What have we learnt from real-life research in asthma and COPD? Standards and novel designs for the future

Real-life research uses many different data sources (e.g., databases, registries) and study designs including pragmatic (more real-life) randomized trials and electronic medical record (EMR)- or registry-based observational studies. Its value is multifactorial, including adaptability of study design to various research questions and inclusion of broad and heterogenous patient populations who are routinely excluded from RCTs due to strict inclusion/exclusion criteria (Figure 1). Real-life research is conducted within routine clinical practice settings, generally using study variables routinely collected in clinical practice or as part of enhanced data collection within registries. Hence, multiple and varied outcomes can be investigated (Figure 1).

On the other hand, randomized controlled trials (RCTs), offer high interval validity by including well-defined, homogeneous populations in rigid settings with patients with tightly defined disease, who demonstrate good adherence to therapy and lack confounders. While therapeutic guidelines still place defined disease, who demonstrate good adherence to therapy. Thus, real-life research and RCTs answer different study questions.

What proportion of severe asthma patients have eosinophilic disease and how do I recognize them? In its 2020 Executive Summary, Global Initiative for Asthma (GINA) considered 50% of asthma patients to be eosinophilic. However, not only did an expert-driven ISAR eosinophil gradient algorithm reveal the prevalence to be much higher at 83.8%, the finding contributed to GINA revising its estimate. ISAR’s eosinophilic gradient algorithm uses variables that

Key learnings from real-life research
- Real-life research has high external validity and determines the effectiveness of clinical interventions in real life. On the other hand, randomized controlled trials (RCTs) have high internal validity and determine the efficacy of interventions in patients with narrowly defined disease and good adherence to therapy. Thus, real-life research and RCTs answer different study questions.
- By using larger numbers of patients, variables that are routinely collected and data from patients who do not qualify for RCTs due to their strict eligibility criteria, real-life research can answer research questions that may also be unfeasible for RCTs.
- Some recent key findings from real-life research are that eosinophilic disease is more common than previously thought in both broad and severe asthma, short-acting beta-agonist (SABA) should not be prescribed alone, and oral theophylline has no value in terms of reducing exacerbations among adults with chronic obstructive pulmonary disease (COPD).
are routinely collected in clinical practice, which enables physicians to easily identify and categorize their severe asthma patients. As a result, physicians can encourage phenotype directed and personalized management strategies for their patients. Eosinophilic patients have been found to have greater comorbidities, asthma attacks, asthma that was difficult to treat, healthcare resource use and to receive more intensive treatment.

- **Is one class of biologic more effective than another for the treatment of asthma?** Anti-IL5/5R therapy is more effective than anti-IgE in decreasing exacerbation rates and long-term oral corticosteroids (OCS) daily dose in severe asthma patients eligible for both biologic classes, although both treatments provided substantial benefit.

- **How are biologics used in real life?** Three-quarters of patients tend to stay on their first biologic despite many having limited improvements. Among the low number of patients who did switch biologics, the most common switch was from Anti-IgE to Anti-IL5/5R therapy. The results of this real-life research should encourage physicians to consider switching biologics when appropriate to optimize response.

- **How accessible are biologics in real life?** Biologics vary in accessibility worldwide, depending on prescription criteria, licensing and reimbursement policies defined by individual countries. The BACS score summarizes biologic accessibility criteria across countries, and should inform guideline recommendations and prescription choices in real life.

Much like registries, EMRs and databases such as the Optimum Patient Care Research Database (OPCRD) and Clinical Practice Research Datalink (CPRD) can also add value to the breadth of research on severe asthma and COPD. The OPCRD database has a median follow-up period of 13 years (with diagnostic information from birth for many patients), offering increased power to study rare adverse events such as pneumonia which RCTs are less able to do. Here are some previously unanswered questions that EMR-based observational studies have now answered:

- **Does lung function decline more rapidly in asthmatics with more frequent exacerbations?** Accelerated lung function decline and repeat exacerbations have been found to have associations, especially in younger patients in a broad asthma population. This suggests earlier intervention with biologics in appropriate patients may be beneficial.

- **Are short doses of OCS associated with adverse events?** Cumulative OCS exposures of 0.5–<1 g, equivalent to four lifetime systemic corticosteroid courses, increases the risk
of adverse outcomes in a broad asthma population. Additionally, even short courses of OCS increase the risk for long-term adverse effects such as osteoporosis, diabetes and cataracts. Consequently, GINA 2022 cited this study in its recommendation that despite response to OCS for Type 2 inflammation in patients with severe asthma, alternate treatments should be considered due to their serious adverse effects.

- Should SABA be prescribed alone? No, GINA 2022 no longer recommends prescribing SABA alone; inhaled corticosteroids (ICS)-containing controller treatment should be used to control symptoms and reduce risk of serious exacerbations in adults and adolescents with asthma. As-needed ICS-formoterol can be taken for relief of symptoms in mild asthma. At this point, the following two studies must be noted to illustrate the importance of assessing treatment adherence in real life. A controlled, double-blind trial setting (SYGMA 1) found similar rates of exacerbation with maintenance ICS and as-needed ICS-formoterol. However, in the real-life setting of a pragmatic trial (PRACTICAL), lower rates of exacerbations were found with ICS-formoterol than maintenance ICS, as a result of lower adherence to maintenance ICS.

- Do fine-particle fluticasone-containing ICS formulations have implications in the clinical management of patients with COPD? In real-life research, patients treated with a fluticasone-containing ICS formulation were found to have an increased risk of pneumonia, in comparison to patients treated with extrafine beclomethasone. The study’s findings emphasize the need for clinicians to be aware of fine-particle fluticasone-containing ICS formulations and their different adverse effects when selecting treatments.

Along with registries and observational studies, real-life research also encompasses pragmatic trials. Here is an example of a previously unanswerd research question addressed by a pragmatic trial:

- Does low-dose oral theophylline reduce exacerbations among adults with COPD? Real-life research found that the addition of low-dose oral theophylline to ICS did not reduce exacerbations among adults with COPD at high risk of exacerbation. This therapeutic option has now been removed from COPD clinical guidelines and physicians should no longer prescribe low-dose oral theophylline.

Pragmatic trials can also take the form of cluster randomized trials where groups of patients rather than individuals are randomized. This innovative study design is practical, financially viable and enables patient factors such as adherence to be assessed. The PREVAIL study (NCT05306743) is a pragmatic cluster randomized trial that evaluates the effectiveness of quality improvement standards among COPD patients at risk of exacerbations, who are often undiagnosed or missed in primary care. As primary care teams are the clusters that are randomized, the problem of poor case finding, patient follow-up and management of COPD in primary care can be potentially addressed.

The MAGNIFY study (ISRCTN10567920) is a pragmatic cluster randomized trial that aims to examine the benefits of monitoring adherence through technology-based interventions among COPD patients. This novel approach involving a smartphone app and technology-enabled inhalers could improve patient adherence and behaviour due to consistent feedback on inhaler technique, patient reminders and education. The cluster randomized trial study design could also prevent cross-contamination within primary care practices.

In conclusion, real-life research comes in many forms, with the emphasis on matching the study design to the study question. In this way, high quality real-life research has many advantages over RCTs; it can complement and confirm data from RCTs, but also answer questions which are unanswerable or unfeasible for RCTs. Real-life research has delivered important findings for patients with asthma and COPD, as well as their treating physicians. Real-life research has an important role in the incorporation of real-world evidence into guidelines, and setting quality standards for patient care.

KEYWORDS
chronic obstructive pulmonary disease, clinical guidelines, real-life research, severe asthma

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CONFLICTS OF INTEREST
David Price has advisory board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals, Therofisher; consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Novartis, Pfizer, Teva Pharmaceuticals, Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, UK National Health Service; payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma, Novartis; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis, Therofisher; funding for patient enrolment or completion of research from Novartis; stock/stock options from AKL Research and Development Ltd which produces
phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding in Timestamp which develops adherence monitoring technology; is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology Assessment; and was an expert witness for GlaxoSmithKline. Thendral Uthaman has none to declare.

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