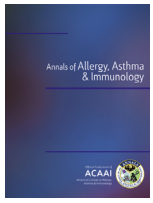
Ann Allergy Asthma Immunol xxx (2015) 1–7

Contents lists available at ScienceDirect



Review

Emerging therapeutic options for the treatment of patients with symptomatic asthma

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ARTICLE INFO

Article history:
Received for publication May 1, 2015.
Received in revised form June 25, 2015.
Accepted for publication July 13, 2015.

ABSTRACT

Objective: Asthma is a chronic inflammatory disorder of the airways with increasing worldwide prevalence. Despite treatment according to guidelines, a considerable proportion of patients with asthma remain symptomatic. Different potential therapeutic options for the treatment of these patients are currently in development and undergoing clinical trials, and it is important to regularly review their status.

Data Sources: A search of ClinicalTrials.gov was performed and supported by a PubMed literature search and restricted to the previous 10 years to ensure currency of data. The results were manually filtered to identify relevant articles.

Study Selections: Emerging therapies that are currently in phase 2 and 3 development include anti-interleukin agents (benralizumab, reslizumab, dupilumab, brodalumab, lebrikizumab, and mepolizumab), a chemoattractant receptor-homologous molecule expressed on a T-helper type 2 lymphocyte antagonist (OC000459), a phosphodiesterase-4 inhibitor (roflumilast), and long-acting muscarinic antagonists (glycopyrronium bromide, umeclidinium bromide, and tiotropium bromide).

Results: The clinical trial program of the long-acting muscarinic antagonist tiotropium is currently the most advanced, with data available from different phase 2 and 3 studies. Results demonstrate that it is an efficacious add-on to at least inhaled corticosteroid maintenance therapy across severities of symptomatic asthma.

Conclusion: The results of ongoing and future studies will help to determine whether these emerging therapeutic options will help address the unmet need for improvement in asthma management.

Introduction

Asthma is an inflammatory disease of the airways, with multifactorial pathophysiology. It is one of the most common chronic conditions, with a global prevalence of up to 18%, and is expected to affect approximately 400 million people worldwide by 2025.[1] Current Global Initiative for Asthma guidelines recommend stepwise treatment to achieve and maintain asthma control.[2] After initial treatment with inhaled corticosteroids (ICS), an increase in the ICS dose or the addition of another controller therapy, including long-acting β_2-agonists (LABAs), leukotriene modifiers, or theophylline, is recommended to achieve control. In patients with more severe disease where control cannot be achieved add-on therapy with anti-immunoglobulin E or oral glucocorticosteroids is recommended.

Despite treatment according to current guidelines, such as the Global Initiative for Asthma guidelines, at least 40% of patients with asthma remain symptomatic.[3–6] In the United States, the Asthma Control Characteristics and Prevalence Survey Studies reported uncontrolled asthma in 58.8% and 49.7% of adult and pediatric patients, respectively,[7] whereas the European REcognise Asthma and LInk to Symptoms and Experience survey reported uncontrolled asthma in 45% of respondents.[8] Poorly controlled asthma puts patients at risk of future exacerbations and thus has a significant impact on patients' lifestyles and on the use of health care resources and health care costs.[9–13] It is important to recognize that although the degree to which a patient's asthma is controlled might be related to disease treatment or severity, it also might be affected by different variables, including comorbidities such as allergic rhinitis and gastroesophageal reflux, poor treatment adherence, incorrect inhaler technique, allergen exposure, or concurrent smoking.[14]

There is an ongoing need for improvements in the management and control of asthma. This review examines recently published clinical data on emerging therapeutic options for the treatment of patients with symptomatic asthma.

Emerging Therapeutic Options for the Treatment of Asthma

Different promising therapeutic options are currently in development and undergoing clinical trials for the

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Disclosures: Dr McIvor has received CME honoraria and grants from Boehringer Ingelheim, Novartis, and AstraZeneca.

Funding: Funded by Boehringer Ingelheim.

http://dx.doi.org/10.1016/j.anai.2015.07.011

treatment of symptomatic asthma, including anti-interleukin (IL) agents, chemoattractant receptor-homologous molecules expressed on T-helper type 2 lymphocyte (CRT_H2) antagonists, phosphodiesterase-4 inhibitors, and long-acting muscarinic antagonists (LAMAs). The emerging anti-IL agents benralizumab, reslizumab, dupilumab, brodalumab, lebrikizumab, and mepolizumab, the CRT_H2 antagonist OC000459, the phosphodiesterase-4 inhibitor roflumilast, and the LAMAs glycopyrronium bromide, umeclidinium bromide, and tiotropium bromide were identified for inclusion based on recent literature.

Search Strategy

A search of ClinicalTrials.gov was performed using the drug names listed earlier AND *asthma* as search terms (Table 1). A PubMed literature search also was performed using the Boolean string *asthma** [title/abstract] AND *drug name* [title/abstract] AND *clinical trial* [ptyp] and was restricted to the previous 10 years to ensure currency of data (June 2015). The results were manually filtered to identify relevant articles or studies with data from well-designed clinical trials of the treatment of interest in human patients.

Anti-IL Agents in the Treatment of Asthma

Anti-IL agents are monoclonal anticytokine agents that decrease airway inflammation and prevent eosinophil activation.[15,16] The literature search provided 16 publications relating to the anti-IL agents benralizumab, reslizumab, dupilumab, brodalumab, lebrikizumab, and mepolizumab (eTable 1A).

Benralizumab

An initial phase 1 study in 27 patients with asthma found that single-dose intravenous and multiple-dose subcutaneous benralizumab (anti−IL-5) decreased airway, bone marrow, and peripheral blood eosinophil counts, with comparable safety profiles.[17] In a phase 2 study in 108 patients with acute asthma, a single dose of intravenous benralizumab was found to decrease the rate (1.82 vs 3.59 [total number of exacerbations per total duration of person-year follow-up], $P = .01$) and severity (0.65 vs 1.62 [total number of exacerbations per total duration of person-year follow-up], $P = .02$) of asthma exacerbations compared with placebo and had an acceptable safety profile.[18] Patients with severe asthma are currently being recruited for additional phase 3 studies (Table 1).

Reslizumab

In a study of 106 patients with severe eosinophilic asthma, treatment with monthly reslizumab infusions (anti−IL-5) showed a trend toward improved asthma control ($P = .0541$), significantly decreased sputum eosinophils ($P = .0068$), and significantly improved lung function, as measured by forced expiratory volume in 1 second (FEV_1; $P = .0023$), percentage of predicted FEV_1 ($P = .0010$), and forced vital capacity (FVC; $P = .0054$), compared with placebo.[15] The results from the first phase 3 trials in 953 adult and adolescent patients (489 patients in study 1 and 464 patients in study 2) with moderate to severe eosinophilic asthma (NCT01287039 and NCT01285323) showed that monthly intravenous reslizumab significantly decreased the frequency of asthma exacerbations ($P < .0001$ in the 2 trials) and had a similar adverse-event profile compared with placebo.[19] Additional phase 2 and 3 trials of reslizumab in adult and pediatric patients with eosinophilic asthma are currently ongoing (Table 1).

Dupilumab

Dupilumab (anti−IL-4) showed efficacy in a 12-week phase 2 trial of 104 patients with moderate to severe eosinophilic asthma (NCT01312961). Significant decreases in the incidence of asthma exacerbations ($P < .001$) and significant improvements in most measurements of lung function (FEV_1, $P < .001$) and asthma control (5-question Asthma Control Questionnaire [ACQ-5], $P = .001$) were observed after once-weekly subcutaneous administration of 300 mg of dupilumab compared with placebo; dupilumab also was found to decrease biomarkers associated with T-helper type 2 (T_H2)-driven inflammation.[16] A phase 2 trial and follow-on phase 3 trial are currently ongoing to evaluate the efficacy and safety of different doses and treatment regimens of dupilumab in patients with moderate to severe asthma (Table 1).

Brodalumab

In a 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 (anti−IL-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 ($P = .02$; no adjustment for multiplicity) in patients with high bronchodilator reversibility (post-bronchodilator FEV_1 improvement $\geq$20%).[20] A second phase 2 study of brodalumab in patients with high bronchodilator reversibility is currently recruiting patients (Table 1).

Lebrikizumab

Lebrikizumab (anti−IL-13) at 250 mg, administered subcutaneously every 4 weeks, showed improved lung function in a phase 2

Table 1
Summary of emerging therapeutic options in the treatment of asthma, listed on ClinicalTrials.gov

Therapeutic class	Mode of administration	Mechanism of action	Drug name	Sponsor	Development phase
Anti-interleukin agents	injection	anti-inflammatory	benralizumab	AstraZeneca	3
				Kyowa Hakko Kirin Company	2
				MedImmune	1/2
			reslizumab	Teva	2/3
				GlaxoSmithKline	3
			dupilumab	Sanofi	2/3
			brodalumab	Amgen	2
			lebrikizumab	F. Hoffmann-La Roche	2/3
				Genentech	2
			mepolizumab	GlaxoSmithKline	2/3
CRT_H2 antagonists	oral	anti-inflammatory	OC000459	Oxagen	2
				Atopix Therapeutics	1
Phosphodiesterase-4 inhibitors	oral	anti-inflammatory	roflumilast	Takeda	2/3
Long-acting muscarinic antagonists	oral	bronchodilator	glycopyrronium bromide	Chiesi	1/2
			umeclidinium bromide	GlaxoSmithKline	1/2
			tiotropium bromide	Boehringer Ingelheim	2/3

Abbreviation: CRT_H2, chemoattractant receptor-homologous molecules expressed on T-helper type 2 lymphocytes.