Systematic Review and Meta-Analysis

Medicine

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A comparison of the efficacy of tocilizumab versus azathioprine for neuromyelitis optica spectrum disorder

A study protocol for systematic review and meta-analysis

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Abstract

Background: Neuromyelitis optica spectrum disorder (NMOSD) is a chronic inflammatory disease of the nervous system, which is frequently accompanied by a pathological humoral immune response against aquaporin-4 water channel. The most common feature of the disorder is recurrent episodes of longitudinally extensive transverse myelitis and optic neuritis. Frequent relapse leads to the gradual accumulation of neurological dysfunction. Azathioprine (AZA) is an empirical attack -preventive immunotherapies drug to prevent the relapse of NMOSD, and tocilizumab (TCZ) has been also reported reduce the activity of NMOSD. Therefore, we designed this systematic review and meta-analysis to evaluate the efficacy between TCZ and AZA in the treatment of NMOSD patients.

Methods: This study followed the PRISMA guidelines. We searched the English literature between 2000 and 2022 by using relevant medical subject heading and entry terms in PubMed, MEDLINE, Embase and CENTRAL databases. A meta-analysis of drug efficacy was performed using expanded disability status scale score and annualized relapse rate (ARR) as the primary outcome indicators.

Results: The literature search found a total of 1546 articles about TCZ and AZA in the treatment of NMOSD, 27 of which were included in this study after a series of screening. 930 and 148 patients with NMOSD were enrolled, who had been treated with AZA and TCZ, respectively. The pooled standardized mean difference (SMD) of expanded disability status scale score before and after AZA treated was -0.40 (95%CI: -0.50, -0.30) (I^2 = 65.4%, P < .001), before and after TCZ treated was -0.84 (95%CI: -1.08, -0.60) (I^2 = 45.6%, P = .076). The SMD of ARR before and after AZA treated was -1.01 (95%CI: -1.12, -0.90) (I^2 = 83.4%, P < .001), before and after TCZ treated was -1.27 (95%CI: -1.52, -1.03) (I^2 = 52.7%, P = .039). In addition, TCZ reduce ARR more significantly compared with AZA (P = .031).

Conclusion: The results of this study showed that the treatment of NMOSD patients with AZA and TCZ are associated with decreased number of relapses and disability improvement as well. In addition, compared with AZA, TCZ more significantly reduce ARR.

Abbreviations: ARR = annualized relapse rate, AZA = azathioprin, EDSS = expanded disability status scale, NMO = neuromyelitis optica, SD = standard deviation, TCZ = tocilizumab.

Keywords: annualized relapse rate, azathioprine, expanded disability status scale, meta-analysis, neuromyelitis optica spectrum disorders, tocilizumab

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a chronic inflammatory disease of the nervous system, which is frequently accompanied by a pathological humoral immune response against aquaporin-4 water channel. The most common feature of the disorder is recurrent episodes of longitudinally extensive transverse myelitis and optic neuritis.[1,2] Frequent relapse leads to the gradual accumulation of neurological dysfunction. Therefore, it is very important to prevent

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The datasets generated during and/or analyzed during the current study are publicly available.

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the relapse of NMOSD.[3] Tocilizumab (TCZ) is a humanized anti-IL-6R monoclonal antibody, which can effectively reduce the annual relapse rate (ARR) and improve neurological dysfunction in patients with NMOSD.[4,5] Azathioprin (AZA) is a kind of thiopurine, which acts as an antagonist of endogenous purine of DNA, RNA and some coenzyme components. It has immunosuppressive effect and is an empirical attack-preventive immunotherapies drug for the treatment of NMOSD. It can also effectively reduce the relapse of patients and improve neurological dysfunction.[6,7] Recently, more studies are published regarding safety and efficacy of TCZ and AZA. Therefore, we designed this systematic review and meta-analysis to compare the efficacy of the 2 drugs in the treatment of NMOSD patients.

2. Methods

2.1. Study selection

This meta-analysis was carried out based on the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was registered on the international prospective register of systematic reviews (PROSPERO) CRD42022346673.

Two of us (Tang and Yao) independently searched PubMed, MEDLINE, Embase and CENTRAL databases using medical subject heading and related entry terms with the search strategy shown in Figure 1, and then collected relevant data using a standardized data extraction form. medical subject heading include: Neuromyelitis optic and Tocilizumab or AZA; Entry terms

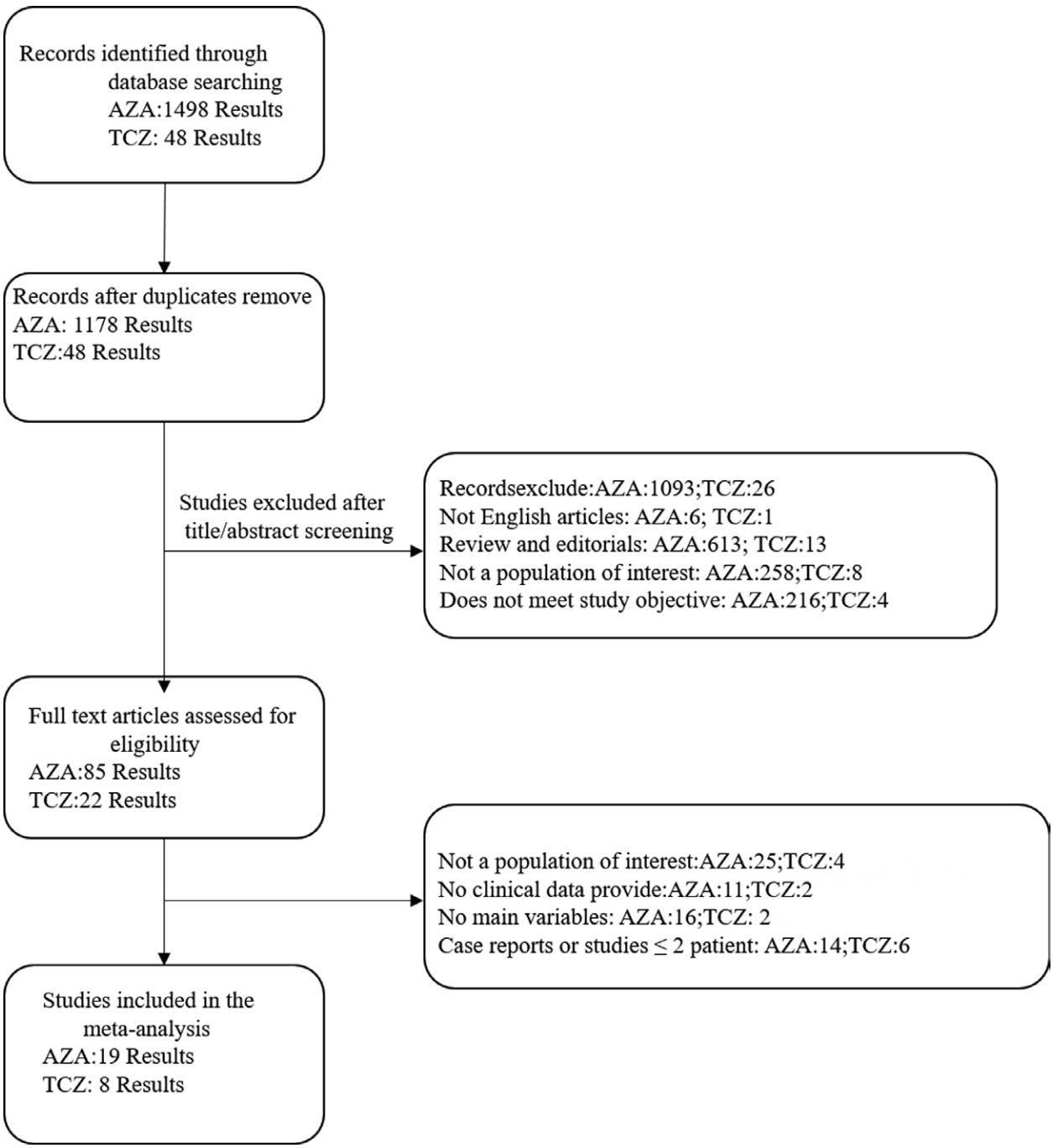

Figure 1. Study selection according to preferred reporting items for systematic reviews and meta-analyses.

include: neuromyelitis optica (NMO) Spectrum Disorder, NMO Spectrum Disorders, NMO Spectrum Disorder, Neuromyelitis Optica Spectrum Disorders, Devic Neuromyelitis Optica, Neuromyelitis Optica, Devic, Devic's Disease, Devic Syndrome, Devic's Neuromyelitis Optica, NMO Spectrum Disorders, atlizumab, monoclonal antibody MRA, BAT-1806, MSB11456, RG-1569, RO-4877533, RHPM-1, AZA sodium, AZA sulfate. Ji and Wang then reexamined the inconsistent data and resolved the differences through discussion and consensus.

2.2. Inclusion and exclusion criteria for the literature

All searched documents were read to assess their suitability for inclusion in the meta-analysis. Inclusion criteria: Meeting the study objectives; NMOSD patients meeting the diagnostic criteria for NMOSD in 2006 or 2015; English language articles; The article provides the mean ± standard deviation (SD) or median (IQR) of the expanded disability status scale (EDSS) scores or ARR ratios. Exclusion criteria: Case reports and studies including fewer than 2 patients; Reviews, editorials, or meta-analyses; Studies with no population of interest.

2.3. Primary efficacy outcome

In the present study, the ARR ratio (mean [SD]) and EDSS score (mean [SD]) were used as the main indicators to evaluate the effect of medications. In the absence of fever or infection, a new neurological deficit that increased the EDSS score by at least half a point or worsened 2 functional systems by 1 point or 1 functional system by 2 points and lasted for at least 24 hours was considered a relapse. ARR is the ratio of the number of relapses to the time from the start of first-line immunosuppressive therapy to the end of follow-up.

2.4. Statistical analysis

Data analysis was performed using STATA (Version 15.0, https://www.stata.com). Fix Inverse Variance effects model with inverse variance was used. Inconsistency (I^2) was calculated for heterogeneity evaluation. Means and standard deviation were calculated if EDSS score and ARR ratio were reported as median (IQR) in the included articles.[8]

3. Results

3.1. Literature search and study selection

The literature search identified a total of 1546 relevant English-language publications (published from January 1, 2000–July 21, 2022) on AZA and TCZ for NMOSD from MEDLINE, PubMed, and Embase databases. After a series of screening, 27 of these articles were included in this study

In the combined data of all studies, the total number of patients treated with TCZ was 148 (136 women and 12 men) and the total number of patients treated with AZA was 930 (802 women and 128 men). The main characteristics of the included studies are shown in Table 1. The average age of patients treated with TCZ was 42.3 ± 14.1 years and the average age of patients treated with AZA was 37.5 ± 11.8 years. There were 127 AQP4 antibody seropositive patients in the TCZ treatment group, accounting for 85.8% of the total. In the AZA treatment group, there were 363 patients known to be seropositive for AQP4 antibodies and 406 patients for whom the serum AQP4 antibody status was not known.

3.2. Efficacy on the EDSS score and ARR ratio

Figure 2 shows a forest plot of EDSS scores and ARR ratios before and after drug treatment. (A)The pooled SMD of EDSS score before and after AZA treated was -0.40 (95%CI: -0.50, -0.30) (I^2 = 65.4%, P < .001), before and after TCZ treated was -0.84 (95%CI: -1.08, -0.60) (I^2 = 45.6%, P = .076). (B) The SMD of ARR ratio before and after AZA treated was -1.01 (95% CI: -1.12, -0.90) (I^2 = 83.4%, P < .001), before and after TCZ treated was -1.27 (95%CI: -1.52, -1.03) (I^2 = 52.7%, P = .039). The results showed that both AZA and TCZ could effectively reduce the ARR ratio of NMOSD. AZA could improve the EDSS score of NMOSD patients, but there was no significant difference in EDSS score before and after TCZ treatment.

3.3. Publication bias and sensitivity analysis

The Egger test revealed no publication bias among the studies in the meta-analysis with EDSS score (Fig. 3A) and ARR ratio (Fig. 3B) as the 2 main variables (P = .168; 95 % CI, -2.8952–0.5376 and P = .051; 95 % CI, -3.9562–0.0060). A sensitivity analysis revealed that there is no significant heterogeneity between the studies (Fig. 3C, D).

3.4. Quality assessment of included studies

No major quality defects were included in this paper. The quality assessment is shown in Table 2.

3.5. The curative efficacy of Tocilizumab is better than that of AZA in NMOSD

We analyzed the significant differences in SMD of ARR among AZA and TCZ in this article according to the method provided by Douglas G,[9] the results are shown in Table 3. The results showed that TCZ significantly reduced ARR compared with AZA (P = .0314).

4. Discussion

In this study, the efficacy of AZA and TCZ in the treatment of NMOSD was analyzed by meta-analyzed, and the differences in reducing the annual relapse rate were compared between the 2 drugs. Several conclusions can be drawn from the current meta-analysis. First, both AZA and TCZ can significantly reduce the ARR ratio of NMOSD. Second, compared with AZA, TCZ has more significant efficacy in reducing ARR ratio. Third, AZA can effectively improve EDSS score. However, there was no significant difference in EDSS score before and after TCZ treatment. We speculate that the reason for this result may be related to the small sample size included.

NMOSD is a rare and crippled autoimmune disease of the central nervous system, which can be treated with a variety of immunosuppressants and biological drugs, such as anti-complement C5 monoclonal antibody eculizumab,[10] anti-CD19 monoclonal antibody inebilizumab,[11] anti-IL-6 receptor monoclonal antibody satralizumab,[12] rituximab,[13] mycophenolate mofetil,[14] etc. Since the degree of disability in NMOSD patients accumulates with the relapse of the disease, prevention of the relapse of NMOSD is critical.

IL-6 is a multi-effector cytokine produced by multiple types of cells and plays a role in multiple pathophysiological processes. Recent studies have found that IL-6 signaling plays a role in the pathogenesis of NMOSD.[15,16] The levels of IL-6 in CSF of NMOSD patients were significantly higher than those of other neurological diseases,[17]and serum IL-6 levels were correlated with CSF white blood cell count and EDSS score.[18,19] Tocilizumab is a humanized monoclonal antibody targeting the IL-6 receptor. Due to the potential role of IL-6 in the pathogenesis of NMOSD, Tocilizumab has been used in clinical trials for the treatment of NMOSD and has shown good therapeutic efficacy.[5,20,21] AZA is an empirical

Table 1

Clinical and demographic characteristics of patients from studies included in the systematic review.

Reference (study)	publish yr	Research type	patient No. (F/ M)	Age of onset	AQP4-Ab (+)	Duration of disease (yr/mo)	Follow-up (yr/mo)
TCZ							
Ayzenberg[1]	2013	Retrospective	3(3/0)	35.0(7.8)	3	6.7(3.7) y	47.2(23.3) m
Araki[2]	2014	Retrospective	7(6/1)	28.7(15.8)	7	NA	NA
Ringelstein[3]	2015	Retrospective	8(8/0)	29.4 (9.1)	8	7.9(7.7) y	30.9(15.9) m
Lotan[4]	2020	Retrospective	12(11/1)	46.9 (14.5)	7	6.8(4.5) y	31.8(18.8) m
Rigal[5]	2020	Retrospective	4(4/0)	41.5(16.9)	4	10.7 (3.9) y	23(4–50) m
Zhang[6]	2020	RCT	59(55/4)	48.1(13.4)	50	6.0(2.9) y	78.9(58.3–90.6) m
Du[7]	2021	Retrospective	19(16/3)	44.7(15.8)	12	NA	1.33 (0.63) y
Ringelstein[8]	2022	Retrospective	36(33/3)	36.1 (15.2)	36	5.5(2.5) y	NA
AZA							
Bichuetti[9]	2010	Retrospective	36(28/8)	32.3(11.0)	7	7.3(4.2) y	47.2(23.3) m
Costanzi[10]	2011	Retrospective	99(79/20)	40(5–83)	64	2(1–27) y	22(12–180) m
Elsone[11]	2014	Retrospective	103(91/12)	42.4 (2.8–76.8)	NA	NA	18(0.01–256) m
Mealy[12]	2014	Retrospective	32(29/3)	39.5 (3–70)	16	3(1–24) y	23.5(7–148) m
Qiu[13]	2015	Retrospective	77(73/4)	32 (4–65)	NA	32 (2–197) m	20(6–51) m
Balasa[14]	2015	Prospective	13(9/4)	31.8(11.3)	NA	4.64(5.4) y	3.74(1.8) y
Torres[15]	2015	Retrospective	22(19/3)	39(13–68)	14	16 (5–108) m	21 (12–46) m
Xu[16]	2016	Prospective	119(110/9)	35.7 (14.0)	NA	23.0 (0.6–220.3) m	NA
Chen[17]	2017	Prospective	105(99/6)	41.6 (11.9)	89	2.7 (0.1–17.1) y	3(0.5–6.5) y
Nikoo[18]	2017	RCT	35(28/7)	32.3 (9.5)	20	6.12 (5.54) y	NA
Zhang[19]	2017	Retrospective	34(24/10)	42.2(16.9)	28	4.1(2.1) y	2.3(1)y
Shi[20]	2017	Retrospective	16(16/0)	22.9(4.3)	13	NA	NA
Yang[21]	2018	Prospective	22(20/2)	39.6(12)	8	9(0.2–180) m	NA
Zhou[22]	2019	Retrospective	23(22/1)	14 (10–17)	23	54 (16–175) m	NA
Drulovic[23]	2019	Retrospective	74(63/11)	40 (7–68)	NA	35 (0.4–256) m	NA
Shi[24]	2020	Prospective	58(52/6)	37 (14)	51	1.8 (0.1–21.5) y	NA
Poupart[25]	2020	Retrospective	23(16/7)	39.1(14.2)	12	0.4(1)y	NA
Lim[26]	2020	Retrospective	20(19/1)	38.5(26.3–47.8)	NA	57 (20.8–80.3) m	NA
Gomes[27]	2021	Retrospective	19(17/2)	44 (28–61)	18	15 (10–39) y	NA

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AQP4-Ab = aquaporin 4 autoantibody, NA = no available, RCT = randomized clinical test, TCZ = tocilizumab.

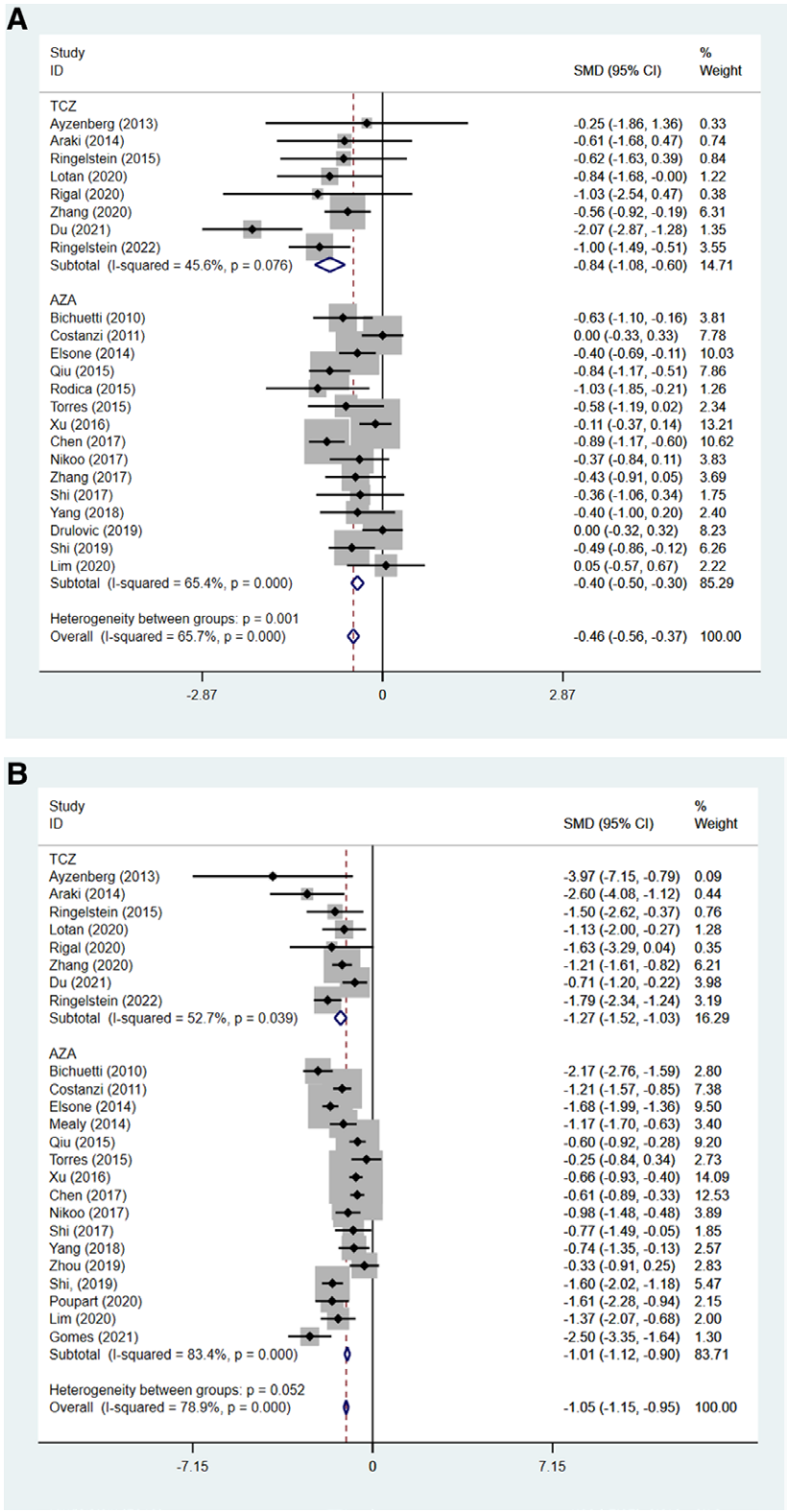

Figure 2. Forest plot showing the standardized mean difference and 95% confidence interval for the reduction in EDSS score and ARR ratio. ARR = annualized relapse rate, EDSS = expanded disability status scale.

attack -preventive immunotherapies drug for the treatment of NMOSD, can also effectively reduce the relapse of patients and improve neurological dysfunction.[22,23] A randomized clinical trial by Zhang et al[24] found that TCZ was associated with a significantly reduced risk of relapse in patients with NMOSD compared with AZA, which is consistent with our findings. Unfortunately, we did not find that TCZ was associated with significantly lower EDSS score in NMOSD patients, which may be related to fewer studies being included. Further research may be needed.

Limitations of this study are: Although the search criteria were relatively well developed, it cannot be excluded that

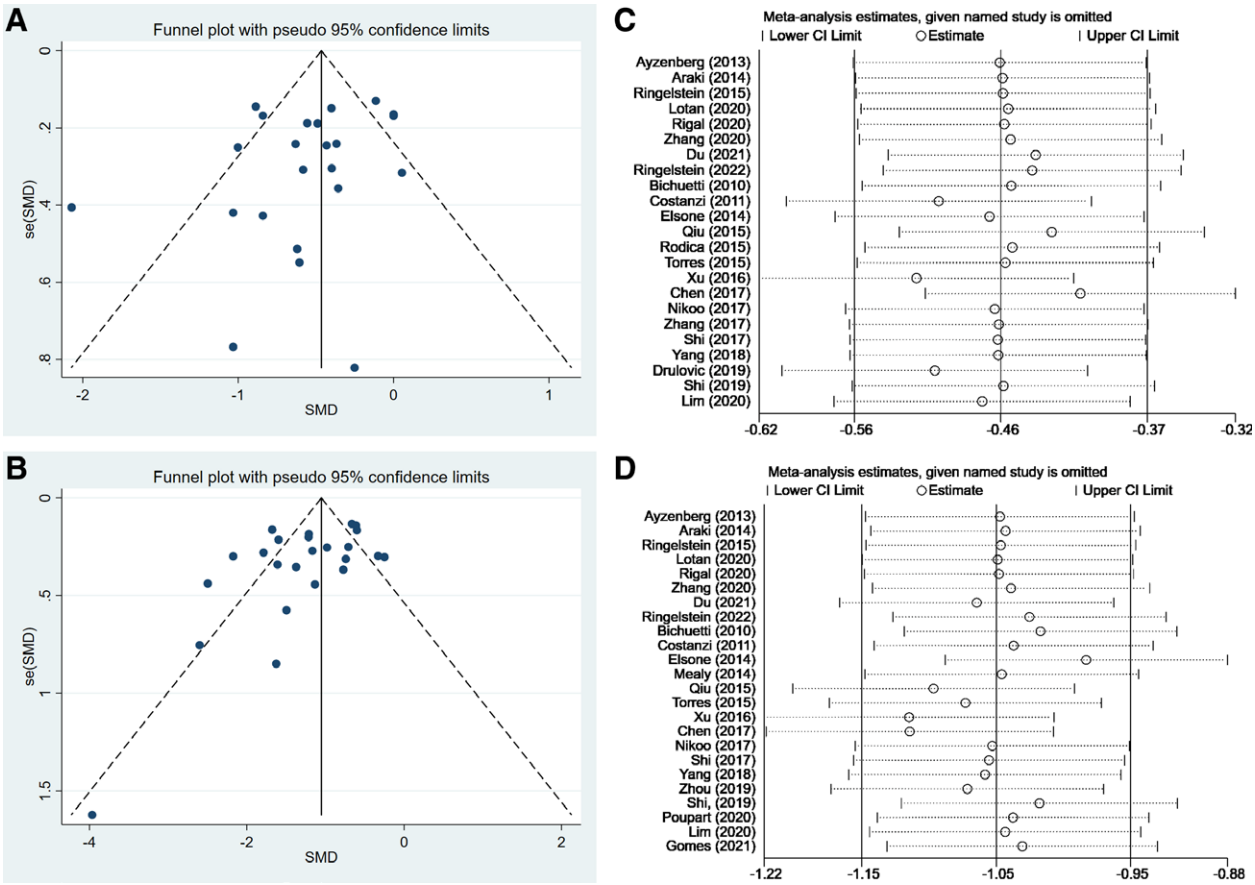

Figure 3. Publication bias and sensitivity analysis of included studies.

Table 2

The quality assessment of 27 observational studies by using Newcastle–Ottawa Scale.

Study	Selection	Comparability	Outcom
AZA			
Bichuetti et al 2010	****	**	***
Costanzi et al 2011	****	**	***
Elsone et al 2014	****	**	***
Mealy et al 2014	****	**	***
Qiu, Wei et al 2015	****	**	**
Rodica et al 2015	****	**	***
Torres, Jose et al 2015	****	**	***
Xu, Yan et al 2016	****	**	**
Chen, H et al 2017	****	**	**
Nikoo et al 2017	****	**	***
Zhang et al 2017	****	**	***
Shi et al 2017	****	**	**
Yang et al 2018	****	**	***
Zhou et al 2019	****	**	***
Drulovic et al 2019	****	**	***
Shi, Ziyan et al 2020	****	**	***
Poupart, J et al 2020	****	**	***
Lim et al 2020	****	**	**
Gomes et al 2021	****	**	**
TCZ			
Ayzenberg et al 2013	**	*	**
Araki et al 2014	**	*	***
Ringelstein et al 2015	**	*	***
Lotan et al 2020	**	**	**
Rigal et al 2020	**	*	***
Zhang et al 2020	**	*	***
Du et al 2021	**	*	***
Ringelstein et al 2022	**	*	***

TCZ = tocilizumab.

Table 3

calculations for comparing to estimated standardized mean difference of ARR ratio.

Group	TCZ	AZA
\SMD\	1.27	1.01
log \SMD\	0.104(E1)	0.013(E2)
95%CI for \SMD\	1.03–1.52	0.90–1.12
95%CI for log\SMD\	0.013–0.182	-0.046–0.049
Width for CI	0.167	0.095
SE [=Width/(2*1.96)]	0.0426	0.0242
Difference between log standardized mean differce		
d_{12}[=E1–E2]	0.091	
SE_{12}	0.049	
CI_{12}	0.005–0.187	
Test of interaction		
	z value	*P* value
AZA vs TCZ	1.86	.0314 (*)

AZA = azathioprine, TCZ = tocilizumab.

* $P < 0.05$.

eligible literature was not included in this study; Most patients receive other immunotherapies before and after TCZ treatment, so the benefits and risks of treatment using a single drug are inaccurate; Our research mainly included in retrospective studies and case series and thus a large sample of multicenter studies was lacking in the included studies.

5. Conclusions

The results of this study show that AZA and TCZ treatment of NMOSD patients can reduce the number of relapses and

improve disability. In addition, compared with AZA, TCZ more significantly reduce ARR.

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Conceptualization: Yupeng Wang, Wenbo Ji.
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Investigation: Yupeng Wang, Wenbo Ji.
Methodology: Qi Tang, Mengyuan Yao.
Project administration: Yupeng Wang, Wenbo Ji.
Resources: Mengyuan Yao, Yuanyuan Huang, Jiangping Bian.
Software: Yuanyuan Huang, Jiangping Bian.
Supervision: Yupeng Wang, Wenbo Ji.
Validation: Yupeng Wang, Wenbo Ji.
Visualization: Mengyuan Yao.
Writing – original draft: Qi Tang Mengyuan Yao.
Writing – review & editing: Yupeng Wang, Wenbo Ji.

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