Efficacy and safety of biological agents in the treatment of patients with Takayasu arteritis: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: We aimed to systematically review biological agents' efficacy and safety in patients with Takayasu arteritis (TAK).

MATERIALS AND METHODS: A systematic literature search of 7 electronic databases, including MEDLINE (via PubMed), EMBASE, Elsevier ScienceDirect, EBSCO, Springer Link, Web of Science, and Cochrane Library on the efficacy of biological agents on patients with TAK was conducted. Only studies published in English and with a sample size >5 patients with TAK were included. Two reviewers independently selected studies, extracted data and assessed its methodological quality. Random effects meta-analyses of various effect measures were performed.

RESULTS: According to the title and abstract, 961 studies were identified and screened. Subsequently, 31 studies from 29 observational studies and 2 randomized-controlled trials (RCTs), which included a total of 517 patients with TAK that met the inclusion and exclusion criteria, were selected. Observational studies showed a high risk of bias. Pooled remission rates of biological agents were 66% (95% CI: 58%-73%; I2=59%), and the remission rates of anti-tumor necrosis factor (TNF) agents and tocilizumab (TCZ) were similar: 65% (95% CI: 56%-73%; I2=49%) and 70% (95% CI: 55%-86%; I2=69%), respectively. Pooled relapse rates were 23% (95% CI: 15%-31%; I2=66%). The relapse rate was 28% (95% CI: 16%-40%; I2=68%) for anti-TNF agents and 17% (95% CI: 7%-26%; I2=49%) for TCZ. The remission rate of TCZ was slightly higher (*p*>0.05), but the relapse rate was statistically significantly lower than that of anti-TNF agents (*p*=0.017). Furthermore, biological agents significantly decreased the doses of glucocorticoid (GC) and levels of acute phase inflammation markers (ESR, CRP) while the proportion of patients with new angiographic lesions or progression of previously noted lesions were 11% (95% CI: 4%-18%; I2=59%). RCTs with a small sample size showed abatacept was ineffective, and TCZ was underpowered to detect a difference in time to relapse compared to placebo. The most common adverse event of biological agents was infection (6%, 95%CI: 2%-10%). No deaths were reported.

CONCLUSIONS: Although the beneficial effects of biological agents are encouraging in enhancing disease remission, reducing the levels of acute phase inflammation markers and decreasing the treatment doses of GC in patients with TAK, there is still a risk of relapse. More refined studies with larger cohorts are necessary before drawing a definitive opinion.

Key Words:
Takayasu arteritis, Biological agents, TNF, Tocilizumab, Efficacy, Adverse events.

Introduction

Takayasu arteritis (TAK), also known as aortic arch syndrome, non-specific aortic arteritis or pulseless disease, encompasses a variety of chronic, non-specific inflammatory disease of unknown etiology. It appears to be more common in Asia compared to North America[1,2]. Two epidemiologic studies[3,4], one from western Turkey, reported an incidence of 1.1 per million, while another study from northwestern Turkey indicated a higher incidence of 3.4 per million, based on the population aged 16 and over. TAK predominantly affects females compared to males with a ratio of 6.6 to 1, and its onset age is usually below 40 years old. Confounding factors of TAK include race, gender, genetics, infection, endocrine and immunological dysregulations[1,5,6]. Physiologically, TAK affects a wide range of arteries causing various inflammatory responses and tissue inju-

ries between different individuals. Patchy granulomatous polyarteritis of the aorta and its major branches are typical of TAK, resulting in local pain, stenosis, occlusion, and aneurysm formation. End-organ ischemia due to these vascular changes and non-specific systemic symptoms caused by sterile inflammation are responsible for most of the clinical manifestations, such as weakened pulse, unequal blood pressure on both limbs, intermittent claudication, angina, abdominal pain, dizziness, hemiplegia, low fever, weight loss, joint pain, etc.[7,8].

In recent years, TAK has received much attention due to the high relapse rate, extensive vascular complications, and increase in mortality[9]. The first-line medication recommended for TAK currently is a glucocorticoid (GC). Although GC therapy alone may achieve clinical remission in almost 60% of patients, it is prone to relapse when GC doses are tapered. Therefore, traditional disease-modifying anti-rheumatic drugs (DMARDs, i.e., cyclophosphamide, methotrexate, mycophenolate mofetil) are also prescribed during the onset of treatment[10]. Despite this, up to 10% of patients remain with an active TAK disease, and many suffer from frequent adverse events or/and severe sequelae[11,12]. On the other hand, scientists have also explored the therapeutic potential of biologics in TAK. It is encouraging several recent studies[13,14] have reported that anti-IL-6 agents (such as tocilizumab [TCZ]) can be more effective than traditional DMARDs (most cyclophosphamide [CTX]) in mitigating vascular inflammation and remodeling arterial structure of TAK patients.

Biological agents have been demonstrated to be an effective treatment regimen for various autoimmune disorders[15,16] and are increasingly used to treat TAK patients who are insufficiently responsive to GC or GC+ DMARDs[17]. Some of these biologics, such as anti-tumor necrosis factor (TNF) agents (infliximab [IFX], adalimumab [ADA], etanercept [ETN]), TCZ, anti-CD20 agents (rituximab [RTX]), CTLA4-Ig (abatacept [ABA]), and tofacitinib citrate have been shown to significantly improve the clinical and imaging indices of TAK[18,19]. Other studies found that the administration of anti-TNF agents in refractory TAK patients who had already received GC and DMARDs treatment could result in highly varied inflammatory responses and high relapse rates[20]. However, we noted that these data were mostly derived from small observational studies and case studies. To date, there is no definitive evidence available that favors one treatment over another for TAK. In this meta-analysis study, a) we have chosen more researches, including those with anti-IL-6 and non-anti-IL-6 agents; b) the establishment of disease remission and relapse in TAK patients were chosen as primary outcomes meanwhile the reduction of GC use after the addition of these agents and their adverse events were chosen as secondary outcomes. Our objective is to assess the efficacy and safety of biological agents in patients with TAK through a meta-analysis and to provide physicians with a clinical medication guidance for TAK.

Materials and Methods

Literature Search and Study Selection

A systematic literature search was conducted using MEDLINE (via PubMed), EMBASE, Elsevier ScienceDirect, EBSCO, Springer Link, Web of Knowledge, and Cochrane Library from inception to June 2020 without limitations for age and with a study design using the search terms: Takayasu arteritis or Takayasu disease (aortic arch syndrome, non-specific aorto-arteritis or pulseless disease); interleukin-6/IL-6; tumor necrosis factor/TNF; rituximab; trastuzumab; certolizumab; tocilizumab; adalimumab; etanercept; abatacept; tofacitinib; infliximab; biologics or biological agents. We also included randomized controlled trials (RCTs) and observational studies (case-control, cohort studies, and case series) if they included TAK patients receiving a biological agent. Case reports of case series with <5 subjects and non-English language papers/abstracts were excluded. When there were multiple studies of the same cohort with the same outcomes, only the largest study was included. Two authors (Shuai Z and Zhang C) independently reviewed the studies according to the inclusion and exclusion criteria. Disagreements between the reviewers were resolved by consensus (Ge S). Any unresolved issues were referred to the arbiters.

Data Extraction and Quality Assessment

Data extraction was performed by Shuai Z and Zhang C independently using standardized forms. The following data were extracted: study design, patient demographics (age, disease duration, gender), treatment duration, inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) before and after biological agent therapy, follow-up periods, primary (effica-

cy) and secondary (safety) outcomes. To obtain consistent reporting of outcomes, we applied the Hozo's method[21] to estimate mean and standard deviations based on the median, range and sample size. The quality of observational studies and RCTs were assessed using the Newcastle-Ottawa score and Cochrane Risk of Bias (RoB) tool[22,23].

Statistical Analysis

Median values (range) and mean (standard deviation [SD]) were calculated for patient age, disease duration, follow-up periods, levels of ESR, CRP, and GC doses before and after receiving a biological agent, disease progression on imaging were summarized in Table I. We also performed random effects meta-analysis (Der-Simonian and Laird random) for the most reported outcome measures. When there were too few RCTs for meta-analysis, the results of these studies are described in the systematic review.

Diagnosis of TAK was based on the criteria established by the American College of Rheumatology[24]. Disease activity was defined according to the National Institutes of Health (NIH) criteria in most studies[25]. Remission was defined as a complete resolution of clinical symptoms and physical exam findings of TAK and no evidence of disease activity. Some studies also included improvements in vascular imaging (ultrasound, computed tomography angiography [CTA], magnetic resonance angiography [MRA]). Relapses were defined as new or recurrent TAK symptoms and the disease becoming active again, therefore requiring a change of the treatment regimen and/or disease progression on imaging. Heterogeneity between studies was reported using I[2], and publication bias and sensitivity analysis of observational studies were assessed using funnel plots and Egger's regression test[26]. All statistical tests and construction of forest plots were performed by the Review Manager (RevMan) software (version 5.3, Copenhagen. The Nordic Cochrane Centre) and Comprehensive Meta-Analysis (CMA) software (version 3.3.070, Englewood, USA).

Results

Study Inclusion and Basic Characteristics of Studies

We identified 961 potential articles through the initial search strategy and 231 duplicates were excluded across databases. After reviewing the titles and/or abstracts, 496 articles were excluded, and 234 full-text articles were retrieved for further evaluation. Next, after full-text identification, 203 articles were excluded for one or more of the following reasons: review articles; outcome not of interest, sample size <5. Ultimately, 29 observational studies and 2 RCTs were retained for further analysis (Figure 1). The study design and parameters determined in these observational studies and RCTs are detailed in Table I and Table II, respectively. Among the 29 observational studies, 16/29 included anti-TNF agents (infliximab, Kenilworth, New Jersey, USA; etanercept, Ingel-
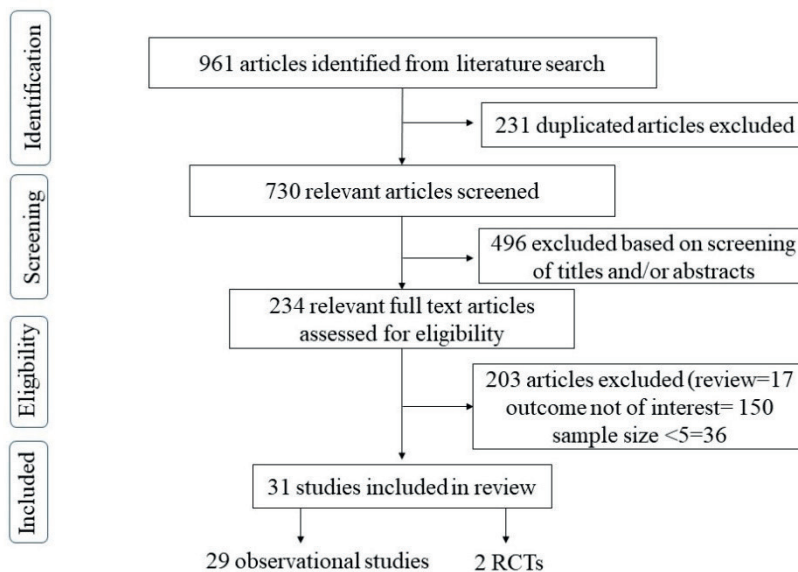

Figure 1. Meta-analysis study selection. Studies identified by database searches with reasons for exclusion, and number of observational and RCTs included in the systematic review and meta-analysis. RCTs, randomized controlled trials.
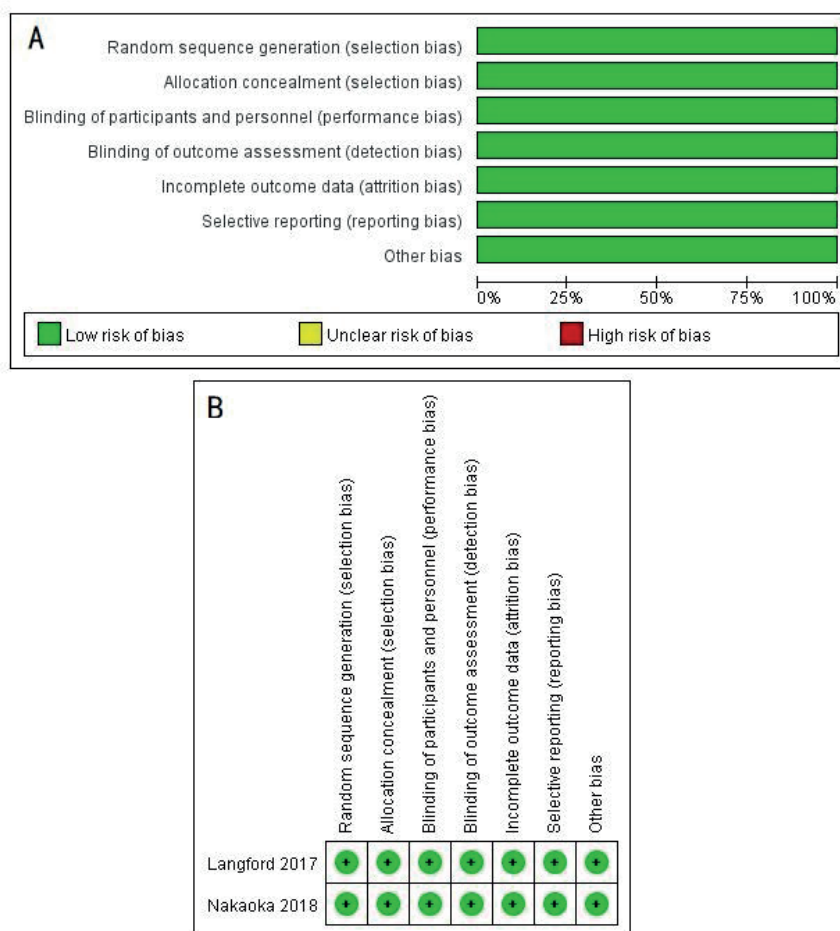
Figure 2. The overall risk of bias graph and summary of RCTs. The overall risk of bias in the RCTs was low (green). RevMan software (version 5.3, Copenhagen). RCTs, randomized controlled trials.

heim, Germany; adalimumab, Boca Raton, Florida, USA)[17,18,20,27-39], 12/29 included TCZ (Ramsey Road Shirley, New York, USA)[12-15,36,38,40-47], 2/29 included anti-TNF agents and TCZ simultaneously[36,38], and 1/29 was on RTX (Basel, Switzerland)[48] only. All patients were treated with concomitant GC, and patients in 26/29 studies had been previously administered with DMARDs.

The study subjects ranged from 3 to 61 years of age and were predominately female (76%-100%). The median disease duration of subjects ranged from new disease onset to a median of 158 months. The median duration of follow-up ranged 3 to 74 months. Newcastle-Ottawa Score showed that the risk of selection bias of observational studies was high or the derivation of the cohort was not described.

There were two double-blind placebo-controlled RCTs[49,50], of which one was on TCZ and the other on ABA (Brooklyn, New York, NY, USA).

The study subjects ranged from 19 to 59 years of age. In both studies, patients were followed for 12 months and with an identical prednisone tapering regimen. They received GC, but without other DMARDs or biological agents. RevMan was used to assess the risk of bias in RCTs. The overall risk of bias graph and summary are shown in Figure 2. Only the random sequence generation and incomplete outcome data were judged as having an unclear risk of bias. No parameters were assessed as a high risk of bias. The overall risk of bias in the ABA/TCZ trial was low.

Effect of Biological Agents on Clinical Outcomes in Observational Studies

Nineteen studies with 22 treatment groups (total N=333) examined the effects of biological agents on remission in TAK. The pooled remission rate (Figure 3A) for biological agents was 0.66 (95% CI: 0.58-0.73; I^2=59%) and the relapse
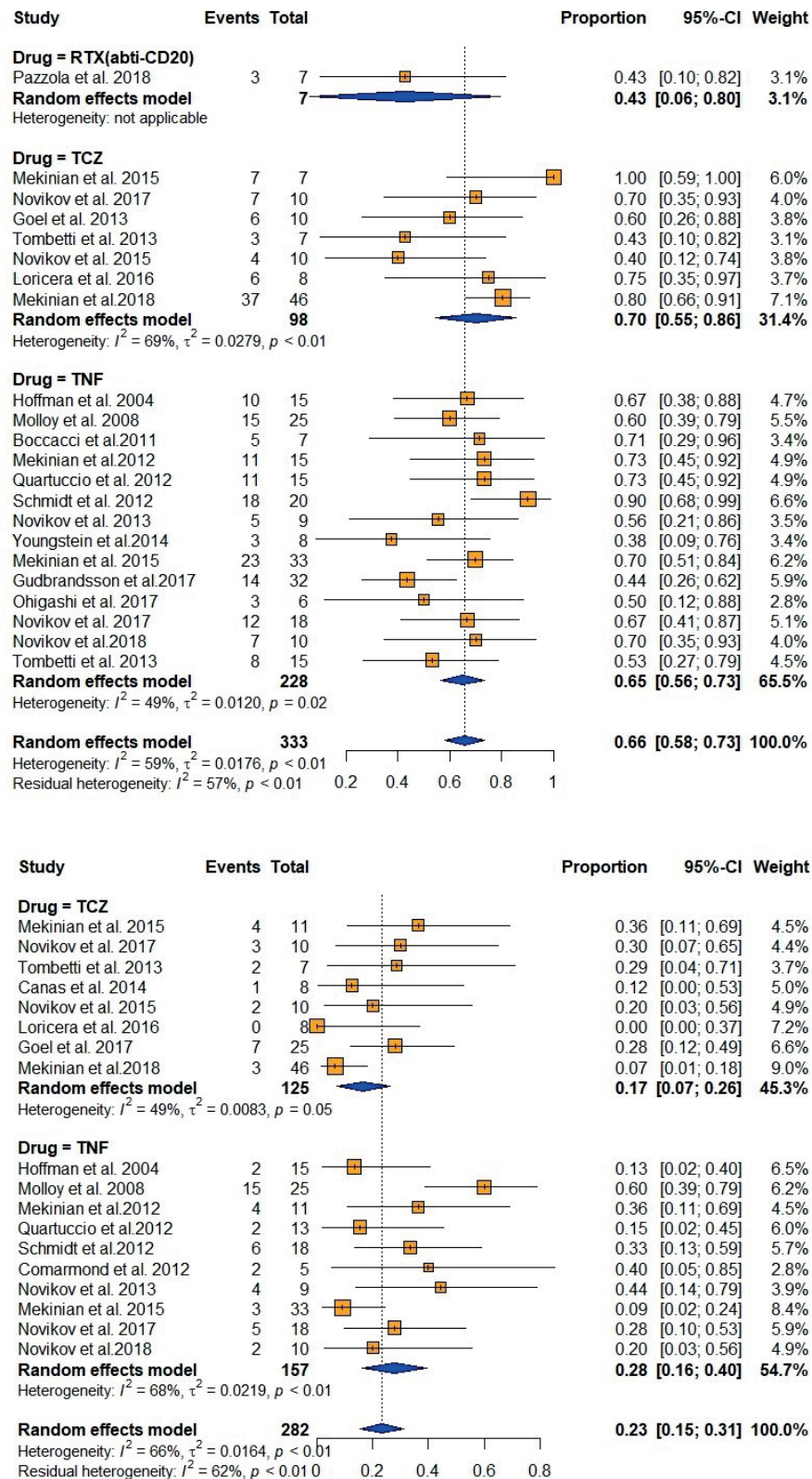
Figure 3. Clinical effectiveness of biologic therapies. Meta-analysis of the proportion of patients achieving remission (**A**) and relapsing (**B**). RTX, rituximab; TCZ, tocilizumab; TNF, anti-tumor necrosis factor; CI, confidence interval. Events, the number of patients achieving remission (**A**) and relapsing (**B**).
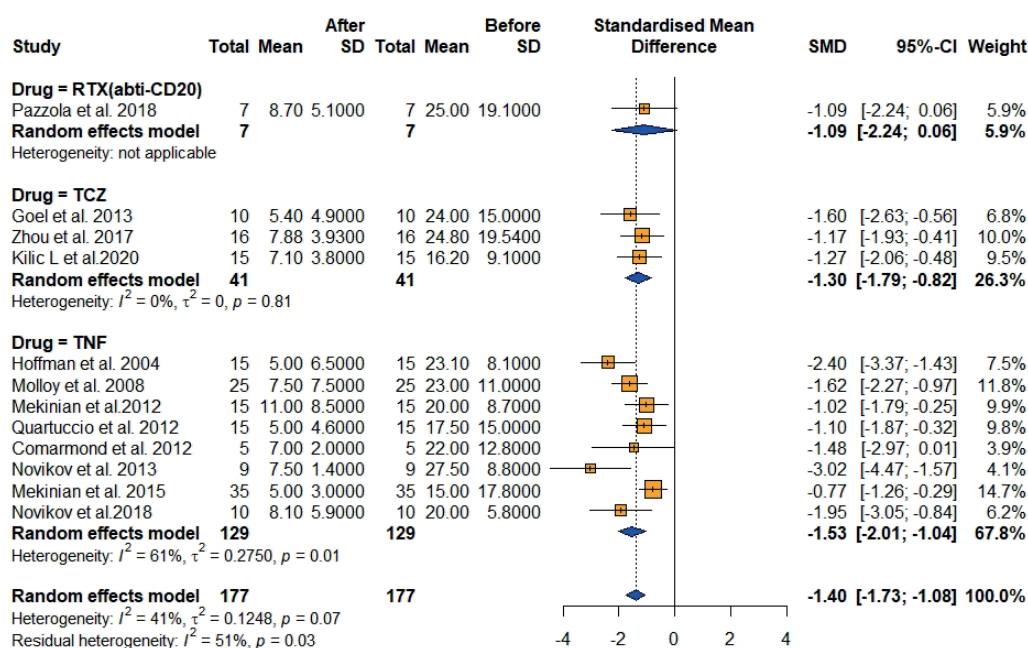
Figure 4. Effect of biological agents on GC doses. Meta-analysis of the GC dose changes after initiation of biologics. GC, glucocorticoid; RTX, rituximab; TCZ, tocilizumab; TNF, anti-tumor necrosis factor; CI, confidence interval. SD, standard deviation; SMD, standardized mean difference. Before: glucocorticoid dose before treatment of biological agents; After: glucocorticoid dose after treatment of biological agents.

rate (Figure 3B) (16 studies with 18 treatment groups; total N=282) was 0.23 (95% CI: 0.15-0.31; I^2=66%). In order to better observe the effect of different types of biological agents on TAK, we conducted a subgroup analysis of the two drugs. The results showed that the remission rates and relapse rates of anti-TNF agents and TCZ were: 0.65 (95% CI: 0.56-0.73; I^2=49%) and 0.28 (95% CI: 0.16-0.40; I^2=68%) for anti-TNF agents, 0.70 (95% CI: 0.55-0.86; I^2=69%) and 0.17 (95% CI: 0.07-0.26; I^2=49%) for TCZ, respectively (Figure 3A and 3B). From the original articles (12 studies, N=177), we learned that the dose of GC was significantly reduced, and that there was a significant statistical difference between before and after treatment of biological agents (-1.40, 95CI: -1.73 to -1.08, I^2=41%), when analyzed by random effects model (Figure 4). There was 1 case series of rituximab with 3/7 (43%) patients achieving remission but it did not report the frequency of relapse. GC doses significantly decreased (from 25 mg/day to 8.7 mg/day, *p*=0.0122) with rituximab treatment[48]. With data only from one article, the meta merge value of rituximab is non-committal.

From a total of nineteen studies involving 21 treatment groups with anti-TNF agents and TCZ (N=313), there were fifty-two adverse events, with infection as the most common, 0.06 (95% CI: 0.02-0.10; I^2=42%). The proportion of infection is 0.11 (95% CI: 0.04-0.19; I^2=61%) for anti-TNF agents and 0.02 (95% CI: 0.00-0.06; I^2=0.00%) for TCZ (Figure 5). Infections included pneumonia, mycobacterium tuberculosis, EBV infections, and others. Infusion reactions were the second most common adverse event. In addition, allergic reactions and neutropenia were also reported. Notably, there were 4 cancers: lung cancer in a smoker, breast cancer in a patient with family history, a case of pancreatic cancer, and another case of breast cancer. No deaths were reported.

Influence of Biological Agents on ESR, CRP, and Imaging in Observational Studies

Twelve studies (N=117) investigated the impact of biological agents on ESR. The results showed that ESR was significantly decreased with a statistical difference between before and after treatment of biological agents (-2.12, 95CI: -2.78 to -1.46, I^2=70%, Figure 6A). Because TCZ is an IL-6 inhibitor and directly affects CRP, we analyzed the influence on CRP of anti-TNF agents (5 studies, N=74) and TCZ (7 studies, N=111; Figure 6B) separately: -2.10 (95CI: -3.48 to -0.71, I^2=88%) for
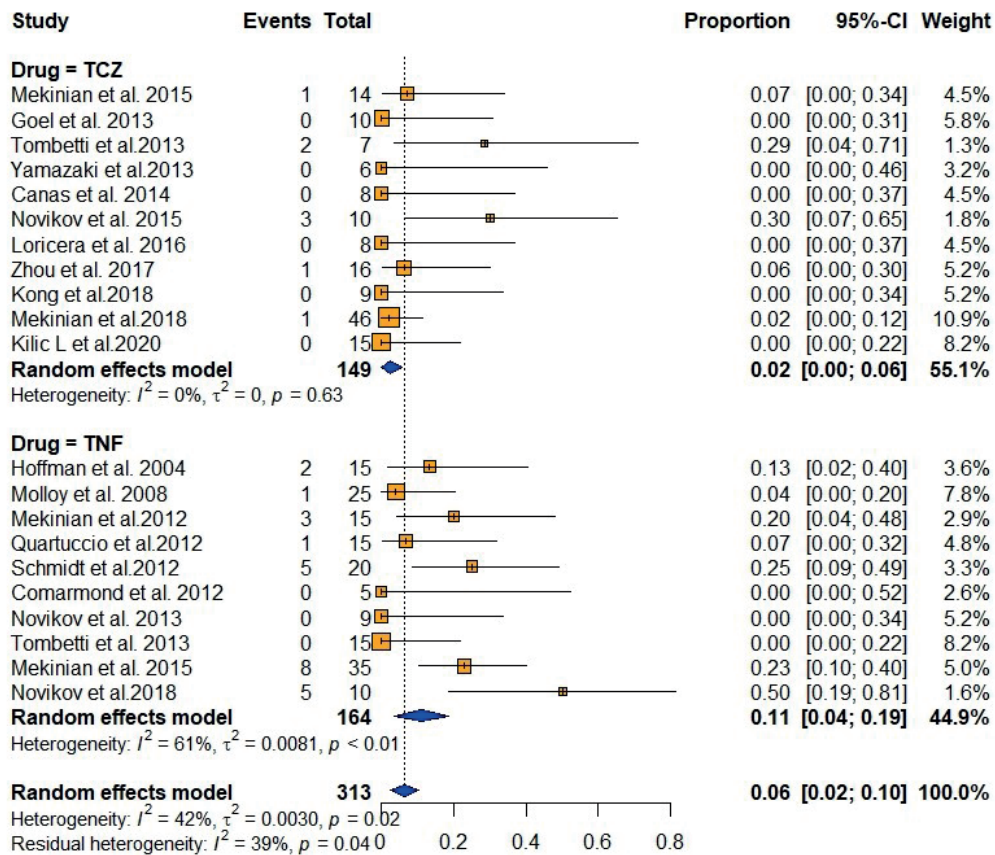
Figure 5. Adverse events (infection) of biological agents on patients with TAK. TCZ, Tocilizumab; TNF, anti-tumor necrosis factor; CI, confidence interval. Events, the number of patients occurred infection.

anti-TNF agents and -2.52 (95CI: -4.03 to -1.01, $I^2=93\%$) for TCZ. There was a statistical difference in CRP between before and after treatment of biological agents ($p<0.01$).

The proportion of patients with new angiographic lesions or progression of previously noted lesions were noted in 13 studies (total N=178): 0.11 (95% CI: 0.04-0.180; $I^2=59\%$), in which the proportion of anti-TNF agents and TCZ were 0.08 (95% CI: 0.00-0.15; $I^2=54\%$) and 0.19 (95% CI: 0.04-0.340; $I^2=64\%$), respectively (Figure 7).

Results of RCTs of Biological Agents

In a double-blind RCT from Japan[49], 36 patients with refractory TAK who had relapsed within the previous 12 weeks were induced into remission with GC therapy alone. They were then randomly assigned 1:1 to receive TCZ (162 mg/weekly) + GC and placebo + GC subcutaneously. GC was tapered 10% weekly to a minimum of 0.1 mg/kg/day until 19 patients relapsed. In the intention-to-treat analysis, TCZ (50.6%, 95% CI: 25.4 -75.8%) failed to show difference in relapse-free

survival when compared to placebo (22.9% ,95% CI: 0.4-45.4%). The most common adverse events in both groups were infections and infestations: 9/18 (50.0%) for the TCZ-treated group and 6/18 (33.3%) for the placebo-treated group with no significant difference; no serious adverse events were attributed to TCZ. In another RCT from the USA[50], 34 patients (newly-diagnosed or relapsing TAK who had active disease within the prior 2 months) were treated with ABA 10 mg/kg by intravenous infusion on days 1, 15, 29, and week 8 together with GC (40-60 mg/day) followed by a standardized tapering schedule. Patients attaining remission at 12 weeks were randomized to either receive placebo (n= 15) or monthly abatacept (n = 11) and were followed up until 12 months. All patients were on prednisone 20 mg/day with tapering continuing, and both treatment arms discontinued prednisone at week 28. There was no statistical difference in the primary outcome of relapse-free survival: 22% for ABA *vs*. 40% for placebo ($p>0.05$) and in the median duration of remission among those who received ABA (5.5
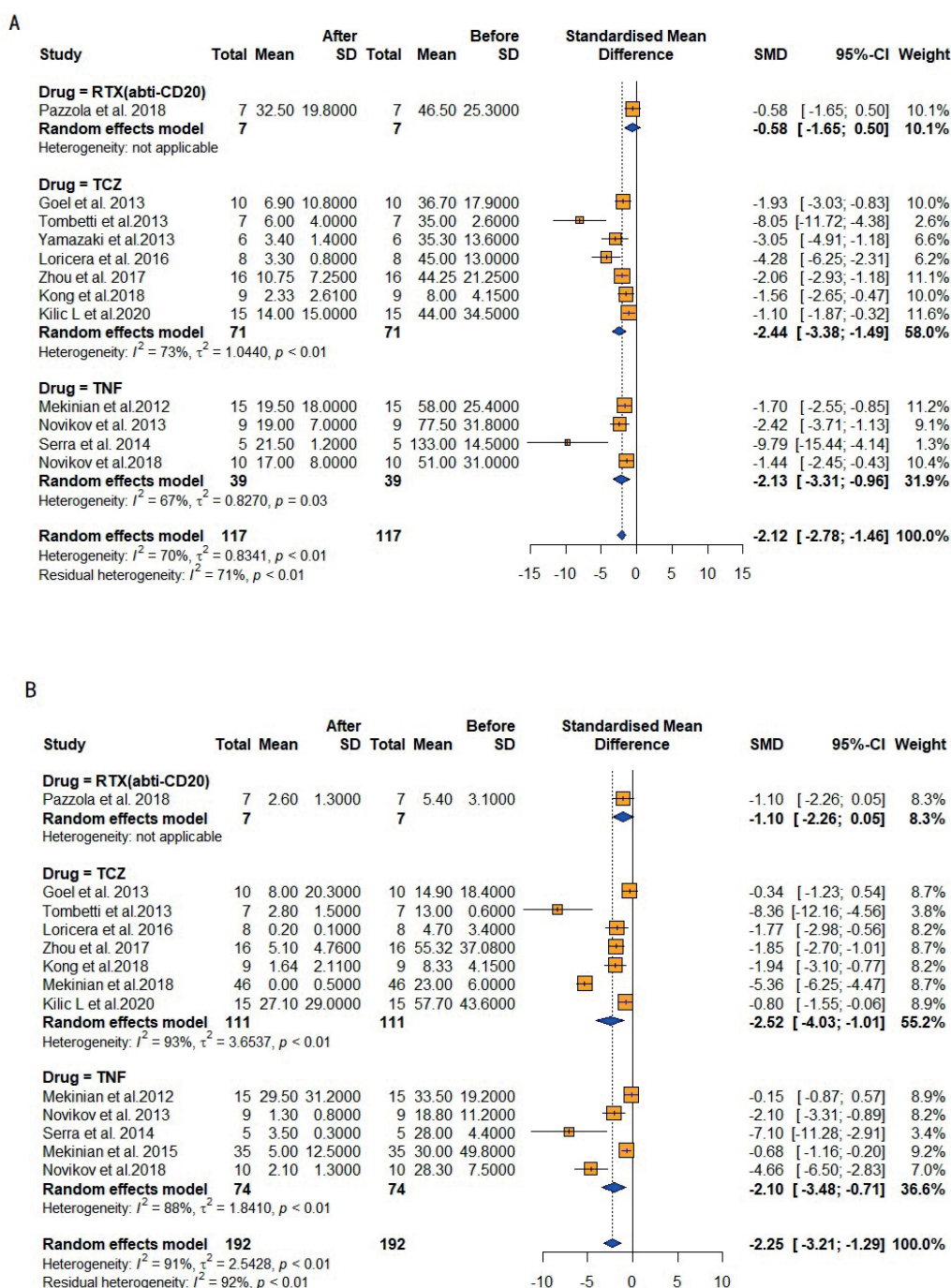
Figure 6. Effect of biologics on acute phase reactants. Meta-analysis the influence on ESR level from treatment of biologics (**A**); meta-analysis the influence on CRP level from treatment of biologics (**B**). ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RTX, rituximab; TCZ, tocilizumab; TNF, anti-tumor necrosis factor; CI, confidence interval. SD, standard deviation; SMD, standardized mean difference. Before, ESR/CRP levels before treatment of biological agents; After, ESR/CRP levels after treatment of biological agents.

months) compared to those who received placebo (5.7 months, $p>0.05$). The most common adverse event was infections (13 in ABA *vs.* 36 in the placebo group), and there no statistically significant difference for the infections between the two groups ($p>0.05$).
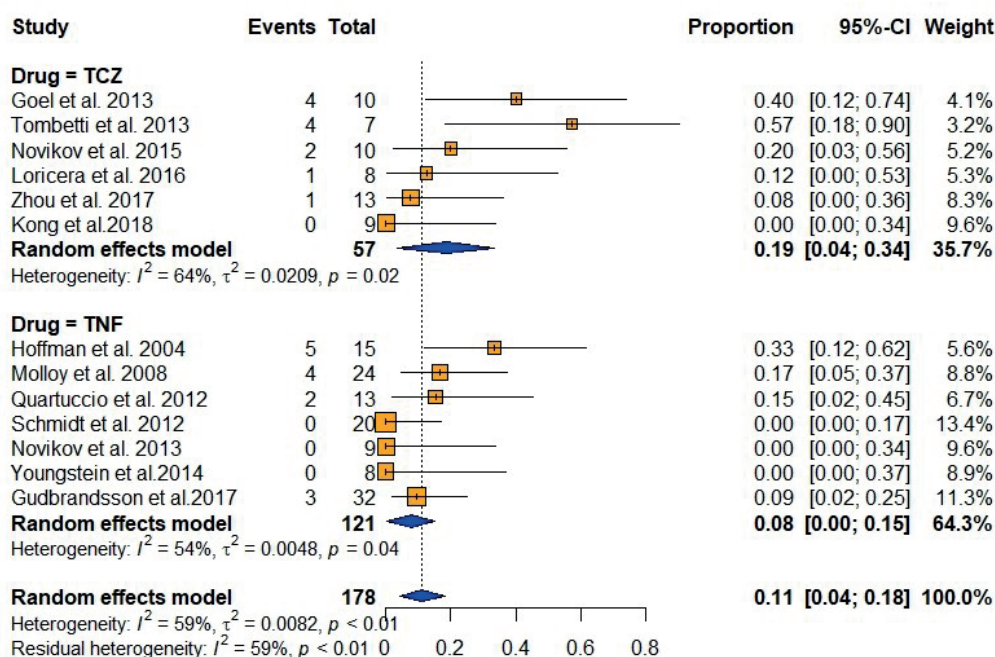
Figure 7. Effect of biological agents on angiographic disease progression. Meta-analysis of the proportion of patients experiencing new angiographic lesions or progression of existing lesions by various imaging modalities at follow-up after initiation of biologics. TCZ, Tocilizumab; TNF, anti-tumor necrosis factor; CI, confidence interval. Events, the number of patients occurred new angiographic lesions or progression of existing lesions.

Analysis of Sensitivity and Publication Bias

A sensitivity analysis was performed by the sequential omission of individual studies. The result revealed that the significance estimate of the overall pooled RD was not affected by omitting any single study (data not shown). Funnel plots showed evidence of asymmetry, and Egger's regression test showed $p < 0.05$, suggesting there is a publication bias.

Discussion

To date, there is no consensus on the ideal pharmacological management of TAK. Current clinical practice guidelines recommend GC as the mainstay of remission. However, an observational study[37] showed that more than 70% of TAK patients fail GC monotherapy. Moreover, with a high relapse rate of 50% in TAK patients on GC dose tapering, DMARDs (most cyclophosphamide) and/or biological agents are also added to the treatment regimen[10]. Regrettably, direct evidence supporting their usefulness is sparse and generally of low quality. This review and meta-analysis summarized the available data on the efficacy and safety of various biological therapies for the management of TAK, and aimed to provide TAK patients with a clinical medication guidance.

Briefly, observational studies showed that approximately 66% of patients achieved remission with GC combined with biological agents. Anti-TNF agents had a lower rate of remission (65% *vs.* 70%, $p > 0.05$) compared to TCZ. Acute phase reactants (ESR, CRP) and daily GC doses declined significantly over the course of follow-up after treatment of biological agents. The pooled relapse rates were 23%, which is lower than 53.9% in DMARDs[50], and with a significant difference between anti-TNF agents (28%) and TCZ (17%, $p=0.017$). However, this does not mean that TCZ had an advantage over anti-TNF agents because of the variations in duration of treatment and follow-up, study design, disease severity, GC regimens and prior exposure to other biological agents. Mekinian et al[36] reported that the proportion of complete or partial responses are similar in TAK patients treated with either anti-TNF agents or TCZ. CRP level and the GC daily dose tended to be lower at 12 months in TAK patients treated with TCZ. The 3-year relapse-free survival in patients on anti-TNF agents and those on TCZ was 91% and 85.7%, respectively ($p > 0.05$). Given the inherent weakness of case series and retrospective studies

and the risk for publication bias in our review, these results should be interpreted cautiously.

Recently, 2 RCTs of biologic therapies for TAK have been published. The RCT of ABA *vs.* placebo did not show a benefit in TAK despite including a pre-randomization phase where non-responders were excluded[50]. A single-center RCT comparing TCZ with placebo in a Phase 3 TAKT trial in Japan, demonstrated a trend toward relapse suppression in favor of TCZ over placebo (51% *vs*. 23%). Additionally, TCZ group showed numerically favorable (though not statistically significant) trends for improvement in objective systemic symptoms, subjective systemic symptoms, inflammation marker levels, vascular lesions, and ischemic symptoms[49]. However, the small sample size of the TAKT trial may not reflect the true differences between treatment and control group. Moreover, there is no evidence of long-term efficacy and safety of TCZ and ABA in this study population. Although the included RCTs in this review were assessed as having a low risk of bias, we should be very cautious when interpreting the overall conclusion. A larger and comprehensive designed RCT is necessary to assess the efficacy of biological agents in TAK.

Some observational studies suggest a benefit of biological agents on angiographic disease progression[12,42]. In this review, 13 studies reported the effect of biological agents on angiographic disease progression. The proportion of patients with biological agents experiencing new angiographic lesions or progression of existing lesions was 11%, which was lower than DMARDs (21.9%)[51].

The adverse events for biological agents were sparse. Twenty-one studies (total N=313) reported fifty-two adverse events. The top two were infections and infusion reactions. Ten studies reported 25 case infections (N=164) in anti-TNF agents, and eleven studies reported 8 case infections (N=149) in TCZ. Some studies[13,20,46] also reported adverse events such as thrombocytopenia, hypertension, and dizziness, but were not serious. Mekinian et al[36] reported that there was no significant difference between anti-TNF agents (23.2%) and TCZ (21.4%) with regard to safety.

It is worth noting that of the 31 studies we included, 2 studies reported the occurrence of 2 cases of breast cancer. Although one of the patients had a family history of breast cancer (breast cancer in sister), the authors could not determine whether its occurrence is related to TCZ[14]. Furthermore, another

breast cancer case occurred in a 52-year-old woman after 41 months of IFX (anti-TNF agents) therapy, and it was judged to possibly be related to IFX[20].

However, we noted some limitations of our analysis. Firstly, there are too few RCTs on biologic treatment for TAK to conduct a meaningful meta-analysis; therefore, we included observational studies. Given the rarity of the disease, the sample size was small in most of the studies. Some studies did not describe the procedures for inclusion, which can introduce selection bias. Moreover, the differences in characteristics of subjects, disease severity, duration of treatment, and follow-up, can introduce outcome bias and publication bias **(Supplementary materials)**. Secondly, while disease activity was defined according to clinical and laboratory parameters in some studies, the progression of vascular lesions and presence of histologically active disease were found in about half of the TAK patients despite clinical and laboratory remission[52,53]. Therefore, future studies should standardize disease activity[54].

Conclusions

In general, literature has shown a high efficacy in the use of biological agents in treating patients with TAK (especially refractory TAK) with an acceptable safety profile. TCZ and anti-TNF agents seem to have equivalent efficacy and tolerance. Although data from two small RCTs, TCZ indicated a trend towards prolonging the time to relapse while ABA was reported as not effective in maintaining remission in TAK, it is still inconclusive. Larger RCTs involving multiple centers with standardized definitions of disease characteristics and outcomes are necessary to improve the clinical management and quality of life in patients with TAK.

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