced thrombocytopenia is more frequent comparing with TNF inhibitor or abatacept but tolerable.

The risk factors associated with the development of tocilizumab-induced thrombocytopenia have not been determined. In a previous study, advanced patient age and a low platelet count at baseline are risk factors for the development of thrombocytopenia induced by antibiotics or anticonvulsants [9,15]. Elderly patients are frequently treated with multiple drugs, which can affect thrombocytopenia and drug metabolism or cause a decline in organ function [16]. Similarly, in the present study, advanced patient age and a low platelet count prior to tocilizumab treatment were associated with the development of thrombocytopenia after treatment.

Three patients with platelet count less than lower normal limit at baseline were included in the present study. After treatment, two patients showed >30% reduction in thrombocytopenia compared to that at baseline. Among these patients, a 71-year-old female patient with baseline platelet count of 142,000/μL was treated with intravenous tocilizumab (320 mg) for 10 consecutive months. The platelet count decreased to 78,000/μL and tocilizumab was discontinued. After discontinuation, the platelet count did not recover to the pretreatment range for 30 months. Thus, careful monitoring of platelet count is recommended in older patients with low platelet count at the time of initiation of treatment with tocilizumab.

The present study has some limitations. Firstly, this was a single-cohort retrospective study. Thus, we cannot exclude the possibility of selection bias. Secondly, it was prudent to conclude that the development of thrombocytopenia was directly related to treatment with tocilizumab; it might be affected partially by the administration of other concomitant treatments.

CONCLUSION

In conclusion, the present findings demonstrate that tocilizumab-induced thrombocytopenia is tolerable. However, the development of thrombocytopenia was associated with old age, and inversely related to higher platelet count at baseline. Careful monitoring of platelet counts is recommended in patients with recognized risk factors.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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