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Risk of psychiatric disorders and all-cause mortality with belimumab therapy in patients with systemic lupus erythematosus: a meta-analysis of randomised controlled trials

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ABSTRACT

Objectives To evaluate the risk of psychiatric disorders and all-cause mortality associated with belimumab therapy in patients with SLE.

Methods A literature search of four electronic bibliographic databases, including PubMed, EMBASE, Scopus and Cochrane databases, was conducted for randomised controlled trials (RCTs) reporting adverse reactions between belimumab and placebo. OR and 95% CI were calculated using the Mantel-Haenszel method with fixed-effects or random-effects model, depending on the heterogeneity test.

Results In total, 11 eligible RCTs including 8824 patients with SLE were randomised into belimumab (5160 patients with 5552 patient-years) and placebo (3664 patients with 3985 patient-years) groups, respectively. Overall, no increased risk was identified with belimumab therapy at all dosages compared with placebo in patients with SLE regarding all psychiatric disorders (OR 0.89, 95% CI 0.64 to 1.23, I^2=58%) and all-cause mortality (OR 1.10, 95% CI 0.64 to 1.89, I^2=0%). The subgroup analysis of psychiatric disorders also revealed no statistically elevated risks in serious psychiatric disorders (OR 1.15, 95% CI 0.77 to 1.70, I^2=47%), non-serious psychiatric disorders (OR 0.83, 95% CI 0.60 to 1.16, I^2=52%), suicidal ideation or behaviour (OR 0.87, 95% CI 0.57 to 1.33, I^2=0%), and depression (OR 1.29, 95% CI 0.90 to 1.85, I^2=15%). Secondary analysis restricting belimumab at approved dose of 10 mg/kg only yielded similar results.

Conclusion Belimumab therapy overall does not increase psychiatric events and all-cause mortality risks, whereas the results from Belimumab Assessment of Safety in SLE Study are suggestive of increased risk of psychiatric adverse events with belimumab exposure. Consequently, post-marketing data are needed to ascertain its psychiatric safety, especially serious mental disorders.

Key messages

What is already known about this subject?

- Belimumab has been licensed worldwide for the treatment of SLE, but the risk of psychiatric disorders and all-cause mortality associated with belimumab therapy remains undetermined.

What does this study add?

- This is the first meta-analysis, based on the best available datasets, showing belimumab therapy is not associated with significantly increased risk of psychiatric events and mortality, relative to placebo.

How might this impact on clinical practice or future developments?

- Belimumab therapy is not associated with increased risk of psychiatric events and mortality, but in consideration of the result of Belimumab Assessment of Safety in SLE Study, post-marketing data are decidedly needed to ascertain the psychiatric safety of belimumab, especially serious mental disorders.
- Special caution is needed when initiating belimumab therapy in patients with existing mental problems, such as depression, suicidal ideation or behaviour until more information becomes available.
- The search of risk factors for developing serious mental disorders and the characteristics of mental disorders associated with belimumab are urgently required.

INTRODUCTION

Belimumab is a humanised monoclonal antibody that inhibits the activity of B cell activating factor. Based on the promising efficacy and satisfactory safety in the pivotal clinical programmes of SLE, belimumab has been licensed worldwide for the treatment of adult as well as paediatric patients with active and autoantibody-positive SLE despite standard treatment.[1 2] Besides, the beneficial effects of belimumab on renal outcomes in patients with lupus nephritis were also demonstrated in the Belimumab International Study in Lupus Nephritis.[3]

Belimumab is the first biological agent approved for SLE treatment in more than 50 years. Nevertheless, in 2019, the Medicines and Healthcare products Regulatory Agency

raised an alarm of increased risk of serious psychiatric events, such as depression, suicidal ideation or behaviour in patients with SLE receiving belimumab compared with those receiving placebo based on interim findings from a randomised trial of Belimumab Assessment of Safety in SLE (BASE). Very recently, the published data of BASE Study showed patients with SLE with belimumab exposure had increased risks of psychiatric disorders, including serious depression, treatment-emergent suicidality, and sponsor-adjudicated serious suicide or self-injury events.[4] In a recent phase III, open-labelled continuation study for up to 7 years, favourable safety profiles and treatment response were observed in 142 Japanese and Korean patients with SLE receiving belimumab therapy, with median duration of belimumab exposure of 1171 days and a total belimumab exposure of 458.9 patient-years. Regarding the psychiatric disorders, one serious event of depression was reported (0.2 events/100 patient-years) and no completed suicides or suicide attempts were observed.[5] But owing to the relatively low frequency of psychiatric event, it is difficult to assess the psychiatric impact of belimumab in patients with SLE based on an individual randomised controlled trial (RCT) unless an adequate population is available. To fill the gap, we performed this meta-analysis of RCTs to evaluate the risk of psychiatric disorders and all-cause mortality associated with belimumab treatment in patients with SLE.

METHODS

This article is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[6] The methods were stipulated in a protocol that was registered with the PROSPERO (registration number: CRD42021234298).

Data sources

Four electronic bibliographic databases, including PubMed, EMBASE, Scopus and Cochrane databases, were searched without language restrictions from inception through 20 January 2021 and an updated search was conducted on 21 August 2021. Studies were identified using the search terms belimumab and synonyms. The details of search strategy are available in online supplemental appendix S1. The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov), major annual meetings in 2015–2020 and reference lists of all included studies were searched for additional trials.

Study selection

We included double-blind RCTs that reported adverse events in patients with SLE receiving belimumab or placebo during the randomised controlled phase. Exclusion criteria included non-randomised design, single-arm extension study, observational studies, case report, editorial, review or no adverse events reported. Two investigators (WX, HH) independently screened all titles and abstracts for potential inclusion. Discordances were resolved by a third experienced investigator (ZZ).

Data extraction and outcome assessment

Two review authors (WX, HH) independently extracted data and assessed the quality of selected studies. Data extraction included first author, publication year, patients' demographics, clinical characteristics and study outcomes. The Cochrane quality assessment tool was used to assess the quality of included RCTs.[7]

The primary outcome was the risk of all psychiatric disorders and all-cause mortality associated with belimumab at all dosages or approved dose of 10 mg/kg compared with placebo. The secondary outcomes included serious psychiatric disorders, non-serious psychiatric disorders, suicidal ideation or behaviour, and depression.

Statistical analysis

To summarise the findings of the selected studies, the OR with 95% CI was calculated as an effect measure. Meta-analysis was performed using a Mantel-Haenszel random-effects or fixed-effects model according to heterogeneity between studies, assessed using the I^2 statistic (low, I^2 <25%; moderate, 25%–50%; high, I^2 >50%). We conducted sensitivity analyses with the Peto method for the rare outcome and with exclusion of conference abstracts. Funnel plot analysis was used to detect the potential publication bias. For statistical significance, two-sided α was set at p=0.05. All data were recorded in a Microsoft Excel spreadsheet and analysed using Review Manager V.5.3 software (Cochrane Collaboration).

RESULTS

Study selection and characteristics

In total, 11 RCTs comprising 8824 patients with 9537 patient-years were included. The details of the study selection are summarised in figure 1.[3 4 8–16] There were 5160 patients with 5552 patient-years and 3664 patients with 3985 patient-years randomised into belimumab and placebo groups, respectively. The included RCTs were mostly international multicentre studies, with a median observation period of 52 weeks, ranging from 15 to 104 weeks. All included studies were published in peer-reviewed journals with full-text, except for one conference abstract.[16] All studies were performed in adult SLE, except one study conducted in paediatric patients with SLE.[14] Baseline characteristics of included patients were generally comparable regrading age, sex composition, disease duration and disease activity across most arms (online supplemental table S1).

Overall, the numbers of all psychiatric disorders and death during the controlled phase of these studies are summarised in table 1. The crude incidence rates of psychiatric disorders and all-cause mortality in belimumab and placebo groups were 6.430, 0.576 and 5.094, 0.501 per 100 patient-years, respectively.

All psychiatric disorders and all-cause mortality

For comparison of belimumab against placebo, pooled analysis of 11 trials found no increased risk of all psychiatric disorders (OR 0.89, 95% CI 0.64 to 1.23, I^2=58%)

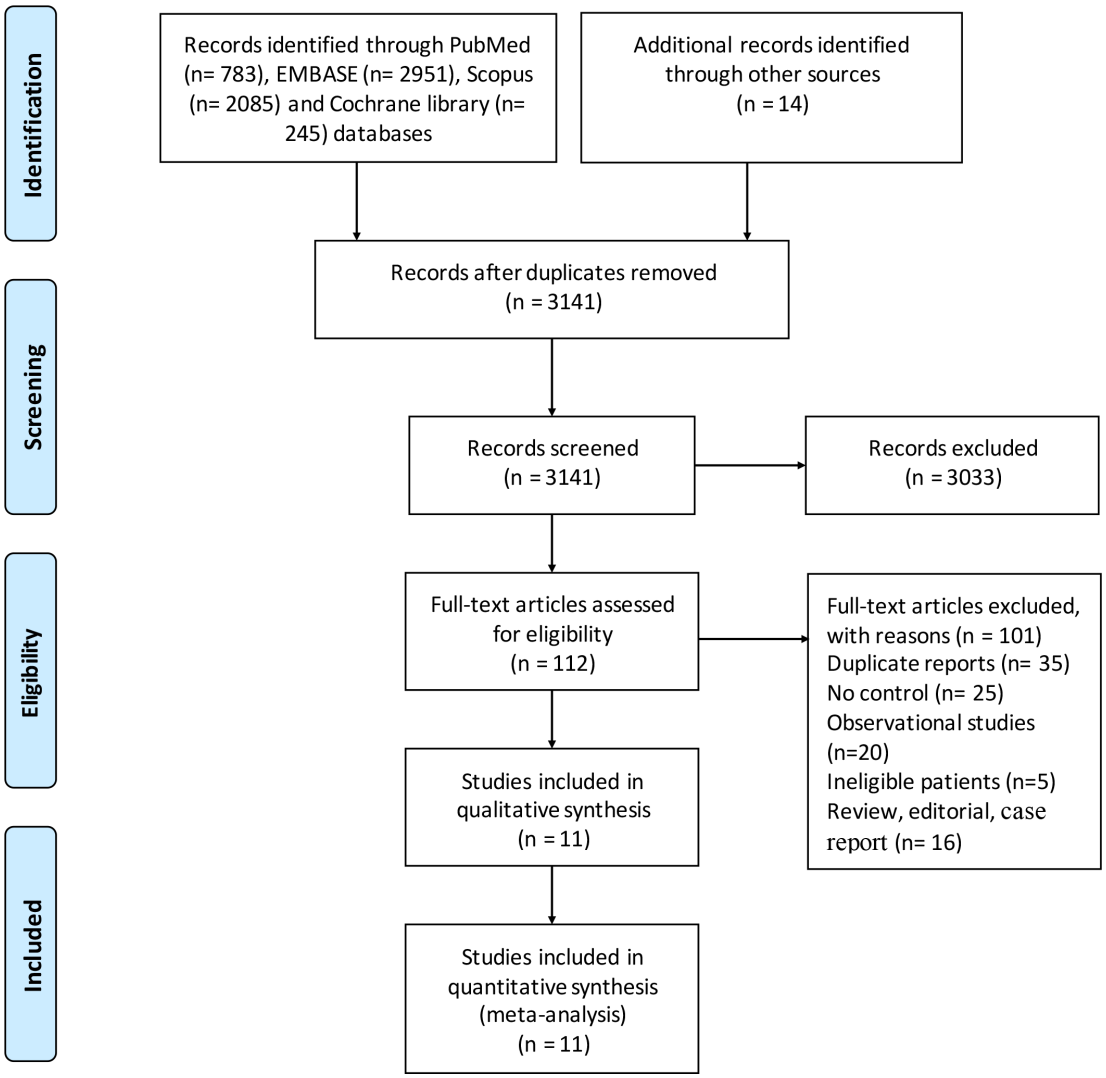

Figure 1 PRISMA flow diagram of study selection for systematic review and meta-analysis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

and all-cause mortality (OR 1.10, 95% CI 0.64 to 1.89, I^2=0%) with belimumab therapy at all dosages in general (figures 2 and 3). Furthermore, no statistical difference in all psychiatric disorders and all-cause mortality was observed between belimumab 10 mg/kg group and placebo group (all psychiatric disorders: OR 0.88, 95% CI 0.64 to 1.22, I^2=54%; all-cause mortality: OR 1.14, 95% CI 0.66 to 1.98, I^2=0%) (online supplemental table S2). In addition, the sensitivity analyses showed similar results using the Peto method for all-cause mortality (<1%) (OR 1.19, 95% CI 0.68 to 2.08, I^2=0%) or exclusively inclusion of full-text articles (all psychiatric disorders: OR 0.89, 95% CI 0.64 to 1.25, I^2=62%; all-cause mortality: OR 1.10, 95% CI 0.64 to 1.89, I^2=0%) (online supplemental figure 1–3).

Subgroup analysis of psychiatric disorders

No significantly elevated risk was identified with belimumab exposure, relative to placebo, regarding serious psychiatric disorders (OR 1.15, 95% CI 0.77 to 1.70, I^2=47%), non-serious psychiatric disorders (OR 0.83, 95% CI 0.60 to 1.16, I^2=52%), suicidal ideation or behaviour (0.87, 95% CI 0.57 to 1.33, I^2=0%), and depression (OR 1.29, 95% CI 0.90 to 1.85, I^2=15%) (figure 4). Of note, considering serious psychiatric disorders, suicidal ideation or behaviour, and depression as rare events (<1%), we further applied Peto method and found no statistically increased risk (serious psychiatric disorders: OR 1.20, 95% CI 0.80 to 1.79, I^2=60%; suicidal ideation or behaviour: OR 0.92, 95% CI 0.59 to 1.43, I^2=30%; depression: OR 1.30, 95% CI 0.92 to 1.83, I^2=30%) (online supplemental figure 4–6). Similar findings were also generated in the comparison of belimumab at 10 mg/kg dose with placebo regarding the above-mentioned outcomes (online supplemental table S5).

Risk of bias assessment

Of the 11 included articles, 7 RCTs adequately reported the generation of random sequence and adequately described the concealed allocation. Blinding of participants, personnel and outcome assessor was also performed in seven RCTs. Incomplete data of outcome were well

Table 1 Summary of the numbers of psychiatric disorders and death in randomised controlled trials

Author	Year	NCT number	Patients	Phase	Duration (weeks)	Interventions	No of patients	No of patient-years	No of death	No of psychiatric disorders		
										All	Serious	Non-serious
Furie *et al*[8]	2008	NCT00657007	Adults	Phase 1	15	Placebo	13	4	0	0	0	0
						Belimumab 1 mg/kg	15	4	0	3	3	0
						Belimumab 4 mg/kg	14	4	0	0	0	0
						Belimumab 10 mg/kg	14	4	0	0	0	0
						Belimumab 20 mg/kg	14	4	0	0	0	0
						Belimumab combined	57	16	0	3	3	0
Wallace *et al*[9]	2009	NCT00071487	Adults	Phase 2	52	Placebo	113	113	0	25	0	25
						Belimumab 1 mg/kg	114	114	1	29	2	27
						Belimumab 4 mg/kg	111	111	0	25	0	25
						Belimumab 10 mg/kg	111	111	1	22	0	22
						Belimumab combined	336	336	2	76	2	74
Navarra *et al*[10]	2011	NCT00424476	Adults	Phase 3	52	Placebo	287	287	3	19	5	14
						Belimumab 1 mg/kg	288	288	2	9	0	9
						Belimumab 10 mg/kg	290	290	4	26	5	21
						Belimumab combined	578	578	6	35	5	30
Furie *et al*[11]	2011	NCT00410384	Adults	Phase 3	72	Placebo	275	381	0	33	0	33
						Belimumab 1 mg/kg	271	375	2	60	4	56
						Belimumab 10 mg/kg	273	378	1	45	3	42
						Belimumab combined	544	753	3	105	7	98
Stohl *et al*[12]	2017	NCT01484496	Adults	Phase 3	52	Placebo Subcutaneous	280	280	2	30	0	30
						Belimumab 200 mg Subcutaneous	556	556	3	35	2	33
Zhang *et al*[13]	2018	NCT01345253	Adults	Phase 3	52	Placebo	226	226	1	7	7	0
						Belimumab 10 mg/kg	451	451	0	11	11	0
Bae[16]	2019	NCT02119156	Adults	Phase 3	52	Placebo	39	39	0	2	0	2
						Belimumab 10 mg/kg	29	29	0	1	0	1
Furie *etal*[11]	2020	NCT01639339	Adults	Phase 3	104	Placebo	224	448	5	34	16	18
						Belimumab 10 mg/kg	224	448	6	21	11	10
Brunner *etal*[14]	2020	NCT01649765	Children	Phase 3	52	Placebo	40	40	1	8	3	5
						Belimumab 10 mg/kg	53	53	0	1	0	1
Sheikh *etal*[4]	2021	NCT01705977	Adults	Phase 4	52	Placebo	2002	2002	8	24	6	18
						Belimumab 10 mg/kg	2001	2001	10	35	22	13
Ginzler *etal*[15]	2021	NCT01632241	Adults	Phase 3	52	Placebo	165	165	0	21	2	19
						Belimumab 10 mg/kg	331	331	2	34	1	33

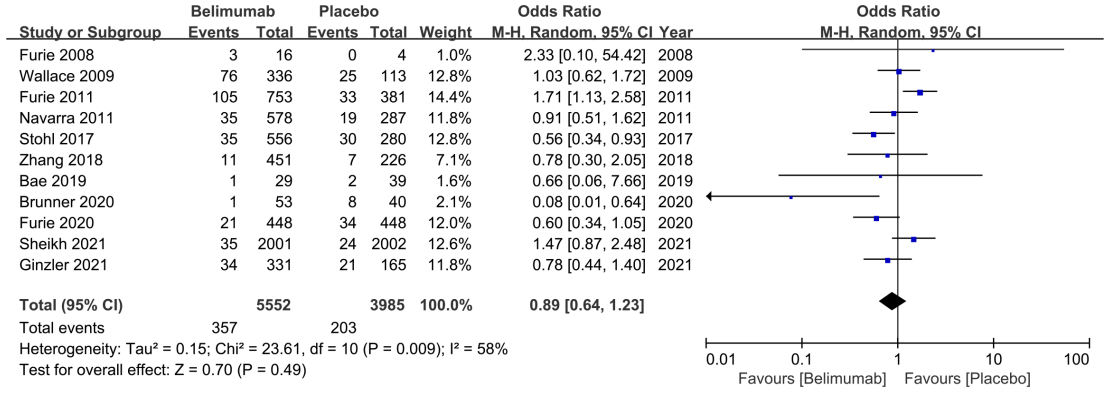

Figure 2 OR of all psychiatric disorders in patients with SLE receiving belimumab compared with placebo in randomised controlled trials.

balanced with no suggestion of selective outcome reporting in all included studies. Baseline characteristics of patients in all intervention groups were well balanced (figure 5). Funnel plot analysis showed no evidence of publication bias in all comparisons (online supplemental figure S7).

DISCUSSION

Belimumab has been approved for the treatment of adult and paediatric SLE, but there are residual uncertainties including psychiatric safety.[1–3 17] Due to the variable psychiatric events observed in SLE clinical programmes, an additional BASE trial was required. The latest results of BASE Study indicated similar safety profiles between belimumab and placebo groups, except for higher frequency of hypersensitivity reactions and serious psychiatric events.[4] To our knowledge, this is the first meta-analysis assessing the risk of psychiatric disorders and all-cause mortality associated with belimumab exposure. According to our results, belimumab treatment does not increase overall risks of psychiatric events and all-cause mortality relative to placebo. Subgroup analyses of psychiatric events revealed no significantly excess risk with belimumab exposure. Based on the best available datasets, this work reveals that belimumab is not associated with increased risk of psychiatric events and mortality. But in consideration of the results of BASE Study, further attention is needed to confirm the psychiatric safety. Due to the limited observational period in clinical trials and low frequency of serious psychiatric events, long-term observation in real-life setting is necessary to precisely measure such risks associated with belimumab therapy.

Currently, how belimumab triggers mental disorders is unclear. Further pharmacogenetic and pharmacogenomic investigations are required to explore the potential mechanism involved in psychiatric adverse effects associated with belimumab exposure. At moment, unravelling the characteristics of and risk factors for developing serious mental disorders associated with belimumab therapy should be performed either using pooled analysis of existing patient-level data in practice or using large sample of patients with SLE in future. Many practical problems need to be resolved, including the median (minimum, maximum) time from the start of belimumab therapy to the onset of the psychiatric event and the possibility of time-dependent effect of belimumab treatment. According to the results from the BASE Study, belimumab-treated patients who developed psychiatric events had longer SLE duration, high baseline SLE disease activity, and more past or current psychiatric disorder, as compared with placebo-treated patients who developed these events and overall patient population.[4] These would

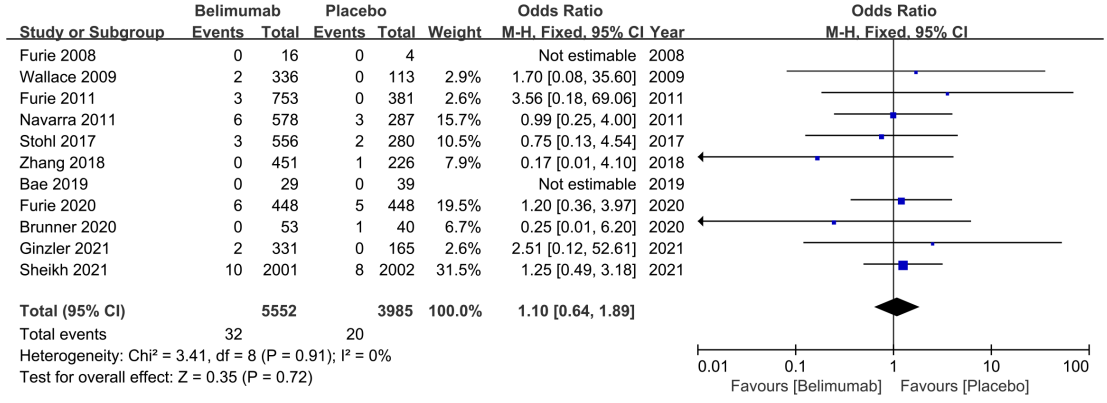

Figure 3 OR of all-cause mortality in patients with SLE receiving belimumab compared with placebo in randomised controlled trials.

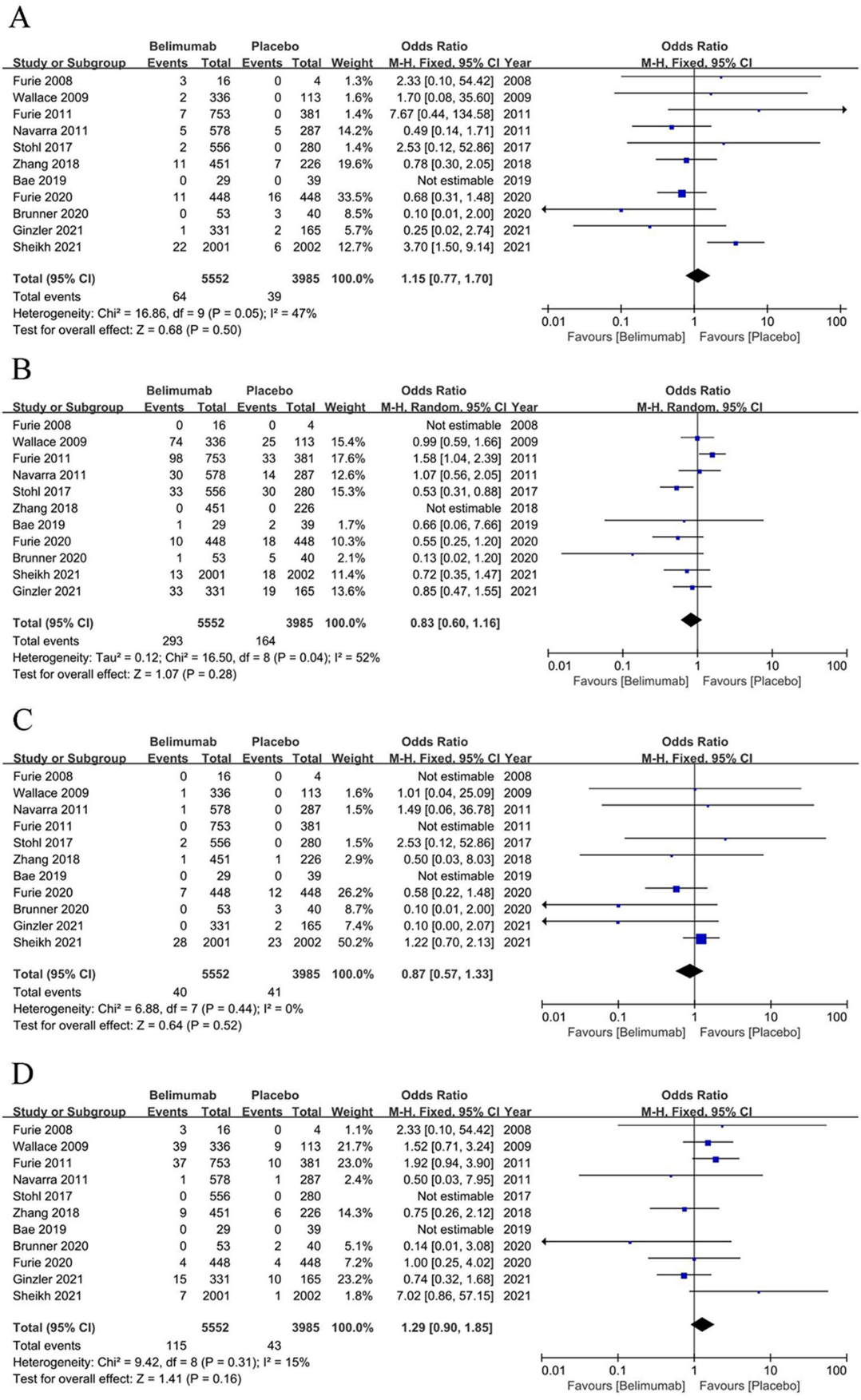

Figure 4 OR of psychiatric events in patients with SLE receiving belimumab compared with placebo in randomised controlled trials: (A) serious psychiatric disorders, (B) non-serious psychiatric disorders, (C) suicidal ideation or behaviour, and (D) depression.

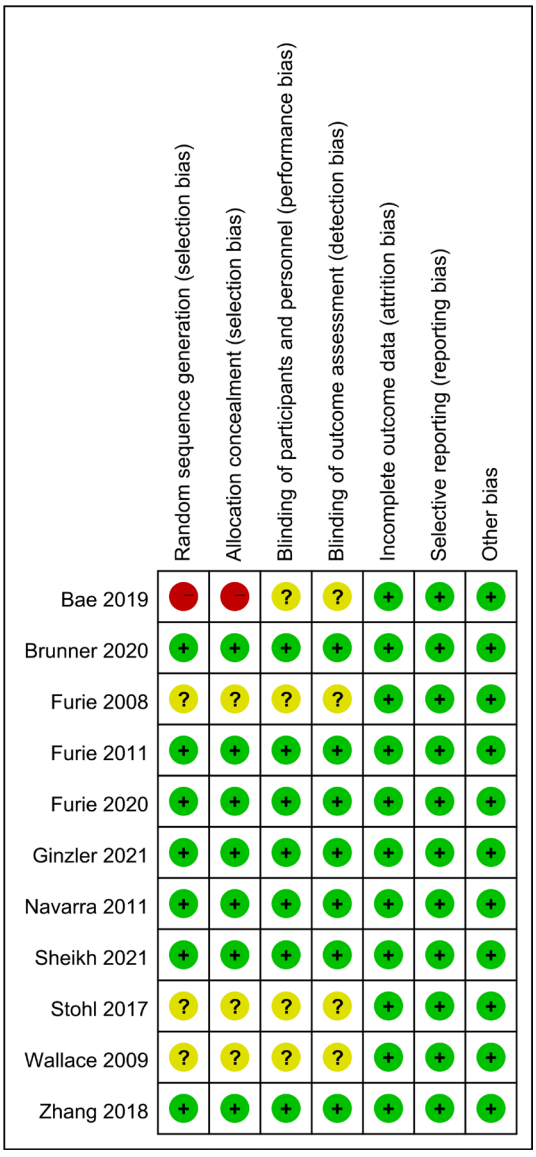

Figure 5 Risk of bias assessment for randomised controlled trials.

be helpful for physicians to identify the patients at risk of developing serious psychiatric adverse events. At present, we may need to assess the psychiatric risk (eg, history of mental disorders) before initiating belimumab therapy, and rheumatologists should seek advice from a psychiatrist if clinically necessary. Additionally, considering the increased risk of psychiatric disorders in patients with SLE and difficulties in diagnosing or excluding neuropsychiatric lupus even in randomised trials, an independent psychiatric safety endpoint adjudication committee reviewing all potential psychiatric events should be routinely established in future clinical trials. At present, special caution is needed when initiating belimumab therapy in patients with existing mental problems, such as depression, suicidal ideation or behaviour until more information becomes available.

We are aware of the major limitation of our meta-analysis. The rarity of serious psychiatric disorders may be inadequately addressed in the context of limited observation duration in RCT. Although both Mantel-Haenszel and Peto methods were applied, which for sure strengthened the statistical power, the low frequency of psychiatric events in relatively short placebo-controlled period of included trials precluded us from a definite conclusion. Moreover, the possibility of bias in the selection of patients in RCTs could not be excluded, and therefore, the findings may not be generalisable to the real-world population.

In summary, based on the best available evidence from RCTs, the present meta-analysis indicates belimumab therapy in general dose not increase the risk of psychiatric events and all-cause mortality. Continuous post-marketing surveillance is imperative to comprehensively clarify the psychiatric effect of belimumab therapy in patients with SLE, especially serious mental disorders, because BASE Study suggested increased risk of psychiatric adverse events associated with belimumab exposure.

Contributors ZZ is the guarantor of this article who conceived the study, participated in its design and coordination, and critically revised the manuscript. WX had full access to all the data collection, analysis and interpretation, and drafted the manuscript. HH contributed to the data collection as a study investigator. SZ provided helpful assistance of statistical information. All authors read and approved the final manuscript.

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