

The Efficacy and Safety of Antiinterleukin 13, a Monoclonal Antibody, in Adult Patients With Asthma

A Systematic Review and Meta-Analysis

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Abstract: Effects of antiinterleukin 13 therapies in patients with asthma remain inconsistent. Therefore, we aimed to further clarify the efficacy and safety of antiinterleukin 13 therapies in adult asthmatics by a systematic review and meta-analysis.

Randomized controlled trials which reported pulmonary functions, fraction of exhaled nitric oxide (FeNO), Asthma Control Questionnaire (ACQ), rescue use of short-acting- β -agonist (SABA), and rate of asthmatic exacerbation and adverse events were identified in Pubmed, Embase, Medline, Cochrane Central Register of Controlled Trials (CENTRAL), American College of Physician (ACP) Journal Club, and ISI Web of Science, reference lists and by manual searches. Randomized-effect models were used in meta-analysis to calculate pooled mean difference and relative risks (RR).

Eight studies with 957 patients were enrolled. Systematic review showed that treatment with antiinterleukin 13 antibodies could significantly improve peak expiratory flow (PEF), decrease FeNO and asthmatic exacerbation, but could not decrease blood and sputum eosinophil levels, improve FEV₁, inhibit methacholine PC₂₀, or reduce ACQ scores. Two studies reported opposite results in reducing rescue use of SABA. Meta-analysis showed that antiinterleukin 13 monoclonal therapies could significantly decrease asthmatic exacerbation (RR 0.55, 95% CI: 0.31–0.96, $z=2.10$, $P=0.04$), but did not significantly improve the FEV₁ (95% CI: -1.03 to 2.22 , $z=0.72$, $P=0.47$) or increasing adverse events (RR 1.00, 95% CI: 0.91–1.10, $z=0.00$, $P=1.00$).

Antiinterleukin 13 monoclonal therapies could be safely used to improve PEF, decrease FeNO and asthmatic exacerbation, and probably reduce rescue use of SABA, but could not decrease blood and sputum eosinophil levels, improve FEV₁, inhibit methacholine PC₂₀, or reduce ACQ scores.

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Abbreviations: ACP = American College of Physician, ACQ = Asthma Control Questionnaire, AHR = airway hyperresponsiveness, Arg I = arginase I, CENTRAL = Cochrane Central Register of Controlled Trials, CI = confidence interval, cNOS = constitutive NOS, FeNO = fraction of exhaled nitric oxide, FEV₁ = forced expiratory volume in 1 second, IL = interleukin, INF- γ = interferon- γ , iNOS = inducible NOS, methacholine PC₂₀ = provocation concentration of methacholine causing a 20% fall in FEV₁, NO = nitric oxide, NOS = nitric oxide synthase, OAT = ornithine aminotransferase, ODC = ornithine decarboxylase, PEF = peak expiratory flow, RCT = randomized controlled trial, RR = risk ratio, SABA = short-acting- β -agonist, SD = standard deviation, STAT = signal transducers and activators of transcription, Th lymphocytes = T helper lymphocytes, TNF- α = tissue necrosis factor- α .

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements evolved, such as eosinophils and mast cells, as well as interleukin-4 (IL-4), IL-13, interferon- γ (INF- γ), and tissue necrosis factor- α (TNF- α) released from T helper (Th) lymphocytes.¹ Recently, an increasing number of animal studies have demonstrated that IL-13 plays an important role in the pathogenesis of asthma by markedly activating arginase I (Arg I) expression in pulmonary macrophages via the transcription factors CCAAT-enhancer binding protein and signal transducers and activators of transcription (STAT) 6.^{2–4} The mechanisms of Arg I in the development of asthma have been well studied which include the following 2 major pathways: firstly, it may contribute to airway remodeling through converting L-arginine to L-ornithine, and then to polyamines and L-proline with the catalytic action of ornithine decarboxylase (ODC) and ornithine aminotransferase (OAT), respectively. It has been identified that polyamines may contribute to proliferation of structural cells in airways by promoting histone acetyltransferase activity and chromatin hyperacetylation, while L-proline is the precursor of collagen which can induce subepithelial fibrosis in asthmatic airways.^{5–7} Secondly, it may aggravate the allergen-induced airway hyperresponsiveness (AHR) by decreasing the production of bronchodilating nitric oxide (NO) and increasing the formation of procontractile and proinflammatory peroxynitrite via suppressing the L-arginine bioavailability to nitric oxide synthase (NOS).^{8,9} Therefore, treatment targeting IL-13 may have potential clinical values in attenuating IL-13-induced AHR, alleviating asthmatic symptoms, decreasing exacerbation, and improving pulmonary function in patients with asthma.

It was firstly reported by Singh et al¹⁰ that IL-13 blockage therapy could be safely administered in patients with asthma. In the study, they compared three different doses of CAT-354, that is tralokinumab, with placebo in mild to moderate asthma, and

the results showed that the maximum serum medication concentration and area under the curve were dose-dependent, and few adverse events related to study medication happened. Since then, a great variety of IL-13 antagonists have emerged, especially the humanized IgG-type monoclonal antibodies that compete with IL-13 receptors for specifically binding to IL-13 and result in neutralizing their functional activities, such as lebrikizumab and GSK679586.^{11,12} Two randomized, double-blind, placebo-controlled studies compared placebo with lebrikizumab and GSK679586 in patients with asthma, respectively, and they demonstrated that the mean increase in forced expiratory volume in 1 second (FEV₁) was 5.5% higher in lebrikizumab group ($P=0.02$) and the mean decrease in level of fraction of exhaled nitric oxide (FeNO) was greater in GSK679586 group than in placebo group.^{11,13} However, in the studies by de Boer et al⁸ and Corren et al,¹¹ they reported a negative effect of antiinterleukin 13 on improving symptoms and decreasing Asthma Control Questionnaire (ACQ) scores in patients with asthma. Therefore, from bench to clinic, the exact effects of antiinterleukin 13 on patients with asthma still do not reach a consensus thus necessitating further evaluations.

Based on the controversial conclusions from different studies, we conducted a systematic review and meta-analysis of all randomized, double-blinded, placebo-controlled trials and aimed to further clarify the efficacy and safety of antiinterleukin 13 therapies in adult patients with severe asthma.

METHODS

Study protocol was approved by the Institutional Ethical Committee for Clinical and Biomedical Research of West China Hospital (Sichuan, China) and the corresponding institutional review board in each enrolled trial. Written informed consent was obtained from all participants before enrolment.

Search Strategies

We conducted a comprehensive computer search, from 1946 to June 2015, in Pubmed, Embase, Medline, Cochrane Central Register of Controlled Trials (CENTRAL), American College of Physician (ACP) Journal Club, and ISI Web of Science using “anti-interleukin,” “anti interleukin,” or “monoclonal antibody” and “asthma.” Publication type of randomized controlled trials (RCTs) was limited. A review of references listed in the identified articles and a manual search of the related articles were performed to identify all relevant and eligible studies and minimize publication bias.

Inclusion and Exclusion Criteria

Eligible clinical trials were defined based on the following criteria: study design was randomized, double-blinded, placebo-controlled trial; adult patients with an age ≥ 18 years old; severe asthma was diagnosed by physicians with at least 12% increase in the FEV₁ after inhalation of a short-acting bronchodilator and a pre-bronchodilator FEV₁ between 35% and 85% of the predicted value at the time of randomization; intervention treatment was antiinterleukin 13 monoclonal antibody therapy with comparison with placebo, regardless of the different drug names and doses; outcome measures included blood and sputum eosinophils count, pulmonary functions such as FEV₁, peak expiratory flow (PEF) and the provocation concentration of methacholine causing a 20% fall in FEV₁ (methacholine PC₂₀), FeNO, ACQ, rescue use of short-acting- β -agonist (SABA), and rate of asthmatic exacerbation and adverse events. We did not

include trials that were nonrandomized controlled, observational, cohort, or case control.

Study Selection

Two investigators conducted study selection independently in 2 phases. Firstly, they discarded duplicated and nonrandomized controlled studies by screening titles and abstracts. Secondly, eligible studies were extracted by reviewing full texts according to the study inclusion criteria. Any disagreement was solved by mutual consensus in the presence of a third investigator.

Data Extraction

The 2 investigators used a standardized data extraction form to extract related data from each eligible study independently, which included authors, publication year, study design, study population, patient demographic characteristics (age, gender, etc.), details of intervention treatment (drug name, dose, and administration routine), and outcome measures and study results.¹⁴ Differences in opinion were resolved by reaching a consensus or by inquiring a third investigator.

Quality Assessment

The standard bias tool recommended by Cochrane was used to assess the risk of potential biases in the methods and outcomes reported by each enrolled study, which included: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of related outcomes assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other bias.¹⁴ These processes were performed by 2 independent investigators, but mutual consensus was reached with a third investigator if any disagreement presented.

Statistical Analysis

Statistical analysis was conducted by an independent statistician using Cochrane systematic review software Review Manager (RevMan; Version 5.3.5. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We defined z -value and P -value <0.05 as statistical significance with Mann–Whitney U test, and the results of the hypothesis tests were displayed in Forest plots. While for data that could not be pooled in the meta-analysis, we conducted a systematic review.

Dichotomous variables were reported as frequency and proportion, while continuous were shown as mean and standard derivation (SD). Random-effects model was applied in all data analysis regardless of the statistical heterogeneity. For dichotomous data we calculated risk ratio (RR) and 95% confidence interval (CI), while for continuous data we calculated mean difference and 95% CI. Moreover, as for FEV₁ and incidence of exacerbation and adverse events, we separately performed subanalysis in different drugs.

We tested the clinical, methodological, and statistical heterogeneities using the χ^2 test with $P < 0.1$ and $I^2 > 50\%$ indicating significance. Sensitivity analysis was also conducted to substitute alternative decisions or ranges of values for decisions that were arbitrary or unclear.

RESULTS

Initially we identified 525 records in the electronic databases and extracted another 7 records from the reference lists. After screening the titles and abstracts, 510 studies were

discarded, of which 128 studies were duplicated, 178 studies were not RCTs, 50 studies did not enroll asthmatic patients, and 154 studies did not administer antiinterleukin monoclonal antibody as intervention treatment. The remaining 22 studies were searched for full-text articles and eventually 8 trials^{10,11,13,15-19} were included in the final analysis, because the discarded 14 studies did not apply antiinterleukin 13 (12 trials administered antiinterleukin 5 while 2 trials prescribed antiinterleukin 9) (Figure 1).

Study Description

All studies enrolled were randomized, double-blind, placebo-controlled trials, of which 3 studies^{11,16,19} used lebrikizumab as intervention drug, 2 studies^{13,18} used GSK679586, 2 studies^{10,17} used tralokinumab (CAT-354), and 1 study¹⁵ used both IMA-638 and IMA-026. Five studies^{11,15-17,19} administered drugs via subcutaneous injection, while 3 studies^{10,13,18} via intravenous infusion.

Two studies^{15,18} reported eosinophils count, 6 studies reported pulmonary functions, of which 4 studies^{11,16-18} presented FEV₁, 3 studies^{11,16,17} presented PEF and 2 studies^{15,19} presented methacholine PC₂₀, 3 studies^{11,13,16} reported FeNO, 4 studies^{11,16-18} reported ACQ, 2 studies^{16,17} rescue use of SABA, 4 studies^{11,16-18} reported rate of asthmatic exacerbation, and all studies^{10,11,13,15-19} reported adverse events. In terms of FEV₁ and rate of exacerbation and adverse events, relevant studies showed the exact data, thus we pooled the studies and conducted a meta-analysis, while for the other outcome measures, we performed a systematic review.

A total of 957 patients with asthma were studied, among which, 591 (61.8%) received antiinterleukin 13 while 366 (38.2%) received placebo. Details of patients' characteristics, intervention strategies, and outcomes are summarized in

Table 1, and baseline characteristics of the patients enrolled are described in Table 2. Quality assessment of the 8 studies showed that although unknown risks of attrition and reporting biases existed, no biases in selection, blinding of participants and personnel, or blinding of outcome assessment were identified (Figures 2 and 3). Sensitivity analysis showed that none of these 8 studies was excluded for low quality or dubious decisions, and the funnel plot of the 8 studies evaluated the effect of antiinterleukin 13 on adverse events appeared to be symmetrical through visual examination (Figure 4).

Heterogeneity

No statistical heterogeneity was found either in FEV₁ ($I^2 = 26\%$, $\chi^2 = 2.71$, $P = 0.26$) (Figure 5), or in rate of adverse events ($I^2 = 0\%$, $\chi^2 = 6.36$, $P = 0.50$) (Figure 7), whereas significant statistical heterogeneity was found in rate of exacerbation ($I^2 = 61\%$, $\chi^2 = 7.66$, $P = 0.05$) (Figure 6). For the other outcome measures, we did not evaluate the heterogeneity due to the incomplete data, which could not be pooled in the meta-analysis.

Findings and Outcomes

Eosinophil Count

Eosinophils play a predominant role in the development of chronic airway inflammation, and a bulk of allergic asthmatics have elevated levels of eosinophil in peripheral blood and sputum. Out of the 8 studies enrolled, 2 trials compared the blood eosinophil levels between antiinterleukin 13 treatment and placebo.^{15,18} From the results reported, both studies showed no essential change of eosinophil level in blood after monoclonal therapy with antiinterleukin 13, regardless of the different drugs they used, which draw a conclusion of no effect of antiinterleukin 13 antibody on blood eosinophils (Table 3).

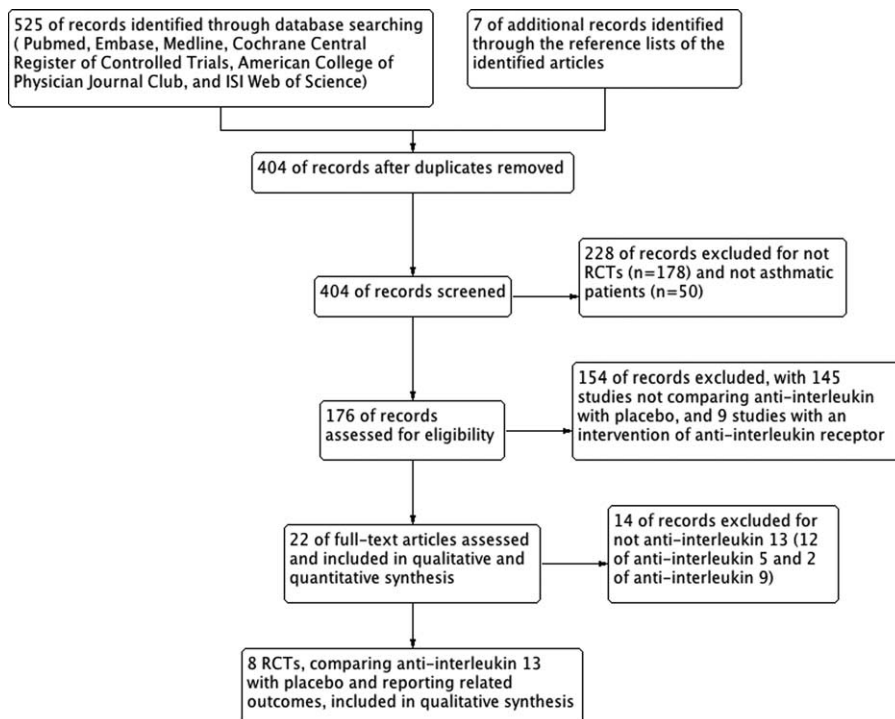


FIGURE 1. Study flow diagram. RCT = randomized controlled trial.

TABLE 1. Details of the 8 Studies Reviewed

Refs.	No.	Patients	Intervention				Control	Duration	Follow-Up	Outcomes*
			Drug	Dose	Routine	Dose				
Corren et al ¹¹	219	Uncontrolled asthma	Lebrikizumab	250 mg, every 4 wk	SC	Placebo	24 wk	32 wk	3, 4, 6, 7, 10, 11	
Noonan et al ¹⁶	210	Asthmatic patients not receiving inhaled corticosteroids	Lebrikizumab	125, 250, or 500 mg, every 4 wk	SC	Placebo	12 wk	20 wk	3, 4, 6, 7, 9, 10, 11	
Scheerens et al ¹⁹	29	Mild asthma	Lebrikizumab	5 mg/kg, every 4 wk	SC	Placebo	12 wk	28 wk	5, 11	
Hodsman et al ¹³	28	Mild intermittent asthma	GSK679586	2.5, 10, or 20 mg/kg, every 4 wk	IV	Placebo	8 wk	56–192 d	6, 11	
De Boever et al ¹⁸	198	Severe asthma	GSK679586	10 mg/kg, every 4 wk	IV	Placebo (NS)	8 wk	32 wk	1, 3, 7, 10, 11	
Singh et al ¹⁰	23	Mild to moderate asthma	Tralokinumab (CAT-354)	1, 5, or 10 mg/kg, every 4 wk	IV	Placebo (PBS)	56 d	147 d	11	
Piper et al ¹⁷	194	Moderate-to-severe asthma	Tralokinumab (CAT-354)	150, 300, or 600 mg, every 2 wk	SC	Placebo	12 wk	24 wk	3, 4, 7, 8, 9, 10, 11	
Gauvreau et al ¹⁵	Study 1: 27; Study 2: 29	Mild atopic asthma	Study 1: IMA-638; Study 2: IMA-026	2 mg/kg, every wk	SC	Placebo	2 wk	24 wk	1, 2, 5, 11	

ACQ = Asthma Control Questionnaire, AQLQ = asthma quality of life questionnaire, FeNO = fraction of exhaled nitric oxide, FEV1 = forced expiratory volume in 1 second, IV = intravenous, methacholine PC₂₀ = the provocation concentration of methacholine causing a 20% fall in FEV₁, No = number, NS = normal saline, PBS = phosphate-buffered saline, PEF = peak expiratory flow, SABA = short-acting-β-agonist, SC = subcutaneous.

* Outcomes reported in enrolled studies: (1) blood eosinophils; (2) sputum eosinophils; (3) FEV₁; (4) PEF; (5) methacholine PC₂₀; (6) FeNO; (7) ACQ; (8) AQLQ; (9) rescue use of SABA; (10) exacerbation rate; (11) adverse events.

TABLE 2. Baseline Characteristics of Patients in the 8 Studies Included

Refs.	No.*	Sex (Male, %)*	Age (Mean ± SD, y)*	Weight (Mean ± SD, kg)*	Blood Eosinophils (Mean ± SD, ×10 ³ /μL)*	FEV ₁ % Predicted (Mean ± SD, L)*	PEF (Mean ± SD, L/min)*	FeNO (Mean ± SD, ppb)*
Corren et al ¹¹	107	35 (32.7)	45 ± 12	87 ± 19	NM	64 ± 12	NM	31.0 ± 24.6
Noonan et al ¹⁶	158	57 (36.1)	39.3 ± 12.1	82.9 ± 17.5	0.2 ± 0.2	72.6 ± 6.8	375 ± 112	41.8 ± 41.9
Scheerens et al ¹⁹	13	6 (46.2)	36 ± 11	NM	0.258 ± 0.169	84.3 ± 13.6	NM	NM
Hodsmann et al ¹³	21	21 (100.0)	29 ± 10	NM	NM	105 ± 14	NM	35 ± 15
De Boever et al ¹⁸	99	48 (48.5)	51 ± 11	NM	0.27 ± 0.02	55 ± 12	NM	NM
Singh et al ¹⁰	19	12 (63.2)	43.3 ± 14.5	78.3 ± 20.7	NM	90.7 ± 9.5	NM	NM
Piper et al ¹⁷	146	63 (43.2)	47.4 ± 11.1	NM	NM	61.2 ± 12.3	313.2 ± 112.3	NM
Gauvreau et al ¹⁵	Study 1: 14; Study 2: 14	Study 1: 7 (50.0); Study 2: 7 (50.0)	Study 1: 26.1 ± 1.7; Study 2: 33.1 ± 3.3	NM	NM	Study 1: 93.0 ± 3.4; Study 2: 90.6 ± 2.8	NM	NM

FeNO = fraction of exhaled nitric oxide, FEV₁ = forced expiratory volume in 1 second, NM = not mentioned, No = number, PEF = peak expiratory flow, SD = standard deviation.
* Data on all patients who received antiinterleukin 13.

Lung Function

Three out of 4 studies reported the accurate data of FEV₁ change from baseline, thus making it possible to conduct a meta-analysis.^{11,16,17} Figure 5 shows that lebrikizumab could not significantly improve the FEV₁ in patients with asthma compared with placebo (95% CI: -1.34 to 5.45, *z* = 1.19, *P* = 0.24), neither did the pooled data analysis (95% CI: -1.03 to 2.22, *z* = 0.72, *P* = 0.47).

Three trials depicted the change of PEF after treatment with antiinterleukin 13, of which 2 trials used lebrikizumab as intervention drug while 1 trial used tralokinumab.^{11,16,17} Results from the studies illustrated that both lebrikizumab and tralokinumab could significantly improve PEF compared with placebo (Table 3). Meanwhile, another 2 studies showed the results in methacholine PC₂₀,^{15,19} however, both demonstrated that there was no difference between antiinterleukin 13 treatment with lebrikizumab, IMA-638 and -026 and placebo in terms of methacholine PC₂₀ values (Table 3).

FeNO

Of the 3 studies^{11,13,16} reporting FeNO, 2 showed that lebrikizumab was associated with a 19% to 49% mean decline in FeNO from baseline compared with placebo (*P* < 0.001), and 1 demonstrated that GSK679586 can also reduce FeNO relatively to the baseline (Table 3).

ACQ

Four trials^{11,16-18} with 3 different antiinterleukin 13 antibodies reported ACQ scores. However, a similar outcome was identified that antiinterleukin 13 could not significantly improve asthmatic symptoms though ACQ scores were slightly decreased after antiinterleukin 13 treatment (Table 3).

Rescue Use of SABA

Two out of 8 trials evaluated the effect of antiinterleukin 13 antibodies on SABA use: Noonan study showed that the reductions in reliever medication use were similar between lebrikizumab and placebo (-0.3 vs -0.6, *P* = 0.29), whereas Piper study resulted in significant reduction in β₂ agonist use in tralokinumab treatment group compared with placebo (-0.68 vs -0.10, *P* = 0.020) (Table 3).

Asthmatic Exacerbation and Adverse Events

The meta-analysis of the effect of antiinterleukin 13 monoclonal therapies on exacerbation in patients with asthma are summarized in Figure 6. The pooled RR was 0.55 (95% CI: 0.31-0.96), which showed that antiinterleukin 13 could significantly decrease asthmatic exacerbation compared with placebo (*z* = 2.10, *P* = 0.04). The incidence of adverse events in the treatment of antiinterleukin 13 are shown in Figure 7, from which we could identify that there was no significant difference in adverse events between antiinterleukin 13 and placebo (RR 1.00, 95% CI: 0.91-1.10, *z* = 0.00, *P* = 1.00).

DISCUSSION

In our systematic review and meta-analysis, we found that treatment with antiinterleukin 13 monoclonal antibodies could be safely used in patients with asthma to improve PEF, decrease FeNO and asthmatic exacerbation, and even probably reduce rescue use of SABA, but could not decrease blood and sputum eosinophil levels, improve FEV₁, inhibit methacholine PC₂₀, reduce ACQ scores.

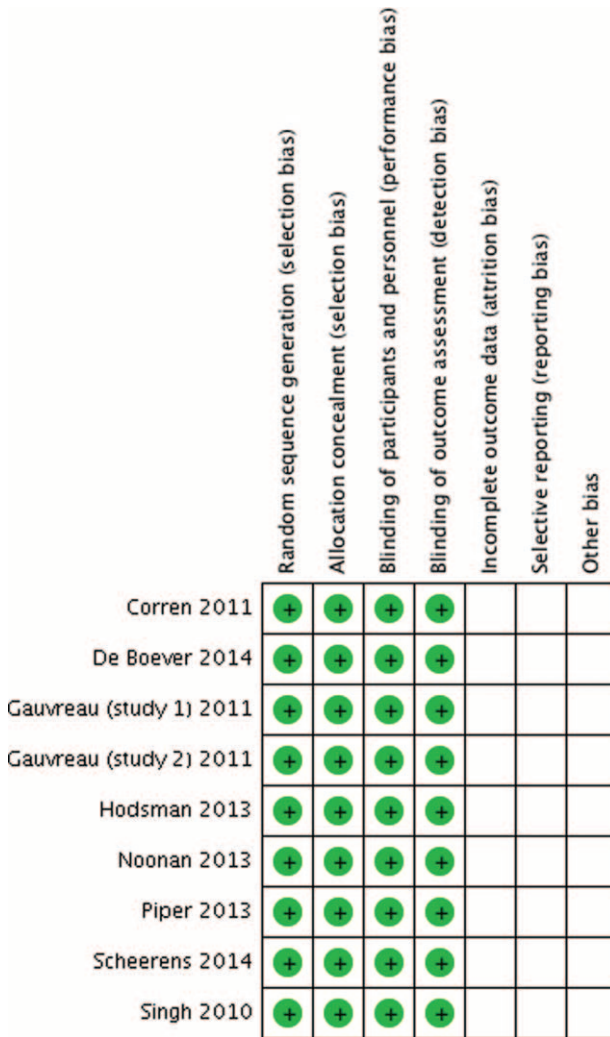


FIGURE 2. Risk of bias graph.

Reversible airflow limitation is the clinical and pathological hallmark of asthma, and lung function test nowadays remains not only the gold standard in diagnosis, but also the important measurements in evaluating treatment efficacy, in which the change of FEV₁ and PEF, as well as Methacholine PC₂₀ are mostly used.¹ In terms with FEV₁, an inconsistent conclusion was drawn from four studies with different anti-interleukin 13 antibodies. De Boever et al¹⁸ firstly reported the treatment of GSK679586 in patients with severe asthma, but they did not find a statistically significant improvement in

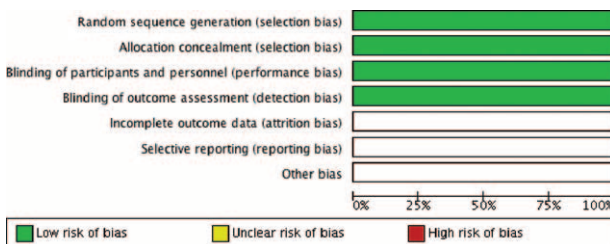


FIGURE 3. Risk of bias summary.

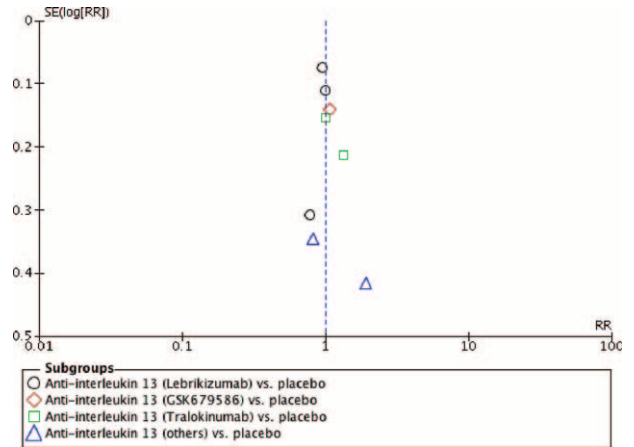


FIGURE 4. Funnel of the enrolled studies. RR = risk ratio, SE = standard error.

FEV₁. While in the following studies applying other antiinterleukin 13 antibodies, that is tralokinumab and lebrikizumab, FEV₁ was significantly improved.^{11,16,17} In our meta-analysis, the result showed that antiinterleukin 13 therapies could not significantly improve FEV₁, which favored in the conclusions reported by De Boever. Potential explanations for the lack of efficacy of antiinterleukin 13 therapies on improving FEV₁ may due to the following reasons: inconsistent drug properties: in the studies included in our final analysis, different drugs with various bioavailability, pharmacokinetics and pharmacodynamics were administered and different status of asthmatic patients were enrolled, thus might induce biases in the results and outcomes; insufficiency of only blocking IL-13: in patients with severe asthma, IL-13 imbalance may merely be one of the underlying pathogenesis in FEV₁ decline due to a long term of taking high-dose corticosteroids or functional redundancy with IL-4 or other mediators of asthma.¹⁸ Moreover, in our systematic review, we found that antiinterleukin antibodies could improve PEF, but had no effect on methacholine PC₂₀. However, we could not draw exact conclusions in these two parameters, because insufficient data could be extracted from the original studies to perform the pooling meta-analysis.

FeNO is measured by the large amount of NO produced by inducible NOS (iNOS), which is a noninvasive parameter reflecting the airway inflammation.²⁰ An increasing number of evidence have revealed that arginase plays a central role in the pathophysiology of asthma, and arginase activity has been shown to be associated with the L-arginine bioavailability to NOS thus influencing the production of NO in an animal experiment, in which arginase antagonist fully reversed the AHR to methacholine while NOS antagonist further prevented that effect.^{9,21} Therefore, antiinterleukin 13 antibodies could theoretically decrease NO in the exhaled breath produced by iNOS and improve lung function by increasing bronchodilating NO via constitutive NOS (cNOS). Our study showed that treatment with antiinterleukin antibodies could significantly decrease FeNO, which further demonstrated the underlying mechanisms mentioned above and the potential clinical values of antiinterleukin 13 antibodies in patients with severe asthma.

ACQ is a patients-reported outcome widely used in clinical trials, which comprised of 5 comprehensive questions that is night-time waking, symptoms on waking, activity limitation, shortness of breath and wheezing. It has been verified to have strong evaluative and discriminative properties and can be used

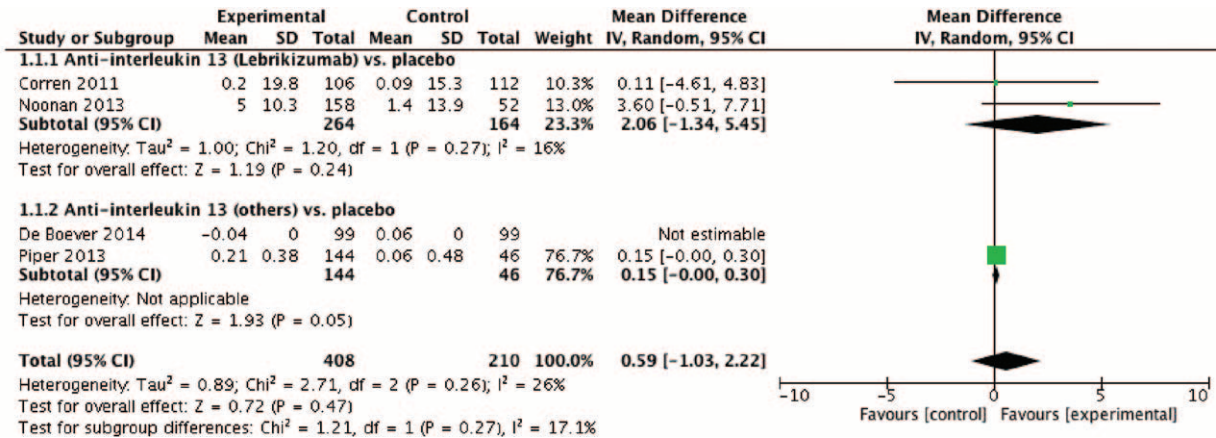


FIGURE 5. The effect of antiinterleukin 13 versus placebo on FEV₁. CI = confidence interval; FEV₁ = forced expiratory volume in 1 second; SD = standard derivation.

with confidence to measure asthma control.²² SABA is one of the most important relievers to rapidly dilate the bronchial smooth muscle and relieve the asthmatic symptoms via activating the β₂ receptors in airways. Numbers of rescue use of SABA has already been recommended as one of measurements to assess the levels of asthma control and severity.¹ In our study, we did not find significant reduction in ACQ scores after treatment with antiinterleukin 13 antibodies, while the effect on reducing rescue use of SABA was elusive, which we considered to be resulted from the insignificant improvement in lung functions and unchanged levels of eosinophil in peripheral blood and sputum. However, compared with placebo, a slight decrease of ACQ scores was observed after treatment of antiinterleukin 13 although without significance, which suggested that antiinterleukin 13 therapies were able to provide some evidence of pharmacology specially located in the lung.

Acute exacerbations are major causes of morbidity and mortality in patients with asthma, and IL-13-induced AHR may be the underlying mechanism.^{3,23} Yang et al³ found that, in vitro, IL-13-induced activation of Arg I significantly correlated

with the AHR, and inhibition of the function of Arg I specifically alleviated IL-13-induced AHR. In the in vivo study by Corren et al,¹¹ they compared antiinterleukin 13 antibodies with placebo in 219 adult patients with asthma and firstly demonstrated a trend of lower exacerbations in the antiinterleukin 13 group. In our pooled meta-analysis, we found that asthma exacerbations were significantly decreased after treatment with antiinterleukin 13 antibodies but without increasing the incidence of adverse events, which further strengthen and supported the clinical application of antiinterleukin 13 therapies in patients with severe asthma. However, interpretation of our result should be cautious due to significant statistical heterogeneity in the pooled data of enrolled studies.

Limitations of our study are as follows: Firstly, the name, dose, administration routine, and duration of the intervention drugs were not identical in the enrolled studies, which may result in performance biases. Secondly, the baseline characteristics of the patients were not completely provided which may lead to selection biases. Thirdly, arginase and NOS levels were not measured which made it elusive to understand the

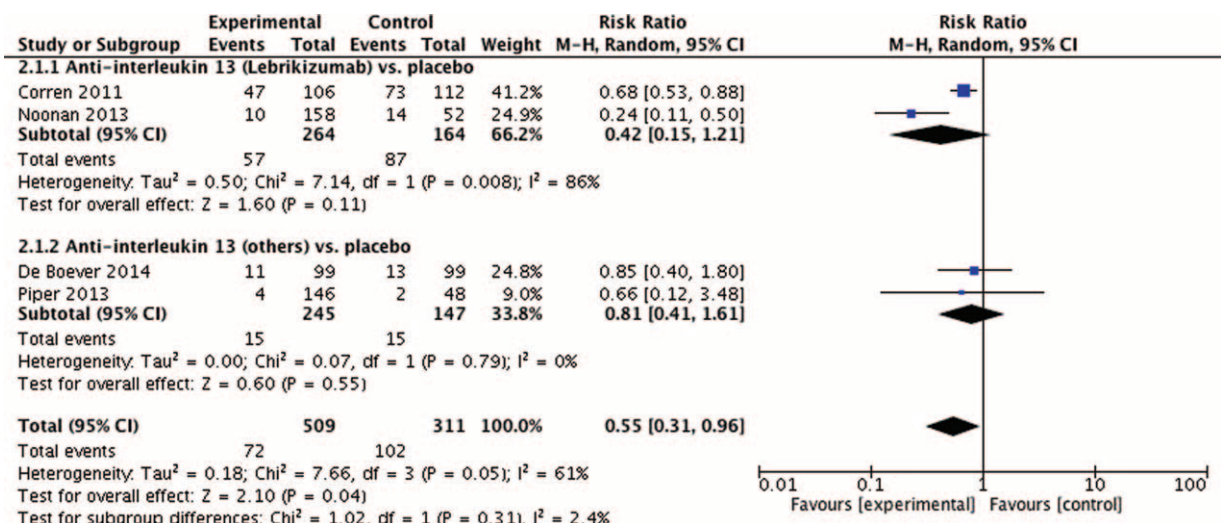


FIGURE 6. The effect of antiinterleukin 13 versus placebo on exacerbation. CI = confidence interval; M.-H = Mantel-Haenszel.

TABLE 3. Results of Eosinophil Count, PEF, Methacholine PC₂₀, FeNO, ACQ, and Rescue Use of SABA

Refs.	Patients	No.*	Sex (Male, %)*	Age (Mean ± SD, y)*	Intervention	Result	Conclusion
Eosinophil count De Boever et al ¹⁸	Severe asthma	99	48 (48.5)	51 ± 11	GSK679586	Mean blood eosinophil counts tended to be slightly higher for GSK679586 than placebo	Blood eosinophil counts remained essentially unchanged after treatment of GSK679586
Gauvreau et al ¹⁵	Mild atopic asthma	Study 1: 14; Study 2: 14	Study 1: 7 (50.0); Study 2: 7 (50.0)	Study 1: 26.1 ± 1.7; Study 2: 33.1 ± 3.3	Study 1: IMA-638; Study 2: IMA-026	There was no effect of IMA-638 or IMA-026 on the levels of eosinophil in peripheral blood; There was no effect of either IMA-638 or IMA-026 on sputum eosinophils after allergen challenge	There was no effect of anti-IL-13 antibody on blood or sputum eosinophils
PEF Corren et al ¹¹	Uncontrolled asthma	107	35 (32.7)	45 ± 12	Lebrikizumab	Absolute change in PEF (baseline to week 12): lebrikizumab: -0.49; placebo: -3.73; difference between lebrikizumab and placebo: 3.24 (95% CI: -11.34-17.81)	Lebrikizumab treatment was associated with improved lung function
Noonan et al ¹⁶	Asthmatic patients not receiving inhaled corticosteroids	158	57 (36.1)	39.3 ± 12.1	Lebrikizumab	Change in morning prebronchodilator PEF: 6.3% for lebrikizumab vs -0.1% for placebo, <i>P</i> = 0.03	Increases among lebrikizumab-treated patients were seen for change in morning prebronchodilator PEF
Piper et al ¹⁷	Moderate-to-severe asthma	146	63 (43.2)	47.4 ± 11.1	Tralokinumab (CAT-354)	Change from baseline: 31.8 ± 62.0 for tralokinumab vs 14.2 ± 60.1 for placebo	PEF measured by spirometry at study visits improved in the combined tralokinumab group compared with placebo
Methacholine PC ₂₀ Scheerens et al ¹⁹	Mild asthma	13	6 (46.2)	36 ± 11	Lebrikizumab	The arithmetic mean of the methacholine doubling dose in the lebrikizumab group was 0.33 doubling doses higher than that of the placebo group mean (1.58 vs 1.25, 95% CI: -0.64 to 1.30)	The difference of methacholine PC ₂₀ between lebrikizumab and placebo group was not clinically meaningful inhibition
Gauvreau et al ¹⁵	Mild atopic asthma	Study 1: 14; Study 2: 14	Study 1: 7 (50.0); Study 2: 7 (50.0)	Study 1: 26.1 ± 1.7; Study 2: 33.1 ± 3.3	Study 1: IMA-638; Study 2: IMA-026	The PC ₂₀ values for most subjects decreased after each allergen challenge	There was no difference between the treatment groups in terms of PC ₂₀ values
FeNO Corren et al ¹¹	Uncontrolled asthma	107	35 (32.7)	45 ± 12	Lebrikizumab	Lebrikizumab was associated with a 19% mean decline in FeNO at week 12, as compared with a 10% increase with placebo (<i>P</i> < 0.001)	Lebrikizumab treatment can significantly decrease FeNO

Refs.	Patients	No.*	Sex (Male, %)*	Age (Mean ± SD, y)*	Intervention	Result	Conclusion
Noonan et al ¹⁶	Asthmatic patients not receiving inhaled corticosteroids	158	57 (36.1)	39.3 ± 12.1	Lebrikizumab	Mean percentage change from baseline: lebrikizumab: -49%; placebo: 11%; difference: $P < 0.001$	Lebrikizumab treatment can significantly decrease FeNO
Hodsman et al ¹³	Mild intermittent asthma	21	21 (100.0)	29 ± 10	GSK679586	FeNO were reduced relative to baseline in all GSK679586 treatment groups at both 2 weeks and 8 weeks, whereas FeNO levels remained essentially unchanged over time in the placebo group	FeNO can be significantly reduced by GSK679586
ACQ Corren et al ¹¹	Uncontrolled asthma	107	35 (32.7)	45 ± 12	Lebrikizumab	Change in ACQ5 score at week 12: lebrikizumab: -0.93 vs placebo: -0.88; difference between lebrikizumab and placebo: -0.05 (95% CI: -0.32 to 0.22)	Treatment with lebrikizumab had no significant effects on the ACQ5 score
Noonan et al ¹⁶	Asthmatic patients not receiving inhaled corticosteroids	158	57 (36.1)	39.3 ± 12.1	Lebrikizumab	Mean change in ACQ score: lebrikizumab: -0.2 vs placebo: -0.4 ($P = 0.21$)	The reductions in ACQ scores were similar among lebrikizumab- and placebo-treated patients
De Boever et al ¹⁸	Severe asthma	99	48 (48.5)	51 ± 11	GSK679586	Decrease in ACQ-7 scores over 12 wk: GSK679586: -0.31 vs placebo: -0.17; estimated treatment difference: -0.14 (95% CI: -0.28 to 0.00, $P = 0.58$)	GSK679586 did not demonstrate a clinically meaningful improvement in asthma control
Piper et al ¹⁷	Moderate-to-severe asthma	146	63 (43.2)	47.4 ± 11.1	Tralokinumab (CAT-354)	Change of ACQ-6 from baseline at week 13: tralokinumab: -0.76 ± 1.04 vs placebo: -0.61 ± 0.90, $P = 0.375$	The addition of tralokinumab to existing asthma controller medication showed no significant improvement in ACQ-6 score
Rescue use of SABA Noonan et al ¹⁶	Asthmatic patients not receiving inhaled corticosteroids	158	57 (36.1)	39.3 ± 12.1	Lebrikizumab	Mean change in reliever medication use: lebrikizumab: -0.3 vs placebo: -0.6, $P = 0.29$	The reductions in reliever medication use were similar among lebrikizumab- and placebo-treated patients
Piper et al ¹⁷	Moderate-to-severe asthma	146	63 (43.2)	47.4 ± 11.1	Tralokinumab (CAT-354)	Reduction in β_2 -agonist use: tralokinumab: -0.68 ± 1.45 vs placebo: -0.10 ± 1.49, $P = 0.020$	Subjects in the tralokinumab group showed a significantly greater reduction in β_2 -agonist use compared with placebo

ACQ = Asthma Control Questionnaire, CI = confidence interval, FeNO = fraction of exhaled nitric oxide, methacholine PC₂₀ = the provocation concentration of methacholine causing a 20% fall in FEV₁, No = number, PEF = peak expiratory flow, SABA = short-acting- β -agonist, SD = standard deviation.
 * Data on all patients who received anti-interleukin 13.

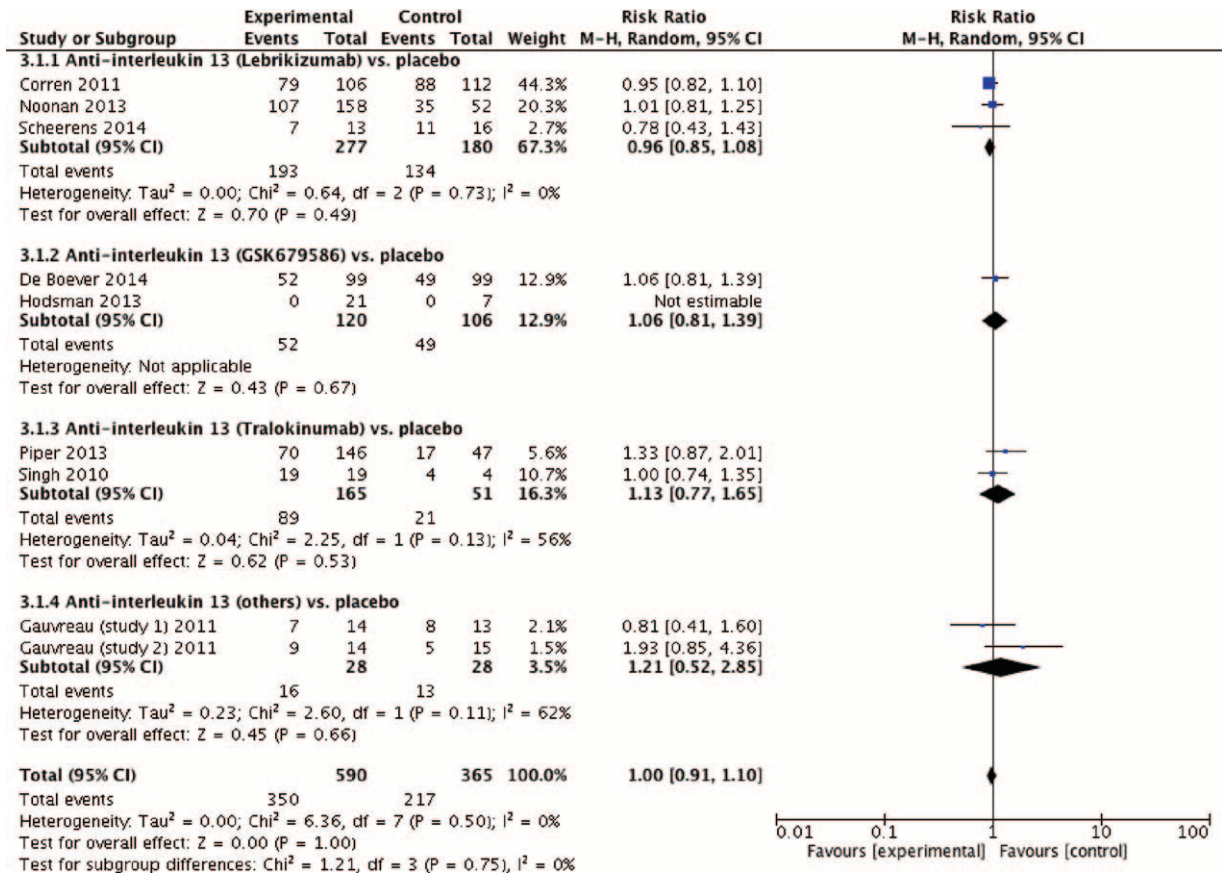


FIGURE 7. The effect of antiinterleukin 13 versus placebo on adverse events. CI = confidence interval; M-H = Mantel-Haenszel.

mechanism of antiinterleukin 13 in treatment of asthmatics. Finally, our study focused specially on the IL-13-induced AHR rather than the pathway of airway remodeling via production of polyamines and L-proline, which was also the fundamental mechanism of severe asthma with refractory symptoms and nonresponsiveness to corticosteroids. Therefore, future studies involving and dealing with these issues are urgently needed.

CONCLUSIONS

Antiinterleukin 13 monoclonal therapies could be safely used to improve PEF, decrease FeNO and asthmatic exacerbation, and probably reduce rescue use of SABA, but could not decrease blood and sputum eosinophil levels, improve FEV₁, inhibit methacholine PC₂₀, or reduce ACQ scores. Based on our systemic review, we suggest using antiinterleukin 13 as a final add-on treatment in uncontrolled asthmatics nor as a substitute of bronchodilators or corticosteroids.

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REFERENCES

1. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA), 2012. Available at www.ginasthma.org

2. Zimmermann N, King NE, Laporte J, et al. Dissection of experimental asthma with DNA microarray analysis identifies arginase in asthma pathogenesis. *J Clin Invest.* 2003;111:1863-1874.

3. Yang M, Rangasamy D, Matthaei KI, et al. Inhibition of arginase I activity by RNA interference attenuates IL-13-induced airways hyperresponsiveness. *J Immunol.* 2006;177:5595-5603.

4. Gray MJ, Poljakovic M, Kepka-Lenhart D, et al. Induction of arginase I transcription by IL-4 requires a composite DNA response element for STAT6 and C/EBPbeta. *Gene.* 2005;353:98-106.

5. Hobbs CA, Gilmour SK. High levels of intracellular polyamines promote histone acetyltransferase activity resulting in chromatin hyperacetylation. *J Cell Biochem.* 2000;77:345-360.

6. Ricciardolo FL, Zaagsma J, Meurs H. The therapeutic potential of drugs targeting the arginase pathway in asthma. *Expert Opin Investig Drugs.* 2005;14:1221-1231.

7. Howell JE, Mcanulty RJ. TGF-beta: its role in asthma and therapeutic potential. *Curr Drug Targets.* 2006;7:547-565.

8. de Boer J, Meurs H, Flendrig L, et al. Role of nitric oxide and superoxide in allergen-induced airway hyperreactivity after the late asthmatic reaction in guinea-pigs. *Br J Pharmacol.* 2001;133:1235-1242.

9. Maarsingh H, Bossenga BE, Bos IS, et al. L-arginine deficiency causes airway hyperresponsiveness after the late asthmatic reaction. *Eur Respir J.* 2009;34:191-199.

10. Singh D, Kane B, Molfino NA, et al. A phase 1 study evaluating the pharmacokinetics, safety and tolerability of repeat dosing with a

- human IL-13 antibody (CAT-354) in subjects with asthma. *BMC Pulm Med.* 2010;10:1–8.
11. Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med.* 2011;365:1088–1098.
 12. LaPorte SL, Joo ZS, Vaclavikova J, et al. Molecular and structural basis of cytokine receptor pleiotropy in the interleukin-4/13 system. *Cell.* 2008;132:259–272.
 13. Hodsman P, Ashman C, Cahn A, et al. A phase I, randomized, placebo-controlled, dose-escalation study of an anti-IL-13 monoclonal antibody in healthy subjects and mild asthmatics. *Br J Clin Pharmacol.* 2013;75:118–128.
 14. Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0 [Updated March 2011]. Oxford: The Cochrane Collaboration; 2011. Available at: www.cochrane-handbook.org. Accessed 20 March 2011
 15. Gauvreau GM, Boulet LP, Cockcroft DW, et al. Effects of interleukin-13 blockade on allergen-induced airway responses in mild atopic asthma. *Am J Respir Crit Care Med.* 2011;183:1007–1014.
 16. 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.e12–574.e12.
 17. Piper E, Brightling C, Niven R, et al. A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. *Eur Respir J.* 2013;41:330–338.
 18. De Boever EH, Ashman C, Cahn AP, et al. Efficacy and safety of an anti-IL-13 mAb in patients with severe asthma: a randomized trial. *J Allergy Clin Immunol.* 2014;133:989–996.
 19. 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.
 20. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med.* 2011;184:602–615.
 21. Maarsingh H, Pera T, Meurs H. Arginase and pulmonary diseases. *Naunyn Schmiedebergs Arch Pharmacol.* 2008;378:171–184.
 22. Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. *Eur Respir J.* 1999;14:902–907.
 23. Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy.* 2004;59:469–478.