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Biological Therapy in Bronchial Asthma: Case Reports

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ABSTRACT

Asthma is a common, chronic airway inflammatory disease affecting nearly 300 million people world-wide and found in 1-18% of the population in different countries. Bronchial asthma is known to be a heterogenous chronic respiratory disease. It is characterised by chronic inflammation of the bronchi, bronchoconstriction, increased bronchial reactivity or hyperresponsiveness and mucus hypersecretion. Severe eosinophilic allergic and non-allergic bronchial asthma presents a complex challenge for both patients and healthcare professionals. Finding the right treatment often involves navigating individual needs and variable responses. This study explores the potential of two promising biological therapies, benralizumab and omalizumab in specifically targeting this form of severe bronchial asthma. By exploring the therapeutic application, efficacy and clinical effectiveness of these agents, this research aims to empower healthcare professionals with valuable insights. This knowledge can translate into personalized and more effective treatment plans for patients struggling with severe eosinophilic bronchial asthma. To provide a comprehensive understanding, the research first delves into the underlying inflammatory mechanisms of this condition, drawing upon current research findings. It then explores the existing landscape of available biological therapies for this patient population, paving the way for a focused analysis of benralizumab and omalizumab. Finally, I was able to present two different case reports to substantiate my claim. I focused on two biological agents, benralizumab and omalizumab based on my case reports, and demonstrated their use and effectiveness in diverse patient contexts. By considering individual asthma endotypes, phenotypes, concomitant conditions, and clinical manifestations, I aimed to illustrate how these targeted therapies can be tailored to achieve optimal outcomes. In conclusion, these case studies provide a compelling demonstration of the effectiveness of biological therapies, particularly benralizumab and omalizumab, in the management of severe eosinophilic allergic bronchial asthma. Notable improvements in asthma control, lung function, and quality of life were evident in both patients. It is strongly recommended that patients with severe bronchial asthma seek consultation with both pulmonologists and allergists to determine the most appropriate biological agents based on individual asthma characteristics. Additionally ongoing research is crucial to explore and develop novel treatment approaches for this challenging condition.

KEYWORDS

Bronchial asthma, phenotypes, endotypes, biological agents, benralizumab, omalizumab, and biological therapy.

ABBREVIATIONS

AAAI=The American Academy of Allergy, Asthma, and Immunology; ACAAI=The American College of Allergy, Asthma, and Immunology; ACQ=Asthma Control Questionnaire; ADCC= Antibody-dependent cell-mediated cytotoxicity; ANA= Antinuclear Antibody; ANCA= Anti-Neutrophil Cytoplasmic Antibody; ATS= American Thoracic Society; EAACI= European Academy of Allergy and Clinical Immunology; ERS= European Respiratory Society; EMA= European Medicine Agency; EU= European Union; FeNO= Fractional Exhaled Nitric Oxide; FEV1= Forced Expiratory Volume in one second; FDA= American Food and Drug Administration; FVC= Forced Vital Capacity; GINA= Global Initiative of Asthma; ICS= Inhaled Corticosteroids; IgE= Immunoglobulin E; IL= Interleukin; ILC2= Innate Lymphoid Cells type2; LABA= Long-Acting Beta Agonists; LTRA= Leukotriene Receptor Antagonists; Mini AQLQ = Mini Asthma Quality of Life Questionnaire ; NICE= National Institute for Health and Care Excellence; OCS= Oral Corticosteroids; RCT= Randomized Control Trial; SARP= Severe Asthma Research Program; Th2 (T2) = T-helper cells; TSLP= Thymic Stromal Lymphopoietin; USA= United States of America; UTI= Urinary Tract Infection.

INTRODUCTION

DEFINITION AND DESCRIPTION

Bronchial asthma is a heterogenous chronic respiratory disease characterised by chronic inflammation of the bronchi, bronchoconstriction, increased bronchial reactivity or hyperresponsiveness, and mucus hypersecretion. Asthma causes symptoms such as wheezing, breathlessness, chest tightness, cough and it causes reversible airway obstruction [1]. It is a common, chronic airway inflammatory disease which affected nearly 300 million people world-wide; and predicted to affect a more 100 million people by the year 2025 [2].

The prevalence of severe asthma among individuals with current asthma has been estimated to be 3.6% according to the definition of the US Severe Asthma Research Program (SARP), 4.8 % as per the European Respiratory Society (ERS) and American Thoracic Society (ATS) Taskforce definition, and 6.1% based on the Global Initiative for Asthma (GINA) definition [3]. Both asthma symptoms and airway obstruction vary in intensity over time and provoked by other factors such as allergens, exercise, viral respiratory infection, colds, or even weather and environmental changes [1]. Asthma symptoms may improve or even disappear spontaneously, or with medication, for weeks and in some cases months at a time. However, these periods of calm can be interrupted by flare-ups of asthma which can be dangerous and even life-threatening. According to ATS and ERS Task force, the severity of asthma should not be a static label. Instead, it should be reassessed regularly based on the level of treatment needed, to control symptoms and prevent flare-ups [4]. Mark L. Levy et al. define severe asthma as a subset of difficult-to-treat asthma. It is characterized by uncontrolled asthma symptoms despite optimal management, including high-doses of inhaled corticosteroids (ICS) combined with long-acting beta agonists (LABA), proper inhaler technique, and addressing contributory factors like comorbidities and environmental triggers. Additionally, reducing the doses of these medications can worsen symptoms in patients with severe asthma [1].

The Global Initiative of Asthma (GINA) has published a guideline outlining a universal approach to the diagnosis, management, and prevention of asthma. According to this guideline, the long-term goals of asthma managements are symptoms control, fewer exacerbations, reduction in risk of future asthma-linked mortality and adverse-effects of therapy [1]. Furthermore, The ATS/ERS has guidelines that describe the diagnosis and management of severe bronchial asthma [4]. Asthma treatment can be ineffective due to the diverse phenotypes and endotypes of the asthma and the variability in patient response to existing medications. Furthermore, some patients may experience ongoing difficulties in achieving adequate symptoms control despite receiving appropriate therapy.

The recent advanced knowledge of aetiology and pathophysiological mechanism of different phenotypes and endotypes of severe asthma has provided the tools to know the accessibility of inventive therapies, one of such is biological therapy in severe bronchial asthma that has been in use in the last few years. By working against molecules involved in type 2 inflammatory pathway, this therapy modifies the natural course of the disease by decreasing airway inflammation without the most adverse effect caused by oral corticosteroids.

The primary goals of these case reports are to present compelling evidence supporting the effectiveness of benralizumab and omalizumab in the management of severe uncontrolled eosinophilic allergic bronchial asthma.

In pursuit of this goal, my methodology involves elucidating the following aspects in accordance with contemporary scholarly literatures:

(1) Assessing the inflammatory mechanism of severe bronchial asthma involves a comprehensive evaluation.

(2) Evaluate the present recommendations for the management of asthma.

(3) Elaborate on the approach of biological therapy, the agents presently available, and the circumstances under which they are used in the context of severe bronchial asthma.

(4) Discuss patient's characteristics for biological therapy-severe asthma.

(5) Elaborate on the methods used to assess the effectiveness of biological therapy in the management of severe bronchial asthma.

(6**)** Exploring the role of biological agents in patients with severe asthma during COVID-19 era and alongside the treatment for COVID-19 infection.

Finally, I will corroborate these findings with the inclusion through the case reports and initiate a discussion concerning the observed outcomes.

METHODS

LITERATURE SEARCH STRATEGY

To find the latest and the most relevant research for this thesis, I conducted an extensive search through online databases like PubMed and Google Scholar. This search spanned from the database inception dates to March 2023. To ensure a comprehensive exploration, I employed a variety of keywords (listed below) in various combinations.

Focusing on contemporary insights, I limited my search to studies published in English within the past five years. To capture additional relevant sources, I carefully reviewed the reference lists of the retrieved articles, following a technique known as the "snowball method".

Additionally, I included articles recommended by my university supervisor and her colleagues to gain a more comprehensive perspective.

To guarantee I only selected truly relevant studies, I implemented a two- steps screening process. First, I scanned the titles of all retrieved articles to identify those potentially aligned with my research theme. Next, I read abstracts of these shortlisted articles to get a better sense of their content. Finally, I thoroughly evaluated the full text of these articles to confirm their thematic relevance to the case reports under study.

Throughout this research journey, I relied on the Mendeley Reference Manager to keep track of and organize my references. This software proved invaluable in streamlining the citation management process, ultimately boosting my efficiency and effectiveness during the literature review process.

The specific keywords I utilised in my search included terms related to: Bronchial asthma, phenotypes, endotypes, biological agents, benralizumab, omalizumab, and biological therapy.

INFLAMMATORY MECHANISMS AND TARGET FOR TREATMENT OF BRONCHIAL ASTHMA

Concerning of pathogenesis, severity of symptoms, clinical manifestation, and outcomes of treatments, asthma is an extremely heterogeneous and chronic airway inflammatory disease. Diversity of different cells are elaborated in the process of airway inflammation of asthma. This includes innate and adaptive immune responses in particular eosinophils, mast cells, basophils, T-lymphocytes, neutrophils, and dendritic cells.

Two major groups of asthma phenotypes have been identified, referred to as T2 high and T2 low, which are recognized based on the inflammatory pathways they entail. Our conception of T2 low (non-T2 inflammation) asthma remains limited [5]. According to the recent review authored by Fitzpatrick et al [5], precise pathways for T2-low asthma are currently absent, although potential involvement of IL-8 and IL-17, metabolic dysfunctions, obesity, and other exposures may play a role. Consequently, at present, there are no established biomarkers for T2-low asthma although sputum neutrophilia characterizes the airway inflammatory response.

T2-high asthma, characterized by early-onset allergic asthma and long-onset non-allergic eosinophilic asthma, is primarily driven by inflammation linked to the T2 immune response.

In contrast, neutrophilic asthma falls under the T2-low category [6]. In allergic asthma, dendritic cells acting as alarm system, presenting allergens to naïve immune cells called CD4+T cells. These T cells then mature into specialized Th2 (T-helper) cells, fuelling the inflammatory response. In non-allergic eosinophilic asthma, the alarm is tiggered by various stimuli including respiratory viruses, bacteria or even pollutants, directly activating the airway lining. This activation leads to the release of respiratory epithelium-originated special cytokines, and chemokines like TSLP, IL-25 and IL-33 which are also called alarmins [7]. Alarmins in turn activate other immune cells called type-2 innate lymphoid cells (ILC2s). Following activation, both activated cells (Th2 and ILC2s) release key player cytokines such as IL-4, IL-5, and IL-13, driving the T2-related inflammation. Notably, IL-5 plays a crucial role by summoning eosinophils, white blood cells involved in allergic response, from the bone marrow to the airways, further amplifying the inflammatory response [8]. Furthermore, by sharing a common receptor sub chain, IL-4 and IL-13 trigger the production of special antibodies called IgE, which react to specific allergens. This reaction leads to the release of various chemicals from immune cells like eosinophils, mast cells, and basophils, causing inflammation and changes in the airways. We can measure this T2 inflammation using various biomarkers including total and antigen specific IgE, eosinophil counts, and fractional exhaled nitric oxide (FeNO). These markers generally indicate the presence of T2 inflammation in asthma and help identifying patients who might benefit from targeted therapies like biological agents, which specifically target the T2 pathway. Many patients with severe asthma experience a specific type of inflammation driven by the immune system’s T2 pathway. This makes it a prime target for new, innovative biological agents currently available [9].

BIOLOGICALS, AND MECHANISMS OF ACTION

BIOLOGICALS

Biological agents, also known as biologicals, are therapeutic substances synthesized by living organisms through advanced biotechnology and other cutting-edge technologies. Biological agents typically consist of large-molecular-weight substances, such as monoclonal antibodies (mAb), which specifically target cytokines or receptors. These distinguishes them from chemical compounds and small molecular weight agonists or antagonists. The unique

features of biological agents make them well-suited for the realm of ‘personalized’ or ‘precision’ medicine[10]. However, the use of biologicals requires comprehensive knowledge of the pathophysiology, endotypes, and phenotypes of the diseases.

INITIATION OF BIOLOGICAL THERAPY FOR SEVERE BRONCHIAL ASTHMA

The management of severe asthma, characterized by inadequate symptoms control and frequent exacerbations, has seen a paradigm shift with the introduction of biological therapies. By focusing on specific inflammatory pathways, biological therapies aim to achieve significant improvements in lung function, reduce exacerbations, and improve quality of life.

Currently, five T2-targeted biological treatments have been approved for the management of severe bronchial asthma. This treatment can be broadly classified into three main pathways that target specific cytokines: the IL-5 pathway (eosinophils), the IgE pathway, and the IL-4/ IL-13 pathway. In addition, Tezepelumab, a novel TSLP-targeting biological, has recently gained regulatory approval [11]. To select the most suitable biological therapy, patients undergo careful assessment based on the presence of severe asthma and the presence of T2 inflammatory biomarkers. These biomarkers serve as valuable indicators of who is likely to benefit from these targeted treatments.

The main goals of adding biological therapies to the treatment regimen of patients with severe asthma are to significantly reduce the frequency and severity of exacerbations, improve pulmonary functions, minimize the reliance on systemic corticosteroids, alleviate asthma symptoms, and enhance quality of life [9]. The first monoclonal anti-IgE antibody is omalizumab, working over diverse mechanisms of allergic pathways by binding to IgE. Mepolizumab and reslizumab are biologicals which target interleukin-5 (IL-5), whereas the receptors of interleukin-5 (IL-5) targeting biological is benralizumab. Lastly, the receptor of interleukin-4 (IL-4) targeting biological is dupilumab which block the signalling lane of IL-4 and IL-13. Furthermore, Tezepelumab works against TSLP, while itepekimab is an interleukin-33 targeting biological agent. Conversely, astegolimab targets the receptors of interleukin-33 in its biological mechanisms [11]

BIOLGICALWHICH TARGET IgE

OMALIZUMAB

Omalizumab, a pioneering biological agent targeting immunoglobulin E (IgE), was approved by both the European Medicine Agency (EMA) and American Food and Drug Administration (FDA) for the treatment of severe bronchial asthma. This recombinant monoclonal antibody binds specifically to circulating IgE, resulting in a marked reduction in blood IgE levels. Furthermore, omalizumab depletes FCRI receptors on inflammatory cells, such as mast cells and basophils. Consequently, this dual action of omalizumab leads to the reduction of asthma exacerbations by mitigating allergic responses and enhancing the antiviral immune response [12][13]. According to GINA, EMA, and FDA guidelines, omalizumab can now be used by patients aged 6 years and above with moderate-to severe persistent allergic bronchial asthma. To qualify, patients must have a positive skin-prick test or allergen-specific IgE reactivity to perennial aeroallergen. Furthermore, the eligible patients for omalizumab treatment are those whose asthma symptoms persist uncontrolled regardless of adherence to GINA step 4/5 recommendations, alongside having IgE sensitization to perennial allergens [1][12][13].

Omalizumab is administered subcutaneously every 2-4 weeks, with the specific dosing regimen tailored to each patient's body weight and circulating IgE levels. As defined in the European label for omalizumab, the medication is deemed suitable for long-term use, offering a sustained treatment option for eligible patients. To assess the effectiveness of omalizumab therapy, patients typically undergo a re-evaluation after 16 weeks of treatment. This comprehensive assessment considers various factors, including changes in asthma symptoms, lung function, and quality of life. Based on the re-evaluation findings, the healthcare providers and patient can collaboratively decide whether to continue, adjust, or discontinue of omalizumab therapy [13] A randomised controlled trial by Hanania et al. demonstrated a significant reduction of 25% in the rate of asthma exacerbations in patients treated with omalizumab compared to a placebo control group. Additionally, the omalizumab group experienced improvements in quality of life, decreased reliance on daily as-needed medications, and a reduction in the mean Asthma Symptoms Score[14]. These findings highlight the potential of omalizumab as an effective treatment for severe asthma, offering benefits beyond mere symptom control.

A Prospective real-world study by Casale et al. evaluated the safety profile of omalizumab in adults and adolescents with severe asthma. Out of 801 participants in the study, 11.2% (or 90 individuals) experienced a serious adverse event (SAE). This translates to a slightly higher rate in adults (11.6% or 85 individuals) compared to adolescents (7.2% or 5 individuals). Among these, the most common SAEs were asthma (3.2%), pneumonia (1.4%), anaphylactic events (0.5%), chronic obstructive pulmonary disease (0.5%), as well as incidences of pulmonary embolism and status asthmaticus (0.4%). It is crucial to note that all anaphylactic events were mild to moderate and occurred exclusively in the adult population. Additionally, seven fatal adverse events were reported but none were attributed to omalizumab treatment [15].

BIOLOGICAL AGENTS WHICH TARGET IL-5

IL-5 plays a pivotal role in the pathogenesis of asthma. It serves as a key regulator, governing the activation, migration, differentiation, effector function, and overall survival of eosinophils [16]. Remarkably, high eosinophil levels correlate strongly with the severity of asthma symptoms and susceptibility to asthma exacerbations, providing their crucial involvement in the pathophysiology of asthma [16]. Recognizing this significant contribution, recent research has focused on developing novel biological agents targeting either IL-5 itself or its receptor (IL-5Rα) expressed on effector cells, aiming to disrupt the IL-5 pathway and provide new therapeutic options. Presently, three such biological agents have been approved for their efficacy in countering the IL-5 pathway: mepolizumab, reslizumab, and benralizumab.

MEPOLIZUMAB

Mepolizumab, a monoclonal antibody of the IgG1 class with high affinity for IL-5, represent a treatment option for severe eosinophilic asthma. In the EU, it is approved for patients aged 6 years and above while in the USA, its indication is limited to patients aged 12 years and older. This therapeutic is specifically recommended for patients with severe eosinophilic asthma who remain uncontrolled despite adhering to GINA-defined step 4/5 treatment guideline. Eligibility criteria for mepolizumab treatment include a blood eosinophil count of ≥150 cells/μl before the initial administration or ≥ 300 cells/μl within the presiding year, alongside a history of at least two asthma exacerbations requiring systemic corticosteroid

within the past year [17]. Mepolizumab is administered subcutaneously at a consistent dosage of 100 mg, every 4 weeks [17].

Multiple studies and clinical assessments have consistently demonstrated the effectiveness of mepolizumab in improving the outcomes of patients with uncontrolled severe eosinophilic bronchial asthma. These studies have shown an overall enhancement of asthma control, marked by a reduction in the frequency of severe exacerbations, emergency room visits, hospital admissions, and corticosteroid use. Additionally, mepolizumab treatment has been shown to improve lung function and quality of life in these individuals [18][19]. While generally well tolerated, common adverse-effects associated with mepolizumab include fatigue, itching, headache, injection-side reactions, flu-like symptoms, eczema, urinary tract infections (UTIs), abdominal pain and muscles spasms [18][19].

International guidelines differ regarding the optimal duration of mepolizumab treatment before assessing its effectiveness in the severe eosinophilic asthma. The GINA suggests a trial period of approximately four months may provide sufficient information. However, the NICE recommends continuing treatment for at least one year with annual evaluation. Importantly, NICE also advices discontinuing mepolizumab treatment after one year, if asthma symptoms remain inadequately controlled [20].

RESLIZUMAB

Reslizumab, a monoclonal antibody (mAb) of the IgG4 class, received approval from both the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) in 2016. This antibody exhibits high binding affinity for interleukin-5 (IL-5), a key regulator of eosinophil development and function. As its primary mechanism of action, reslizumab reduces blood eosinophil counts by interacting with and inhibiting IL-5, leading to decreased in eosinophil production and activity. Notably, this mechanism of action closely resembles that of another IL-5 targeting monoclonal antibody, mepolizumab [21]. Reslizumab received approval as an additional therapy for adult patients with severe, uncontrolled eosinophilic asthma, requiring treatment with high dose of inhaled corticosteroids (ICS), and at least one other controller medication. This biological therapy is particularly recommended for patients with severe asthma who have experienced asthma exacerbations within the preceding year and demonstrably high blood eosinophil counts, equal to or exceeding 400 eosinophils per microliter (μl) [22]. Reslizumab is administered intravenously with the dosage determine based

on the patient's weight. The recommended dosage is 3 milligrams per kilogram (mg/kg) of body weight, and this medication is administered once every month.

Clinical studies evaluating the efficacy of reslizumab have demonstrated a notable outcome. Administration of this biological agent significantly reduced the frequency of asthma exacerbations in patients with elevated blood eosinophil levels. Additionally, these studies demonstrated improvements in both asthma symptom control and lung function parameters within the study population [21][23]. In a study conducted by Murphy et al. [24] the safety index of reslizumab was evaluated over a period of 24 months. The finding of this study indicated a favourable safety profile of reslizumab usage. Reported adverse effects were predominantly mild, including headache, cough, sinusitis, and nasopharyngitis [24]. While reslizumab exhibits notable clinical efficacy, its intravenous administration presents a significant distinction from subcutaneous mepolizumab and benralizumab, potentially impacting patient comfort. However, investigations into a subcutaneous fixed-dose (110 mg) formulation of reslizumab have not shown significant improvements in reducing acute exacerbations or oral corticosteroids dependence in patients with severe uncontrolled eosinophilic asthma [25].

BENRALIZUMAB

Benralizumab is a monoclonal antibody, belonging to IgG1 class that has been humanized and rendered afucosylated, received approval in 2017. These means it's a highly specific, engineered antibody designed to target a particular molecule involved in asthma. Originally derived from non-human species, benralizumab undergoes a process called humanization to make it more compatible with the human immune system. This mitigates the risk of an immune response, a potential side-effect of using non-human antibodies. Benralizumab specifically targets the alpha subunit of interleukin-5 receptor (IL-5R) on eosinophils, a type of white blood cell linked to allergic inflammation. Furthermore, this monoclonal antibody works by triggering a process called antibody-dependent cell-mediated cytotoxicity (ADCC), where natural killer cells attack and eliminate eosinophils. This mechanism ultimately leads to a significant reduction in circulating eosinophil levels [26][27].

This biological agent has been approved as an additional treatment option for uncontrolled severe eosinophilic bronchial asthma in adults by the European Medicine Agency (EMA), and in patients aged 12 years and above by the U.S. Food and Drug Administration (FDA).

Eligibility criteria include a blood eosinophil count of equal to or exceeding 300 eosinophils per microliter (μl) [28]. The recommended administration regimen involves subcutaneous injection at a monthly dose of 30 mg for the initial three months. Following this initial period, the administration frequency is adjusted to once every 8 weeks [28].

Extensive clinical studies involving phage analysis in patients with moderate to severe bronchial asthma treated with benralizumab have shown promising results. These studies documented a significant reduction in the frequency of asthma exacerbations, enhancements in lung function parameters, and decreased reliance on oral corticosteroids (OCS) [26][27][29]. Furthermore, a comprehensive analysis of these research investigations has identified several factors associated with a positive treatment response. These predictors include a history of at least four asthma exacerbations in the past year, adult-onset asthma, the presence of nasal polyps, and a pre-bronchodilator forced expiratory volume in one second (FEV1) below 65% of the predicted value [26][27][29]. This combination of findings provides valuable insights for optimizing patient selection for benralizumab therapy in severe bronchial asthma, informing clinical decision-making. Common adverse effects of benralizumab therapy include headache, post-initial dose fever, nasopharyngitis and in some cases worsening of asthma. [26][27][29]. Remarkably, benralizumab depletes blood eosinophils almost completely within 24 hours, comparable to the comprehensive reduction achieved by mepolizumab in airway eosinophils [30] [31]. Additionally, benralizumab demonstrates sustained efficacy, suppressing nasal eosinophils completely after 6 months of treatment.

BIOLOGICALS TARGETTING IL-4 AND IL-13

IL-4 and Il-13 are key orchestrators of type-2 inflammation, a major contributor to asthma pathogenesis. IL-4 promotes the differentiation of T helper (Th) cells into the type-2 (T2) subset, which in turn drives B-cell to swich antibody production towards IgE, an immunoglobulin class crucial for allergic responses. Additionally, IL-4 facilitates eosinophil migration from the bloodstream into tissues. On the other hand, IL-13 exerts direct effects on airway smooth muscle, leading to increased responsiveness (Hyperresponsiveness) to triggers excessive mucus production and airway remodelling, characterized by structural changes that further exacerbate airway obstruction [32] [33]. Currently, dupilumab remains the only approved biological agent specifically targeting both IL-4 and IL-13.

DUPILUMAB

Dupilumab, a fully human IgG4 monoclonal antibody introduced in 2018, represents a significant therapeutic advancement. This antibody effectively inhibits signalling from both interleukin-4 (IL-4) and interleukin-13 (IL-13) by binding to their shared receptor alpha subunit. This biological agent is approved as an additional therapy for uncontrolled severe asthma in patients aged 12 years and older who have received the highest level of standard treatment as defined by GINA 4/5 guidelines. Eligible patients must demonstrably exhibit type 2 inflammation, marked by elevated blood eosinophil levels and/or increased fractional exhaled nitric oxide (FeNO), and/or patients who are reliance on OCS. Dupilumab is administered subcutaneously, with an initial loading dose of either 400 mg (two 200 mg injections) followed by 200 mg every two weeks, or 600 mg (two 300 mg injections) followed by 300 mg every two weeks [34]. The European Medicines Agency (EMA) guidelines recommended a 600 mg dupilumab dosage regimen for two distinct patient groups: patients with severe bronchial asthma requiring oral corticosteroids, and those diagnosed with atopic dermatitis [34].

However, dupilumab demonstrates remarkable efficacy in multiple aspects of severe asthma management. It significantly reduces the frequency of asthma exacerbations, improves lung function and overall asthma control, and importantly, allows for a reduction in reliance on oral corticosteroids (OCS). Remarkably, these positive effects are observed regardless of blood eosinophil counts, broadening its potential application in diverse severe asthma phenotypes [35] [36] [37] [38]. Certainly, while initiating dupilumab therapy, some patients experience a temporary increase in blood eosinophil count. This phenomenon is likely not due to increased production of eosinophils, but rather their impeded migration from the bloodstream into tissues [38]. Furthermore, treatment efficacy with dupilumab can be assessed through T2 inflammatory markers including a reduction in total serum immunoglobulin E (IgE) levels and fractional exhaled nitric oxide (FeNO) measurements. However, potential adverse effects including injection sites reactions, upper respiratory tract infections as well as conjunctivitis, and other associated conditions have been reported [35] [36] [37] [38].

ANTIBODIES TARGETING EPITHELIAL CYTOKINES

Airway epithelial cells, triggered by allergens, viruses, or even pollutants, release specific cytokines like TSLP (thymic stromal lymphopoietin), IL-25, and IL- 33, fuelling the flames of inflammation in asthma [39]. This has led to the hypothesis that targeting these “upstream”

cytokines with specific biological agents, compared to broader approaches targeting downstream type 2 cytokines, could offer benefits for a wider range of asthma patients [39] [40]. The idea is to intervene earlier in the inflammatory cascade, potentially leading to better symptom control and management of related conditions. Recent studies have yielded promising results for novel therapeutic agents targeting specific epithelial cytokines in severe asthma. These include: an anti-TSLP human monoclonal antibody called Tezepelumab, an anti-interleukin-33 human monoclonal antibody known as Itepekimab and a human monoclonal antibody targeting interleukin-33 receptors also known as suppressor of tumorigenicity 2 (ST2), called as astegolimab [41] [42] [43]. These agents demonstrate potential for improved asthma outcomes in various patient populations, offering a more targeted approach compared to broader type 2 cytokine inhibition.

Tezepelumab, a powerful weapon in the fight against severe asthma, targets a key player in the disease process: thymic stromal lymphopoietin (TSLP). This monoclonal antibody of human origin, belonging to the IgG2 class, specifically inhibits the activity of TSLP, a cytokine produced by airway epithelial cells known to fuel asthma development [39]. Designed to mimic the body's natural immune response, Tezepelumab is precisely engineered from a single immune cell clone using advanced technology. Tezepelumab is approved for use in patients aged 12 years and above with severe asthma. It is administered subcutaneously every four weeks at a dose of 210 mg.

A phase 3 randomized controlled trial (RCT) evaluated the effectiveness of Tezepelumab, a new drug targeting a key player in asthma, TSLP. This study, involving adults and adolescents with severe, uncontrolled asthma, demonstrated a significant reduction in annual asthma exacerbations. Among participants with baseline eosinophil levels below 300 per microliter, Tezepelumab administration at a subcutaneous dosage of 210 mg every 4 weeks for a year led to a remarkable 56% reduction in asthma exacerbations compared to those who did not receive the drug. Even for those with baseline eosinophil levels at or exceeding 300 per microliter, Tezepelumab still exhibited a significant 41% decrease in the yearly asthma exacerbations [41]. This innovative drug, compared to a placebo, delivered significant benefits for diverse asthma subtypes, including those with high and low levels of type 2 inflammation. Patients experienced fewer asthma flare-ups, leading to improved control of their asthma, better lung function and an overall enhanced sense of wellbeing. Moreover, Tezepelumab exhibited a gradual decline in total IgE levels in the blood, indicating a dampening of allergic response.

It also led to rapid decreases in blood eosinophil levels and FeNO, and reduced airway hyperresponsiveness, a key feature of asthma [44]. Tezepelumab exhibited a similar safety profile to both the active treatment and placebo groups in the study [41]. In a bronchoscopy study, Tezepelumab demonstrated a significant reduction in the number of eosinophils within the airway submucosa. However, Tezepelumab did not have a notable effect on the number of mast cells, neutrophils, or T-cells in the same submucosal region [44]. This suggests that Tezepelumab primarily targets eosinophils, while having minimal effects on other inflammatory cell types in the airways.

Furthermore, Itepekimab emerged as a novel monoclonal antibody specifically targeting interleukin-33, a key upstream alarmin intricately involved in the inflammatory response. A phase 2 clinical trial involving patients diagnosed with moderate to severe asthma revealed that the administration of Itepekimab at a subcutaneous dosage of 300 mg every 2 weeks over a span of 12 weeks effectively curbed the loss of asthma control and enhanced lung functions compared to a placebo control group. Additionally, this treatment resulted in a significant reduction in the continued use of inhaled corticosteroids (ICS) in combination with long-acting beta agonists (LABA) [42].

Moreover, Astegolimab emerges as a human monoclonal antibody belonging to the IgG2 class, specifically designed to inhibit IL-33 signalling. The mechanism of action of this monoclonal antibody revolves around targeting the IL-33 receptor, known as ST2. A phase 2b randomized controlled trials (RCTs) focused on patients with severe asthma characterized by low eosinophils count revealed that astegolimab, administered subcutaneously at doses of 70 mg, 210 mg, or 490 mg every 4 weeks, effectively reduced asthma exacerbations compared to a placebo control group. These findings indicate that astegolimab may hold promise as a treatment option for patients experiencing severely uncontrolled asthma with low eosinophil counts, particularly in terms of reducing exacerbations [43].

SELECTING APPROPRIATE INITIAL BIOLOGICAL AGENTS

Currently, there is a paucity of head-to-head RCTs that provide comparative data on the efficacy, real-world effectiveness, and safety profile of various monoclonal antibodies for the

treatment of severe asthma. This dearth of high-level evidence presents a significant gap in guiding clinical decision-making for healthcare providers.

Despite the availability of various biological agents for the treatment of severe uncontrolled bronchial asthma, physicians must carefully consider several key factors before selecting the most appropriate medications for individual patients. These factors include accurate diagnosis of severe asthma, identification of the specific asthma phenotypes and endotypes, thorough assessment of clinical biomarkers such as blood or sputum eosinophils, IgE levels and fractional inhaled nitric oxide (FeNO) and considering of patient-centered aspects (as depicted in Fig.1). Moreover, the decision-making process should incorporate additional criteria such as dosing frequency, the route of administration (subcutaneous and intravenous), the age at onset of asthma, relevant biomarkers, the presence of coexisting conditions like atopic dermatitis and nasal polyposis, the need for ongoing monitoring by healthcare professionals, cost of medications, insurance coverage considerations, risk-benefit profile, and patient preferences. These factors collectively inform the selection of an appropriate and available biological agents for the individual patient's unique asthma management needs [45].

In the management of patients with severe bronchial asthma, stratification based on specific asthma phenotypes, endotypes and biomarkers is paramount for making effective treatment decisions. For patients experiencing an allergic phenotype and eosinophilic severe asthma characterised by elevated blood IgE levels and confirmed sensitivity to perennial aeroallergens, omalizumab emerges as the initial treatment of choice [45]. Conversely, in cases where patients exhibit a non-allergic eosinophilic phenotype, the utilization of an anti-IL-5 biological agent emerges as a more appropriate choice. Furthermore, for patients with severe type 2 eosinophilic asthma who are dependent on oral corticosteroids (OCS) for disease control, the consideration of IL-4/IL-13 targeted therapies becomes particularly beneficial. This approach effectively addresses the unique needs of patients with severe asthma who require OCS to maintain diseases management [45]. This stratified treatment approach considers the distinct asthma subtypes, biomarkers, and OCS dependence, offering a more personalized and effective therapeutic strategy for patients with severe bronchial asthma.

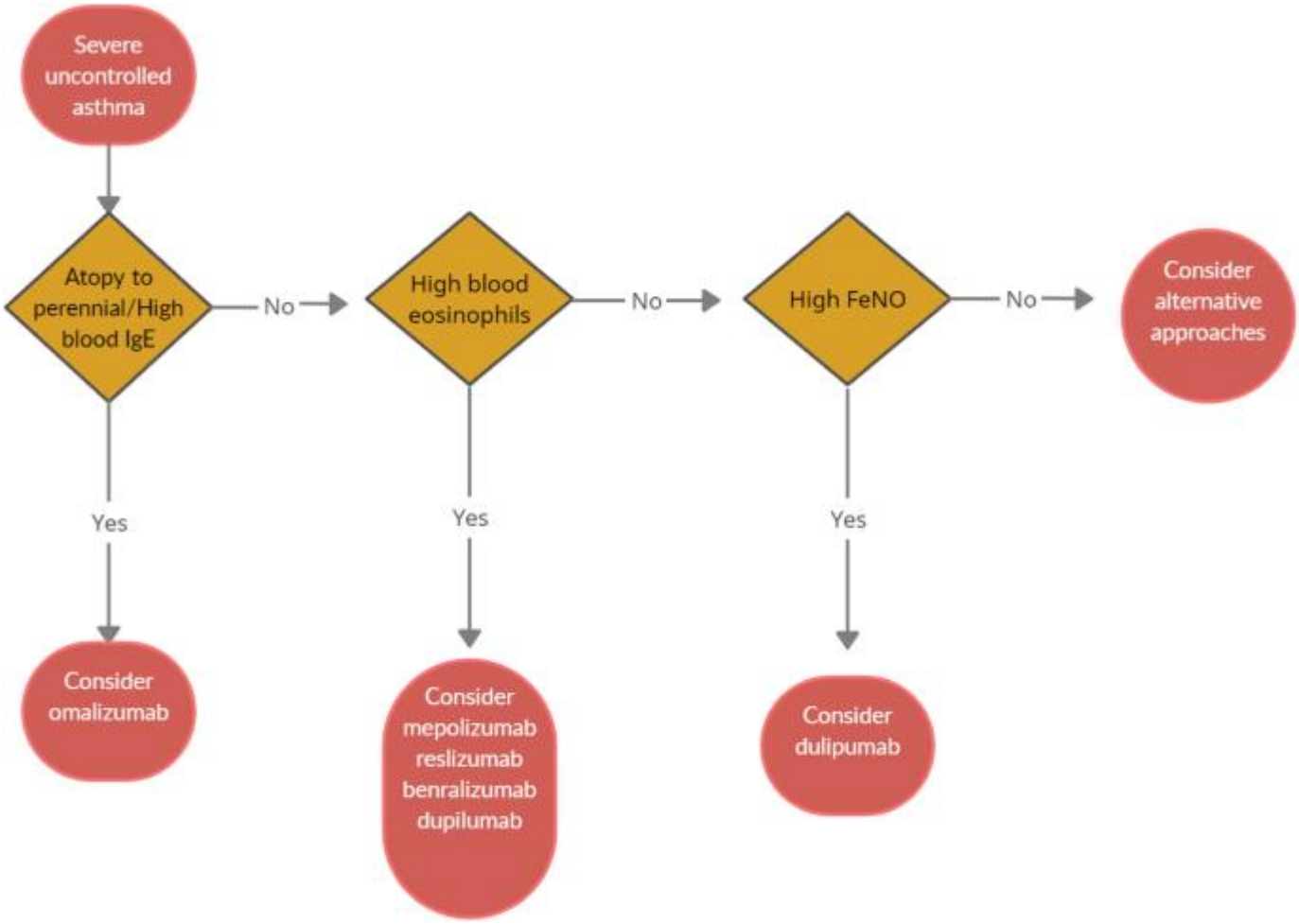


Figure 1. Algorithm for Selecting Initial Biological Agents for severe uncontrolled asthma [22]

Currently, there are significant gaps in our ability to make specific recommendations regarding which anti-IL-5 biological agent is the best choice among the available options. Comparative studies have not yet provided enough conclusive data to guide us in this regard. Consequently, the decision on the most appropriate anti-IL-5 biological agents is often based on practical experience and involves a collaborative effort between the patient and their physicians. As a result of the lack of clear comparative evidence, the selection of the appropriate anti-IL-5 biological agent is influenced by clinical judgement, individual patient factors, and active patient involvement in the decision-making process. Patients play a crucial role in decision-making process by sharing their preference and concerns. This highlights the

importance of tailoring treatment choices to the unique needs and preferences of each patient while considering available options and expert medical guidance.

THE USE OF BIOLOGICAL AGENTS FOR SEVERE ASTHMA DURING COVID-19 ERA

The GINA guidelines advised patients diagnosed with asthma to continue using all asthma controller medications, including inhaled corticosteroids, to maintain optimal asthma control in the context of the Covid-19 pandemic. Furthermore, the use of biological therapies was recommended for patients with severe asthma who are eligible for this therapy, aiming to minimize the need for oral corticosteroids (OCS) as far as possible [46]. These guidelines underscore the importance of maintaining effective asthma management, particularly in severe cases, to reduce reliance on OCS and potentially enhance COVID-19 susceptibility.

The American Academy of Allergy, Asthma, and Immunology (AAAI) provided crucial observations indicating that there is currently no substantial evidence to suggest that the immune response to COVID-19 will be impaired in asthma patients receiving anti-IL-5 (anti-IL-5Ra), anti-IL-4/Il-13, or anti-IgE medications. Given the absence of any data indicating potential harm, the continued administration of biological therapies during the COVID-19 pandemic is considered reasonable, particularly for patients for whom these therapies are clearly indicated and have previously demonstrated efficacy [47].

The American College of Allergy, Asthma, and Immunology (ACAAI) emphasized the importance for continuing asthma medication regimens, including inhaled corticosteroids and biologicals, for patients with severe asthma. This recommendation was based on the absence of evidence suggesting that these medications increase the risk of contracting COVID-19. Furthermore, given the current lack of information regarding the discontinuation of biological agents for severe asthma, the ACAAI recommended to maintain this treatment especially for patients with severe asthma who may face an elevated risk of COVID-19 infection. Ensuring optimal control of their chronic condition is crucial to minimize the risk of asthma exacerbations, which could potentially worsen CODID-19 outcomes [47].

In response to frequent questions raised during the onset of COVID-19 pandemic, the European Respiratory Society (ERS) and European Lung Foundation (ELF) provided crucial recommendations regarding the use of anti-IL-5, and omalizumab. Their guidance emphasized the importance of maintaining ongoing asthma medication regimens including biological agents without interruption or modification due to concerns related to COVID-19. Cessation of these medications could pose a significant risk of worsening asthma control, potentially leading to the need for medical intervention and hospital admissions. Additionally, it was highlighted that anti-IL-5 administration should not impact the risk of contracting COVID-19. Continuous administration was considered theoretically beneficial in reducing the risk of an asthma exacerbation if a patient were to contract the virus. Regarding omalizumab, the recommendation underscored the importance of patients continuing all regular asthma treatments, including omalizumab, to prevent asthma attacks during the COVID-19 pandemic [47]. These recommendations prioritize asthma control and patient well-being during the ongoing public health crisis.

British Thoracic Society (BTS) strongly advised to continue the biological treatment for patients with severe asthma during the COVID-19 pandemic. Additionally, they emphasized the crucial role of transition efforts, specially, in enabling the shift from clinic-based administration to home-based care. Patients are provided with guidance and support to self-administer biological agents in a home-based setting to ensure the uninterrupted continuation of their treatments [47]. This approach adjusts with the goal of maintaining adequate asthma management while minimizing the need for clinical visits in person during the COVID-19 pandemic.

In their study, Morais et al. further emphasized the potential adverse consequences of discontinuing biological therapies during Covid-19 pandemic. Abruptly halting biological treatment could lead to a heightened risk of asthma exacerbations, necessitating increased reliance on systemic corticosteroids. Furthermore, patients may experience a higher frequency of emergency room visit and hospitalizations. These adverse outcomes not only pose a significance health risk for patients but also represent potential risk factors for contracting SARS-CoV-2 infection. [47]. This underscores the importance of maintaining consistent and effective asthma management, including the continued use of biological therapies to mitigate these risks during the ongoing pandemic.

Furthermore, Hanon and colleagues conducted an analysis of a cohort of 676 adult patients with severe asthma who were undergoing treatment with biological agents, including 129 who were receiving omalizumab. This analysis revealed that despite a few cases of COVID-19 infection were found within this cohort, none of these infections resulted in fatalities or led to a notably severe disease course. Importantly, this study found no evidence to suggest that treatment with biological agents for severe allergic or severe eosinophilic asthma was associated with a higher risk of SARS-CoV-2 infection or a more severe form of COVID-19 [48]. These findings provide robust support for the current clinical practice of continuing biological treatment in severe asthma cases during the COVID-19 pandemic.

CAN BIOLOGICAL THERAPY BE USED IN PATIENT WITH ASTHMA ALONGSIDE TREATMENT FOR COVID-19 INFECTION?

Lommatzsch et al. presented a case report of a 52-year-old man with severe allergic asthma who contracted SARS-CoV-2 infection. The patient received biological treatment with omalizumab while under home quarantine. Despite the infection, the patient's asthma symptoms remained stable, and no adverse effects related to the therapy were observed. The authors concluded from this observation that patients with allergic asthma may have a reduced risk of COVID-19 and suggested that omalizumab, an anti-IgE antibody could potentially enhance the immune response against viral infections. [49]

Furthermore, Morais et al. emphasized that the decision of whether to continue or temporarily suspend biological therapy for severe asthma in the context of a patient infected by SARS-CoV-2 should be a case-by-case basis. This decision should be guided by a multidisciplinary healthcare team, considering a comprehensive evaluation of the patient's clinical status, including the severity of asthma and any co-existing medical conditions. Such a decision-making process should be informed by available information and evidence, ensuring that it aligns with the unique needs and circumstances of each patient [47].

Extensive research on the pathogenesis of tissue injury related to cytokine storm in COVID-19 has revealed a predominant role of pro-inflammatory cytokines associated with type 1 and type 3 responses. These cytokines promote inflammatory activation and neutrophilia. Intriguingly, it has been observed that the type 2 immune response and regulatory

T-cell (Treg) response can counterbalance these pro-inflammatory effects and may have a positive impact on disease outcomes [50]. Considering this context, it is crucial to recognize that suppressing the type 2 response in severe and critical COVID-19 cases could potentially aggravate the disease. Therefore, in exceptionally severe cases, discontinuation of biological agent targeting the type 2 immune response may be considered. This decision should be made carefully, considering the individual patient's specific clinical presentation and severity of COVID-19 infection, accompanied by close monitoring and medical supervision to ensure the best possible outcome.

In accordance with the guidelines provided by the European Academy of Allergy and Clinical Immunology (EAACI), it is strongly recommended that all patients who have contracted a SARS-CoV-2 infection, irrespective of the severity of the infection, should temporarily suspend the administration of biological therapies until they have fully recovered. This period of suspension of biological treatment should extend a minimum of two weeks. Upon confirming the recovery from the disease through a negative SARS-CoV-2 test result, the resumption of biological therapies should be initiated. Notably, the re-initiation of biological therapies should not occur sooner than two weeks after the onset of the disease or the initial positive test result (as depicted in Figure 2) [51]. Adhering to this recommended timeframe is crucial to ensure a safe and effective approach to re-introducing biological treatments for individuals who have experienced a SARS-CoV-2 infection.

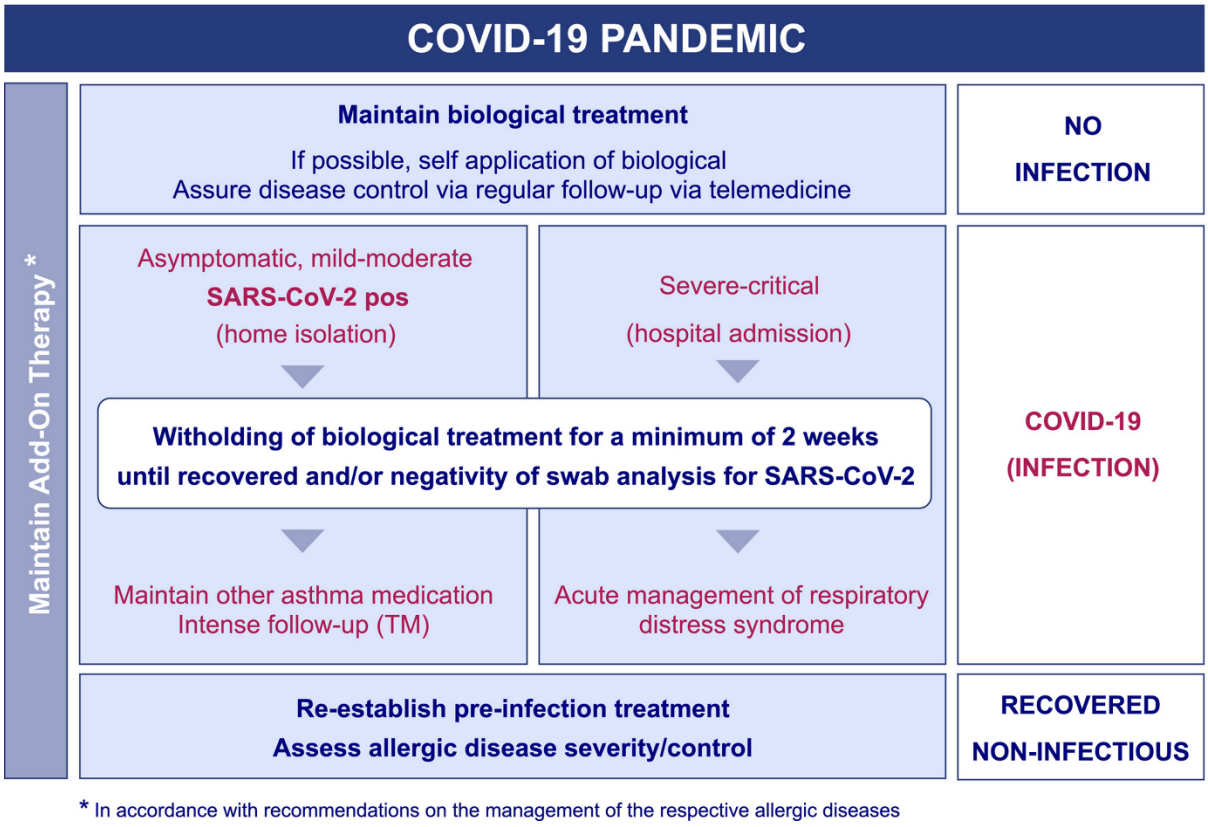


Fig. 2: Clinical algorithm on the use of biologicals for the treatment of allergic disease in the context of COVID-19 [51].

CURRENT GIDELINE APPROACH MANAGEMENT AND CHARACTERISTICS OF SEVER ASTHMA

The GINA distinguishes between two categories of asthma: difficult-to-treat and severe asthma, with specific guidelines and recommendations for each.

Difficult-to treat asthma: in this group, suboptimal asthma control is associated with factors such as incorrect inhaler technique, limited adherence to medication use, patient's comorbidities (including conditions like obesity), modifiable risk factors (such as smoking), and medication side effects. These factors contribute to suboptimal asthma managements and control [52].

Severe asthma: severe asthma is characterized by persistent poor symptom control despite optimised adherence to treatment involving high-dose inhaled corticosteroids (ICS) in

combination with long-acting-beta-agonists (LABA) and proper inhaler technique. Patients with severe asthma continue to experience inadequate asthma control despite their best efforts. Recent focus for biological therapies has been on patients exhibiting severe eosinophilic bronchial asthma, as this specific phenotype represents a subgroup that may benefit from these specialized treatments. The GINA 2022 asthma guideline provides a comprehensive recommendation tree for the diagnosis, management, and prevention of asthma. Within this framework as the severity of asthma increases, there is a stepwise escalation in the primary treatment medications, including inhaled corticosteroid plus a secondary controller such as long-acting beta agonist, leukotriene modifiers and/or long-acting anti muscarinic agents [52].

While significant progress has been made in achieving disease control in patients with low or mild asthma, approximately 3-10% of asthma population remains uncontrolled despite adherence to optimised ICS-LABA therapy. Additionally, reducing optimal treatment can exacerbate contributory factors or symptoms, especially in cases of severe asthma. For patients with severe bronchial asthma at GINA 4/5 treatment levels, the current approach involves the addition of biological agents to their treatment regimen (as depicted in Fig. 3). This modification reflects a shift in care strategies for severe asthma to enhance control and improve the quality of life for these patients [52]. In situation where patients continue to experience persistent symptoms and/or exacerbations despite being prescribed high doses of inhaled corticosteroids (ICS), it is crucial to assess the clinical or inflammatory phenotype. This evaluation serves as a crucial step in determining the potential need for add-on biological therapy to enhance asthma management [52]

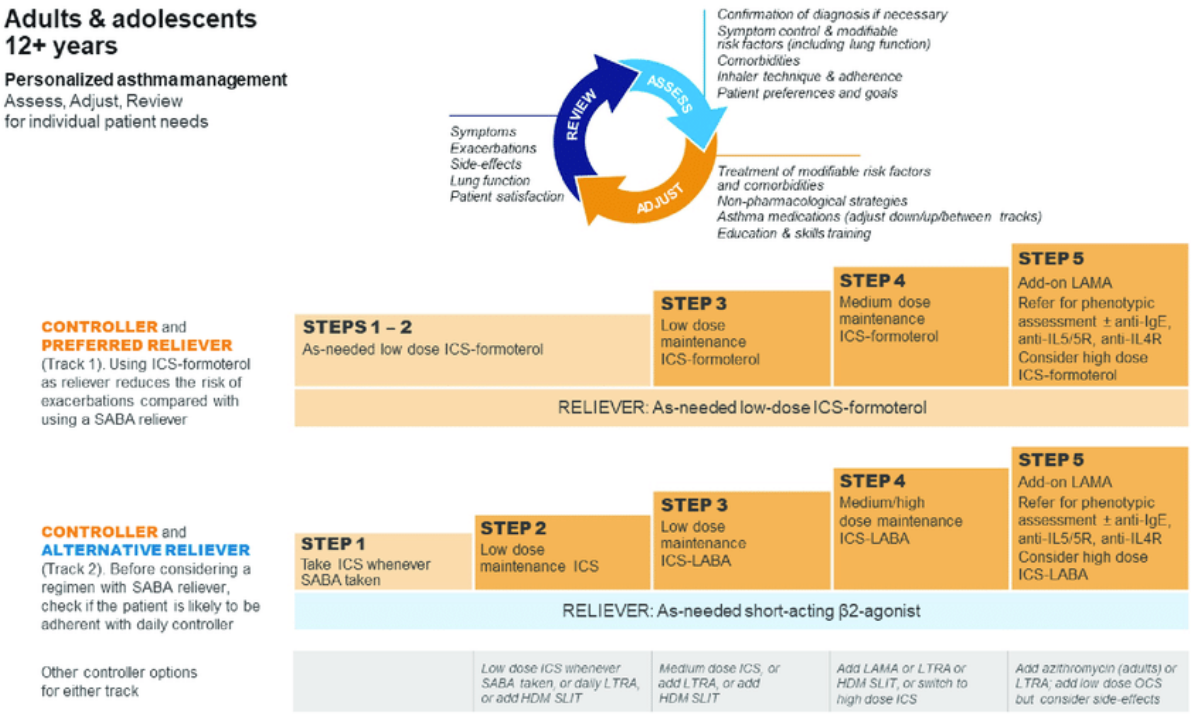
Furthermore, by identifying the specific asthma phenotype such as T2 inflammatory severe asthma, which may involve characteristics such as elevated eosinophil levels, allergic triggers, or other pertinent factors (as depicted in Fig. 4), healthcare professional can make informed and tailored decisions regarding the incorporation of additional biological therapies [9] [52]. This personalized approach is crucial to improve asthma control and enhance the overall quality of care for these individuals.

The primary criteria for initiating first-line add-on biological therapy for severe asthma are based on the evaluation of specific biomarkers and predictors of asthma treatment response. This decision-making process also considers various factors including the presence of comorbidities, dosing frequency, route of administration (subcutaneous or intravenous) and patient preferences. Following the initiation of biological therapy, the patient's response is

assessed after a period of four months. During this assessment, several critical factors must be considered. These factors include the reduction of asthma exacerbations, utilization of health care services, degree of enhancement of lung-function, effect on coexisting condition, the percentage reduction in the glucocorticoid dose while maintaining of asthma control, adverse-effects associated with the chosen asthma management strategy and patient satisfaction with treatment, including their perception of symptoms control and overall well-being. If a favourable response to the treatment is observed, therapy continuation is warranted, and subsequent re-evaluations are typically conducted at intervals of every 3 to 6 months.[52]. This comprehensive approach ensures that the selection and administration of biological therapies align with patient-specific factors, optimize asthma management, and provide ongoing assessment to maintain treatment efficacy.

Moreover, the GINA 2022 guidelines provide recommendations for switching to alternative biological therapies if a patient does not respond adequately to their initial agent but remains eligible for T2 targeted therapy. However, these guidelines do not specify precise criteria for defining a "good response". Instead, the decision to pursue alternative biological therapies is based on a comprehensive evaluation that considers multiple factors.

In cases where a patient exhibits an inadequate response with persistent symptoms or exacerbations, it is crucial to consider potential factors such as suboptimal adherence to background controller therapy or the biological agent itself before considering a switch to a different biological agent. Additionally, inadequate management of coexisting condition (e.g., obesity and rhinosinusitis) and development of neutralizing antidrug antibodies may contribute to suboptimal responses to biological therapy. Furthermore, before deciding to transition to another biological agent, it is essential to reassess the asthma phenotype including biomarkers such as blood eosinophil count, serum IgE levels, and fractional exhaled nitric oxide (FeNO) [52] Additionally, the considerations for transition to a different biological therapy encompass the intensity of patient's treatment, including their oral corticosteroids (OCS) doses, as well as any side effects associated with the medications. Evaluations also include assessment of symptoms control, the frequency of exacerbations, lung function, and, importantly, the patient's preference [52]. By weighting these various factors, healthcare professionals can make informed decisions regarding the selection of alternative biological therapies, ensuring that the chosen treatment is tailored to the patient's individual needs and optimizes their asthma management.



Figur-3: Personalized asthma management for adults and adolescents to control symptoms and minimize prospective risks associated with asthma [52].

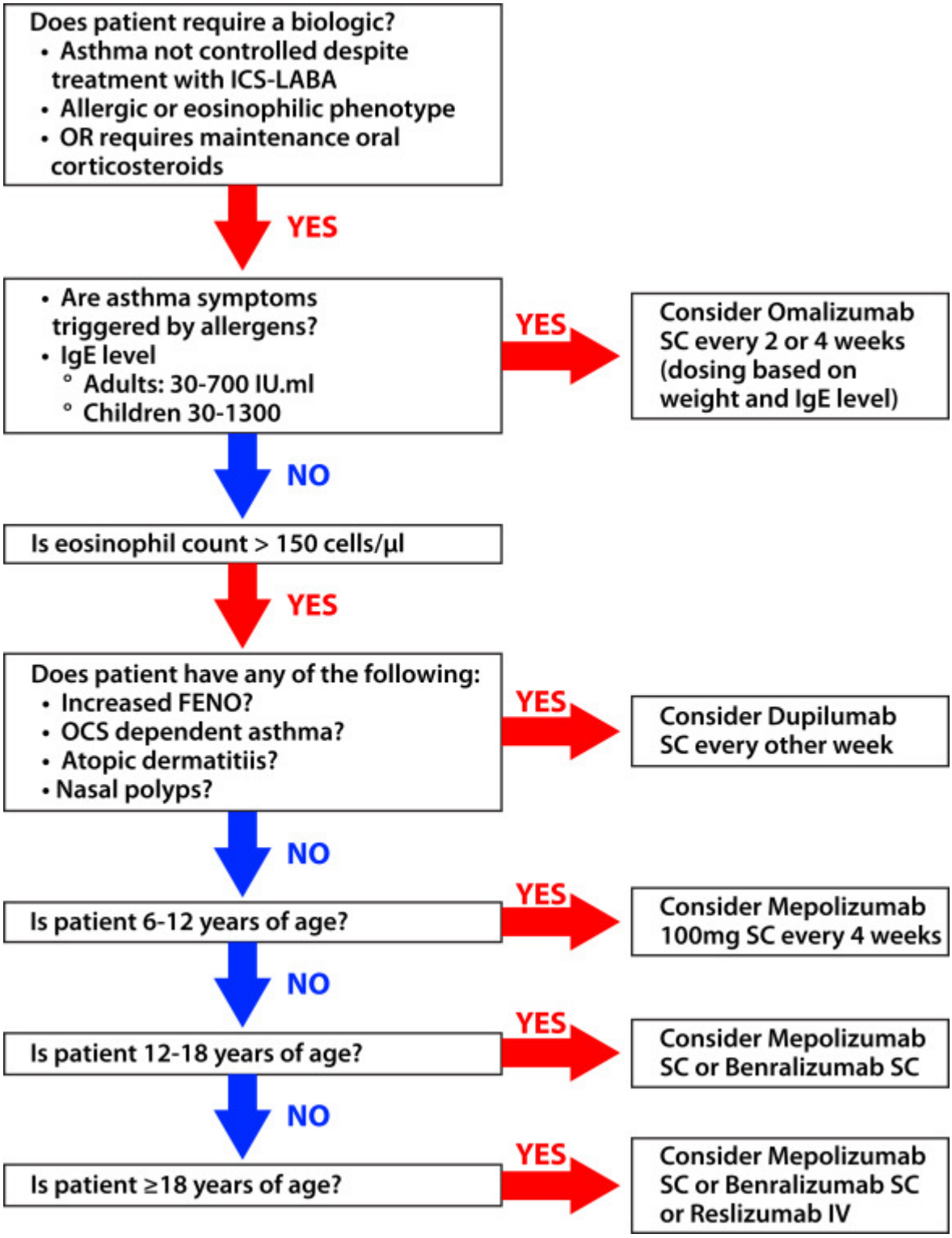


Figure-4: Suggested algorithm for decision-making process in selecting a biologic for the treatment of T2 severe asthma [9]. (SC-subcutaneously, IV-intravenously).

CASE REPORTS

CASE 1

A 58-years-old female patient was referred to an allergist's clinic in July 2020 due to her persistent struggle with severe asthma. The patient presented with a cluster of symptoms, including dyspnoea during physical exertion, and 2-3 times per week at nighttime, chest tightness, wheezing, difficulty in clearing her airways, nasal congestion, and sneezing.

The patient's medical history reveals that she was initially diagnosed with allergic bronchial asthma in 1995, following a hospital admission due to prolonged episodes of shortness of breath. Remarkably, after her initial diagnosis, she remained free of symptoms and did not require or use any asthma medications until the year 2017. However, in 2019, she resumed asthma treatment with inhaled corticosteroids due to the recurrence of frequent shortness of breath episodes, which re-emerged following a prior episode of pneumonia. Over the past six months, her condition has escalated, characterised by four severe asthma exacerbations requiring hospitalization on two occasions. During these exacerbations, the patient received treatment with oral corticosteroids (OCS) to manage her asthma attacks effectively.

Furthermore, the patient's medical history includes the effective management of chronic rhinosinusitis using mometasone furoate nasal spray. Additionally, she has been receiving angiotensin-converting enzyme inhibitors to regulate her hypertension. It is noteworthy that she had a 20-years history of smoking, which she successfully quit one year ago. Her current body mass index (BMI) is indicative of obesity with a value of 40.2 kg/m^2. Moreover, her family history reveals a notable presence of bronchial asthma as both her father and granddaughter have been diagnosed with this condition. This comprehensive compilation of patient's medical history provides essential background information for understanding her overall well-being, which may influence the management of her asthma and the decisions regarding treatment options.

The patient's spirometry results revealed severe lung obstruction, with a Forced Expiratory Volume in 1 second (FEV1) of 0.78 Liters, representing only 32% of her predicted value. The presence of eosinophilic inflammation was confirmed by elevated blood eosinophil levels of 0.73 × 109/L (7.8%) (Normal value 0,02-0,50 x109/l), as well as eosinophils detected in bronchial aspirate at a level of 22%. Additionally, the patient had positive skin prick tests for

various aeroallergens, including Dermatophagoides pteronvssinus (2+), Dermatophagoides farinae (4+), and dog hair (2+), which further supported the diagnosis. Fibro bronchoscopy findings indicated chronic bronchitis. Laboratory tests for Antinuclear Antibody (ANA) and Anti-Neutrophil Cytoplasmic Antibody (ANCA) were negative, and no helminths were detected in the patient's faeces. Elevated Total IgE levels of 418 U/ml (normal value 0-100 U/ml) were observed. Moreover, a thoracic computed tomography (CT) scan revealed mild bronchiectasis in the lower parts of the lungs.

Considering these comprehensive assessments, the patient was diagnosed with severe, uncontrolled eosinophilic allergic bronchial asthma, coexisting with bronchiectasis and perennial allergic rhinitis.

Following this diagnosis, the patient was referred to a dietitian for dietary guidance and physical activity counselling as part of an integrated management plan.

The patient's treatment regimen was progressively intensified by pulmonologist, culminating in the administration of high-dose inhaled corticosteroids (ICS) combined with long-acting-beta-agonist (LABA) therapy. Formoterol/budesonide 4.5/160 mcg was administered as two puffs three times daily, while budesonide 400 mcg was prescribed additionally twice daily for maintenance therapy (1200mcg+400mcg=1600mcg- high dose according to GINA). To manage acute symptoms, ipratropium bromide/fenoterol hydrobromide 20/50 mcg was prescribed as needed, with up to four to six times permitted throughout the day. Furthermore, the patient was advised to use a nasal spray containing mometasone furoate 50 mcg, administered as two puffs daily, to address concurrent allergic rhinitis.

Despite the intensified treatment regimen, proper inhaler technique and reported adherence to therapy, the patient continued to experience frequent asthma symptoms and elevated blood eosinophil levels. Furthermore, In the last six months, she experienced four asthma exacerbations, with two requiring hospitalizations. Due to these concerns, her doctor prescribed a short-term OCS (Prednisolone) regimen of 10 mg, which the patient only took during exacerbations. The patient experienced dyspnoea even on minimal physical activity, and persistent poor asthma symptoms control despite receiving optimal asthma treatment. Spirometry results further confirmed the presence of lung obstruction, with a low FEV1/FVC

ratio of 46% and an FEV1 of 32%. These clinical findings highlighted the challenging nature of the patient's asthma and the need for alternative therapeutic approaches.

Subsequently, on October 7, 2020, the patient's treatment regimen was augmented with subcutaneous injections of benralizumab, a monoclonal antibody that targets the alpha subunit of the IL-5 receptor. She received 30 mg of benralizumab every 4 weeks for the initial 3 months, and after 3 months- every 8 weeks. Following four months of benralizumab treatment, significant improvements were observed in the patient's pulmonary function parameters compared to the pre-benralizumab treatment period. While airflow limitation persisted (FEV1 50%, FEV1/FVC ratio 60%), the patient's asthma control markedly improved, with no further exacerbations reported. This resulted in the cessation of the use of systemic oral corticosteroids (OCS), and a reduction in the required ICS dosage. Additionally, the patient's blood eosinophil levels significantly reduced to zero, indicating a substantial reduction in eosinophilic inflammation. Furthermore, the patient's quality of life significantly improved as assessed through the Mini Asthma Quality of Life Questionnaire (Mini AQLQ). In the light of these positive outcomes, benralizumab treatment was continued, and the patient's progress was systematically re-evaluated at 12-month intervals.

On January 4, 2021, after three months of benralizumab therapy, the patient developed a fever of 39°C. Subsequent RT-PCR testing confirmed SARS-CoV-2 infection on January 8, coinciding with her husband's COVID-19 diagnosis. The patient's condition deteriorated, leading to the onset of dyspnoea on January 14. She was subsequently hospitalized in the COVID-19 department of the Centre of Infectious Disease on January 15 and received medical care for seven days, resulting in improved health. In response to the COVID-19 symptoms and a confirmed SARS-CoV-2 infection, the administration of benralizumab was temporarily postponed for two weeks. Subsequently, after receiving a negative SARS-CoV-2 test, benralizumab treatment was resumed.

After 12 months of benralizumab treatment, the patient underwent a comprehensive reassessment, demonstrating sustained improvement in asthma control with no documented exacerbations during this period. Notably, the patient remained free from any significant adverse effects associated with benralizumab treatment throughout the 12-month period. These favourable outcomes underscore the potential benefits of benralizumab in managing severe, uncontrolled eosinophilic allergic bronchial asthma in this patient, even in the presence of a SARS-CoV-2 infection.

CASE 2

A 51-year-old woman presented to an allergist with a constellation of respiratory and allergic symptoms, including a persistent dry cough, nocturnal dyspnoea (shortness of breath at night), nasal congestion, eye itching, and hyposmia (reduced sense of smell). Physical examination and comprehensive medical history revealed a consistent pattern of respiratory clinical manifestations, including episodes of coughing, shortness of breath, wheezing, and the presence of nasal polyps.

The patient's medical history reveals a diagnosis of allergic bronchial asthma at the age of 18 years, followed by a diagnosis of allergic rhinitis at the age of 30 years, Additionally, nasal polyps were identified as part of her clinical presentation. Over the last two years, she has experienced a high frequency of asthma exacerbation, requiring ongoing treatment with an inhaler containing formoterol/budesonide, a nasal spray containing mometasone furoate, and systemic corticosteroids, which have been administered almost continuously due to the recurrence and severity of these exacerbations.

Moreover, the patient's comprehensive medical history reveals several important facets of her health. She is currently under treatment for arterial hypertension, using medications such as angiotensin converting enzyme inhibitors (ACEIs) and verapamil. Additionally, her medical history includes two surgical procedures for vertebral hernias. On an occasional basis, she relies on medications such as gabapentin, carbamazepine, amitriptyline, and non-steroidal anti-inflammatory drugs (NSAIDS) to manage various medical needs.

Furthermore, the patient has a history of experiencing episode of urticaria, a skin condition characterized by hives and itching. This episode was effectively managed using loratadine, an antihistamine medication. Importantly, it's noteworthy that the patient has a family history of allergic asthma, as her sister also suffers from this condition. The patient keeps guineapigs at her home. This comprehensive medical history provides valuable context for understanding the patient's overall health and may have implications for her asthma management and treatment choices.

The patient's comprehensive clinical evaluation included various diagnostic tests to assess her medical condition. Notably, positive skin prick tests revealed strong reactions to guineapig

(4+), birch (4+), and mug wort (2+), indicating an elevated sensitivity to these allergens. However, her total IgE levels remained within the normal range at 53.2 U/ml, and her blood eosinophil count was also within the normal limits at 0,40 x10 ^{9}/l (6,7%).

Furthermore, ancillary test for Anti-nuclear Anti-body (ANA), and Anti-Neutrophil Cytoplasmic Antibody (ANCA) yielded negative results. Additionally, no helminths were detected in her faecal samples. Fibro bronchoscopy results indicated the presence of chronic bronchitis, while computed tomography of thorax revealed no significant abnormalities.

Moreover, spirometry revealed a severe obstruction in pulmonary function. The pre-bronchodilator forced expiratory volume in 1 sec (FEV1) was measured at 1.71liters, representing merely 54% of her predicted value. Notably, a significant reversibility of 25% in FEV1 was observed after bronchodilator.

Considering these comprehensive diagnostic evaluations, the patient was diagnosed with severe, uncontrolled eosinophilic allergic bronchial asthma, coexisting with perennial severe allergic rhinitis and nasal polyps.

The patient's treatment regimen was intensified involving the use of a high-dose inhaled corticosteroids (ICS) combined with long-acting beta agonist (LABA), specifically, Formoterol/budesonide 4.5/160 mcg, administered as two puffs three times daily (daily dose of budesonide 1200 mcg). Additionally, a daily nasal spray of mometasone furoate 50 mcg, administered as two puffs, was prescribed to address her rhinitis.

Despite meticulously adhering to the prescribed treatment regimen and demonstrating proper inhaler technique, the patient's symptoms remained uncontrolled. Her asthma exacerbations continued to occur at a concerning frequency. Considering this unrelenting symptomatology and the recurrent nature of asthma exacerbations, a decision was made by pulmonologist to initiate a regular OCS regimen, starting with 10 mg daily, as part of her treatment and she took OCS with a short pause for the last two years.

In response to the ongoing asthma exacerbations and inadequate symptoms control despite optimal treatment regimen, subcutaneous injections of anti-IgE antibody, omalizumab, were initiated on May 15, 2018. The prescribed dosage of omalizumab was 150 mg administered every four weeks, adjusted according to the patient's weight and total IgE levels. After four months of omalizumab therapy, significant improvements were observed in various

asthma-related outcomes. These included symptoms severity, overall asthma control, lung function, reduction of asthma attacks and exacerbations, and decreased use of rescue medications. Additionally, the patient reported relief from nasal symptoms, and a reduction in the frequency of acute rhinosinusitis episodes.

The omalizumab treatment was continued, and the patient's progress was systematically re-evaluated at 12 and 18-month intervals. Throughout the 18-month observational period, the patient experienced no significant adverse effects attributable to omalizumab treatment. Notably, the patient contracted a Covid-19 infection in November 2020, two years after initiating omalizumab therapy. However, the patient experienced mild COVID-19 symptoms and did not require hospitalization.

RESULTS

The evidence substantiating the effectiveness of biological therapy:

This study, employing case reports, investigated the potential benefits of benralizumab and omalizumab therapy in managing patients with severe uncontrolled eosinophilic allergic bronchial asthma and enhancing their general well-being. The key findings highlighting the effectiveness of both therapies will be presented in the following tables.

The following table summarizes the key findings of benralizumab therapy in Case Report 1.

Parameter	Before the treatment with Benralizumab	After 4 months treatment with Benralizumab (following one month of COVID-19 infection) 2020.02	After 12 months of treatment with Benralizumab (some days after upper airway infection)	Outcomes

ACQ (Asthma Control Questionnaire)	3.3	1.7	2.6	Enhanced asthma control
Mini AQLQ (Asthma Quality of Life Questionnaire)	3.9	5.1	5.5	Improved quality of life
FEV1 L (%)	0.78 (32)	1.24 (50)	1.10 (45)	Improved pulmonary functions
FEV1/FVC %	46	60	59	Improved
PEF mean (l/min)	270	300	270	The same as initial
Blood eosinophil levels (x 109/l)	0.73	0.00	Not done	Significantly reduced to zero.
Asthma exacerbations	4 times during the last 6 months	No exacerbations	No exacerbations	Reduced exacerbation frequency
Utilization of OCS	10 mg of Prednisolone daily	No OCS needed	No OCS needed	Achieved OCS-free asthma control
Adverse effects		No adverse effects were observed	No adverse effects were observed	Benralizumab treatment was continued

Table-1: The effectiveness of benralizumab treatment in the management of severe uncontrolled eosinophilic allergic bronchial asthma.

The results of omalizumab therapy in Case Report 2 are presented in the following table (table-2)

Parameter	Before the initiation of Omalizumab	After 4 months of treatment with Omalizumab	After 12 months of treatment with Omalizumab	After 18 months of treatment with Omalizumab	Outcomes
ACQ	4.4	1.7	3	1.6	Enhanced asthma control
Mini AQLQ	3.1	6	3.7	4.7	Improved quality of life
FEV1 L (%)	1.71 (54)	2.11 (66)	1.95 (62)	Not done	Improved pulmonary functions
FEV1/FVC %	57	66	59	Not done	Improved
PEF average	280	380	380	380	Improved (from initial)
Asthma exacerbation	Frequently	No exacerbations	No exacerbations	No exacerbations	No exacerbation since biological therapy started

Utilization of OCS	10 mg of Prednisolone daily	No need for OCS usage	No need for OCS usage	No need for OCS usage	Achieved OCS-free asthma control
Adverse effects		No adverse effects were observed	No adverse effects were observed	No adverse effects were observed	Omalizumab treatment was continued

Table-2: The effectiveness of omalizumab therapy in the management of severe uncontrolled eosinophilic allergic bronchial asthma.

DISCUSSION

Two distinct case reports are presented, each illustrating the effectiveness of biological therapy in managing severe bronchial asthma. Case 1 demonstrates the effectiveness of benralizumab in a patient with severe, uncontrolled eosinophilic allergic bronchial asthma, concomitant bronchiectasis, and perennial allergic rhinitis. Case 2 showcases the benefits of omalizumab in a severe, uncontrolled eosinophilic allergic bronchial asthma, concomitant perennial severe allergic rhinitis, and nasal polyposis.

Eosinophils play a central role in the pathogenesis of asthma, and their infiltration into the airways is a hallmark of the disease. Elevated blood eosinophil levels are a common characteristic of various human disease, and interleukin (IL) 5, a key cytokine regulating eosinophil function, is consistently associated with these conditions. Additionally, IL-5 is often co-expressed with other T2 cytokines including IL-4 and IL-13, which are known to promote eosinophil activation and proliferation. Remarkably, this co-expression of cytokines is strongly linked to increased IgE production, a hallmark of atopic individuals, further emphasizing the importance of IL-5 in the development of allergic asthma [53][54].

Eosinophilic asthma is characterised by an aberrant T2 inflammatory response, driven by the production of T2 cytokines, particularly IL-4, IL-5, and IL-13, with eosinophils serving as the dominant effector cell in this inflammatory cascade [55]. This eosinophilic inflammation

has been consistently associated with increased asthma severity, higher frequency of exacerbations, and accelerated lung function decline [56].

Blood eosinophils level serve as a readily measurable and generally reliable biomarker, exhibiting significant correlations with treatment efficacy, disease control, and clinical response to biological therapies [57] [58]. Furthermore, management strategies focused on targeting sputum eosinophilia have demonstrated effectiveness in reducing the risk of asthma exacerbations [59]. While less commonly employed in clinical practice, airway eosinophil counts have shown a closer association with disease control compared to blood eosinophil levels [60][61]. Persistent airway eosinophilia can further promote the recruitment and activation of type 2 inflammatory cells at the tissue level, exacerbating asthma symptoms. In a seminal study, Travers J et al. demonstrated that, eosinophils are recruited and activated by IL-5, leading to the release of mediators that contribute to the initiation of inflammation, epithelial cell damage, and modulation of smooth muscle function [62]. These findings underscore the critical role of eosinophils and associated cytokines in the pathogenesis of eosinophilic asthma, emphasizing the importance of targeting these pathways for the development of effective therapeutic strategies.

Patients with eosinophilic asthma, characterized by blood eosinophil levels exceeding 150 × 109/ml or >0.15× 109/l, and who experience severe disease refractory to conventional GINA step 4/5 treatment and/or requiring maintenance treatment with OCS, can significantly benefit from targeted therapeutic interventions such as benralizumab, mepolizumab, reslizumab, and/or dupilumab. Similarly, patients with moderate to severe allergic asthma who fail to achieve adequate control despite adhering to GINA step 4/5 guidelines, can drive substantial benefit from omalizumab (anti-IgE) therapy. Additionally, patients with severe asthma may experience significant improvement in symptom control and lungs function from therapeutic administration of anti-thymic stromal lymphopoietin (anti TSLP) [52] .

Benralizumab exerts its therapeutic effect by directly binding to IL-5 receptors on eosinophils, leading to their depletion and a significant reduction in blood eosinophil counts. In contrast, omalizumab selectively targets circulating IgE antibodies, the key mediator of allergic inflammation in asthma, resulting in a decrease in IgE levels in the bloodstream. These biological agents have consistently demonstrated their efficacy in reducing asthma exacerbations, decreasing the reliance on corticosteroids, and improving overall asthma control.

In Case 1, the patient's treatment with benralizumab resulted in a remarkable clinical and biological response. This positive response was characterized by significant improvement in pulmonary function, enhanced asthma symptom control, reduced exacerbation frequency, and a significant reduction in blood eosinophil levels. Notably, these improvements were paralleled by a reduction in airway eosinophilic inflammation, further solidifying the effectiveness of benralizumab in managing severe eosinophilic asthma.

Benralizumab, a novel monoclonal antibody, specifically targets IL-5 receptors on eosinophils, effectively inhibiting their proliferation and survival while promoting their apoptosis. Its unique afucosylated IgG1κ structure enhances binding affinity, enabling antibody-dependent cell-mediated cytotoxicity (ADCC). This dual mechanism of action leads to a rapid and significant reduction in eosinophil levels, ultimately achieving nearly complete depletion in bone-marrow and tissues [63] [64]. This unique mechanism of action underscores the remarkable efficacy of benralizumab in selectively targeting and effectively reducing eosinophilic inflammation, a hallmark of severe bronchial asthma.

Benralizumab has consistently demonstrated superior efficacy in reducing both airways and blood eosinophil levels compared to mepolizumab. A prior study conducted by Oriano M. et al. revealed that patients with severe eosinophilic asthma and bronchiectasis who received combined treatment with benralizumab and mepolizumab exhibited a significant decrease in exacerbation rates [65]. Furthermore, in a randomised controlled trial conducted by Rademacher J. et al., the use of a monoclonal anti-eosinophilic antibody as an adjunct anti-inflammatory therapy for patients with clinically significant bronchiectasis and an eosinophilic endotype was deemed clinically warranted [66]. Moreover, Nolasco et al. documented rapid clinical and functional improvement in patients with severe eosinophilic asthma and bronchiectasis following treatment with benralizumab [67]. Additionally, Cook et al. presented a case report in which a patient unresponsive to mepolizumab due to refractory airway eosinophilia, exhibited a positive response to benralizumab [68]. Furthermore, it is noteworthy that benralizumab demonstrated a steroid-sparing effect in these case reports, consistent with the findings of the phase 3 ZONDA trial, which evaluated benralizumab's efficacy in severe eosinophilic asthma [27].

The present study corroborates previous findings, reaffirming the effectiveness of benralizumab in managing severe eosinophilic allergic bronchial asthma and concomitant bronchiectasis.

The case report for Case 2 provides compelling evidence of the efficacy of omalizumab treatment in various aspect of asthma management, including symptoms control, lung function improvement, enhanced asthma control, reduced asthma exacerbation frequency, decreased reliance on rescue medications and enhanced quality of life. These remarkable improvements were observed in a patient with uncontrolled severe eosinophilic asthma, characterized by a clinically significant allergic phenotype despite being on multiple maintenance medications, including long-term systemic corticosteroids. Furthermore, Omalizumab therapy also demonstrated a positive impact on nasal symptoms and significantly reduced the incidence of acute rhinosinusitis.

It is important to note that a study conducted by Tiotiu et al. demonstrated consistent results with omalizumab, indicating improvements in both asthma outcomes and sinonasal symptoms, while not significantly affecting nasal endoscopy polyps scores [69]. However, in our patient evaluations, we solely relied on clinical assessment of symptoms and did not employ specific scoring systems for nasal polyposis.

Omalizumab is a humanised monoclonal IgG1 antibody that targets free circulating IgE. By binding to IgE, omalizumab prevents its interaction with mast cells and basophils, thereby suppressing the release of inflammatory mediators [70]. Furthermore, Omalizumab downregulates the expression of FcεRI, the high-affinity IgE receptors found on these cells (mast cells, basophils, and dendritic cells) and reduces the in vivo expression of FcεRI on dendritic cells. These actions contribute to the prevention of allergic inflammation by mitigating the activation of eosinophils [71].

Omalizumab is recommended as an additional therapeutic option for severe asthma cases that exhibit evidence of an allergic phenotype [52]. Phase 3 clinical trials have demonstrated that omalizumab can significantly reduce the frequency of severe exacerbations and enhance asthma control in patients with severe allergic asthma [14]. Additionally, omalizumab has demonstrated a sparing effect on oral corticosteroids (OCS) use. However, the reduction in daily inhaled corticosteroid use compared to a placebo in omalizumab studies has been modest [72]. Furthermore, randomized controlled trials conducted by Bousquet J. et al. consistently demonstrated that omalizumab treatment significantly improved the global evaluation of treatment effectiveness, lung function, and reduced asthma exacerbations and the need for oral corticosteroids in patients with severe allergic asthma [73]. Similarly, in an observational real-world study by Heffler E. et al. confirmed that the addition of omalizumab for the treatment of

severe allergic asthma effectively improved asthma control, lung function and contributed to a reduction in exacerbations, even among patients with concomitant chronic rhinosinusitis with nasal polyps [74]. These findings provide substantial clinical evidence supporting the efficacy of omalizumab in managing severe allergic asthma, demonstrating its ability to enhance overall asthma control, lung function, and reducing exacerbation rates, including in patients with co-existing conditions like chronic severe rhinosinusitis with nasal polyps.

The findings of our current study corroborate the existing evidence, further reinforcing the consistent efficacy of omalizumab in effectively managing severe eosinophilic allergic bronchial asthma, even in patients with co-existing chronic severe rhinosinusitis and nasal polyposis.

Both case studies have provided compelling evidence of a steroid-sparing effect. However, it is crucial to recognize the critical role of corticosteroids in the management of asthma. Studies have consistently demonstrated their efficacy in reducing asthma exacerbations while being cost-effective. Despite their effectiveness, corticosteroids are associated with undesirable side-effects [75] [76]. Furthermore, it is essential to recognize that there is a dose-response relationship between the intensity of steroid dosage and the risk of developing complications [77]. Therefore, it is paramount to increase awareness of strategies that can reduce the reliance on oral corticosteroids (OCS), as these strategies have proven efficacy. This can potentially lead to a positively shift in prescribing practice in the future [78].

Both patients in these case studies were diagnosed with Covid-19 infection. In Case 1, the patient experienced moderate to severe Covid-19 symptoms, requiring hospitalization for seven days. Conversely, Case 2 involved a patient with mild Covid-19 symptoms who did not require hospitalization.

Recent studies have provided compelling evidence indicating that individuals with asthma may have a reduced risk of contracting Covid-19 and, if they do contract the disease, they may experience milder symptoms of the disease as evidenced by several research publications [79][80]. Notably, a study by Zhang JJ et al. demonstrated that asthma is not a significant risk factor for SARS CoV-2 infection [81]. This observation may be attributed to the downregulation of ACE2, a crucial receptor for SARS-CoV-2 entry, in the respiratory airways of individuals with asthma and allergies [82]. Furthermore, it has been hypothesized that individuals with severe allergic asthma receiving treatment with the anti-IgE antibody

omalizumab, may experience reduced susceptibility to severe Covid-19 disease manifestation. Gill Ma et al. reported that omalizumab can augment the anti-viral immune response by downregulating high-affinity IgE receptors on plasmacytoid dendritic cells [83].

This study, in agreement with prior research findings, provides support for the hypothesis that the milder COVID-19 symptoms experienced by Case 2 may have been influenced by their biological therapy with omalizumab. Further research is warranted to fully elucidate the implications of this observation for patient care.

CONCLUSION AND PROPOSITIONS

In summary, this case study provides a comprehensive evaluation of the application and effectiveness of biological therapies, particularly benralizumab and omalizumab, while considering divers factors such as asthma endotypes, phenotypes, concomitant conditions, and clinical presentations of the patients.

The study highlights significant improvements in asthma exacerbations, asthma control, lung function, corticosteroids usage, and overall quality of life among individuals with severe, uncontrolled eosinophilic allergic bronchial asthma who were treated with benralizumab (as seen in Case 1) and omalizumab (as seen in Case 2).

Furthermore, this study strongly recommends that, prior to initiating biological therapy, all patients with severe bronchial asthma should seek consultation with both pulmonologists and allergologists. These consultations are essential to identify the most appropriate and suitable biological agents tailored to the individual patient's asthma phenotypes, endotypes, clinical presentation and any coexisting medical conditions.

Moving forward, it is crucial to undertake comprehensive comparative research to enhance our understanding of the optimal utilization of tailored novel biological agents for individuals with severe bronchial asthma. This research will pave the way for refined treatment strategies and ultimately lead to substantial improvements in the management of this complex medical condition.

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