Safety and Efficacy of IL-6 Inhibitors in the Treatment of Neuromyelitis Optica Spectrum Disorders. A Meta-analysis

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Abstract

Background

Interleukin-6 (IL-6) inhibitors like Tocilizumab and Satralizumab are showing promising results in the treatment of Neuromyelitis Optica spectrum disorder (NMOSD). We aimed to investigate the efficacy and safety of various IL-6 inhibitors in the management of NMO/NMOSD.

Methods

PubMed, Embase, and The Cochrane Library were systematically searched for suitable studies. Change in Annualized Relapse Ratio (ARR), Change in Extended Disability Status Scale (EDSS) s, the proportion of relapse-free patients, on trial relapse risk, and proportion of patients with adverse events, including serious adverse events and mortality were the parameters considered for the meta-analysis. Mean difference (MD) with 95% CI was used to quantify the change in ARR and change in EDSS-before and after treatment. While pooled risk ratio between the intervention group and placebo group was used in Randomized Controlled Trial (RCTs). A forest plot was prepared to indicate the efficacy outcomes.

Results

A total of nine studies with 202 patients were included in our meta-analysis. IL-6 inhibitors found a good proportion (75%,95% CI: 0.62–0.89; p<0.001) of relapse free patients at follow up. It also significantly reduced mean ARR (mean difference: -2.6 95% CI: -2.71 to -1.68; p<0.001) and on trial relapse risk (RR: 0.46; 95% CI: 0.32-0.66; P< 0.001) but did not show significant difference in change in EDSS score (mean difference=-0.79, 95% CI: -1.89 to -0.31; p=0.16). Also, the toxicity profile of IL-6 inhibitors was acceptable considering the proportions of patients with adverse events (72%, 95% C.I.;0.59-0.84, I^2=85.29%, p<0.001), proportions of patients with serious adverse events (18%;95% C.I.; -3.68 to 4.04, I^2=0%, p=0.93) and zero treatment related deaths. In subgroup analysis, we found subcutaneous administration to be superior (81%;95% CI:0.74-0.82) than intravenous route (67%; 95% CI:0.67-0.89) in relapse free maintenance.

Conclusion

IL-6 inhibitor therapy showed significant benefits in reducing mean ARR, relapse risk and increasing the number of relapse-free patients with acceptable adverse events profile.

Background

Neuromyelitis Optica Spectrum Disorder (NMOSD), previously called Devic's disease is an Aquaporin-4-Immunoglobulin G (AQP4-IgG) antibody-associated autoimmune inflammatory disease of the Central Nervous System mostly involving the optic nerve and spinal cord.[1] Similarly, involvement of cerebrum, diencephalon, or brainstem are also frequently observed, in about 80% of patients.[2] Myelin oligodendrocyte glycoprotein (MOG) antibody found in AQP-4 negative NMOSD patients, has also been recently described.[3] Several studies have shown the prevalence rate of NMOSD ranging from 0.37 to 4.1 per 100,000 persons and up to 10 per 100,000 persons in certain racial groups.[4,5] Females, people with age greater than 35 years, and Asian or African races are particularly at an increased risk for developing NMOSD.[6]

The primary aim of treatment in NMOSD is to reduce the severity of acute attacks, prevent relapses, and maintain remission.[7] To achieve this, various groups of drugs have been used. For the prevention of relapses, immunosuppressive drugs such as azathioprine and mycophenolate mofetil are used and are also found effective. However, it comes with the cost of inevitable adverse effects because of prolonged or long-life immunosuppression.[8,9]

To counterfeit this issue, humanized recombinant monoclonal antibody drugs like eculizumab, inebilizumab, and satralizumab targeting different receptors like anti-CD-20, IL-6, complement-5(C-5), etc. are being widely used and studied.[10] IL-6 inhibitors like Tocilizumab and Satralizumab, are now being considered as good options for treatment of NMO/NMOSD and potential therapeutic effects of two anti-IL-6 agents Tocilizumab and Satralizumab have been investigated via clinical trials and have shown promising results in the treatment of active NMOSD case, however, summarized data is lacking.[11] To establish IL-6 inhibitors drugs as efficacious and tolerated treatment options in the management of NMO/NMOSD, this meta-analysis is done with the aim of finding the combined effect size of their efficacy and safety from real-world studies.

Methods

This systematic review and meta-analysis were carried out and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[12] Our meta-analysis aims to explain the role of IL-6 inhibitors or Anti-Interleukin Receptor drugs (Tocilizumab and Satralizumab) for the treatment of patients with Neuromyelitis Optica Spectrum Disorder (NMOSD).

Study Registration and Protocol

The study protocol, with well-defined methodology and inclusion criteria, was registered on PROSPERO with reference number ID: CRD42021226900.

Inclusion and exclusion criteria

All original research studies in the English language published until December 5, 2020, discussing the efficacy and/or safety of IL-6 inhibitors (Tocilizumab, Satralizumab) administered in any doses (either low or high dose) and in any form (Intravenous or subcutaneous) for the treatment of NMOSD/NMO patients were considered eligible for inclusion. Studies reporting data on the use of these drugs given to patients of any age or nationality as monotherapy or in combination with other add-on therapies were included. The objective outcomes needed (at least one) in the study for inclusion were: Change in Annualized Relapse ratio (ARR), Change in EDSS score, the proportion of relapse-free patients, on trial relapse risk, and proportion of patients with adverse events, including serious adverse events and mortality.

Studies involving any of these were excluded from the meta-analysis: 1) Studies with insufficient or unclear information 2) in vitro or animal studies 3) case reports, case series with ≤ 2 cases, conference abstracts, reviews, meta-analysis, editorials and commentaries, and 4) non-English studies.

Search strategy and selection criteria

We searched PubMed, Embase and The Cochrane Library from the inception dates to December 5, 2020. Boolean logic was used for conducting a database search, and Boolean search operators "AND" and "OR" were used to link search terms. A combination of the following keywords was included: “neuromyelitis spectrum disorder”, “optic neuritis”, “NMOSD”, “Aquaporin 4 antibody”, “Devic’s disease”, “Anti-interleukin-6”, “anti-IL-6”, “IL6 receptor blockade”,” Tocilizumab” and “Satralizumab”. For advanced PubMed search, the medical subject headings (MeSH) database was used to find MeSH terms for the aforementioned search terms. Similarly, for advanced Embase search, Emtree terms were used for the aforementioned search terms. The search strategy is described in supplementary file 1. To find additional articles, manual searching of reference lists from selected articles was done. The search was also broadened to include preprint servers and thesis repositories while experts in the field were also inquired about ongoing studies. These additional searches were included in our analysis if they fulfilled our eligibility criteria.

Data extraction

Two reviewers (SK and SS) imported all the above records to ENDNOTE v9 and ran duplicate searches. The duplicate records were then removed. Then, they evaluated remaining records by their titles and abstracts independently and assessed in detail the full texts of any potentially relevant articles against the eligibility criteria. Any disagreements or uncertainties were resolved through discussion with the help of a third author (RO). Two reviewers then independently extracted data from studies selected for inclusion, and any discrepancies resolved through discussion and with help of a third reviewer (RO).

Following this, two reviewers (SK and SS) used a pre-designed standardized data extraction format to extract data under the following headings: Authors, year of publication, IL-6 inhibitors used, type of study, regions/countries where studies were conducted, sample size, follow-up period, number of females/males patients, mean age or range of patients, mean disease duration, number of Aquaporin-4 Ab positive patients, doses of drugs used, Add-on drugs and/or previously used drugs. The corresponding authors of the respective papers were contacted for clarification if required data were missing, not reported in the paper, or reported in an unusual form. Supplementary material associated with the main paper was also explored in cases whenever deemed necessary.

Statistical Analysis

The meta-analysis was conducted using the STATA software version 16 (StataCorp). A random-effects or fixed-effect model was used to pool the data, and statistical heterogeneity was evaluated using the I^2 statistic. When I^2 was ≤ 50%, a fixed-effect model was used for meta-analysis. When I^2 was > 50%, DerSimonian, and Laird random-effects model was used for meta-analysis. Meta-analysis of the proportion of patients with relapse-free at last follow-up and proportion of patients with adverse events, serious adverse events were expressed as a pooled proportion with 95% confidence interval (CI). Meta-analysis for change in ARR and Change in EDSS-before and after treatment was expressed as a mean difference (MD) with 95% CI. While meta-analysis for on-trial relapse risk among randomized control trials (RCTs) studies was expressed as pooled Risk ratio between the intervention group and placebo group. Forest plots with 95% CIs were created to show individual study results and weights as well as overall weighted mean estimates. Subgroup analysis was performed and to check the heterogeneity meta-regression analysis was done on different headings. Sensitivity analysis was also done to check the robustness of studies.

Publication bias was evaluated by visual inspection of the funnel plot and Egger’s test. We used the Duval and Tweedie trim and fill method to calculate the adjusted effect size accounting for potential publication bias in one of the analyses. A P-value of < 0.05 was considered statistically significant.

Risk of Bias

To assess the risk of bias in individual studies for the primary outcome, a standardized critical appraisal instrument, the Cochrane Collaboration’s risk of bias tool (https://training.cochrane.org/handbook/current) was used for RCT. While the Newcastle Ottawa scale (NOS) for the observational study was used for observational studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Two reviewers (SK and SS) independently assessed the risk of bias based on sequence generation, allocation concealment, blinding of participants' personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Disagreements were resolved by discussion.

Results

Search results and study characteristics

Altogether, 165 studies were obtained from electronic database searches. Out of this, 115 studies were screened by title and abstract after removal of duplicates. The remaining 30 full-text articles were then assessed as per the eligibility criteria. Finally, only 9 studies with a total of 202 patients were included

in the analysis. (Fig. 1)

The characteristics of the patients included in our analysis are summarized in Table 1. The included studies consisted of six retrospectives observational studies,[13–19] and three randomized controlled trials.[19–21] Of these, only 2 studies used Satralizumab,[20,21] while the remaining seven studies used Tocilizumab.[13–18] The studies were done in different parts of Asia, Europe, and North America. The sample size of the patients ranged from 3 to 63 with female predominance with mean age ranging from 29.4 years to 50 years. The average follow-up duration ranged from 12 months to 31.8 months. The most commonly used dose was 8 mg/kg for 4 weeks intravenously and 120 mg subcutaneously in specified dosage pattern. Add-on drugs were used in all the observational studies, of which the most common were azathioprine and mycophenolate mofetil while in RCTs, only one study assessing monotherapy used no placebo drugs.[21]

Table 1
Detail characteristics of studies included

Authors	Year	IL-6 inhibitors used	Type of study	Regions/Countries	Sample Size	Followup	Sex (Female/Male)	Mean age/Range	Mean disease Duration	AQ ab pos
Ayzenberg	2013	Tocilizumab	Retrospective study	Germany	3	18 months	3/0	39 years (26–40 years)	8.2 years (2.5–9.4 years)	3(1
Araki	2014	Tocilizumab	Pilot study	Japan	7	12 months	6/1	12–60 years	NA	7(1
Ringelstein	2015	Tocilizumab	Retrospective Study	Germany	8	30.9+-15.9 months	8/0	29.4 years (25–49 years)	7.9+-7.7	8(1
Guarnizo	2018	Tocilizumab	Retrospective Study	Spain	5	NA	3/2	50+-5.3 years	2.3 years	2(4
Lotan	2019	Tocilizumab	Retrospective study	USA	12	31.8+-18.8 months	11/1	46.9+-14.5(26–68) years	6.8+-4.6 years	7(5
Rigal	2020	Tocilizumab	Retrospective study	France	4	23 months	4/0	35.75 years (20–63 years)	7.85(2–15 years)	4(1
Zhang	2020	Tocilizumab	Randomized Controlled Trial	6 centers in China	59	60 weeks	55/4	48.1+-13.4 years	6+-2.9 years	50(
Yamamura	2019	Satralizumab	Randomized Controlled Trial	34 centers in 11 countries	41	NA	37/4	40.8+-16.1 years (13–73 years)	NA	27(
Traboulsee	2020	Satralizumab	Randomized Controlled Trial	44 centers in 13 countries	63	NA	46/17	45.3 ± 12.0 (21–70 years)	NA	41(

NOS scale used for observational studies[13–18] found the score ranging from 5 to 7. All the studies were included in the analysis. While for RCTs, two trials [20,21] had a low risk of bias while the remaining trial[19] had a high risk of bias under the domain deviation from the intended intervention and unclear bias under the domain missing outcome data.(Appendix 2 and 3 supplementary file)

Efficacy Outcomes

Proportions of relapse-free patients

The events of patients before and after IL-6 inhibitor therapy was reported in all nine studies(n = 152). As the heterogeneity between studies was high (I^2 = 89.33%, p = < 0.001), we conducted a meta-analysis using a random effect model. Our analysis showed that number of relapse-free patients at follow-up with use of IL-6 inhibitors was 75% (95% CI: 0.62–0.89; p < 0.001) among which pooled proportion was 69% (95% CI: 0.43–0.94; I^2 = 82.95%, p = < 0.001) in observational studies (n = 38) and 79% (95% CI: 0.69–0.89; I^2 = 61.32%, p = 0.08) in RCTs (n = 163), with no subgroup difference (p = 0.44). Similarly, pooled proportion was 75% (95% CI: 0.65–0.85; I^2 = 36.71%, p = 0.21) in Satralizumab groups (n = 104) while 76% (95% CI: 0.43–0.94; I^2 = 84.39%, p < 0.001) in Tocilizumab groups (n = 97) with no subgroup difference(p = 0.91). (Fig. 2). Thus, differences in effect size according to the study types, the treatment used, duration of follow-up, percentage of Aquaporin-4 Ab positivity, and site of injection are given in subgroup analysis in Table 2.

Table 2
Subgroup Analysis in proportion of relapse free patients

Subgroups			
Study type	Effect size (95% C.I.)	I^2	Subgroup difference
Observational Study	69% (95% CI: 0.43–0.94), p < 0.001	82.95%	0.44
Randomized Controlled Trial	79% (95% CI: 0.69–0.89), p < 0.001	61.32%	
Treatment used			
Satralizumab	75% (95% CI: 0.65–0.85), p < 0.001	36.71%	0.91
Tocilizumab	76% (95% CI: 0.43–0.94), p < 0.001	84.93%	
Duration of follow-up			
< 20 months	74% (95% CI:0.49–0.98), p < 0.001	53.54%	0.89
> 20 months	71% (95% CI:0.33–1.09), p < 0.001	89.55%	
Percentage of AQP-4 positivity			
All (100%)	65% (95% CI:0.27–1.02), p = 0.001	86.32%	0.47
Not All (100%)	79% (95% CI: 0.71–0.87), p < 0.001	34.72%	
Site of Injection			
Intravenous	67% (95% CI:0.67–0.89), p < 0.001	64.68%	p < 0.001
Subcutaneous	81% (95% CI:0.74–0.82), p < 0.001	0%	

To explore the possible cause of heterogeneity, meta-regression was done, which showed no significant correlation between the outcome and following variables: study types(p = 0.167), treatment/drug used(p = 0.152), duration of follow up(p = 0.51) and percentage of AQP-4 positivity(p = 0.940). While a significant correlation was found between the outcome and the site of injection(p = 0.016). The information for meta-regression analysis is given in Table 3.

Table 3
Meta Regression for subgroups of relapse free patients

Variables	**Coef.**	**Std. Err.**	**z**	**P>|z|**	**[95% Conf. Interval]**
Study type	0.3806221	0.275608	1.38	0.167	− .1595597 .920804
Treatment used	0.4811561	0.3362744	1.43	0.152	− .1779296 1.140242
Duration of followup	0.083989	0.1641929	0.51	0.609	− .2378232 .4058013
AQP-4 positivity	-0.015244	0.2018352	-0.08	0.94	− .4108338 .3803457
Site of injection	0.1994568	0.0829793	2.4	0.016	.0368204 .3620932
_cons	0.0178725	0.4507015	0.04	0.968	− .8654862 .9012313

Sensitivity analysis done showed stable overall effect size after testing. The inspection of the funnel plot and egger's test (p = < 0.001) showed significant publication bias. (Supplementary Fig. 1). The adjusted proportion using the Duval and Tweedie trim and fill method was 83% of patients (95% CI: 0.71–0.95, 3 studies imputed)

Change in ARR

Changes in ARR before and after IL-6 inhibitor therapy was reported in 5 studies (n = 35), and only in the Tocilizumab group. None of the studies report mean and standard deviation (SD). For those, individual data, mean and SDs were calculated, and in studies reporting as a median, range, and interquartile range, it was converted into mean and SD.[22]

As there was no heterogeneity between the studies (I^2 = 0%, p = 0.80), we conducted a meta-analysis using a fixed-effect model. Our analysis showed that the use of IL-6 inhibitor therapy significantly reduced ARR at follow-up by 2.6 (95% CI: -2.71 to -1.68; p < 0.001) (Fig. 3). Publication bias was not conducted because of a small number of studies.

Change in EDSS score

Changes in EDSS before and after IL-6 inhibitor therapy was reported in 4 studies (n = 23), and only in the Tocilizumab group. As there was no heterogeneity between the studies (I^2 = 0%, p = 0.74), we conducted a meta-analysis using a fixed-effect model. Our analysis showed that the IL-6 inhibitors therapy group did not significantly influence EDSS scores at follow-up. (MD=-0.79, 95% CI: -1.89 to -0.31; p = 0.16) (Fig. 4). Considering a small number of studies, Publication bias was not conducted.

On trial Relapse Risk

3 RCTs reported on trial relapse risk between Treatment groups (Tocilizumab and Satralizumab, n = 163) and Placebo groups(n = 133). Because of the presence of heterogeneity between the studies (I^2 = 30.32%, p = 0.24), we conducted a meta-analysis using a fixed-effect model. Our analysis showed a significant difference between the two treatment groups showing less relapse risk among IL-6 inhibitor therapy used groups than placebo (RR: 0.46; 95% CI: 0.32-0.66; P < 0.001) with no subgroup differences based on the type of drug used (p = 0.12). (Fig. 5)

Safety Outcomes

Proportions of patients with adverse events

Adverse events were reported among (n = 198) patients in nine studies. The pooled proportions of patients with adverse events were 72% (95% C.I.;0.59–0.84, I^2 = 85.29%, p < 0.001) among which 48% (95% C.I.;0.26–0.69, I2 = 56.16%, p < 0.04) was in observational studies and 94% (95% C.I.;0.91–0.98, I^2 = 7.20%, p = 0.34) in RCTs with significant subgroup difference(p = < 0.001) was seen. Similarly, in Satralizumab group, it was 91% (95% C.I.;0.86–0.97, I^2 = 0%, p = 0.75) and in Tocilizumab group was 56% (95% C.I.;0.27–0.85, I^2 = 88.95%, p < 0.001) with significant subgroup differences (p = 0.02). (Fig. 6a)

Most common adverse effects were upper respiratory tract infections(n = 49), Urinary tract infections(n = 43), hypercholesterolemia(n = 13), Leucopenia(n = 12), Fatigue(n = 20), and anemia (n = 19).

Proportions of patients with serious adverse events

Serious adverse events are those that interrupt the patient's daily activities and may lead to systemic medication or other treatment. Serious Adverse events were reported among (n = 180) patients in six studies. Bacterial infections like pneumonia and Deep Vein Thrombosis were the common serious adverse events. The pooled proportions of patients with serious adverse events were 18% (95% C.I.; -3.68 to 4.04, I^2 = 0%, p = 0.93) and a significant subgroup difference was not seen based on study type and type of drug used (p > 0.99). (Fig. 6b)

Mortality

Two patients died in two studies, both in the Tocilizumab group. One with cervical myelitis and another with relapse of longitudinally extensive transverse myelitis. Both the deaths were not related to the treatment complications.

Discussion

To the best of our knowledge, this is the first meta-analysis to evaluate the effectiveness and safety of IL-6 inhibitors in the treatment of NMOSD.

Satralizumab and Tocilizumab are humanized monoclonal antibodies targeting IL-6 receptor or IL-6 which act by promoting differentiation of inflammatory cells inducing morbific antibodies production in NMOSD as a pro-inflammatory cytokine.[20] With the use of antibody recycling technology, Satralizumab has better pharmacokinetics than Tocilizumab.[23] CSF and serum IL-6 levels are found to be increased in patients with NMOSD. IL-6 promotes plasmablast survival, stimulating the secretion of AQP-4 IgG, reducing blood-brain barrier (BBB) integrity and functionality, and enhancing proinflammatory T-lymphocyte differentiation and activation; a driving factor for disease severity in NMOSD. Thus, IL-6 inhibition is now being considered to improve disease severity and control.[24] Among them, tocilizumab is found to have a shorter dosing interval than Satralizumab. Similarly, Satralizumab was tested both as a monotherapy versus placebo and in combination with basic therapeutic agents. [25]

Our analysis showed a promising result. We found that following IL-6 inhibitor therapy, a significant proportion of patients was relapse-free (75%), mean ARR reduced by 2.6 at follow-up and a significant decrease in relapse risk among treatment groups than placebo groups. Barros et al. showed a correlation between baseline serum IL-6 levels and risk of relapses and severity. During a 2-year disease follow-up period in these patients, an increase of 8-fold relapse risk was observed in patients with IL-6 serum concentrations above baseline during remissions.[26] Uzawa et al. found patients with high CSF IL-6 levels to have shorter relapse-free duration than with low levels after relapse ($p = 0.079$).[27] Similarly, it also found an only modest improvement in disability of patients with high IL-6 levels.[27] A recent meta-analysis of Xue et al. analyzed the safety and efficacy of different monoclonal antibodies used in NMOSD among RCTs. Sub-group analysis of this study found a significant decrease in on-trail relapse risk and a significant difference in mean difference in mean ARR and EDSS at follow-up (analysis of two trials of Satralizumab) among the treatment groups and placebo group. IL-6 inhibitors was also found to be superior to other monoclonal antibodies in reducing EDSS.[28] A meta-analysis describing the safety and efficacy of Tocilizumab has similar therapeutic outcomes as compared to our analysis considering results in a change in mean ARR and EDSS score following treatment as only more studies of Tocilizumab treatment were added in our analysis with no availability of data following Satralizumab treatment.[29]

Between the subgroups of study type (Observational studies and RCTs) and drug use (Tocilizumab and Satralizumab), our analysis found no significant subgroup difference in efficacy outcomes. Individual trail[20] has shown significant reduction in relapses for AQP-4 Ab positive patients and significant increase with duration of treatment/follow up but in our analysis mean duration of follow up and percentage of AQP-4 positivity neither had a significant difference on the effectiveness of therapy. However, considering the route of administration of the drug (intravenous vs subcutaneous), studies with subcutaneous injection found a greater proportion of relapse-free patients (74%) than those with intravenous administration. This finding cannot be generalized because both have been used inconsistently. But, a study by Iotan et al found subcutaneous injections equally effective as IV formulations while subcutaneous injections more advantageous due to ease of in-home administration.[17]

In terms of safety issues, the proportion of patients with adverse events and serious adverse events was 72 % and 18%. The frequency of most common adverse events like Upper respiratory tract infections, Urinary Tract Infections, hypercholesterolemia, and serious adverse events are similar to studies by Xie et al. and Xue et al.[28,29] Though, cardiovascular disease is the main safety of concern in Anti-IL-6 receptor drugs like Satralizumab and Tocilizumab as a result of an increase in cholesterol levels; recent trials[20] have shown no increase in the risk of cardiovascular disease.[30] In subgroups, RCTs and Satralizumab used studies had greater patients with adverse events than observational and Tocilizumab used studies respectively. Most of the adverse events in these studies were caused by drug effect and accidental occurrence mainly during relapse and there was a very small mortality rate. These evidences suggest that IL-6 inhibitor therapy is safe and well-tolerated with an acceptable adverse effects profile.

Recently, Satralizumab has been approved by the US Food and Drug Administration (FDA) for the treatment of NMOSD based on two RCTs; SAkuraSky and SAkuraStar trial. Canada also approved subcutaneous Satralizumab for the treatment of NMOSD in adults and children aged ≥ 12 years with AQP-4 seropositivity.[31] While Tocilizumab is still used off-label in some case studies and in clinical studies. Tocilizumab, however, is considered a safe and effective alternative to azathioprine in controlling relapses with the need for further trials.[19] Comparison of safety and efficacy of satralizumab and Tocilizumab was not effective in our study, as ideally, head-to-head trials should be conducted for direct comparative analysis and evaluation. Though, IL-6 inhibitors have established themselves as an important class of monoclonal antibodies in the field of treatment of relapses of NMOSD, the road ahead is long, as the benefits are only applicable to a large subset of AQP4-Ab seropositive patients leaving behind the important hurdle to find a drug that can impact the disease course of AQP-4 Ab seronegative groups.[10]

Our meta-analysis has several strengths. We have systematically collected all evidence including real-world data and RCTs for the efficacy and safety of IL-6 inhibitors. Our meta-analysis included 9 studies with 202 patients receiving IL-6 inhibitor therapy. Errors in the calculation of data used in the previous meta-analysis were rectified, if present. The main limitation of our analysis is heterogeneity among studies in two analyses; the proportion of Relapse free patients and adverse events with publication bias in the initial one. Variability in sample size, follow time, drug use, AQP-4 positivity rate, and sites of injection causing heterogeneity is another limitation. The use of different add-on drugs like immunosuppression to reduce relapses may also add on to heterogeneity.

Conclusions

Our meta-analysis showed IL-6 inhibitor therapy showed significant benefits in reducing mean ARR, relapse risk and increasing the number of relapse-free patients with acceptable adverse events profile. However, more long-term trials and placebo-controlled trials including large subsets of both AQP4-Ab seropositive and AQP4-Ab seronegative NMOSD patients are needed.

Abbreviations

IL-6: Interleukin-6

INMOSD: Neuromyelitis Optica spectrum disorder

IARR: Annualized Relapse ratio

IEDSS: Extended Disability Status Scale

IMD: Mean difference

IRCT: Randomized Controlled Trial

IAQP4-IgG: Aquaporin-4-Immunoglobulin G

IMOG: Myelin oligodendrocyte glycoprotein

INOS: Newcastle Ottawa scale

ISD: Standard Deviation

IBBB: Blood Brain Barrier

IFDA: Food and Drug Administration

Declarations

Declaration of Conflict of Interest:

Authors declare no conflict of interest

Acknowledgment:

None

Competing Interest:

None to declare.

Availability of data and Materials:

All the necessary data and information are within the article. Supplementary file with the search strategy has been provided.

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Not applicable.

Authors Contributions:

SK and SS were involved in conceptualization of the study along with designing the study search strategy, reviewed study abstracts, extracted data from full text articles, and drafted the initial manuscript. SK did all the statistical analysis. RO, NH and RG were involved in editing and revising the manuscript. All the authors read and approved the final version of the manuscript.

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Figures

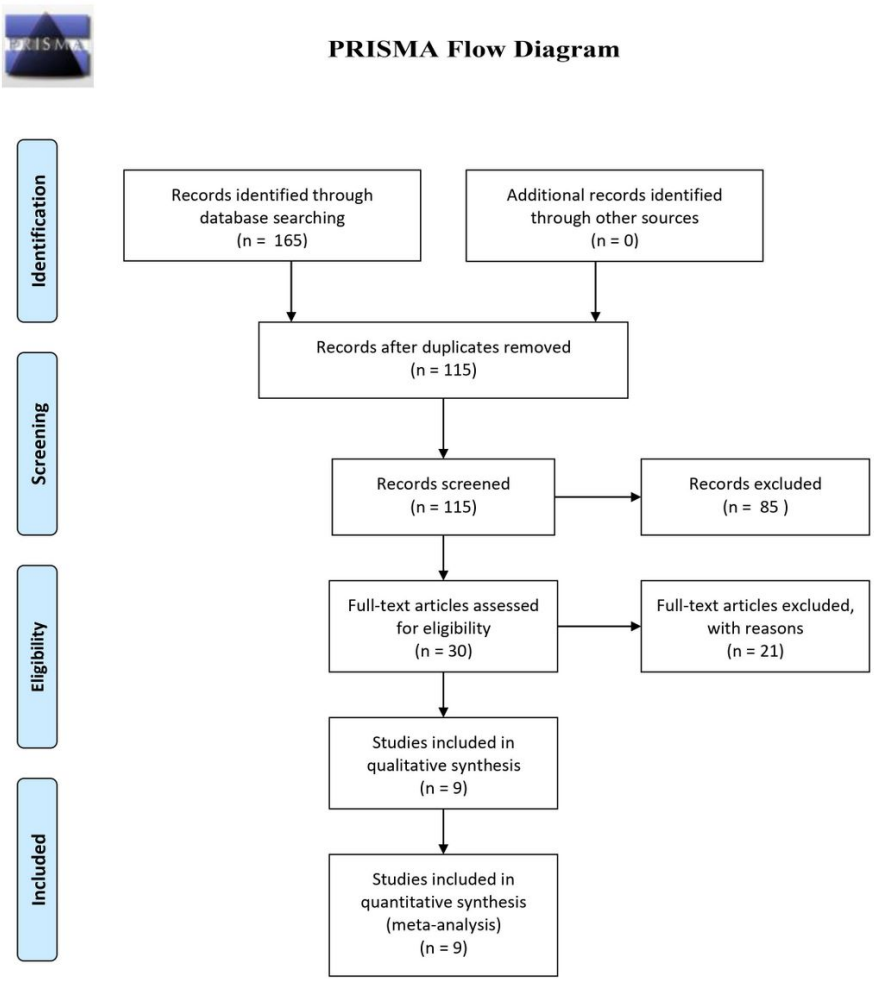

Figure 1

Prisma diagram showing the selection and identification of study.

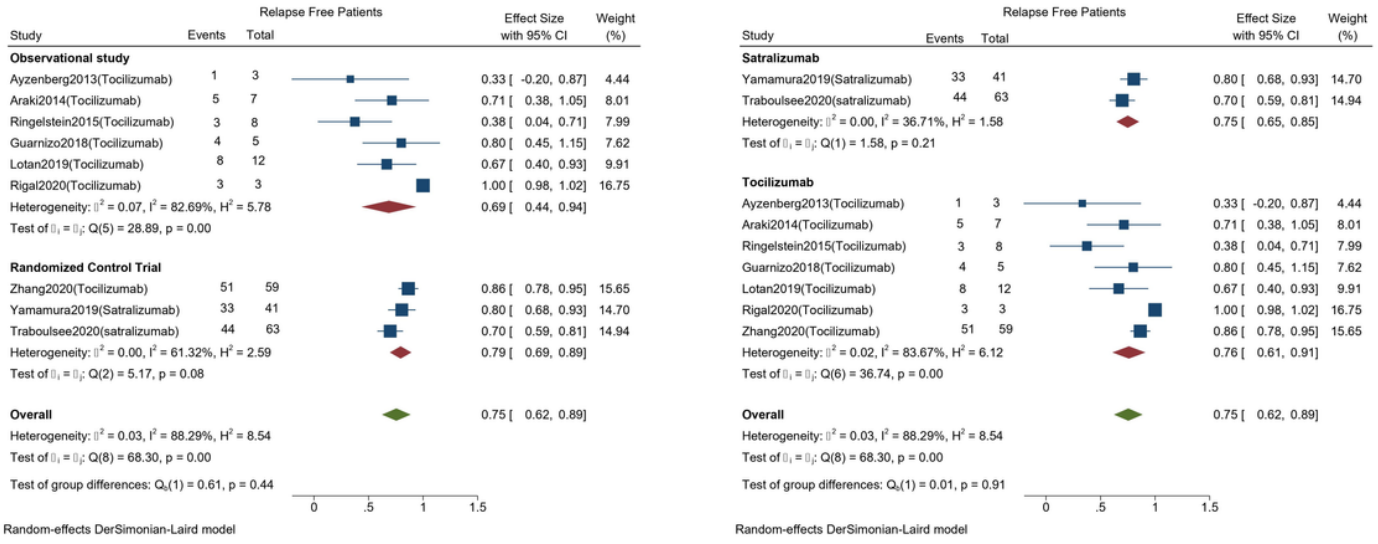

Figure 2

Forest plot with 95% CI for meta-analysis of proportion of patients who were relapse free. The area of each square is proportional to the study's weight in the meta-analysis, while the diamond shows the pooled result. The horizontal lines through the square illustrate the length of the confidence interval. The width of

the diamond serves the same purpose. The overall meta-analyzed measure of effect is imaginary vertical line passing through diamond. A: Subgroup Analysis according to study type B: Subgroup Analysis according to treatment used.

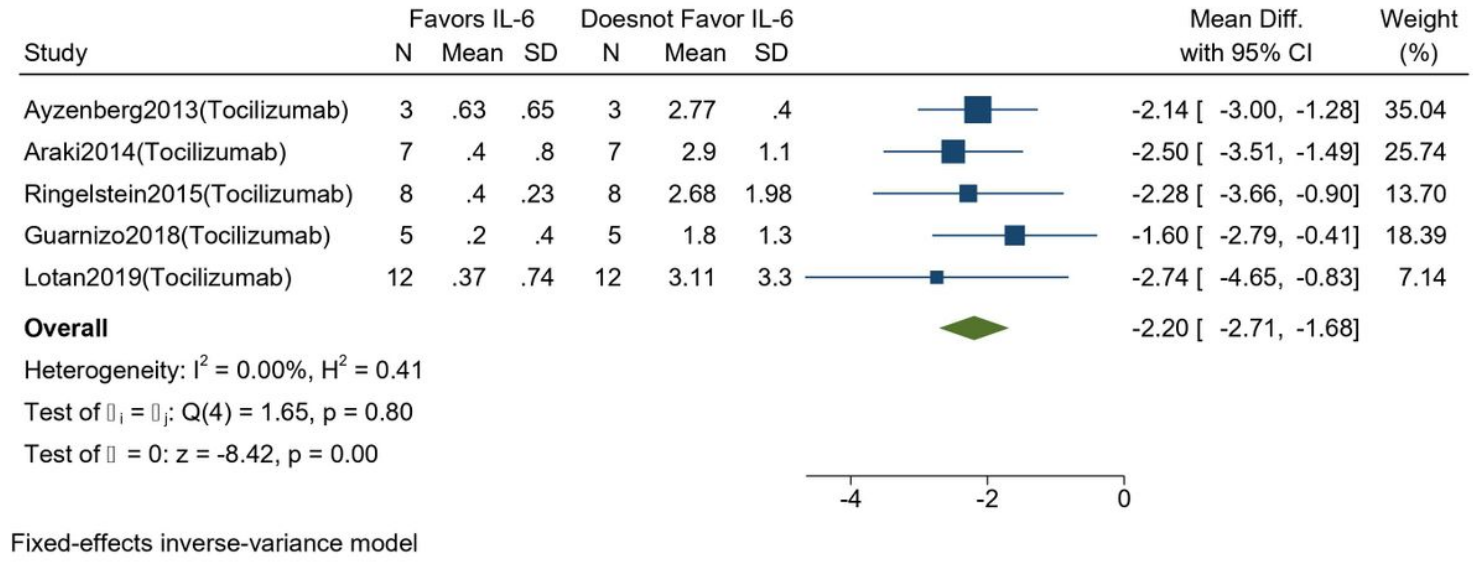

Figure 3

Forest plot with 95% CI for meta-analysis of efficacy on the mean ARR reduction. The square shows the mean difference for each study. The diamond at the bottom of the graph shows the average effect size of included studies.

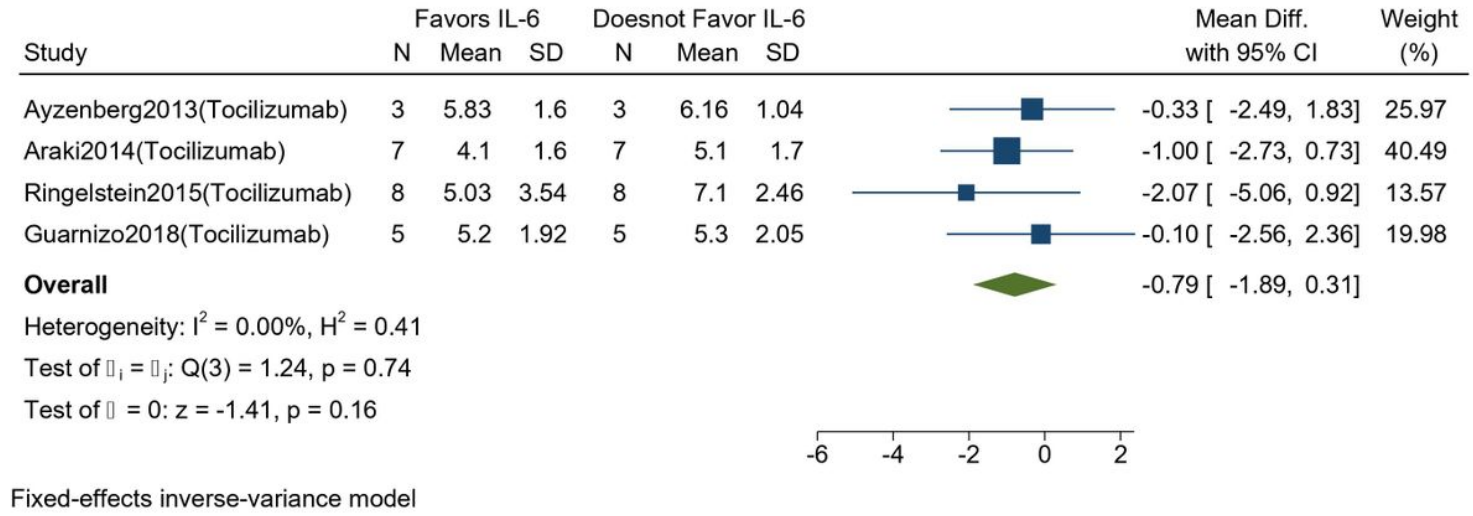

Figure 4

Forest plot with 95% CI for meta-analysis of efficacy on the mean EDSS reduction. The square shows the mean difference for each study. The diamond at the bottom of the graph shows the average effect size of included studies.

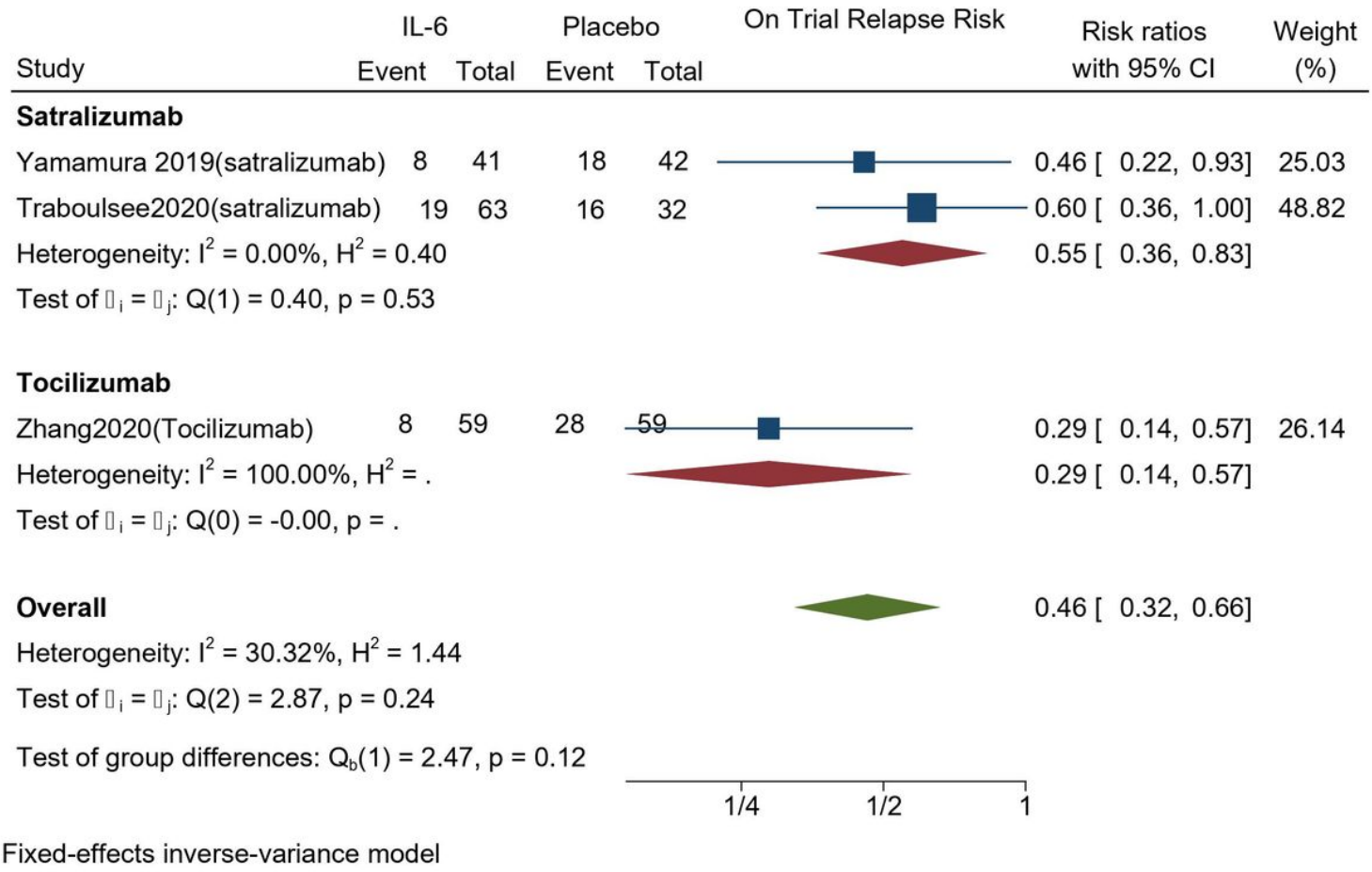

Figure 5

Forest plot with 95% CI for meta-analysis of efficacy on the on-trial Relapse risk among RCT studies. The square shows the risk ratios for each study. The diamond at the bottom of the graph shows the average effect size of included studies.

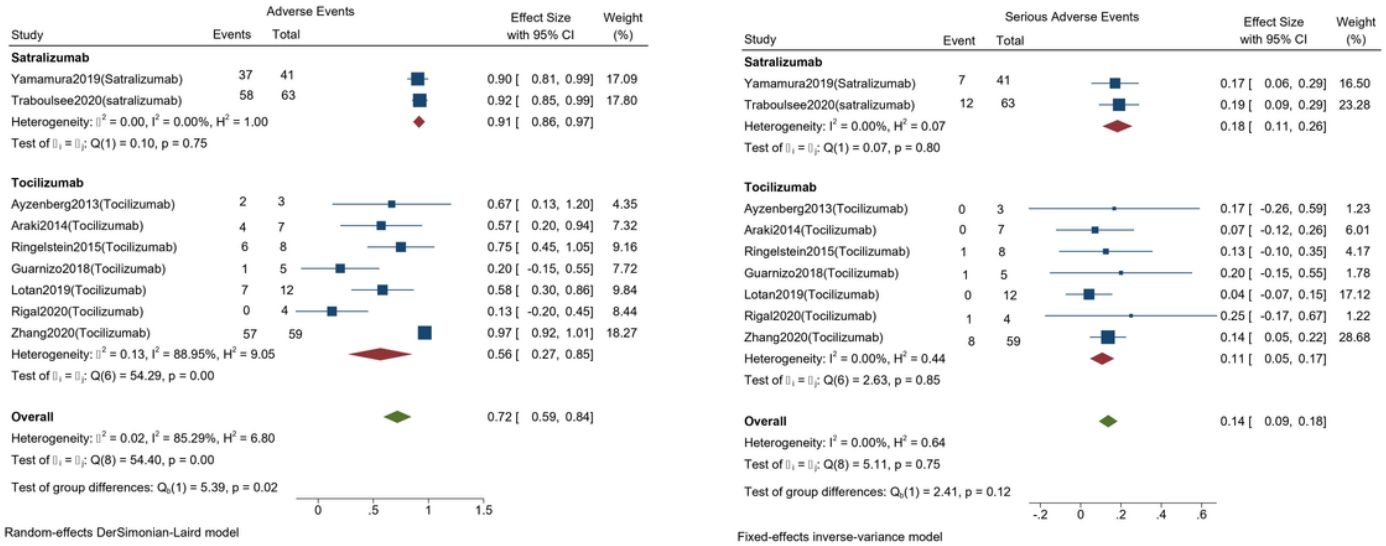

Figure 6

Forest plot with 95% CI for meta-analysis of proportion of patients who experienced adverse effects. The area of each square is proportional to the study's weight in the meta-analysis, while the diamond shows the pooled result. The horizontal lines through the square illustrate the length of the confidence interval.

The width of the diamond serves the same purpose. The overall meta-analyzed measure of effect is imaginary vertical line passing through diamond. A: incidence of Adverse effect B: incidence of serious adverse effect

Supplementary Files

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