

Meta-analysis of randomized controlled trials for the efficacy and safety of anti-interleukin-13 therapy with lebrikizumab in patients with uncontrolled asthma

Ying Liu, M.D., SuZhong Zhang, M.D., Ruie Chen, M.D., Jieshu Wei, M.D., Guanheng Guan, M.D., Manru Zhou, M.D., Nan Dong, M.D., and Yingnan Cao, Ph.D.

ABSTRACT

Background: Several studies have evaluated the efficacy and safety of lebrikizumab treatment with uncontrolled asthma. However, most of these studies were small and conclusions were inconsistent. Furthermore, whether serum periostin can act as a good predictor of the response to lebrikizumab treatment is still not certain.

Method: We conducted a systematic review and meta-analysis of randomized controlled trials to evaluate the efficacy and safety of lebrikizumab treatment with uncontrolled asthma. Trials were searched in PubMed, Embase, Web of Science and Cochrane. Outcome measures were the rate of asthma exacerbations, relative changes in the forced expiratory volume in the first second of expiration (FEV1) of predicted value (%) and incidence of adverse events.

Result: Five trials were finally included. Compared with placebo lebrikizumab treatment significantly decreased the rate of exacerbations (risk ratio [RR] 0.66 [95% confidence interval {CI}, 0.54–0.80]; $p < 0.0001$; $n = 2039$) and increased FEV1% of predicted value (weighted mean difference [WMD] 5.46 [95% CI, 2.48–8.43]; $p < 0.0003$; $n = 351$). Patients with high levels of serum periostin had greater exacerbation rate reductions (RR 0.59 [95% CI, 0.50–0.70]; $p < 0.00001$; $n = 1157$) and FEV1 of predicted value improvement (WMD 7.18 [95% CI, 2.93–11.42]; $p < 0.0009$; $n = 177$) than patients with low periostin levels in exacerbation rate reductions (RR 0.73 [95% CI, 0.47–1.14]; $p < 0.17$; $n = 882$) and FEV1 of predicted value improvement (WMD 3.79 [95% CI, 0.39–7.97]; $p < 0.08$; $n = 174$). There was no significant difference in the incidence of adverse events in patients with lebrikizumab compared to placebo (RR 1.03 [95% CI, 0.99–1.06]; $p < 0.11$; $n = 2056$).

Conclusion: In patients with uncontrolled asthma, lebrikizumab treatment significantly decreased the rate of exacerbation and improved lung function, especially for patients with high periostin levels.

(Allergy Asthma Proc 39:332–337, 2018; doi: 10.2500/aap.2018.39.4149)

Asthma is a complex disease with marked heterogeneity in the clinical course and in the response to treatment.¹ Despite management with standard-of-care therapies, a proportion of patients' asthma remains uncontrolled and at high risk of life-threatening exacerbations and disease worsening.^{1,2} Phenotypic characterization of patients with asthma has led to great advances in the "personalization" of treatment.^{2–4}

Interleukin (IL) 13, a T-helper type 2 cytokine, has been shown to be a central mediator in T-helper type 2 inflammatory response and has a prominent role in the pathophysiology of asthma.⁵ It has been established

that IL-13 is implicated in driving airway inflammation, remodeling, and hyperresponsiveness.^{5,6} IL-13 can contribute to resistance to glucocorticoids; some patients with uncontrolled asthma continue to have elevated levels of IL-13 in the sputum, despite the use of systemic and inhaled glucocorticoids.^{7,8} IL-13, therefore, has been demonstrated as a potential therapeutic target in patients with uncontrolled asthma and higher concentrations of type 2 biomarkers.⁹

Periostin, previously known as osteoblast-specific factor 2, is an extracellular protein that is expressed in multiple cellular lines.¹⁰ IL-13 induces bronchial epithelial cells to secrete periostin and can be detected in serum. Periostin is highly expressed in the lungs of patients with asthma and contributes to mucus secretion, airway fibrosis, and remodeling.^{11–13} Much attention has been paid to periostin as a serum marker of T-helper type 2 driven inflammation in asthma.¹⁴

Patients with severe asthma that is not controlled despite taking effective therapy are most in need of new treatment approaches. Lebrikizumab is an immunoglobulin G4 humanized monoclonal antibody that specifically binds to IL-13 and inhibits its function.^{15,16} Several randomized controlled clinical

From the College of Pharmacy, Xinhua College of Sun Yat-sen University, Guangzhou, PR China

This study was supported by Education Department of Guangdong Province (No. 2017KQNCX257)

The authors have no conflicts of interest to declare pertaining to this article

Address correspondence to Ying Liu, M.D., College of Pharmacy, Xinhua College of Sun Yat-sen University, No. 19, Huamei Road, Tianhe District, Guangzhou 510000, PR China or Yingnan Cao, Ph.D., College of Pharmacy, Xinhua College of Sun Yat-sen University, No. 19, Huamei Road, Tianhe District, Guangzhou 510000, PR China

E-mail address: caoyingnan@xhsysu.cn or YingLiu@xhsysu.cn

Copyright © 2018, OceanSide Publications, Inc., U.S.A.

Table 1 Characteristics of included randomized controlled trial

Study, y	Population	Intervention, Lebrikizumab Dose, mg	No. Subjects (L/P)	Age, mean $\pm$ SD, y	Outcomes	Follow up, wk
Corren <i>et al.</i> , ¹⁷ 2011	Uncontrolled asthma	250	107/112	45.0 $\pm$ 12.0	Asthma exacerbation, AEs, FEV ₁ % changes	24
Noonan <i>et al.</i> , ²⁰ 2013	Stable asthma	125	53/52	37.6 $\pm$ 12.4	Asthma exacerbation, AEs, FEV ₁ % changes	20
		250	53/52	40.0 $\pm$ 12.4		
		500	52/52	40.6 $\pm$ 11.4		
Hanania <i>et al.</i> , ¹⁹ 2015	Uncontrolled asthma	37.5	117/116	48.7 $\pm$ 13.1	Asthma exacerbation, AEs, FEV ₁ % changes	24
		125	112/116	46.8 $\pm$ 13.4		
		250	118/116	47.9 $\pm$ 11.9		
Hanania <i>et al.</i> , ¹⁸ 2016 (LAVOLTA I)	Uncontrolled asthma	37.5	360/362	51.4 $\pm$ 12.9	Asthma exacerbation, AEs; FEV ₁ % changes	52
		125	359/362	51.0 $\pm$ 12.6		
Hanania <i>et al.</i> , ¹⁸ 2016 (LAVOLTA II)	Uncontrolled asthma	37.5	356/354	50.9 $\pm$ 12.9	Asthma exacerbation, AEs, FEV ₁ % changes	52
		125	357/354	50.2 $\pm$ 12.6		

AE = Adverse event; FEV₁ = forced expiratory volume in the first second of expiration; L/P = Lebrikizumab/Placebo.

studies evaluated the efficacy and safety of lebrikizumab in the treatment of uncontrolled moderate-to-severe asthma.^{17–20} The MILLY study indicated that patients with uncontrolled asthma lebrikizumab improved forced expiratory volume in the first second of expiration (FEV₁) and reduced the rate of exacerbations in patients with high periostin levels.¹⁷ However, The LAVOLTA II study showed the different results.¹⁸ Whether serum periostin can act as a predictor of lebrikizumab therapy in patients with uncontrolled moderate-severe asthma is still uncertain. We performed a systematic review and meta-analysis to evaluate the efficacy and safety of lebrikizumab, and to assess whether periostin can act as a prediction response to lebrikizumab therapy in patients with uncontrolled and/or moderate-severe asthma.

METHOD

Data Sources and Search Strategy

We performed a systematic search of PubMed, EMBASE, the Cochrane Controlled Trials Registry, and the Web of Science by using the following keywords: anti-interleukin-13 or lebrikizumab or monoclonal antibody, combined with asthma. Searches were restricted to studies published in the English language.

Inclusion and Exclusion Criteria

Inclusion criteria were patients with uncontrolled or moderate-to-severe asthma. Intervention was monthly subcutaneous lebrikizumab. The control was placebo. Outcomes were the rate of asthma exacerbations, rela-

tive changes in the FEV₁% of predicted value, and the incidence of adverse events.

Data Extraction

For selected studies, two reviewers (YL and YC) extracted data independently by using a standard data extraction form and were cross-checked. Data were collected at the start of the study, including the first author, year of publication, number of subjects, mean age, intervention characteristics of the trial, and outcome measures. The information is presented in Table 1. All data were obtained from tables or figures if no direct data were available from the article text. Disagreements about data extraction were resolved by discussion with a review author until consensus was reached. All analyses were based on previous published studies, thus no ethical approval or patient consent was required.

Assessment of Study Quality

Two researchers (SZ and RC) independently assessed the quality of the included studies. The risk of bias was evaluated by using the Cochran manual.¹⁶ Evaluation categories included (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias), and (7) other bias. Each category included three levels: low risk, unclear risk, and high risk. Disagreements about study quality were resolved by discussion with a review author

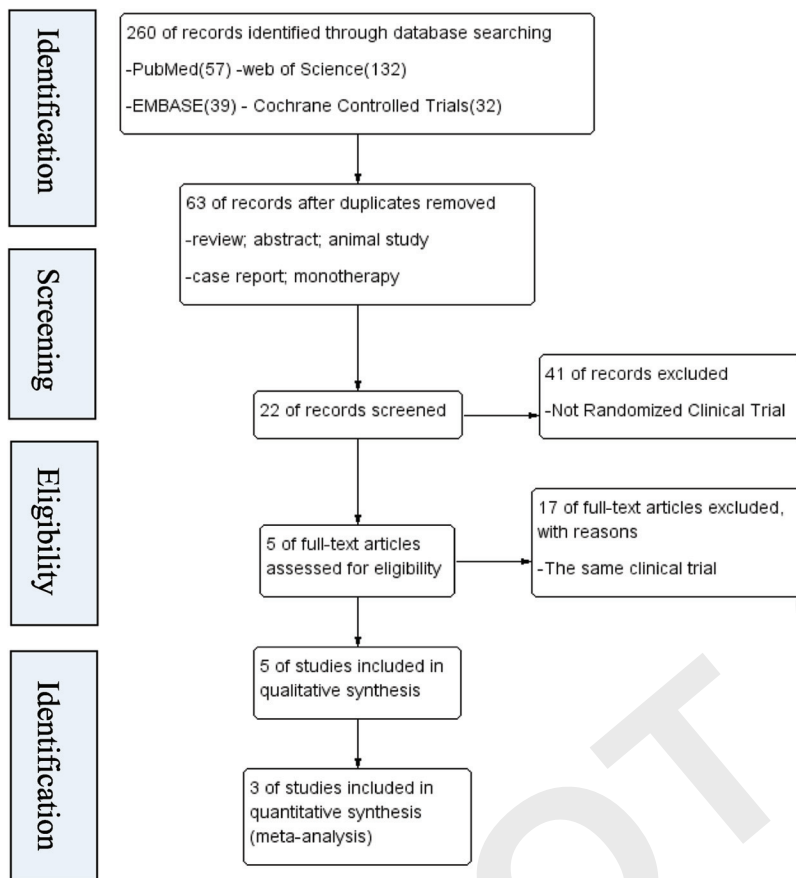


Figure 1. Flow diagram shows the process of literature selection.

until consensus was reached. The selection of included studies and the statistical methodology were verified by a certified statistician from Sun Yat-Sen University.

Statistical Analysis

Data were analyzed by using RevMan 5.3. Weighted mean differences (WMD) and their associated 95% confidence intervals (CI) were calculated for the continuous outcome of the relative change in FEV₁ of the predicted value. Risk ratios (RR) and their associated 95% CIs were calculated for the dichotomous outcomes of the rate of asthma exacerbations and incidence of adverse events. To assess the heterogeneity among studies, the I^2 index was calculated. Low and high levels of heterogeneity were considered as $I^2 \leq 50\%$ and $I^2 > 50\%$, respectively. We used a fixed-effects model on the conditions of $p < 0.05$ and $I^2 \leq 50\%$, otherwise, a random-effects model was used.

RESULTS

Search Results and Baseline Characteristic

The study selection process is shown in Fig. 1. Initially, 260 articles were included in our search strategy, among which five studies met the inclusion criteria to be included in the pooled analysis.^{17–20} The basic features of the five studies included are listed in Table 1.

The mean age of the subjects ranged from 40 to 52 years. Patients were randomly assigned to receive subcutaneous injections of lebrikizumab once every 4 weeks. The assessment of risk of bias is shown in Figs. 2 and 3; no obvious bias was detected.

Asthma Exacerbation Rates

Compared with placebo, lebrikizumab treatment significantly decreased the risk of exacerbation (RR 0.66 [95% CI, 0.54–0.80]; $p < 0.0001$; $n = 2039$). Subgroup analysis stratified by serum periostin levels showed that lebrikizumab treatment significantly decreased the risk of exacerbation in patients with high periostin levels (RR 0.59 [95% CI, 0.50–0.70]; $p < 0.00001$; $n = 1157$) but with no significant difference in the patients with low periostin levels (RR 0.73 [95% CI, 0.47–1.14]; $p = 0.17$; $n = 882$) (Fig. 4). Our meta-analysis demonstrated that the efficacy of lebrikizumab on asthma exacerbation had a significant relationship with serum periostin levels.

Lung Function (FEV₁% of predicted value)

Three studies assessed the relative changes of FEV₁% of predicted value to treatment with lebrikizumab.^{17,19,20} Compared with placebo, lebrikizumab treatment significantly increased FEV₁% of predicted value (WMD 5.46 [95% CI, 2.48–8.43]; $p = 0.0003$; $n =$

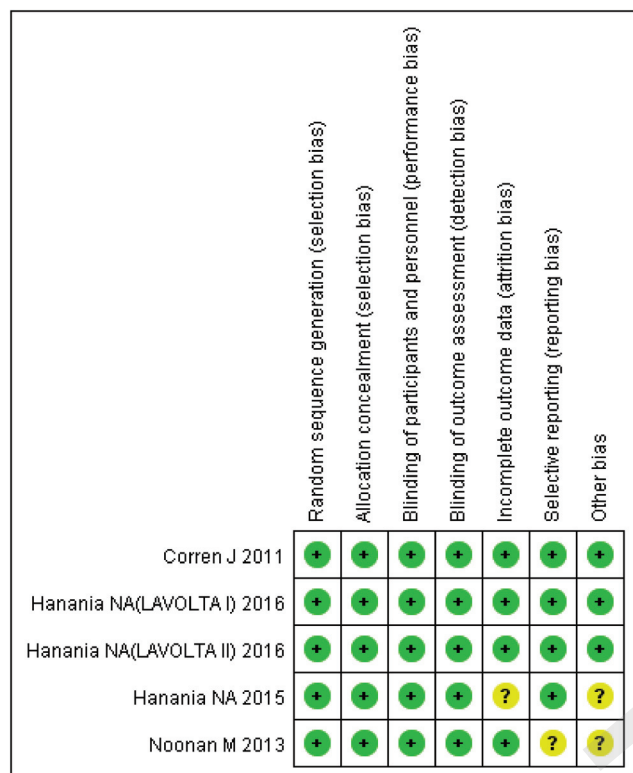


Figure 2. The risk of bias graph. Risk of bias summary. + = Low risk; ? = unclear risk; - = high risk.

351). Subgroup analysis stratified by serum periostin levels showed that lebrikizumab treatment significantly increased FEV₁% of predicted value in the patients with high periostin levels (WMD 7.18 [95% CI, 2.93–11.42]; $p = 0.0009$; $n = 177$) but with no significant difference in patients with low periostin levels (WMD 3.79 [95% CI, -0.39 to 7.97; $p = 0.08$; $n = 174$) (Fig. 5). Our meta-analysis demonstrated that the efficacy of lebrikizumab on FEV₁% of predicted value had a significant relationship with serum periostin levels.

Safety

Lebrikizumab was well tolerated. No significant difference in the incidence of adverse events was found in the patients treated with lebrikizumab and in those on placebo (RR 1.03 [95% CI, 0.99–1.06]; $p = 0.11$; $n = 2056$) (Fig. 6).

DISCUSSION

We systematically reviewed the available five randomized controlled trials and found that lebrikizumab significantly decreased the rate of exacerbation and increased lung function in patients with uncontrolled moderate-to-severe asthma. Our meta-analysis demonstrated that patients with asthma and with higher concentrations of serum periostin benefited most from lebrikizumab treatment. Periostin can act as a prediction response to lebrikizumab in patients with unstable asthma, despite Inhaled corticosteroids therapy.

Our results were in line with MILLY study and other study.^{17–21} Similarly, the omalizumab study ($n = 850$) also showed that serum periostin could be a predictive marker of responses to omalizumab, an anti-IgE antibody, in patients with severe asthma.²² Although the LAVOLTA II study reported that lebrikizumab did not consistently show a significant reduction in asthma exacerbations in patients with a high biomarker (serum periostin of at least 50ng/mL), the exacerbation rates were also reduced (lebrikizumab 37.5 mg: RR 0.74 [95% CI, 0.54–1.01]; $p = 0.0609$; and lebrikizumab 125 mg: RR 0.74 [95% CI, 0.54–1.02]; $p = 0.0626$), which is considered to represent a clinically meaningful rate reduction compared with placebo. Furthermore, the study showed that pharmacokinetics and pharmacodynamics data indicated that lebrikizumab blocked IL-13 by affecting IL-13-related pharmacodynamics biomarkers; clinically relevant changes of lebrikizumab could not be ruled out.¹⁸

Approximately 50% of patients with uncontrolled moderate-to-severe asthma demonstrate evidence of asthma based on the presence of type 2 inflammation.²³ Phenotypic characterization of patients with asthma has led to great advances in the “personalization” of treatment.^{24,25} With the aid of biomarkers, patients can receive targeted therapy, thus, which potentially yields improved outcomes.²⁶ Biologics have a great effect on patients with uncontrolled asthma, but not all patients can afford the expense. Therefore, identifying patients who are most likely to benefit from biologic treatment with biomarkers (*e.g.*, blood eosinophil, fractional ex-

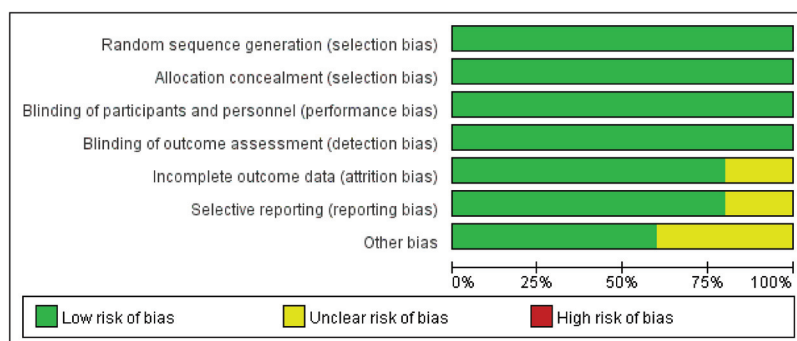


Figure 3. Risk of bias summary.

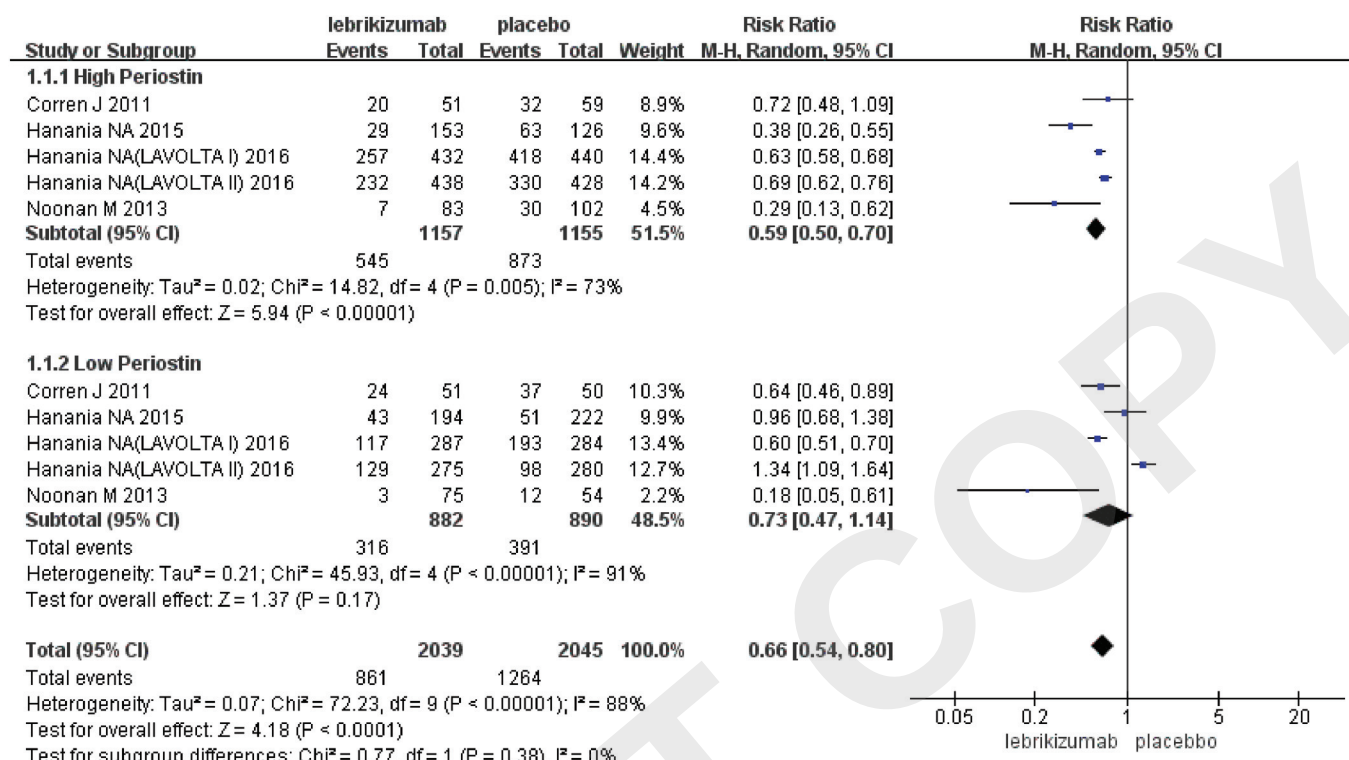


Figure 4. Incidence of asthma exacerbations: Overall and subgroup analyses stratified by serum periostin level.

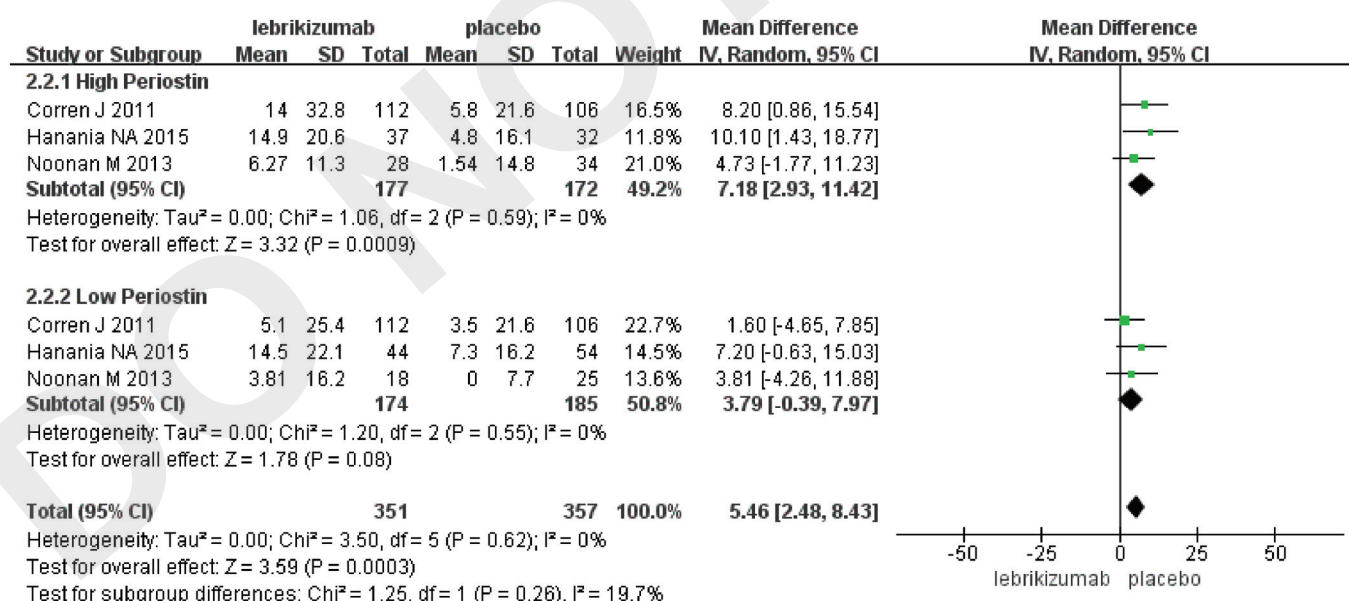


Figure 5. Relative change in FEV₁% of predicted value: overall and subgroup analyses stratified by serum periostin level. FEV₁ = forced expiratory volume in the first second of expiration.

haled nitric oxide[FeNO], and serum periostin) is necessary to efficient cost saving.

This study had some limitations. First, the meta-analysis was limited to five studies; the sample size was not large enough. Second, the drug administration dosage and treatment duration differed in some trials involved in our meta-analysis, which may have caused some bias. Third, the statistical heterogeneity of the

continuous outcome was significant. However, we performed subgroup analysis and sensitivity analysis, and the results remained robust.

CONCLUSION

In patients with uncontrolled asthma, lebrikizumab treatment significantly decreased the rate of exacerba-

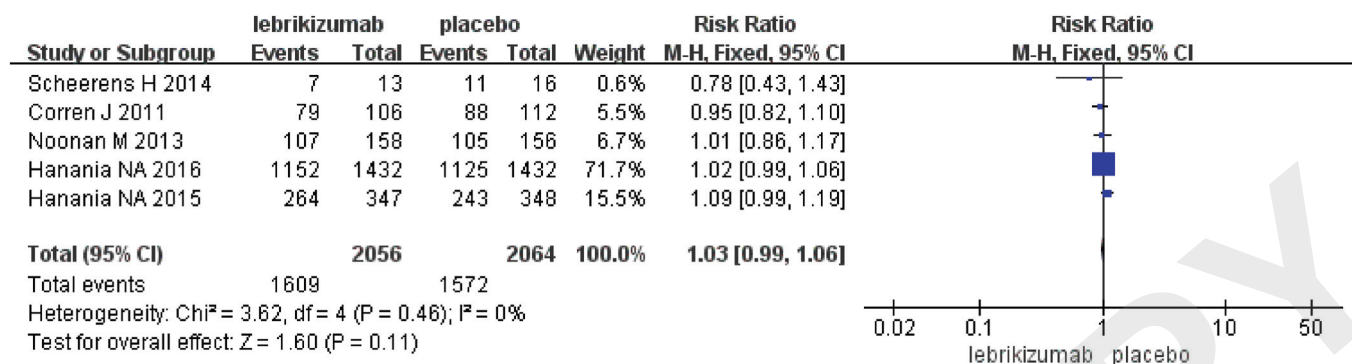


Figure 6. Incidence of adverse events.

tion and improved lung function. Patients with high periostin levels had greater exacerbation rate reduction and lung function improvement with lebrikizumab than did patients with low periostin levels. Serum periostin can act as a good predictor of the response to lebrikizumab in patients with uncontrolled asthma despite Inhaled corticosteroids therapy.

REFERENCES

- Becker AB, and Abrams EM. Asthma guidelines: the Global Initiative for Asthma in relation to national guidelines. *Curr Opin Allergy Clin Immunol*. 2017; 17:99–103.
- Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med*. 2010; 181:315–323.
- Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet*. 2008; 372:1107–1119.
- Agbetile J, and Green R. New therapies and management strategies in the treatment of asthma: patient-focused developments. *J Asthma Allergy*. 2011; 4:1–12.
- Fichtner-Feigl S, Strober W, Kawakami K, Puri RK, and Kitani A. IL-13 signaling through the IL-13alpha2 receptor is involved in induction of TGF-beta1 production and fibrosis. *Nat Med*. 2006; 12:99–106.
- Saha SK, Berry MA, Parker D, et al. Increased sputum and bronchial biopsy IL-13 expression in severe asthma. *J Allergy Clin Immunol*. 2008; 121:685–691.
- Hakonarson H, Bjornsdottir US, Halapi E, et al. Profiling of genes expressed in peripheral blood mononuclear cells predicts glucocorticoid sensitivity in asthma patients. *Proc Natl Acad Sci U S A* 2005; 102:14789–14794.
- Barnes PJ, and Adcock IM. Glucocorticoid resistance in inflammatory diseases. *Lancet*. 2009; 373:1905–1917.
- Blanchard C, Mishra A, Saito-Akei H, Monk P, Anderson I, and Rothenberg ME. Inhibition of human interleukin-13-induced respiratory and oesophageal inflammation by anti-human-interleukin-13 antibody (CAT-354). *Clin Exp Allergy*. 2005; 35: 1096–1103.
- Izuhara K, Arima K, Ohta S, Suzuki S, Inamitsu M, and Yamamoto K. Periostin in allergic inflammation. *Allergol Int*. 2014; 63:143–151.
- O'Dwyer DN, and Moore BB. The role of periostin in lung fibrosis and airway remodeling. *Cell Mol Life Sci*. 2017; 74: 4305–4314.
- Parulekar AD, Atik MA, and Hanania NA. Periostin, a novel biomarker of TH2-driven asthma. *Curr Opin Pulm Med*. 2014; 20:60–65.
- Parulekar AD, Diamant Z, and Hanania NA. Role of T2 inflammation biomarkers in severe asthma. *Curr Opin Pulm Med*. 2016; 22:59–68.
- Matsumoto H. Serum periostin: a novel biomarker for asthma management. *Allergol Int*. 2014; 63:153–160.
- Parulekar AD, Kao CC, Diamant Z, and Hanania NA. Targeting the interleukin-4 and interleukin-13 pathways in severe asthma: current knowledge and future needs. *Curr Opin Pulm Med*. 2018; 24:50–55.
- Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011; 343:d5928.
- Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med*. 2011; 365:1088–1098.
- Hanania NA, Korenblat P, Chapman KR, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med*. 2016; 4:781–796.
- Hanania NA, Noonan M, Corren J, et al. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. *Thorax*. 2015; 70:748–756.
- Noonan M, Korenblat P, Mosesova S, et al. Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids. *J Allergy Clin Immunol*. 2013; 132:567–574.e12.
- Scheerens H, Arron JR, Zheng Y, et al. The effects of lebrikizumab in patients with mild asthma following whole lung allergen challenge. *Clin Exp Allergy*. 2014; 44:38–46.
- Hanania NA, Wenzel S, Rosén K, et al. Exploring the effects of omalizumab in allergic asthma: An analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med*. 2013; 187:804–811.
- Wenzel SE. Emergence of biomolecular pathways to define novel asthma phenotypes. Type-2 immunity and beyond. *Am J Respir Cell Mol Biol*. 2016; 55:1–4.
- Lauer S, and Renz H. The Advance of Personalized and Stratified Therapies in Bronchial Asthma: Phenotypes - Endotypes - Biomarkers. *EJIFCC*. 2013; 24:113–125.
- Fajt ML, and Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: the next steps toward personalized care. *J Allergy Clin Immunol*. 2015; 135:299–310; quiz 311.
- Tabatabaian F, Ledford DK, and Casale TB. Biologic and New Therapies in Asthma. *Immunol Allergy Clin North Am*. 2017; 37:329–343.

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.