The comparative effectiveness across severe asthma biologic classes (Anti-IL5 versus Anti-IgE) in patients eligible for both therapies

Describing the profile of severe asthma patients eligible for Anti-IgE and Anti-IL5 and assessing the comparative effectiveness of initiating Anti-IL5 versus Anti-IgE, in terms of exacerbation rates, oral corticosteroids load and hospitalizations.

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TITLE	The comparative effectiveness across severe asthma biologic classes (Anti-IL5 versus Anti-IgE) in patients eligible for both therapies
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Country of study	ISAR Countries
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Introduction

Approximately 358 million people worldwide are diagnosed with asthma [1], of whom 1% to 3% have a severe form of the disease [2]. Despite this relatively low prevalence, severe asthma contributes disproportionately to morbidity, mortality, and healthcare costs [3], accounting for approximately 50% of its total asthma healthcare costs [4]. Patients with severe asthma require treatment with high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids (SCS) to achieve adequate control [5].

Severe asthma specialists administer monoclonal antibody therapies, mostly when patients are refractory to or dependent upon long-term oral corticosteroid treatments. In the last five years, multiple classes of monoclonal antibodies that target three main pathways of severe asthma pathophysiology have been introduced: 1) immunoglobulin E (IgE) with anti-IgE, 2) interleukin-5 (IL-5) with anti-IL-5 or anti-IL-5 receptor (anti-IL-5R), and 3) interleukin-4 (IL-4) and interleukin-13 (IL-13) with anti-interleukin-4 receptor α (anti-IL4Rα) [6-8].

Two of the most administered biologic classes are anti-IgE and anti-IL-5/5R. While the specific eligibility criteria for these biologics differ between payers and locality, their criteria overlap in areas, such as clinical indicators (e.g. exacerbations), elevated levels of total serum IgE, or blood eosinophil counts [22]. In clinical practice, patients may present with overlapping phenotypic characteristics making them eligible for both treatments, which either neutralise IL-5 (reducing peripheral and tissue eosinophils) or reduce levels of IgE (targeting the allergic component), or both. The relative size of this population that is eligible for both treatments of anti-IL-5/5R and anti-IgE are poorly understood [10].

A meta-analysis of 25 observational studies showed that omalizumab (anti-IgE) is associated with improved lung function, quality of life, reduction in ICS and SCS use, and reduction in exacerbations when used as an add-on to ICS or ICS/long-acting beta agonist (LABA) combination therapy [7]. Recently, it was demonstrated that mepolizumab (anti-IL-5), reduces exacerbations, improves asthma control, lung function and health-related quality of life (HRQOL) while sparing the use and adverse effects of oral steroids [11-14]. Three clinical trials have shown that benralizumab (anti-IL5 receptor) reduced asthma exacerbations and the use of long-term corticosteroids compared to placebo while maintaining asthma control, and improved lung function and disease control in patients with severe, uncontrolled asthma compared to placebo [15-17].

Approximately half of patients with severe asthma exhibit persistent eosinophilic and allergic phenotypes [31] and one third of patients with severe asthma are eligible for both biologic treatments (anti-IgE and anti-IL-5/5R) [10, 18-20]. Although there is some overlap in treatment eligibility, severe asthma patients who were subsequently prescribed with mepolizumab had a different prevalence of certain comorbidities, and had greater disease burden, asthma-related healthcare resource utilisation (HRU) and healthcare cost in the 12 months prior to prescription than those subsequently prescribed with omalizumab [21]. As there is some evidence of a subgroup of patients that can have an efficacious response to anti-IgE and anti-IL-5/5R, it has become increasingly important to understand and assess the clinical effectiveness of these two classes among those that are eligible for both. The GINA 2019 guidelines have called for head on comparisons of different biologics in patients eligible for both [22].

Information on the relative clinical effectiveness between these two biologic classes is limited. In a systematic literature review plus indirect treatment comparison (ITC) of patients with severe asthma with a history of exacerbations, no difference in the comparative effectiveness and tolerability of anti-IL5 and anti-IgE was observed [20]. On the other hand, a multi-centre open-label study of patients (n=145) with severe asthma who were eligible for both biologic treatments but who were not optimally controlled with anti-IgE showed that these patients experienced improvements in asthma control, health status and exacerbation rate after directly switching from anti-IgE to anti-IL-5/5R [24]. Currently, a study examining the comparative effectiveness of initiating omalizumab versus mepolizumab, benralizumab or reslizumab amongst severe asthma patients who are eligible for both modalities is not yet available. Therefore, it has become increasingly important to assess the clinical response of initiating an anti-IL-5/5R versus anti-IgE among those that are eligible for both.

The prospectively collected data from a large cohort of severe asthma patients from the International Severe Asthma Registry (ISAR) allows for a through comparative effectiveness study between Anti-IL5 and Anti-IgE across real-life settings worldwide. This study will provide real-life evidence on the effectiveness of initiating anti-IL-5 versus anti-IgE (reference group) in severe asthma patients eligible for both biologic treatments and a description of these patients.

1.1 Study aims

The overall aim of the study is to describe the effectiveness of initiating anti-IL-5/5R versus anti-IgE in patients with severe asthma who meet the common eligibility criteria in clinical practice and are eligible for both modalities.

1.2 Study objectives

Objective 1: To describe the demographic and clinical features of the severe asthma population in the International Severe Asthma Registry who are eligible for both anti-IL-5/5R and anti-IgE, based on most frequent eligibility criteria (including those eligible and did not start biologic), at or before the date of initiating of the treatment, overall and per country.

Objective 2: To compare clinical outcomes of patients receiving anti-IL-5/5R versus anti-IgE in terms of oral corticosteroids, exacerbation rates, and hospitalisations.

Materials and Methods

Data Source

Data was sourced from the International Severe Asthma Registry (ISAR) [30]. The ISAR registry is a multi-country, multicentre, observational epidemiologic data repository, with retrospective and prospective data of severe asthma patients. The key feature of the registry is its standardised data fields irrespective of data source. ISAR includes a combination of existing and new severe asthma registries (N ~ 9000 patients), where primary data are collected via electronic Case Report Forms (eCRF) on a web-based platform. Anonymized person-level data from 20 countries (Argentina, Bulgaria, Canada, Colombia, Denmark, Greece, Japan, Kuwait, Ireland, Italy, India, Japan, Mexico, Saudi Arabia, South Korea, Taiwan, Spain, United Arab Emirates, USA, UK) as defined by the inclusion criteria in section 2.2, will be used for this analysis. ISAR has governance provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG) [30].

Study Design and Sample

A prospective cohort study used anonymised real-world data from the International Severe Asthma Registry (ISAR). The duration of the study was from the time of patient enrollment into the registry to the time of the most recent data extraction (September 2020). The follow-up period was from the time of initiating the therapy (either anti-IL-5/5R or anti-IgE) to the time of recent data extraction. Patient inclusion for the study per objective are described below in Figure 1.

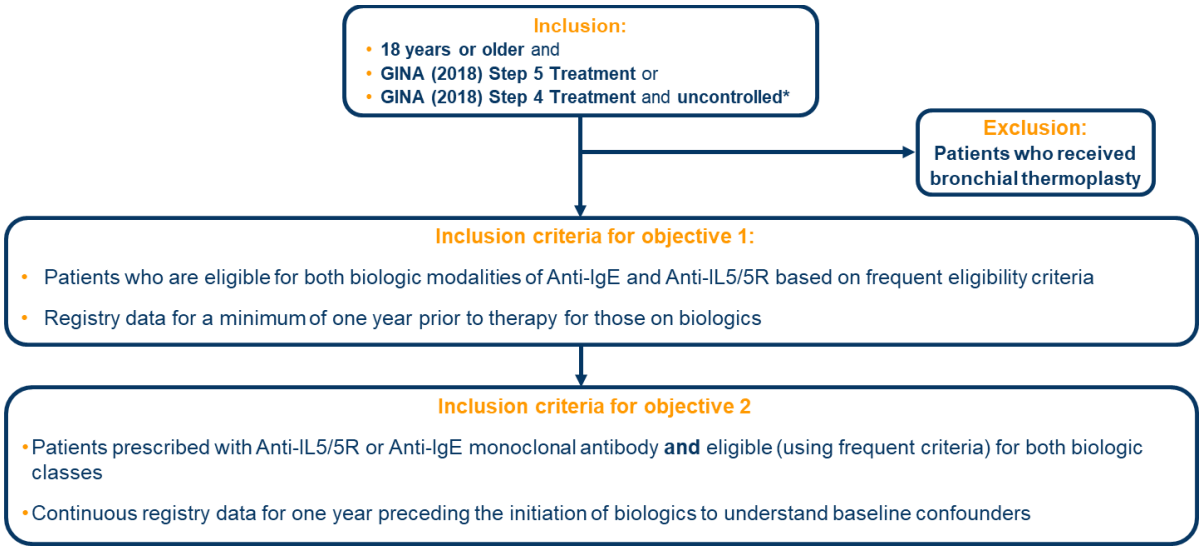

Figure 1 Inclusion and exclusion criteria.

* Uncontrolled is defined as having severe asthma symptoms or frequent exacerbations requiring systemic corticosteroids.

For the purposes of this study, a patient is deemed eligible for both drugs if they have:

- A positive skin prick test or allergen positive test to perennial environmental aeroallergens (having atopic asthma would be used in lieu of missing information on allergen tests. A patient is labeled as having atopic asthma if they report a comorbidity of allergic rhinitis or eczema). These allergens include HDM, moulds, cockroach, pets and feather
- Pre-therapy total serum IgE level above or equal to 30 IU/mL
- Pre-therapy BEC above or equal to 150 cells/μL if patient is on long-term OCS with no requirement for exacerbations OR
- Pre-therapy BEC above or equal to 300 cells/ μL in lieu of long-term OCS while also having 2 or more yearly exacerbations pre-therapy

Depending on the type of drug the patient had initiated, assumptions were made for each drug type used by the patient.

Table 3: Eligibility Criteria for both Anti-IgE and Anti-IL5

Criteria	**For those on anti-IgE**	**For those on anti-IL5/5R**	**For those who were not on biologics**
Background therapy AND	Assumed to be met	Assumed to be met	Assumed to be met
Positive Allergen test AND	Assumed to be met	Needs to be ever met*	Needs to be ever met*
IgE levels ≥ 30 IU/mL AND	Assumed to be met	Needs to be ever met*	Needs to be ever met*
BEC≥ 150 cells/µL with mOCS OR ≥ 300 cells/µL without mOCS AND	Needs to be ever met*	Assumed to be met	Needs to be ever met*
Exacerbation	Assumed to be met	Assumed to be met	Ever exacerbation (≥2) OR On mOCS

Statistical analysis

For the first part of the study, the full eligible population was described. This was done by producing summary statistics produced such as Sample size (n), Percentage of the non missing, Mean , Standard deviation (SD). Range (minimum- maximum), Median and Inter-quantile range (25^{th} and 75^{th} percentile) for count variable. For categorical variables, the summary statistics will include:Sample size (n), Range (if applicable) and Count and percentage by category (distribution). Tables will be annotated with the total population size relevant to that treatment, including any missing observations. Characteristics of study groups was be compared and tested for statistical significance via Chi-square tests for comparison of counts data, t-test, or one-way analysis of variance (ANOVA) for continuous variables. Statistical significance will be defined as $p < 0.05$.

Stata version 14.2 (College Station, TX, USA) will be used to conduct all statistical analyses and data manipulations.

1.3 Study objective 2 – Comparative Effectiveness Analyses

Comparing the two treatments of anti-IgE and anti-IL-5/5R with different indications can be difficult since patients may differ in disease severity and outcome risk. As such some approaches can be used to minimise this potential bias by indication. While the best method of matching will be decided after objective one is fulfilled, the propensity score matching methods is discussed here as this might be the most appropriate for this study.

Matching process via propensity score matching

Estimation of propensity score

We will first describe the two groups before we proceed with propensity scoring. From objective 1, as the study progresses to objective 2, only patients who were eligible for both modalities and eventually initiate either therapy will be studied. First the two populations will be described in detail using the index date of initiation of first biologic. Factors mentioned in tables 4 and 5 will be used to describe the two therapy groups. Then, we will proceed to understand the differences between this two groups.

To ensure that the two groups are comparable, first, we will perform a logistic regression to estimate the propensity score, which is the probability of initiating on a biologic therapy as a function of measured pre-therapy covariates. Following best practice recommendations [30], we select covariates that are prognostically important or confound the relationship between treatment (Anti-IgE or Anti-IL5) and outcomes (yearly rate of exacerbation, and health resource utilization). The results from objective one will also enable the finalizing of the list of covariates that may modify or confound the outcomes of interest. Some probable covariates of interest are included in the table below.

Table 7. Baseline covariates for propensity score estimation.

Variable Name	**Description**
Socio-demographics	**In the past 12 months of index date**
Age Gender Ethnicity Occupation	Patient age in years, gender, ethnicity (Caucasian, Asian, African, Mixed, Other, Unknown)
Obesity	Defined as the ratio of weight (kg) to squared height (m^2): Categorised as obese if BMI $\geq$ 30 kg/m^2
Smoking status	Categorised as non-smoker, current smoker, or ex-smoker
Pack years	Defined as the number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked
Asthma severity	**In the past 12 months of index date**

ISAR inclusion (GINA[1] guidelines)	Patient on GINA (2018) Step 5 treatment OR Patient on GINA Step 4 treatment with (a) Severe asthma symptoms (b)Severe asthma exacerbations requiring systemic corticosteroids
Fractional exhaled nitric oxide (FeNO)	Measurements of FeNO concentration in exhaled breath, measured in parts per billion (ppb) at a flow rate of 50mL/s
Number of invasive ventilations for severe asthma	Count of episodes of invasive ventilation ever
Asthma complications	**In the past 12 months of index date**
Presence of comorbidity	Composite variable of prevalent or incident cases of self reported or diagnosis for allergic rhinitis, Chronic rhinosinusitis, Eczema, Nasal polyps, Obstructive sleep apnea, Renal failure Anxiety/depression, Overall circulatory diseases, Heart Failure, Myocardial infarction, Stroke, Pulmonary embolism, Thromboembolism, Osteoporosis, Diabetes, Peptic ulcer, Pneumonia, Cancer
Assessibility to biologics	
Country licensing	Countries that reimburse both biologic classes

Next the propensity score will be checked to ascertain the level of balance between the two therapy groups and check that the covariates are sufficiently balanced between them. Standardized differences or graphs can be used to examine the distributions of the scores. Then, matching will be conducted between each therapy groups based on the propensity score.

Primary outcome: Rate of exacerbations

An asthma exacerbation will be defined as the occurrence of the following events (ERS/ATS task force definition):

- asthma-related hospital attendance/admission primary care consultation; AND/OR
- asthma-related A&E attendance; AND/OR
- an acute oral corticosteroid course of 3 days or more
- separate recordings of exacerbations within 14 days of each other will be treated as the same exacerbation.

A time-to-event analysis will be performed to analyse the association between treatment and time to first exacerbation with right censoring at the time of death or loss to follow-up or switching to another biologic or treatment. Kaplan-Meier curves will be used to describe event-free survival over time and comparisons. Conditional cox regression will be performed with

[1] Global Initiative for asthma 2018: GINA Stepwise approach for asthma control

time to the first exacerbation as the outcome variable to estimate Hazard Ratios (HR) with 95% confidence intervals (CI) of the treatment effect. The proportional hazard assumption will be evaluated visually by means of a log-log plot of survival. Conditional negative binomial regression* will be used to compare yearly exacerbation counts per treatment. However, this is contingent on the feasibility of using count data to effectively assume yearly exacerbation rates, An intention to treat design will be used, thus allowing patients in the two treatment groups to change their therapy during follow-up, without being censored or otherwise removed from the analyses.

Secondary outcome: OCS dose

For patients on long-term OCS and anti-IgE or anti-IL-5/5R, a pre/post design or comparative analysis will be used to compare the differences in dose of OCS between those on the two therapies. Using descriptive analyses such as percentages, the dose reduction/ discontinuation will be shown for those on long-term OCS and either therapy. If using a comparative analysis model, the model will be split to keep only patients concurrently on long term OCS and either biologic class and compared using a GLM.

Secondary outcome: Healthcare resource utilisation

Healthcare resource utilization in the form of emergency room visits, hospital admissions and invasive ventilations will be compared between the treatment groups using the same methodology as the primary outcome: exacerbations.

Exploratory outcome: Lung function

A change in lung function is defined as an increase in the FEV1 (L) or FEV1 % predicted between anti-IL-5/5R users and anti-IgE users. A generalized linear model with GEE estimation can be considered for this outcome. However, for this to be feasible as per previous ISAR research, patients require at least 3 readings prior to therapy and 3 reading post therapy.

Other exploratory outcomes: The ISAR team is currently working on quantifying super responders in a separate study. It will be a composite variable including factors such as exacerbations, OCS use, treatment persistence and more. The differences in super responders between the two biologic groups will also be assessed via a logistic regression model. Other composite variables which might be feasible in the later parts of the study will also be considered to study the differences in outcomes between the two biologic classes.

* Appropriate statistical analysis methods will be discussed further based on feasibility and assumptions

2.0Regulatory and ethical compliance

This study was designed and will be implemented and reported in accordance with the criteria of the "European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study" and follows the ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol has been agreed and reviewed by the advisory group, this study will be registered with www.encepp.eu. Governance will be provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG, https://www.regresearchnetwork.org/adept-committee/) to govern the standard of research conducted on internationally recognised databases.

All sites will enter into a regulatory agreement in compliance with the specific data transfer laws and legislation pertaining to each country and its relevant ethical boards and organisations.

Further, all data extracted to be transferred from sites will be hashed and will enter the research database in the form of anonymized patient IDs. The data will be retrieved by OPC data analysts and utilised as an anonymized dataset to perform the analysis according to protocol.

The study will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices.

3.0 Data dissemination

Distinct results from this study will be submitted in abstract form for REG 2021, ATS 2021 and ERS 2021. The manuscript from this study will be submitted to a severe asthma focused peer-reviewed scientific journal in due course.

4.0 Advisory group

Project Steering Committee Members	**Country**
Liam Heaney Andrew Menzies-Gow David Jackson Peter Pfeffer	United Kingdom
Giorgio Walter Canonica Enrico Heffler Daniela Morrone	Italy
Richard Costello	Ireland
Nikos Papadopoulous	Greece
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6.0 Timelines

Projected timeline for the study is as follows:

Action	Timeline
Protocol finalization	June 2020
Data extraction & preparation	July and August 2020
Analysis	August – November 2020
First draft of paper	December 2020

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8.0APPENDIX

8.1 Appendix: Abbreviations

ATS	American Thoracic Society
BMI	Body Mass Index
ENCePP	European Network Centres for Pharmacoepidemiology and Pharmacovigilance
ERS	European Respiratory Society
FEV1	Forced expiratory volume in the first second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
IgE	Immunoglobulin E level
ICS	Inhaled Corticosteroid
IL5	Interleukin-5
ISAR	International Severe Asthma Registry
LABA	Long-Acting β-adrenoreceptor
OPCRD	Optimum Patient Care Research Database
OCS	Oral corticosteroids
SCS	Systemic corticosteroids
REG	Respiratory Effectiveness Group