






Difficult-To-Treat and Severe Asthma: Can Real-World Studies On Effectiveness of Biological Treatments Change the Lives of Patients?

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Abstract: Many different phenotypes that characterize severe asthma are supported by intricate pathomechanisms called endotypes. The latter are driven by molecular interactions, mediated by intercellular networks. With regard to the biological treatments of either allergic or non-allergic eosinophilic type 2 asthma, real-world studies have confirmed the positive effects of currently available antibodies directed against immunoglobulins E (IgE), interleukin-5 (IL-5) and its receptor, as well as the receptors of interleukins-4 (IL-4) and 13 (IL-13). The best way to treat severe asthma should be chosen based on the peculiar phenotypic and endotypic traits of each patient. This will lead to relevant improvements in both clinical and functional outcomes. In particular, biological therapies can change the lives of asthma patients with a strong impact on quality of life. Unfortunately, patients with severe non-type-2 asthma, who continue to have pertinent unmet needs, are not receiving satisfactory advances within the context of biological treatments. It is also hopeful that in the next future new therapeutic strategies will be specifically implemented for these people, perhaps offering them the opportunity to improve their current, mostly inadequate asthma management.

Keywords: type 2 severe asthma, monoclonal antibodies, pro-inflammatory cytokines, quality of life

Introduction

Asthma is one of the most common diseases in the world, as it affects about 300 million people. It is characterized by respiratory symptoms such as wheezing, difficult breathing, chest tightness, and coughing, which are usually associated with variable airflow limitations.¹ In particular, a subset of patients with severe uncontrolled asthma (5–10%) pose the heaviest medical, social, and economic burden.^{2–5} Different subgroups of severe asthma are currently recognized: allergic eosinophilic, nonallergic eosinophilic, mixed eosinophilic and neutrophilic, neutrophilic, and paucigranulocytic.⁶ The bronchial epithelium of asthmatic patients is often fragile and highly permeable to environmental noxious agents. As a consequence, injured airway epithelial cells release high amounts of innate cytokines including thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25), and interleukin-33 (IL-33).⁷ These alarmins drive the tight crosstalk between innate and adaptive immune responses, which induce the development and progression of type 2 airway inflammation. Within this pathogenic context, group 2 innate lymphoid cells (ILC2) and T helper 2 (Th2) lymphocytes produce huge quantities of type 2 cytokines such as interleukin-5 (IL-5), interleukin-4 (IL-4), and interleukin-13 (IL-13). The latter trigger and amplify the differentiation and activation of eosinophils, as well as their recruitment inside inflamed airways.⁸

With regard to severe asthma, updated Global Initiative for Asthma (GINA) guidelines recommend at step 5 the addition of biological drugs to maximized and optimized standard treatments.⁹ Several monoclonal antibodies are

currently available for biologic therapies of severe asthma. Omalizumab targets human immunoglobulins E (IgE), thus being indicated for treatment of severe allergic asthma.¹⁰ Other monoclonal antibodies target either IL-5 (mepolizumab, reslizumab) or its receptor (benralizumab), thereby providing very effective anti-eosinophilic therapies.^{11–15} Dupilumab is a dual receptor antagonist of both IL-4 and IL-13, and its specific mechanism of action guarantees an effective biologic treatment of severe type 2 asthma.¹⁶ Tezepelumab is a specific inhibitor of TSLP, which appears to be involved in the pathobiology of both T2-high and T2-low pheno/endotypes of asthma. Therefore, this drug is currently the only biologic which can be prescribed to severe asthmatic patients with either type 2 or non-type 2 disease.¹⁷

Severe asthma and its multiple comorbidities negatively impact on quality of life.^{18–20} The Asthma Quality of Life Questionnaire (AQLQ) is used to assess quality of life in asthma patients.^{21,22} This score considers 4 domains: symptoms (12 items), activity limitation (11 items), emotional function (5 items), and environmental stimuli (4 items). To each domain 7-point scale (7 = not impaired at all; 1 = severely impaired) is assigned, with higher scores indicating a better quality of life. However, in large clinical trials a greater efficiency is provided by the Mini Asthma Quality of Life Questionnaire (Mini-AQLQ). In addition to AQLQ, another important tool for assessing the health status of asthmatic patients is the Asthma Control Test (ACT).²³ It consists of 5 questions on different domains (activity, shortness of breath, night or morning symptoms, medication use as needed, subjective control) on a scale of 1 to 5 points. ACT score ranges from 5 (poor asthma control) to 25 (complete asthma control), with higher scores reflecting greater asthma control. An ACT score >19 indicates that asthma is well controlled

On the basis of the above-mentioned considerations, the aim of this review is to evaluate the real-world impact of biological therapies on quality of life in patients with severe asthma (Table 1).

Table 1 Main Real-World Positive Therapeutic Effects of Biological Drugs in Patients with Severe Asthma

Real-World Study	Biological Drug	Main Results
Su N et al ²⁴	Omalizumab	↑ AQLQ, ↓ Exacerbations, ↑ FEV ₁
Rojo-Tolosa S et al ²⁵	Omalizumab	↑ ACT, ↓ Exacerbations, ↓ OCS, ↑ FEV ₁
Menzella F et al ²⁶	Omalizumab	↑ AQLQ, ↓ Exacerbations, ↑ FEV ₁
Menzella F et al ²⁷	Omalizumab	↑ AQLQ, ↑ ACT, ↓ Exacerbations, ↓ OCS
Campisi R et al ²⁸	Omalizumab	↑ ACT, ↓ Exacerbations, ↑ FEV ₁
Pilette C et al ²⁹	Mepolizumab	↓ ACQ-5, ↓ Exacerbations, ↓ OCS, ↓ WPAI
Pavord I et al ³⁰	Mepolizumab	↑ ACT, ↓ Exacerbations, ↓ OCS, ↑ FEV ₁
Rojo-Tolosa S et al ³¹	Mepolizumab	↑ ACT, ↓ Exacerbations, ↓ OCS, ↑ FEV ₁
Korn S et al ³²	Mepolizumab	↓ Exacerbations, ↓ OCS
González-Pérez R et al ³³	Mepolizumab	↑ ACT, ↓ Exacerbations, ↓ OCS, ↑ FEV ₁
Jackson DJ et al ³⁴	Benralizumab	↑ AQLQ, ↓ ACQ-6, ↓ Exacerbations, ↓ OCS
Di Bona D et al ³⁵	Benralizumab	↑ AQLQ, ↑ ACT, ↓ Exacerbations, ↓ OCS, ↑ FEV ₁
Martínez-Moragón E et al ³⁶	Benralizumab	↑ AQLQ, ↑ ACT, ↓ Exacerbations, ↓ OCS
Vultaggio A et al ³⁷	Benralizumab	↑ ACT, ↓ Exacerbations, ↓ OCS, ↑ FEV ₁
Scioscia G et al ³⁸	Benralizumab	↑ AQLQ, ↑ ACT, ↓ OCS, ↑ FEV ₁
Dupin C et al ³⁹	Dupilumab	↑ ACT, ↓ Exacerbations, ↓ OCS, ↑ FEV ₁

(Continued)

Table 1 (Continued).

Real-World Study	Biological Drug	Main Results
Campisi R et al ⁴⁰	Dupilumab	↑ ACT, ↓ Exacerbations, ↓ OCS, ↑ FEV ₁
Fukunaga K et al ⁴¹	Dupilumab	↓ Exacerbations, ↓ OCS
Pelaia C et al ⁴²	Dupilumab	↑ ACT, ↓ Exacerbations, ↓ OCS, ↑ FEV ₁
Pelaia C et al ⁴³	Dupilumab	↑ ACT, ↓ Exacerbations, ↓ OCS, ↑ FEV ₁

Abbreviations: AQLQ, asthma quality of life questionnaire; FEV₁, forced expiratory volume in one second; ACT, asthma control test; OCS, oral corticosteroid; ACQ, asthma control questionnaire; WPAI, work productivity and activity impairment.

Omalizumab

Omalizumab was the first biologic therapy authorized by regulatory bodies for the add-on treatment of severe asthma.⁴⁴ Omalizumab inhibits IgE interactions with high-affinity receptor (FcεRI) and low-affinity receptor (FcεRII)/CD23 receptors by specifically binding to the constant region of human IgE.⁴⁵ Omalizumab is thus particularly efficient in blocking the biological effects of IgE at the level of immune/inflammatory and structural cells within the airways.⁴⁶ Allergic patients with impaired lung function, who are treated with high dosages of inhaled corticosteroids, but do not control asthma symptoms and experience frequent asthma exacerbations, are eligible to receive omalizumab.⁴⁷

Several real-world studies conducted all around the globe have proven the positive therapeutic advantages of omalizumab.⁴⁸ Specifically, these real-world studies have shown that omalizumab decreases oral corticosteroids (OCS) consumption and the number of missed work and school days, in addition to markedly decreasing the likelihood of asthma exacerbations and hospital ward visits.^{24,25,49} Additionally, empirical data clearly indicates that omalizumab may provide substantial and long-lasting improvements in forced expiratory volume in one second (FEV₁), detectable up to 16 years after the initiation of anti-IgE treatment.^{26,27,50} Severe asthmatics patients under treatment with omalizumab manifest a high degree of treatment adherence, which can be explained by the above positive clinical and functional effects.²⁸ Omalizumab also has a long-lasting, favourable safety and tolerability profile, which contributes to improve the quality of life of asthmatic patients.⁵¹

Mepolizumab

Mepolizumab is a humanized monoclonal antibody which specifically binds to IL-5, thus preventing its interaction with IL-5 receptor expressed by eosinophils. As a consequence, mepolizumab inhibits the proliferation and survival of these cells, thereby suppressing eosinophilic inflammation. This biological drug can be prescribed to people complaining of uncontrolled eosinophilic asthma, with a blood eosinophil count ≥ 150 cells/ μ L before the first administration and ≥ 300 cells/ μ L in the previous year, and with at least 2 asthma exacerbations requiring oral steroids in the past year. In addition to severe eosinophilic asthma, mepolizumab is also indicated for other three eosinophil-driven diseases, including chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic granulomatosis with polyangiitis (EGPA), and hyper-eosinophilic syndrome (HES).⁵² Mepolizumab is administered by a subcutaneous injection at a fixed dose of 100 mg every 28 days. During these years, lots of studies analysed mepolizumab about its efficacy in uncontrolled severe eosinophilic asthma, showing very positive effects on symptom control, exacerbation rate, OCS maintenance dose, hospitalization number, lung function.^{29,53} Furthermore, mepolizumab is characterized by a very safe profile.³⁰ In particular, several studies suggest that patients treated with mepolizumab can achieve real-life clinical benefits regardless of the presence of a range of common comorbidities, including upper and lower airway diseases, atopic disorders, chronic sinusitis, chronic obstructive pulmonary disease, nasal polyps, obesity, anxiety, and depression.⁵⁴ These investigations focused on the impact that this biological therapy has on quality of life. Indeed, a significant change in the ACT questionnaire score and an improvement in pulmonary function were found in all studies.^{31–33,55} All these considerations highlight that treatment with mepolizumab improves the quality of life in a real-world setting.³²

Benralizumab

Benralizumab is a humanized monoclonal antibody (IgG1k) that binds very strongly to the α subunit of IL-5 receptor, thus impeding its interaction with IL-5. Moreover, the molecular structure has been engineered without fucose sugar residues in the CH2 domain of the constant region, thus enhancing the affinity binding for Fc γ RIIIa (CD16a) expressed by natural killer (NK) cells. As a consequence, antibody-dependent cell-mediated cytotoxicity (ADCC) of eosinophils and basophils results to be markedly potentiated.⁵⁶

Real-life experiences with benralizumab in patients with severe eosinophilic asthma (SEA) showed that overall disease control was much better after anti-IL5 receptor treatment. In particular, it was reported that there was a drastic reduction in annualized exacerbation rate and OCS intake, with associated improvements in lung function, Asthma Control Questionnaire (ACQ) score, ACT score and mAQLQ score.^{34–36} Another real-world study conducted on a large SEA population evaluated the effectiveness of benralizumab. This drug dramatically decreased the frequency of exacerbations, improved asthma control and lung function. The proportion of patients achieving well-controlled asthma increased from 16.7% at baseline to 78.7% after 96 weeks of therapy. Moreover, long-term treatment with benralizumab has proven to promote OCS elimination, thereby reducing OCS median daily dosage by 100% at both 48 and 96 weeks.³⁷

In addition to retrospective real-world studies, an Italian observational real-life study enrolled 10 consecutive patients that began treatment with benralizumab. During the follow-up, ACT score enhanced from 13.5 ± 1.5 (baseline) to 20.3 ± 1.4 (12 weeks) and to 24.2 ± 0.6 (24 weeks), ACQ score reduced from 3.48 ± 0.65 (baseline) to 2.32 ± 0.57 (12 weeks) and to 1.42 ± 0.92 (24 weeks), EuroQol-Visual Analogue Scales (EQ-VAS) increased from 44.5 ± 7.7 (baseline) to 60.5 ± 6.6 (12 weeks) and to 86.7 ± 7.2 (24 weeks), and Beck Depression Inventory scale (Beck DI) reduced from 14.6 ± 3.68 (baseline) to 9.1 ± 1.64 (12 weeks) and to 3.7 ± 1.8 (24 weeks). Moreover, AQLQ total score improved from 3.65 ± 0.56 (baseline) to 4.61 ± 0.67 (12 weeks) and to 5.17 ± 0.87 (24 weeks). The percentage of patients complaining of serious problems in all domains of the EuroQol-5Dimensions-3Levels (EQ-5D-3L) at baseline significantly decreased after both 12 and 24 weeks of treatment. Lastly, FEV₁ significantly increased during the follow-up.³⁸

Dupilumab

Dupilumab is a fully human IgG4 monoclonal antibody that binds to IL-4R α , thereby functioning as an IL-4 and IL-13 dual receptor antagonist. Dupilumab is beneficial for severe asthmatics with a blood eosinophil count of at least 150 cells/ μ L and/or fractional exhaled nitric oxide (FeNO) concentration of at least 25 parts per billion (ppb), who also eventually begin long-term OCS treatment regimens. Dupilumab exerts positive therapeutic action, such as timely and significant improvements in asthma exacerbations, symptom control, airflow limitation, lung hyperinflation, and OCS consumption.^{57,58} Nowadays, dupilumab may be suggested as an add-on biological treatment for people with nasal polyposis or atopic dermatitis, two major conditions that often coexist with asthma, as well as for people with severe asthma.^{39–41,59,60} When evaluating dupilumab's practical effects on severe asthma, it is important to keep in mind that nasal polyposis and chronic rhinosinusitis are both significantly impacted by its mode of action. In fact, a study showed how a group of 20 individuals had substantial improvements in both nasal polyposis and severe asthma within only 4 weeks.⁴² Specifically, there was a substantial reduction in Sinonasal Outcome Test-22 (SNOT-22) score, as well as a significant increase in ACT score. Within 4 weeks, OCS consumption was interrupted. Moreover, forced vital capacity (FVC) and FEV₁ significantly increased at week 4. Furthermore, dupilumab increased forced expiratory flow between 25% and 75% of FVC (FEF_{25–75}) and decreased residual volume, respectively. Another real-life investigation assessed the effects of 6-month treatment with dupilumab in 127 patients affected by severe asthma, eventually associated with nasal polyps.⁴³ Asthma exacerbations and daily intake of prednisone zeroed during the follow-up period. SNOT-22 score decreased from 55.84 to 19.76, and ACT score improved from 14 to 22. These results were paralleled by an improvement of lung function, in terms of FEV₁, FVC and FEF_{25–75}.

Conclusions

The recent advances in our understanding of the pathomechanisms underlying severe asthma have driven the development of several biologic medications, including omalizumab, mepolizumab, benralizumab, and dupilumab. Randomized

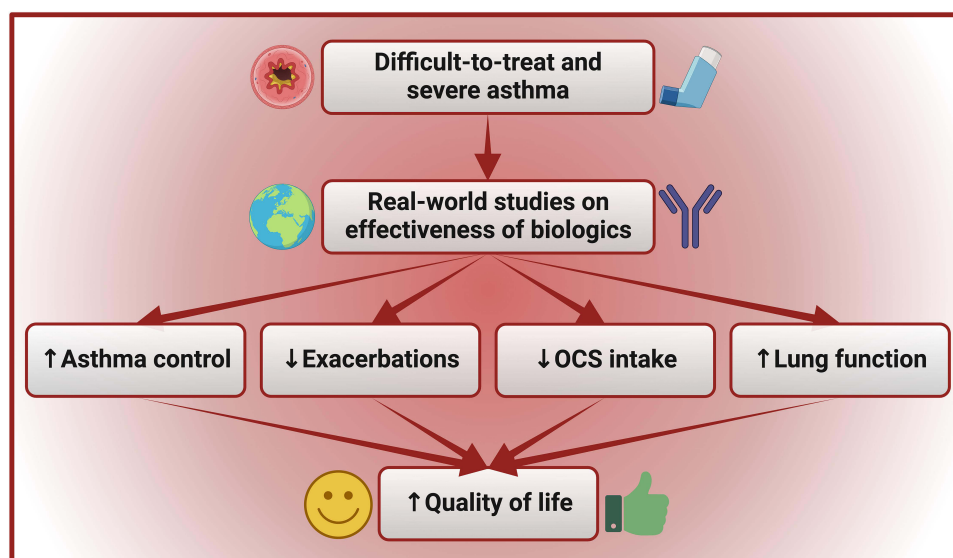


Figure 1 Real-world treatment effectiveness of biological therapies for severe type 2 asthma contribute to improve quality of life of patients. Omalizumab, mepolizumab, benralizumab, and dupilumab are able to reduce exacerbations and daily oral corticosteroid (OCS) intake, ameliorating lung function and asthma control test (ACT) score. These positive effects translate into notable improvements in terms of quality of life. Created with BioRender.com.

controlled trials and observational real-life data have provided compelling evidence for the safety and effectiveness of these antibodies as additional therapies for type 2 airway inflammation. Furthermore, the aforementioned biologic treatments are capable of inducing noteworthy advantages in the management of several asthma comorbidities, namely nasal polyposis. In particular, real-world studies have confirmed the positive therapeutic effects of biological drugs in patients with severe asthma, highlighting great improvements also in quality of life and global health status (Figure 1).

Overall, the very relevant therapeutic benefits enjoyable by patients with type 2 severe asthma and related comorbidities, treated with biological therapies, can be summarized as follows: (i) suppression of eosinophilic inflammation and restoration of airway epithelium; (ii) decrease of severe asthma exacerbations; (iii) decrement of OCS use; (iv) improvement of asthma symptom control; (v) improvement of lung function; (vi) reduction of emergency visits and hospitalizations; (vii) improvement of health status and quality of life; (viii) remarkable attenuation of the social and economic burden associated with severe asthma.

Unfortunately, individuals with predominant neutrophilic bronchial inflammation are not taking advantage by the considerable treatment prospects now enjoyed by subjects with allergic and eosinophilic asthma. Thus, more studies are needed to attain improved outcomes in the therapy of severe T2-low asthma as well.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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