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Original Article

Biomarkers and Choice of Biologic Agent: A Comparison of the Efficacy of Tocilizumab and Etanercept in Rheumatoid Arthritis Patients Presenting with Leukocytosis or Thrombocytosis

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Abstract

Objective: The aim of this study was to evaluate the relative efficacy of tocilizumab (TCZ) and etanercept (ETN) in patients with rheumatoid arthritis (RA) presenting with upper normal limit or high white blood cell (WBC) and platelet counts, and the relative roles of inflammatory cytokines TNFα and IL-6 on the appearance of these hematological abnormalities, by comparing laboratory results from RA patients pre and post administration of TCZ or ETN.

Methods: The influence of TCZ on white blood cell (WBC) and platelet (Plt) counts in 33 RA patients was compared to that of ETN in 38 RA patients at Weeks 0, 12, and 24. The relationship between the presence or absence of WBC>9000 (high normal/leukocytosis) or Plt>35x10^4 (high normal/thrombocytosis) before treatment, and the rate of clinical complete remission by DAS-28 CRP at Week 24 in 33 patients treated with TCZ and 38 treated with ETN was investigated.

Results: In the 33 RA patients treated with TCZ, the pre-treatment mean WBC count (7708/μL) and plt count (29.4×10^4/μL) were significantly decreased to 5970/μL (22.5%↓)and 20.8×10^4/μL (29.3%↓) respectively at Week 12. In the 38 RA patients treated with ETN, initial WBC (7804/μL) and plt (31.7×10^4/μL) counts were also reduced to 6911/μL (11.4%↓)and 25.4×10^4/μL (20.0%↓) respectively at Week 12. The decrease in mean plt count was significantly greater in RA patients treated with TCZ than in those treated with ETN at Week 12 ($p<0.05$). Twelve of the 14 (85.7%) RA cases presenting WBC↑or Plt↑ treated with TCZ achieved complete remission by Week 24, however, only 5 of the 20 (25.0%) cases treated with ETN achieved complete remission by this time. This difference was statistically significant with a X^2 score of 6.6526 ($P<0.01$).

Conclusion: TCZ may be more suitable than ETN as a first-line therapeutic option for RA patients that have upper normal limit platelet count, WBC, thrombocytosis and/or leukocytosis, parameters which may be influenced by IL-6.

Keywords: Tocilizumab; IL-6; Etanercept; TNFα; Rheumatoid Arthritis (RA); Cytokine; Biological Agents

Introduction

Although the etiology of rheumatoid arthritis (RA) is not well understood, both genetic and environmental factors are considered to be involved. Patients with HLA-DRB1 shared epitope alleles exhibit a poorer prognosis than patients with other haplotypes [1,2]. Environmental factors, including several bacterial, viral, and mycoplasma infections have also been implicated in the etiology of the disease. These microbes are recognized by Toll-like receptors (TLRs) expressed on the surface of a wide variety of cells including macrophages, and elicit an innate immune response [3]. Since class II major histocompatibility complex (MHC) loci, such as HLA-DR, are known to promote TLR-triggered innate immunity [4], involvement of innate immunity and subsequent production of cytokine-mediated inflammatory responses are considered keys to the pathogenesis of RA.

Cytokines including tumor necrosis factor alpha (TNFα) and interleukin 6 (IL-6) form the crux of the inflammatory process that drives joint destruction in RA [5]. IL-6 is present in great quantities in the serum and synovial fluid of RA patients, and levels reflect disease activity well [6]. IL-6 is released by lymphocytes and monocytes that infiltrate the synovium, causing inflammation and joint destruction by influencing multiple other cell types (Refer Supplementary Figures (1 and 2)) [5]. This cytokine has been implicated in the development of anemia [6] and leukocytosis [7] in RA patients, and is also known to affect megakaryocytopoiesis, with RA patients with thrombocytosis exhibiting higher IL-6 levels than patients with normal platelet counts [8]. Similarly, TNFα has a broad range of action on many cell types, including macrophages, activated T-cells, B-cells, synovial lining cells and endothelial cells, with myriad pro-inflammatory effects. Like IL-6, TNFα is a key mediator of joint destruction and inflammation in RA. [9].

TNFα inhibitor infliximab (IFX) [10] has been available for the treatment of RA for approximately 11 years in Japan, and more recently, etanercept (ETN) [11], adalimumab (ADA) [12], golimumab [13] and certolizumab pegol have become available. These TNFα inhibitors were proven to be effective in clinical trials of large cohorts in Japan, although their efficacy in combating leukocytosis and thrombocytosis has not yet been examined. Moreover, in Japan the IL-6 receptor inhibitor tocilizumab (TCZ) and the T-cell blocker abatacept [14] have been used as second-line therapeutic options for RA over the last 7 years and the last 4 years, respectively. In addition, these two biologic agents were approved as first line drugs in 2013. The inflammatory cytokines TNFα and IL-6 both play very important roles in disease progression and outcomes of RA; however, the difference in disease response to these agents is not well understood.

While treating RA patients with methotrexate (MTX) and/or biological therapies, a subset of RA patients that presented high normal platelet counts, high normal WBCs, leukocytosis, thrombocytosis, and/or severe anemia were noted at our clinic. Most were in a very clinically active stage of established RA, although some had early RA. Of note, these patients had no evidence of underlying infections or severe iron-deficiency anemia, and it was hypothesized based on the biology of IL-6 action that this hematological disturbance was predominantly due to IL-6 activity rather than TNFα, and as such IL-6 inhibitors may be more effective in this patient group.

In this study, clinical and laboratory responses to TCZ or ETN, including WBC count and platelet count, were compared in 71 RA patients randomized to each treatment group. It was hypothesized that IL-6 may play a greater role in the pathogenesis of thrombocytosis, leukocytosis, anemia, and/or the production of acute-phase reactants (CRP and serum amyloid A protein) than TNF-α although IL-6 levels were not assessed in this study. Results of this study suggest that TCZ used as a first-line biologic agent could be more effective for the treatment of RA patients who present with increased WBC or platelet counts than ETN.

Materials and methods

Patients

In this study, 71 RA patients treated with biological therapies were enrolled. They included 33 patients treated with TCZ at the Keigu Clinic (Yokohama) and the Saiseikai Yokohama City Eastern Hospital (Group 1), and 38 treated with ETN at the Keigu Clinic (Group 2). Owing to different approaches in the enrollment of patients with established RA, the disease parameters of Group 1 and Group 2 differed as evidenced by the differences in disease duration, functional class, and other parameters (Table 1). In order to compare responses in patients with similar disease status, we selected 17 patients with early RA (7 patients from Group 1 and 10 patients from Group 2). 76.8% of Group 1 patients and 71.1% of Group 2 patients were concurrently treated with MTX, respectively. Biologic monotherapy was only considered in cases of MTX intolerance or toxicity. 48.5% of Group 1 and 65.7% of Group 2 patients received steroids.

All patients included in this study were provided with an explanation of the purpose of the study, and gave their written and/or oral consent prior to enrollment. This study was approved by the Yokohama Society of Rheumatology.

RA diagnosis

Established RA patients were diagnosed by close adherence to the 1987 American College of Rheumatology criteria [15]. However, early RA patients were more recently diagnosed according to the 2010 American College of Rheumatology/Eu-

ropean League against Rheumatism criteria [16]. If erosions were not observed on bilateral X-rays of the hands and feet, a classification of early RA was allowed if 6 points or greater were obtained.

Medical and biological drugs

MTX at a dose of 6 to 15 mg/wk was routinely administered in early or established RA cases. MTX was not implemented or was discontinued for some RA patients who complained of persistent nausea or dizziness or who had a history of interstitial pneumonia or hematological disturbances.

In Group 1, 8 mg/kg of TCZ every 4 weeks was used as a second-line biological agent for 17 patients with established RA. Seven patients with early RA and 9 patients with established disease were given 8 mg/kg of TCZ every 4 weeks as a first-line biological agent, which was reduced to 4 mg/kg every 4 weeks after 1 year.

In Group 2, ETN at a dose of 25 mg twice a week for 6 consecutive months was used in 28 patients with established RA. In 10 early RA patients who had favorable clinical responses, 25 mg of ETN twice a week were used for 1 or 2 months and then reduced to 25 mg once a week.

Laboratory tests

In this study, white blood cell count (WBC count), platelet count, and hemoglobin (Hb) were assessed at Weeks 0, 12, and 24. In order to include patients with more subtle hematological disturbances, the slightly lower values WBC>9000 and Plt>35x10^4 were used as cut-offs for leuko- and thrombocytosis instead of WBC>9100 and Plt>36.9x10^4. Changes in parameters in the 33 RA patients treated with TCZ (Group 1) were compared at Weeks 0, 12, and 24 with changes in parameters in the 38 RA patients treated with ETN (Group 2). Anti-CCP antibody was usually tested once at the initial visit, and in accordance with Japanese clinical practice guidelines was not retested thereafter.

Evaluation of efficacy

The clinical response to biologics was evaluated by using the 28-joint disease activity score DAS28-CRP [17] and the Boolean complete remission criteria [18]. Clinical complete remission was considered to be achieved in TCZ patients with a DAS28-CRP score < 2.3, and in ETN patients with a score < 2.6. A lower score was used in the TCZ group, as TCZ is known to inhibit CRP, as has been done in previous studies [17]. Patients achieving Boolean complete remission fulfilled all of the following criteria: tender joint count ≤1, swollen joint count ≤1, CRP level of ≤1 mg/dL, and patient global assessment of ≤1 cm on a 0 to 10 visual analogue scale (VAS).

Statistical Analysis

Patient baseline characteristics were summarized using mean (± standard deviation), median (interquartile range), or *n* (%). The last observation carried forward (LOCF) method was used in each analysis. Statistical significance was determined by Student's *t*-test (for continuous variables) and paired-samples *t*-test. In addition, X^2 test was used for the comparison of the efficacies of TCZ and ETN in patients with RA.

Results

Comparison of treatment group demographics

The demographics of the study patients are shown in Table 1. There were several differences between Group 1 (TCZ) and Group 2 (ETN) with respect to patient background. First, the 7.2 year observation period from diagnosis of RA to initiation of biologic therapies in Group 1 was significantly shorter than the 10.1 years in Group 2. Second, there was a higher percentage of patients with advanced RA (Steinbrocker functional class 3 or 4) in Group 2 (78.9%, 30/38) than in Group 1 (54.5%, 18/33). Finally, the percentage of patients in Group 2 using ETN as the first-line biologic was higher (81.6%) than that of patients in Group 1 (48.5%) using TCZ as a first-line therapeutic agent.

Table 1. Patient demographics.

Cases	Group 1 TCZ (*n*=33)	Group 2 ETN (*n*=38)
Age (yr), mean (range)	64.0(39~81)	63.9(23~90)
Disease duration, yr	7.2(0.2~27.3)	10.2(0.2~40)
Steinbrocker radiographic stage (I:II:III:IV)	(4:5:16:8)	(1:10:18:9)
Steinbrocker functional class (1:2:3:4)	(1:14:18:0)	(0:8:28:2)
Steroid use, %	48.5	65.7
Mean dose of steroid, mg	2.2	3.3
MTX use, %	76.8	71.1
Mean dose of MTX, mg	6.9	7.5
Positive RF, %	76	81.2
Biologic naïve	48.5	81.6
DAS28-CRP	4.64	5.04
peripheral blood examination		
Mean WBC (/μl)	7708	7804
Mean Platelet (/μl)	29.4	31.7
Mean Hb (mg/ml)	11.5	12.4

These differences may be due to the different times at which TCZ and ETN became available in Japan; as ETN was approved four years prior to TCZ, it is more commonly used as a first line agent. In addition, TCZ has only been available as a first line agent since 2013.

Comparison of WBC counts in Group 1 and 2 at Weeks 0, 12, and 24

The mean WBC count of 7708±2767/μL before treatment with TCZ was significantly decreased to 5970±2728/μL (↓22.5%) at Week 12 and to 6258±2668/μL(↓18.8%) at Week 24 (p<0.05). By comparison, the mean WBC count of 7804±1783/μL before treatment with ETN was significantly reduced to 6911±2009/μL (↓11.4%) at Week 12 and to 6811±1739/μL (↓12.7%) at Week 24 (p<0.05*)*. Interestingly, the decrease in mean WBC count at Week 12 appeared to be greater in the group treated with TCZ than in the group treated with ETN (Figure 1), however, this difference was not statistically significant because of a wide standard deviation.

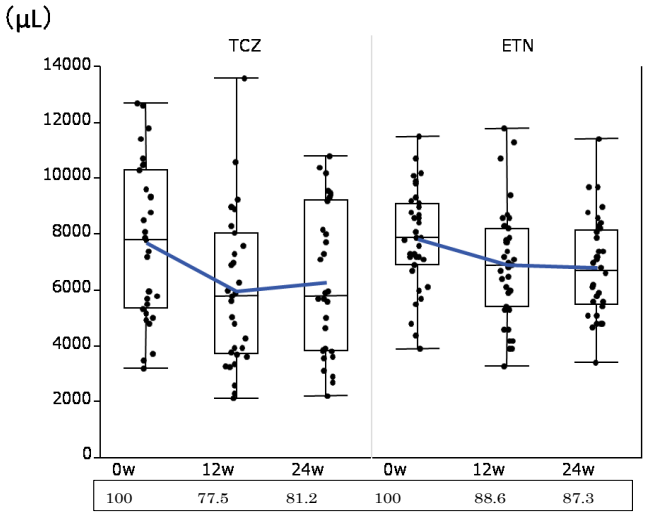

Figure 1: Serial WBC counts of 33 patients treated with TCZ and 38 patients treated with ETN—comparisons at Weeks 0, 12, and 24

Comparison of platelet counts in Group 1 and 2 at weeks 0, 12 and 24

The mean platelet count of 29.4±9.5×10⁴/μL before treatment with TCZ was significantly reduced to 20.8±6.3×10⁴/μL (↓29.3%) at Week 12 and to 22.9±9.9×10⁴/μL (↓22.1%) at Week 24 (p<0.05). Similarly, the mean platelet count of 31.7±9.6×10⁴/μL before treatment with ETN was significantly reduced to 25.4±6.85×10⁴/μL (↓20.0%) at Week 12 and to 24.3±6.07 ×10⁴/μL (↓23.3%) at Week 24 (p<0.05). Interestingly, the decrease in mean platelet count at Week 12 was statistically significantly greater in the group treated with TCZ than in the group treated with ETN (p<0.05) (Figure 2).

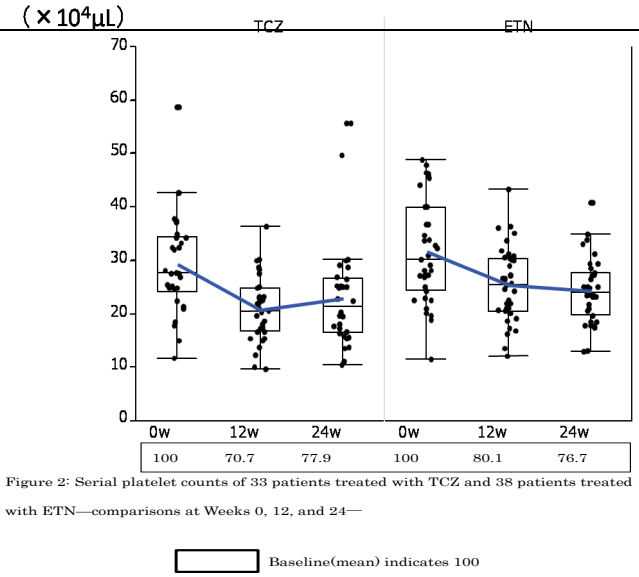

Figure 2: Serial platelet counts of 33 patients treated with TCZ and 38 patients treated with ETN—comparisons at Weeks 0, 12, and 24—

Comparison of hemoglobin levels in Group 1 and 2 at weeks 0, 12 and 24

The mean hemoglobin level was 11.5±1.4mg/ml before treatment with TCZ, and was significantly increased to 12.1±1.5mg/ml (↑5.22%) at Week 12 and to 12.2±1.6 mg/ml (↑6.09%) at Week 24 (p<0.05). By comparison, the mean hemoglobin level of 12.4±1.7mg/ml before treatment with ETN was only marginally increased to 12.7±1.6mg/ml (↑2.42%) at Week 12 and to 12.6±1.6mg/ml (↑1.61%) at Week 24. The difference in hemoglobin increase between the two groups at Week 24 did not reach statistical significance (Figure 3).

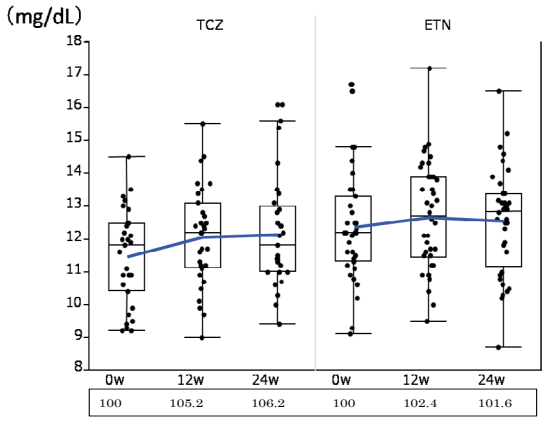

Figure 3: Serial hemoglobin levels of 33 RA patients treated with TCZ and 38 RA patients treated with ETN—comparison at Weeks 0, 12 and 24—

Comparison of achievement of Boolean's complete remission in Group 1 and 2

Of 33 RA patients treated with TCZ, 5 (15.1%) achieved Boolean's complete remission within 3 months, two of whom had early RA. Eleven of 33 (33%) patients in this group achieved

remission within 1 year. All patients with early RA in this group obtained Boolean's complete remission within 2 years, except 2 patients who failed to achieve a patient global assessment VAS score of less than 1cm. Of the 38 RA patients treated with ETN, 7 (18.4%) achieved complete remission within 3 months, five of whom had early stage RA. Ten of 38 (26.3%) achieved remission within 1 year. Patients with an inadequate response to TCZ and ETN, as determined by a CRP> 1mg/ml, were changed to other biologic agents. (Table 2). Eight cases were lost to follow up in Group 1 and two cases in Group 2.

Table 2. Comparison of achievement of Boolean's complete remission in RA patients treated with TCZ and ETN.

Biologics Type	No of Pts	Months to Achieve ≦3	3＜ ≦6	6＜ ≦12	12＜ ≦24	No Achievement	Dropped Out
TCZ	33 (7)	5(2)	4(2)	2(1)	2(2)	12	8
ETN	38 (11)	7(5)	2(1)	1(1)	2(1)	24	(2)

TCZ: Tocilizumab, ETN: Etanercept

( ) : No of early RA

Relationship between the presence or absence of high WBC and/or plt count before treatment and the rate of clinical complete remission by DAS-28 CRP at Week 24 in Group 1 and 2

TCZ and ETN were used in 14 and 20 RA patients presenting with WBC >9000/μl (upper normal/leukocytosis) or platelet count plt>35x10^4/μl (upper normal/thrombocytosis), respectively. In both groups, high normal WBC /leukocytosis and high normal platelets/thrombocytosis were evident before commencing the biologic agents. Surprisingly, 12 of the 14 (85.7%) RA cases treated with TCZ achieved complete remission by DAS 28- CRP: 2.3 at Week 24, however, only 5 of the 20 (25%) cases treated with ETN achieved complete remission by DAS28–CRP: 2.6 at Week 24. This difference was statistically significant with a X^2 score of 6.6526 (P<0.01).

In contrast, TCZ and ETN were used in 19 and 18 RA patients not presenting with high normal WBC/leukocytosis or high normal platelet count/thrombocytosis, respectively. Twelve of the 18 (66.7%) cases of RA treated with ETN reached complete remission by Week 24, however, only 10 of the 19 (52.6%) cases of RA treated with TCZ achieved complete remission. Furthermore, of the 33 cases of RA treated with TCZ, the proportion of patients achieving remission was higher in the group that presented with high normal WBC/leukocytosis or high normal platelets/thrombocytosis (87.5%, 12/14) than in patients without these abnormalities (52.6%, 10/19). However, this difference was not statistically significant (Table 3).

Table 3. Relationship between the presence or absence of leukocytosis or thrombocytosis before treatment and the rate of clinical complete remission by DAS-28 CRP at Week 24 in Group 1 and 2.

TCZ(33)				ETN(38)			
WBC↑ or Plt↑	DAS28-CRP <2.3	Total	Remission rate %	WBC↑ or Plt↑	DAS28-CRP <2.6	Total	Remission rate %
Yes	Yes	12	12/14(87.5%)	Yes	Yes	5	5/20 (25%)
Yes	No	2		Yes	No	15	
No	Yes	10	10/19(52.6%)	No	Yes	12	12/18 (66.7%)
No	No	9		No	No	6	

TCZ ( ): Tocilizumab (total patients), ETN ( ): Etanercept (total patients)

WBC ↑: >9000/μl, Plt ↑: >35x10^4/μl

DAS: Disease Activity Score

Limitations

This trial was conducted on a relatively small patient cohort, all of whom were ethnically Japanese. These results therefore may not be generalizable beyond this population, and further studies should be considered to confirm this. In addition, while in early RA it is easier to attribute leuko- and/or thrombocytosis to the disease, patients with established RA may have multiple other possible causes for these abnormalities such as infection or steroid use. This may reduce the reliability of using WBC or platelet count as a biomarker for selection of an appropriate biologic agent.

Discussion

Interleukin 6 (IL-6)/B cell stimulating factor 2 (BSF-2) was first discovered and cloned in 1986 [19]. IL-6 was found to stimulate the proliferation of myeloma cells [20] and to promote platelet production in mice [21], and is known to contribute to anemia, leukocytosis and thrombocytosis in RA patients (6,7,8). TCZ is a humanized antibody targeting the IL-6R that was first produced in Japan for the treatment of RA, and is distinct from TNFα inhibitors. In previous studies of patients with Castleman disease and systemic juvenile idiopathic arthritis, diseases in which overproduction of IL-6 is a key feature [22], IL-6R inhibitors have been shown to markedly reduce WBC and plt count within one month [23,24].

The differing efficacies of the wide range of available biologic agents have been the subject of many studies. The efficacy of TCZ and ADA monotherapy were compared in a large, randomized, double-blind controlled trial (the ADACTA study); TCZ monotherapy was found to be more effective [25]. TCZ was also shown to be more effective than MTX in another trial;

49.2% of patients given TCZ monotherapy achieved an ACR50 response and 29.5% achieved ACR70 at 24 weeks, in contrast with MTX monotherapy where only 10.9% achieved an ACR50 response and 6.3% achieved ACR70 [26]. DAS28-ESR scores of <2.6 were attained by 47.2% of RA patients treated with TCZ monotherapy and by 2.8% treated with MTX. These results indicate that efficacy of TCZ monotherapy in RA is superior to therapy with MTX alone. In addition, another study showed the mean modified total Sharp score (mTSS) of 2.3 obtained in RA patients treated with TCZ monotherapy at 52 weeks was significantly lower than the mTSS of 6.1 in RA patients treated with MTX (6–8 mg/wk) alone over the same period [27]. TCZ plus MTX versus TCZ alone has also been examined in one study, in which patients who did not tolerate MTX + TCZ were given TCZ monotherapy; TCZ alone was found to be equally effective [28].

However, ETN or ADA combined with MTX has been shown to be more effective than ETN or ADA monotherapy [29,30], and monotherapy with ETN or ADA is not as effective as MTX monotherapy [30].

TCZ has been shown as an appropriate choice for inadequate responders to MTX. In a randomized placebo-controlled trial of TCZ in MTX inadequate responders, the rate of accomplishment of DAS28-ESR<2.6 in the TCZ 8 mg/kg group (47.2%) was much higher than that of the placebo group (7.9%). TCZ was also found to have an adequate safety profile [31]. Likewise, in RA patients with disease refractory to TNF blockers, TCZ 8mg/kg proved safe and effective in another randomized placebo-controlled trial [32].

Administration of TCZ is associated with neutropenia in RA patients; however, it remains unclear why leukocyte recruitment from bone marrow to the peripheral circulation is affected by treatment with TCZ. WBC counts have been shown to be markedly reduced on the first day of treatment [33], and although WBC counts return to the normal range over time, they do not recover to initial levels for two to three months. As IL-6 enhances platelet release from megakaryocytes directly, the phenomenon of decreased platelet count following TCZ therapy is more easily understood. In the present study, the decrease in levels of leukocytes and platelets was significantly greater in patients on TCZ therapy than in those on ETN therapy, suggesting that TCZ has a more direct effect on bone marrow than ETN.

In addition, although not statistically significant, recovery from anemia was quicker in patients receiving TCZ treatment than in those on ETN. This may be related to the effect of TCZ on the blockade of hepcidin production, and on aberrant regulation of absorption of iron in the intestine and release of iron from the spleen [34].

It is known that both TNF-α and IL-6 are involved in the pathogenesis of RA, however, while undoubtedly some pathways are shared, it is likely that both cytokines also have independent pathogenic effects. While TNFα has been reported to be the primary cytokine responsible for the pathogenesis of RA [35], and that IL-6 is dependent upon TNFα, this may not be the case. In the RISING study, a randomized double-blind trial, patients treated with infliximab (IFX) were found to be divisible into two groups. The first group (80% of patients) maintained therapeutic IFX concentrations (>1μg/ml), and IL-6 was suppressed to less than 10pg/ml. These patients achieved good disease control. The second group (20%) also maintained therapeutic IFX concentrations, but IL-6 was not suppressed (>10pg/ml). These patients did not achieve good disease control [36]. This suggests that TNFα suppression does not always result in IL-6 suppression; as such, in these patients IL-6 is able to act independently. Should this be the case, identifying which cytokine plays a greater role in the disease process of each patient may assist with choosing a more effective biologic agent. This study's demonstration of the benefit of TCZ over ETN for RA patients with high normal WBC/leukocytosis and high normal platelets/thrombocytosis may suggest that different patients with RA may be more affected by overactivity of one cytokine than another (IL-6 dominant or TNFα dominant disease). As IL-6 is more directly involved in megakaryocytopoiesis and is known to increase circulating platelet count (8), and can also contribute to increased WBC (7), it may be that patients with "IL-6 dominant" RA are more likely to present with thrombo- or leukocytosis, and consequently are also more likely to respond to TCZ.

TCZ has been shown in many studies to be an effective, safe treatment for patients with RA. The results of this study suggest that in patients who present with high normal WBC/leukocytosis or high normal platelets/thrombocytosis, TCZ may be more effective than the TNFα inhibitor ETN. This may be due to relatively high IL-6 activity in these patients causing hematological disturbances. Accordingly, TCZ is likely a more effective choice of first-line agent in early or established RA patients presenting with high normal platelets/thrombocytosis [37], high normal WBC/leukocytosis, or severe anemia.

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Conflict of interest

None declared

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