REVIEW ARTICLE

EFFICACY AND SAFETY OF OLOKIZUMAB IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS- A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Olokizumab (OKZ) is a monoclonal antibody against the interleukin receptor-6 that has shown promise in recent phase II and III trials in patients of rheumatoid arthritis (RA). This meta-analysis aims to evaluate the efficacy and safety of Olokizumab in managing rheumatoid arthritis. **Methods:** We searched different databases until March 2023 for randomized controlled trials inspecting the effects of OKZ on various outcomes in RA patients inadequately controlled with anti-TNF or methotrexate. Data were analyzed via Review Manager-v 5.4.1. Relative risks (RR) with 95% confidence intervals were calculated. **Results:** We evaluated five trials with 2761 patients under four treatment groups: 60mg OKZ administered 2-weekly, 64mg 2-weekly, 64mg 4-weekly, and 120mg 2-weekly. Clinical response as measured by ACR 20, 50, and 70 showed statistically significant improvement with the use of OKZ. A 50% disease improvement was seen across all 4 treatment groups (OKZ 64 mg q2w: RR= 2.96, $p<0.0001$, OKZ 64mg q4w: RR= 3.06, $p=0.0002$, OKZ 60 mg q2w: RR=5.06, $p=0.007$, and OKZ 120mg q2w: RR= 3.63, $p=0.04$). Moreover, 20% and 70% improvements were also noted with OKZ in doses 64mg 2-weekly and 4-weekly. Disease remission, as indicated by DAS28 <2.6 was also significantly higher than placebo across all groups. Safety data showed comparable mortality rates in treatment and placebo groups (OKZ 64mg q2w: $p=0.48$, OKZ 64 mg q4w: $p=0.93$). **Conclusion:** In conclusion, Olokizumab has shown significant improvement in disease activity compared to placebo with a favourable safety profile. However, further larger and longer-term studies are required to confirm these findings.

Keywords: Rheumatoid arthritis; Olokizumab; Methotrexate; Monoclonal antibody; Meta-analysis

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes destructive changes in bone and cartilage, as well as persistent synovitis with synovial cell proliferation in multiple joints, greatly affecting the quality of life of those affected. It affects millions of people worldwide, with women being more susceptible to developing RA than men. If left untreated, RA can potentially result in permanent joint damage, disability, and other issues. Although there is no known cure for RA, several treatments are available that can help manage symptoms and prevent the disease's progression.[1,2] If initial treatment with methotrexate alone proves ineffective, adding a biologic disease-modifying antirheumatic medication or a Janus kinase inhibitor has been recommended.[3,4]

Interleukin-6 (IL-6), a pro-inflammatory cytokine that plays a role in the activation of T cells, the proliferation of B cells, the commencement of an acute phase response, and the development of osteoclasts, all of which contribute to joint destruction, is an important mediator of inflammation in RA.[5] Olokizumab, a monoclonal antibody, is designed to target IL-6. By suppressing IL-6, Olokizumab reduces inflammation and helps alleviate RA symptoms.[6] Although several clinical trials have assessed Olokizumab's efficacy and safety in treating RA, the results have been mixed. Olokizumab has been shown to reduce the severity of RA symptoms and the rate at which the illness progresses.[7,8]

Therefore, a systematic review and meta-analysis is necessary to determine the overall effectiveness and safety of Olokizumab for RA. However, the previous meta-analysis only covered a limited number of outcomes and subgroups of different doses.[9] To address this gap, our study aims to provide a more comprehensive and up-to-date analysis of the available evidence, including a wider range of outcomes and different doses of

Olokizumab. This will lead to more robust and nuanced insights into the efficacy and safety of Olokizumab, with potential implications for clinical decision-making and future research.

MATERIAL AND METHODS

We carried out this meta-analysis in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines.[10] We conducted a systematic literature search to identify studies related to the safety and efficacy of Olokizumab in the management of rheumatoid arthritis that were published from the inception of databases until March 2023. Our search was conducted on different online databases, namely PubMed/MEDLINE, clinicaltrials.gov, Cochrane-Central library and google scholar. To ensure that we identified the most relevant articles for our review, we used the following MeSH terms: (Olokizumab OR CDP6038 OR Anti-IL-6 Antibody) AND (Rheumatoid Arthritis) AND (safety of Olokizumab OR efficacy of Olokizumab) AND (RA inadequately controlled by anti-TNF OR RA inadequately controlled by methotrexate).

The identified papers were initially screened for relevance by title and abstract, and subsequently, the full text was assessed for eligibility by two independent, skilled reviewers, AK and ST. To resolve any dispute regarding article inclusion, a third reviewer, JT was consulted. To identify any additional studies, we also searched the reference lists of the included studies.

For this review, we included studies that satisfied the following conditions: 1) Studies published in English language; 2) Randomized control trials that included rheumatoid arthritis patients who were not adequately managed by Anti-TNF (Tumour Necrosis Factor or Methotrexate; 3) Rheumatoid arthritis patients who were given Olokizumab (OKZ); and 4) Stated incidence of adverse events after taking OKZ. Thus, the studies that did not satisfy these conditions were excluded from our analysis. Furthermore, studies that were subset of other studies were excluded to avoid data duplication.

The data was extracted from the selected studies by three independent reviewers, JT, AK and ST and was recorded using Microsoft Excel. The data that was extracted from the selected studies included a range of variables that were relevant to our research question. These variables included the baseline characteristics of the patient population, including disease duration, dose and duration of OKZ, prior failed TNF treatment, concomitant MTX therapy, MTX dose and duration, and outcomes like American College of Rheumatology 20% (ACR20) response, ACR50, ACR70, Disease Activity Score 28-joint count C-reactive protein DAS28 (CRP) <2.6, DAS28(CRP) ≤3.2, Clinical Disease Activity Index (CDAI) ≤10.0, change in Health Assessment Questionnaire-Disability Index (ΔHAQ-DI), change in Tender Joint Count (ΔTJC), change in Swollen Joint Count (ΔSJC),treatment emergent adverse events (TEAE), treatment emergent serious adverse events (TESAE) and mortality. The risk of bias in individual studies was evaluated by an independent author, SK using the Cochrane Risk of Bias tool in RCTs.[11]

The statistical analysis was performed using Review Manager-v 5.4.1. Relative risks (RR) in the included studies were calculated with 95% confidence intervals. A random effects model was used to pool the effect sizes across studies. In addition to the overall analysis, we conducted a subgroup analysis based on four different doses of the intervention (60mg OKZ administered 2-weekly, 64mg 2-weekly, 64mg 4-weekly, and 120mg 2-weekly). By analyzing the subgroups, we aimed to identify any differences in treatment effects between different doses of the intervention.A p value of <0.05 was considered significant. We assessed heterogeneity using the I2 statistic and considered heterogeneity significant if I2 was greater than 75%. Additionally, publication bias was assessed using funnel plots.

RESULTS

The initial electronic literature search of databases identified 878 articles. After a detailed evaluation of these articles according to the inclusion criteria, 5 RCTs were selected for analysis involving 2761 patients. The PRISMA flow chart (Figure-1) summarizes results of our literature search. Quality assessment using the Cochrane risk of bias assessment tool for RCTs demonstrated good quality studies (Table-S1)**.**

In this meta-analysis, five trials, including a total of 2761 unique patients, were examined. Of these, 50 patients were given 60 mg OKZ every two weeks (q2w), 702 patients received 64 mg OKZ every two weeks (q2w), and 740 patients got 64 mg OKZ every four weeks (q4w), and 46 patients were the recipient of OKZ 120 every two weeks (q2w) in the respective trials.[7–8, 12–14] In this meta-analysis, the mentioned trials were divided into four treatment groups, namely OKZ 64 mg q2w, OKZ 64 mg q4w, OKZ 60 mg q2w (one study by Takeuchi *et al.*[13] administered 60 mg Q2W and 120 mg Q4W), and OKZ 120mg q2w (Takeuchi *et al.*[13] Injected 120 mg Q2W and 240 mg Q4W). Characteristics of the included trials are summarized in Table-1. Study

drugs were administered subcutaneously in all the included trials.

Efficacy outcomes

a) ACR20

OKZ 64 mg q2w and q4w showed that OKZ was significantly superior to placebo (RR=1.85, 95% CI [1.45,2.35], I2 =64%, p<0.00001) for q2w, and (RR=1.91, 95% CI [1.40, 2.59], I2 =78%, p<0.0001) for q4w, respectively. However, OKZ 60mg q2w and OKZ 120mg q2w groups showed insignificant results (RR=1.78, 95% CI [0.60,5.29], I2 =71%, p=0.30) for 60mg q2wand (RR = 1.57, 95% CI [0.89, 2.78], I2=0%, p=0.12) for 120 mg q2w compared to the placebo group.

b) ACR50

In contrast to the placebo group, the Olokizumab group had a significantly higher incidence of American College of Rheumatology 50, as reported by the four treatment groups (RR=2.96, 95% CI [1.78, 4.90], I2=71%, p<0.0001) for OKZ 64mg q2w, (RR= 3.06, 95% CI [1.69, 5.56], I2=79%, p=0.0002) for OKZ 64mg q4w, (RR=5.06, 95% CI [1.56, 16.42], p=0.007) for OKZ 60 mg q2w, and (RR=3.63, 95% CI [1.06, 12.42], p=0.04) for OKZ 120mg q2w.

c) ACR70

This outcome is reported only in two treatment groups (OKZ 64 mg q2w and q4w), shown in Table-2. (RR=5.37, 95% CI [1.98, 14.60], p=0.0010) for OKZ 64 mg q2w and (RR=4.81, 95% CI [1.01, 22.85], p=0.05) for OKZ 64 mg q4w showed that the incidence of ACR70 was significantly greater in the OKZ group as compared to the placebo group, with the heterogeneity of 41% and 75%, respectively.

d) HAQ-DI

OKZ 64 mg q2w was associated with the most statistically significant improvement in HAQ-DI score compared with placebo (MD, -0.25; 95% CI, -0.35, -0.16, I2=46%, p<0.00001) followed by OKZ 64mg q4w (MD, -0.21; 95% CI, -0.35, -0.07; I2= 100%, p=0.004). Whereas, OKZ 60mg q2w and OKZ 120mg q2w treatment groups showed statistically non-significant improvements (MD, -2.01; 95% CI, -5.68, 1.66; I2 =89%, p=0.28). (Table-3)

e) DAS28 (CRP) < 3.2

Three treatment groups (OKZ 64 mg q2w, OKZ 64 mg q4w, and OKZ 60 mg q2w) showed that the incidence of DAS28 (CRP) < 3.2 was significantly greater in the OKZ group as compared to the placebo group (RR=4.53, 95% CI [2.79, 7.36], I2=48%, p<0.00001) for 64mg q2w, Vs. (RR= 4.42, 95% CI [2.23, 8.78], I2=72%, p<0.00001), Vs.(RR = 2.72, 95% CI [1.23, 6.00], I2=0%, p=0.01). Only one treatment group (OKZ 120 mg q2w) showed no statistically significant results (RR=2.17, 95% CI [0.96, 4.92], p=0.06), with heterogeneity (I2) of 0%.

f) DAS28 (CRP) < 2.6

All four treatment groups (OKZ 64mg q2w and q4w, OKZ 60 mg q2w, and OKZ 120mg q2w) reported that the incidence of DAS28 (CRP) <2.6 was significantly greater in the OKZ group as compared to the placebo (RR=5.70, 95% CI [2.79, 11.68], p<0.00001) for OKZ 64mg q2w, (RR= 5.85, 95% CI [2.69, 12.75], p<0.00001) for OKZ 64mg q4w, (RR= 5.86, 95% CI [1.15, 29.76], p=0.03) for OKZ 60 mg q2w, and (RR=5.12, 95% CI [1.16, 22.60], p=0.03) for OKZ 120mg q2w. Heterogeneity was not considered significant in any of the groups. (Table-2)

g) CDAI ≤ 10.0

Only two treatment groups (OKZ 64 mg q2w and q4w) reported this outcome. OKZ 64mg q2w was significantly superior to placebo RR = 3.46, 95% CI [1.59, 7.54], I2=77%, p=0.002. Additionally, OKZ 64mg q4w was significantly superior to placebo; RR= 3.29, 95% CI [1.13, 9.5], I2=58%, p=0.03.

h) ΔTJC

With regards to ΔTJC, two (OKZ 60 mg q2w and OKZ 120 mg q2w) out of four treatment groups reported this outcome. The analysis showed insignificant results as (MD=4.47, 95% CI [-35.06, 44.01], I2=76%, p=0.82) for OKZ 60mg q2w Vs. (MD= -37.99, 95% CI [-108.44, 32.46], I2=0%, p=0.29) for OKZ 120 mg q2w group. (Table-3)

i) ΔSJC

Out of the four treatment groups in the meta-analysis, two groups (OKZ 60 mg q2w and OKZ 120 mg q2w) displayed data on ΔSJC that showed no statistically significant results (MD= -29.44, 95% CI [-82.27, 23.39], I2=85%, p=0.27) for OKZ 60mg q2w Vs. (MD= -18.92, 95% CI [-59.75, 21.91], I2=8%, p=0.36) for OKZ 120 mg q2w (Table-3).

Safety outcomes

Safety assessments included recording treatment-emergent adverse events (TEAEs), serious TEAEs (TESAEs), and mortality. Reported adverse events with OKZ 64mg q2w (RR, 1.14; 95% CI, 1.02 to 1.27, p=0.02; I2=14%) and OKZ 64mg q4w (RR, 1.22; 95% CI, 1.11 to 1.33, p<0.0001; I2=0%) were higher than placebo. The frequency of adverse events was comparable to placebo in both the OKZ 60mg q2w and OKZ 120mg q2w treatment groups (RR, 0.89; 95% CI, 0.73 to 1.09, p=0.27 [OKZ 60mg q2w]; and RR, 0.85; 95% CI, 0.68,1.06, p=0.16 [OKZ 120 mg q2w]).

Reported serious adverse events in all four treatment groups (OKZ 64mg week 2 and 4, OKZ 60mg week 2, and OKZ 120 mg week 2) showed insignificant results (Table-2). Only two treatment groups (OKZ 64 mg q2w and q4w) reported the data for mortality. These groups showed that the incidence of mortality in the OKZ group was similar to placebo (RR, 1.95; 95% CI, 0.31 to 12.30, p=0.48) for OKZ 64mg q2w Vs. (RR, 1.11; 95% CI, 0.10 to 12.20, p=0.93) for OKZ 64mg q4w.

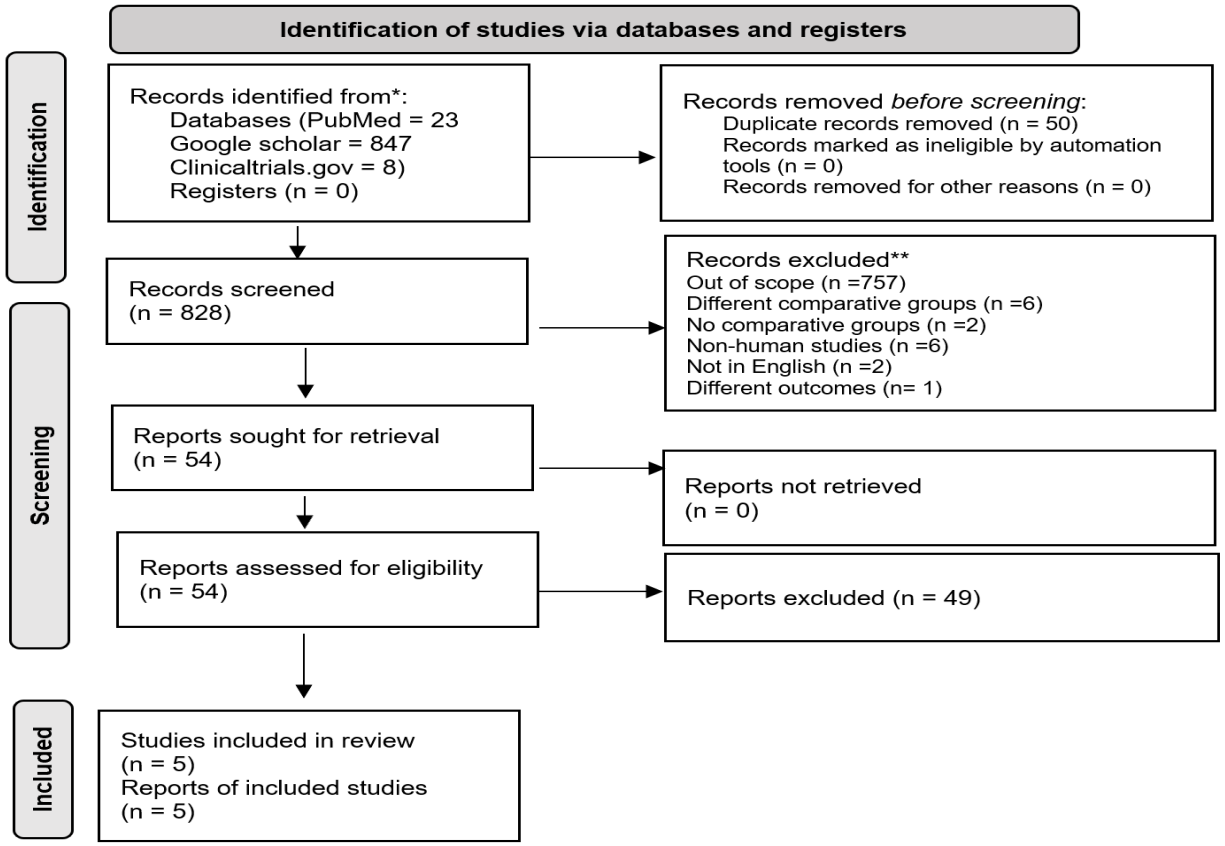

Figure-1: PRISMA Flow Chart

Table-1: Baseline characteristics of included patients.

Author	Phase of study	Total patients	Patients in olokizumab group	Patients in control group	Dose and duration	Age, years mean (SD)	Female gender, n (%)	Prior failed TNF treatment, n%	Duration of prior MTX use, months;	Disease duration in years, Median (IQR)	RF+ (≥20 IU/mL), n %	Anti-CCP+ (>10 U/mL), n%	CRP mg/L, mean (SD)
Feist [8]	III	368	OKZ q2w: 138 OKZ q4w: 161	PBO: 69	OKZ 64mg q4w OKZ 64mg q2w	OKZ q2w: 53.4 (12.7) OKZ q4w: 53.9 (11.7) PBO: 53.0 (13.7)	OKZ q2w: 122 (88.4) OKZ q4w: 130 (80.7) PBO: 55 (79.7)	-	OKZ q2w: 74.7 (68.2) OKZ q4w 71.3 (56.7) PBO 66.3 (56.7)	OKZ q2w: 11.8 (9.2) * OKZ q4w: 12.7 (8.8) * PBO: 9.8 (7.0) *	OKZ q2w: 105 (76.1) OKZ q4w: 128 (79.5) PBO: 55 (79.7)	OKZ q2w: 96 (69.6) OKZ q4w: 124 (77.0) PBO: 58 (84.1)	OKZ q2w: 20.7 (21.7) OKZ q4w: 21.4 (24.3) PBO: 19.4 (20.2)
Nasanov [14]	III	427	OKZ q2w: 143 OKZ q4w: 142	PBO: 143	OKZ 64mg q2w OKZ 64mg q4w	OKZ q2w: 52.0 (11.8) OKZ q4w: 49.1 (12.1) PBO: 52.7 (11.3)	OKZ q2w: 81.1 OKZ q4w: 83.1 PBO: 83.9	OKZ q2w: 0 OKZ q4w: 0 PBO: 4 (2.8)	OKZ q2w: 46.3 (53.4) OKZ q4w: 36.2 (38.1) PBO: 48.3 (47.9)	OKZ q2w: 8.7 (8.0) * OKZ q4w: 7.3 (7.0) * PBO: 8.4 (7.8) *	OKZ q2w: 115 (80.4) OKZ q4w: 122 (85.9) PBO: 127 (88.8)	OKZ q2w: 110 (76.9) OKZ q4w: 115 (81.0) PBO: 117 (81.8)	OKZ q2w: 23.5 (23.1) OKZ q4w: 22.7 (22.7) PBO: 25.8 (28.7)

Author	Phase of study	Total patients	Patients in olokizumab group	Patients in control group	Dose and duration	Age, years mean (SD)	Female gender, n (%)	Prior failed TNF treatment, n%	Duration of prior MTX use, months; mean (SD)	Disease duration in years, Median (IQR)	RF+ (≥20 IU/mL), n %	Anti-CCP+ (>10 U/mL), n%	CRP mg/L, mean (SD)
Genovese [12]	IIb	198	OKZ 60mg q2w: 18 OKZ 120mg q2w: 20 OKZ 240mg q2w: 21 OKZ 60mg q4w: 16 OKZ 120mg q4w: 21 OKZ 240mg q4w: 21	PBO q4w: 20 PBO q2w: 21 TCZ q4w: 43	OKZ 60mg q4w OKZ 120mg q4w OKZ 240mg q4w OKZ 60mg q2w OKZ 120mg q2w OKZ 240mg q2w	PBO q2w: 59.36 OKZ 60mg q2w: 55.50 OKZ 120mg q2w: 53.09 OKZ 240mg q2w: 55.48 PBO q4w: 58.18 OKZ 60mg q4w: 52.64 OKZ 120mg q4w: 53.52 OKZ 240mg q4w: 54.55 TCZ 8mg/kg q4w: 56.58	PBO q2w: 86.4 OKZ 60mg q2w: 80.0 OKZ 120mg q2w: 86.4 OKZ 240mg q2w: 91.3 PBO q4w: 77.3 OKZ 60mg q4w: 90.9 OKZ 120mg q4w: 87.0 OKZ 240mg q4w: 77.3 TCZ 8mg/kg q4w: 86.0	PBO q2w: 12 (54.5) OKZ 60 mg q2w: 14 (70.0) OKZ 120 mg q2w: 12 (54.5) OKZ 240 mg q2w: 14 (60.9) PBO q4w: 12 (54.5) OKZ 60 mg q4w: 12 (54.5) OKZ 120 mg q4w: 12 (52.2) OKZ 240 mg q4w: 13 (59.1) TCZ 8mg/kg q4w: 25 (58.1)	-	PBO q2w: 10.56 OKZ 60 mg q2w: 12.30 OKZ 120 mg q2w: 8.07 OKZ 240 mg q2w: 8.22 PBO q4w: 7.45 OKZ 60 mg q4w: 10.89 OKZ 120 mg q4w: 11.58 OKZ 240 mg q4w: 7.83 TCZ 8mg/kg q4w: 10.55	-	-	-
Smolen [7]	III	1648	OKZ q2w+ MTX: 463 OKZ q4w+ MTX: 477	Adalimumab 40mg q2w+ MTX : 462 PBO q2w+ MTX : 243	OKZ 64 mg q4w + PBO + MTX OKZ 64 mg q2w + MTX Adalimumab 40 mg q2w + MTX PBO q2w + MTX	OKZ 64 mg q4w+PBO +MTX:53.7 (12.09) OKZ 64mg q2w+MTX: 53.3 (11.92) Adalimumab 40mg q2w+MTX: 54.3 (12.32) PBO q2w+MTX: 54.7 (11.85)	OKZ 64mg q4w+PBO +MTX: 378 (78.9) OKZ 64mg q2w+MTX : 352 (75.9) Adalimumab 40mg q2w+MTX : 363 (78.6) PBO q2w+MTX : 190 (78.2)	-	OKZ 64 mg q4w+PBO +MTX: 44.0 (49.6) OKZ 64 mg q2w+MTX: 43.4 (52.8) Adalimumab 40 mg q2w+MTX: 46.5 (55.5) PBO q2w+MTX: 45.0 (53.2)	OKZ 64 mg q4w+PBO +MTX: 7.4 (0.3–40.5) OKZ 64 mg q2w+MTX: 7.5 (0.3–38.9) Adalimumab 40 mg q2w+MTX: 7.4 (0.3–40.2) PBO q2w+MTX: 6.9 (0.3–42.5)	OKZ 64 mg q4w+PBO +MTX: 355 (74.1) OKZ 64 mg q2w+MTX: 352 (75.9) Adalimumab 40 mg q2w+MTX: 343 (74.2) PBO q2w+MTX: 181 (74.5)	OKZ 64 mg q4w+PBO +MTX: 361 (75.4) OKZ 64 mg q2w+MTX: 355 (76.5) Adalimumab 40 mg q2w+MTX: 324 (70.1) PBO q2w+MTX: 188 (77.4)	OKZ 64 mg q4w+PBO +MTX: 18.4 (18.6) OKZ 64 mg q2w+MTX: 19.0 (21.1) Adalimumab 40 mg q2w+MTX: 18.6 (18.5) PBO q2w+MTX: 17.1 (17.2)
Takeuchi [13]	II	119	OKZ 60mg q4w: 32 OKZ 120mg q4w: 32 OKZ 240mg q4w: 13 OKZ 60mg q2w: 16 OKZ 120mg q2w: 13	PBO q2w: 29	OKZ 60mg q4w OKZ 120mg q4w OKZ 240mg q4w OKZ 60mg q2w OKZ 120mg q2w PBO q2w	OKZ 60mg q4w: 53.9 (10.6) OKZ 60mg q2w+OKZ 120 mg q4w: 55.7 (10.8) OKZ 120mg q2w+OKZ 240mg q4w: 56.7 (11.0) PBO q2w: 52.6 (11.3)	OKZ 60mg q4w: 96.9 OKZ 60mg q2w+OKZ 120mg q4w: 81.3 OKZ 120mg q2w+OKZ 240mg q4w: 80.8 PBO q2w: 86.2	OKZ 60 mg q4w: 25 (78.1) OKZ 60 mg q2w+OKZ 120 mg q4w: 24 (75.0) OKZ 120 mg q2w+OKZ 240 q4w: 22 (84.6) PBO q2w: 24 (82.8)	-	OKZ 60 mg Q4W: 7.6 (0.7-69.7)† OKZ 60 mg Q2W+OKZ 120 mg Q4W: 6.9 (1.05-39.6) † OKZ 120 mg Q2W+OKZ 240 mg Q4W: 6.9 (1.1-18.0) † PBO Q2W: 6.5 (1.1-28.9)†	-	-	-

*mean (SD) † median (min-max)

Abbreviations: OKZ = elotuzumab; PBO = placebo; TNF = Tumor necrosis factor; MTX = methotrexate; TCZ= tocilizumab; RF+ = rheumatoid factor positivity; anti-CCP+ = anti-cyclic citrullinated peptide positivity; CRP = C reactive protein; q2w = once every 2 weeks; q4w= every four weeks.

Table-2: Summary of results stratified by different OKZ doses compared with Placebo corresponding to respective dichotomous outcomes

Outcomes	Studies Included (n)	RR	Lower 95% CI	Upper 95% CI	p-value	I^2
ACR 20						
All Treatment Groups						
OKZ 64mg q2w	3	1.85	1.45	2.35	<0.0001	64%
OKZ 64mg q4w	3	1.91	1.40	2.59	<0.0001	78%
OKZ 60mg q2w	2	1.78	0.60	5.29	0.30	71%
OKZ 120mg q2w	2	1.57	0.89	2.78	0.12	0%
ACR 50						
All Treatment Groups						
OKZ 64mg q2w	3	2.96	1.78	4.90	<0.0001	71%
OKZ 64mg q4w	3	3.06	1.69	5.56	0.0002	79%
OKZ 60mg q2w	2	5.06	1.56	16.42	0.007	0%
OKZ 120mg q2w	2	3.63	1.06	12.42	0.04	0%
ACR 70						
All Treatment Groups						
OKZ 64mg q2w	2	5.37	1.98	14.60	0.0010	41%
OKZ 64mg q4w	2	4.81	1.01	22.85	0.05	75%
DAS28(CRP)≤3.2						
All Treatment Groups						
OKZ 64mg q2w	3	4.53	2.79	7.36	<0.00001	48%
OKZ 64mg q4w	3	4.42	8.78	5.56	<0.0001	72%
OKZ 60mg q2w	2	2.72	1.23	6.00	0.01	0%
OKZ 120mg q2w	2	2.17	0.96	4.92	0.06	0%
DAS28(CRP)<2.6						
All Treatment Groups						
OKZ 64mg q2w	2	5.70	2.79	11.68	<0.00001	0%
OKZ 64mg q4w	2	5.85	2.69	12.75	<0.00001	15%
OKZ 60mg q2w	2	5.86	1.15	29.76	0.03	14%
OKZ 120mg q2w	2	5.12	1.16	22.60	0.03	0%
CDAI≤10.0						
All Treatment Groups						
OKZ 64mg q2w	2	3.46	1.59	7.54	0.002	58%
OKZ 64mg q4w	2	3.29	1.13	9.57	0.03	77%
Any TEAE						
All Treatment Groups						
OKZ 64mg q2w	3	1.14	1.02	1.27	0.02	14%
OKZ 64mg q4w	3	1.22	1.11	1.33	<0.0001	0%
OKZ 60mg q2w	2	0.89	0.73	1.09	0.27	0%
OKZ 120mg q2w	2	0.85	0.68	1.06	0.16	6%
TESAE						
All Treatment Groups						
OKZ 64mg q2w	3	1.53	0.61	3.85	0.36	40%
OKZ 64mg q4w	3	1.18	0.65	2.12	0.58	0%
OKZ 60mg q2w	2	0.49	0.11	2.12	0.34	0%
OKZ 120mg q2w	2	1.37	0.16	11.56	0.77	24%
Mortality						
All Treatment Groups						
OKZ 64mg q2w	3	1.95	0.31	12.30	0.48	0%
OKZ 64mg q4w	3	1.11	0.10	12.20	0.93	Not applicable

Abbreviations: OKZ = olokizumab; RR = Relative risk; q2w = once every 2 weeks; q4w= every four weeks; ACR 20, 50, 70 = American College of Rheumatology 20%, 50% and 70% response respectively; DAS28(CRP) = Disease Activity Score 28-joint count C-reactive protein; CDAI = Clinical Disease Activity Index; TEAE = Treatment emergent adverse effect; TESAE= Treatment emergent serious adverse effects.\

Table-3: Summary of results stratified by different OKZ doses compared with Placebo corresponding to respective continuous outcomes

Outcomes	Studies Included (n)	MD	Lower 95% CI	Upper 95% CI	P value	I^2
ΔHAQ-DI						
All Treatment Groups						
OKZ 64mg q2w	3	-0.25	-0.35	-0.16	<0.00001	46%
OKZ 64mg q4w	3	-0.21	-0.35	-0.07	0.004	100%
OKZ 60mg q2w	2	-2.01	-5.68	1.66	0.28	89%
OKZ 120mg q2w	2	-2.01	-5.68	1.66	0.28	89%
ΔTJC						
All Treatment Groups						
OKZ 60mg q2w	2	4.47	-35.06	44.01	0.82	0%
OKZ 120mg q2w	2	-37.99	-108.44	32.46	0.29	76%
ΔSJC						
All Treatment Groups						
OKZ 60mg q2w	2	-29.44	-82.27	23.39	0.27	85%
OKZ 120mg q2w	2	-18.92	-59.75	21.91	0.36	8%

Abbreviations: OKZ = olokizumab; MD = Mean Difference; q2w = once every 2 weeks; q4w= every four weeks; ΔHAQ-DI = change in Health Assessment Questionnaire-Disability Index; ΔTJC = change in Tender Joint Count; ΔSJC = change in Swollen Joint Count.

DISCUSSION

In this systematic review and meta-analysis, we evaluated the efficacy and safety of Olokizumab for treating RA in patients with inadequate response to methotrexate and anti TNF therapy. The analysis included RCTs that compared Olokizumab with placebo or other treatment in patients with active RA. A total of five RCTs were included in the analysis, including 2761 patients. A meta-analysis by Mahmoud AM[9] included five RCTs with 2277 patients evaluated the efficacy and safety with limited number of outcomes and different dose-related subgroups, we therefore conducted a comprehensive meta-analysis including a wider range of outcomes and different doses of Olokizumab to evaluate its efficacy and safety.

Rheumatoid arthritis is a chronic inflammatory disease that can lead to substantial disability, morbidity and mortality, if it is not treated appropriately.[1,2] IL-6 is an important cytokine involved in the pathophysiology of RA. Its concentrations are elevated in the serum and synovial fluid of patients with RA and overproduction of IL-6 is associated with clinical abnormalities seen in RA.[15,16] The fact that targeting IL-6 signaling pathway improves inflammation in RA has already been established by the approval of tocilizumab.[17,18] Tocilizumab is a humanized monoclonal anti IL-6 receptor antibody that prevents binding of IL-6 to its receptor and blocks downstream signalling pathway.[19,20] Olokizumab also targets this pathway but with slightly different mechanism. It directly binds to IL-6 at a specific site and renders it unable to form hexamer at cell surface necessary for signal transduction.[21] The trials that made up this analysis tested Olokizumab at various dosages. The participants were divided into four treatment groups, each receiving an OKZ dose ranging from 60 to 240 mg once every two weeks (q2w) or once every four weeks (q4w). The groups are as follows: OKZ 64 mg q2w, OKZ 64 mg q4w, OKZ 60 mg q2w, and OKZ 120 mg. The duration of the trials varied from three to six months.

The summary result of this study indicates that Olokizumab at all the dosage regimens included in this study improved the clinical severity scores as compared to placebo. This is in line with the previous meta-analysis results. However, the tenderness and swelling couldn't get eliminated completely and the number of joints involved before and after Olokizumab administration remained the same. The subjects with dosage regimen of 64mg q2w and 64mg q4w had comparable sample sizes and effect sizes. This is because only these two regimens were selected by the authors of phase 3 trials in their studies, the rationale being the achievement of efficacy with least possible side effects with minimum dose possible.[14] However, the study by Genovese *et al.*[12] showed greater improvement in efficacy endpoints with higher doses without any significant rise of TEAE but this study had a serious limitation of very small sample size in each of the treatment groups. Therefore, we recommend conducting phase 3 trials to study the efficacy and side effect profile of higher dose regimens to determine the maximum effect at an appropriate tolerable dose.

The results of the 60mg q2w and 120mg q2w dose regimens are limited by their small sample sizes and cannot be used to draw meaningful conclusions. The 64mg q2w and 64mg q4w groups had similar efficacy profiles, but the 64mg q2w group had a relatively higher incidence of TESAE, likely due to the rise in cumulative serum concentrations of OKZ with frequent administrations.[6] Surprisingly, the 60mg q2w group did not show a significant rise in TEAE, but this may be due to the small sample size in the said subgroup. Moreover, the trials had a maximum duration of only six months and this limits the evidence of safety provided by these RCTs. In contrast, to colizumab, the similar agent has been extensively studied in the trials.[22] Hence, we would recommend to conduct longer trials to study the TEAE and TESAE.

Furthermore, OKZ was used in patients taking methotrexate without adequate response and previously failed anti TNF therapy. The term 'inadequate response' by these RCTs might have varying levels of unresponsiveness and this meta-analysis couldn't account for that. Furthermore, the patients have been exposed to anti TNF therapy before OKZ administration and so the effect on biologic naïve patients is under question. Additionally, comparison between switching to OKZ vs OKZ add-on treatment groups would help delineate individualized OKZ effects from OKZ add-on. Other IL-6 signaling pathway inhibitor, tocilizumab, should be compared to Olokizumab for efficacy, adverse effect profile and cost effectiveness.

CONCLUSION

In conclusion, Olokizumab has shown significant improvement in disease activity compared to placebo with a favorable safety profile. However, further larger and longer-term studies are required to confirm these findings.

Research and Publication Ethics

Conflict of Interest: None

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AUTHORS' CONTRIBUTION

SK: Conceptualization, Manuscript drafting and Critical Revision. LI: Data collection, Data analysis, Manuscript writing, Supplementary documentation. MU: Manuscript writing, Data collection. JT: Manuscript Writing, Data collection. AK: Manuscript Writing, Data analysis. ST: Manuscript Writing, Data collection. AA: Critical Revision

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