

Monoclonal Antibodies for the Management of Severe Asthma

Renata Rubinsztajn and Ryszarda Chazan

Abstract

Asthma is a heterogeneous inflammatory disease. Most patients respond to current standard of care, i.e., bronchodilators, inhaled glucocorticosteroids and other anti-inflammatory drugs, but in some adequate asthma control cannot be achieved with standard treatments. These difficult-to-treat patients would be the target population for new biological therapies. At present, omalizumab is the only biological agent approved for the treatment of early-onset, severe IgE-dependent asthma. It is safe, effective, and well tolerated. Also, discovery of asthma subtypes suggests new treatments. Half of patients with severe asthma have T-helper type 2 (Th-2) inflammation and they are expected to benefit from monoclonal antibody-based treatments. The efficacy of the investigational monoclonal antibody mepolizumab which targets IL-5 has been well documented in late onset non-atopic asthma with persistent eosinophilic airway inflammation. Anti-IL-4 and IL-13 agents (dupilumab, lebrikizumab, and tralokinumab) which block different Th-2 inflammatory pathways and agents targeting the Th-17 inflammatory pathway in severe refractory asthma are under development. In clinical trials, these drugs reduce disease activity and improve lung function, asthma symptoms, and quality of life. However, studies on larger groups of patients are needed to confirm their safety and efficacy.

Keywords

Airway inflammation • Asthma • Interleukins • Monoclonal antibodies • Omalizumab • Pulmonary function • Therapy

R. Rubinsztajn and R. Chazan (✉)
Department of Internal Medicine, Pneumology
and Allergology, Medical University of Warsaw,
1A Banacha Street, 02-097 Warsaw, Poland
e-mail: ryszarda.chazan@wum.edu.pl

1 Introduction

Asthma is a chronic inflammatory disease which affects growing numbers of people worldwide. Several biological pathways have been shown to

play a role in asthma pathogenesis. Exploring the mechanisms involved in inflammation and identifying asthma phenotypes could be a step toward individualized treatment. The pathways leading to inflammation in asthma, especially severe asthma, are only partly understood. Endobronchial tissue gene expression analyses revealed three major clusters of the disease: Th2 high; Th17 high; Th2/Th17 low (Newcomb and Peebles 2013). Many patients with severe asthma require regular treatment with oral glucocorticosteroids in addition to high-dose inhaled therapy. The long-term use of systemic glucocorticosteroids can be associated with serious and often irreversible adverse effects. It is recognized that different asthma phenotypes respond differently to asthma treatments. Allergic Th-2 driven immunoglobulin E (IgE)-dependent asthma is the most common sub-phenotype. A search for new drugs which would alter the natural history of the disease is underway with the focus on novel biological candidates for use in the treatment of severe refractory asthma.

2 Omalizumab

A relationship between risk of asthma and serum IgE level has been observed. In 2007, approximately 60 % asthma patients in the US were found to have evidence of atopy (Arbes et al. 2007). Omalizumab is the first biological targeted therapy approved for the treatment of IgE-dependent asthma and it is recommended by GINA guidelines as step 5 treatment of severe asthma (GINA Report 2015). Omalizumab (XOLAIR) is a recombinant DNA-derived humanized IgG 1_K monoclonal antibody that selectively binds free IgE in the blood, thereby inhibiting IgE binding to high-affinity IgE receptors (FcεRI) on mast cells and basophils, which mitigates the allergic response. Omalizumab also inhibits binding of IgE to FcεRI on dendritic cells and to FcεRII on lymphocytes T and B, eosinophils, and on other cells (Sarinho and Cruz 2006). This binding reduces the expression of receptors on the

effector cells. In MacGlashan et al.'s (1997) study, expression of FcεRI receptors decreased from 220,000 to 8300 *per* basophile after 3 months' omalizumab treatment. Omalizumab is indicated for the treatment of adults and adolescents (12 years of age and older), with moderate-to-severe persistent asthma, who have a total IgE between 30 and 1500 IU/ml and a positive skin test or *in vitro* reactivity to an aeroallergen, when the symptoms are inadequately controlled with a high dose of inhaled corticosteroids.

2.1 Clinical Efficacy

Clinical efficacy of omalizumab in allergic asthma is well documented based on studies in different populations. In the INNOVATE (Investigation of Omalizumab in Severe Asthma Treatment) trial of add-on omalizumab *vs.* placebo, conducted in patients aged 12–75 years with severe asthma, omalizumab significantly reduced the rate of severe asthma exacerbations (0.24 *vs.* 0.48) and emergency visits (0.24 *vs.* 0.43), and significantly improved asthma-related quality of life, morning peak expiratory flow, and the asthma symptoms score (Humbert et al. 2005). In a study by Novelli et al. (2015) in 306 patients under omalizumab treatment for a median of 32 months, good asthma control (according to GINA guidelines) was achieved in 25.2 %, partial control in 47.1 %, and poor control in 24.5 % of patients. The authors found that co-morbidities such as obesity, gastroesophageal reflux disease, aspirin intolerance, and chronic sinusitis or mental disorders could be responsible for an inadequate response to the treatment. In another multicenter, prospective study conducted in the US and Canada, in patients aged 12–75 years, with inadequately controlled asthma despite treatment with a high-dose inhaled corticosteroids (ICS) plus long-acting β₂-agonists (LABAs), with or without other controllers, omalizumab for 48 weeks reduced the number of exacerbations and mean daily albuterol puffs, decreased asthma symptoms, and improved results in the Asthma

Quality of Life Questionnaire (AQLQ [S]) compared with placebo (Hanania et al. 2011). In Mexican patients with uncontrolled asthma, three years of omalizumab treatment, improved the result of the asthma control test (ACT) (12.4 vs. 20.5 points), increased forced expiratory volume in 1 s of predicted (FEV₁%) (from 66.3 to 88.45 %), and reduced the mean beclomethasone dose (from 1750 to 766 µg/day), emergency room visits, hospitalization, and intensive care therapy (López Tiro et al. 2015). In German adult patients with uncontrolled asthma, six months' treatment with omalizumab had marked beneficial effects on daily and nocturnal symptoms, and the number of exacerbations, unscheduled health care contacts, and hospitalizations (Korn et al. 2009). In the PERSIST study, the physician-rated global evaluation of treatment effectiveness (GETE) score after 16 and 52 weeks' therapy was good and very good in 82 % and 72 % of patients, respectively. The treatment improved the quality of life and reduced the number of exacerbations compared with the baseline level (Brusselle et al. 2009). The longitudinal EXCELS study has shown that patients on omalizumab vs. non-omalizumab therapy experience similar, significant reductions in asthma-related work, school, and activity impairment, regardless of asthma severity (Zazzali et al. 2015). The authors conclude that omalizumab improves asthma control, which becomes evident within 6 months of therapy and persists for five years. Omalizumab therapy has reduced the number of emergency visits, hospitalizations, and the dose of systemic and inhaled corticosteroids in asthma patients in other studies as well (Grimaldi-Bensouda et al. 2013; Lafeuille et al. 2012). In a review on safety and tolerability of omalizumab by Corren et al. (2009), which encompassed 15 randomized trials and 7500 patients, severe adverse events have been reported in 10.8 % of patients treated with omalizumab vs. 12.6 % in controls and serious adverse events in 4.2 % of patients treated with omalizumab vs. 3.8 % in controls. In the placebo-controlled studies, 1.3 % of omalizumab-treated patients and 1.5 % of placebo-treated

discontinued therapy. On the other hand, in the standard treatment-controlled studies, more patients treated with omalizumab (3.1 %) than those on standard treatment (0.3 %) discontinued therapy. The most frequently reported adverse events are cold symptoms, sinusitis, cough, sore throat, headache, stomach problems, muscle pain, fever, and insomnia. Anaphylactic reaction occurs in 0.14 % of patients on omalizumab vs. 0.07 % in placebo groups. There is no evidence of increased risk of malignant neoplasia or thrombocytopenia by omalizumab (Corren et al. 2009). The numbers of major congenital anomalies, prematurity, low birth weight, and small size for gestational age due to omalizumab therapy noted in the EXPECT registry are consistent with the findings in other asthma populations (Namazy et al. 2015). According to a meta-analysis of 25 trials that evaluated omalizumab as add-on therapy in patients with moderate-to-severe asthma out of control with inhaled corticosteroids, the following observations have been made (Normansell et al. 2014):

- reduction in asthma exacerbation episodes (odds ratio (OR) 0.55, 95 % confidence intervals (CI) 0.42–0.60), ten studies;
 - reduction in the number of hospitalizations (OR 0.16, 95 % CI 0.06–0.42);
 - significantly more patients are able to completely withdraw ICS (OR 2.50, 95 % CI 2.00–3.13);
 - small but statistically significant reduction in a daily dose of ICS, (weighted mean difference – 118 µg) beclomethasone dipropionate equivalent per day, (95 % CI 154–84);
 - no difference in the number of patients who are able to withdraw from oral corticosteroid therapy (OR 1.18, 95 % CI 0.53–2.63);
 - small but statistically significant reduction in rescue beta2-agonist medication (mean difference (MD) 0.39 puffs per day, 95 % CI 0.55–0.24, nine studies, 3524 participants).
- This benefit is present in both moderate-to-severe (MD 0.58, 95 % CI 0.84–0.31) and severe (MD 0.30, 95 % CI 0.49–0.10) asthma subgroups on a background ICS therapy.

However, no appreciable benefit is apparent in patients with severe asthma receiving a background therapy of inhaled plus oral corticosteroids.

- significantly fewer serious adverse events (OR 0.72, 95 % CI 0.57–0.91; 15 studies, 5713 patients), but more injection site reactions (9.1 % of omalizumab-treated patients vs. 5.6 % of placebo-treated patients).

A meta-analysis performed by Lai et al. (2015) has shown that omalizumab, used for as long as 52 weeks, is well tolerated but lacks a mitigating effect on asthma exacerbations. Omalizumab treatment is associated with higher costs than conventional therapy, but the cost actually pays off in case of severe allergic asthma.

3 Other Anti-IgE Antibodies

Ligelizumab is a humanized anti-IgE antibody that has a 50-fold higher affinity for IgE than omalizumab. This agent suppresses free IgE more than omalizumab does in atopic patients. It may benefit patients unable to receive, or sub-optimally treated with, omalizumab (Arm et al. 2014).

Quilzumab is another humanized monoclonal antibody targeting the M1 prime epitope of human membrane IgE. In allergic rhinitis and mild asthma, quilzumab reduces total and allergen-specific serum IgE; the effect persists for at least 6 months after treatment cessation. In asthma patients, subjected to allergen challenge, quilzumab inhibits generation of new IgE, and reduces allergen-induced early and late airway responses and sputum eosinophilia (Gauvreau et al. 2014).

3.1 Mepolizumab

Persistent eosinophilia, the most important factor of the late-onset phenotype of severe refractory asthma, is associated with fixed airway limitation and it correlates with disease severity and

recurrent asthma exacerbation. Targeting the eosinophils with anti-IL-5 agents is effective therapy for patients with eosinophilic asthma.

Mepolizumab is a humanized monoclonal antibody of IgG1k type which targets human IL-5 and prevents its interaction with the α -chain of IL-5 receptor (Abonia and Putnam 2011). This agent reduces peripheral blood and sputum eosinophilia; the response also observed after allergen challenge in patients with allergic asthma (Leckie et al. 2000). Treatment with mepolizumab vs. placebo in asthmatic patients with eosinophilia and a history of severe asthma exacerbations has been associated with fewer severe exacerbations, improved score of Asthma Quality of Life Questionnaire, and lower eosinophil counts in the blood and sputum (Haldar et al. 2009). Mepolizumab enables a dose reduction of prednisone in patients who have asthma-related eosinophilia despite prednisone treatment (Nair et al. 2009). In a study by Ortega et al. (2014), intravenous and subcutaneous mepolizumab has been compared with placebo effects in 576 patients. Mepolizumab significantly reduced the rate of asthma exacerbations; the reduction was by 47 % with intravenous route and 53 % with subcutaneous route of administration. Emergency visits and hospitalizations also were reduced by 32 % and 61 %, respectively. These positive effects were accompanied by increased mean forced expired volume in 1 s (FEV1), improved control of asthma symptoms, and better quality of life. In another study, mepolizumab had a significant glucocorticoid sparing effect, reduced exacerbations and improved asthma symptoms in 135 patients requiring daily oral glucocorticoid therapy to achieve asthma control (Bel et al. 2014). The DREAM study has demonstrated that mepolizumab reduces the risk of exacerbation in asthma patients with eosinophilia, with the safety profile akin to that of placebo (Pavord et al. 2012). In a meta-analysis by Powell et al. (2015), including eight studies and 1707 participants, mepolizumab has improved the health-related quality of life and reduced asthma exacerbations in patients suffering from severe eosinophilic asthma. The

authors conclude that longer and larger studies with licensed treatment regimens are required to establish mepolizumab's role in asthma therapy (Powell et al. 2015).

3.2 Reslizumab

Reslizumab is a humanized anti-IL-5 monoclonal antibody that disrupts eosinophil maturation and promotes programmed cell death. The results of two multicenter, double-blind, parallel-group, randomized, placebo-controlled phase 3 trials which enrolled patients with uncontrolled asthma aged 12–75 years show that reslizumab significantly reduces asthma exacerbations (Castro et al. 2015).

3.3 Benralizumab

Benralizumab targets eosinophils by binding IL-5 receptor α , inducing apoptosis through antibody-dependent cell-mediated cytotoxicity. Single-dose intravenous and multiple-dose subcutaneous benralizumab reduce eosinophil counts in airway mucosa/submucosa, sputum, bone marrow, and peripheral blood (Laviolette et al. 2013). One dose of benralizumab added to the usual management reduces the rate and severity of exacerbations during 12 weeks' observation in patients presented to the emergency unit with acute asthma (Nowak et al. 2015).

3.4 Anrukinzumab/Lebrikizumab/ Tralokinumab

Interleukin-13 is involved in several aspects of allergic inflammation such as IgE synthesis, proliferation of bronchial fibroblasts, and recruitment of eosinophils and basophils (Gallelli et al. 2013). Anrukinzumab significantly inhibits allergen-induced late asthmatic response within 14, but not 35, days after its administration (Gauvreau et al. 2011).

Lebrikizumab is a humanized monoclonal antibody that binds to soluble IL-13 with high

affinity and blocks signaling through the active IL-4R α /IL-13R α 1 heterodimer (Ultsch et al. 2013). This agent has been used in asthmatic patients with inadequately controlled disease despite glucocorticosteroid treatment and improved lung function in a subset of patients with a high serum periostin level before onset of treatment (Corren et al. 2011). Lebrikizumab also has reduced the number of exacerbations and improved lung function; the results being again more pronounced in patients with a high periostin level (Hanania et al. 2015).

Tralokinumab is a human IgG4 anti IL-13 monoclonal antibody which is effective in a subset of asthma patients characterized by the highest sputum IL-13 levels (Antohe et al. 2013). In phase 2b study, tralokinumab regimens had an acceptable safety and tolerability profile, but did not significantly reduce asthma exacerbation rates in patients with severe uncontrolled asthma. An improvement in FEV₁ with tralokinumab given every 2 weeks and the results of *post-hoc* subgroup analyzes suggest a positive treatment effect in patients with higher than the population baseline median serum periostatin and dipeptidyl peptidase-4 (DPP-4) concentrations (Brightling et al. 2015).

3.5 Daclizumab

Daclizumab a humanized IgG1 monoclonal antibody against IL-2R chain of activated lymphocytes that improves asthma score and lung function (Busse et al. 2008).

3.6 Dupilumab

Dupilumab is a fully human monoclonal antibody binding to the α subunit of IL-4 receptor. This agent reduces the number of exacerbations by 82 % in patients with persistent moderate-to-severe eosinophilic asthma, increases FEV₁, and improves asthma control despite discontinuation of LABAs and inhaled glucocorticoids. Dupilumab reduces the concentration of

biomarkers associated with Th2-driven inflammation (Wenzel et al. 2013).

3.7 T helper (Th) cytokines

The expression of bronchial tissue genes stratifies asthmatics into Th2 high and Th17 aggregations which are distinctly regulated by IL-13 and IL-17. Neutralization of either interleukin increases the number of Th17 cells and promotes neutrophilic lung inflammation. In contrast, neutralization of both IL-13 and IL-17 has a protective effect on eosinophilia and inflammation. Thus, combination treatment targeting both pathways seems to optimize therapeutic efficacy (Choy et al. 2015). The pro-inflammatory role of Th17 cells is supported by other investigations. Park and Lee (2010) have found that Th17 play a role in airway hyperresponsiveness by recruiting both eosinophils and neutrophils. In sputum of asthmatic patients, expression of IL-17 mRNA correlates with the number of neutrophils (Bullens et al. 2006). Anti-IL-17 agents demonstrate a clinical efficacy in psoriasis (Brown et al. 2015).

3.8 Brodalumab

Brodalumab is a human, anti-IL-17 receptor A (IL-17RA) monoclonal antibody (IgG2). It binds with high affinity to human IL-17RA and blocks the biological activity of the 17A, 17 F, 17A/F, and 17E heterodimers. In a randomized, placebo-controlled study brodalumab in a range of trial doses of 140, 210, or 280 mg has improved the score in the Asthma Control Questionnaire (ACQ) in a subset of patients displaying a high reversibility of obstruction (post-bronchodilator FEV1 improvement $\geq 20\%$) and only in the 210 mg subgroup (Busse et al. 2013).

4 Other Candidate Anti-Inflammatory Drugs with Potential Therapeutic Effect in Asthma

In a mouse study, a neutrophil elastase inhibitor has shown a mitigating effect on airway hyperresponsiveness in response to inhaled methacholine, which indicates potential usefulness of this line of agents as modulators of the immune/inflammatory response in both neutrophil- and eosinophil-dominant phases of response to secondary allergen challenge (Koga et al. 2013). In another experimental study in mice, anti-proteinase-activated receptor 2 (PAR₂) antibody has inhibited ovalbumin and cockroach extract-induced airway hyperresponsiveness and airway inflammation, which also might be of potential interest for asthma therapy (Asaduzzaman et al. 2015). IL-33 and its receptor have been found to play a role in the development of asthma and allergic airway inflammation. In a mouse model, vaccination against IL-33 has inhibited house dust mite-induced development of airway hyperresponsiveness and decreased the production of inflammatory cytokines (Lei et al. 2015).

Asthma is a heterogeneous disease underlain by different molecular processes. Most of the studies outlined in this review article have been performed without previous phenotyping of patients; the procedure that is currently an essential precondition for identifying potential responders to targeted therapy, as similar disease symptoms may be due to different pathogenetic mechanisms. Advances in the understanding of asthma pathobiology and in the development of anti-cytokine agents have a great research potential which, when translated into clinical medicine, may cause a turnaround in the global scenario of optimal asthma treatment.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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