Biologics in severe asthma: the role of real-world evidence from registries

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Data on long-term efficacy and safety of biologics in severe asthma cannot be obtained by RCTs alone. Real-life studies should be a valuable source of this kind of information.
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Abstract

Asthma is one of the most common noncommunicable diseases; in the majority of patients it is well controlled with inhaled bronchodilators and inhaled corticosteroids, but the management of severe asthma has been a significant challenge historically. The introduction of novel biologic drugs in the past few decades has revolutionised the field, presenting physicians with a variety of biologic drugs with different mechanisms for the treatment of severe asthma.

It is of crucial importance to evaluate the effectiveness of these drugs by following their "real-life" effectiveness rather than relying solely on their efficacy, established in carefully designed clinical trials, which therefore do not necessarily match the profile of the real-life patient. Understanding the actual effectiveness of the specific drugs in real-life patients is a crucial part of tailoring the right drugs to the right patients. Registries serve as an important tool in obtaining real-life evidence, since they are in effect observational studies, following the entire patient population.

Introduction

Asthma is one of the most common noncommunicable diseases, affecting >330 million individuals worldwide. It is characterised by variable expiratory airflow limitation and chronic airway inflammation, leading to respiratory symptoms such as dyspnoea, wheezing, chest tightness and cough that evolve over time and in intensity [1]. Its treatment is based on chronic use of anti-inflammatory drugs (mainly inhaled corticosteroids) often combined with bronchodilators (long-acting β_2-agonists), with the aim of achieving disease control. However, 5–10% of patients, whose asthma remains uncontrolled despite high-dose controller therapy and in whom "difficult-to-control" asthma has been excluded (*e.g.* through optimisation of medication adherence, inhaler technique and comorbidities), are classified as "severe asthmatics" [2]. Severe asthma presents in heterogeneous ways, leading to the need to investigate the underlying phenotypes and endotypes, and develop novel biologic drugs targeting the causative mechanisms in each patient using the personalised medicine approach [3, 4].

There has been a breakthrough in severe asthma management in the past few decades with the emergence of novel biologic drugs targeting the specific mechanisms underlying the disease [5]. To date, several of these biologic drugs have been approved for use in severe asthmatics with targets including IgE, interleukin (IL)-5/IL5-receptor and IL-4/IL-13 [6]. Omalizumab works by binding to free circulating IgEs, thus preventing their attachment to mast cells and basophils, resulting in reduced histamine release [7]. The anti-IL-5 monoclonal antibodies mepolizumab and reslizumab, and the anti-IL-5 receptor monoclonal

antibody benralizumab, inhibit the proliferation and activation of eosinophils [6, 8]. The anti-IL-4 receptor monoclonal antibody dupilumab interrupts both the IL-13 and IL-4 signalling pathways [9].

When determining whether a drug should be used for the treatment of severe asthma, there are many different methods guiding the physician's decision and each one of these methods has its strengths and weaknesses. As advocated by the Respiratory Effectiveness Group, the two important methods that should be used complementarily in determining the effectiveness of a drug are randomised controlled clinical trials (RCTs) and real-life research [10]. All the aforementioned biologics have gone through rigorous RCTs and were proven effective in terms of reduction of asthma exacerbation and systemic corticosteroid treatment, and improvement of lung function and health-related quality of life [11–28]. Nevertheless, it is still important to distinguish the drugs' efficacy, which is their effect in controlled conditions (established by the selection of patients based on inclusion and exclusion criteria and controlled environments in those RCTs), from the drugs' effectiveness, which is their actual effects in the real world. The effectiveness of drugs cannot be established using the results of RCTs alone; it requires in addition the pragmatic observation of patients in real life, in environments not specifically engineered to maximise the drugs' effects, and in patient populations that are not pre-selected for optimal response to the drug. It is important to investigate the effects across different age groups, different body mass index (BMI) values and during pregnancy. In an article analysing patients with uncontrolled asthma in the general population in comparison to patients recruited for RCTs leading to biological medications approval in asthma, those in the trials were more likely to be Caucasians, never-smokers, with a lower BMI [29–31]. Therefore, real-life and pragmatic studies can inform drug effectiveness and play a role in post-marketing surveillance phase IV studies. The aforementioned statements can be grouped together under the umbrella term "efficacy–effectiveness gap" referring to the discrepancies between the outcomes reported in RCTs and those observed in real-word clinical practice [32–34]. In summary, figure 1 illustrates the strength of evidence of drug efficacy and effectiveness from real-life research and RCTs. Nonetheless, registries present with some limitations in respect to RCTs: they don't provide a randomisation of patients; there might be missing or incomplete data; enrolment of patients in registries is less supervised compared with randomised trials (as previously mentioned, this can also be a strength); and, lastly, follow-up presents a lower grade of standardisation in comparison to randomised trials [35].

The role of registries in real-life research of severe asthma

Real-life research relies on properly designed and executed registries that are able to provide a real-world view of clinical practice, patient outcomes and safety over time, and comparative effectiveness. Registries structure data in a comprehensive and consistent manner, producing generalisable outcomes that are

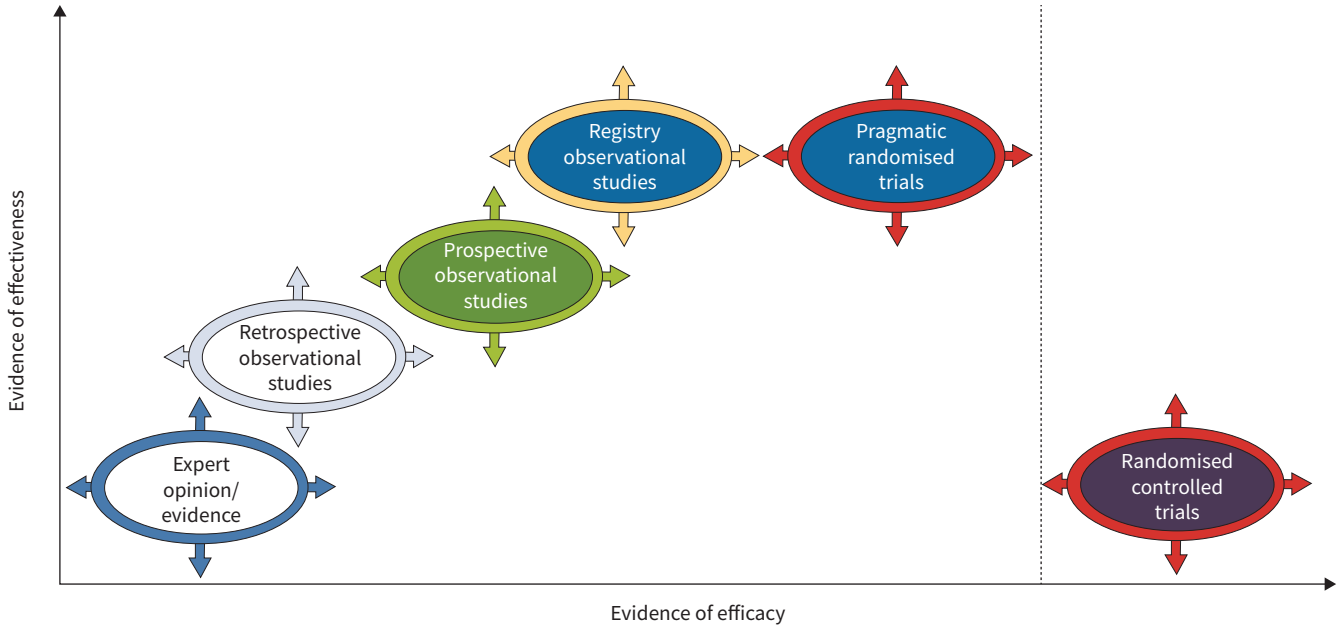

FIGURE 1 Strength of evidence of drug efficacy and effectiveness from real-life research and randomised controlled trials.

valuable in evaluating care [36]. There are many regional and national registries for severe asthma designed with the purpose of achieving better understanding of its epidemiology, inflammatory profile, different phenotypes and treatment characteristics. There are a few examples of such registries across Europe: in 2014 the Belgian Severe Asthma Registry (BSAR) investigated the different asthma phenotypes making up its registry [37] and more recently looked into the chronic use of oral corticosteroid and persistent eosinophilia in severe asthmatics [38]. In Germany, the national registry (German Asthma Net (GAN); www.germanasthmanet.de) was used to investigate the different phenotypes in severe asthma starting from demographic data [39]. The UK Severe Asthma Registry (UKSAR) characterised patients with severe asthma and provided insight across different research areas highlighting substantial unmet needs leading to poor asthma control in some of the patients [40]. In addition, as shown in a study based on the British Thoracic Society Severe Asthma Registry, patients with severe refractory asthma aged ⩾65 years had better clinical and healthcare outcomes and lower blood eosinophils than those aged <65 years [37, 41–50].

From the Italian point of view, data extrapolated from the Severe Asthma Network in Italy (SANI; www.sani-asma.org) provides us with a real-life snapshot of the state of severe asthmatics in Italy [42]. These data highlight the high prevalence of bronchiectasis among severe asthmatics [51] and the excessive use of oral corticosteroids (OCS) [52]. The latter finding is especially important considering the numerous side-effects of OCS overuse; chief among them, increased mortality [53–57].

Further analysis of the SANI data reveals that 40.6% of patients with severe asthma present with chronic rhinosinusitis with nasal polyps as a comorbidity. In this subpopulation of patients, the proportion of long-term OCS users is significantly higher, with doubling of the days of treatment per year when compared with severe asthmatics without nasal polyps [58].

Following these observations, the cost resulting from OCS overuse was calculated. A budget impact model estimated the total annual cost due to OCS-related adverse events to be EUR 242.7 million for severe asthmatics, which is an incremental expenditure of approximately EUR 110.6 million and EUR 75.2 million, when compared with nonasthmatic and moderately asthmatic populations, respectively [59].

The aforementioned study, together with additional literature evidence about OCS toxicity and cost, has called attention to the need to reduce OCS use in severe asthma treatment [52, 59, 60]. Such reduction is currently considered a primary outcome in patients with severe asthma. Novel biologics in asthma have an important corticosteroid-sparing effect, in addition to their other benefits in decreasing exacerbation rates and increasing quality of life [52].

The role of biologics in real life

Despite the extensive research into biologics since the early 2000s [61], resulting in a plethora of novel and effective drugs, clinical algorithms that can identify the right biologic for the right patient are yet to be established [62, 63]. Furthermore, new and substantially more data are required to characterise the heterogeneous phenotypes in asthma, in order to identify treatable traits and deliver precision treatment [64–68]. Table 1 shows the estimated numbers of published real-world clinical studies for the five biologics approved for use in severe asthma. The relatively large numbers of existing studies for omalizumab and mepolizumab may be due to their earlier approvals for use in severe asthma.

TABLE 1 Estimated numbers of existing real-world clinical studies published on monoclonal antibodies for severe asthma

	Retrospective	Prospective	Registry
Benralizumab	9	3	0
Dupilumab	4	0	0
Mepolizumab	18	12	3
Omalizumab	30	13	5
Reslizumab	4	2	0

Data are presented as n. The studies are categorised as retrospective, prospective and registry studies. To obtain these data, we used the search string on PubMed: "omalizumab/dupilumab/reslizumab/mepolizumab/benralizumab asthma real world". The search was performed in November 2021.

United States Food and Drug Administration approval was granted to omalizumab in 2003 [69], mepolizumab in 2015 [70], reslizumab in 2016 [71], benralizumab in 2017 [72] and dupilumab in 2018 [73].

Real-world evidence on the use of the new biologics allows us to assess whether the data from RCTs are matched with the effectiveness of biologics in the broader population of asthmatics, and further deepens the understanding of long-term efficacy and safety of biologics.

The quest for evidence of effectiveness rather than efficacy of these drugs has already begun worldwide. The analysis of real-world data from the Australian Mepolizumab Registry (https://toolkit.severeasthma.org.au/registries) established the effectiveness of mepolizumab in improving the lung function and control of asthma symptoms in patients with severe eosinophilic asthma [74, 75].

Similarly, a real-life study from the Spanish registry has confirmed the efficacy and tolerability of omalizumab in patients with uncontrolled severe asthma [76].

Nevertheless, even though regional and national severe asthma registries provide valuable country-specific information, their use is limited by their small populations of interest and by their broader definitions of severe asthma, leading to insufficient statistical power to answer many research questions.

The role of the International Severe Asthma Registry

To overcome the aforementioned limitations, the International Severe Asthma Registry (ISAR) was created [77–79]. ISAR (www.isaregistries.org) is the first global adult severe asthma registry aiming to achieve sufficient statistical power to answer important research questions, and to standardise data, making them comparable across countries and regions. The global reach of ISAR is achieved by the already established collaboration with 25 countries, including national or regional registries from Europe, plus registries from the Americas, Asia, the Middle East and the Australasian Severe Asthma Web-based Database registry of Australia, New Zealand and Singapore [78]. ISAR's research is overseen by the ISAR steering committee (ISC), consisting of global severe asthma experts, and is governed by the Respiratory Effectiveness Group *via* the Anonymised Data Ethics and Protocol Transparency committee [78]. ISAR is cofunded by Optimum Patient Care Global and AstraZeneca; however, ISAR is open to independent projects not funded by AstraZeneca. Participating countries may also have multiple additional sources of funding. Core variables for standardised data collection were derived from a modified Delphi process [79]; additional variables are also collected from some countries to assess patient safety and the impact of steroid reduction. Prospective data collection for the ISAR registry was initiated in 2018 in Italy, the United States, South Korea (www.severeasthmawg.com) and the United Kingdom (UK) to better standardise data fields, increase the accuracy of cross-country comparisons and reduce any data incongruence in datasets [80].

Real-world evidence has emerged from ISAR's research programme ENLIGHTEN, which encompasses projects on "what severe asthma looks like", "appropriate care for severe asthma" and the "effectiveness of biologics". ISAR's first global publication on "what severe asthma looks like" described the demographic and clinical characteristics of severe asthma patients globally; for example, there were variations in biomarker expression, exacerbation rates and healthcare resource utilisation across countries [80]. The Biomarker Relatability in the International Severe Asthma Registry project further characterised biomarker expression in adults with severe asthma and identified five clusters exhibiting unique clinical profiles [81]. In a project investigating the role of exacerbations on lung function trajectory, data from the Optimum Patient Care Research Database (OPCRD; www.opcrd.co.uk) in the UK demonstrated that repeat exacerbations were associated with lung function decline in a broad asthma population, and that the decline was significantly more pronounced in younger patients [82]. Additionally, data from ISAR allowed for the development of an evidence-based and consensus-driven eosinophil gradient algorithm that uses variables readily accessible in real life, enabling physicians to ascertain their patients' asthma phenotypes and any treatable traits [83]. The eosinophilic phenotype was predominant in severe asthma: 83.8% of patients were most likely eosinophilic and 1.6% of patients were non-eosinophilic [83]. The predominance of the eosinophilic asthma phenotype was also observed when the ISAR eosinophil gradient algorithm was applied to a primary care cohort in the UK: 72.5% of patients had most likely or likely eosinophilic phenotypes, and 5.6% of patients were non-eosinophilic [84]. Therefore, asthma phenotyping should become part of routine clinical care to enable the delivery of phenotype-targeted treatment to patients across all asthma severities [83, 84]. Additional research projects on "what severe asthma looks like" include the PATH project, which differentiates severe asthma phenotypes by age of asthma onset [85], and the EMBER project, which evaluates the demographic and clinical characteristics of severe asthma patients with non-type 2 asthma [86].

To provide insights into "appropriate care for severe asthma", ISAR's research has elucidated the importance of biologics accessibility and collaboration between primary and specialist care in reducing OCS use. The Biologic Accessibility Score (BACS) project showed that although biologic prescription criteria such as the annual total exacerbation number were similar in many countries, access to biologics varied globally because of country-specific factors such as biologics licensing and reimbursement [87]. The SUNNIE project, which described biologic utilisation patterns globally, found that three-quarters of severe asthma patients continued treatment with their first prescribed biologic; of the minority of patients who switched therapy, the most common switch was from anti-IgE to anti-IL5/5R therapy [88]. Additionally, data from both ISAR and the OPCRD illustrated that of the 8% of asthma patients in UK primary care who have potential severe asthma, 72% were thought to be unreferred for specialist care [46]. Therefore, the collaboration between primary and specialist care is essential to identify hidden severe asthma patients who may benefit from biologic therapy, thereby reducing unnecessary treatment with long-term OCS. Another research project, Relationship between Socioeconomic Status and Asthma Outcome (RADIANT), sheds light on the association between socioeconomic status and clinical outcomes in severe asthma patients [89]. Patients who were most socioeconomically deprived were more likely to have uncontrolled asthma or exacerbations than those who were least deprived, yet the rates of respiratory referrals remained similar; this suggests that more deprived patients may have greater need for specialist reviews and biologic treatment [90].

The research projects recently prioritised by the ISC aim to study the "effectiveness of biologics" in severe asthma patients. In 2019, the ISC prioritised the FIRE project comparing the effectiveness of anti-IL5/5R *versus* anti-IgE therapy in severe asthma patients eligible for both biologic classes [91], as well as the Impact of Comorbidity in Severe Asthma (PRISM) project describing the prevalence of comorbidities in severe asthma patients and the association between type 2 comorbidities and response to biologics [92]. Phase I results from FIRE demonstrated that anti-IL5/5R patients tended to have greater disease severity pre-biologic initiation than anti-IgE patients [93]. Phase II results from FIRE showed that after matching for baseline characteristics, both biologic classes reduced exacerbation rates and long-term OCS daily dose, although anti-IL5/5R therapy was comparatively more effective than anti-IgE therapy [94]. In 2020, the ISC prioritised the BEAM research project, which defines and characterises biologic treatment responders and nonresponders in severe asthma patients [95], and the LUMINANT research project, which describes clinical outcomes before and after biologic initiation in severe asthma patients [96]. Phase I results from BEAM illustrated that severe asthma patients who initiated anti-IL5/5R therapy tended to have poorer asthma control and greater likelihood of receiving long-term OCS than those who initiated anti-IgE therapy [97]. In 2020, the ISC also approved three additional research projects: 1) the PASS project, a post-authorisation safety study of the incidence of malignancy in severe asthma patients receiving benralizumab compared with those receiving other biologics and those not receiving biologics [98]; 2) the CLEAR project on assessing biologic usage patterns, clinical outcomes and healthcare utilisation in severe asthma patients [99]; and 3) the GLITTER project on describing the impact of initiating biologics in patients on long-term OCS or frequent rescue steroids [100]. Phase I results from GLITTER demonstrated that 71% of ISAR patients with high exposure to OCS initiated biologics, and that biologic initiators were more likely to be eosinophilic and have uncontrolled asthma compared to those who did not initiate biologics [101].

The role of the Severe Heterogeneous Asthma Research Collaboration, Patient-Centred

To facilitate the generation of real-world evidence on severe asthma using a patient-centred approach, the European Respiratory Society (ERS) Clinical Research Collaboration (CRC) created SHARP (Severe Heterogeneous Asthma Research Collaboration, Patient-Centred) [102]. The goals of SHARP are to minimise the reliance on OCS for disease control; reduce exacerbations; provide all severe asthma patients with access to severe asthma specialists; understand the heterogeneous mechanisms of severe asthma; and prevent severe asthma [103]. Recently, the first study [104] by the ERS SHARP CRC, which aimed to compare the characteristics and treatments of severe asthma patients using data from 11 national severe asthma registries in Europe, demonstrated the heterogeneity of severe asthma in these two aspects. There are three major implications: first, it is challenging to integrate results coming from different European registries; second, the definition of severe asthma in the ERS/American Thoracic Society guidelines cannot be applied due to major discrepancies in the application of the aforesaid guidelines in the real world; and last, the concordance of the databases across Europe and the long-term follow-up of severe asthmatic patients are important and urgently needed.

Evidence from RCTs and real-life research is complementary

Registries, RCTs and other study designs, together with different data sources, should all be considered in order to try and create higher quality evidence, as long as their limitations and hierarchy are weighted and

put into context [105]. RCTs are still considered the gold standard for high-quality research, as they present lower risk of bias. Nevertheless, RCTs have limitations, such as strict inclusion criteria, making their findings difficult to apply to real-life and larger populations [10]. Real-world evidence from nonrandomised studies apply directly to the populations, interventions, comparators and outcomes that constitute the clinical environment, leading to the now affirmed concept of personalised medicine [105]. Despite that, the higher risk of bias that comes with real-world evidence must be acknowledged, and thus even the "most direct real-world evidence is not sufficient to provide certainty" [105]. Therefore, a certain level of quality must be achieved in both real-world evidence and RCTs using tools such as Grading of Recommendations Assessment, Development, and Evaluation (GRADE). The GRADE working group had developed a system to assess the certainty of evidence of effects and strength of recommendations; it broadened the system to support the process of using evidence to guide healthcare decision-making [106].

With regards to asthma, the Real Life Evidence Assessment Tool (RELEVANT) is a new user-friendly quality appraisal tool developed in order to support quality review of observational asthma comparative effectiveness research with the purpose of informing asthma guidelines and supporting decision-makers. The major difference between GRADE and RELEVANT is that the former automatically downgrades observational study designs and upgrades RCTs [107]. Another important tool is the Cochrane Collaboration's Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) [108]. It is designed to identify evidence that is robust enough (*i.e.* low risk of bias) to inform clinical practice and to warrant consideration by guideline bodies.

Therefore, RCTs are irreplaceable, but a hierarchy for real-world evidence is increasingly necessary and has already been proposed in the assessment of allergen immunotherapy, where, with the contribution of GRADE, RELEVANT and ROBINS-I tools, pragmatic trials and registry data are positioned at the highest levels of evidence [109].

The major difference between allergen immunotherapy and biologics used in asthma is the greater availability of registries for the latter.

Conclusion

Research priorities envisage the integration of evidence from nonrandomised studies with that from RCTs when supplementary and sequential evidence from nonrandomised studies is of particular relevance. Future research should also define the types of nonrandomised studies that should be considered for the contribution of evidence, and determine the criteria to appraise research quality with this additional evidence [105].

In conclusion, data on long-term efficacy and safety of biologics in severe asthma cannot be obtained by RCTs alone. Real-life studies should be a valuable source of this kind of information. Ideally, a long-term real-life study comparing biologics to standard treatment would provide data on their safety and effectiveness, including symptom control and steroid-sparing effect. These studies would also be essential in providing input parameter data for modelling in pharmacoeconomic studies.

Obviously, for ethical reasons, these studies are unfeasible. Therefore, it is impossible to design a real-life study comparing biologics to standard treatment. However, registries could be very useful in providing this missing piece of information. Subjects who refuse treatment with biologics for whatever reason, despite fulfilling the indication for this treatment, could serve as the control group for studies comparing biologics *versus* standard treatment over a long period. Given the large number of patients included in the already available asthma registries (SANI, BSAR, (GAN)UKSAR, ISAR, SHARP, *etc.*), theoretically, it could be possible to identify two comparable groups, *e.g.* by propensity scoring or other tools. This would integrate and confirm the information from RCTs on a large scale and in real-life populations, leading to more generalisable and complete results. These studies could later be analysed using other tools such as RELEVANT or ROBINS-I, to assess whether their strength and quality are sufficient for guideline developers. Currently, we should use our best data from severe asthma registries and possibly prospective observational studies to provide high-quality research that complement RCTs, thereby improving the care of patients with severe asthma.

In future, registries will enable the investigation of severe asthmatic phenotypes, comparison of the effectiveness of various treatments and their economic impact. Moreover, the creation of verified real-life databases linked to digital phenotyping using electronic patient-reported outcomes will enable the establishment of patient-centred outcome measures. When it comes to therapies, new products should not

only provide the desired effectiveness, but also considerable cost savings when compared to the best existing standards of care.

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