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Combination treatment with monoclonal antibodies for the management of severe asthma and immune-mediated inflammatory diseases: a comprehensive review

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Abstract

Biological drugs have revolutionized the management of severe asthma, and a tailored treatment approach has made it possible to consider remission as an achievable treatment target. The incidence of autoimmune diseases is increasing worldwide. Patients suffering from severe asthma, eligible for or already treated with an asthma-approved biologic agent, may suffer from another immune-mediated inflammatory disease (IMID) that could require the simultaneous use of a second monoclonal antibody. The real-life studies available in the literature describing the concurrent administration of an asthma-approved biologic agent with another biologic for a different immune disease, obtained through a systematic search on online databases based on monoclonal antibodies, were collected and analyzed. In this review, 26 articles were included according to the prespecified inclusion and exclusion criteria. All included papers were retrospective in nature. Study designs were case reports (n=18), case series (n=3), retrospective chart reviews (n=3), retrospective observational studies (n=1), and cohort studies (n=1). The study is intended to present, within the current literature, all the administered combinations of severe asthma-approved biologics with monoclonal antibodies for a different indication. Those were grouped according to the IMID for whom the second biologic agent, with a different mechanism of action, was prescribed. The combinations prescribed to the cohort of patients specifically treating uncontrolled severe asthma were more deeply evaluated in the discussion section, since an analysis of these therapeutic combinations deriving from real-life experiences may be useful to optimize the management of patients with severe asthma, ultimately leading to improved patient care and outcomes. Prospective registries and future studies are required to assess the safety and efficacy of combination therapies for severe asthmatic patients who suffer from an IMID.

Key words: severe asthma, immune-mediated inflammatory diseases, biologics, combination therapy.

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Introduction

The introduction of biological therapies has brought a great improvement in the treatment of many severe or difficult-to-treat diseases across a wide range of medical specialties, in particular in respiratory, rheumatological, gastroenterological, and dermatological fields [1,2]. The role of biologic agents in severe asthma is critical, since they have revolutionized the management of the disease by significantly reducing exacerbations and the need for oral corticosteroids (OCS), improving lung function and quality of life [3]. Nowadays, the role of biologics in the management of severe asthma has pushed the scientific community to move forward with the concept of disease control towards increasingly ambitious goals, such as disease-modifying interventions or even clinical remission [4,5]. The burden of autoimmune diseases is progressively rising worldwide and is predicted to further increase in the coming decades [6], perhaps due to changes in exposures to environmental factors or behavioral changes, and also the COVID-19 pandemic has been recently linked to an increased risk of developing autoimmune diseases [7]. As a consequence, new drugs that target specific cytokines of the immunological pathways involved in the diseases are being studied and developed [8]. At the same time, in clinical practice, we saw an expansion of the population of patients who are candidates for or undergoing biological therapy for severe asthma. This raised the possibility of identifying patients eligible for biological therapies across different indications, and these patients could undergo therapeutic schemes involving the use of two biological drugs. The administration of a combination of two biologics has been recently described in severe asthma patients suffering from uncontrolled severe asthma with evidence of both allergic and eosinophilic phenotypes or severe asthma and type-2 comorbidities. However, no guideline recommends this strategy, due to insufficient data about efficacy

and safety, and also due to the high costs [9]. Some preliminary data derived from real-life studies are available in the literature, describing the concurrent administration of an asthma-approved biologic agent with another biologic for a different autoimmune disease. It can be hypothesized that these cases will become more frequent in the near future, not only due to a greater incidence of these pathologies, but also due to the improved detection and the possibility of better and targeted treatments. Real-world data reporting the concurrent treatment with two biologics for severe asthma or a T2 comorbidity and for a second autoimmune disease have not been systematically explored and need to be described and examined to assess the efficacy and the potential long-term risks deriving from different combinations of biologic therapies across several diseases. This review aims to collect and summarize the experiences regarding the combinations of asthma-approved biologics alongside another biologic agent to treat a different autoimmune disease. No general consideration about the safety and effectiveness of such combinations is made, and evidence deriving from existing literature is analyzed with specific reporting of indications, biologic drugs, efficacy, and safety for each study. Cases that describe the combinations of asthma-approved biologics administered for uncontrolled severe asthma and another biologic drug are presented and discussed.

Materials and Methods

A comprehensive review is a systematic, scientifically designed review of a defined literature base that employs the rigor of original research to limit outcome bias. A rigorous search of the literature was performed to identify the literature that meets the inclusion criteria as defined for the review.

Search strategy

A systematic search was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify the current literature about the combination of biological therapies with asthma-approved biologics and other monoclonal antibodies (mAbs) for the treatment of another concomitant condition. The search was conducted on the online databases MEDLINE (PubMed), Scopus, and Cochrane Library, from inception to April 2024, and was followed by manual literature searches in the reference lists of the included articles to identify additional articles about this topic. The research string was as follows: (Benralizumab OR Dupilumab OR Mepolizumab OR Omalizumab OR Reslizumab OR Tezepelumab) AND (Dual OR Combination OR Simultaneous OR Combining OR Combined OR Concomitant OR Add-on) AND (Abatacept OR Adalimumab OR Alemtuzumab OR Anakinra OR Anifrolumab OR Belimumab OR Bimekizumab OR Brodalumab OR Canakinumab OR Certolizumab OR Etanercept OR Golimumab OR Guselkumab OR Infliximab OR Ixekizumab OR Natalizumab OR Ocrelizumab OR Ofatumumab OR Risankizumab OR Rituximab OR Sarilumab OR Secukinumab OR Tildrakizumab OR Tocilizumab OR Ustekinumab OR Vedolizumab).

Study selection

We included clinical trials, observational studies, case series, case reports, letters, published in English, that met the following criteria: i) cases of combination of benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab, and tezepelumab with a second biologic agent; ii) the second biologic agent was prescribed to treat a different IMID. Small-molecule tyrosine kinase inhibitors were not considered for inclusion. Included studies were not restricted to patient demographics; studies with both adult and pediatric patients have been considered, without any publication date restriction. Review articles, studies unavailable as full-texts, and abstract-only papers were classified as ineligible for inclusion. Studies describing combinations of asthma biologics for the treatment of severe asthma uncontrolled with a biologic monotherapy or for the treatment of severe asthma and type 2 comorbidities were excluded, as well as studies reporting combinations with a mAb approved for the treatment of malignancies.

Data extraction

Data extraction was conducted by one author (LC) to be subsequently discussed and checked by a second author (AC). Extracted data included the following items: author/year, study design, population size, pathologies for which dual biologic therapy was administered, prescribed biologic agents, follow-up, efficacy, and safety.

Data synthesis

The data were extracted and qualitatively synthesized. Because of the limited number of reports and the restricted total number of patients, also in consideration of the design of the studies and the heterogeneous nature of outcome measures, a quantitative analysis was not conducted. In particular, the focus of the paper is on patients with severe asthma receiving a second biological agent for a concomitant condition. Other associations deriving from the existing literature, obtained through a systematic search based on mAbs, will be presented in the results section and in dedicated tables, even when asthma was not the indication; these data are to be considered separately and will not be further analyzed in the discussion.

Results

The initial literature search generated 475 potentially eligible articles from the aforementioned databases, plus 6 records identified additionally by manual search. A total of 68 duplicates were identified and removed. After excluding 387 articles, 26 articles were included in this review according to the prespecified inclusion and exclusion criteria. A flow chart showing the study selection is presented in Figure 1.

Study characteristics

All included papers were retrospective in nature. Study designs were case report (n=18), case series (n=3), retrospective chart reviews (n=3), retrospective observational study (n=1), and cohort studies (n=1). Across all studies, the observation period ranged from 0.13 years to 4 years. A total of 87 patients were identified. Three patients, all belonging to the study by Gisondi *et al*. [10], were excluded from the current analysis, since 2 of them received a combination of two asthma-approved biologics (dupilumab and omalizumab) and 1 patient received dupilumab in combination with cetuximab for the treatment of colorectal cancer, which is beyond the scope of this article. A detailed summary of study characteristics is presented in *Supplementary Tables 1-5*. Studies were grouped according to IMIDs' indications. *Supplementary Table 1*

for dermatological pathologies (psoriasis and hidradenitis suppurativa) [11-24], *Supplementary Table 2* for inflammatory bowel diseases (IBDs) [10,12,14,25-28], *Supplementary Table 3* for rheumatoid arthritis (RA) [10,14,26,29-31], *Supplementary Table 4* for ankylosing spondylitis (AS) [10,12,14]. Six patients received two or more mAbs, of which at least one was not prescribed for an autoimmune disease, while the other 29 patients received two different biologics to treat one uncontrolled pathology; therefore, the data of these patients were separated and described in a different section, *Supplementary Table 5* [10,14,32-36]. Table 1 shows the reasons and how many patients received an asthma-approved biologic, and Table 2 describes the number of patients suffering from each autoimmune disease that required the co-administration of a second biologic agent. In Table 3, all the combinations of mAbs administered in the studies included in the review and the number of patients who received such a combination are described in detail, grouped depending on asthma biologics.

Efficacy

The efficacy of the combination therapy was examined by the authors of the included studies through an independent evaluation of the outcomes for each pathology treated with a biologic agent. Responses were evaluated at various time points using several validated clinical scores, specific to each disease. In some studies,

Table 1. Indications for receiving an asthma-approved biologic drug.

Indications	Number of patients (n=87)
CSU	47
AD	24
Asthma	12
HES	1
Prurigo Nodularis	1
Systemic mastocytosis	1
Bullous Pemphigoid	1

CSU, chronic spontaneous urticaria; AD, atopic dermatitis; HES, hypereosinophilic syndrome.

Table 2. Immune-mediated inflammatory disease for whom monoclonal antibodies in combination with an asthma-approved biologic drug were administered.

Indications	Number of patients (n=87)
Psoriasis	56
Inflammatory bowel disease	18
Rheumatoid arthritis	8
Ankylosing spondylitis	3
Hidradenitis suppurtiva	2

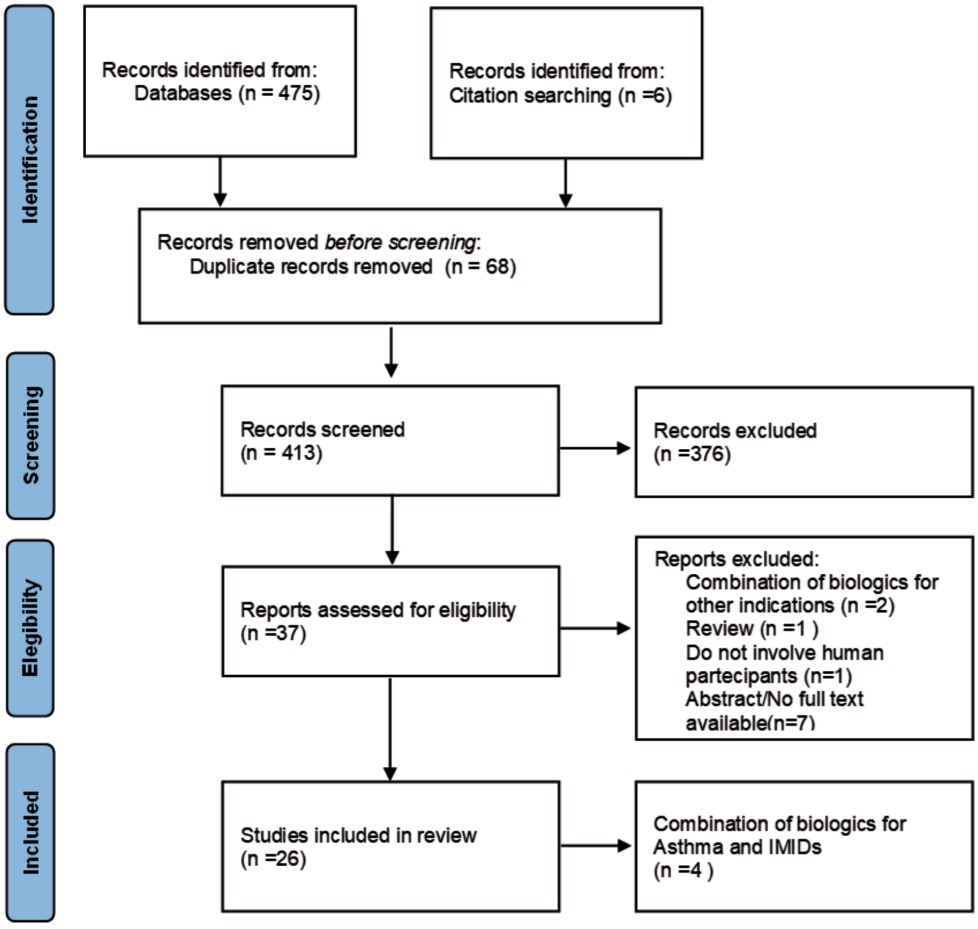

Figure 1. PRISMA 2020 flowchart diagram of the selected articles.

Table 3. Biologics administered concurrently with omalizumab, dupilumab, mepolizumab, and benralizumab.

Biologic agent combined with omalizumab	Number of patients (n=50)	Biologic agent combined with dupilumab	Number of patients (n=30)	Biologic agent combined with mepolizumab	Number of patients (n=4)
Secukinumab	20	Guselkumab	8	Rituximab	1
Adalimumab	7	Ustekinumab	7	Infliximab	1
Ixekizumab	7	Secukinumab	3††	Etanercept	1
Etanercept	6	Vedolizumab	3	Ustekinumab	1
Ustekinumab	4	Infliximab	3	Biologic agent combined with beralizumab	Number of patients (n=3)
Infliximab	3	Tildrakizumab	2‡	Etanercept	2
Tocilizumab	1	Abatacept	1	Golimumab	1
Tildrakizumab	1	Brodalumab	1		
Guselkumab	1†	Etanercept	1		
		Adalimumab	1		

†The patient, during omalizumab treatment, received different biologics, but we considered the last administered biologic. Table 1, Benko *et al.* [22]. ††The patient received benralizumab first, later switched to dupilumab. We considered the last administered biologic and included her under this list. Table 1, Mahar *et al.* [20]. ‡One patient received brodalumab first, later switched to tildrakizumab. We considered the last administered biologic and included her under this list. Table 1, Gerger *et al.* [15].

efficacy data were descriptive and/or in photographic form, and in others, it was not possible to assess due to study design or data presentation.

Adverse events

Overall, 19 of the included studies reported no adverse events. In 7 studies, adverse events were described, in most cases, of minor severity. They are all presented in the specific tables.

Discussion

Asthma inflammation develops as a result of a complex interaction between the innate and the adaptive immune system. The main pathogenic mechanisms are often described as T2-high and T2-low [37]. T2-high endotypes have an immune-inflammatory response driven by T helper type 2 cells and type 2 innate lymphoid cells and mediated by type 2 cytokines, such as interleukin (IL)-4, IL-5, and IL-13, each with different roles in the inflammatory cascade. IL-4 drives immunoglobulin E (IgE) production and B-cell class switching, IL-13 causes mucus production, airway remodeling, and bronchial hyperresponsiveness, and IL-5 is responsible for eosinophil differentiation, activation, and survival [38]. T2-low asthma is either driven by neutrophilic (dependent on a Th1/Th17-mediated immune response) or paucigranulocytic inflammation [39]. Asthma biologics target cytokines within the T2 inflammatory pathway. These drugs interfere with T2-inflammation in different ways: omalizumab targets IgE; mepolizumab and reslizumab target IL-5; benralizumab targets the IL-5 receptor; and dupilumab targets IL-4 and IL-13. Tezepelumab, recently approved, targets thymic stromal lymphopoietin, an epithelial-derived cytokine released in response to multiple triggers, preventing its interaction with the receptor and thus inhibiting multiple downstream inflammatory pathways, and at the moment, it is the only mAb approved for patients with either high or low levels of T2 biomarkers [40]. Autoimmune diseases are characterized by dysregulation of the immune system with aberrant activation of the adaptive immune system cells. Biological agents available for the treatment of autoimmune diseases have targets that include cytokines and their receptors, or cell subsets with a view to altered trafficking, modulation of cellular activation state, or cellular depletion [1]. The classes of biological disease-modifying anti-rheumatic drugs currently available for use in psoriatic arthritis, RA, and AS are anti-tumor necrosis factor (TNF)-α, IL inhibitors, T cell co-stimulation inhibitors, and B cell depletion therapy. Psoriasis can be treated with anti-TNF-α agents and IL inhibitors. Anti-TNF-α, IL inhibitors, and integrin blockers are the biologic agents available for the treatment of IBDs. In view of the foregoing, it is evident that mAbs approved for severe asthma and for IMIDs have different therapeutic targets and distinct mechanisms of action. Table 4 summarizes the major mechanisms of action of the mAbs approved for severe asthma and IMIDs that were included in the search string.

IMIDs have been recognized to share some similar pathogenic mechanisms; in particular, the dysregulation and over-expression of the pro-inflammatory cytokine TNF have been recognized to play a pivotal role in the pathophysiology of IMIDs [41,42]. In both Crohn's disease and ulcerative colitis, TNF-α is secreted with other cytokines, such as IL-1, IL-6, and IL-17, by Th1 cells, causing the accumulation of immune cells in the gut [43,44]. TNF-α is considered the major inflammatory cytokine involved in the pathogenesis of RA, as it is secreted from Th1 cells and macrophages and activates synovial fibroblasts and recruits other inflammatory cells [45]. In the pathogenesis of psoriasis, TNF-α is secreted from stressed keratinocytes, and together with interferon-γ and IL-17 causes keratinocyte hyperproliferation and epidermal changes [46,47].

Patients with IBD have a significantly increased prevalence of respiratory symptoms, asthma, and chronic rhinosinusitis compared to those without IBD [48]. Recent studies highlighted the association between asthma and RA [49,50]. Interestingly, lung inflammation is thought to be involved in the pathogenic mechanisms leading to the development of RA, since inflammation of the mucosa of the respiratory system upregulates citrullination, which could trigger immunity and the production of anti-citrullinated protein antibodies (ACPAs) [51]. Therefore, the possible connections between asthma, T2 diseases, and other inflammatory conditions have not been fully explored, and understanding these potential links is important for advancing understanding of the underly-

ing mechanisms of pathology. For example, TNF-α has been linked to a delay of eosinophil apoptosis *via* TNF-receptor 1, changing the longevity of these cells [52]. Eosinophils have been described to be involved in the development of IBD, not only altering the structure and protective functions of the mucosal barrier and causing mucosal injury, but also playing an immunomodulatory role [53]. Interestingly, an increase in serum eosinophil cationic protein values was observed in patients with RA compared with healthy subjects, and higher levels were associated with a more aggressive course [54]. Moreover, eosinophilia at diagnosis could affect the treatment response of RA patients [55].

Patients who have received omalizumab or dupilumab as asthma-approved biologics represent the vast majority of the population included in the review. This is due to the fact that these medications are commonly used in dermatology to treat skin conditions uncontrolled with conventional therapies (chronic spontaneous urticaria, atopic dermatitis, bullous pemphigoid, prurigo nodularis). Since the role of type 2 inflammation in skin conditions is well documented [56], the large use of these mAbs in clinical practice should not be surprising. Psoriasis was the most common IMID within the studies included in the review. It is noteworthy that biologics are approved for moderate to severe psoriasis, and it represents the pathology with the widest list of biologic agents available (TNF-α inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, and IL-23 inhibitors), enabling treatment to be personalized according to patient-related factors and comorbidities [57]. These could have been some of the reasons for the high prevalence of psoriasis among patients treated with a combination of biologic therapies, as well as the high rate of comorbidities of psoriatic patients [58]. Although biologics for the treatment of multiple sclerosis were included in the search string, cases of combination with an asthma-approved biologic agent have not been detected and are not available in the literature to our knowledge.

The cohort of patients receiving biologics for severe asthma is the focus of our dissertation. An analysis of these therapeutic com-

Table 4. Mechanism of action of biological drugs included in the review.

Biological drugs	Mechanism of action	Biological drugs	Mechanism of action
Benralizumab	Anti-IL-5 receptor α antibody; prevents the interaction between IL-5 and its receptor and promotes antibody-dependent cell-mediated cytotoxicity (ADCC) enhancing eosinophil apoptosis	Etanercept	TNF receptor fusion protein; binds and neutralizes TNF-α
Dupilumab	Anti-IL-4Rα antibody; inhibits IL-4 and IL-13 signaling	Golimumab	Anti-TNF-α antibody; inhibits TNF-α signaling
Mepolizumab	Anti-IL-5 antibody; binds to IL-5 and prevents IL-5 from binding to its recepto	Guselkumab	Anti-IL-23p19 antibody; inhibits IL-23 signaling
Omalizumab	Anti-IgE antibody; inhibits the binding of IgE to its receptor on mast cells and basophils	Infliximab	Anti-TNF-α antibody; blocks TNF-α
Reslizumab	Anti-IL-5 antibody; binds to IL-5 and prevents IL-5 from binding to its receptor	Ixekizumab	Anti-IL-17A antibody; blocks IL-17A signaling
Tezepelumab	Anti-TLSP (thymic stromal lymphopoietin) antibody; prevents interaction with TLSP receptor complex and inhibits TLSP signaling upstream in the inflammatory cascade	Natalizumab	Anti-α4 integrin antibody; inhibits leukocyte adhesion and migration across the blood-brain barrier
Abatacept	CTLA-4-Ig fusion protein; inhibits T-cell activation by blocking CD80/CD86 on antigen presenting cells	Ocrelizumab	Anti-CD20 antibody; depletes B-cells
Adalimumab	Anti-TNF-α antibody; blocks TNF-α signaling	Ofatumumab	Anti-CD20 antibody; depletes B-cells
Alemtuzumab	Anti-CD52 antibody; depletes T and B lymphocytes	Risankizumab	Anti-IL23p19 antibody; inhibits IL-23 signaling
Anakinra	IL-1 recptor antagonist; blocks IL-1 signaling	Rituximab	Anti-CD20; depletes B-cells
Anifrolumab	Anti-IFNAR1 (type I intereferon receptor) antibody; inhibits type I interferon signaling	Sarilumab	Anti-IL-6 receptor antibody; blocks IL-6 signaling
Belimumab	Anti-BAFF (B-cell activating factor) antibody; inhibits the survival of B-cells	Secukinumab	Anti-IL-17A antibody; blocks IL-17A signaling
Bimekizumab	Anti-IL-17A and IL-17F antibody; blocks IL-17A and IL-17F pathways	Tildrakizumab	Anti-IL23p19 antibody; inhibits IL-23 signaling
Brodalumab	Anti-IL-17RA antibody; blocks IL-17 receptor, inhibiting IL-17 signaling	Tocilizumab	Anti-IL-6 receptor antibody; blocks IL-6 signaling
Canakinumab	Anti-IL-1β antibody; block IL-1β signaling	Ustekinumab	Anti-IL-12 and IL-23p40 antibody; inhibits IL-12 and IL-23 signaling
Certolizumab	Anti-TNF-α antibody fragment (Fab); blocks TNF-α	Vedolizumab	Anti-α4β7 integrin antibody; inhibits T-cell migration into the gut

IL, interleukin; IgE, immunoglobulin E; TSLP, thymic stromal lymphopoietin; CTLA4-Ig, cytotoxic T-lymphocyte-associated protein 4-immunoglobulin;; TNF, tumor necrosis factor; IFNAR1, interferon-1 receptor subunit 1; BAFF, B cell-activating factor.

binations deriving from real-life experiences may be of fundamental importance to optimize the management of patients with severe asthma, ultimately leading to improved patient care and outcomes, including quality of life. Mahar *et al*. report the case of a woman treated for psoriasis and psoriatic arthritis with the IL-17 inhibitor secukinumab, who successfully received a second biologic agent for severe asthma and nasal polyps, with great improvement in asthma control [20]. It is noteworthy that the previous discontinuation of each biological individually had caused a relapse of the disease. The case series by Lommatzsch *et al*. described 25 patients treated with several biologic combinations [14]. A total of 15 patients concomitantly received two biologics approved for severe asthma, and another 10 patients received one biologic for asthma plus another for the treatment of a concomitant but different disease. In this second group, which we are examining, the efficacy of the combination treatment was determined by evaluating the impact on asthma exacerbations, OCS use, asthma control (as measured with the asthma control test) and lung function (as measured with the forced expiratory volume in the first second, forced expiratory volume in 1 second, in % of the predicted value), before and during dual treatment. The study by Malik *et al.* presents the cases of three patients with asthma and rheumatic diseases, who have benefited from different combined biologic therapies, providing data for each patient [26]. Two patients, the former with CD and asthma and the latter with RA and asthma, obtained full control of both diseases. One patient affected by severe asthma and RA, despite improvement in both diseases, could not discontinue OCS, but reduced the dose to 11 mg/daily. The patient described by Yamada *et al*. [30], after the administration of a combination of biologics for severe asthma and AR, experienced a great improvement in respiratory function and quality of life, and did not require OCS courses. Both diseases were well controlled using the respective biologic agents, but relapsed following discontinuation, thus it was decided to administer the two mAbs simultaneously.

Regarding side effects, a mild adverse event was described by Mahar *et al*. [20], with occasional sweating episodes and rhinorrhea under the combination of dupilumab and secukinumab. Also, a mild γ-glutamyl transferase increase was observed in this patient, but was considered related to hepatic steatosis and not attributable to either secukinumab or dupilumab. No other relevant side effects were described in the other studies with asthmatic patients.

The analyzed existing data have some limitations, in particular related to the design of the studies (most of the literature consists of case reports and case series, and no prospective studies or randomized controlled trials were found), to the small numbers of patients included, and to the heterogeneous follow-up duration. Moreover, publication bias may be present, contributing to uncertainty in the evaluation of the literature. Considering all these factors, it is not possible to provide any data or general consideration about the safety profile when biologics were combined.

Treatment adherence is particularly important in severe asthma [59]. The consequences deriving from the necessity to receive two mAbs to treat two different pathologies could represent an additional factor to consider when designing the model of care of this group of patients. The psychological burden of this intervention, deriving also from administration-related factors (*i.e.*, the increased frequency of injections), has not been explored yet, and future studies of patient acceptability are needed to examine perceptions and perspectives of patients receiving a combination of biologics [60]. The costs might represent the main limitation to combinations of biologic agents for severe asthma and IMIDs, in particular in middle- and low-income countries. Finally, regular clinical and laboratory monitoring of these patients is recommended to early detect potential significant side effects, such as an increased risk of infection, other disorders of the immune system, or malignancies. However, when treating these complex patients, these potential risks must be balanced carefully against the risks deriving from uncontrolled severe diseases and the consequences deriving from ongoing therapies (as in the case of systemic side effects due to long-term OCS therapy for severe asthma). Moreover, the difference in therapeutic targets and the distinct mechanisms of action of biologics approved for severe asthma and for IMIDs should be kept in mind, since this consideration could provide reassurance to clinicians regarding the risk of side effects and infections when comorbid patients require the simultaneous administration of two mAbs for uncontrolled diseases.

The production of new real-life data would be valuable, and in this sense, international registries could play a crucial role, enabling researchers and healthcare professionals to analyze disease trends, treatment strategies, and outcomes, including safety profiles.

Conclusions

The introduction of biologic therapies enabled a paradigm shift toward an era of precision medicine [61]. Previously, asthma treatment aimed for disease control rather than remission. However, the development of new biologic therapies allowed clinicians to set new ambitious goals, such as the possibility of achieving and maintaining asthma remission [62]. It is very likely that cases of severe asthmatic patient candidates or those undergoing biological therapy and requiring a second biologic agent for a different indication will be more frequent in the near future. Clinicians should be sensitized and prepared to manage patients with asthma and a concomitant IMID, to aim to achieve clinical remission for both diseases. Further studies on a larger number of patients are required to assess the safety and efficacy of combination therapies for severe asthmatic patients who suffer from an immune-mediated inflammatory disease. Web-based observatory registries collecting demographic, clinical, functional and inflammatory data, treatments (including biologics) and comorbidities of these patients could be valuable to demonstrate whether the outcomes and the safety profile observed so far in real-world studies are replicable.

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Online supplementary material:

Supplementary Table 1. Combination of benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab, tezepelumab with a second biologic agent to treat dermatological immune-mediated inflammatory disease.

Supplementary Table 2. Combination of benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab, tezepelumab with a second biologic agent to treat inflammatory bowel diseases.

Supplementary Table 3. Combination of benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab, tezepelumab with a second biologic agent to treat rheumatoid arthritis.

Supplementary Table 4. Combination of benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab, tezepelumab with a second biologic agent to treat ankylosing spondylitis.

Supplementary Table 5. Other combinations of asthma-approved biologics with monoclonal antibodies of different nature with their respective indications, not suitable for inclusion in previous groups.

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