Efficacy and safety of tocilizumab in treatment of Takayasu arteritis: A systematic review of randomized controlled trials

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Running Title

Tocilizumab in Takayasu arteritis

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Abstract

Background: Takayasu arteritis (TAK) is a chronic immune vasculitis in which Interleukin-6 (IL-6) receptors play a key role in pathogenesis. Tocilizumab (TCZ), an IL-6 receptor antagonist with a favorable safety and efficacy profile, has been tried as an option for patients with TA. This systematic review analyzed the evidence from randomized control trials (RCT) assessing the safety and efficacy of TCZ in patients with TAK.

Methods: MEDLINE, Embase, the Cochrane Library, and clinical trial registries were searched from inception to July 2018. We included RCTs assessing the efficacy and safety of TCZ versus placebo/other comparators for the treatment of patients with TAK. The risk of bias (RoB) was assessed using Cochrane RoB tool.

Results: 2799 identified articles were screened as per abstract and title; 42 selected full-texts articles were assessed for the potential inclusion. One trial, reported in two publications, comparing subcutaneous TCZ (162 mg/week) versus matching placebo in 36 patients with TAK was included. The relapse-free rate at 24 weeks was 50.6% and 22.9% in TCZ and placebo arm, respectively. The hazard ratio (HR) for time to first relapse was statistically significant in the per-protocol population (HR 0.34 [95.41% CI, 0.11-1.00]; $p = 0.0345$), while non-significant in the intention-to-treat population (HR 0.41 [95.41% CI, 0.15-1.10]; $p = 0.0596$). The serious adverse events were higher in the placebo arm.

Conclusions: This systematic review finds the existing evidence from RCTs on efficacy and safety profile of TCZ in TAK to be promising but limited. Additional evidence is required to draw a stronger conclusion.

Keywords: Takayasu Arteritis; Large Vessel Vasculitis; Systematic Review; Tocilizumab; Meta-Analysis

Introduction

Takayasu arteritis (TAK) is a chronic immune vasculitis that is characterized by inflammation of the aorta and its primary branches.¹ TAK is a rare disorder seen worldwide and is more common in Asia and the Middle East.² Limited data is available on the global and regional epidemiology of the disease. The estimated prevalence ranged from 40 per million in Japan to 0.9 per million in the US.³ In the European population, the prevalence of TAK ranged from 4.7 to 33 per million.³ TAK predominantly affects young women with age of onset between 10-40 years.⁴ TAK leads to a significant decrease in quality of life with a profound decline in social functioning and physical and mental health.⁵⁻⁷

Typical medical management of TAK mainly focuses on remission induction, remission maintenance and treatment of relapse by controlling the inflammatory process and the associated complications that develop. Oral glucocorticoids (GCs) are currently the mainstay of treatment for TAK.^{8,4,9} Patients with TAK often require high maintenance GC dosing and are often at risk for chronic steroid toxicity.¹⁰⁻¹² Furthermore, due to the high relapse rate of up to 50% in patients undergoing dose tapering, often immunosuppressant agents such as azathioprine, cyclophosphamide, methotrexate, or mycophenolate mofetil are added to the treatment regimen.^{13,14} The toxicity of these drugs remains the main cause of concern. Relapses are frequent even with these drugs suggesting the need for further studies exploring the treatments with novel mechanisms of action.

The pathogenesis of TAK is poorly understood; however, interleukin 6 (IL-6) is thought to play a key role in the pathogenesis. Cell-mediated mechanisms are thought to be the cause of the thickening and narrowing of the affected vessels, resulting in various symptoms.^{1,15,16} Increased levels of inflammatory cells (Th17, and Th1) and cytokines (IL-6, TNF- α) are observed in

patients with TA.^{17,18} While the presence of IL-6 is known to increase the production of Th17 cells and action of transforming growth factor β (TGF- β),¹⁹ the patients with TAK are often present with higher expression of Th17-related cytokines.¹⁷ Hence, the Th17-related cytokines may contribute to the pathogenesis or symptoms of TA.^{17,19} Therefore, inhibition of the IL-6 receptor seems to be a potential target for the treatment of patients with TA, which also presents a different mechanistic approach than that of GCs.²⁰

Attributable to the IL-6 receptor antagonist's action, favorable toxicity profile, and good efficacy, tocilizumab has been studied as a therapeutic agent for patients with TA.²¹⁻²⁴ Tocilizumab is the first humanized monoclonal antibody targeting the IL-6 receptor subunit alpha (IL-6R α). Tocilizumab not only helps to control the disease activity but allows for the reduction of steroid dose (steroid-sparing property).²⁵ Numerous observational studies and subsequent systematic reviews of observational studies have demonstrated a positive effect of tocilizumab in the treatment of patients with TA.²⁵⁻³⁰ To our knowledge, there is no published systematic review of randomized control trials (RCTs) explicitly assessing the efficacy and safety of tocilizumab for the treatment of TA. Hence, the objective of this study is to systematically review the existing literature of RCTs evaluating the efficacy and safety of tocilizumab in patients with TA.

Methods

Protocol

Prior to conducting this study, the protocol was registered with PROSPERO (Registration No-CRD42017064542).³¹ This systematic review was reported in accordance with the Preferred

Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Supplementary Table S1).³²

Search strategy/data sources

The published RCTs investigating the efficacy and safety of tocilizumab in TAK were searched comprehensively in the major databases including MEDLINE via PubMed, Embase, and the Cochrane Library (inception to 12th July, 2018) (search strategy available in Supplementary Table S2). To identify ongoing and unpublished RCTs, clinical trial registries (ClinicalTrials.gov, UMIN-CTR, ChiCTR, EU Clinical Trials Register, ANZCTR, CriS, Thai Clinical Trials Registry, CTRI, and WHO International Clinical Trials Registry Platform (ICTRP)) were searched. The major conference proceedings (European League Against Rheumatism (EULAR), American College of Rheumatology/Association of Rheumatology Health Professionals (ACR/ARHP) Annual Meetings, Society for Vascular Medicine (SVM) Annual Scientific Session, European Society for Vascular Medicine (ESVM) Congress, International Society on Thrombosis and Haemostasis (ISTH) Congress, Scientific and Standardization Committee (SSC) Meeting of the ISTH) of the last five years were also queried.

The authors of relevant published and registered RCTs were contacted to request clinical outcome data for inclusion in the systematic review as per the primary and secondary outcomes specified in the registered protocol. The bibliographies of potentially eligible studies and relevant systematic reviews were reviewed to identify any unpublished or ongoing research. Well-known researchers in this clinical area were consulted to identify any other potentially relevant articles not otherwise indexed or discoverable.

Study selection and exclusion criteria

All published and unpublished RCTs assessing the safety and efficacy of tocilizumab treatment in patients with TAK were considered for inclusion. Non-randomized trials, observational studies (case-control, cohort studies, and case series) and single-patient case reports or studies only having a single TAK patient treated with tocilizumab were excluded. The major clinical trial registration sites were searched to identify the relevant ongoing RCTs assessing the safety and efficacy of tocilizumab treatment in the patients with TAK.³¹

Studies were selected based on the pre-specified inclusion criteria outlined in the registered protocol (CRD42017064542).³¹ Two reviewers (Ambrish Singh, Salman Hussain) independently reviewed potential studies for inclusion. Disagreements between the reviewers were resolved by consensus. Any unresolved issues were referred to the arbiters.

Data extraction

Two reviewers (SH, AS) independently extracted data from the included studies, including information on the study population, disease duration before tocilizumab initiation, age at tocilizumab initiation and duration of tocilizumab, previous and concomitant immunosuppressive agents, primary (efficacy) and secondary (safety) outcomes, and analyses performed in the studies. The data were collected using a standardized extraction template.

Assessment of risk of bias and quality of reporting

The risk of bias in the included study was assessed using the Cochrane Risk of Bias (RoB) tool. The Consolidated Standards of Reporting Trials (CONSORT) is used for reporting randomized trials in journal and conference abstracts.^{33, 34} Quality of the reporting in the included study was assessed using CONSORT guidelines. Review Manager version 5.3 (RevMan) was used for the assessment of the risk of bias.³⁵

Results

Literature search/Search output

The search strategy details were presented in the supplement S2 and the results in the PRISMA flow diagram (Figure 1). The search identified 2,799 potential articles through various database searching. No article was identified from other sources (bibliography search, clinical trial registries search, and grey literature search). After removing 418 duplicates, we screened 2,382 articles for potential inclusion. Two thousand and forty-one (2,041) articles were excluded based on the title and abstract screening. The full-texts of the remaining 42 articles were reviewed for inclusion, and 40 articles were excluded. Eight articles were excluded due to study design, 21 due to the population not of interest, and 11 due to outcome not of interest. Two articles reporting the same RCT published as conference abstract and full-text qualified for inclusion in the systematic review.

Included studies characteristics

Two articles, one conference abstract³⁶ and one full-text article by Nakaoka *et al.*³⁷, reporting the same RCT was found eligible for inclusion in the systematic review (Table 1). This randomized, double-blinded, placebo-controlled, phase 3 trial enrolled 36 patients of age ≥ 12 years receiving GC therapy (≥ 0.2 mg/kg/d prednisolone equivalent) who had relapsed ≤ 12 weeks before enrollment in the study. The patients were required to be on stable GC dose at $\geq 2\times$ dose at relapse and to be in remission for 1 week before the randomization. The patients were randomly assigned 1:1 to receive subcutaneous tocilizumab 162 mg or matching placebo every week. The GC dose was tapered during the study at a rate of 10% per week starting from week 4. The time to first relapse to TAK on the per-protocol defined criteria in the intention-to-treat (ITT) population assessed through the Kaplan-Meier analysis method using log-rank test stratified by

age (<18 years, 18–64 years, ≥ 65 years) was the primary outcome of the study. The time to relapse by Kerr's definition was the secondary endpoint of the study.

Excluded studies characteristics

The majority of studies were excluded at the title and abstract screening and full-text screening stages. The key criteria for exclusion were population not of interest (n= 21), outcome not of interest (n= 11), and study design not of interest (n= 8). Table 2 presents the characteristics of the notable studies excluded from the systematic review.

Assessment of risk of bias

The overall risk of bias graph and summary is shown in Figure 2A and 2B, respectively. Along with the parameters assessed, only the random sequence generation, incomplete outcome data, and the other potential sources of bias were judged as having an unclear risk of bias; whereas, none of the parameters were assessed as the high risk of bias.

Assessment of quality of reporting

The quality of reporting in the included study was assessed using the CONSORT checklist. Nakaoka *et al.*³⁷ reported all the major required items as per the CONSORT reporting guideline for full-text articles except the setting/locations where the data was collected and the details on random sequence generation. In addition, the study did not provide the patients' disposition using a participant flow diagram that is strongly recommended in the reporting of RCTs. (Supplementary Table 3)

Statistical analysis

There was no scope for meta-analysis in this study because only one study qualified the inclusion criteria.³⁸⁻³⁹ The primary outcome of the study was to assess the efficacy of tocilizumab based on

the time to first relapse and the secondary outcome was to assess the safety parameters. The review, therefore, consists of a qualitative assessment and narrative analysis.⁴⁰⁻⁴¹

Evaluation of efficacy

The only study included in this systematic review did not assess many of the primary outcomes of the systematic review (C-reactive protein levels and erythrocyte sedimentation rate) as listed in our review protocol (CRD42017064542). Table 3 provides a summary of the efficacy outcome assessed by Nakaoka *et al.*³⁷ study.

Time to relapse

As per the protocol definition and Kerr's definition, eight patients of tocilizumab arm relapsed compared to 11 in the placebo arm in the intent-to-treat (ITT) population, while seven patients of tocilizumab arm relapsed compared to 11 in the placebo arm in the per-protocol population (PPP) (Table 1). The time to relapse for the tocilizumab arm was not statistically significant in the primary endpoint of the included TAKT trial (time to first protocol-defined relapse in the ITT population, HR = 0.41; 95.41% CI 0.15–1.10; P = 0.0596). However, the time to relapse for the tocilizumab arm was significantly longer than the placebo arm, as per the PPP analyses (HR=0.34, 95.41% CI 0.11 to 1.00; p=0.0345) (Table 3). The relapse-free rate at 24 weeks follow-up was, 50.6% and 22.9% in ITT analysis, and 51.7% and 16.7% for PPP analysis in the tocilizumab and placebo arm, respectively (Table 3). The study examined the GC tapering effect with mandatory GC tapering in both study arms. The reduction in GC dose to its minimum, without disease relapse, was observed in eight patients in the tocilizumab arm compared to three patients in the placebo arm.

Other outcomes

The analysis of various subgroups such as gender, prednisolone-equivalent GC dose category at randomization, disease duration, history of Disease-modifying Antirheumatic Drugs (DMARDs)/immunosuppressant treatment, and HLA-B52 status consistently demonstrated the longer time to relapse for tocilizumab arm compared to the placebo arm.

Evaluation of safety

A higher number of patients from the tocilizumab arm reported the adverse events (AEs) than that of patients from placebo arm (Table 4). However, the observed safety profile in this study was comparable to AEs reported with tocilizumab therapy in RA and GC therapy in giant cell arteritis. Moreover, only one patient reported serious AEs from the tocilizumab arm compared to two from the placebo arm. None of the patients had injection site reactions or systemic injection reactions, and no death was reported during the study.

Discussion

This is the first systematic review of RCTs of tocilizumab therapy for the treatment of patients with TAK. The single RCT identified in our systematic review assessing the effect of tocilizumab in patients with TAK reported data only on a few of the pre-specified outcomes for this review. The evidence supported the use of tocilizumab with reduced time to relapse in adult patients with TAK compared to placebo with no additional safety concerns. No data were available for the pre-specified primary outcome of C-reactive protein levels and erythrocyte sedimentation rate as mentioned in the review protocol (CRD42017064542).³¹ However, our study reported the primary outcome of time to relapse as described in the included RCT. Other key clinical efficacy outcomes reported were, relapse-free rate and number of patients decreasing GC dose. The reported safety profile was comparable with that of tocilizumab therapy in RA and GC therapy in giant cell arteritis.⁴²

Many observational studies, primarily case series studies, have assessed the efficacy and safety of tocilizumab in patients with TAK.^{43-45,27,46,23,47-49,29} Furthermore, the systematic reviews comprising these non-randomized studies have confirmed the safety and efficacy of tocilizumab in patients with TAK.^{21,50} Our review also found that the use of tocilizumab demonstrated efficacy with no additional evidence of notable AEs in patients with TAK. Nonetheless, the current evidence is based on one single-center RCT comparing tocilizumab with placebo (TAKT trial) in a study with a relatively smaller sample size (n=36). Phase 3 TAKT trial demonstrated a trend toward relapse suppression in favor of tocilizumab over placebo in the primary outcome measure analysis (time to first protocol-defined relapse was not statistically significant in the ITT population).³⁷ However, the sensitivity analyses in the PPP reported a statistically significant superiority of tocilizumab over placebo. Additionally, tocilizumab arm showed numerically favorable (though not statistically significant) trends for improvement in objective systemic symptoms, subjective systemic symptoms, elevated inflammation marker levels, vascular lesions, and ischemic symptoms accompanied by organ lesions.³⁷ Based on TAKT trial³⁷, tocilizumab was approved in August 2017 for the treatment of TAK in Japan.

Biological therapies are normally used as second-line treatment in current practice and options such as mycophenolate mofetil and methotrexate are shown to be effective in minimizing GC-associated toxicity in patients with TAK.^{13,8} Hence, in the included study, choice of placebo as a comparator to tocilizumab should also be considered while interpreting the results. The applicability of the evidence to broader healthcare settings with a heterogeneous population is yet to be established. Furthermore, the evidence on long-term efficacy and safety of tocilizumab in this population is lacking. Although the included RCT (Nakaoka et al.³⁷) in this review was assessed as having a low risk of bias, we advise caution while interpreting the overall conclusion.

The small sample size of the included study may not reflect the true differences between treatment and control arms.

A strength of our systematic review is that we worked to minimize the bias by following the published systematic review protocol. We not only conducted the systematic search of key databases for RCTs, but also scanned the major clinical trial registries, grey literature, and other possible sources of relevant data. As per the need, we contacted authors of the primary study and other opinion leaders to obtain relevant methodological and/or clinical outcome data. None of the authors from the included study was involved in selection or data extraction for this systematic review. A limitation of our review is that we only included studies published in English.

Overall, with our study, we established a clear gap in evidence from RCTs to confirm the efficacy of tocilizumab in patients with TA. Although, tocilizumab appears to have an acceptable safety profile and promising clinical efficacy in patients with TA, a sufficiently powered multi-center RCT assessing the outcomes such as GC-sparing effect, remission and reduction in relapse is eagerly awaited to provide definite evidence to answer this research question.

Conclusion

Tocilizumab has shown promising results as a treatment option for patients with TAK in numerous observational studies and subsequent systematic reviews of such studies. However, we identified only one RCT that has explored the safety and efficacy of tocilizumab in this population. Although few of the outcomes assessed in this RCT were encouraging, our systematic review demonstrated a clear evidence gap and found existing evidence from RCTs on efficacy and safety of tocilizumab in patients with TAK to be limited to make a strong

conclusion. Larger RCT assessing the key outcomes for the treatment of patients with TAK is warranted.

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Figure Legends

Fig.1 PRISMA flow diagram

Fig.2 The overall risk of bias graph and summary

Tables

Table 1: Characteristics of the included studies

Study, year, country	Study design	Sample size (ITT population)		Age, years, mean (SD)		Female, n (%)		Median Disease Duration (years)		GC dose at randomization, Mean (SD) [mg/kg/d]		HLA-B52 positive (%)		Relapse rate, n (%)	
		TCZ	Placebo	TCZ	Placebo	TCZ	Placebo	TCZ	Placebo	TCZ	Placebo	TCZ	Placebo	TCZ	Placebo
Nakaoka <i>et al.</i> , 2018, Japan ³⁷	Double blind Placebo- Controlle d RCT	18	18	31.1 (18.1)	30.8 (13.1)	16 (88.9)	15 (83.3)	3.3 3	2.89	0.57 (0.19)	0.52 (0.16)	38.9	72.2	8 (44.4%)	11 (61.1%)

ITT: Intention to treat; GC: Glucocorticoid; TCZ: Tocilizumab;

Table 2: Characteristic of the key excluded studies

Author, year, country	Study design	Study Population				Study Outcome	
		<i>Sample size</i>	<i>Female, %</i>	<i>Age, median</i>	<i>Median disease duration, month</i>	<i>Efficacy Results</i>	<i>Safety Results</i>
Seitz <i>et al.</i> , 2011, Switzerland ⁴⁸	Case series	2	50	34	57	All patients achieved a rapid and complete clinical response and normalization of the acute phase proteins	No drug-related side effects were noted
Unizony <i>et al.</i> , 2012, United States ²⁹	Case Series	2	NR	41	20	All patients achieved and maintained clinical remission. Serologic and radiologic improvements were also observed	Transaminitis and mid neutropenia were noticed in four patients.
Salvarani <i>et al.</i> 2012, Italy ⁴⁷	Case report	4	50	47	NR	All patients showed significant clinical improvement	No serious drug-related side effects were noted
Goel <i>et al.</i> 2013, India ²⁴	Case series	10	NR	24.5	25.5	Immediate response good in all, but only 60% of patients maintained clinical response at	No major adverse events were noticed

						the last visit. TCZ acted as a steroid-sparing, fast-acting and stopgap option to tide over disease flare.	
Tombetti et al. 2013, Italy ⁴⁹	Case series	7	100	24	66	Complete response was achieved in less than 50% of the patients	Recurrent respiratory infections (n=2) and severe maculopapular rash (n=1) were the most common reported adverse event
Osman et al. 2015, Canada ²³	Case series	3	66	29	23	All patients clinically, biochemically and radiographically	No drug-related side effects were noted
Loricera et al. 2016, Spain ²⁶	Case series	8	100	36	NR	90% of patients experienced significant clinical improvement	Mild thrombocytopenia and systemic lupus erythematosus were noticed in a single patient.
Batu et al. 2017, Turkey ⁴³	Case series	4	100	14.5	30	All patients achieved a complete response	No drug-related side effects were noted
Mekinian et al. 2018, France ⁴⁶	Case Series	46	35	43	NR	A total of 89% of patients achieved the treatment response	Event-free survival was better in comparison to DMARDs

DMARDs: Disease-Modifying Antirheumatic Drugs; NR: Not Reported

Table 3: Summary of the study outcomes

Study, year, country	Relapse-free rates at 24 weeks, % (95% CI)				Hazard ratio		AEs, n (%)		SAEs, n	
					ITT	PP populati on				
	TCZ		Placebo				TCZ	Placebo	TCZ	Placebo
	ITT	PP	ITT	PP						
Nakaoka <i>et al.</i> , 2016, Japan ³⁷	50.6 (25.4-75.8)	51.7 (25.3-78.0)	22.9 (0.4-45.4)	16.7 (0.0-37.5)	0.41 [95.41% CI, 0.15-1.10] <i>p</i> = 0.0596	0.34 [95.41% CI, 0.11-1.00] <i>p</i> = 0.0345				

AEs: Adverse Events; ITT: Intention-To-Treat; PP: Per Protocol; SAEs: Serious Adverse Events; TCZ: Tocilizumab

Table 4: Detailed safety outcome

Characteristics	TCZ (n=18)	Placebo (n=18)
Patients with ≥ 1 AE, n (%)	14 (77.8)	11 (61.1)
Events, n	38	31
Patients with ≥ 1 adverse drug reaction, n (%)	5 (27.8)	3 (16.7)

<i>Most frequent AEs by SOC*</i>		
<i>Infections and infestations, n (%)</i>	9 (50.0)	6 (33.3)
<i>Gastrointestinal disorders, n (%)</i>	3 (16.7)	5 (27.8)
<i>Skin and subcutaneous tissue disorders, n (%)</i>	6 (33.3)	1 (5.6)
<i>Eye disorders, n (%)</i>	1 (5.6)	2 (11.1)
<i>Nervous system disorders, n (%)</i>	2 (11.1)	1 (5.6)
<i>Respiratory, thoracic and mediastinal disorders, n (%)</i>	0	3 (16.7)
<i>Investigations, n (%)</i>	0	2 (11.1)
<i>Psychiatric disorders, n (%)</i>	1 (5.6)	1 (5.6)
Patients with ≥ 1 SAE, n (%)	1 (5.6)	2 (11.1)
Events, n	1	3
<i>SAEs by SOC</i>		
<i>Eye disorders, n (%)</i>	1 (5.6)	1 (5.6)
<i>Gastrointestinal disorders, n (%)</i>	0	1 (5.6)
<i>Vascular disorders, n (%)</i>	0	1 (5.6)

*AEs reported in >1 patient in either treatment group. AE: Adverse Event; SAE: Serious Adverse Event; SOC: System Organ Class; TCZ: Tocilizumab