Roles of real-world evidence in severe asthma treatment: challenges and opportunities

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When using real-world data to evaluate treatment effectiveness in severe asthma, it is important to decide which real-world data are "fit for purpose" to address a specific clinical question https://bit.ly/3unZQaj

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Abstract

Recent advances in asthma research have led to the development of novel biologicals that hinder the pathological actions of key molecules in severe asthma. Traditional randomised controlled studies (RCTs), the gold standard for evaluating the efficacy and safety of medical interventions with excellent internal validity, have proven the clinical benefits and favourable safety profiles of type 2 biologicals in severe asthma. However, RCTs are not always ideal because of shortcomings such as limited external validity and practical issues in the management of severe asthma that cannot be solved through strictly designed clinical trials. Thus, the applicability of their findings may be questioned because treatment adherence is frequently poor in the real world. Real-world evidence includes a wide range of real-world data (RWD) collected from multiple sources in clinical practice, such as electronic medical records, healthcare insurance claims and retrospective or prospective patient registries. RWD may help clinicians decide how to manage patients with severe asthma. Real-world evidence is also gaining attention in addressing clinical questions not answered by traditional RCTs. Because there are various types of RWD with different possibilities and limitations, it is important to decide which type of RWD could be "fit for purpose" to address a specific question. This narrative review discusses the challenges and opportunities of RWD for evaluating the effectiveness and clinical outcomes of biological treatments for severe asthma.

Introduction

Asthma is a common chronic airway inflammatory disease that affects more than 300 million patients worldwide [1, 2]. Patients with severe asthma (SA) only account for about 5–10% of all asthma patients; however, SA imposes a substantial burden on patients, their family, physicians and society owing to persistent or recurrent symptoms, frequent exacerbations, lung function decline, need for high-intensity treatments and treatment complications [3–10].

SA is a heterogeneous condition with diverse phenotypes and endotypes [1]. Recent advances have led to the identification of key molecules such as interleukin (IL)-4, IL-5, IL-13 and IgE, which drive chronic type 2 (T2) inflammation in asthmatic airways, and the development of biologicals targeting the specific molecules or pathways in patients with SA [11, 12]. Biologicals targeting T2 airway inflammation significantly reduced asthma exacerbations and oral corticosteroid (OCS) use and had favourable safety profiles in randomised controlled trials (RCTs) of patients with SA [13–18].

However, many questions remain unanswered regarding optimal treatment of SA in the real world. Traditional RCTs are the gold standard for determining treatment efficacy, but their external validity is questionable owing to the stringent participant selection criteria [19]. According to recent analyses, participants of traditional RCTs may represent only about 5–10% of patients in the real world [20–22]. Furthermore, the gaps between RCTs and real-world settings may be more prominent for asthma than for other chronic disorders because treatment adherence, particularly to inhalers, is low in asthmatic patients [23]. Adherence to controller therapy is frequently poor, even in patients with SA [24]. Novel biologicals are usually expensive and not readily accessible, and the treatment effects depend on patient phenotypes [25, 26], highlighting the need to investigate real-world evidence (RWE) to validate treatment effects. This narrative review aims to evaluate opportunities and challenges of real-world data (RWD) studies for evaluating the effectiveness and clinical outcomes of biological treatments for SA.

RWE: overview

RWE is gaining attention in every aspect of the medical field, with advances in collecting, assorting and processing RWD. RWE is practically defined by what it is not [27] and includes a wide range of evidence not generated by traditional RCTs. There are many sources of RWD, including primary studies (prospective observational cohort or registry studies) and secondary data analyses (retrospective cohort studies, routinely collected electronic medical records (EMRs) or healthcare claims data analyses). Compared with traditional RCTs, the main strength of real-world studies lies in their external validity (table 1), which is usually attributable to the large-scale, heterogeneous or unselected nature of patient recruitment from the real world [28]. Their selection criteria are usually generous (*i.e.* patients are not excluded based on smoking history or comorbidities).

Most real-world studies in the field of SA have been performed using retrospective patient registries or routinely collected databases (RCDs) such as EMRs or healthcare insurance claims databases [29–32]. Retrospective analyses are more convenient and less time-consuming than prospective studies and can help generate hypotheses or in the rapid response to epidemic issues such as the coronavirus disease pandemic [33]. However, they can also provide clinical insights; well-designed national or international patient registry studies can produce generalisable and valuable data and identify unmet clinical needs and associated socioeconomic risk factors [34]. The issue of OCS overuse and morbidity burden was highlighted by national and international SA registry studies [35–37]. In addition, ethnic, demographic and geographic disparity in asthma management has been recently addressed by the UK Severe Asthma Registry study [38, 39]. These disparities are a critical issue in SA patient care because access to specialist treatment and biologicals is key to favourable clinical outcomes.

However, multiple types of bias are intrinsic to observational study design, and they are usually more frequent in retrospective studies. These include confounding, selection bias, information bias, recall bias and missing data, which sometimes seriously weaken the internal validity [40–42]. The operational

TABLE 1 Comparison of randomised controlled trials and real-world studies

	Randomised controlled trial	Real-world study
Strength	Internal validity	External validity
Design	Prospective	Retrospective or prospective
Inclusion criteria	Strict	Generous
Study population	Usually homogeneous	Heterogeneous
Comparator	Present (usually placebo controls)	Usually absent (or historical controls)
Outcomes	Focused and pre-determined	Various (depending on type of study or database)
Treatment regimen	Fixed	Variable (based on clinical practice and patient–physician decision)
Treatment adherence	Controlled (as planned)	Uncontrolled (resulting from various factors that patients and physicians experience, including efficacy, adverse effects, ease of use and costs)
Risk of bias and confounder	Usually controlled	Usually uncontrolled
Long-term follow-up	Relatively short (<1 year)	Follow-up for years is relatively common

definitions of SA and clinical outcomes, such as exacerbations or asthma control status, are other challenging issues in healthcare database analyses [43]. Moreover, healthcare claims data cannot easily capture SA and exacerbations. Patient-reported outcomes (PROs) can be helpful in clinical decision-making, and if integrated into RCDs, they can increase the value and utility of RWD [44, 45]; however, PROs are not routinely measured in most real-world practices.

Despite these issues, large-scale RWD analyses may be valuable in specific contexts, such as the evaluation of healthcare utilisation, rare diseases or outcomes, or long-term prognoses. In this regard, deciding which type of RWD is "fit for purpose" to address a specific question and evaluate the creditability in a specific context is essential (figure 1).

Retrospective RWE in the evaluation of biological treatments

Traditional RCTs demonstrated the benefits of T2 biological treatments over placebos in patients with SA [13–18]. How confident can we be that the findings of RCTs apply to SA patients in clinics? Healthcare claims databases usually represent a national or large population and have strength in studying long-term health outcomes that are rare in incidence or not readily captured in clinic-based studies, such as mortality. The databases contain large-scale information regarding drug prescriptions, outpatient visits or hospitalisations and may help in evaluating the cost-effectiveness of a biological or the treatment-associated changes in healthcare utilisation, or in comparing different biological treatments [46–49]. However, claims databases have systemic biases inherent to the nature of databases, including selection bias and information bias (*i.e.* incorrect classification of exposure and outcomes). They also frequently lack relevant clinical information associated with treatment decisions or effects, such as disease severity, patient phenotypes, biomarkers or socioeconomic status. Current biologicals are usually costly (although insurance systems vary between countries), and patients who can afford treatments may be more likely to have better socioeconomic and health statuses. Thus, the effects of unmeasured confounders cannot be excluded in effectiveness analyses based on claims databases.

Retrospective analyses of institutional EMRs or patient registries usually include detailed clinical information such as disease severity, biomarkers or lung function data and thus may overcome the limitations of healthcare claims database analyses. They may also be helpful for rapidly exploring treatment effectiveness and generating hypotheses. However, retrospective RWD frequently lack

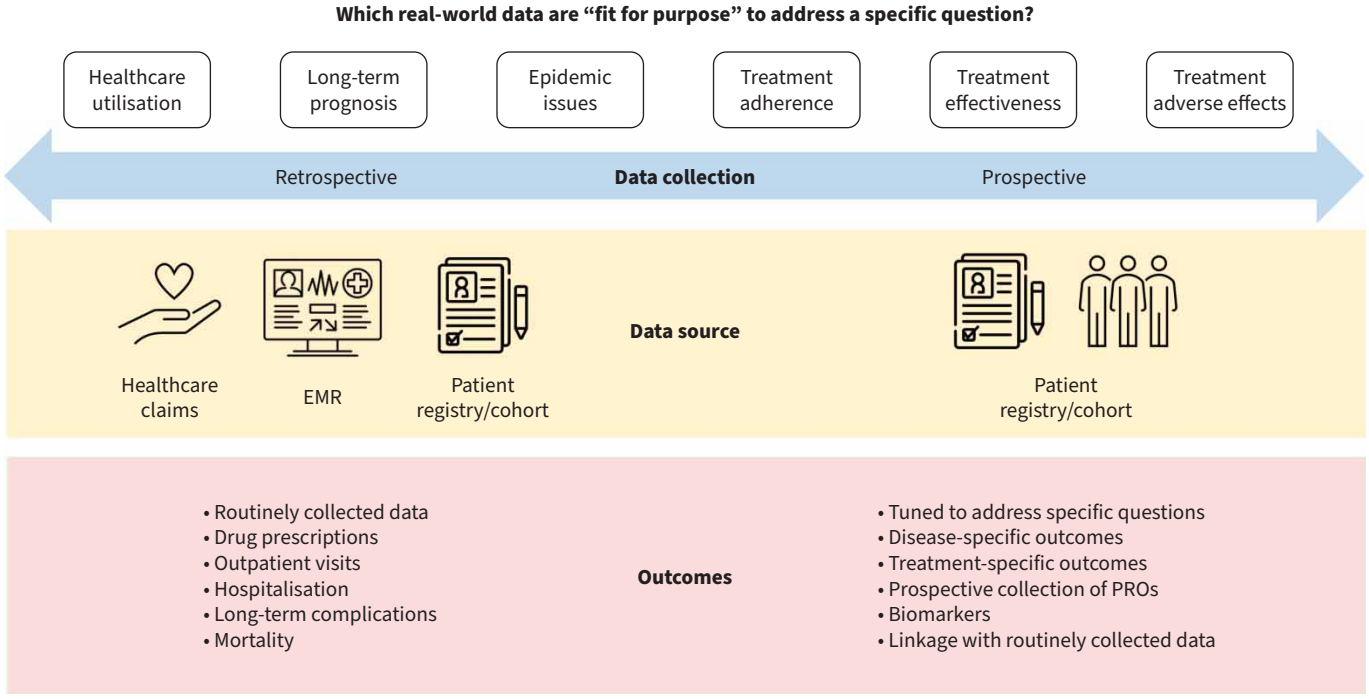

FIGURE 1 Types of real-world data. There are different possibilities and limitations, depending on the type of data, and thus it is essential to decide which real-world data are "fit for purpose" to address a specific question. EMR: electronic medical record; PRO: patient-reported outcome.

pre-specification of analytic plans and may selectively report favourable findings. Furthermore, the study inclusion criteria (or treatment decision criteria) are often unclear, resulting in confounding by indication. PROs are usually lacking in retrospective analyses of RCDs such as EMRs. Handling missing data is another challenge. In real-world observational studies, the treatment responses appear to be larger than those observed in RCTs [44, 50–53]; several factors may underlie the gap, such as different baseline severity, comorbidity or background treatment. However, it is difficult to explain the gaps in retrospective studies. Therefore, retrospective RWE has inherently limited value in validating the findings of RCTs, and well-designed prospective real-world studies should be conducted to inform specific treatment decisions.

Prospective RWE in the evaluation of biological treatments

Successful RCTs are followed by prospective real-world studies. Several prospective observational studies have been conducted with omalizumab [54–74], mepolizumab [70, 75–86], reslizumab [80, 87] and benralizumab [70, 88, 89] in patients with SA. We conducted a semi-systematic literature search to identify prospective observational studies of biological treatment in patients with SA and summarise their outcome measurements in table 2. We searched PubMed for articles published in English from database inception until 21 April 2022, and updated on 11 October 2022, with the search terms “severe asthma” combined with “omalizumab”, “mepolizumab”, “reslizumab”, “benralizumab”, “dupilumab”, “tezepelumab” and “biologics”. Additional searches were performed using Google Scholar and cross-referenced articles. Only prospective observational or non-randomised studies in adults with SA that reported asthma exacerbations or quality of life (QoL) as effectiveness outcomes of T2 biologicals were included. When there was duplication of study protocols and populations, a single paper was chosen where possible.

Roles of prospective RWE

The primary role of these prospective observational studies is to cross-validate the efficacy findings of RCTs in real-world populations. This is important because patients with SA in the real world may have different profiles from those in RCTs in terms of age, disease severity, airway reversibility, smoking history, comorbidities, socioeconomic status or adherence [55, 57, 59, 61, 78, 97, 98]. When the inclusion criteria of RCTs were applied to a SA patient cohort in a real-world setting in France, most cohort participants (89.3–99.7%) did not meet these criteria [97]. Their ineligibility was due to insufficient airflow reversibility (73%) and a lower exacerbation rate (58%), followed by smoking, obesity and comorbidities. A strength of prospective studies is that they can be tuned to a specific research question. To validate treatment effects, they can prospectively characterise patients and collect and follow up proper clinical outcomes or PROs in a similar fashion to traditional RCTs, such as exacerbations, QoL, medication use or hospitalisation. The treatment effect size in the real world can then be compared with that in RCTs. However, there are many pitfalls in interpreting such observational studies [42], including a few more specific issues in SA studies.

Challenges in RWE interpretation

First, regression to the mean effects or spontaneous improvement is a major concern in interpreting observational studies. Regression to the mean is a common statistical phenomenon that may occur in longitudinal studies with repeated outcome measures because extreme measurements are likely to move closer to the mean when subjects are followed up [99]. At the time of study inclusion or treatment initiation, patients are likely to have severe disease.

Placebo effects are another concern and may be substantial even among patients with SA. In a pooled analysis of five RCTs, spontaneous improvements or placebo effects were substantial in analyses of clinical outcomes of patients with SA and were largest for risk reduction of healthcare utilisation, including hospitalisation (66% risk reduction, range 61–74%), emergency department visits (50% risk reduction, range 36–82%) and exacerbations (31% risk reduction, range 19–56%), followed by improvements of PROs such as the Asthma Control Questionnaire score (25% improvement, range 18–30%) and St George’s Respiratory Questionnaire score (19.5% improvement, range 19–20%) [100].

Methods suggested to reduce regression to the mean, spontaneous improvement or placebo effects during the study design stage include 1) employment of a proper control group and 2) selection of participants based on multiple measurements (*i.e.* recruitment of patients with persistently severe disease) [101]. However, to our knowledge, most prospective real-world studies with T2 biologicals only used historical controls (comparing patients before *versus* after treatment) or were based on a single baseline measurement (table 2). Furthermore, given the fluctuating clinical course of asthma, the study inception point should be specified, tied to treatment initiation and matched to baseline measurement.

TABLE 2 Summary of treatments of interest, comparisons and measurements of asthma exacerbations or QoL in prospective observational cohort or registry studies reporting type 2 biological treatment effectiveness in adults with severe asthma

Study	Measurement of asthma exacerbation		Measurement of QoL	
	Method	Definition and comparison	General health-related QoL	Asthma-specific QoL
Omalizumab				
Molimard *et al.* 2008 [54]	Patient self-reported questionnaire	Exacerbations requiring OCS, ED visits or hospitalisations: before (recall of 12 months) *versus* during treatment (for >5 months)	–	–
Korn *et al.* 2009 [56]	Patient self-reported questionnaire	Exacerbations (defined by FEV_1<60% of personal best, intermittent treatment with OCS, unscheduled healthcare visits, emergency treatments or hospitalisations due to asthma): before (recall of 12 months) *versus* after treatment (for 6 months)	–	Mini-AQLQ: recall of 12 months before *versus* measurement at 6 months after treatment
Brusselle *et al.* 2009 [55]	Retrospective assessment by physicians at study visit	Severe exacerbations (requiring OCS, ED visit or hospitalisation): 52 weeks before *versus* after treatment (at 16 and 52 weeks)	EQ-5D: baseline *versus* 52 weeks	AQLQ: baseline *versus* 16 and 52 weeks
Cazzola *et al.* 2010 [57]	Retrospective assessment by physicians at study visit	Asthma-related events (exacerbations, hospitalisation and ED visits): 12 months before (retrospective review) *versus* after treatment	–	–
Schumann *et al.* 2012 [59]	Retrospective assessment by physicians at study visit	Severe exacerbations (worsening of asthma requiring systemic corticosteroids, ED visit, hospitalisation or reduction of FEV_1 to <60% of personal best): 16 weeks before (retrospective review) *versus* after treatment	–	–
Braunstahl *et al.* 2013 [61]	Retrospective assessment by physicians at study visit	Clinically significant exacerbations (any worsening of asthma requiring systemic corticosteroids) and severe exacerbations (if reduction of PEF to <60% of personal best): before (retrospective review of 12 months data) *versus* after treatment (at 12 and 24 months)	-	AQLQ or mini-AQLQ: baseline *versus* 12 and 24 months
Chen *et al.* 2013 [73], Long *et al.* 2009 [90]	Electronic data capture of patient reporting (healthcare utilisation)	Asthma-related ED visits, overnight hospitalisations, unscheduled office visits, intubations or need for mechanical ventilator assistance, and oral or intravenous corticosteroid bursts: Omalizumab *versus* non-omalizumab treatment groups	–	–
Grimaldi-Bensouda *et al.* 2013 [71]	Medical chart review by clinical research associates (independent reviewers)	Severe exacerbations (exacerbation requiring ED visits or hospitalisation): Omalizumab *versus* non-omalizumab prescribed groups	–	–
Vieira *et al.* 2014 [72]	Retrospective assessment by physicians at study visit	Clinically significant exacerbation (worsening of asthma symptoms requiring treatment with systemic corticosteroids or a doubling of the inhaled steroids dose in addition to unscheduled healthcare utilisation resources): 12 months before (retrospective review) *versus* after treatment	-	Asthma Life Questionnaire: baseline *versus 16* weeks and every 4 months

Continued

TABLE 2 Continued

Study	Measurement of asthma exacerbation		Measurement of QoL	
	Method	Definition and comparison	General health-related QoL	Asthma-specific QoL
Gouder *et al*. 2015 [63]	Retrospective assessment by physicians at study visit (every 4 or 8 weeks)	Exacerbations, hospitalisations, unscheduled healthcare visits, number of OCS courses prescribed: 12 months before (retrospective review) *versus* after treatment	–	–
Sousa *et al*. 2015 [62]	Structured questionnaire at routine visit	Exacerbations (unscheduled healthcare utilisation or increases in OCS intake because of asthma): no comparison group	–	–
Hew *et al*. 2016 [91]	Based on medical records	Exacerbations (measurement details were not described in the paper): before (retrospective review) *versus* after treatment (at 6 months)	–	AQLQ: baseline *versus* 6 months
Niven *et al*. 2016 [64]	Based on routinely collected data of healthcare use	Hospital exacerbations (when patients attended ED or were admitted) and dose exacerbations (when OCS dose increased by ⩾10 mg at any point for at least 3 days): 12 months before (retrospective review) *versus* after treatment	EQ-5D: baseline *versus* 16 weeks, 8 months and 12 months	AQLQ: baseline *versus* 16 weeks, 8 months and months
Kupryś-Lipińska *et al*. 2016 [65]	Retrospective assessment by physicians at study visit	Exacerbations (measurement details were not described in the paper): before (retrospective review of 6–12 months data) versus after treatment (for 16 weeks)	–	AQLQ: baseline *versus* 16 weeks
Gibson *et al*. 2016 [92]	–	– (reported as safety outcome)	–	AQLQ: baseline *versus* 6 months
Canonica *et al*. 2018 [67]	Retrospective assessment by physicians at study visit	Number of exacerbations and proportion of patients with at least one episode of asthma exacerbation during the 12 months study period: 12 months before (retrospective review) *versus* after treatment	EQ-5D: baseline *versus* 6 and 12 months	–
Adachi *et al*. 2018 [74]	(Not described in the paper)	Exacerbations (worsening of asthma symptoms requiring hospitalisation, ED visit, OCS therapy, unscheduled doctor visit or absenteeism): before (retrospective review) *versus* after treatment (for 52 weeks)	–	–
Casale *et al*. 2019 [68], Soong *et al*. 2021 [93]	Monthly retrospective assessment of patient self-reporting	Exacerbations (worsening of asthma symptoms requiring the use of OCS, ED visit or hospitalisation): 12 months before (retrospective review) *versus* after treatment	–	AQLQ: baseline *versus* 6 and 12 months
Jung *et al*. 2021 [69]	–	–	–	KAQLQ: baseline *versus* 16 and 24 weeks
Mepolizumab				
Schleich *et al*. 2020 [79]	Retrospective assessment by physicians at study visit	Exacerbation (a course of OCS for at least 3 days in case of asthma worsening): before (retrospective review of 12 months data) *versus* after treatment (for 18 months)	–	AQLQ: baseline *versus* 6, 18 and 30 months
Langton *et al*. 2020 [85]	Researcher assessment with OCS use record	Exacerbation requiring OCS (measurement details were not described in the paper): mepolizumab *versus* bronchial thermoplasty treatment groups (comparing 6 months before *versus* after each treatment)	–	–

Continued

TABLE 2 Continued

Study	Measurement of asthma exacerbation		Measurement of QoL	
	Method	Definition and comparison	General health-related QoL	Asthma-specific QoL
Harvey *et al*. 2020 [78], Thomas *et al*. 2021 [83]	Retrospective assessment at study visit (3, 6 and 12 months)	Severe exacerbation requiring documented use of systemic corticosteroids (OCS initiated or increased for at least 3 days, or parenteral corticosteroids) prescribed/supervised by a physician: 12 months before (retrospective review) *versus* after treatment	–	AQLQ: baseline *versus* 3, 6 and 12 months
Harrison *et al*. 2020 [76], Renner *et al*. 2020 [77], Pini *et al*. 2021 [81], Pilette *et al*. 2022 [94]	Monthly assessment during routine care visit	Clinically significant exacerbation (requiring rescue medication with OCS for at least 3 days or a single systemic steroid injection, and/or ED visits and/or hospitalisations (×2 increase in maintenance OCS dose for 3 days in patients with OCS maintenance therapy): 12 months before (retrospective review) *versus* after treatment	–	–
Izumo *et al*. 2020 [88]	–	–	–	AQLQ: baseline *versus* 4 and 12 weeks
Pertzov *et al*. 2021 [86]	Medical record assessment during routine care visit	Exacerbation (ED visit or OCS treatment prescribed by general practitioner): 12 months before (retrospective review) *versus* after treatment	Using a scale of −2 to 2	-
McDowell *et al*. 2021 [82]	Retrospective assessment during routine care visit (patient reporting)	Severe asthma symptoms worsening outside of a patient's normal daily variation and occurring any time: no comparison group	–	–
McDowell *et al*. 2022 [84]	Monthly retrospective assessment by research nurse specialist	Exacerbations (measurement details were not described in the paper): 12 months before (retrospective review) *versus* after treatment	EQ-5D: baseline *versus* 12 months	mini-AQLQ and SGRQ: baseline *versus* 12 months
Kallieri *et al*. 2022 [95]	Prospective multicentre, non-interventional observational study	Clinically significant exacerbations (symptoms deterioration requiring the use of systemic corticosteroids or increase from maintenance dose for ⩾3 days and/or emergency visit or hospital admission): 12 months before (retrospective review) *versus* 12 and 24 months after treatment	–	–
Reslizumab				
Pérez de Llano *et al*. 2019 [87]	Retrospective assessment by physician during routine care visit	Severe exacerbation (clinically judged worsening of asthma control as evidenced by worsening symptoms and that resulted in use of systemic corticosteroids and/or hospitalisation): before (retrospective review) *versus* after treatment (for 24 weeks)	–	AQLQ: baseline *versus* 4, 12 and 24 weeks
Benralizumab				
Scioscia *et al*. 2021 [89]	Retrospective assessment at 24 weeks	Number of exacerbations for 24 weeks (measurement details were not described in the paper): 24 weeks before (retrospective review) *versus* after treatment	EQ-5D: baseline *versus* 12 and 24 weeks	AQLQ: baseline *versus* 12 and 24 weeks

Continued

TABLE 2 Continued

Study	Measurement of asthma exacerbation		Measurement of QoL	
	Method	Definition and comparison	General health-related QoL	Asthma-specific QoL
Jackson *et al*. 2022 [96]	Retrospective assessment at 48 weeks	Number of exacerbations for 48 weeks (worsening in asthma control requiring ⩾3 days of OCS), OCS dose reduction: 48 weeks before (retrospective review) *versus* after treatment	-	AQLQ: baseline *versus* 48 weeks

QoL: quality of life; OCS: oral corticosteroid; ED: emergency department; FEV_1: forced expiratory volume in 1 s; AQLQ: Asthma Quality of Life Questionnaire; EQ-5D: EuroQoL five-dimensional instrument; PEF: peak expiratory flow; KAQLQ: Quality of Life Questionnaire for Adult Korean Asthmatics; SGRQ: St George's Respiratory Questionnaire.

When designing an external comparator group, employment of an active treatment comparator with a similar indication and treatment modality as the target treatment population is recommended over the use of a non-user comparator because non-user groups may differ from the target treatment population in baseline severity, socioeconomic status or treatment indications (leading to confounding by indication) [102]. In the case of SA treatments, employing different T2 biologicals as comparators may mitigate the risk of unmeasured confounding and is preferred. Indeed, such a comparison is more relevant to real-world decision-making. The Risk of Bias In Non-Randomized Studies – of Interventions (ROBINS-I) is a major tool to assess the risk of bias in Cochrane Reviews for non-randomised studies of interventions [42]. The Real Life Evidence Assessment Tool (RELEVANT) is a quality assessment tool developed by a joint task force between the Respiratory Effectiveness Group and the European Academy of Allergy and Clinical Immunology (www.regresearchnetwork.org/relevant-tool-2) [103]. The ROBINS-I evaluates the level of evidence of observational studies as in ideal RCTs. The RELEVANT has a simple and user-friendly checklist scoring system and can be used to assess the comparative effectiveness of asthma research. These tools should be used not only in judging the validity of studies that are already published but also when considering the design of real-world studies of treatments to reduce the risk of bias.

Another challenge is the transparency of RWD studies. In the case of RCTs, detailed study protocols should be registered in public clinical trial databases before recruiting study participants. Such registration ensures that the results do not influence or modify measurements, analyses and reporting. There is increasing consensus that protocols for prospective real-world studies should be pre-registered to ensure transparency, trust and replicability, which will facilitate the use of RWE in practice guidelines or policy decision-making [104].

Opportunities for real-world studies in SA

Despite their limitations, real-world studies can address scientific or clinical research questions that are not answered by RCTs. First, because treatment decision-making is based on different factors, including disease characteristics, effectiveness, patient preference, adherence and socioeconomic status, real-world studies can investigate factors related to treatment initiation, dose adjustment or discontinuation and examine switching patterns. Biological treatment discontinuation or switch is frequent in patients with SA, and RWD may help clarify patient factors or clinical outcomes associated with treatment changes [105–109]. Some patients who do not respond to one biological agent may achieve a significant clinical improvement with other biologicals [110]. RWD may also provide an opportunity to examine different dosing; in the Australian Xolair Registry study, it was suggested that omalizumab treatments beyond the recommended dosing criteria might provide further clinical improvement [111]. Furthermore, the effects of a combination of different biologicals can be evaluated. Some patients eligible for T2 biologicals may have overlapping phenotypic features (*e.g.* allergic eosinophilic asthma) and respond better to a particular drug or multiple T2 biologicals. However, RCTs directly comparing different biologicals or regimens are still limited, and only indirect comparisons *via* network meta-analysis have been performed [111–114].

Second, real-world studies can explore treatment effectiveness in patient subgroups with overlapping but distinct clinical problems. For example, in the case of T2 biologicals, treatment effectiveness can be examined in SA patients with features of aspirin-exacerbated respiratory diseases, eosinophilic granulomatosis with polyangiitis (EGPA) or fungal sensitisation [115–120]. Fortunately, mepolizumab has

recently been approved for treating patients with EGPA. However, ongoing unmet needs exist to manage these conditions, because such patients have rarely been prospectively trialled. Furthermore, patients with fixed airflow obstruction or cardiovascular comorbidities who are ineligible in many RCTs with T2 biologicals can be examined in real-world studies.

Third, long-term clinical outcomes can be evaluated with treatments or after discontinuation. Little is known about the long-term benefits and safety of T2 biologicals in SA. Executing an RCT requires enormous resources and extending the study period to several years or longer is more consuming. In most RCTs with T2 biologicals, the study period was 1 year or shorter, although some extended the study period to a few years to assess long-term efficacy and safety [15, 121–125]. In a recent phase 3, open-label, safety extension study with benralizumab in patients with severe uncontrolled eosinophilic asthma, long-term eosinophil depletion was not associated with adverse events and the treatment effects were well maintained [126]. Another long-term study appraised mepolizumab in patients with severe eosinophilic asthma for over 3 years and demonstrated favourable clinical efficacy in reducing exacerbations or asthma control [122]. However, further studies are warranted to confirm that responders will have consistently good clinical responses for a longer duration or maintain their status after discontinuation of the treatment [126]. It also remains to be tested if T2 biologicals have disease-modifying effects. Moreover, given the impact of SA on diverse health outcomes, such treatments should be evaluated to determine if they improve general health-related QoL, treatment complications or mortality.

Last, because biologicals are far more expensive than conventional asthma therapy, cost-effectiveness should be sought in real-world studies. A systematic review of cost-effectiveness analyses of treatments reported controversial results based on the type of biological and its target population [127]. Another recent retrospective analysis of claims data in Germany described that the average cost of asthma treatment per patient increased by more than three times after the initiation of biological therapy [32]. The cost-effectiveness of biologicals is as critical as the clinical efficacy for continuing biological therapy, and better-designed investigations with multiple aspects of economic analyses also will inform selection of the proper biological agent for each patient.

Outcomes in real-world studies of SA

The final section of this review discusses outcome measurements in prospective real-world studies of SA. The selection of core outcomes depends on the study purpose, but they should be relevant to addressing unmet patient needs and thus may not differ much from the outcomes in RCTs.

Morbidity related to OCS use

SA is not just “bad or uncontrolled” asthma because its health outcomes may extend beyond the respiratory system [10, 128]. Patients with SA may experience severe physical and emotional distress from repeated asthma exacerbations, feel helpless because of their failed efforts, live a restricted life and frequently rely on systemic steroids, despite being aware of their adverse effects and hoping to avoid OCS [10]. Thus, a major burden of SA is the future risk of adverse health outcomes [1, 129], which can be addressed in long-term observational studies. Some patients stated that taking OCS is like “biting the bullet” [10], and therefore OCS-induced morbidity is a particular concern and may be reduced by novel biological treatments. A recent series of RWD studies using healthcare claims databases and patient registries reported that the risk of complications of systemic corticosteroids might increase in a dose-dependent manner but occur even upon low-dose steroid exposure [130–134]. RCTs have shown that T2 biologicals may help reduce OCS use in patients with SA without loss of asthma control [135–138]. Also, in extension studies, T2-biological-treated patients successfully achieved long-term OCS reduction or elimination and recovered adrenal functions [139].

However, the use of OCS is a proxy marker and, therefore, the next question is whether T2 biologicals can reduce OCS complications and improve long-term health outcomes in the real world. In a recent longitudinal, real-world, prospective, single-centre cohort study of 101 patients from the UK with SA who commenced mepolizumab treatment, changes in glucocorticoid toxicity were evaluated after 12 months of treatment [84]. The outcome of interest was the glucocorticoid toxicity index: a composite scoring tool developed to capture a range of glucocorticoid toxicities [140]. Of the 83 study participants on maintenance OCS, this treatment was completely withdrawn from 30 patients, and only 21 patients remained on this treatment for asthma control. The median (interquartile range) prednisolone dose per year decreased from 4280 mg (3082–3475 mg) at baseline to 2450 mg (1242–3360 mg) after mepolizumab treatment for 1 year, while the number of asthma exacerbations declined from a median (interquartile range) of five (two to seven) to one (zero to two). Notably, there were also meaningful reductions in body

mass index, blood pressure, lipid profile, haemoglobin A1C and depressive symptoms and improvements in general health-related QoL [84]. Further studies are warranted to address longer-term or rarer outcomes of SA, but the results are promising and suggest further roles of RWD studies in evaluating the effectiveness of novel treatments to reduce future risks.

Exacerbation

Exacerbation is a defining factor of SA and is a core outcome in RCTs and real-world studies with biological treatments. However, it is challenging to collect exacerbations, especially in real-world studies. In secondary analyses of routinely collected claims databases, an asthma exacerbation is usually identified by a working definition based on a visit to the emergency department, hospital admission or OCS prescription plus registration of asthma diagnostic codes. However, the definition may not differentiate healthcare utilisation for reasons other than asthma exacerbations, and a diagnostic code may not precisely represent SA. Thus, another working definition for SA is needed [141].

Asthma exacerbation has been evaluated in many prospective real-world studies with T2 biologicals in SA. However, these evaluations are mostly based on retrospective assessments of patient reports or medical records of healthcare utilisation (table 2). This can be more problematic because patient follow-up intervals are usually 3–6 months, and follow-ups are not strictly controlled in observational studies. The definition of asthma exacerbation is rather subjective [142]; therefore, retrospective assessment at the time of patient visits may increase the risk of misclassification or recall bias. Use of digital technology or telemedicine might help to increase the precision of detection *via* prospective real-time measurement.

Quality of life

General health-related QoL is perceived to be one of the most important clinical outcomes by SA patients [128]. However, it has not been frequently measured in prospective real-world studies (table 2). Furthermore, although the EuroQoL five-dimensional instrument (EQ-5D) is one of the most widely used tools to measure general health-related QoL, the items are not specific to asthmatic patients' experiences and may not be sufficiently sensitive to capture clinical changes before *versus* after biological treatments [143, 144]. Therefore, tools that were designed to measure SA patients' experiences, such as the Severe Asthma Questionnaire, are becoming more popular in real-world studies [145].

Mortality risk

Treatment complications and mortality are also important outcomes in SA [129], but the differences by treatment may not be evident in short-term studies. In a recent Danish nationwide population register analysis (1999–2018), asthma-specific mortality was significantly associated with OCS use and dosage, but mortality rates were generally low at 0.15 (95% CI 0.11–0.20) and 0.04 (95% CI 0.02–0.06) per 1000 person-years in OCS-users and non-users, respectively [146]. In the National Health Insurance Sharing Service database in Korea (2002–2015), the asthma mortality rates ranged from 16.2 to 28.0 deaths per 100 000 population per year [8]. However, large RCD studies have inherent limitations in identifying true cases or specific patient characteristics associated with worse outcomes; thus, linkage of prospective patient registries with national health databases is likely to be a way forward.

Conclusion

RWE studies have gained attention for regulatory and clinical decision-making purposes. For clinicians, proper RWE is valuable to judge whether a novel treatment is applicable to patients in daily clinics. Treatment adherence is a frequent issue in SA; therefore, RWE findings may be more relevant than RCTs for helping clinicians make decisions about patient management. Different types of RWD are used in SA studies, with different possibilities and limitations, and thus there are no general rules for evaluating RWE or translating it to clinical practice. It is important to decide which RWD are "fit for purpose" to address a specific clinical question. Prospective real-world studies may be more advantageous than other types of RWD analyses for validating the findings of RCTs because they can be prospectively tuned to address a specific research question. They can also collect clinical outcomes or PROs, similar to RCTs. However, there are methodological pitfalls in observational studies, including regression to the mean effects or limited outcome measurements, which should be properly addressed in future studies of treatment effectiveness in SA. This will ensure the value and impact of prospective RWE and enable it to be used in guiding clinical and political decision-making for treatment of patients with SA in clinics.

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