Biologicals in the management of bronchial asthma

Deepa Shrestha

Overview of the seminar

- Burden of asthma and need of biologicals
- Immunology of asthma
- Possible targeted therapy
- Available biologicals used in asthma
- Evidence in favour of different biologicals used in asthma
- Take home message

Burden of moderate to severe asthma

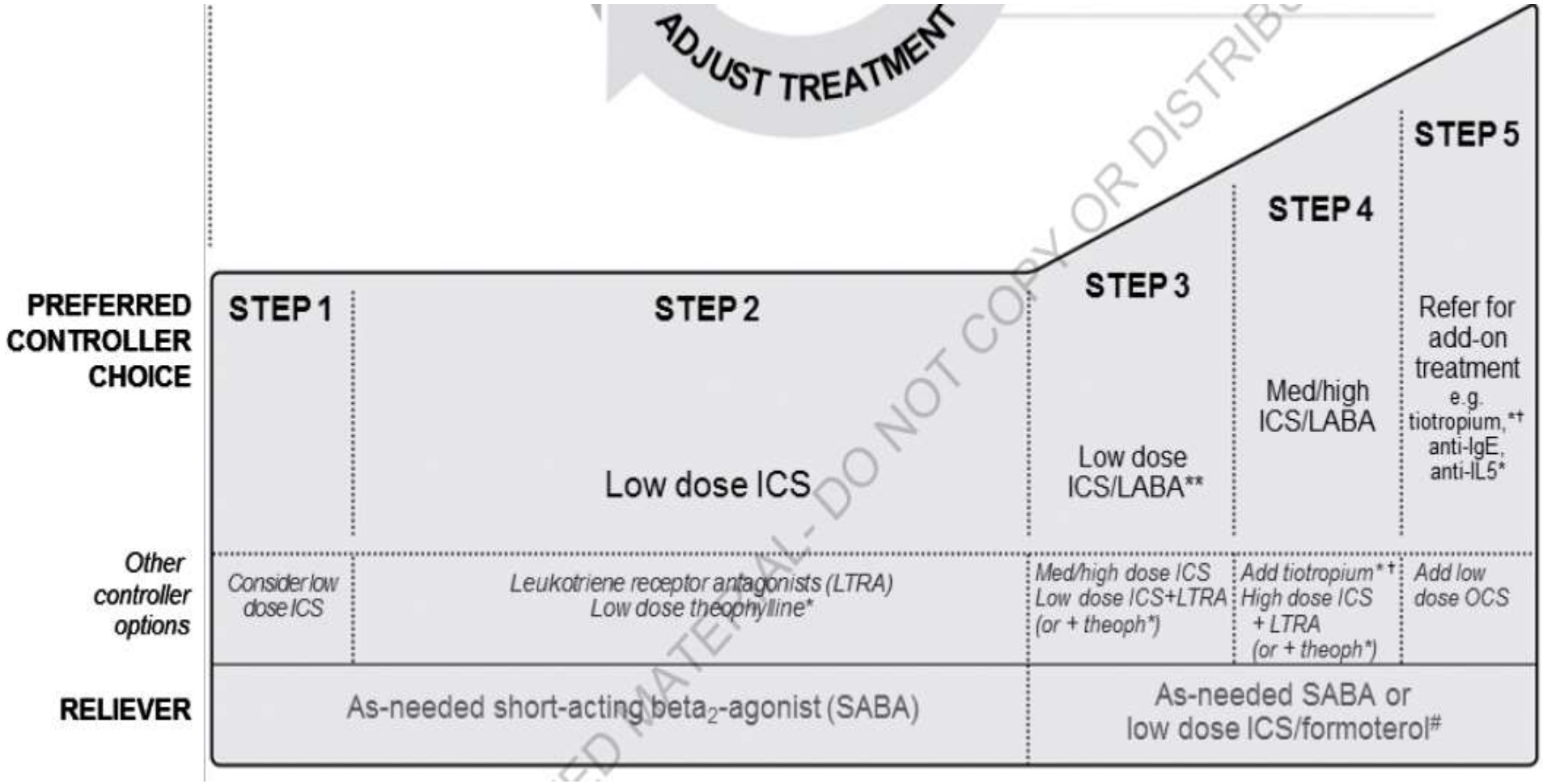
- Global prevalence of up to 18%, and is expected to affect approximately 400 million people worldwide by 2025
- 5–10% of people with asthma remains symptomatic and inadequately controlled
- High risk of serious morbidity and mortality→ large share of economic resources and health-care services, including emergency visits, hospitalizations and additional consumption of drugs for recurrent exacerbations
- Frequent absences from school and work
- Patients with difficult-to-treat disease are often prone to anxiety and depression
- Poor quality of life

International ERS/ATS Guidelines on Definition, Evaluation, and Treatment of Severe Asthma 2013
Ann Am Thorac Soc Vol 13, Supplement 1, pp S68–S77, Mar 2016

Need of biologicals in asthma

- Heterogeneous disease that includes several different phenotypes:
  - Allergic asthma
  - Non-allergic asthma
  - Late-onset asthma
  - Asthma with fixed-airflow limitation
  - Asthma with obesity
- Appreciation of heterogeneity
- Different therapeutic targets (targeted and nontargeted therapies)
- Knowledge of molecular targets that are relevant to each phenotypic subgroup of asthma based primarily on cluster analyses, molecular phenotyping, biomarkers, and differential responses

"Asthma is both easy and hard to treat. It is easy to treat because the vast majority of patients require little medication for a lot of benefit."



GINA 2017

Severe asthma

- Defined for age 6 years and older as asthma that requires:

(1) Treatment corresponding to GINA step 4(i.e., medium/high dose of controller medication such as ICS and LABA and reliever as needed) and step 5 (i.e., step 4 treatment scheme plus referral for add-on treatment such as anti–immunoglobulin E [IgE] or IL-5) or

(2) Systemic corticosteroid (CS) for at least 50% of the previous year, to prevent asthma from becoming uncontrolled or that remained uncontrolled despite this therapy

International ERS/ATS Guidelines on Definition, Evaluation, and Treatment of Severe Asthma 2013
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Immunology of asthma

- Chronic inflammation and tissue remodelling
- TH2–high patients: Triggered by immune-inflammatory response driven by T helper type 2 (TH2) lymphocytes
- Commitment to TH2 lineage driven by IL-4, released from mast cells, T cells, eosinophils and basophils
- Innate cytokine thymic stromal lymphopoietin (TSLP) secreted by bronchial epithelial cells and mast cells→ TH2-adaptive responses
- Induce dendritic cells to release chemokines CC motif chemokine 17 (CCL17) and CCL22→ recruit TH2 cells upon binding to their receptor: CCR4

Fajt ML. et al. J Allergy Clin Immunol Feb 2015

Immunology….

- Main cytokines involved in TH2 are interleukins (IL)-2, 4, 5, and 13
- Agents such as monoclonal antibodies (eg, to IL-5, 13, thymic stromal lymphopoietin) and antibodies to receptors (eg, IL-2, IL-5, IL-4) that interfere with these cytokines or deplete cells expressing these receptors
- TH2 low patients:
  - Neutrophilic inflammation of airways
  - Often associated with most severe clinical phenotypes of asthma
  - Induced by other subsets of TH cells

Fajt ML. et al. J Allergy Clin Immunol Feb 2015

Immunology….

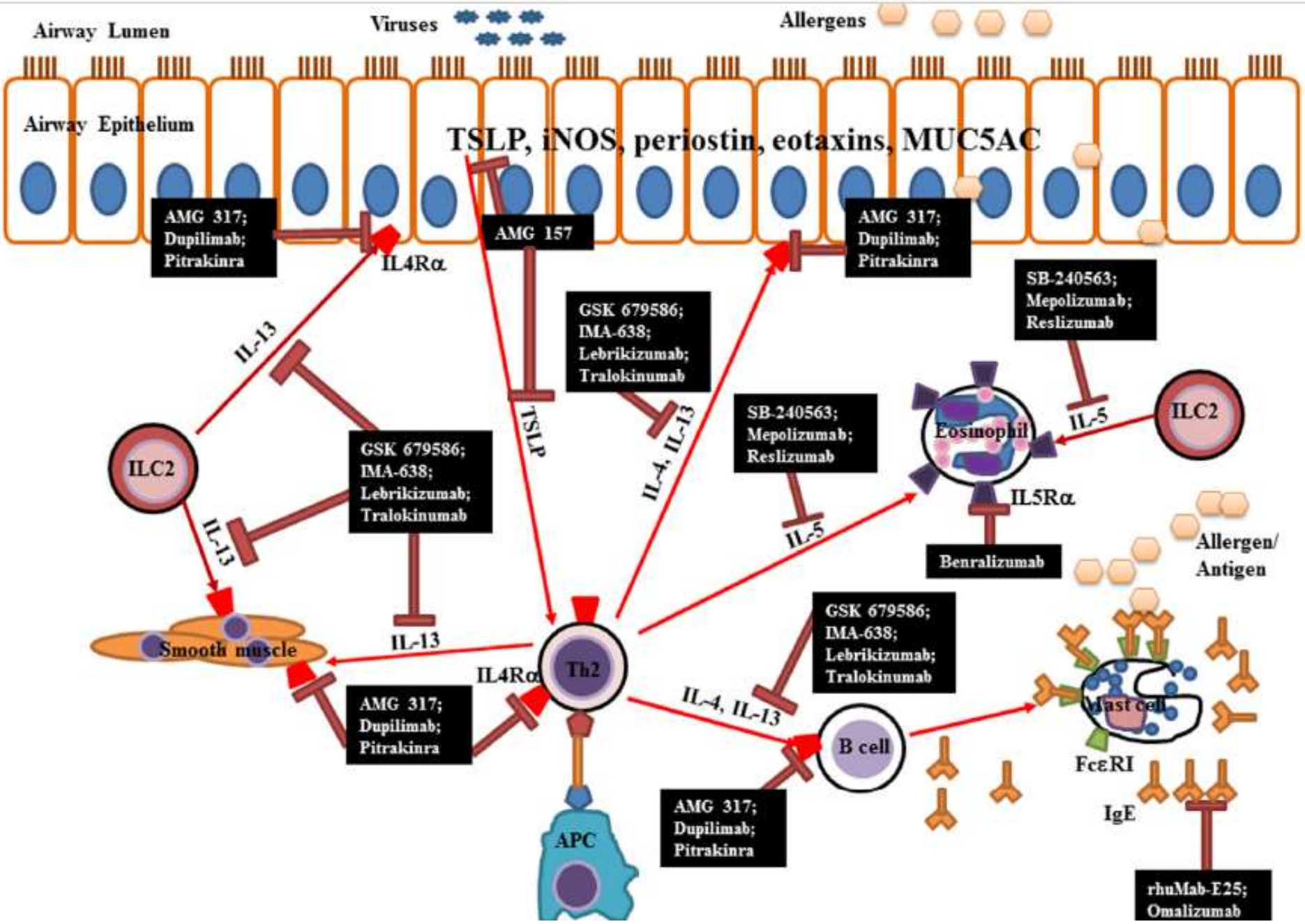
- Specific lineage of CD4+ effector T lymphocytes, which express IL-17 and called TH17 cells
- Have a pivotal role in bronchial neutrophilia
- Airway eosinophilia— which is predominantly mediated by TH2 cells — is responsible for mild and moderate allergic asthma
- Whereas concomitant activation of both TH2 cells and TH17 cells is associated with mixed eosinophilic and/or neutrophilic inflammatory phenotype that underlies more severe forms of disease

Fajt ML. et al. J Allergy Clin Immunol Feb 2015

Immunology….

Allergic asthma	Non-allergic asthma
Childhood onset	Adult
History of atopy present	No atopy Associated with obesity, postinfectious, neutrophilic, and smoking-related factor
Eosinophilic inflammation	Neutrophilic /eosinophilic(paucigranular)
Usyally responds well to ICS	Often responds less to ICS
IL-4, IL-5, and IL-13	IL-17
FENO levels Blood/Sputum eosinophilia Serum periostin	No specific biomarkers
Mild to moderate asthma	Severe form
Managed by targeted therapy	Targeted therapy difficult

Fajt ML. et al. J Allergy Clin Immunol Feb 2015



Fajt ML. et al. J Allergy Clin Immunol Feb 2015

Prefix
Random

Substem B
Target class

-b(a)-	bacterial
-c(i)-	cardiovascular
-f(u)-	fungal
-k(i)-	interleukin
-l(i)-	immunomodulating
-n(e)- (under discussion	neural
-s(o)-	bone
-tox(a)	toxin
t(u)	tumour
-v(i)-	viral

Substem A
Source species

a	rat
axo (pre-sub-stem)	rat/mouse
e	hamster
i	primate
o	mouse
u	human
xi	chimeric
-xizu- (under discussion)	chimeric/humanized
zu	humanized

Suffix
-mab

Omalizumab= Oma+li+zu+mab

- Benralizumab= Benra+li+zu+mab

WHO 2009 General policies for monoclonal antibodies

Different classes of biologicals

- Anti-IgE antibody
- Anti-IL-2R antibody
- Anti-IL-4 receptor alpha subunit antibody
- Anti-IL-5 monoclonal antibodies
- Anti-IL-5 receptor alpha antibodies
- Anti-IL-13 antibodies
- Anti-thymic stromal lymphopoietin
- Anti-TNF-alpha agents

TABLE I. Summary of DBPC trials using biologic medications in patients with T_H2/type 2–high asthma

Target	Biologic therapies used	Type of study	Major outcome
IgE	Anti-IgE mAb (rhuMAb-E25, omalizumab)	Allergen challenge: mild-to-moderate allergic asthma	↓ Early and late asthmatic response, ↓ serum free IgE
		Chronic moderate-to-severe allergic asthma	↓ Asthma exacerbations, ↓ serum free IgE
		Chronic severe allergic asthma	↓ Asthma exacerbations greater when subanalyzed by type 2–high phenotypes (↑ FENO levels, blood eosinophil counts, or serum periostin levels)
IL-4 and IL-13	Mutant IL-4 (pitrakinra); IL-13 antibody (IMA-638)	Allergen challenge: mild allergic asthma	↓ Late asthmatic response
	IL-4Rα mAb (AMG 317); mutant IL-4 (pitrakinra)	Chronic moderate-to-severe asthma	No effect on prespecified clinical asthma outcomes in "all comers," + SNPs of IL-4Rα gene associated with clinical response (pitrakinra)
	IL-13 mAb (lebrikizumab, tralokinumab)	Chronic moderate-to-severe asthma	↑ FEV_1; greatest clinical benefit when subanalyzed by type 2–high phenotypes (↑ periostin and sputum IL-13^+)
	IL-13 mAb (GSK679586)	Very severe asthma	No effect on prespecified clinical asthma outcomes
	IL-4Rα mAb (dupilumab)	Chronic moderate-to-severe asthma with type 2–high phenotype (blood eosinophils ≥300 cells/μL or sputum eosinophils ≥3%)	↓ Asthma exacerbations, ↓ FENO, ↓ β-agonist use, ↑ FEV_1

Fajt ML. et al. J Allergy Clin Immunol Feb 2015

IL-5	Anti–IL-5 (SB-240563)	Allergen challenge: mild allergic asthma	No effect on clinical asthma outcomes despite ↓ in blood and sputum eosinophil counts
	Anti–IL-5 (mepolizumab)	Mild-to-moderate allergic asthma	No effect on clinical asthma outcomes despite ↓ in blood, sputum, bone marrow, and airway eosinophil counts
	Anti–IL-5 (mepolizumab; reslizumab)	Chronic, refractory, severe asthma with type 2–high phenotype (sputum eosinophils >3%, or ↑ blood eosinophil counts or FENO levels)	↓ Asthma exacerbations, ↓ blood/sputum eosinophils, ↑ FEV_1
	Anti–IL-5Rα (benralizumab)	Chronic eosinophilic asthma with type 2–high phenotype (sputum eosinophils ≥2.5%)	↓ Eosinophils in airway mucosa/submucosa, sputum, bone marrow, and blood; clinical measures not evaluated
TSLP	Anti-TSLP mAb (AMG 157)	Allergen challenge: mild allergic asthma	↓ Late asthmatic response, ↓ in blood/sputum eosinophil counts, ↓ FENO levels

Fajt ML. et al. J Allergy Clin Immunol Feb 2015

Immunoglobulin E (IgE)

- Plays central role in mechanism of immediate bronchoconstriction and influx of inflammatory cells in allergic
- Higher elevated circulating immunoglobulin E (IgE) concentrations (levels are adjusted for age)
- Target for therapeutic agents in asthma and other allergic diseases
- Omalizumab, a recombinant humanized monoclonal anti-IgE antibody, is approved for use in asthma
- First received approval from Australian health authorities for treating adults and adolescents with moderate allergic asthma in 2002→ Approved in the US and EU in 2003 and 2005, respectively

Omalizumab MoA

- Binds to third constant domain of IgE heavy chain (C-epsilon- 3), the same site at which IgE normally binds to both high- and low-affinity IgE receptors on mast cells, basophils, and other cell types
- Omalizumab forms complexes with free IgE and prevents its interaction with these receptors
- Omalizumab-IgE complexes cleared by hepatic reticuloendothelial system

The New England Journal of Medicine

December 23, 1999

TREATMENT OF ALLERGIC ASTHMA WITH MONOCLONAL ANTI-IgE ANTIBODY

HENRY MILGROM, M.D., ROBERT B. FICK, JR., M.D., JOHN Q. SU, PH.D., JAMES D. REIMANN, PH.D., ROBERT K. BUSH, M.D., MARC L. WATROUS, PH.D., AND W. JAMES METZGER, M.D., FOR THE RHUMAB-E25 STUDY GROUP*

- Recombinant humanized monoclonal antibody (rhuMAb-E25) forms complexes with free IgE and blocks its interaction with mast cells and basophils
- 317 subjects, who required inhaled or oral corticosteroids (or both) to receive either placebo or one of two regimens of rhuMAb-E25:
  - High-dose rhuMAb-E25 (5.8 μg/kg/ng of IgE per ml) or
  - Low-dose rhuMAb-E25 (2.5 μg μg/kg/ng of IgE per ml)
- Intravenously on days 0 (half a dose), 4 (half a dose), and 7 (full dose) and then once every 2 weeks thereafter for 20 weeks

The New England Journal of Medicine

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- During first 12 weeks of study, corticosteroids continued
- During the next eight weeks, corticosteroids tapered, with effort to discontinue
- Primary outcome: Improvement in the asthma symptom score at 12 weeks
- Improvement was marginal, but statistically significant
- More subjects in the two omalizumab groups were able to decrease or discontinue corticosteroids than in the placebo group

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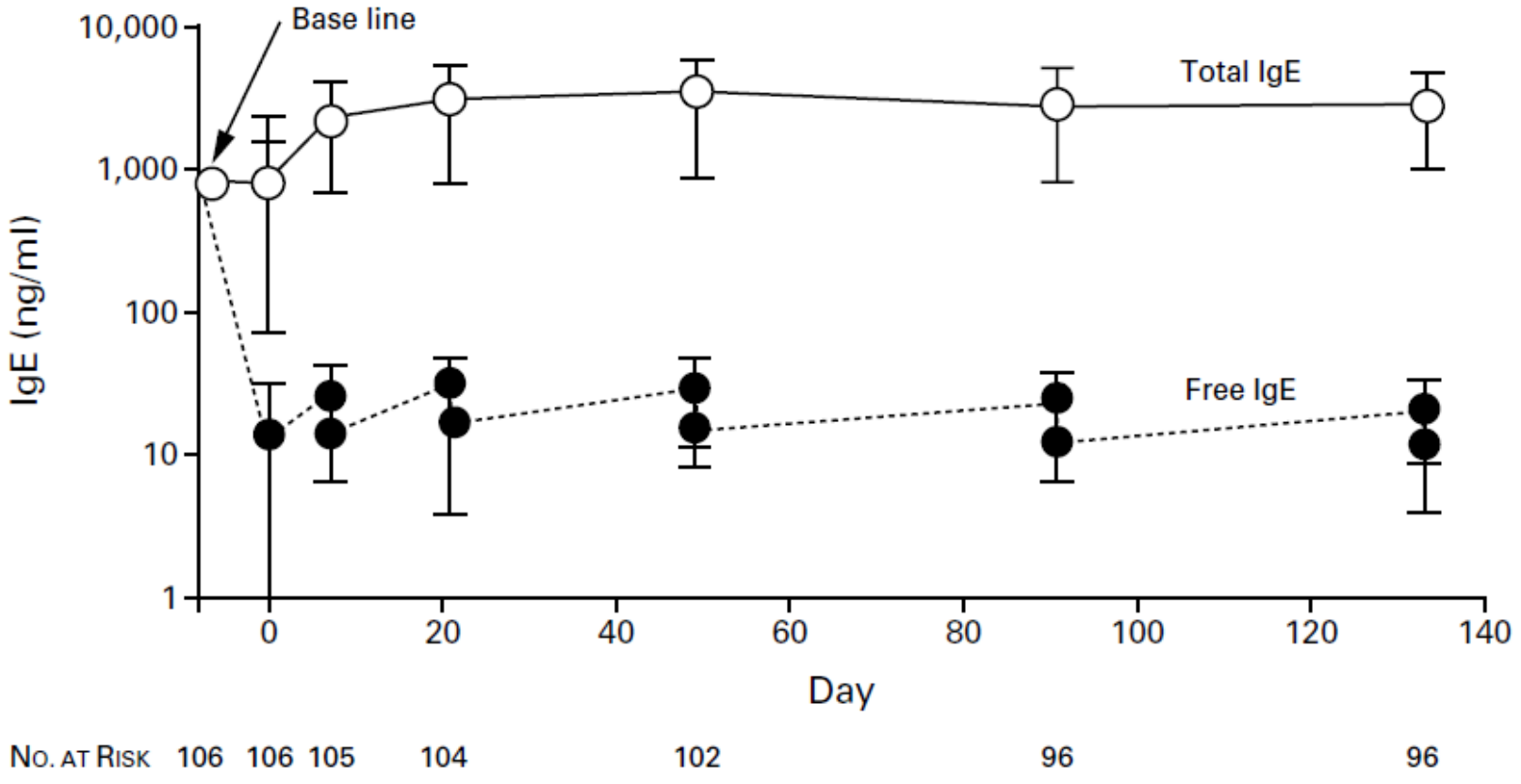


Figure 1. Mean (±SD) Serum Concentrations of Total and Free IgE in Subjects Given a Low Dose of rhuMAb-E25 for 20 Weeks.

Serum free IgE concentrations decreased rapidly by more than 95 percent (base-line level, 1060 ng per milliliter [441.7 IU per milliliter])

Allergy 2005: 60: 309–316

ALLERGY
DOI: 10.1111/j.1398-9995.2004.00772.x

Original article

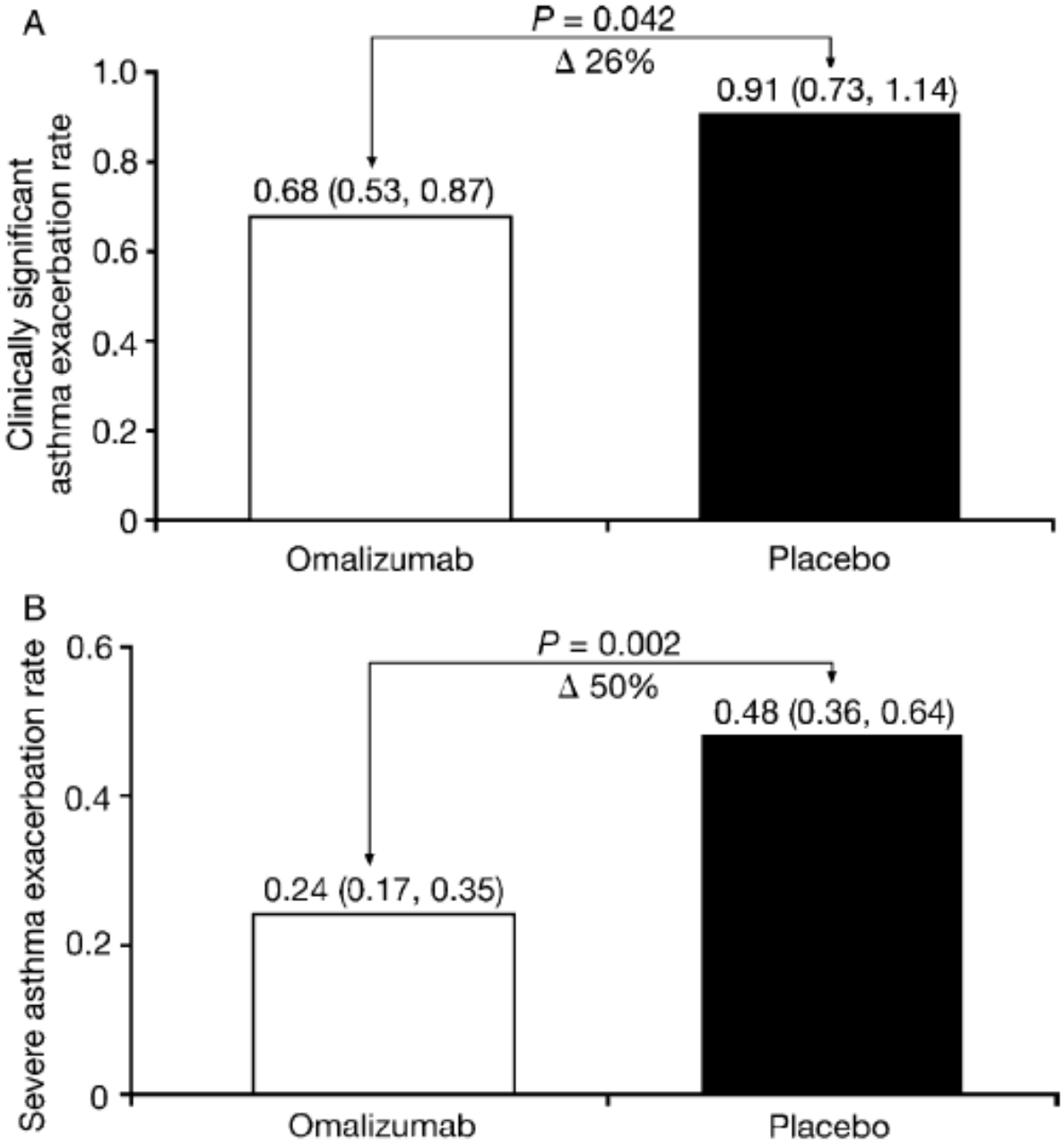
Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE

- Double-blind, parallel-group, multicentre study
- 419 patients included
- Inadequately controlled despite therapy with high-dose inhaled corticosteroids (ICS) and long-acting b2-agonists (LABA) with reduced lung function and recent history of clinically significant exacerbations
- Randomized to receive omalizumab or placebo for 28 weeks

INNOVATE Trial

- Clinically significant asthma exacerbation rate, 0.68 with omalizumab and 0.91 with placebo (26% reduction) during 28-week treatment phase (P= 0.042)
- Significantly reduced severe asthma exacerbation rate (0.24 vs 0.48, P ¼ 0.002) and emergency visit rate (0.24 vs 0.43, P= 0.038)
- Significantly improved asthma-related quality of life, morning peak expiratory flow and asthma symptom scores
- Incidence of adverse events was similar between treatment groups

Humbert et al. Allergy 2005: 60: 309–316



Concluded:
Omalizumab is effective and should be considered as add-on therapy for patients with inadequately controlled severe persistent asthma who have a significant unmet need despite best available therapy

Humbert et al. Allergy 2005: 60: 309–316

Cochrane Database

- Fourteen trials (15 group comparisons) were included, contributing a total of 3143 mild to severe allergic asthmatic participants with high levels of IgE
- Omalizumab led to significant reduction in inhaled steroid (ICS) consumption compared with placebo (-119 mcg/day (95% CI -154 to -83, three trials))
- Significant increases in number of participants who were able to reduce ICS by over 50% (odds ratio (OR) 2.50, 95% confidence interval (CI) 2.02 to 3.10 (four trials)); or
- Completely withdraw daily ICS intake (OR 2.50 (95%CI 2.00 to 3.13; four trials))

Walker S. et al. Cochrane Database Syst Rev. 2006(2):CD003559

Cochrane Database

- Participants treated with Omalizumab were less likely to suffer an asthma exacerbation with treatment as an adjunct to ICS (OR 0.52, 95%CI 0.41 to 0.65, five trials), or as an ICS tapering agent (OR 0.47, 95% CI 0.37 to 0.60, four trials)
- Omalizumab was effective in reducing asthma exacerbations as an adjunctive therapy to inhaled steroids, and during steroid tapering phases of clinical trials
- Omalizumab was generally well tolerated, although there were more injection site reactions with Omalizumab

Walker S. et al. Cochrane Database Syst Rev. 2006(2):CD003559

Cochrane Database: Results

- Omalizumab produced significant reduction in serum free IgE (89% to 99%) (in all trials, except one trial which used inhaled route)
- Omalizumab reduced asthma exacerbations and need for rescue medications when used as an adjunctive therapy to steroids
- Omalizumab use allowed significant reduction of ICS dose
- In subgroup of patients requiring oral steroids, Omalizumab had no significant effect on asthma exacerbations or reduction in daily oral steroid dose
- Omalizumab significantly improved HRQoL
- No consistent effect on lung function

Walker S. et al. Cochrane Database Syst Rev. 2006(2):CD003559

Omalizumab

- Randomized trial of 850 patients with uncontrolled symptoms despite both highdose ICS (≥500 mcg fluticasone twice daily) and LABA therapy
- Treatment with omalizumab or placebo was administered for 12 months, controller therapies not changed
- Patients had IgE levels within specified range and sensitization to perennial allergen
- Primary endpoint: Number of exacerbations requiring systemic glucocorticoids for more than 3 days or requiring an increase in daily dose of ≥20 mg of prednisone (or equivalent) for patients on chronic oral glucocorticoids
- Rates of exacerbations per subject were 0.66 and 0.88 in the omalizumab and placebo groups, respectively, corresponded to 25 percent reduction in incidence rate, statistically significant

Hanania NA. et al. Ann Intern Med 2011; 154:573

CHEST Original Research
ASTHMA

Efficacy and Safety of Subcutaneous Omalizumab vs Placebo as Add-on Therapy to Corticosteroids for Children and Adults With Asthma

A Systematic Review

Gustavo J. Rodrigo, MD; Hugo Neffen, MD; and José A. Castro-Rodriguez, MD, PhD

- Systematic review of placebo-controlled studies performed
- Primary outcomes: Reduction of steroid use and asthma exacerbations
- Secondary outcome: Lung function, rescue medication use, asthma symptoms, health-related quality of life, and adverse effects

CHEST Original Research
ASTHMA

Efficacy and Safety of Subcutaneous Omalizumab vs Placebo as Add-on Therapy to Corticosteroids for Children and Adults With Asthma

A Systematic Review

Gustavo J. Rodrigo, MD; Hugo Neffen, MD; and José A. Castro-Rodriguez, MD, PhD

- Eight trials (3,429 participants) fulfilled selection criteria
- At end of steroid reduction phase, patients taking omalizumab more likely to be able to withdraw from corticosteroids completely compared with those taking placebo (Relative risk [RR]= 1.80; 95% CI, 1.42-2.28; *P=.00001)*
- *Omalizumab showed decreased risk of asthma exacerbations at* end of stable (RR= 0.57; 95% CI, 0.48-0.66; *P= .0001) and adjustable-steroid phases* (RR= 0.55; 95% CI, 0.47-0.64; *P= .0001); post-hoc analysis suggested the effect independent* of duration of treatment, age, severity of asthma, and risk of bias

Rodrigo GJ. et al. Chest. 2011 Jan;139(1):28-35

CHEST Original Research
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- Frequency of serious adverse effects was similar in omalizumab (3.8%) and placebo (5.3%) groups
- Injection site reactions were more frequent in the omalizumab patients (19.9% vs 13.2%)
- No indications of increased risk of hypersensitivity reactions, cardiovascular effects, or malignant neoplasms

Rodrigo GJ. et al. Chest. 2011 Jan;139(1):28-35

Study or Subgroup	Omalizumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Busse 2001	39	268	60	257	15.5%	0.62 [0.43, 0.90]
Holgate 2004	13	126	15	120	4.8%	0.83 [0.41, 1.66]
Humbert 2005	35	246	55	236	14.2%	0.61 [0.42, 0.90]
Lanier 2009	56	384	59	192	18.9%	0.47 [0.34, 0.65]
Milgrom 2001	35	225	25	109	10.4%	0.68 [0.43, 1.07]
Ohta 2009	6	151	18	164	3.0%	0.36 [0.15, 0.89]
Soler 2001	35	274	83	272	16.0%	0.42 [0.29, 0.60]
Vignola 2004	43	209	59	196	17.2%	0.68 [0.49, 0.96]
Total (95% CI)		**1883**		**1546**	**100.0%**	**0.57 [0.48, 0.66]**
Total events	262		374			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.15$, $df = 7$ ($P = 0.32$); $I^2 = 14\%$

Test for overall effect: $Z = 7.06$ ($P < 0.00001$)

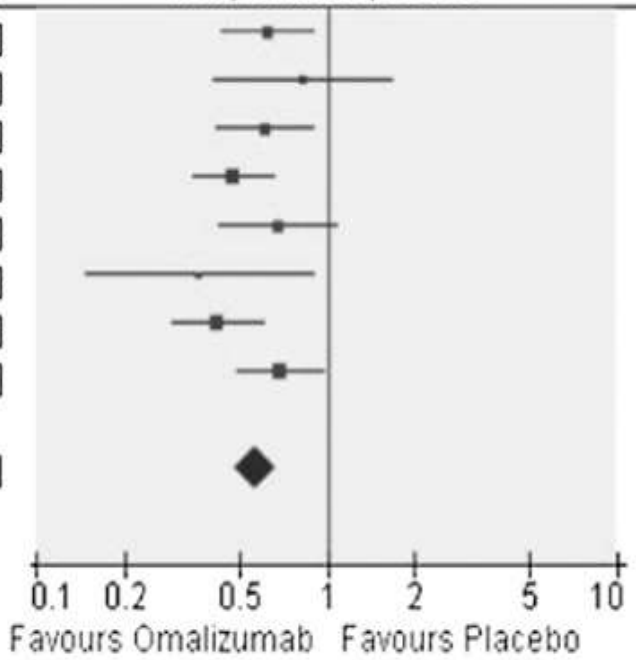

FIGURE 2. Pooled relative risk for the number of patients with at least one asthma exacerbation (with 95% CI) of eligible studies comparing omalizumab with placebo at the end of the stable-steroid phase. M-H = Mantel-Haenszel.

Rodrigo GJ. et al. Chest. 2011 Jan;139(1):28-35

Table 4—*Analysis of Secondary Outcomes (Omalizumab vs Placebo)*

Outcome	No.	Omalizumb vs Placebo	Measure (95% CI)	*P* Value	I^2, %
Rescue medication (stable phase),[11,23,25-27] puffs/d	2,285	2.27 vs 2.76[a]	WMD = −0.52 (−0.79 to 0.25)	.0002	40
Final pulmonary function (FEV_1 or PEF) (stable phase)[23-26,a]	1,651	3.82 vs 3.63[ab]	SMD = 0.07 (−0.03 to 017)[ab]	.15	0
Change from baseline in morning PEF (stable phase),[12,23,27] L/m	1,245	15.0 vs 3.05[a]	WMD = 11.8 (8.1-15.5)	.0001	0
Asthma symptom score (stable phase)[11,23,25-27]	1,893	1.53 vs 1.71[a]	WMD = −0.30 (−0.40 to 0.20)	.0001	13
Change in AQLQ score (stable phase)[23,25-28]	2,131	0.37 vs 0.06[a]	WMD = 0.33 (0.28-0.37)	.0001	53
Rescue medication (steroid-reduction phase),[23,25-26] puffs/d	1,291	2.27 vs 2.76[a]	WMD = −0.73 (−1.04 to 0.42)	.0001	0
Prematurely discontinued patients[11-12,23-28]	3,429	9.6% vs 12.5%	RR = 0.69 (0.50-0.97)	.03	60
Withdrawals due to adverse events[11-12,23-28]	3,429	1.3% vs 1.5%	RR = 0.97 (0.43-2.20)	.95	26
Any adverse effect[11-12,23-28]	3,429	84.9% vs 82.4%	RR = 1.01 (0.97-1.05)	.80	53
Serious adverse effects[11-12,23-28]	3,429	3.8% vs 5.3%	RR = 0.75 (0.52-1.10)	.14	17
Treatment-related adverse effects[11-12,24,27-28]	2,112	5.0% vs 3.2%	RR = 1.61 (1.05-2.47)	.03	0
Urticaria[12,23-28]	2,853	2.5% vs 2.1%	RR = 1.11 (0.53-2.32)	.79	34
Injection site reactions[12,23-28]	2,853	19.9% vs 13.2%	RR = 1.43 (1.15-1.79)	.002	37
Anaphylactic reactions[11,28]	995	0.33% vs 0.24%	RR = 1.08 (0.13-8.74)	.94	0

AQLQ = Asthma Quality of Life Questionnaire; PEF = peak expiratory flow; SMD = standardized mean difference; WMD = weighted mean difference. See Table 3 for expansion of other abbreviation.

[a]Mean value.

[b]Expressed in SD units.

Rodrigo GJ. et al. Chest. 2011 Jan;139(1):28-35

Omalizumab

- Randomized trial included 328 patients with normal lung function aged 12 to 75 years with incompletely controlled atopic asthma despite inhaled glucocorticoids
- Primary endpoint: Reduction in the rate of asthma exacerbations during the six-month treatment period
- Although exacerbation rate was reduced in omalizumab group compared with placebo, difference was not statistically significant in group as a whole, and thus primary endpoint was not met
- However, in high eosinophil group, exacerbation rate was reduced by 45 percent (0.4 to 0.22 exacerbations/patient during treatment period [95% CI 0.25-1.22])

Busse W. et al. J Allergy Clin Immunol 2013; 132:485

A Proof-of-Concept, Randomized, Controlled Trial of Omalizumab in Patients With Severe, Difficult-to-Control, Nonatopic Asthma

Gilles Garcia MD, PhD [a, b, c], Antoine Magnan MD, PhD [d, e, f], Raphaël Chiron MD [g], Cécile Contin-Bordes MD, PhD [h, i, j], Patrick Berger MD, PhD [j, k, l], Camille Taillé MD, PhD [n, o], Gilles Devouassoux MD, PhD [p], Frédéric de Blay MD, PhD [q, s], Louis-Jean Couderc MD, PhD [r], Alain Didier MD, PhD [t], Dermot S. O'Callaghan MD [a, b, c], Pierre-Olivier Girodet MD, PhD [k, u], Isabelle Bourdeix PhD [v], Vincent Le Gros MD [v], Marc Humbert MD, PhD [a, b, c]

- Patients with nonallergic asthma also have local IgE synthesis in airways
- Omalizumab may be beneficial in these patients
- Proof-of-concept pilot study, 41 patients with refractory nonallergic asthma
- Reduction in expression in Fc-epsilon-RI on basophils and significant improvement in FEV1 after 16 weeks of therapy, as well as a trend towards reduction in exacerbations

Garcia G. et al. Chest 2013; 144:411

Omalizumab

- 2014 systematic review included 25 randomized trials of patients with moderate or severe asthma receiving inhaled glucocorticoids, to which subcutaneous omalizumab was added
- Most of the studies involved patients with moderate asthma
- Addition of omalizumab had following effects:
  - Reduced risk of experiencing an exacerbation from 26 to 16 percent over 16 to 60 weeks of treatment
  - Reduced risk of hospitalization for asthma from 3 to 0.5 percent over 28 to 60 weeks
  - Allowed for small but significant reduction in inhaled glucocorticoid dose (weighted mean difference [WMD] -118 mcg beclomethasone dipropionate equivalent per day [95% CI -154 to -84])

Normansell R. et. al. Cochrane Database Syst Rev 2014; CD003559

Omalizumab Indications

- Six years of age and older
- Moderate-to-severe persistent asthma (in the United States)
- Asthma symptoms inadequately controlled with inhaled glucocorticoids (in the United Kingdom, patients must have symptoms despite high doses of inhaled glucocorticoids)
- Total serum IgE level between 30 and 700 (1500 in Europe) international units/mL, which is the range over which the drug can reduce enough free IgE to ensure a therapeutic effect
- Allergic sensitization demonstrated by positive skin testing or in vitro testing for allergen-specific IgE to an allergen that is present year round (a perennial allergen), such as dust mites, animal danders, cockroach, or molds
- 2007 National Asthma Education and Prevention Program (NAEPP) asthma guidelines recommended: omalizumab be considered as adjunctive therapy in step 5 or 6 care for patients with allergies and severe persistent asthma

Anti-IL-2R antibody

- Activation of type 2 helper T lymphocyte (Th2) cells by allergen leads to production of interleukin (IL)-2 and its receptor IL-2R
- Binding of IL-2 to Th2 cells expressing IL-2R leads to proliferation of that clone of specifically sensitized Th2 cells
- Humanized monoclonal antibody to CD25 subunit of IL-2R, daclizumab, inhibits various T cell functions, including T cell proliferation and cytokine production
- Randomized, double-blinded, placebo-controlled
- Moderate to severe persistent asthma

Am J Respir Crit Care Med. 2008;178(10):1002. Epub 2008 Sep 11

Daclizumab

- Examined in a study of 115 patients randomly assigned (3:1) to intravenous daclizumab every two weeks or placebo for 12 weeks
- Daclizumab improved FEV(1) (daclizumab, 4.4 +/- 1.80% vs. placebo, 1.5 +/- 2.39%; P = 0.05), and reduced daytime asthma symptoms (P = 0.018) and short-acting inhaled beta(2)-agonist use (P = 0.009)
- Daclizumab treatment prolonged time to exacerbation (P = 0.024)
- Associated with small improvements in pulmonary function and asthma control
- Potential risks of suppression of IL-2 pathway may limit utility of this type of immunosuppression in asthma

Am J Respir Crit Care Med. 2008;178(10):1002. Epub 2008 Sep 11

Anti-IL-5 monoclonal antibodies

- Potent effect of IL-5 on eosinophil recruitment to airways
- Anti-IL-5 monoclonal antibodies, mepolizumab and reslizumab, have been approved by US Food and Drug Administration for maintenance treatment of severe

A Study to Evaluate Safety and Efficacy of Mepolizumab in Patients with Moderate Persistent Asthma

Patrick Flood-Page[1], Cheri Swenson[2], Isidore Faiferman[3], John Matthews[3], Michael Williams[3], Lesley Brannick[3], Douglas Robinson[4], Sally Wenzel[5], William Busse[2], Trevor T. Hansel[4], and Neil C. Barnes[6], on behalf of the International Mepolizumab Study Group*

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- 362 patients with asthma experiencing persistent symptoms despite ICS (400-1,000 mcg of beclomethasone or equivalent)
- Three 'monthly' IV infusions of Mepolizumab 250mg or 750mg vs placebo
- Follow-up: Till 8wks after last infusion
- Associated with a significant reduction in blood and sputum eosinophils in both treatment groups
- No statistically significant changes in any of clinical end points measured

Flood-Page P. et. al. Am J Respir Crit Care Med. 2007;176:1062e1071

Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma

Pranabashis Haldar, M.R.C.P., Christopher E. Brightling, Ph.D., F.R.C.P., Beverley Hargadon, R.G.N., Sumit Gupta, M.R.C.P., William Monteiro, M.Sc., Ana Sousa, Ph.D., Richard P. Marshall, Ph.D., M.R.C.P., Peter Bradding, D.M., F.R.C.P., Ruth H. Green, M.D., F.R.C.P., Andrew J. Wardlaw, Ph.D., F.R.C.P., and Ian D. Pavord, D.M., F.R.C.P.

- Randomized, double-blind, placebo-controlled, parallel-group study
- 61 subjects who had **refractory eosinophilic asthma and a history of recurrent severe exacerbations**
- Inclusion criteria:
  - Diagnosis of refractory asthma according to ATS criteria
  - Sputum eosinophil more than 3% on at least one occasion in the previous 2 years despite highdose corticosteroid Rx, and
  - At least two exacerbations requiring rescue prednisolone in the previous 12 months

Haldar P. et al. N Engl J Med 2009;360:973-84

Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma

Pranabashis Haldar, M.R.C.P., Christopher E. Brightling, Ph.D., F.R.C.P., Beverley Hargadon, R.G.N., Sumit Gupta, M.R.C.P., William Monteiro, M.Sc., Ana Sousa, Ph.D., Richard P. Marshall, Ph.D., M.R.C.P., Peter Bradding, D.M., F.R.C.P., Ruth H. Green, M.D., F.R.C.P., Andrew J. Wardlaw, Ph.D., F.R.C.P., and Ian D. Pavord, D.M., F.R.C.P.

- 12 infusions (monthly) of either 750 mg of IV mepolizumab or matched placebo
- Background asthma medications not changed during study
- Mepolizumab was associated with significantly fewer severe exacerbations than placebo over 50 weeks (2.0 vs. 3.4 mean exacerbations per subject; RR, 0.57; 95% CI, 0.32 to 0.92; P = 0.02)
- Exacerbations by approximately 48% compared with placebo, with modest effect on asthma quality of life, accompanied by marked decrease in blood and sputum eosinophil counts

Haldar P. et al. N Engl J Med 2009;360:973-84

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

Parameswaran Nair, M.D., Ph.D., Marcia M.M. Pizzichini, M.D., Ph.D., Melanie Kjarsgaard, R.R.T., Mark D. Inman, M.D., Ph.D., Ann Efthimiadis, M.L.T., Emilio Pizzichini, M.D., Ph.D., Frederick E. Hargreave, M.D., and Paul M. O'Byrne, M.B.

- Smaller study of systemic corticosteroid–dependent patients
- Randomized, double-blind, parallel-group trial
- Enrolled 20 patients with persistent sputum eosinophilia (>3%) and symptoms despite steroid Rx (Prednisone 5-25mg and ICS 600-2000mcg fluticasone for 4 wks). (<3% of 800 patients from asthma clinics)
- 9 patients were assigned to receive mepolizumab (5 monthly infusions of 750 mg each) and 11 patients to receive placebo. (2 patients without sputum eosinophilia were included by error)

Nair P. et al. N Engl J Med 2009;360:985-93

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

Parameswaran Nair, M.D., Ph.D., Marcia M.M. Pizzichini, M.D., Ph.D.,
Melanie Kjarsgaard, R.R.T., Mark D. Inman, M.D., Ph.D.,
Ann Efthimiadis, M.L.T., Emilio Pizzichini, M.D., Ph.D.,
Frederick E. Hargreave, M.D., and Paul M. O'Byrne, M.B.

- Prednisone tapered to 2.5-5mg between 6-22wks
- Follow-up: 8wks after last infusion
- 12 asthma exacerbations in 10 patients who received placebo, 9 of whom had sputum eosinophilia at time of exacerbation
- Only one patient who received mepolizumab had an asthma exacerbation, and this episode was not associated with sputum eosinophilia ($P = 0.002$)
- Mepolizumab was associated with significant reductions in OCS dose compared with placebo and baseline, small improvements in symptoms, and reductions in sputum eosinophil counts

Nair P. et al. N Engl J Med 2009;360:985-93

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial

Prof Ian D Pavord DM [a] ✉, Stephanie Korn MD [b], Peter Howarth DM [c], Prof Eugene R Bleecker MD [d], Prof Roland Buhl MD [b], Oliver N Keene MSc [e], Hector Ortega MD [f], Pascal Chanez MD [g, h]

- Multicentre, double-blind, placebo-controlled trial
- Patients with history of recurrent severe asthma exacerbations, receiving high-dose ICS/LABA treatment
- And evidence of eosinophilic inflammation as shown by one or more criteria at study entry or in the previous year:
  - Sputum eosinophil count of 3% or more
  - Exhaled nitric oxide concentration (FENO) of 50 ppb or more
  - Asthma-related peripheral blood eosinophil count of $0{\cdot}3\times10^9$ per L or more

Pavord ID. et al. Lancet 2012;380:651-9

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial

Prof Ian D Pavord DM [a] ✉, Stephanie Korn MD [b], Peter Howarth DM [c], Prof Eugene R Bleecker MD [d], Prof Roland Buhl MD [b], Oliver N Keene MSc [e], Hector Ortega MD [f], Pascal Chanez MD [g, h]

- 621 patients randomised: 159 were assigned to placebo, 154 to 75 mg mepolizumab, 152 to 250 mg mepolizumab, and 156 to 750 mg mepolizumab (13 infusions at 4-weekly intervals)
- Three different doses of mepolizumab were equally effective in decreasing clinically significant asthma exacerbations compared with placebo, with the greatest reductions seen in those with the highest blood eosinophil counts and greatest prior exacerbation history
- Identified blood eosinophil counts of 300/mL or greater as a highly predictive biomarker of treatment response
- No effect on other asthma outcomes, including symptoms and FEV1

Pavord ID. et al. Lancet 2012;380:651-9

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez M.D., Ph.D., for the MENSA Investigators*

- Randomized, double-blind, double-dummy study
- Assigned 576 patients with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high doses of inhaled glucocorticoids to one of three study groups
- 75-mg intravenous dose or a 100-mg subcutaneous dose, or placebo every 4 weeks for 32 weeks
- Rate of exacerbations was reduced by 47% (95% CI, 28 to 60) among patients receiving IV mepolizumab and by 53% (95% CI, 36 to 65) among those receiving SC mepolizumab, as compared with those receiving placebo ($P<0.001$ for both)
- Increased FEV1 and modestly affected symptom and ACQ-5 scores compared with placebo

Ortega HG et al. N Engl J Med 2014;371:1198-207

Mepolizumab

- Mepolizumab studied in patients with systemic corticosteroid–dependent severe asthma, generally of late onset with persistent blood eosinophilia
- Subcutaneous mepolizumab for 20 weeks more effective than placebo in decreasing daily corticosteroid doses
- In patients with very severe eosinophilic asthma, mepolizumab improved asthma control and quality of life and marginally improved FEV1, despite decreased OCS use
- Forty percent of mepolizumab-treated patients reduced their OCS dose by greater than 75%

Bel EH et al. N Engl J Med 2014;371:1189-97

Subcutaneous mepolizumab compared to placebo for asthma

Patient or population: adults with severe eosinophilic asthma
Settings: community
Intervention: subcutaneous (SC) mepolizumab
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	SC mepolizumab				
Change in HRQoL assessed with SGRQ. Scale from: 0 to 100 (lower is better) Follow-up: 32 weeks	The mean HRQoL was −9.0 units	The mean HRQoL - SGRQ in the intervention group was 7 units fewer (10.19 fewer to 3.81 fewer)	-	385 (1 RCT)	⊕⊕⊕◯ moderate[a]	
Rate of exacerbations requiring admission Follow-up: 32 weeks	The mean rate of exacerbations requiring admission on placebo was 0.10 per patient per year	The mean rate of exacerbations requiring ED visit or admission in the intervention group was 0.07 less per patient per year (0.01 less to 0.09 less)	Rate ratio 0.31 (0.11 to 0.91)	385 (1 RCT)	⊕⊕⊕◯ moderate[a]	
Rate of exacerbations requiring ED or admission Follow-up: 32 weeks	The mean rate of exacerbations requiring ED or admission on placebo was 0.20 per patient per year	The mean rate of exacerbations requiring ED or admission in the intervention group was 0.12 less per patient per year (0.03 less to 0.16 less)	Rate ratio 0.39 (0.18 to 0.83)	385 (1 RCT)	⊕⊕⊕◯ moderate[a]	

Powell C. et. Al. Cochrane Database of Systematic Reviews 2015, Issue 7

Rate of clinically significant exacerbations Follow-up: 32 weeks	The mean rate of clinically significant exacerbations on placebo was 1.75 per patient per year	The mean rate of clinically significant exacerbations in the intervention group was 0.93 less per patient per year (0.65 less to 1. 14 less)	Rate ratio 0.47 (0.35 to 0.63)	385 (1 RCT)	⊕⊕⊕◯ moderate[a]
Asthma symptoms measured on Asthma Control Questionnaire Scale from: 0 to 6 (lower is better)[b] Follow-up: 32 weeks	The mean change in asthma symptoms was –0.5 units	The mean asthma symptoms in the intervention group was 0.44 units fewer (0.64 fewer to 0.24 fewer)	-	385 (1 RCT)	⊕⊕⊕◯ low[a,c]

*The basis for the **assumed risk** was the event rate in the placebo arm of the single included study. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **ED**: emergency department; **HRQoL**: health-related quality of life; **RCT**: randomised controlled trial; **SC**: subcutaneous; **SGRQ**: St George's Respiratory Questionnaire.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Powell C. et.Al. Cochrane Database of Systematic Reviews 2015, Issue 7

Reslizumab

- Anti–IL-5 antibody reslizumab studied in patients with poorly controlled asthma taking high-dose ICSs and additional controllers with persistent sputum eosinophils (>3% on 2 occasions)
- Like mepolizumab, intravenous reslizumab decreased both blood and sputum eosinophil counts
- Marginal increases in FEV1 and ACQ scores compared with placebo

CHEST

Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels

A Randomized Phase 3 Study

Leif Bjermer, MD; Catherine Lemiere, MD; Jorge Maspero, MD; Sivan Weiss, MSc; James Zangrilli, MD; and Matthew Germinaro, MD

- Randomized, double-blind, placebo-controlled, parallel-group, fixed-dosage, phase 3 trial
- Randomized to receive reslizumab 0.3 or 3.0 mg/kg or placebo administered once every 4 weeks for 16 weeks (total four doses)
- Reslizumab significantly improved FEV1 (difference vs placebo [reslizumab 0.3 and 3.0 mg/kg], 115 mL [95% CI, 16-215; P= .0237] and 160 mL [95% CI, 60-259; P= .0018])
- Clinically meaningful increases in FVC (130 mL) and FEF25%-75% (233 mL/s) were observed with reslizumab 3.0 mg/kg

CHEST

Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels

A Randomized Phase 3 Study

Leif Bjermer, MD; Catherine Lemiere, MD; Jorge Maspero, MD; Sivan Weiss, MSc; James Zangrilli, MD; and Matthew Germinaro, MD

- Reslizumab improved scores on the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) vs placebo (greater effects seen with 3.0 mg/kg; $P < .05$)
- Scores on Asthma Symptom Utility Index and SABA use improved with reslizumab
- Most common adverse events were worsening of asthma, headache, and nasopharyngitis; most were mild to moderate in severity

CHEST

Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma

Effects Across a Broad Range of Eosinophil Counts

Jonathan Corren, MD; Steven Weinstein, MD; Lindsay Janka, MS; James Zangrilli, MD; and Margaret Garin, MD

- Randomized, double-blind, placebo-controlled, phase 3
- Randomly assigned to intravenous reslizumab 3.0 mg/kg or placebo once every 4 weeks for 16 weeks
- Four hundred ninety-two patients received1 dose of placebo (n= 97) or reslizumab (n= 395)
- Mean FEV1 change from baseline to week 16 not significantly different between reslizumab and placebo, and no significant relationship detected between treatment, baseline blood eosinophils and change in FEV1

CHEST

Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma

Effects Across a Broad Range of Eosinophil Counts

Jonathan Corren, MD; Steven Weinstein, MD; Lindsay Janka, MS; James Zangrilli, MD; and Margaret Garin, MD

- Subgroup of patients with baseline eosinophils < 400 cells/mL, patients treated with reslizumab showed no significant improvement in FEV1 compared with those receiving placebo
- Subgroup with eosinophils more than 400 cells/mL, however, treatment with reslizumab was associated with much larger improvements in FEV1, ACQ-7, rescue SABA use, and FVC compared with the placebo group
- Reslizumab was well tolerated, with fewer overall adverse events compared with placebo (55% vs 73%)

Reslizumab in Eosinophilic Asthma: A Review

Table 1 Efficacy of intravenous reslizumab (3 mg/kg once every 4 weeks) in reducing asthma exacerbations when added to background therapy in patients aged 12–75 years with eosinophilic asthma in two 52-week phase III trials and their pooled analysis [8]

Trial	Treatment (pt no.)	Number of clinical asthma exacerbations per pt per year (rate ratio vs. placebo; 95% CI)		
		All[a]	Requiring systemic CS for ≥3 days	Requiring hospitalization or ER visit
Study 3082	Reslizumab (245)	0.90 (0.5; 0.37–0.67)*	0.72 (0.45; 0.33–0.62)*	0.14 (0.66; 0.32–1.36)
	Placebo (244)	1.80	1.60	0.21
Study 3083	Reslizumab (232)	0.86 (0.41; 0.28–0.59)*	0.65 (0.39; 0.26–0.58)*	0.03 (0.69; 0.29–1.65)
	Placebo (232)	2.11	1.66	0.05
Pooled analysis				
Overall population	Reslizumab (477)	0.84 (0.46; 0.37–0.58)*	0.66 (0.43; 0.33–0.55)*	0.08 (0.66; 0.38–1.16)
	Placebo (476)	1.81	1.54	0.12
Severe asthma subgroup[b]	Reslizumab (383)	0.85 (NR)[c]		
	Placebo (380)	1.95		

All asthma exacerbations were adjudicated by an independent review committee

E. D. Deeks, G. Brusselle. Springer International Publishing Switzerland 2017

Reslizumab in Eosinophilic Asthma: A Review

Table 2 Efficacy of intravenous reslizumab (3 mg/kg every 4 weeks) in improving lung function, when added to background therapy, in patients aged 12–75 years with eosinophilic asthma in three phase III trials and a pooled analysis

Trial	Treatment [no. of pts]	Mean FEV_1 at BL [L]	Mean change from BL in FEV_1 [L] (difference vs. placebo; 95% CI)	
			Over 16 weeks	Over 52 weeks
Study 3081 [9][a]	Reslizumab (106)	2.19	0.29 (0.16; 0.06, 0.26)*[b]	
	Placebo (105)	2.22	0.13[b]	
Study 3082 [8]	Reslizumab (245)	1.89	0.25 (0.14; 0.08, 0.198)**	0.24 (0.13; 0.06, 0.19)**
	Placebo (244)	1.93	0.11	0.11
Study 3083 [8]	Reslizumab (232)	2.13	0.19 (0.09; 0.003, 0.155)*	0.20 (0.09; 0.003, 0.153)*
	Placebo (232)	2.00	0.09	0.11
Pooled (3082 + 3083) [8]	Reslizumab (477)	NR	0.23 (0.12; 0.07, 0.16)**	0.22 (0.11; 0.07, 0.15)**
	Placebo (476)	NR	0.11	0.12

BL baseline, *FEV_1* forced expiratory volume in 1 s, *NR* not reported, *pts* patients

* $p < 0.01$, ** $p < 0.0001$ vs. placebo

[a] This study also contained a reslizumab 0.3 mg/kg q4w arm ($n = 104$)

[b] Primary endpoint

E. D. Deeks, G. Brusselle. Springer International Publishing Switzerland 2017

Reslizumab in Eosinophilic Asthma: A Review

- Indicated in EU as an add-on therapy for adults with severe eosinophilic asthma inadequately controlled despite high-dose inhaled CS plus another medication for maintenance treatment
- In USA as an add-on maintenance treatment for adults (aged C18 years) with severe asthma with an eosinophilic phenotype
- Recommended dosage is 3 mg/kg administered q4w via intravenous infusion (over 20–50 min)
- approved for the treatment of severe eosinophilic asthma on the basis of the BREATH phase III trial programme
- Recommended as an add-on treatment for severe eosinophilic asthma in most recent Global Initiative for Asthma guidelines

E. D. Deeks, G. Brusselle. Springer International Publishing Switzerland 2017

Anti-IL-5 receptor alpha antibodies

- Block activation of eosinophils by IL-5
- Afucosylated anti-IL-5 receptor alpha antibody, benralizumab, depletes IL-5 receptor-bearing cells (eosinophils and basophils) via enhanced antibody-dependent cellular cytotoxicity
- Two multicenter trials demonstrated a reduction in exacerbation rates when benralizumab was given to patients with moderate or severe asthma

Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial

Eugene R Bleecker, J Mark FitzGerald, Pascal Chanez, Alberto Papi, Steven F Weinstein, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Magnus Aurivillius, Viktoria Werkström, Mitchell Goldman, on behalf of the SIROCCO study investigators*

- 1205 adolescent and adult patients with severe asthma and at least two exacerbations in prior year while taking high-dose inhaled glucocorticoids and long-acting beta agonist were randomly assigned to
  - Benralizumab 30 mg every four weeks
  - Benralizumab 30 mg every eight weeks (after 30 mg every four weeks for three doses), or
  - Placebo every four weeks, given subcutaneously for 48 weeks

Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial

*Eugene R Bleecker, J Mark FitzGerald, Pascal Chanez, Alberto Papi, Steven F Weinstein, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Magnus Aurivillius, Viktoria Werkström, Mitchell Goldman, on behalf of the SIROCCO study investigators**

- Peripheral blood eosinophil count ≥300 cells/microL, benralizumab reduced the exacerbation rate in the every four and every eight week groups (rate ratio [RR] 0.55, 95% CI 0.42-0.71, and RR 0.49, 95% CI 0.37-0.64, respectively)
- Improved prebronchodilator FEV and the every eight week regimen reduced asthma symptom scores

Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial

*J Mark FitzGerald, Eugene R Bleecker, Parameswaran Nair, Stephanie Korn, Ken Ohta, Marek Lommatzsch, Gary T Ferguson, William W Busse, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Viktoria Werkström, Magnus Aurivillius, Mitchell Goldman, on behalf of the CALIMA study investigators**

- 1306 adolescent and adult patients with moderate or severe asthma and at least two exacerbations in prior year while taking medium or high-dose inhaled glucocorticoids and a long-acting beta agonist were randomly assigned to
  - Benralizumab 30 mg every four weeks,
  - Benralizumab 30 mg every eight weeks (after 30 mg every four weeks for three doses), or
  - Placebo every four weeks,
  - Given subcutaneously for 60 weeks

Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial

*J Mark FitzGerald, Eugene R Bleecker, Parameswaran Nair, Stephanie Korn, Ken Ohta, Marek Lommatzsch, Gary T Ferguson, William W Busse, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Viktoria Werkström, Magnus Aurivillius, Mitchell Goldman, on behalf of the CALIMA study investigators**

- Annual exacerbation rate was decreased in the every four week benralizumab group (RR 0.64, 95% CI 0.49-0.85) and the every eight week group (RR 0.72 [95% CI 0.54-0.95)
- For those with lower eosinophil counts, the reduction in exacerbations only reached significance with the every eight week dosing regimen
- A/E: Nasopharyngitis and worsening asthma control

ORIGINAL ARTICLE

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

Parameswaran Nair, M.D., Ph.D., Sally Wenzel, M.D., Klaus F. Rabe, M.D., Ph.D., Arnaud Bourdin, M.D., Ph.D., Njira L. Lugogo, M.D., Piotr Kuna, M.D., Ph.D., Peter Barker, Ph.D., Stephanie Sproule, M.Math., Sandhia Ponnarambil, M.D., and Mitchell Goldman, M.D., for the ZONDA Trial Investigators*

N Engl J Med 2017; 376:2448-2458 | June 22, 2017 | DOI: 10.1056/NEJMoa1703501

- 28 week multicenter trial
- 220 patients with severe asthma
- Who had ≥150 eosinophils/mL in peripheral blood and required daily oral glucocorticoids for the previous six months were randomly assigned to one of three treatment arms:
  - Benralizumab 30 mg subcutaneously every four weeks,
  - Benralizumab 30 mg every four weeks for the first three doses then every eight weeks, or
  - Placebo every four weeks

ORIGINAL ARTICLE

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

Parameswaran Nair, M.D., Ph.D., Sally Wenzel, M.D., Klaus F. Rabe, M.D., Ph.D., Arnaud Bourdin, M.D., Ph.D., Njira L. Lugogo, M.D., Piotr Kuna, M.D., Ph.D., Peter Barker, Ph.D., Stephanie Sproule, M.Math., Sandhia Ponnarambil, M.D., and Mitchell Goldman, M.D., for the ZONDA Trial Investigators*

N Engl J Med 2017; 376:2448-2458 | June 22, 2017 | DOI: 10.1056/NEJMoa1703501

- Four weeks after first study dose, oral glucocorticoid dose was reduced according to a predetermined program (2.5 to 5 mg every four weeks)
- At end of 28 weeks, oral glucocorticoid dose decreased by 75 percent from baseline in two benralizumab groups, compared with 25 percent in placebo group
- Odds of reduction in oral glucocorticoid dose with benralizumab every four weeks were 4.09 times (95% CI 2.22-7.57) that of placebo
- Annualized exacerbation rates were lower with benralizumab; marginal rates were 0.83 for benralizumab every four weeks, 0.54 for benralizumab every eight weeks, and 1.83 for placebo
- FEV was not significantly different between groups at 28 weeks

Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial

*Gary T Ferguson, J Mark FitzGerald, Eugene R Bleecker, Michel Laviolette, David Bernstein, Craig LaForce, Lyndon Mansfield, Peter Barker, Yanping Wu, Maria Jison, Mitchell Goldman, on behalf of the BISE Study Investigators**

- To assess safety and efficacy for patients with mild to moderate, persistent asthma
- Randomised, double-blind, placebo-controlled, phase 3 trial
- Receive subcutaneous placebo or benralizumab 30 mg injections every 4 weeks for12 weeks
- Included:
  - Post BDR in FEV1 of at least 12 %
  - Receiving low to medium dose ICS or low dose ICS with LABA
  - Morning pre BDR FEV1 of more than 50-90 % predicted
  - One or more of the following symptoms within 7 days before randomisation: a daytime or night-time asthma symptom score of at least 1 for at least 2 days, rescue short-acting β2 agonist use for at least 2 days, or night-time awakenings due to asthma for at least one night

Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial

*Gary T Ferguson, J Mark FitzGerald, Eugene R Bleecker, Michel Laviolette, David Bernstein, Craig LaForce, Lyndon Mansfield, Peter Barker, Yanping Wu, Maria Jison, Mitchell Goldman, on behalf of the BISE Study Investigators**

- Resulted in an 80 mL (95% CI 0–150; p=0.04) greater improvement in prebronchodilator FEV1 after 12 weeks than did placebo (placebo group: 2246 mL [SD 768] at baseline vs 2261 mL [796] at week 12, change from baseline of 0 mL; benralizumab group: 2248 mL [606] vs 2310 mL [670], 70 mL)
- 44 (42%) patients in benralizumab group had adverse events compared with 49 (47%) in placebo
- Most common adverse events for both groups were nasopharyngitis (eight [8%] patients in each group) and upper respiratory tract infections (five [5%] patients in each group)

Anti-IL-13 antibodies

- IL-13 promotes IgE production by B cells, generation of eosinophil chemoattractants, and contractility of airway smooth muscle cells
- Potential target for asthma therapy
- Preliminary clinical studies have not documented benefit to anti-IL-13 monoclonal antibodies
- **IMA-638 and IMA-026:** fully humanized IgG antibodies that bind to different epitopes and neutralize IL-13 bioactivity

Gauvreau GM. et. al. Am J Respir Crit Care Med 2011;183:1007-14

Anti-IL-13 antibodies

- 2 double-blind, randomized, placebo-controlled, parallel group trials
- Fifty-six subjects with mild, atopic asthma were recruited to compare IMA-638 and IMA-026 IL-13 antibody treatments with placebo treatment
- Drug was administered on Days 1 and 8, and allergen challenges were performed on Days 14 and 35
- Primary outcome variable: Late-phase area under the curve (AUC)
- Secondary outcome variables: Early- and late-phase maximum % fall in FEV, early AUC, allergen-induced shift in airway hyperresponsiveness, and sputum eosinophils

Gauvreau GM. et. al. Am J Respir Crit Care Med 2011;183:1007-14

Anti-IL-13 antibodies

- The treatment difference with IMA-638 on Day 14 was −19.1FEV × hour (95% confidence interval: −36.2, −1.9) for the allergen-induced early AUC and −23.8
- FEV × hour (95% confidence interval: −46.4, −1.2) for the late AUC (both *P < 0.05), but this effect* was lost by Day 35
- Treatment with IMA-026 did not attenuate the asthmatic responses on Day 14 or Day 35
- There was no effect of either antibody on allergen-induced airway hyperresponsiveness or sputum eosinophils
- The frequency of adverse events after administration of the IL-13 antibodies was similar to placebo

Gauvreau GM. et. al. Am J Respir Crit Care Med 2011;183:1007-14

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE N ENGL J MED 365;12 NEJM.ORG SEPTEMBER 22, 2011

Lebrikizumab Treatment in Adults with Asthma

Jonathan Corren, M.D., Robert F. Lemanske, Jr., M.D., Nicola A. Hanania, M.D., Phillip E. Korenblat, M.D., Merdad V. Parsey, M.D., Ph.D., Joseph R. Arron, M.D., Ph.D., Jeffrey M. Harris, M.D., Ph.D., Heleen Scheerens, Ph.D., Lawren C. Wu, Ph.D., Zheng Su, Ph.D., Sofia Mosesova, Ph.D., Mark D. Eisner, M.D., M.P.H., Sean P. Bohen, M.D., Ph.D., and John G. Matthews, M.B., B.S., Ph.D.

- Compared with placebo in 219 subjects with asthma that was inadequately controlled at baseline by medium-to-high dose of inhaled glucocorticoids
- At 12 weeks, subjects who received lebrikizumab had significant increase in FEV (mean 5.5 percent); however, the improvement in FEV was no longer significant at 24 weeks
- Subgroup analysis found that subjects with high initial peripheral blood periostin levels (an indirect measure of baseline IL-13 activity) had a greater response to lebrikizumab than the low-periostin group

Corren J. et. al. N Engl J Med 2011;365:1088-98

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lebrikizumab Treatment in Adults with Asthma

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- More marked improvement in FEV1 (8.2%) compared with those receiving placebo (with a tendency toward decrease exacerbations), whereas those with low levels had no improvement
- High FENO levels (by median split) also predicted a responsive phenotype, whereas high levels of both markers were even more predictive of an FEV1 response
- No differences in asthma exacerbations, symptom scores, or beta agonist rescue use were noted over the 24 weeks of the trial

Corren J. et. al. N Engl J Med 2011;365:1088-98

Journal of Allergy and Clinical Immunology
Volume 132, Issue 3, September 2013, Pages 567-574.e12

Asthma and lower airway disease

Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids

Michael Noonan MD [a], Phillip Korenblat MD [b], Sofia Mosesova PhD [c], Heleen Scheerens PhD [c], Joseph R. Arron MD, PhD [c], Yanan Zheng PhD [c], Wendy S. Putnam PhD [c], Merdad V. Parsey MD, PhD [d], Sean P. Bohen MD, PhD [c], John G. Matthews MB, BS, PhD [c]

- 212 patients with asthma, not taking inhaled glucocorticoids randomly assigned to receive lebrikizumab 125 mg, 250 mg, 500 mg, or placebo SC at monthly intervals for 12 weeks
- No significant improvement was noted in FEV1 at 12 weeks between dose groups or placebo, even after analysis of subgroup with high periostin levels
- In addition, albuterol usage and ACQ scores were not different between lebrikizumab and placebo
- While lebrikizumab protected against treatment failure compared with placebo, the effect was not greater than that expected with inhaled glucocorticoid therapy

Noonan M. et. al. J Allergy Clin Immunol Sept. 2013;132:567-74

FULL TEXT ARTICLE

Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials

Nicola A Hanania Dr, Phillip Korenblat Prof, Kenneth R Chapman Prof, Eric D Bateman Prof, Petr Kopecky MD, Pierluigi Paggiaro Prof, Akihito Yokoyama Prof, Julie Olsson MD, Sarah Gray PhD, Cecile T J Holweg PhD, Mark Eisner MD, Charles Asare MD, Saloumeh K Fischer PhD, Kun Peng PhD, Wendy S Putnam PhD and John G Matthews MB BS

Lancet Respiratory Medicine, The, 2016-10-01, Volume 4, Issue 10, Pages 781-796, Copyright © 2016 Elsevier Ltd

- Replicate, phase 3, randomised, double-blind, parallel, placebo controlled trials with a total of 2148 adults with uncontrolled asthma
- Lebrikizumab (37.5 mg or 125 mg) or placebo was administered subcutaneously every 4 weeks for 52 weeks
- Predetermined stratification by periostin and peripheral blood eosinophil levels
- The trials demonstrated inconsistent results in terms of a clinically meaningful reduction in exacerbations
- Six serious adverse events were reported: one case of aplastic anemia and five cases of increased peripheral blood eosinophil counts

Hanania NA. et. al. Lancet Respir Med 2016; 4:781-796

Tralokinumab

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma

Edward Piper, Christopher Brightling, Robert Niven, Chad Oh, Raffaella Faggioni, Kwai Poon, Dewei She, Chris Kell, Richard D. May, Gregory P. Geba, Nestor A. Molfino

European Respiratory Journal 2013 41: 330-338; **DOI:** 10.1183/09031936.00223411

Tralokinumab

- Investigational human IL-13-neutralising immunoglobulin G4 monoclonal antibody
- Phase IIa, randomised, double-blind, placebo-controlled, parallel-group, multicentre study
- 194 adults with moderate-to-severe uncontrolled asthma despite controller therapies
- Patients randomly assigned to receive tralokinumab (150, 300 or 600 mg) or placebo subcutaneously every 2 weeks for 13 weeks
- At week 13, change from baseline in ACQ-6 was -0.76±1.04 for tralokinumab *versus -0.61±0.90 for placebo (p=0.375)*

Piper E. et. al. Eur Respir J 2013;41:330-8

Tralokinumab

- Increases from baseline in forced expiratory volume in 1s (FEV1) were 0.21±0.38 L versus 0.06±0.48 L (p=0.072), with a dose-response observed across the tralokinumab doses tested
- β -agonist use (puffs per day) was decreased for tralokinumab -0.68±1.45 versus placebo -0.10±1.49 (p=0.020)
- Increase in FEV following tralokinumab treatment remained evident 12 weeks after final dose
- Safety profile was acceptable with no serious adverse events related to tralokinumab

Piper E. et. al. Eur Respir J 2013;41:330-8

Tralokinumab

- Randomized, double-blind, placebo-controlled, parallel-group, multicentre, phase 2b trial
- Patients with severe asthma with 2-6 exacerbations in previous year were randomly assigned (1:1) to one of the two dosing regimen groups:
  - Every 2 weeks or
  - Every 2 weeks for 12 weeks to receive Tralokinumab 300 mg or placebo for 1 year
- Primary endpoint was the annual asthma exacerbation rate (AAER) at week 52 in the intention-to treat-trial

Brightling CE.. et al. Lancet Respir Med 2015 Sep,3(9):692-701

Tralokinumab

- Secondary endpoints included the prebronchodilator FEV1, ACQ-6, and Asthma-quality of life questionnaire-standardized version (AQLQ[S])
- At week 52, percentage change in AAER were not significant with tralokinumab every 2 weeks or every 4 weeks versus placebo (6% [95 % CI -31 to 33; p=0.709] and -2%[-46 to 29; p=0.904], respectively)
- Though had acceptable safety and tolerability profile but did not significantly reduce asthma exacerbation rates in patients with uncontrolled asthma

Brightling CE.. et al. Lancet Respir Med 2015 Sep,3(9):692-701

Phase 3 trials: STRATOS 1 & 2

- Tralokinumab did not meet its primary endpoint of a significant reduction in the annual asthma exacerbation rate (AAER) in the overall population of severe, uncontrolled asthma patients despite ICS plus LABA, compared with placebo
- Clinically relevant in AAER was observed in a sub-population of patients with an elevated biomarker associated with incresed IL-13 activity
- The sub-group will be the focus for future analysis of STRATOS 2, which is ongoing with results expected in 2nd half of 2017

Pitrakinra & AMG 317

- Pitrakinra: mutant IL-4 molecule that blocks ability of human IL-4 or IL-13 to bind to IL-4Ra
- Nebulized pitrakinra for 4 weeks in patients with mild atopic asthma reduced late asthmatic response 3.7-fold compared with placebo
- Pitrakinra did not decrease induced asthma exacerbations compared with placebo when background medication was withdrawn in a population with moderate-to-severe asthma
- Study of humanized mAb to IL-4Ra (AMG 317) for 12 weeks had no effect on asthma outcomes, although it did reduce serum IgE levels, suggesting some biologic activity

Wenzel S. et al. Lancet 2007;370:1422-31
Corren J. et al. Am J Respir Crit Care Med 2010;181:788-96
Slager RE. et al. J Allergy Clin Immunol 2012;130:516-22.e4

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 27, 2013 VOL. 368 NO. 26

Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

Sally Wenzel, M.D., Linda Ford, M.D., David Pearlman, M.D., Sheldon Spector, M.D., Lawrence Sher, M.D., Franck Skobieranda, M.D., Lin Wang, Ph.D., Stephane Kirkesseli, M.D., Ross Rocklin, M.D., Brian Bock, D.O., Jennifer Hamilton, Ph.D., Jeffrey E. Ming, M.D., Ph.D., Allen Radin, M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Graham, M.D., and Gianluca Pirozzi, M.D., Ph.D.

Dupilumab

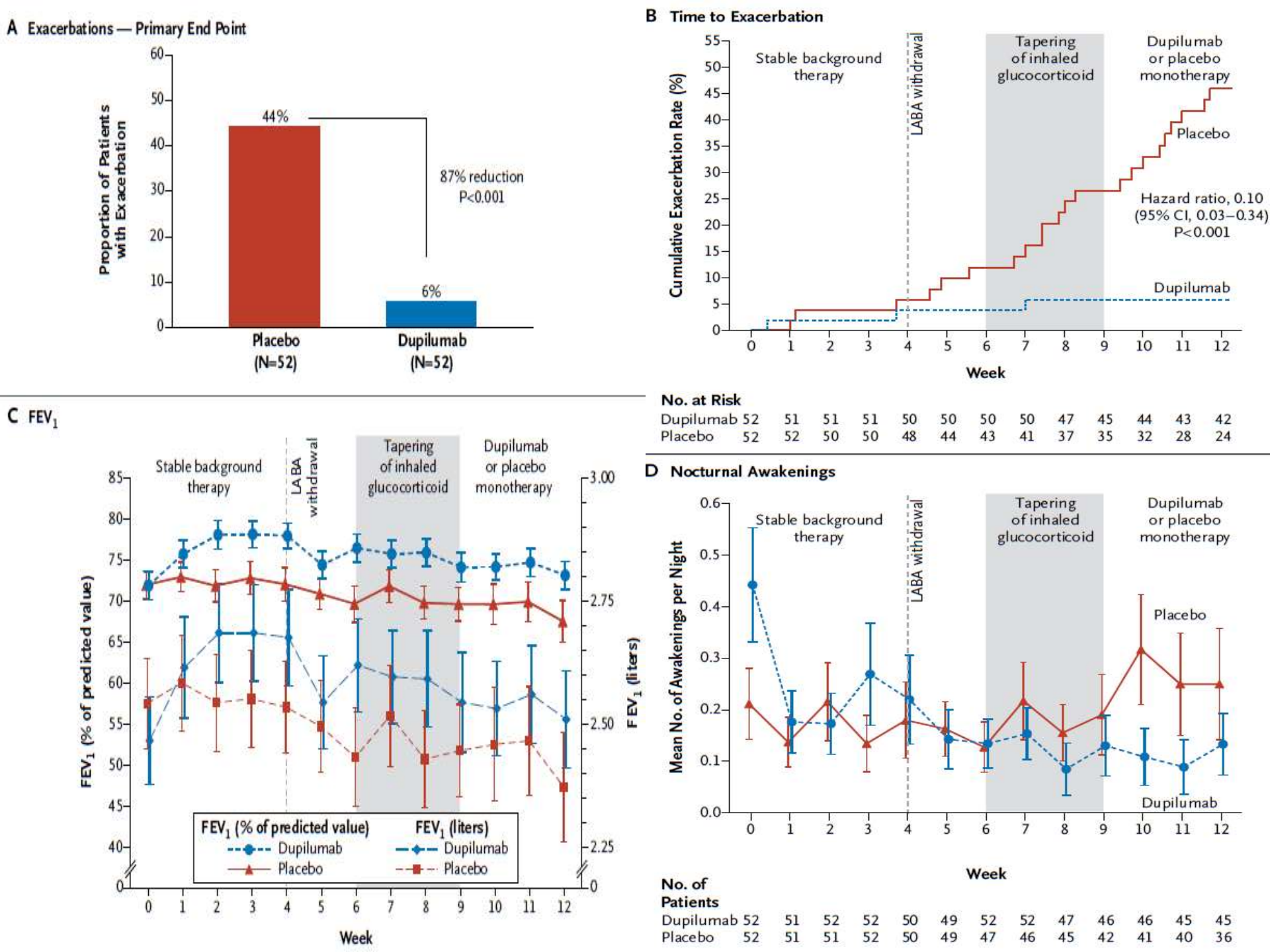
- Fully human monoclonal antibody, binds to alpha subunit of IL-4 receptor
- Inhibits downstream signaling of both IL-4 and IL-13
- Multicenter, phase 2 trial, 12-week study
- Adults with moderate-to-severe asthma→ Symptoms not well controlled with moderate- to high-dose ICS/LABA treatment (approximately 80% on high dose combination)
- Peripheral blood eosinophilia (≥300 cells/microL) or ≥3 percent sputum eosinophils
- Randomly assigned to once-weekly subcutaneous injections of dupilumab (300 mg) or placebo for 12 weeks

Wenzel S. et al. N Engl J Med 2013;368:2455-66

Dupilumab

- After fourth week, LABA discontinued and during weeks six to nine, inhaled glucocorticoids stopped
- Dupilumab associated with fewer "induced" asthma exacerbations (87% reduction compared with placebo, odds of an asthma exacerbation (OR 0.08, 95% CI 0.02-0.28; P<0.001) when LABAs and then ICSs were successively withdrawn
- Improved ACQ scores, symptoms, and FEV1 on top of combination ICS/LABA treatment even when background therapy was withdrawn
- Improvements in upper airway symptoms
- FENO, thymus and activation-regulated chemokine (CCL17), eoxtaxin-3 (Type 2 eosinophilic CC chemokine), and IgE levels decreased

Wenzel S. et al. N Engl J Med 2013;368:2455-66


A Exacerbations — Primary End Point
Proportion of Patients with Exacerbation
44%
6%
87% reduction
P<0.001
Placebo (N=52)
Dupilumab (N=52)
B Time to Exacerbation
Cumulative Exacerbation Rate (%)
Stable background therapy
LABA withdrawal
Tapering of inhaled glucocorticoid
Dupilumab or placebo monotherapy
Placebo
Dupilumab
Hazard ratio, 0.10
(95% CI, 0.03–0.34)
P<0.001
Week
No. at Risk
Dupilumab 52 51 51 51 50 50 50 50 47 45 44 43 42
Placebo 52 52 50 50 48 44 43 41 37 35 32 28 24
C FEV1
FEV1 (% of predicted value)
FEV1 (liters)
Stable background therapy
LABA withdrawal
Tapering of inhaled glucocorticoid
Dupilumab or placebo monotherapy
FEV1 (% of predicted value) Dupilumab
FEV1 (% of predicted value) Placebo
FEV1 (liters) Dupilumab
FEV1 (liters) Placebo
Week
D Nocturnal Awakenings
Mean No. of Awakenings per Night
Stable background therapy
LABA withdrawal
Tapering of inhaled glucocorticoid
Dupilumab or placebo monotherapy
Placebo
Dupilumab
Week
No. of Patients
Dupilumab 52 51 52 52 50 49 52 52 47 46 46 45 45
Placebo 52 51 51 52 50 49 47 46 45 42 41 40 36

Dupilumab

- Efficacy and safety of dupilumab as add-on therapy in patients with uncontrolled persistent asthma, receiving medium-to-high-dose inhaled corticosteroids plus long-acting β agonist assessed
- Randomised, double-blind, placebo-controlled, parallel-group, pivotal phase 2b clinical trial
- Randomly assigned (1:1:1:1:1) to receive subcutaneous dupilumab 200 mg or 300 mg every 2 weeks or every 4 weeks, or placebo, over 24-week period

Wenzel S. et al. Lancet 2016; 388:31

Dupilumab

- Dupilumab resulted in significant increases in FEV at week 12 in overall group
- Effect somewhat greater in prespecified subgroup with peripheral blood eosinophils ≥300 per microL than in those with lower blood eosinophils
- At 24 weeks, increases in FEV continued to be significant relative to placebo except for lowest dose of dupilumab
- Rates of severe asthma exacerbation were reduced in groups receiving dupilumab every two weeks

Wenzel S. et al. Lancet 2016; 388:31

Evaluation of dupilumab in patients with persistent asthma (Liberty Asthma Quest)

- Ongoing Phase 3 trial
- A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dopilumab in patients with persistent asthma
- Primary objective:
  - To evaluate the efficacy of dopilumab in patients with persistent asthma
- Secondary objectives:
  - To evaluate the safety and tolerability of dopilumab in improving patient-reported outcomes including health-related quality of life.
  - To evaluate dupilumab systemic exposure and incidence of antidrug antibodies

Brodalumab

- Phase 2 dose-ranging study in 302 adult patients with moderate to severe asthma (NCT01199289)
- No treatment differences were observed in 7-question ACQ (ACQ-7) scores, lung function, or asthma symptoms after subcutaneous brodalumab (antieIL-17) at 140, 210, or 280 mg or placebo
- Prespecified subgroup analyses showed an improvement in ACQ-7 score beyond the minimal clinically important difference after 210 mg of brodalumab only (P= 0.02; no adjustment for multiplicity) in patients with high bronchodilator reversibility (post-bronchodilator FEV1 improvement 20%)

BusseWW. et al. Am J Respir Crit Care Med. 2013;188:1294e1302

Anti-thymic stromal lymphopoietin

- TSLP: Epithelium derived cytokine, capable of regulating type 2 responses through suppression of dendritic cell–derived IL-12 production, thus skewing TH0 cells toward TH2
- AMG 157 (Human anti-TSLP monoclonal IgG2-lambda), binds human TSLP and prevents receptor interaction
- Randomly assigned 31 patients with mild allergic asthma to receive AMG157 (700 mg) or placebo intravenously, once a month for three doses

Gauvreau GM. et al. N Engl J Med 2014;370:2102-10

Anti-thymic stromal lymphopoietin

- Primary outcome, maximum percentage decrease in FEV during late asthmatic response (3 to 7 hours after allergen inhalation), was 45.9 percent less in AMG 157 group than placebo group on day 84 (***p = 0.02***)
- Methacholine hyperresponsiveness, exhaled nitric oxide, blood and sputum eosinophils also decreased in AMG group
- Associated decreases in blood and sputum eosinophil counts before and after allergen challenge, as well as decreased FENO levels
- No serious adverse effects reported

Gauvreau GM. et al. N Engl J Med 2014;370:2102-10

ORIGINAL ARTICLE

Tezepelumab in Adults with Uncontrolled Asthma

Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

N Engl J Med 2017; 377:936-946 | September 7, 2017 | DOI: 10.1056/NEJMoa1704064

- Moderate-to-severe asthma, particularly those with noneosinophilic inflammation
- Uncontrolled despite treatment with long-acting beta-agonists and medium-to-high doses of inhaled glucocorticoids
- Phase 2, randomized, double-blind, placebo-controlled trial, we compared subcutaneous tezepelumab at three dose levels with placebo over a 52-week treatment period
- Primary end point: Annualized rate of asthma exacerbations (events per patient-year) at week 52

ORIGINAL ARTICLE

Tezepelumab in Adults with Uncontrolled Asthma

Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

N Engl J Med 2017; 377:936-946 | September 7, 2017 | DOI: 10.1056/NEJMoa1704064

- Tezepelumab at dose:
- 70 mg every 4 weeks (low dose; 145 patients), 210 mg every 4 weeks (medium dose; 145 patients), or 280 mg every 2 weeks (high dose; 146 patients) resulted in
- Annualized asthma exacerbation rates at week 52 of 0.26, 0.19, and 0.22, respectively, as compared with 0.67 in placebo group (148 patients
- Exacerbation rates in respective tezepelumab groups were lower by 61%, 71%, and 66% than rate in placebo group ($P<0.001$ for all comparisons)
- Prebronchodilator forced expiratory volume in 1 second at week 52 was higher in all tezepelumab groups than in the placebo group (difference, 0.12 liters with the low dose [$P=0.01$], 0.11 liters with the medium dose [$P=0.02$], and 0.15 liters with the high dose [$P=0.002$])

Anti-TNF-alpha agents

- Pluripotent cytokine identified in innate, type 1, and type 2 immunity
- Expression of TNF-alpha is increased in severe asthmatic airways in association with airway neutrophilia
- Evidence do NOT support a beneficial effect

Infliximab

- Monoclonal antibodies against TNF-a, that bind and neutralize TNF-alpha
- Studied in patients with nonphenotyped asthma
- Small study of patients with moderate symptomatic asthma, infliximab treatment associated with decrease in diurnal peak expiratory flow variation at week 8 and decreased asthma exacerbations

Erin EM. et al. Am J Respir Crit Care Med 2006;174:753-62

Etanercept

- Soluble TNF-alpha receptor fusion protein that binds TNF-alpha and has longer half-life than the native soluble receptor
- Small, randomized, open-label study in patients with corticosteroid-refractory severe asthma, etanercept administered for 12 weeks to 10 patients with refractory asthma, 10 patients with mild-to-moderate asthma, and 10 patients without asthma, reported increased postbronchodilator FEV1 and decreased bronchial hyperresponsiveness compared with placebo
- However, larger follow-up study of patients with severe corticosteroid-refractory asthma, marginally reduced ACQ scores and C-reactive protein levels compared with placebo, without an effect on other outcomes

Berry MA . et al. N Engl J Med 2006;354:697-708
Morjaria JB. et al. Thorax 2008;63:584-91

Golimumab

- Golimumab, fully humanized mAb against TNF-a, that bind and neutralize TNF-alpha
- Large follow-up trial of 309 patients with severe asthma uncontrolled, despite high-dose ICS/LABA treatment (32% receiving OCSs)
- Randomly assigned treatment with golimumab, or placebo for one year
- Trial did not achieve the primary endpoints of reduction in exacerbations and improvement in FEV
- Patients with adult-onset disease, FEV1 reversibility of 12% or greater, and/or chronic sinusitis had a modestly lower risk of asthma exacerbations with golimumab compared with placebo.
- Associated with increase in systemic infections and cancer, trial stopped prematurely

Wenzel SE. et al. Am J Respir Crit CareMed 2009;179:549-58

Take Home Message

- Asthma is both easy and hard to treat
- Ongoing need for improvements in the management and control of asthma
- Knowledge of phenotypic variation needed
- Targeted therapy possible
- Available biologicals with proven efficacy
- Cost factor and availability could be issue
- Many potential therapeutic options for treatment are currently in development and undergoing clinical trials