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

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This manuscript has recently been accepted for publication in the ERJ Open Research. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

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Roles of real-world evidence in severe asthma treatment: challenges and opportunities
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Source of funding: This research was supported by the "National Institute of Health" research project (project No. 2021ER120100) in Korea.

Conflict of interest: WJS is serving as Deputy Chief Editor in the journal. Others have nothing to declare.
Abstract

Recent advances in asthma research have led to the development of novel biologics that hinder the pathologic actions of key molecules in severe asthma (SA). 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-biologics in SA. However, RCTs are not always ideal because of shortcomings such as limited external validity and practical issues in the management of SA that could not be solved through strictly designed clinical trials. Thus, the applicability of their findings may be questioned for asthmatic patients because treatment adherence is frequently poor in the real world. Real-world evidence (RWE) 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. It may help clinicians make decisions about the management of patients with SA. RWE is also gaining attention to address clinical questions not answered by traditional RCTs. Since there are various types of RWD with different possibilities and limitations, and thus it is important to decide which type of RWD could be “fit for purpose” to address a specific question. This narrative review is to discuss the challenges and opportunities of RWD for evaluating the effectiveness and clinical outcomes of biological treatments for SA.

Keywords: severe asthma; real-world; evidence
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 asthmatics; however, SA imposes a substantial burden on patients and family, physicians and society due to persistent or recurrent symptoms, frequent exacerbations, lung function decline, need for high-intensity treatments and treatment complications [3-10].

SA is a highly 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 biologics targeting the specific molecules or pathways in severe asthmatics [11, 12]. Biologics targeting T2 airway inflammation (T2-biologics) significantly reduced asthma exacerbations and oral corticosteroid (OCS) use and had favourable safety profiles in randomised controlled trials (RCTs) of severe asthmatics [13-18].

However, many questions remain unanswered regarding optimal treatments of SA in the real world. Traditional RCTs are the gold standard for determining treatment efficacy, but their external validity is questioned due 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 other chronic disorders because treatment adherence, particularly to inhalers, is low in asthmatic patients [23]. Adherence to controller therapy is frequently poor, even in difficult-to-treat or severe asthmatic patients [24]. Novel biologics 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 has gained increasing 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 rapidly respond 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, the ethnic, demographic, or geographic disparity has been recently addressed by the UK Severe Asthma Registry study [38, 39], which is a critical issue in SA patient care because accessibility to specialist treatment and biologics 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, or missing data, which sometimes seriously weaken the internal validity [40-42]. The operational definitions of SA and clinical outcomes, such as exacerbations or asthma control status, are other challenging issues in extensive 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, the outcomes 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 evaluate the cost-effectiveness of a biologic or the treatment-associated changes in healthcare utilisation or for 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 biologics 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 the effectiveness analyses based on claims databases.

Retrospective analyses of institutional EMRs or patient registries usually include detailed clinical information such as the 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 lacks 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 gaps, 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] or 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 summarized their outcome measurements in Table 2. We
searched PubMed for articles published in English from database inception until April 21, 2022, and updated on October 11, 2022, with the search terms “severe asthma” combined with “omalizumab”, “mepolizumab”, “reslizumab”, “benralizumab”, “dupilumab”, “Tezepelumab”, and “biologics”. Additional searches were performed by using Google Scholar and cross-referenced articles.

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. It 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. When the inclusion criteria of RCTs were applied to a SA patient cohort in the real-world setting of France, most cohort participants (89.3–99.7%) did not meet these criteria. 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 characterize patients and collect and follow up proper clinical outcomes or PROs similar to traditional RCTs, such as exacerbations, quality of life (QoL), medication use, or hospitalisation. Then the treatment effect size in the real world can be compared with that in RCTs. However, there are many pitfalls in interpreting such observational studies, 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. 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 [92]. 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%) [93].

There are methods suggested to reduce regression to the mean, spontaneous improvement or placebo effects during the study design stage, including (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) [94]. However, to our knowledge, most prospective real-world studies with T2-biologics only used historical controls (comparing patients before vs. 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.

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) [95]. In the case of SA treatments, employing different T2-biologics 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 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) [96]. 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 utilized not only in judging the validity of studies that are already published but also should be considered in designing 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. It is now gaining more consensus that protocols for prospective real-world studies should be pre-registered to ensure transparency, trust and replicability, which will facilitate the utilisation of RWE in practice guidelines or policy decision-making [97].

**Opportunities for real-world studies in severe asthma**

Despite their limitations, real-world studies have opportunities to address scientific or clinical research questions that are not answered by RCTs. First, since treatment decision-making is based on different factors, including disease characteristics, effectiveness, patient preference, adherence, and socioeconomic status, real-world studies can offer the opportunity to investigate factors related to treatment initiation, dose adjustment or discontinuation and to examine switching patterns. Biological treatment discontinuation or switch is frequent in
patients with SA, and RWD may help to understand patient factors or clinical outcomes associated with the treatment changes [98-102]. Some patients who did not respond to one biological agent may achieve a significant clinical improvement with other biologics [103]. Also, RWD may 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 [104]. Furthermore, the effects of a combination of different biologics can be evaluated. Some patients eligible for T2-biologics may have overlapping phenotypic features (e.g., allergic eosinophilic asthma) and respond better to a particular drug or multiple T2-biologics. However, RCTs directly comparing different biologics or regimens are still limited, and only indirect comparisons via network meta-analysis have been performed [105-108].

Second, they can explore treatment effectiveness in patient subgroups with overlapping but distinct clinical problems. For example, in the case of T2-biologics, treatment effectiveness can be examined in SA patients with features of aspirin-exacerbated respiratory diseases, eosinophilic granulomatosis with polyangiitis (EGPA), or fungal sensitization [109-114]. Fortunately, mepolizumab has been recently approved for treating patients with EGPA. However, ongoing unmet needs exist to manage these conditions, as such patients have rarely been prospectively trialled. Furthermore, patients with fixed airflow obstruction or cardiovascular comorbidities who are ineligible in many RCTs with T2-biologics 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-biologics 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-biologics, 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, 115-119]. 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 [120]. Another long-term study appraised mepolizumab in severe eosinophilic asthmatics for over 3 years and demonstrated favourable clinical efficacy in reducing exacerbations or asthma control [116]. 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 [121]. It also remains to be tested if T2-biologics have disease-modifying effects. Moreover, given the impact of SA on diverse health outcomes, it should be evaluated if such treatments improve general health-related QoL, treatment complications, or mortality.

Lastly, since biologics are far more expensive than conventional asthma therapy, cost-effectiveness should be sought in real-world studies. A systematic review covering the publications with cost-effectiveness analyses of treatments reported controversial results based on the type of biologics and its target populations [122]. Another recent retrospective analysis of claims data in Germany described that the average cost of asthma treatment per patient increased by more than 3 times after the initiation of biological therapy [123]. The cost-effectiveness of biologics is as critical as the clinical efficacy for continuing biological therapy, and better-designed investigations with multiple aspects of economic analyses also will provide information for selecting 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 systems [10, 124]. 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, 125], 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 or 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 [126-130]. RCTs have shown that T2-biologics may help reduce OCS use in patients with SA without loss of asthma control [131-134]. Also, in extension studies, T2-biologics-treated patients successfully achieved long-term OCS reduction or elimination and recovered adrenal functions [135].

However, the use of OCS is a proxy marker and therefore, the next question is whether T2-biologics can finally 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 (137). Of the 83 study participants on maintenance OCS, this treatment was completely redrawn from 30 patients, and only 21 patients remained on this treatment for asthma control. The median prednisolone dose per
year decreased from 4280 mg (interquartile range: 3082.5–3475 mg) at baseline to 2450 mg (1242.5–3360 mg) after mepolizumab treatment for 1 year, while the number of asthma exacerbations declined from a median of five (2–7) to one (0–2). Notably, there were also meaningful reductions in body mass index, blood pressure, lipid profile, HbA1c, 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 an emergency room visit, 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, which may also not be sufficiently precise [136]).

Asthma exacerbation has been evaluated in many prospective real-world studies with T2-biologics in SA. However, it is mostly based on retrospective assessment of patient reports or medical records of healthcare utilization (Table 2). It can be more problematic because patient follow-up intervals are usually 3–6 months, and follow-ups are not strictly controlled in this type of study. The definition of asthma exacerbation is rather subjective [137]; 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.
**QoL**

General health-related QoL is perceived as one of the most important clinical outcomes by SA patients [124]. However, it has not been frequently measured in prospective real-world studies (Table 2). Furthermore, although the 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 vs. after biological treatments [138, 139]. Therefore, tools that were designed to measure SA patients’ experiences, such as the Severe Asthma Questionnaire, are getting more utilized in real-world studies [140].

**Mortality risk**

Treatment complications and mortality are also important outcomes in SA [125], 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 or higher dosage, but the mortality rates were generally low at 0.15 (95% confidence interval [95% CI] 0.11-0.20) and 0.04 (95% CI 0.02-0.06) per 1,000 person years in OCS-users and non-users, respectively [141]. 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 [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 wide 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 utilised 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 uncontrolled 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.
Table 1. Comparison of randomised controlled trials and real-world studies

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<tr>
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<th>Randomised controlled trial</th>
<th>Real-world study</th>
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<tr>
<td><strong>Strength</strong></td>
<td>Internal validity</td>
<td>External validity</td>
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<tr>
<td><strong>Design</strong></td>
<td>Prospective</td>
<td>Retrospective or prospective</td>
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<tr>
<td><strong>Inclusion criteria</strong></td>
<td>Strict</td>
<td>Generous</td>
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<tr>
<td><strong>Study population</strong></td>
<td>Usually homogeneous</td>
<td>Heterogeneous</td>
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<tr>
<td><strong>Comparator</strong></td>
<td>Present (usually placebo controls)</td>
<td>Usually absent (or historical controls)</td>
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<tr>
<td><strong>Outcomes</strong></td>
<td>Focused and pre-determined</td>
<td>Various (depending on type of study or database)</td>
</tr>
<tr>
<td><strong>Treatment regimen</strong></td>
<td>Fixed</td>
<td>Variable (based on clinical practice and patient-physician decision)</td>
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<tr>
<td><strong>Treatment adherence</strong></td>
<td>Controlled (as planned)</td>
<td>Uncontrolled (resulting from various factors that patients and physicians experience, including efficacy, adverse effects, ease of use, and costs)</td>
</tr>
<tr>
<td><strong>Risk of bias and confounder</strong></td>
<td>Usually controlled</td>
<td>Usually uncontrolled</td>
</tr>
<tr>
<td><strong>Long-term follow-up</strong></td>
<td>Relatively short (&lt; 1 year)</td>
<td>Follow-up for years is relatively common</td>
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Table 2. Summary of treatments of interest, comparisons, and measurements of asthma exacerbations or quality of life in prospective observational cohort or registry studies reporting T2-biologic treatment effectiveness in adults with severe asthma*

<table>
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<tr>
<th>Study</th>
<th>Measurement of asthma exacerbation</th>
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<td></td>
<td>Method</td>
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<td>Patient self-reported questionnaire</td>
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<td></td>
<td>Exacerbations requiring OCS, ER visits, or hospitalizations: Before (recall of 12 months) vs. during treatment (for more than 5 months)</td>
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<tr>
<td>Korn 2009 [56]</td>
<td>Patient self-reported questionnaire</td>
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<td></td>
<td>Exacerbations (defined by FEV1 &lt; 60% of personal best, intermittent treatment with OCS, unscheduled health care visits, emergency treatments, or hospitalizations due to asthma): Before (recall of 12 months) vs. after treatment (for 6 months)</td>
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<tr>
<td>Brusselle 2009 [55]</td>
<td>Retrospective assessment by physicians at study visit</td>
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<td></td>
<td>Severe exacerbations (requiring OCS, ER visit, or hospitalization): 52 weeks before vs. after treatment (at 16 and 52 weeks)</td>
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<tr>
<td>Cazzola 2010</td>
<td>Retrospective</td>
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<td></td>
<td>Asthma-related events (exacerbations, hospitalization,</td>
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<td></td>
<td>EQ-5D: baseline vs. 52 weeks</td>
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<td></td>
<td>AQLQ: baseline vs. 16 and 52 weeks</td>
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* Adapted from Hasani et al. Translational Lung Research 2013.
<table>
<thead>
<tr>
<th>Reference</th>
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<th>Assessment/Outcome</th>
<th>Findings</th>
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<tr>
<td>Schumann 2012 [59]</td>
<td>Retrospective assessment by physicians at study visit</td>
<td>Severe exacerbations (worsening of asthma requiring systemic corticosteroids, ER visit, hospitalization, or reduction of FEV1 &lt; 60% of personal best): 16 weeks before (retrospective review) vs. after treatment</td>
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<tr>
<td>Braunstahl 2013 [61]</td>
<td>Retrospective assessment by physicians at study visit</td>
<td>Clinically significant exacerbations (any worsening of asthma requiring systemic corticosteroids) and severe exacerbations (if reduction of PEF &lt; 60% of personal best): Before (retrospective review of 12 months data) vs. after treatment (at 12 and 24 months)</td>
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<td>Chen 2013 [73], Long 2009 [142]</td>
<td>Electronic data capture of patient reporting (healthcare utilization)</td>
<td>Asthma-related ER visits, overnight hospitalizations, unscheduled office visits, intubations or need for mechanical ventilator assistance, and oral or intravenous corticosteroid bursts: Omalizumab vs. non-omalizumab treatment groups</td>
<td>-</td>
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<tr>
<td>Grimaldi-Bensouda 2013 [71]</td>
<td>Medical chart review by clinical research associates</td>
<td>Severe exacerbations (exacerbation requiring ER visits or hospitalization): Omalizumab vs. non-omalizumab prescribed groups</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Methodology</td>
<td>Outcomes</td>
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<tr>
<td>Vieira 2014</td>
<td>2014</td>
<td>Retrospective assessment by physicians at study visit</td>
<td>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 utilization resources): 12 months before (retrospective review) vs. after treatment</td>
</tr>
<tr>
<td>Gouder 2015</td>
<td>2015</td>
<td>Retrospective assessment by physicians at study visit (every 4 or 8 weeks)</td>
<td>Exacerbations, hospitalizations, unscheduled health care visits, number of OCS courses prescribed: 12 months before (retrospective review) vs. after treatment</td>
</tr>
<tr>
<td>Sousa 2015</td>
<td>2015</td>
<td>Structured questionnaire at routine visit</td>
<td>Exacerbations (unscheduled healthcare utilization or increases in OCS intake because of asthma): no comparison group</td>
</tr>
<tr>
<td>Hew 2016</td>
<td>2016</td>
<td>Based on medical records?</td>
<td>Exacerbations (measurement details were not described in the paper): Before (retrospective review) vs. after treatment (at 6 months)</td>
</tr>
<tr>
<td>Niven 2016</td>
<td>2016</td>
<td>Based on ‘Hospital exacerbations’ (when patients attended ER or ...</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Study Design</td>
<td>Data Collection Method</td>
<td>Measurement Details</td>
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<tr>
<td>[64]</td>
<td>Routinely collected data of healthcare use</td>
<td>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) vs. after treatment</td>
<td>weeks, 8 months, and 12 months vs. 16 weeks, 8 months, and 12 months</td>
</tr>
<tr>
<td>Kupryś-Lipińska 2016 [65]</td>
<td>Retrospective assessment by physicians at study visit (?)</td>
<td>Exacerbations (measurement details were not described in the paper): Before (retrospective review of 6-12 months data) vs. after treatment (for 16 weeks)</td>
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<tr>
<td>Gibson 2016 [143]</td>
<td>-</td>
<td>- (reported as safety outcome)</td>
<td>-</td>
</tr>
<tr>
<td>Canonica 2018 [67]</td>
<td>Retrospective assessment by physicians at study visit</td>
<td>Number of exacerbations and proportion of patients with at least 1 episode of asthma exacerbation during the 12 months study period: 12 months before (retrospective review) vs. after treatment</td>
<td>EQ-5D: baseline vs. 6 and 12 months</td>
</tr>
<tr>
<td>Adachi 2018 [74], Soong 2021 [144]</td>
<td>(Not described in the paper)</td>
<td>Exacerbations (worsening of asthma symptoms requiring hospitalization, ER visit, OCS therapy, unscheduled doctor visit, or absenteeism): Before (retrospective review) vs. after treatment (for 52 weeks)</td>
<td>-</td>
</tr>
<tr>
<td>Casale 2019 [68]</td>
<td>Monthly retrospective assessment of</td>
<td>Exacerbations (worsening of asthma symptoms requiring the use of OCS, ER visit, or hospitalization): 12 months before (retrospective review) vs. after treatment</td>
<td>-</td>
</tr>
<tr>
<td>Study</td>
<td>Reporting Method</td>
<td>Exacerbation Definition</td>
<td>Outcome Measure</td>
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<tr>
<td>Jung 2021 [69]</td>
<td>Patient self-reporting</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>Mepolizumab</td>
<td>-</td>
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<tr>
<td>Schleich 2020 [79]</td>
<td>Retrospective assessment by physicians at study visit</td>
<td>Exacerbation (a course of OCS for at least 3 days in case of asthma worsening): Before (retrospective review of 12 months data) vs. after treatment (for 18 months)</td>
<td>-</td>
</tr>
<tr>
<td>Langton 2020 [85]</td>
<td>Researcher assessment with OCS use record</td>
<td>Exacerbation requiring OCS (measurement details were not described in the paper): Mepolizumab vs. bronchial thermoplasty treatment groups (comparing 6 months before vs. after each treatment)</td>
<td>-</td>
</tr>
<tr>
<td>Harvey 2020 [78], Thomas 2021 [83]</td>
<td>Retrospective assessment at study visit (3, 6, and 12 months)</td>
<td>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) vs. after treatment</td>
<td>-</td>
</tr>
<tr>
<td>Harrison 2020 [76],</td>
<td>Monthly assessment</td>
<td>Clinically significant exacerbation (requiring rescue medication with OCS for at least 3 days or a single -</td>
<td>-</td>
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<tr>
<td>Study</td>
<td>Methodology</td>
<td>Event Description</td>
<td>Comparison</td>
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<tr>
<td>Renner 2020 [77], Pini 2021 [81], Pilette 2022 [145]</td>
<td>during routine care visit</td>
<td>systemic steroid injection, and/or ER visits and/or hospitalizations (x2 increase in maintenance OCS dose for 3 days in patients with OCS maintenance therapy): 12 months before (retrospective review) vs. after treatment</td>
<td></td>
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<tr>
<td>Izumo 2020 [88]</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Pertzov 2021 [86]</td>
<td>Medical record assessment during routine care visit</td>
<td>Exacerbation (ER visit or OCS treatment prescribed by general practitioner): 12 months before (retrospective review) vs. after treatment</td>
<td>Using a scale of -2 to 2</td>
</tr>
<tr>
<td>McDowell 2021 [82]</td>
<td>Retrospective assessment during routine care visit (patient reporting)</td>
<td>Severe asthma symptoms worsening outside of a patient’s normal daily variation and occurring any time: no comparison group</td>
<td></td>
</tr>
<tr>
<td>McDowell 2022 [84]</td>
<td>Monthly retrospective assessment by research nurse</td>
<td>Exacerbations (measurement details were not described in the paper): 12 months before (retrospective review) vs. after treatment</td>
<td>EQ-5D: baseline vs. 12 months</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Exacerbation Definition</td>
<td>Follow-up Period</td>
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<tr>
<td>Kallieri 2022 [146]</td>
<td>Prospective multicenter, non-interventional observational study</td>
<td>Clinically significant exacerbations (symptoms deterioration requiring the use of systemic corticosteroids or increase from maintenance dose for at least 3 days and/or emergency visit or hospital admission): 12 months before (retrospective review) vs. 12 and 24 months after treatment</td>
<td>-</td>
</tr>
<tr>
<td>Pérez de Llano 2019 [87]</td>
<td>Retrospective assessment by physician during routine care visit</td>
<td>Severe exacerbation (clinically judged worsening of asthma control as evidenced by worsening symptoms and that resulted in use of systemic corticosteroids and/or hospitalization): Before (retrospective review) vs. after treatment (for 24 weeks)</td>
<td>-</td>
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<tr>
<td>Benralizumab</td>
<td></td>
<td>Number of exacerbations for 24 weeks (measurement details were not described in the paper): 24 weeks before (retrospective review) vs. after treatment</td>
<td>EQ-5D: baseline vs. 12 and 24 weeks</td>
</tr>
<tr>
<td>Scioscia 2021 [89]</td>
<td>Retrospective assessment at 24 weeks</td>
<td>Number of exacerbations for 24 weeks (worsening in asthma control requiring ≥ 3 days of OCS), OCS dose reduction: 48 weeks before (retrospective review) vs. after treatment</td>
<td>-</td>
</tr>
<tr>
<td>Jackson 2022 [147]</td>
<td>Retrospective assessment at 48 weeks</td>
<td>-</td>
<td>AQLQ: baseline vs. 48 weeks</td>
</tr>
</tbody>
</table>
We searched PubMed for articles published in English from the database inception to April 21, 2022, and updated on October 11, 2022, with the search terms “severe asthma” combined with “omalizumab”, “mepolizumab”, “reslizumab”, “benralizumab”, “dupilumab”, “Tezepelumab”, and “biologics”. Additional searches were performed by using Google Scholar and cross-referenced articles. Only prospective observational or non-randomised studies in adults with severe asthma, reporting asthma exacerbations or quality of life as effectiveness outcomes of T2 biologics, were included. When there is a duplication of study protocols and populations, a single paper was chosen where possible.

Abbreviations: QoL, quality of life; OCS, oral corticosteroid; ER, emergency room; FEV1, forced expiratory volume in 1 second; AQLQ, asthma quality of life questionnaire, PEF, peak expiratory flow; EQ-5D, EuroQoL five-dimensional instrument; KAQLQ, Quality of Life Questionnaire for Adult Korean Asthmatics; SGRQ, St. George’s Respiratory Questionnaire.
**Figure Legend**

**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 records; PRO, patient-reported outcomes.

**Which real-world data are “fit for purpose” to address a specific question?**

- **Healthcare utilisation**
- **Epidemic issues**
- **Long-term prognosis**
- **Treatment adherence**
- **Treatment safety**
- **Treatment effectiveness**

**Data collection**

- Retrospective
- Prospective

**Data source**

- Healthcare claims
- EMR
- Patient registry/cohort

**Outcomes**

- Routinely collected data
- Prescription records
- Outpatient visits
- Hospitalization
- Long-term complications
- Mortality

- Designed to address specific questions
- Validated PROs
- Disease-specific outcomes
- Treatment-specific outcomes
- Biomarkers
- Linkage with routinely collected data
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Farah CS, Badal T, Reed N, et al. Mepolizumab improves small airway function in severe eosinophilic


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