The efficacy and safety of fingolimod plus standardized treatment versus standardized treatment alone for acute ischemic stroke: a systematic review and meta-analysis

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Abstract

Aims Acute ischemic stroke (AIS) is the most common type of stroke. Fingolimod is a sphingosine analog that acts on sphingosine-1-phosphate receptors(S1PR). Recently, the safety and efficacy of fingolimod in both patients with intracerebral hemorrhage and patients with AIS have been investigated in proof-of-concept trials. In this review, we performed a meta-analysis to evaluate the efficacy and safety of fingolimod for AIS. Methods This study was conducted according to the PRISMA (Preferred Reporting Items for Systemic review and Meta-Analysis) statement. We searched for publications on the PubMed, Embase, Cochrane Central Register of Controlled Trials, Clinical trials, CNKI, Wanfang Data, VIP, CBM up to August 2021. We compiled 5 studies; a main Meta-analysis forest plots were conducted for the values of the proportion of patients whose modified Rankin scale(MRS) score was 0-1 at day 90. A sensitivity analysis was performed with a mean difference (MD) of the efficacy of fingolimod plus standardized treatment versus standardized treatment alone. Random effect karyotype is used for Meta-analysis regardless of the I2 index. The methodological quality of each randomized controlled trial (RCTs) was assessed according to the Cochrane Collaboration tool to assess the risk of bias (ROB). Results A meta-analysis of 5 studies with 228 participants was conducted. The risk ratio of patients whose MRS score was 0-1 at day 90 between fingolimod plus standardized treatment and standardized treatment alone was 2.59. Conclusions The Fingolimod plus standard treatment group resulted in more ischemic penumbra rescue and improved clinical function than the standard treatment.

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Abstract

Aims

Acute ischemic stroke (AIS) is the most common type of stroke. Fingolimod is a sphingosine analog that acts on sphingosine-1-phosphate receptors(S1PR). Recently, the safety and efficacy of fingolimod in both patients with intracerebral hemorrhage and patients with AIS have been investigated in proof-of-concept trials. In this review, we performed a meta-analysis to evaluate the efficacy and safety of fingolimod for AIS.

Methods

This study was conducted according to the PRISMA (Preferred Reporting Items for Systemic review and Meta-Analysis) statement. We searched for publications on the PubMed, Embase, Cochrane Central Register of Controlled Trials, Clinical trials, CNKI, Wanfang Data, VIP, CBM up to August 2021. We compiled 5 studies; a main Meta-analysis forest plots were conducted for the values of the proportion of patients whose modified Rankin scale(MRS) score was 0-1 at day 90. A sensitivity analysis was performed with a mean difference (MD) of the efficacy of fingolimod plus standardized treatment versus standardized treatment alone. Random effect karyotype is used for Meta-analysis regardless of the I2 index. The methodological quality of each randomized controlled trial (RCTs) was assessed according to the Cochrane Collaboration tool to assess the risk of bias (ROB).

Results

A meta-analysis of 5 studies with 228 participants was conducted. The risk ratio of patients whose MRS score was 0-1 at day 90 between fingolimod plus standardized treatment and standardized treatment alone was 2.59.

Conclusions

The Fingolimod plus standard treatment group resulted in more ischemic penumbra rescue and improved clinical function than the standard treatment.

Key Words Acute ischemic stroke, Fingolimod, Meta-analysis, Modified Rankin Scale

1.Introduction

Acute ischemic stroke (AIS) is the most common type of stroke. It has the characteristics of high morbidity, high mortality, and high disability, which seriously endangers the health and life of patients. (1) Effective treatment after AIS will directly affect the prognosis of patients. (1)

The devastating, often crippling aftermath of stroke makes it second only to cardiac ischemia as a cause of death worldwide. Therapy for AIS centers first on rapid revascularization of arterial territories, with additional focus on managing blood pressure and cerebral edema.(2)Revascularization is currently achieved by the intravenous administration of tissue plasminogen activator (tPA) and intravascular therapy. However, the benefit of tPA is highly time-dependent, considering that pooled analysis has documented loss of benefit beyond 4.5 h from onset of symptoms.(2-4). Despite numerous clinical trials conducted to salvage cells from death, no significant breakthrough has been made to improve the outcome of stroke patients.(2, 5, 6)

Cerebral ischemia-induced cell death swiftly activates the immune system and initiates inflammation within the brain.(7-11)In an early phase, these immune responses appear to exacerbate neurovascular dysfunction by promoting thrombus formation, and accumulation of blood components in the cerebral microvasculature.(11-13)These changes subsequently exacerbate the ischemic cascade catalyzing neural cell death in the penumbra, resulting in the extension of infarction, which potentially limits the efficacy of pharmacologic or mechanical reperfusion. (11, 14-16)

Fingolimod is a sphingosine analog that acts on sphingosine-1-phosphate receptors(S1PR). It was approved by the US. Food and Drug Administration in 2010 as the first oral disease-modifying therapy for the relapsing-remitting form of multiple sclerosis (MS). (17, 18) Fingolimod inhibits the egress of lymphocytes from lymph nodes and limits their recirculation.(18, 19) Additional effects on the integrity of the blood-brain barrier(BBB) and direct action on neurons and glia that bear sphingosine-1-phosphate receptor may also contribute to its beneficial attributes in MS.(18, 20-22) Recently, the safety and efficacy of fingolimod in both patients with intracerebral hemorrhage and patients with AIS have been investigated in proof-of-concept trials.(2, 18) Fingolimod limited the expansion of infarct volume and ameliorated hemorrhagic transformation in patients with acute ischemic stroke who received intravenous alteplase within 4.5 hours after stroke onset(11, 18), Meanwhile, in patients with acute anterior circulation occlusion who are >4.5 hours after disease onset, fingolimod significantly improved the clinical outcome, reduced secondary lesion growth, and decreased microvascular permeability. (18) In this systematic review, we performed a meta-analysis to evaluate the efficacy and safety of fingolimod for acute ischemic stroke.

2.Methods

Protocol and registration

Our protocol was registered prospectively with the Prospero website(CRD42021272343), the prospective international register of systematic reviews available at https:// www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021272343.

Literature search

This search was restricted only to articles published in English and Chinese language. We searched for publications on the PubMed, Embase, Cochrane Central Register of Controlled Trials, Clinical trials, CNKI, Wanfang Data, VIP, CBM up to August 2021. We did keyword, and Medical Subject Heading (MeSH) searches for our theme, and MeSH terms, keywords, and their synonyms related to "Fingolimod hydrochloride" and "Cerebrovascular Disorders." A flowchart of the search strategy is shown in Fig. 1. One of us used a standardized form of data extraction to extract data; another person checked it, and revisited the data that did not match, and resolved the differences through discussion and consensus.

Inclusion and exclusion criteria for the literature

Studies were included if they fulfilled the following criteria: Published English and Chinese randomized controlled trial in various journals regardless of whether the blind method was used or not; >18 years of age; acute onset of focal neurological deficit consistent with acute ischemic stroke; fingolimod was given 0.5 mg of the drug orally once daily, for 3 consecutive days plus standardized treatment in the test group, standardized treatment was given in control group (standard treatment adhered to current American Heart Association guidelines including the intravenous administration of tPA, intravascular therapy, antiplatelet drugs and so on). Exclusion criterion: Case reports and studies that included fewer than 2 patients, review, meta-analysis; (2)studies from which no data are provided or data are otherwise not extractable; (3)preexisting neurologic disability (a score greater than 2 on the MRS); (4)for studies published in more than one report, the most comprehensive and up-to-date version will be used.

Main variables

Among the 5 articles selected, we extracted the values of the proportion of patients whose MRS score was 0-1 at day 90, the change in National Institutes of Health Stroke Scale (NIHSS) score at 24 hours, the change in NIHSS score at day 7, the change in NIHSS score at day 90, relative infarct lesion growth at 24 hours, relative infarct lesion growth at day 7, the incidence of complications/adverse events.

Data abstraction

The titles and abstracts of studies retrieved during the searches were screened for duplicates by two independent reviewers (PB and PW). Potentially relevant full-texts were then screened according to our inclusion and exclusion criteria. The final included studies were then collated, and the two reviewers used standardized data extraction formats to extract the data. After extraction, both reviewers matched their data with each other and revisited papers where disagreements arose. Any discrepancies were resolved through discussion with other team members. The extracted data included the following: first author, study design, site of study, year of publication, language, number of patients receiving fingolimod, the values of variables If required data was missing, not reported in the paper, or reported in an unusual form, the corresponding authors of the respective papers were contacted for clarification. Supplementary material associated with the main paper was also explored in such cases.

Risk of Bias Assessment and Quality of Evidence

Two authors (PB and PW)individually assessed the methodological quality of RCTs using the Cochrane Collaboration tool for assessing the risk of bias. (23) (24)The criteria were selected a priori and included: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting(including reporting of all outcomes and specifying a primary outcome), and (7) other bias. The evaluated domains were judged as low risk, high risk, or unclear bias per established criteria. In the case of evaluation discrepancies, the authors discussed and came to an agreement.

Statistical analysis

Data analysis of efficacy was performed using statistical software provided by Revman5.3. Data analysis of safety was performed using statistical software provided by Stata16.0. For continuous variables, mean difference (MD) is adopted as the effective index, and the point estimated value and 95% confidence interval(CI) of each effect quantity are given. For the data of median, maximum, and minimum values mentioned in the included study, combined analysis is carried out after transformation according to the formula. (25) The analysis was carried out for categorical variables using the risk ratio (RR), LogRR, and its 95% CI. The heterogeneity included in the study was analyzed by the X^2 test (the test level was axiom 0.1) and evaluated with the I^2 index. Random effect karyotype is used for Meta-analysis regardless of the I^2 index.

The sensitivity analysis was to remove the individual studies in turn, then reconduct the Meta-analysis and evaluate the difference between the results after the exclusion and the original combined results. A p-value of <0.05 was considered statistically significant. (24)

3.Results

Study identification and selection

By searching PubMed, Embase, Cochrane Central Register of Controlled Trials, Clinical trials, CNKI, Wanfang Data, VIP, CBM database dated until August 2021. The database search identified 731 records. After removing duplicates, 692 titles were initially screened, and 9 theme-related abstracts were selected for further screening. 4 studies were excluded because data were not available. Finally, 5 studies were included in this systematic review(Fig. 1).(1, 2, 11, 18, 26) 4 used the values of the proportion of patients whose MRS score was 0-1 at day 90 in total,3 used the change in NIHSS score at 24 hours, 2 used the change in NIHSS score at day 7, 2 used the change in NIHSS score at day 90, 2 used the relative infarct lesion growth at 24 hours, 2 used the relative infarct lesion growth at day 7.

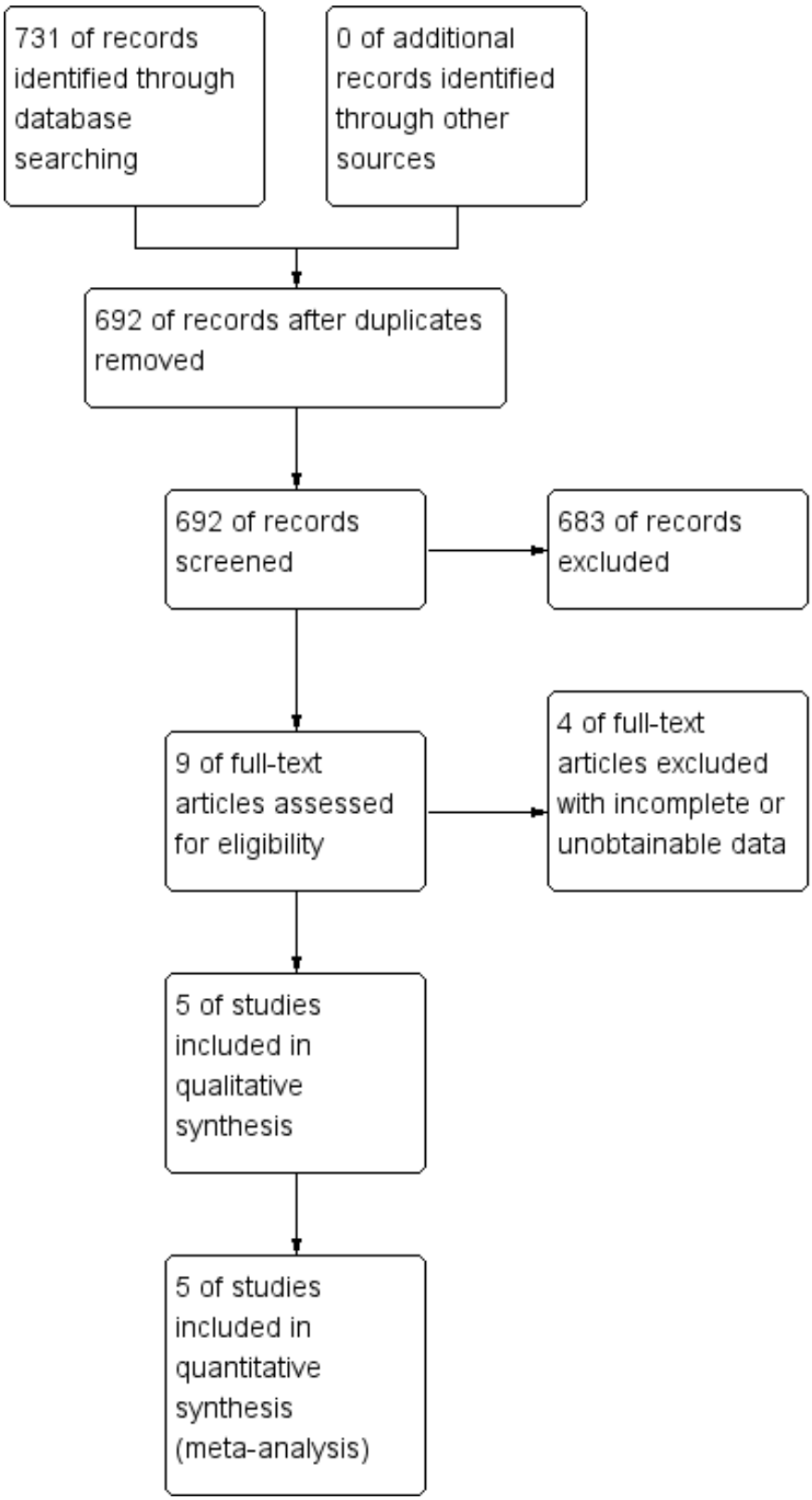

Fig. 1 Flow chart presenting the process of the study selection for fingolimod meta-analysis

Study characteristics and quality assessment

Table 1 lists detailed information from the 5 included studies. The included studies were published between 2014 and 2019. The number of participants per study ranged from 22 to 90, with a total number of 228. Patients have received fingolimod were recorded in 114 of 228 (50%). All studies were randomized controlled trials.

Table 1 Clinical and demographic characteristics of 228 patients from 5 studies included in the systematic review

Reference (study)	Research type	Patient No	Country	Language	Interventions	Outcome measures
					T C	
Zhang Liantao2019	RCTs	90	China	English	FTY720 ST	
De-Cai Tian 2018	RCTs	46	China	English	FTY720 ST	
Zilong Zhu 2015	RCTs	47	China	English	FTY720 ST	
Ying Fu 2014	RCTs	22	China	English	FTY720 ST	
De-Cai Tian 2017	RCTs	23	China	Chinese	FTY720 ST	

RCTs: randomized clinical trials, FTY720:fingolimod, ST: standardized treatment, the proportion of patients whose MRS score was 0,1 at day 90, the change of NIHSS scores over 24 hours,the change of NIHSS scores at day 7, the change of NIHSS scores at day 90, relative infarct lesion growth over 24 hours, relative infarct lesion growth at day 7

Figure 2 shows the risk of bias assessment of the five randomized trials; two trials described adequate methods of random sequence generation, one trial described allocation concealment. In four trials, the participants were blinded. The rate of the dropout was low in all trials. None of these studies had incomplete outcome data or selective outcome reporting. All five studies had no other bias.

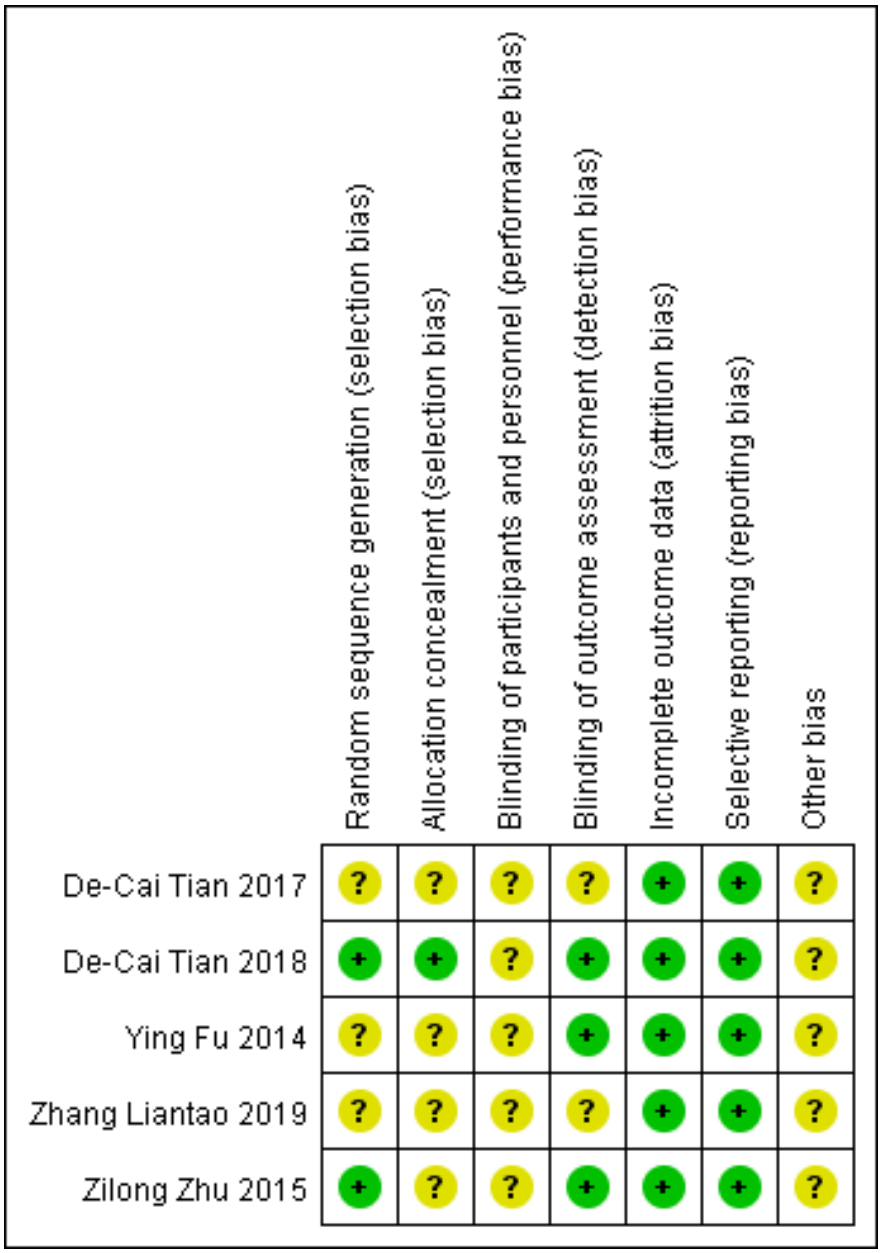

Fig. 2 Risk of bias summary for included studies.

Note: A "+" stands for low risk, "-" for high risk, and "?" for unclear risk.

Figure 3, including four articles, shows a forest plot of the risk ratio of patients whose MRS score was 0-1 at day 90 between fingolimod plus standardized treatment and standardized treatment alone. This finding suggested that the risk ratio of the proportion of patients whose MRS score was 0-1 at day 90 between fingolimod plus standardized treatment and standardized treatment alone was 2.59 (95%CI, 1.48 to 4.56). A random-effect model was used. Sensitivity analyses were performed by removing each study in turn and re-analyzed it. No studies were found to significantly affect heterogeneity.

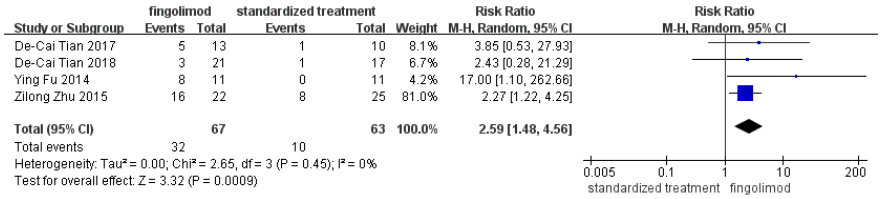

Fig. 3 Forest plot of the risk ratio of the proportion of patients whose MRS score was 0-1 at day 90 between fingolimod plus standardized treatment and standardized treatment alone.

Figure 4(A), including three articles, shows a forest plot of the mean difference in the change in NIHSS score at 24 hours between fingolimod plus standardized treatment and standardized treatment alone. This finding suggested that the mean difference in NIHSS score change at 24 hours of fingolimod plus standardized treatment versus standardized treatment alone was 2.78 (95%CI, 1.46 to 4.10). A random-effect model was used. Sensitivity analyses were performed by removing each study in turn and re-analyzed it. The application of sensitivity analysis showed that the study by De-Cai Tian et al. 2017 significantly affected heterogeneity. Figure 4(B), including two articles, shows a forest plot of the mean difference in the change in NIHSS score at day 7 between fingolimod plus standardized treatment and standardized treatment alone. This finding suggested that the mean difference in NIHSS score change at day 7 of fingolimod plus standardized treatment versus standardized treatment alone was 2.59 (95%CI, -0.27 to 7.26). A random-effect model was used. Figure 4(C), including two articles, shows a forest plot of the mean difference in the change in NIHSS score at day 90 between fingolimod plus standardized treatment and standardized treatment alone. This finding suggested that the mean difference in NIHSS score change at day 90 of fingolimod plus standardized treatment versus standardized treatment alone was 3.98(95%CI, 1.15 to 6.80). A random-effect model was used. Figure 4(D), including two articles, shows a forest plot of the mean difference in the change in relative infarct lesion growth at 24 hours between fingolimod plus standardized treatment and standardized treatment alone. This finding suggested that the mean difference in relative infarct lesion growth change at 24 hours of fingolimod plus standardized treatment versus standardized treatment alone was -26.46(95%CI, -43.64 to -9.28). A random-effect model was used. Figure 4(E), including two articles, shows a forest plot of the mean difference in the change in relative infarct lesion growth at day 7 between fingolimod plus standardized treatment and standardized treatment alone. This finding suggested that the mean difference in relative infarct lesion growth change at day 7 of fingolimod plus standardized treatment versus standardized treatment alone was -17.42(95%CI, -32.67 to -2.18). A random-effect model was used.

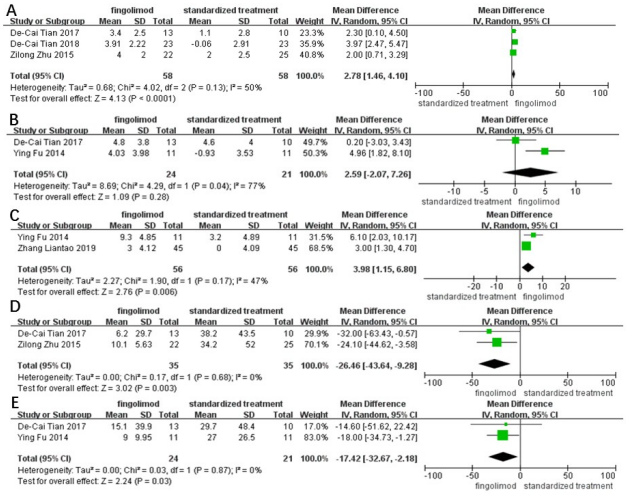

Fig. 4 Forest plot of the mean difference in the change in NIHSS score at 24 hours, NIHSS score at day 7, NIHSS score at day 90, relative infarct lesion growth at 24 hours, relative infarct lesion growth at day 7 between fingolimod plus standardized treatment and standardized treatment alone.

Safety Outcomes:

We combined the data retrieved from the five trials for serious adverse events (SAEs) and adverse events (AEs) such as deaths, myocardial infarctions, recurrent strokes, hernia, hemorrhage of the digestive tract, fever (>38 °C), hemorrhagic transformation at 24 hours, lung infection, urinary tract infection, herpes virus infection, abnormal laboratory liver-function test, gastrointestinal disorders, arrhythmia, and macular edema. The collected data of common AEs are displayed in Table 2. Data analysis was performed using statistical software provided by Stata16.0.We did not find any significant difference between the fingolimod and standardized treatment groups in terms of SAEs and AEs.

Table 2. Safety outcomes in the meta-analysis

	No.of studies	LogRR	95%CI	P value
Complications				
Deaths	5	-1.08	-2.59-0.43	0.16
Myocardial infarctions	5	0.28	-1.37-1.92	0.74
Recurrent strokes	5	0.26	-1.39-1.91	0.75
Hernia	5	-0.97	-2.02-0.07	0.07
Hemorrhage of the digestive tract	5	-0.72	-2.00-0.56	0.27
Hemorrhagic transformation at 24 hours	2	0.94	-0.20-2.08	0.11
Fever (>38 °C)	4	-0.09	-0.89-0.71	0.82
Event				
All events				
At least 1 adverse event	3	-0.12	-0.85-0.61	0.75
Any serious adverse event	4	-0.06	-1.99-1.87	0.95
Frequent or special interest adverse events				
Lung infection	5	0.06	-0.58-0.69	0.86
Urinary tract infection	5	0.02	-0.95-0.99	0.97

	No.of studies	LogRR	95%CI	P value
Abnormal laboratory liver-function test	3	-0.04	-2.26-2.18	0.97
Gastrointestinal disorders	3	-0.04	-2.26-2.18	0.97
Herpes virus infection	4	-0.03	-1.96-1.90	0.98
Arrhythmia	3	0.67	-1.33-2.66	0.51
Macular edema	3	-0.04	-2.26-2.18	0.97

RR, relative risk; CI, confidence interval

4.Discussion

This meta-analysis included 5 trials to assess the efficacy and safety of fingolimod in patients with AIS. Recently, the effectiveness and safety of fingolimod in patients with AIS have been investigated in some RCTs.(1, 2, 11, 18, 26). This systematic review and meta-analysis provide data to support the efficacy and safety of fingolimod for AIS.

Theefficacy of Fingolimod

Our meta-analysis presented that fingolimod resulted in more ischemic penumbra rescue and improved clinical function. Our primary endpoint here is based on a proportion of patients with MRS 0–1 at 90 days, decrease in NIHSS score at 24 hours, decrease in NIHSS score at day 7, decrease in NIHSS score at 90 days, relative infarct lesion growth at 24 hours, and relative infarct lesion growth at 7 days. The sensitivity analysis with analyses of the decrease in NIHSS score at 24 hours and at day 7 showed that the study by De-Cai Tian et al. 2017 significantly affected heterogeneity. It showed no statistically significant differences between fingolimod and standardized treatment in NIHSS score at day 7.

Studies have shown critical linkages between various immunomodulatory mechanisms in ischemic stroke.(18, 27) Ischemic stroke involves neuronal dysfunction and complex interactions between other cells, including vascular endothelial cells, BBB, extracellular matrix, and immune system.(28-30) Early clinical observations suggest a link between inflammation and ischemic stroke. Inflammation predisposes people to ischemic stroke and directly leads to many pathological changes.(29, 31-34) Further understanding of the relationship between immunity and brain tissue in ischemic stroke is helpful to develop new immunomodulatory therapy.

Fingolimod significantly reduced infarct expansion at 24h. Fingolimod not only inhibits lymphocyte infiltration into the brain parenchyma and protects brain tissue from secondary injury but also, at an earlier stage, by reducing the number of cells accumulating in the brain microvasculature. Inhibit the formation of capillary-inflammatory thrombosis and protect the function of the CNS.(35-38)In addition, fingolimod also targets intrinsic cells of the CNS, including vascular endothelial cells. It produces non-immune effects, thereby protecting brain tissue to some extent. The effect of fingolimod on vascular endothelial cells can inhibit the proinflammatory and thrombotic states of endothelial cells and improve the integrity of BBB.(35, 39)

The safety of Fingolimod

Our meta-analysis showed no significant difference in the incidence of complications and adverse events between fingolimod and the standard treatment. Because of the brief fingolimod treatment, this drug does

not necessarily produce an immune-deficient state.

Strengths and limitations

Our meta-analysis aimed to present efficacy and safety data. To date, no meta-analysis has been published about the effects and safety of fingolimod for AIS. Limitations of this study:1) Although the search strategy is relatively complete, it does not rule out that eligible articles are not included 2) A large sample of studies lacked in the included studies 3) the fact that it only includes randomized controlled trials 4) It is not distinguished patients who receive different standard treatments such as the intravenous administration of tPA, intravascular therapy, antiplatelet drugs and so on. 5) Four of the included trials came from the same group of investigators 6) Four of the excluded studies' data are not extractable. The records with unobtainable data may cause bias in the results. 7) None of the included trials were double-blinded(most had a PROBE design). 8) High heterogeneity across studies should not be neglected, though a random-effects model was used for adjustment. Nonetheless, results were broadly similar even if sensitivity analysis which decreased the heterogeneity, were performed. Inherent limitations in the majority of meta-analyses, such as lack of access to raw data and the variety in definitions of outcomes in the included studies, are unavoidable. None of the included studies was adequately sized to evaluate the proposed primary endpoint. 9) The entire data were derived from patients in China. More studies are needed that include other ethnic groups. 10) Different inclusion/exclusion criteria and follow-up periods in the included studies led to high heterogeneity. 10) The treatment of five included studies did not cover intravascular therapy. RCTs with greater patient numbers will be needed for future studies.

5.Conclusion

The Fingolimod plus standard treatment group resulted in more ischemic penumbra rescue and improved clinical function than the standard treatment. A higher proportion of patients with MRS 0–1 at 90 days in the fingolimod plus standard group than the standard treatment group. Fingolimod plus standard treatment showed a decrease in NIHSS score at 24 hours compared with standard treatment. However, the trend did not persist through 7 days, and there was no statistically significant decrease in NIHSS scores at 7 days compared to the standard treatment group. Still, there was a statistically significant decrease at 90 days. The fingolimod plus standard treatment group showed less lesion enlargement at 24 hours than the standard treatment group. The trend continued for 7 days. There was no significant difference in the incidence of complications and adverse events between the standard treatment group and fingolimod plus standard treatment group. Our study shows that it is feasible to use fingolimod to treat AIS.

Abbreviations: AIS: Acute ischemic stroke, PRISMA: Preferred Reporting Items for Systemic Reviews and Meta-Analysis, MRS: Modified Rankin Scale, MD: mean difference, RCTs: Randomized controlled trials,tPA: tissue plasminogen activator, BBB: blood-brain barrier, MeSH: Medical Subject Heading, NIHSS: National Institutes of Health Stroke Scale, CI: confidence interval, RR: risk ratio, SAEs: serious adverse events, AEs: adverse events, S1PR: sphingosine-1-phosphate receptors, MS: multiple sclerosis.CNS: Central nervous system, PB: Peng Bai, NL: Na Li, JY: Jun Yuan, RZ: Runxiu Zhu, PW: Ping Wang, FJ: Feng Jiang, JZ: Jin Zhen, YY: Yuan Yao, CZ: Chenhui Zhao, ZL: Zihong Liang, MW: Meiling Wang, BL: Bin Liu, ML: Min Li.

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Conflict of interest statement

The authors declare no conflict of interest.

Funding information

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Data availability statement

All data analyzed during this study are included in this article.

Contributors:

PB, PW, FJ, BL, ML: designed the study, search and screen the literature, extract and analyzed the data, drafting the manuscript.PB,JZ,YY,NL:collate the data,guide manuscript writing. JY, CZ, ZL, MW: revising the manuscript.

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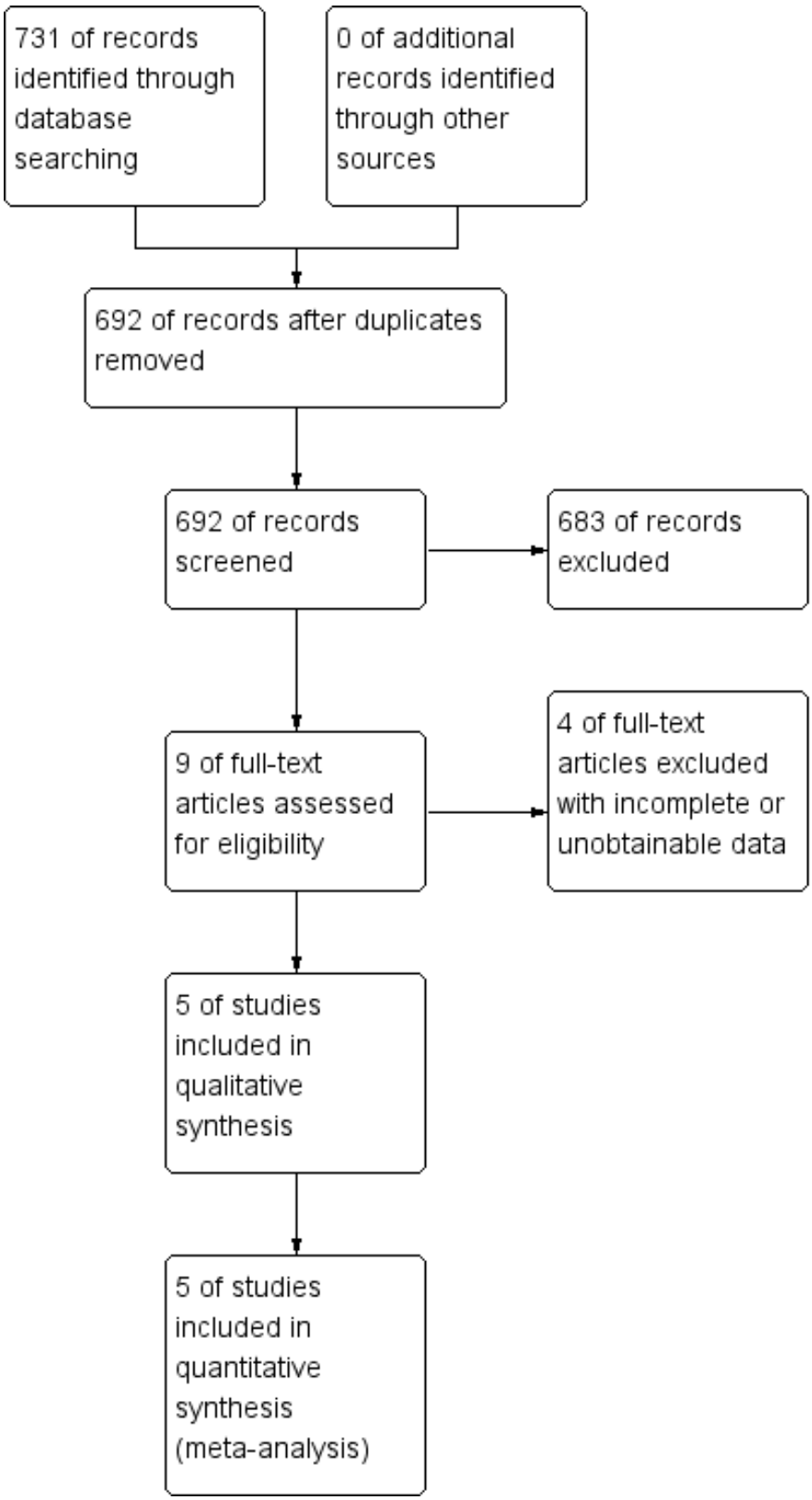

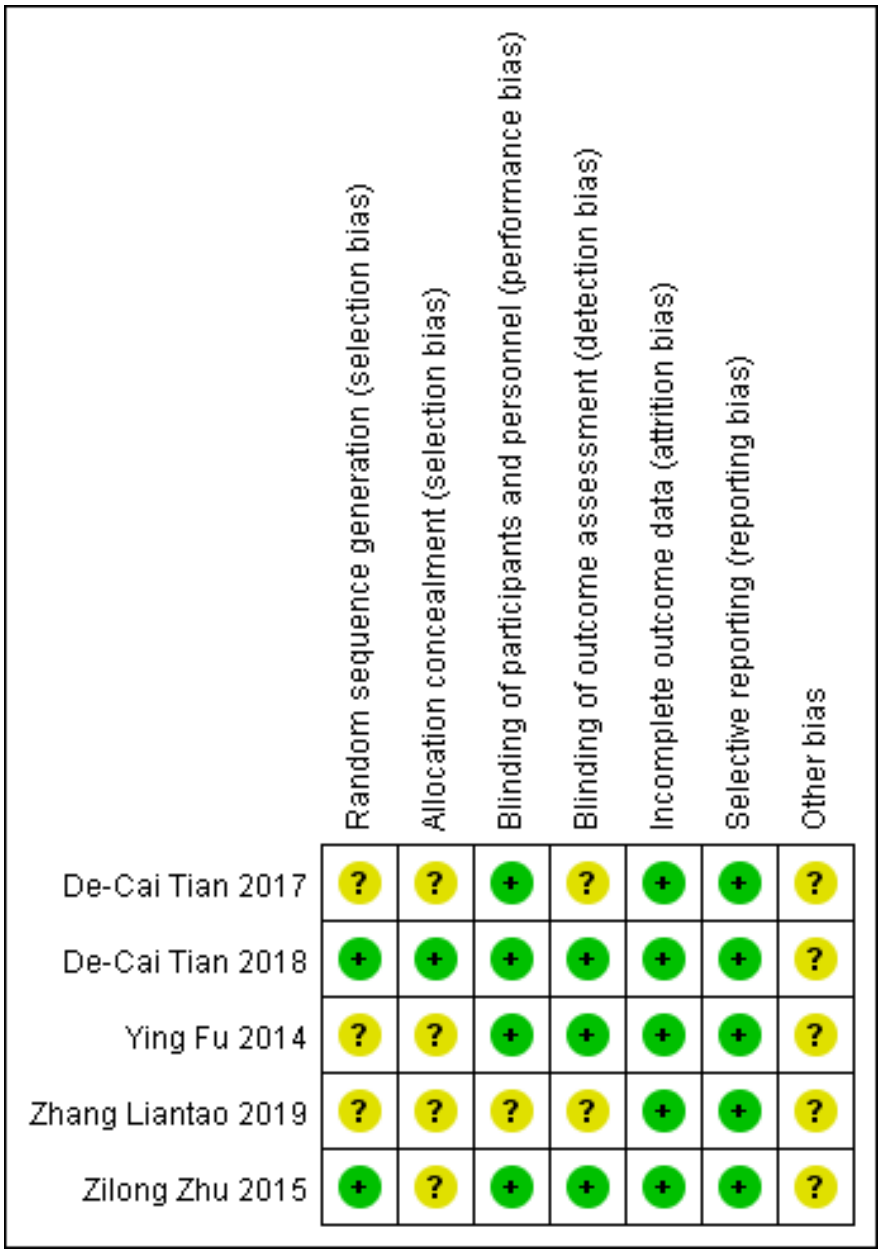

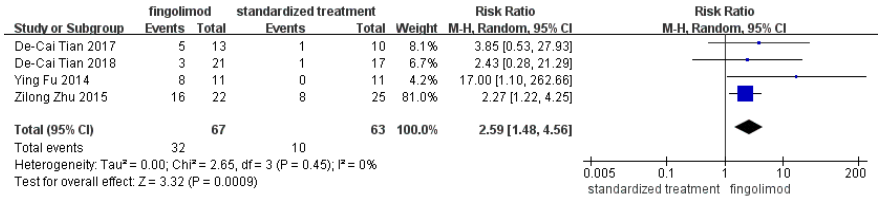

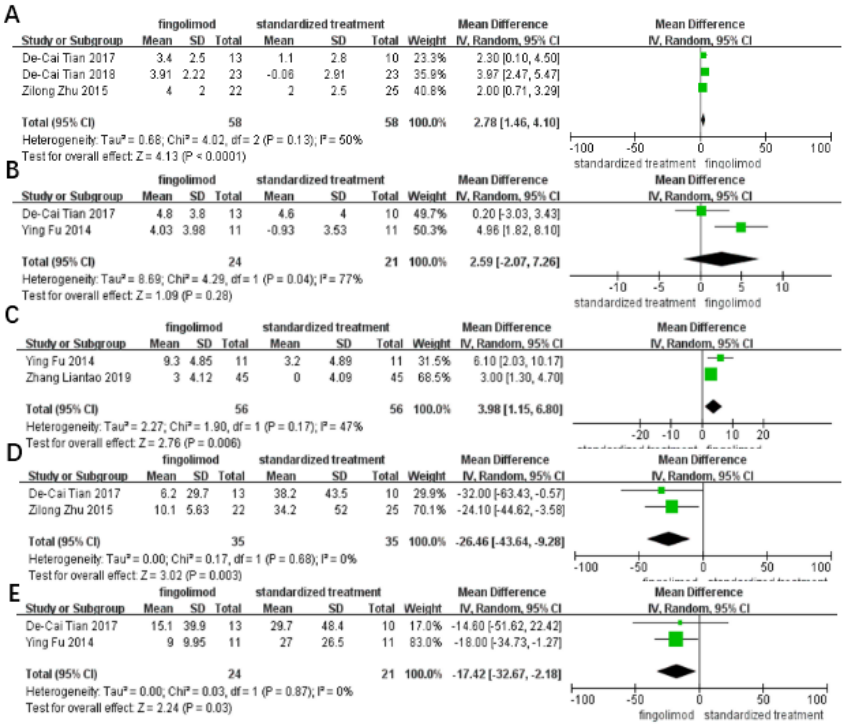

Reference (study)	Research type	Patient No	Country	Language	Interventions		Outcome measure
					T	C	
Zhang Liantao2019	RCTs	90	China	English	FTY720	ST	④
De-Cai Tian 2018	RCTs	46	China	English	FTY720	ST	①②
Zilong Zhu 2015	RCTs	47	China	English	FTY720	ST	①②⑤
Ying Fu 2014	RCTs	22	China	English	FTY720	ST	①③④⑥
De-Cai Tian 2017	RCTs	23	China	Chinese	FTY720	ST	①②③⑤⑥

RCTs: randomized clinical trials, FTY720:fingolimod, ST: standardized treatment, ①the proportion of patients whose MRS score was 0,1 at day 90, ②the change of NIHSS scores over 24 hours,③the change of NIHSS scores at day 7, ④ the change of NIHSS scores at day 90, ⑤relative infarct lesion growth over 24 hours, ⑥ relative infarct lesion growth at day 7

			No.of studies	LogRR	95%CI	P value	
Complications							
Deaths			5	-1.08	-2.59-0.43	0.16	
Myocardial infarctions			5	0.28	-1.37-1.92	0.74	
Recurrent strokes			5	0.26	-1.39-1.91	0.75	
Hernia			5	-0.97	-2.02-0.07	0.07	
Hemorrhage of the digestive tract			5	-0.72	-2.00-0.56	0.27	
Hemorrhagic transformation at 24 hours			2	0.94	-0.20-2.08	0.11	
Fever (>38 °C)			4	-0.09	-0.89-0.71	0.82	
Event							
All events							
At least 1 adverse event			3	-0.12	-0.85-0.61	0.75	
Any serious adverse event			4	-0.06	-1.99-1.87	0.95	
Frequent or special interest adverse events							
Lung infection			5	0.06	-0.58-0.69	0.86	
Urinary tract infection			5	0.02	-0.95-0.99	0.97	
Abnormal laboratory liver-function test			3	-0.04	-2.26-2.18	0.97	
Gastrointestinal disorders			3	-0.04	-2.26-2.18	0.97	
Herpes virus infection			4	-0.03	-1.96-1.90	0.98	
Arrhythmia			3	0.67	-1.33-2.66	0.51	
Macular edema			3	-0.04	-2.26-2.18	0.97	

RR, relative risk; CI, confidence interval