Global Variability in Administrative Approval Prescription Criteria for Biologic Therapy in Severe Asthma

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HIGHLIGHTS BOX

What is already known about this topic?

Five biologics are licensed for severe asthma treatment by the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA). However, accessibility is restricted by clinical, administrative, and reimbursement criteria that differ between countries.

What does this article add to our knowledge?

We developed the Biologic ACcessibility Score (BACS) which compared country-specific biologic prescription criteria across 28 countries in the International Severe Asthma Registry (ISAR), uncovering marked variations in biologic accessibility depending on country of residence.

How does this study impact current management guidelines?

The large international variation in country-specific prescription criteria for biologics, among other factors (not just the gross domestic product), may affect the implementation of personalized medicine. National regulators and payers should focus on minimizing this global variation.

Key words: *Severe asthma; Biologics access; Biologics eligibility*

LIST OF ABBREVIATIONS

BACS: Biologic ACcessibility Score

BEC: Blood eosinophil count

EMA: European Medicines Agency

FDA: U.S. Food and Drug Administration

FeNO: Fractional exhaled nitric oxide

FEV_1: Forced expiratory volume in 1 second

GDP: Gross domestic product

HTA: Health Technology Assessment

ICS: Inhaled corticosteroids

IgE: Immunoglobulin E

IL-4, 5, 13: interleukin-4, 5, 13

ISAR: International Severe Asthma Registry

ISC: ISAR Steering Committee

LABA: long-acting beta agonist

LAMA: long-acting muscarinic antagonist

LTRA: leukotriene receptor antagonist

OCS: oral corticosteroids

RCT: randomized controlled trial

SABA: short-acting beta agonist

SPT: skin prick test

ABSTRACT

BACKGROUND: Regulatory bodies have approved five biologics for severe asthma. However, regional differences in accessibility may limit the global potential for personalized medicine.

OBJECTIVE: To compare global differences in ease-of-access to biologics.

METHODS: In April 2021, national prescription criteria for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab were reviewed by severe asthma experts collaborating in the International Severe Asthma Registry. Outcomes (per country, per biologic) were (1) country-specific prescription criteria and (2) development of the Biologic ACcessibility Score (BACS). The BACS composite score incorporates 10 prescription criteria, each with a maximum score of 10 points. Referenced to European Medicines Agency (EMA) marketing authorization specifications, a higher score reflects easier access.

RESULTS: Biologic prescription criteria differed substantially across 28 countries from 5 continents. Blood eosinophil count thresholds (usually ≥300 cells/μL) and exacerbations were key requirements for anti-IgE/anti–IL-5/5R prescription in around 80% of the licensed countries. Most countries (40% for dupilumab to 54% for mepolizumab) require ≥2 moderate/severe exacerbations, while numbers ranged between none to four. Between 0% (for reslizumab) and 21% (for omalizumab) of countries also required long-term oral corticosteroid use. The BACS highlighted marked between-country differences in ease-of-access. For omalizumab, mepolizumab, benralizumab, and dupilumab, only two, one, four and seven countries respectively scored equal or higher than the EMA reference BACS. For reslizumab, all countries scored lower.

CONCLUSIONS: Although some differences in country-specific biologic prescription criteria and ease-of-access were expected, the substantial differences found in the current study present a challenge to the implementation of precision medicine across the world.

Introduction

Globally, there are currently three major classes of biologics for the treatment of patients with severe asthma licensed for use. These include anti-immunoglobulin E (IgE) (omalizumab), anti–interleukin (IL)-5 (mepolizumab and reslizumab)/anti–IL-5 receptor antagonist (benralizumab) and anti–IL-4Rα, which blocks IL-4 and IL-13 (dupilumab).[1] All have been shown to be effective in large randomized controlled trials (RCT) with carefully selected inclusion and exclusion criteria.[2-5] Some of these criteria differed between biologics, to maximize individual drug response and achieve patient benefits such as reductions in exacerbation rate and oral steroid load.

Following successful trials and subsequent regulatory approval, these biologics are now increasingly available to treat severe asthma, facilitating personalized medicine in this subset of patients with asthma. Notably, it is important to be able to take into account individual patient factors that render patients potentially responsive to biologics.[6] Whilst the principles of personalized or at least stratified medicine are now widely advocated in clinical guidelines, real-world practice and policy may present challenges. Indeed, the European Respiratory Biologics Forum of 2018 noted variation by country in biologic prescriptions due to differences in national healthcare systems regarding referral networks, access and reimbursement policies.[7] All three factors give rise to the hypothesis that despite similar regulatory indications for biologics established by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA), there is a high degree of variation in access criteria across these countries. As such, while the efficacy of biologics has been confirmed, whether or not a patient qualifies for a biologic may very much depend on their country of residence. To document this variation, a systematic global comparison of access criteria for biologics is required. Importantly, recent evidence suggests that the effect of biologics is poorer with more long-standing asthma, and in patients on oral corticosteroids (OCS).[8,9] This suggests that delayed initiation of biologics may have long-term detrimental impacts. This study aimed to analyze national biologic access criteria in countries collaborating with the International Severe Asthma Registry (ISAR; https://isaregistries.org/) and compare these with the wider regulatory indications with the newly developed

Biologic Accessibility Score (BACS). ISAR is a multi-country, multi-center, observational initiative, which collects data prospectively and retrospectively on patients with severe asthma from tertiary care. ISAR has four governing bodies, of which the ISAR Steering Committee (ISC) is one. The ISC comprises 46 experts in severe asthma from 28 ISAR collaborating countries, and medical experts from AstraZeneca (AZ). Due to the cross-disciplinary global nature of ISAR, its structured and uniform data collection, as well as its premise of inclusivity and the expertise of the individuals of the ISC, this collaboration provides an appropriate platform to address essential research questions in severe asthma.[10-13]

Methods

Study design and setting

This study entailed a review of severe asthma biologic prescription criteria and ease of access across 28 countries collaborating with ISAR (Table E1).

Data sources, survey development, and data collection

Several data sources were used to obtain the official prescription criteria per biologic and country (Table E1). First, to obtain an initial list of access criteria, publicly available drug regulation authority websites were searched in June 2020. North and Latin American drug regulation authority websites were found through the World Health Organization (WHO) list of globally identified medicine regulatory authorities. Asian and Oceania drug regulation authorities were compiled from The Regulatory Affairs Professional Society (RASP) list. If an Asian or Oceanian country was known to also have a separate body that determines reimbursement criteria, this body was used instead (e.g., Pharmaceutical Benefits Scheme for Australia, Ministry of Health Drug Advisory Committee for Singapore). For European countries, we used data from Health Technology Assessment agencies (e.g., National Institute for Health and Care Excellence (NICE) for the United Kingdom). If a country had specific reimbursement criteria available, those were

used. If not, the regulatory criteria (e.g., in Europe from the EMA) were used. To determine if a country had a specific guideline and/or licensing criterion available for the biologics, both the drug name and drug trade name were searched in the search engine of each website (e.g., "omalizumab", "Xolair"). All eligibility criteria for biologic initiation were systematically identified from the licensing authorities and aggregated as a table.

Second, to compare these official criteria with the real-life practice of severe asthma specialists, a semi-structured survey (Figure E1 and detailed in next sections) was developed and disseminated to severe asthma specialists from the 29 countries collaborating with ISAR. Responses were received from all countries except India which was eventually removed from the data analysis. This resulted in a response rate of 96.6%. Prior to dissemination, the survey was reviewed, piloted, and then approved by the project steering committee and the ISC chair. Respondents were given two weeks from questionnaire dissemination to complete the survey. In April 2021, tabulated data were re-sent to the ISC members in ISAR countries to check the criteria for all biologics.

Study outcomes

For each of the 28 countries collaborating with the ISAR, we first assessed availability of the five biologics (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) and subsequently assessed (1) all individual access criteria per country, per biologic and (2) the overall ease-of-access to each biologic, as further specified below. The "access" or "accessibility" to severe asthma biologics evaluated in our study refers to the prescription criteria, not to conditions or barriers to access health services in each country.

Biologic ACcessibility Score (BACS)

To summarize and compare overall ease-of-access for licensed biologics in each country, a composite score of biologic access criteria was created, termed the Biologic ACcessibility Score (BACS). To inform the

BACS, we first identified all individual access criteria across countries and biologics. This resulted in a list of 18 initial criteria (age, weight, asthma phenotype, blood eosinophil count [BEC], serum immunoglobulin E [IgE], fractional exhaled nitric oxide [FeNO], allergic asthma diagnostic requirements [e.g., skin prick test [SPT]], background therapy, biologic history, adherence, OCS use, exacerbation history, asthma control, lung function, symptoms, asthma diagnosis, care manager [e.g., severe asthma specialist] and correct inhaler technique). Values within the 18 biologic access criteria were simplified according to frequency of use (e.g., criteria that were only used in one or two countries such as weight were removed) and grouped according to relevancy (e.g., symptoms and asthma control) where possible. This resulted in 10 criteria: (1) Age, (2) Asthma severity and phenotype (e.g., eosinophilic), (3) BEC (serum IgE for omalizumab), (4) FeNO, (5) Background therapy, (6) Adherence (allergic asthma diagnostic requirements for omalizumab), (7) OCS, (8) Number of exacerbations, (9) Asthma control, and (10) Lung function.

Each criterion was then split into clinically-relevant categories and scored between 0 and 10, where '10' represented easiest access and '0' represented most difficult access for each criterion (Table I). The total BACS for each biologic ranged from 0 to 100 and was categorized as 0: no access; 1-20: very difficult access; 21-40: difficult access; 41-60: moderately difficult access; 61-80: neither difficult nor easy access; and 81-100: easy access. Full details on the categorizations and scoring system for each criterion of the BACS per biologic and per country are provided in Tables E2-E6.

To put the score in perspective, the percentage of countries with BACS scores lower than the EMA BACS score (based on EMA regulatory criteria) was calculated for each biologic. Of note, we chose EMA over other regulatory bodies (e.g., FDA, Therapeutic Goods Administration [TGA]) given this is the authority that regulates the highest number of countries collaborating with ISAR. Furthermore, for consistency and ease of interpretation, we preferred to use only a single anchor value for comparison.

Descriptive statistics

Final data on prescribing criteria and access were aggregated and summarized through the use of proportions. The denominator used for each prescription criterion was the number of countries licensing that particular drug. An overview of the BACS per biologic in each country showing each biologic prescribing criteria was visualized using spider plots (Figures E2-E29). To provide a global overview per biologic, colored world maps indicating the total BACS category in each ISAR country were created (Figures 1-5). For each biologic, the relationship between BACS and gross domestic product (GDP) 2019 of the ISAR countries was assessed using Pearson's correlation testing.

Results

Overview of biologics available

At the time of reviewing the biologic prescription criteria in April 2021, omalizumab, mepolizumab, and benralizumab were each licensed in 28 (100%) countries (Tables E2-E4). All three biologics were fully or partially reimbursed in 96.4% (omalizumab), 92.9% (mepolizumab), and 92.9% (benralizumab) of countries in which they were licensed (Table II). As for reslizumab and dupilumab, they were licensed in 15 (54%) and 20 (71%) of the countries respectively (Tables E5 and E6) and either fully or partially reimbursed in 73.3% (reslizumab) and 75.0% (dupilumab) of ISAR countries (Table II).

Biologic prescribing criteria

An aggregated overview of prescription criteria per biologic across the countries is provided in Table III.

Age and phenotype

In the majority of countries, omalizumab and mepolizumab can be prescribed for patients ages ≥6 years, while the other three biologics from either ages 12 or 18 years onwards. In 50% (dupilumab) to 73.3% (reslizumab) of countries, there is a requirement for a diagnosis of severe (persistent or eosinophilic) asthma with type 2 inflammation (or allergic sensitization for omalizumab) (Table III).

IgE, allergic diagnostics, BEC and FeNO

Twenty-five of the 28 countries (89%) required a serum IgE threshold to start omalizumab, with Singapore and Ireland having no criteria in place and Canada being the only exception not requiring a threshold. A threshold of ≥30 or 35 IU/mL was the most common, followed by ≥70, 75, or 76 IU/mL. Twenty-seven of the 28 countries (96%) require a positive serum-specific IgE and/or SPT to common aeroallergens to qualify for omalizumab, with Ireland having no criteria in place (Table III).

While 64.3% and 42.9% of countries utilized a BEC threshold of ≥300 cells/μL in the last 12 months (or ever in the past) for mepolizumab and benralizumab respectively, for reslizumab, the threshold most commonly used to determine eligibility was ≥400 cells/μL in the last 12 months (66.7%) and for dupilumab, it was ≥150 or raised (55.0%). Spain applies a much higher BEC threshold of ≥500 cells/μL, ≥400 cells/μl, and ≥500 cells/μl for mepolizumab, reslizumab, and benralizumab, respectively. Furthermore, three countries (Kuwait, Denmark, and the Netherlands) also included sputum eosinophils (>2 or >3%) as an optional alternative to the BEC criterion. Most countries (80.0-85.7%) did not use FeNO as a criterion to determine eligibility for omalizumab, mepolizumab, reslizumab, and benralizumab. In contrast, ten countries (50.0%) required a FeNO threshold to be considered eligible for dupilumab. Additionally, five countries (25%) stated that either the elevated BEC or the FeNO value can be utilized to be eligible for dupilumab. In countries where FeNO was a criterion, thresholds of ≥20 parts per billion (ppb), ≥25 ppb, or raised were the most common for all countries and biologics.

Adherence, asthma control, and lung function

For all biologics except omalizumab, 40.0%-57.1% of the countries had adherence to background therapy as a prescription criterion. The majority of countries (60.0-82.1%) required evidence of poor asthma control. In most countries, a lung function criterion of forced expiratory volume in one second (FEV_1) ≤80% predicted was most common (46.4%) for omalizumab. For mepolizumab, reslizumab, benralizumab, and dupilumab, only around 13.3-32.1% of countries applied a lung function criterion, with FEV_1≤80% and documented evidence of reversibility as the most common (Table III).

Background therapy

In order to qualify for a biologic, the majority of countries required background therapy of at least a high dose of inhaled corticosteroid (ICS) and long-acting β_2-agonist (LABA), with or without a long-acting muscarinic antagonist (LAMA), leukotriene antagonist (LTRA), or theophylline. Between 0% (reslizumab) and 21% (omalizumab) of countries have the use of long-term OCS as an access criterion (Table III).

Number of exacerbations

In addition to biomarker criteria, approximately half of the countries require ≥2 exacerbations in the previous year (either with hospitalization, emergency department visit, or treatment with OCS) for a biologic prescription (Table III) with differences between countries and biologics (dupilumab: 40%; mepolizumab: 54%). Regarding the number of exacerbations, access to omalizumab in the UK requires ≥4 exacerbations, while in Estonia and The Netherlands, no exacerbations at all are required. In countries such as Australia and Spain, healthcare utilization related to exacerbations is more specified (e.g., ≥2 exacerbations requiring documented use of OCS, or ≥1 severe exacerbation needing hospitalization).

Biologic ACcessibility Score (BACS)

Figures 1 to 5 present the total BACS for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab for countries having the specific biologic available as of April 2021. Detailed data per country are provided in Tables E2-E6.

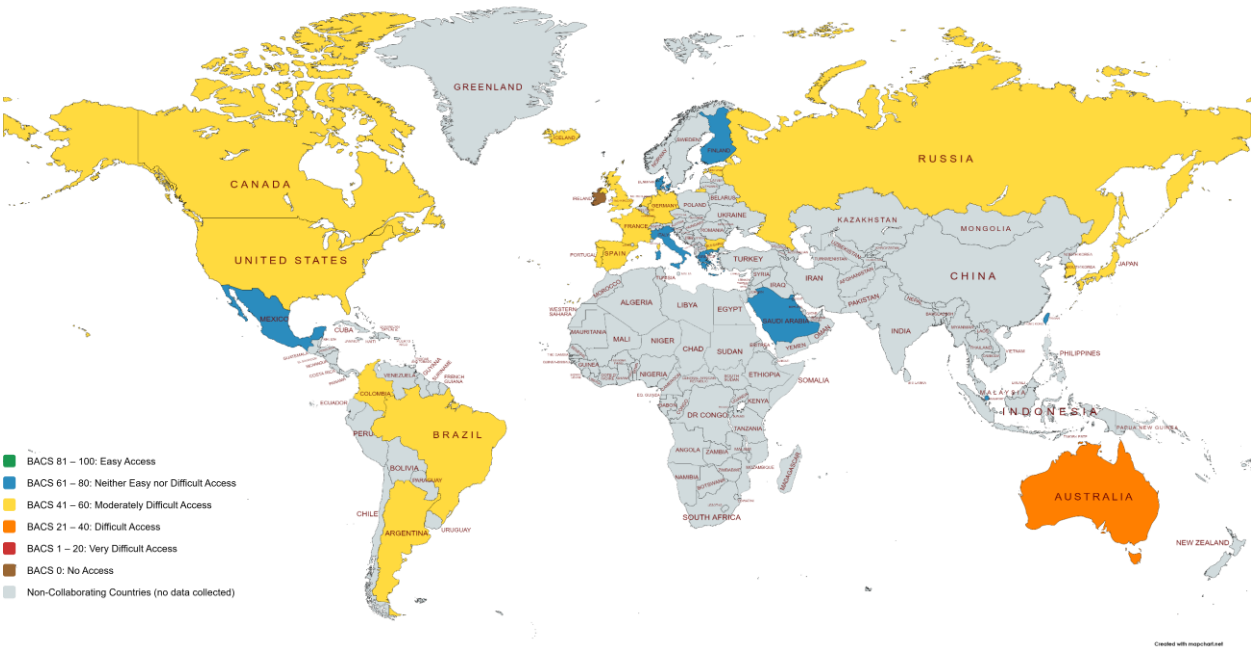

FIGURE 1. Omalizumab BACS for ISAR countries

Omalizumab

Overall, omalizumab is 'neither easy nor difficult' to access in 32% of ISAR countries surveyed (n=9/28), 'moderately difficult' to access in 61% (n=17/28) of ISAR countries, and is 'difficult' to access (i.e., BACS 21-40) in Australia (Figure 1). With the exception of Denmark and Finland, all countries surveyed reported a greater hurdle to omalizumab prescription (i.e., lower BACS) than the EMA BACS of 69. In absolute terms, the BACS for omalizumab ranged from 39 in Australia to 71 in Denmark (mean: 57).

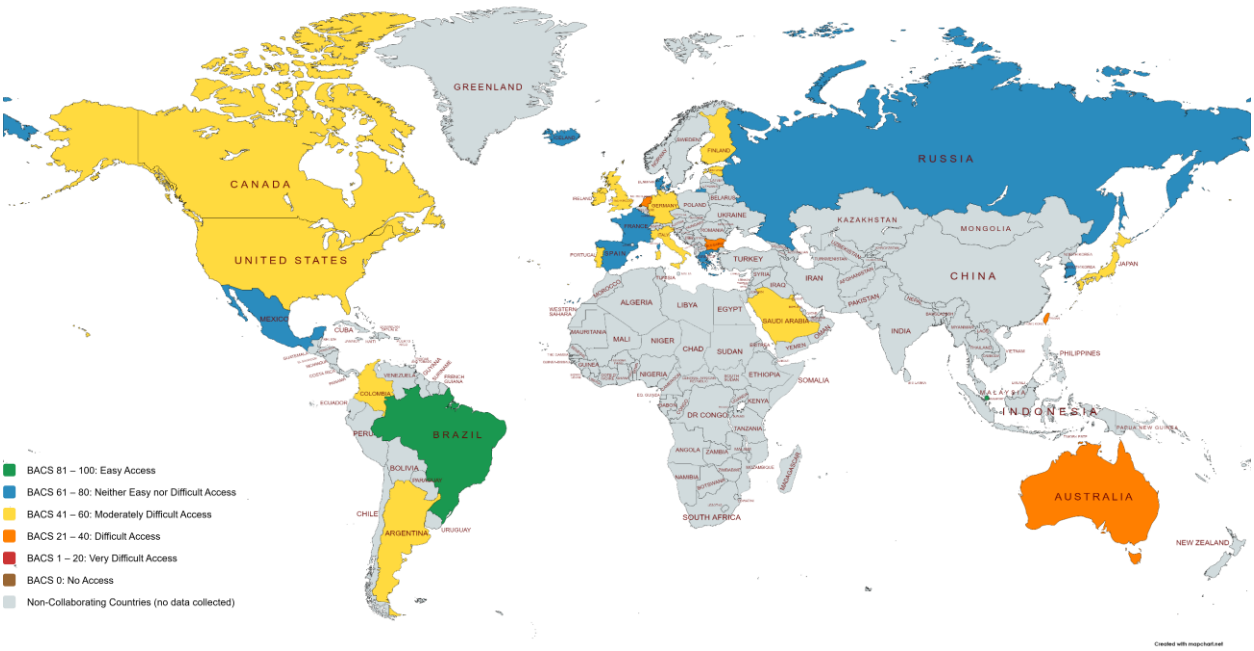

FIGURE 2. Mepolizumab BACS for ISAR countries

Mepolizumab

Mepolizumab is 'difficult' to access in Taiwan, Australia, Bulgaria, and the Netherlands (Figure 2). It is 'neither easy nor difficult' to access mepolizumab in 29% of ISAR countries (N=8/28), and 'moderately difficult' to access mepolizumab in 50% of ISAR countries. Apart from Brazil and Singapore, all countries surveyed reported a greater hurdle to mepolizumab prescription (i.e., lower BACS) than the EMA BACS of 87. Overall, the BACS for mepolizumab ranged from 26 in Bulgaria to 90 in Brazil (mean: 55).

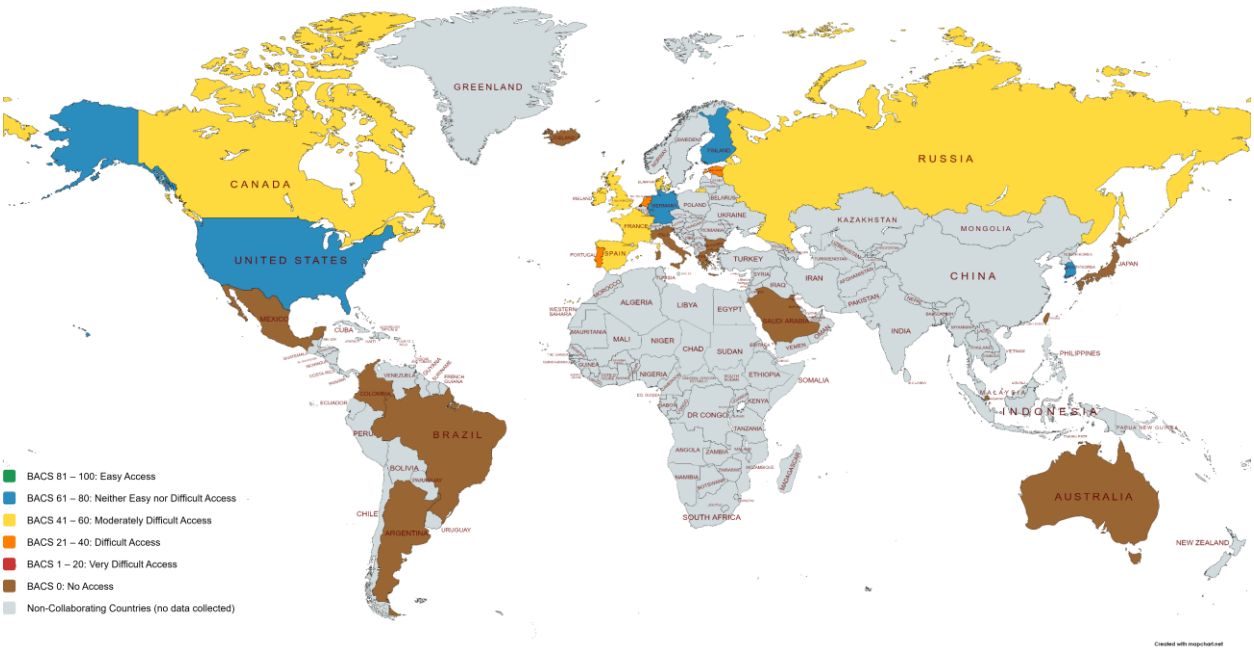

FIGURE 3. Reslizumab BACS for ISAR countries

Reslizumab

Reslizumab is not easily accessible in any ISAR country (Figure 3). It is either 'difficult' or 'moderately difficult' to access in 67% (n=10/15) of countries surveyed that had access, and 'neither easy nor difficult' to access in the US, Germany, South Korea, and Finland. All countries reported stricter prescribing criteria for reslizumab (i.e., lower BACS) than the EMA derived score (BACS=76). The BACS for reslizumab ranged from 36 in The Netherlands to 69 in South Korea (mean 51).

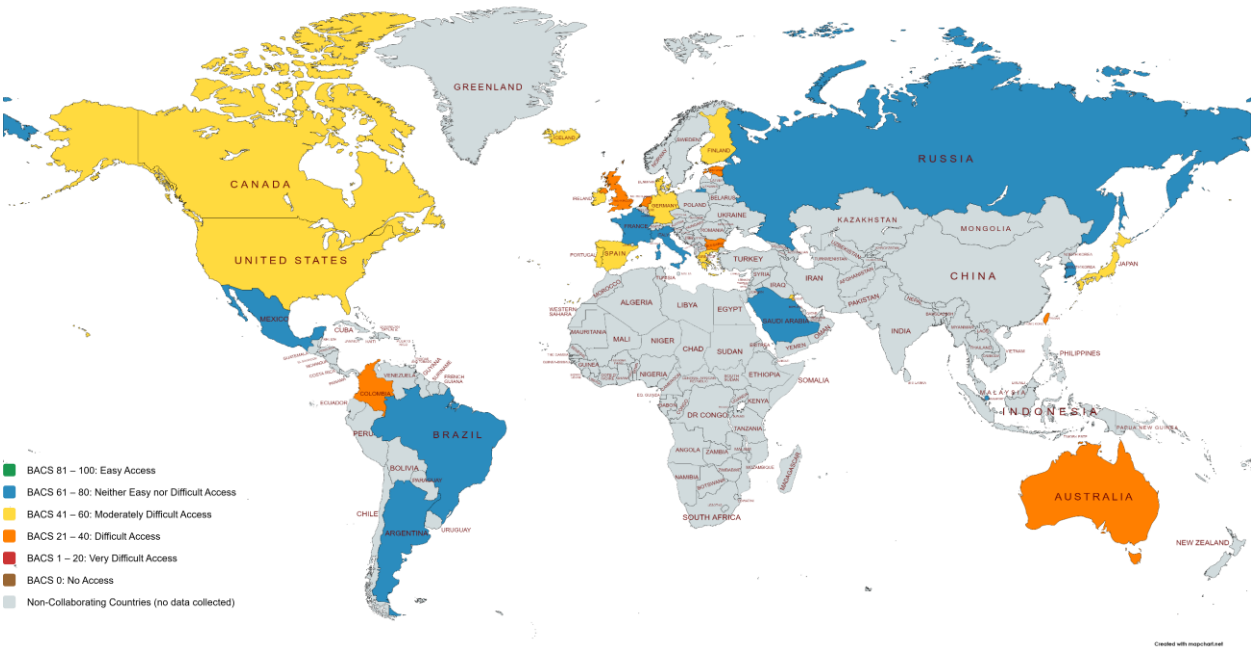

FIGURE 4. Benralizumab BACS for ISAR countries

Benralizumab

Benralizumab is not easily accessible in any ISAR country (Figure 4). It is 'difficult' to access in 7 of the ISAR countries (25%). Overall, it was either 'neither easy nor difficult' or 'moderately difficult' to access in 75% of ISAR countries (n=21/28). With the exception of Mexico, Brazil, South Korea, and Singapore, all other countries surveyed reported a greater hurdle to benralizumab prescription (i.e., lower BACS) than the EMA derived score (BACS=76). The BACS for benralizumab ranged from 30 in Australia to 80 in Mexico (mean: 54).

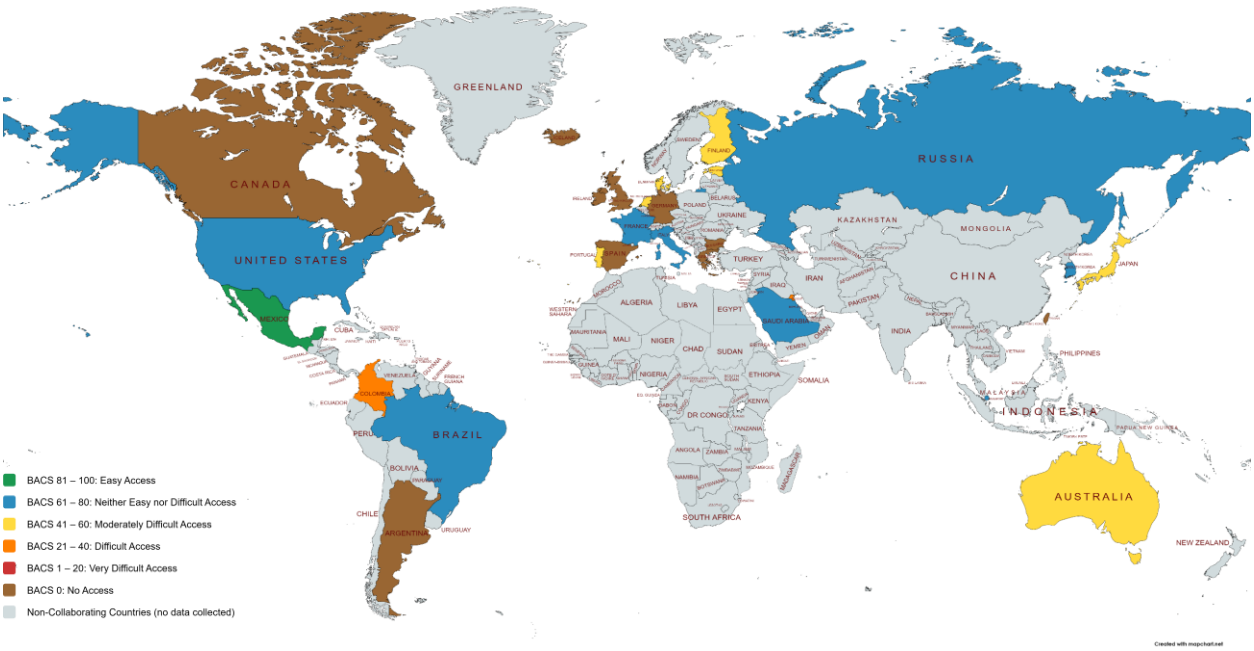

FIGURE 5. Dupilumab BACS for ISAR countries

Dupilumab

Dupilumab is 'difficult' to access in Colombia and Kuwait (Figure 5). Overall, it is either 'neither easy nor difficult' (n=9) or 'moderately difficult' (n=7) to access in 80% of countries that had access (n=6/20), with a BACS lower than the EMA-derived prescription score (BACS=65) in 60% of ISAR countries. In absolute values, the BACS for dupilumab ranged from 33 in Colombia to 88 in Mexico (mean: 59).

Correlation of BACS with GDP

For all biologics, no significant correlations between BACS and GDP were found (Table E7);

Discussion

Main findings

This study has demonstrated wide variations in severe asthma biologic accessibility across the globe. In addition, this study assessed, quantified, and compared the ease-of-access to biologics using the newly developed BACS in the 28 countries collaborating with ISAR. Using the BACS, we found that for omalizumab, mepolizumab, benralizumab, and dupilumab, only two, one, four and seven of the countries respectively had equal or easier access than would be expected from the EMA licensing criteria. Moreover, for reslizumab, we found that all ISAR countries had more stringent access criteria in place than the EMA.

Interpretation

While all ISAR countries assessed in this study had access to the same trial data and follow similar licensing pathways, significant differences in clinical prescription criteria were observed. These differences did subsequently result in biologic accessibility variation across countries. While some of such variation can be attributed to country-specific circumstances, it might also reflect a lack of consensus on which patients benefit the most from which biologic. To our knowledge, no previous studies have systematically compared biologic access across so many countries. Earlier studies have mostly assessed the proportions of patients eligible for one or more severe asthma biologics in single countries such as Canada and Brazil.[14,15] Others looked only at reimbursement and costs of severe asthma biologics over time in Bulgaria.[16] All these single country studies are relevant to inform within-country policy yet limit direct cross country comparisons regarding access or comparisons with our study. The IDEAL study assessed eligibility for three biologics (omalizumab, reslizumab, and mepolizumab) across six countries (Australia, Canada, France, Germany, UK, and the US).[17] In that study, it was found that the percentage of patients eligible for omalizumab was dependent on the country access criteria (e.g., European criteria: 30% and US, Canadian, or Australian criteria: 40% of patients in their cohort would be eligible). A similar variation was found for reslizumab

583 and mepolizumab, but no in-depth comparison of the prescription criteria and their relationship with access
584 was provided.
585
586 Regarding ease of access in our study, there were variations between biologics (the mean BACS ranged
587 from 57 for omalizumab, 55 for mepolizumab, 51 for reslizumab, 54 for benralizumab, to 59 for dupilumab)
588 and between countries (BACS ranging from 26 in Bulgaria to 90 in Brazil for mepolizumab). Numerous
589 countries had no access at all (corresponding to a BACS of 0 shown in Figures 1-5). Multiple factors may
590 play a role in the eligibility for reimbursement including (1) clinical drug characteristics (e.g., efficacy,
591 safety), (2) clinical guideline recommendations, (3) economic implication of the drugs (e.g., cost, cost-
592 effectiveness, budget impact) and (4) regulatory systems (e.g., financing of health systems and health
593 technology assessment (HTA) guidelines, and time between regulatory approval and reimbursement).
594 Importantly, we should note that regulatory procedures are usually not aligned with reimbursement
595 procedures. Licensing is often a central procedure (e.g., by EMA or FDA) yet reimbursement is a national,
596 state, or even insurer or health plan-specific procedure. This means that patients with similar clinical criteria
597 may have different accessibility to biologics (i.e., where prescription criteria are based on provincial or state
598 reimbursement policies such as in Canada, the USA, or France) due to different reimbursement criteria.
599
600 Looking more closely at the criteria underlying the BACS, we observed large variation in clinical criteria
601 applied with the main drivers of differences being biomarkers (BEC, FeNO, IgE thresholds), exacerbation
602 requirements (ranging from zero to four), need for long-term OCS, severity, asthma control, and adherence
603 to background therapy. Interestingly, some prescription criteria included OCS use although registration
604 trials did not show a steroid-sparing effect.[18] These different clinical factors may be partly driven by
605 differences in clinical trial inclusion/exclusion criteria, as well as national severe asthma guidelines and
606 restrictive criteria initiated at a local level. Notably, the process for evidence ranking in these guidelines
607 can be different, but also the frequency of updates may differ so that some guidelines may take some more
608 recent RCT and real-world evidence into account when making their recommendations than others. Lastly,

creating guidelines is often a matter of consensus where experience, expertise, and opinions of individual committee members may be different across countries especially in the absence of head-to-head comparisons between these biologics. Regarding "overall wealth of a country" being an explanation for BACS variation, we first assessed whether GDP per capita might be a factor: yet both a visual inspection and formal correlation testing of our data did not show any significant trend (Table E6). In fact, some countries with higher GDP, such as the UK, have stricter HTA guidelines in place, making biologics actually more difficult to access than in countries with lower GDP such as Colombia. Therefore, we hypothesize that payer system factors, such as HTA criteria, whether the state (e.g., UK) or private insurance of regional system (e.g., in the US or Canada) pays for the biologic, plays a role. One other observation supporting the importance of wider system factors is that the oldest biologic, i.e., omalizumab (Table II) is also the easiest to access. Given that this is also the biologic available in the highest number of countries, the relatively long time that reimbursement has been available may partly explain this higher BACS.

Generally, we hypothesize that many of the additional access criteria are employed to enhance cost-effectiveness and lower the budget impact of biologics. Indeed, most of the biologics have not been shown to be cost-effective in the full trial population, but are only cost-effective when carefully targeted.[19] Here, we should however acknowledge that many of the cost-effectiveness analyses may not be able to capture the full benefit of biologics including avoidance of the long-term complications of OCS and work productivity-related outcomes.[20] Also, most long-term cost-effectiveness analyses may not take into account the lowering of biologics prices in the future, e.g., driven by the development of biosimilars. Still, we see that these additional criteria may significantly restrict real-world use of biologics within some countries with health disparities partially depending on income and access to specialists.[21]

Another final comment should be made on the incorporation of adherence to background therapies as a prescription criterion. In several severe asthma national guidelines, non-adherence to ICS should be ruled

out before a severe asthma diagnosis is made. Recent studies showed that low adherence rates to ICS/LABA were observed before the start of additional severe asthma treatments.[22,23] Additionally, loss of adherence to ICS during use of mepolizumab is associated with a suboptimal response to treatment.[24] As such, in order to ensure biologics are used in the most appropriate patients and in the most cost-effective manner, objective and effective methods (e.g., use of smart inhalers or FeNO suppression) to identify and manage poor adherence to inhaled therapies as well as ensuring good inhaler technique and appropriate treatment of comorbidities should be required before considering a biologic.[25-28]

Strengths & limitations

A major strength of this study is that we included 28 countries spread over five continents, thus providing the world's largest systematic overview of biologic prescription criteria. Structured reviews of health authority databases and guidelines, combined with the use of a survey with local prescribers of biologics to verify real-world practice, ensured data quality and representativeness. This included the use of a quantitative consensus-based BACS based on a transparent set of clinical access criteria which can be used for future benchmarking of ISAR countries and can also be expanded to other countries.

Some limitations should also be noted. Firstly, this survey provides a snapshot of the current status of reimbursement and access criteria for the biologics as they may vary over time. The BACS was calculated only for a country having the specific biologic available per April 2021 using criteria as reported by severe asthma specialists (i.e., not reimbursement agencies). To overcome this potential limitation, the BACS will be periodically updated and will be available at the ISAR website (https://isaregistries.org/) to ensure access to up-to-date information and future benchmarking. Secondly, although we aimed for clinically relevant categories within the scoring of each access criterion, there is still some level of arbitrariness involved which may require further validation, wider consensus in the scoring of the BACS and establishing associations of the BACS with better asthma care outcomes. Thirdly, regarding generalizability, we should note that although in most countries, access criteria are uniformly applied (e.g., the UK), some countries

had variability within the country, depending on (local) health plans (e.g., the US, Canada) which warrant caution in interpretation. Although detailed payor plans were beyond the scope of the current manuscript that focused on general prescriptions criteria, this may be addressed in BACS updates. Besides prescription criteria, one of the methods used to further enhance cost-effectiveness and affordability is the use of stopping criteria for biologics. This means that after a certain number of weeks, effectiveness should be established by a specialist physician before the biologic should be continued. We acknowledge the existence of differences in biologic stopping criteria, but this was beyond the focus of this study.

Recommendations for future research, policy, and research

In its current form, the BACS allows clinicians and regulators to assess ease-of-access to biologics in their own country and by its provision of insights into inter-country variation, it may serve to push harmonization of access criteria and help support international biologic access equality. Importantly, to validate the BACS and expand its future use, the association of the BACS with national asthma outcomes (e.g., OCS usage, hospital admissions) should be addressed in future studies. Ultimately, the BACS may then become useful as an educational tool to encourage timely and appropriate biologic prescription to improve outcomes and reduce costs. Structured and comparable real-world data as collected in ISAR could contribute to these outcome studies. Countries not covered in the ISAR survey are also encouraged to further external validation of the BACS.

Conclusions

This study showed a high degree of variability in the criteria utilized to prescribe severe asthma biologics globally. These differences resulted in profound differences in ease of access to biologics across countries. To ensure the availability of personalized treatment options for patients with severe asthma independently of country of residence, standardization of prescribing and access criteria is recommended.

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759 **TABLE I.** The BACS scoring system.

Criterion	Score
Age (years)	
Not required/undecided	10
≥6	8
≥12	4
≥18	0
Severity/Phenotype	
Not required/undecided	10
IgE mediated OR type II driven OR eosinophilic	8
Bronchial asthma refractory OR uncontrolled allergic	6
Moderate to severe (persistent, eosinophilic, OR OCS dependent)	4
Severe (persistent, eosinophilic, with type II inflammation OR allergic)	2
Severe (uncontrolled, uncontrolled + eosinophilic, uncontrolled allergic, refractory, refractory + eosinophilic)	0
Serum IgE (IU/ml)	
Not required/undecided	10
≥30, 35, or elevated	8
≥70, 75 or 76	4
≥150	2
≥400	0
BEC (cells/µL)	
Not required/undecided	10
≥150 or raised	8
≥150 in last 12 months	7
≥150 in last 1 month	6
≥300 or ≥150 on long-term OCS	5
≥300 in last 12 months or historical	4
≥300 x2 in last 12 months	3
≥400 or in last 12 months	2
≥500	0
FeNO (ppb)*	
Not required/undecided	10
≥20 or 25 or raised	5
≥50	0
Allergic Asthma	
Not required/undecided	10
SPT or RAST	5
SPT and RAST	0
Background Therapy	
Not required/undecided	10
ICS	8

High dose ICS (+/- LABA or long-term OCS or xanthine or LTRA)	6
Medium dose ICS/LABA (+/- LTRA)	5
High dose ICS/LABA (+/- LAMA or LTRA)	4
High dose ICS/LABA (+/- long-term OCS)	
High dose ICS/LABA + ≥ 1 other controller (not OCS)	2
High dose ICS/LABA + long term OCS	0
OCS†	
Not required/undecided	10
Long term OCS use	0
Exacerbations†	
Not required/undecided	10
≥1	8
≥1 requiring hospital admission, emergency room visit, or rescue OCS	6
≥2	4
≥2 requiring hospital admission, emergency room visit, or rescue OCS	3
≥3	2
≥4	0
Asthma Control	
Not required/undecided	10
Required	0
Lung Function	
Not required/undecided	10
FEV_1 ≤80%	8
≥12% reversibility +/- > 200 ml FEV_1	6
FEV_1 ≤80% & evidence of reversibility	4
FEV_1 ≤80% & 12% reversibility & AHR	2
FEV_1 ≤60%	0
Adherence	
Not required/undecided	10
Required	0

AHR: airway hyperresponsiveness; BEC: blood eosinophil count; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; HCP: healthcare professional; ICS: inhaled corticosteroids; IgE: immunoglobulin E; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene antagonist; OCS: oral corticosteroids; RAST: radioallergosorbent test; SPT: skin prick test.

*In countries where either the elevated BEC or the FeNO criteria can be used to be eligible for dupilumab, the BEC criteria instead of FeNO criteria was used to compute the BACS, and "not required" was stated for FeNO for dupilumab, as there is a more specific gradient in the scoring system for BEC. Otherwise, if BEC criteria is not available, the FeNO criteria was used to compute the BACS for dupilumab.

†In countries where there is specification of the operator "OR" between chronic OCS use and exacerbation criteria to be eligible for a particular biologic, the exacerbation criteria instead of the OCS criteria was used to compute the BACS, and "not required" was stated for OCS for that particular biologic, as there is a more specific gradient in the scoring system for exacerbations. When there is chronic OCS use and exacerbation criteria without specification of the operators "OR" or "AND" to determine eligibility for the biologic, it was assumed to be an "OR" operator. Thus, scoring favored the exacerbation criteria and OCS was not indicated as a requirement to be prescribed a particular biologic.

Rules were formulated to account for blanks and ISC/GL conflicts during the generation of the BACS from the survey.

GL: guidelines; ISC: ISAR Steering Committee; EMA: European Medicines Agency

For data pertaining to each criterion per biologic:

- **Blanks**
  - Assumed not required and given a score of 10 (categorized under "Criteria not decided" in Table III).
  - If criteria were left blank by ISC members, blanks were supplemented with the GL criteria (if available).
  - If criteria were left blank by European ISC members, blanks were supplemented with the EMA criteria as EMA is the lowest threshold.
- **If both GL <u>and</u> ISC members completed, and there is**
  - No overlap in responses: The GL criteria were used to fill in gaps/blanks in ISC responses.
  - Overlap and consensus: No further action required; scored as normal.
  - Overlap and disagreement: Scoring was done separately to illustrate multiple prescription criteria, and the "best" score was taken, either between the GL and ISC member's responses, or between two conflicting ISC members' responses (i.e., the highest score), to reflect the true on-the-ground hurdle to biologic prescription and to also not artificially inflate the BACS.

TABLE II. Biologics license dates and reimbursement status in ISAR countries with market authorization for respective biologic (per April 2021)

Biologic	**Omalizumab**	**Mepolizumab**	**Reslizumab**	**Benralizumab**	**Dupilumab**
License dates					
EMA license date	25 October 2005	2 December 2015	16 August 2016	8 January 2018	1 March 2019*
FDA license date	20 June 2003	4 November 2015	23 March 2016	14 November 2017	19 October 2018†
Reimbursement status	n (%)	n (%)	n (%)	n (%)	n (%)
No reimbursement	1 (3.6) SG	2 (7.1) SK, SG	4 (26.7) BR, CN, FR, SK	2 (7.1) SK, SG	5 (25.0) BR, IE, PT, SK, SG
Partial reimbursement	4 (14.3) CN, JP, RU, US	6 (21.4) AR, CN, JP, MX‡, RU, US	2 (13.3) RU, US	5 (17.9) CN, JP, MX‡, RU, US	4 (20.0) JP, MX§, RU, US
Full reimbursement	23 (82.1) AR, AU, BR‖, BG¶, CO#, DK, DE, ES, EE, FI§§, FR, GR, IS, IE**, IT, KW, MX††, NL, PT, SA, SK, TW, UK	20 (71.4) AU, BR‖, BG¶, CO#, DK, DE, ES, EE, FI§§, FR, GR, IS, IE, IT, KW, NL, PT, SA, TW, UK	9 (60.0) DK, DE, ES, EE, FI§§, IE**, NL, PT, UK	21 (75.0) AR‖‖, AU, BR‡‡, BG¶, CO#, DK, DE, ES, EE, FI§§, FR, GR, IS, IE, IT, KW, NL, PT, SA, TW, UK	11 (55.0) AU, CO#, DK, DE, EE, FI§§, FR, IT, KW, NL, SA
Total (N)	**28**	**28**	**15**	**28**	**20**

*date of extension of indication to severe asthma (first approval 26 September 2017 for atopic dermatitis).

†date of extension of indication to severe asthma (first approval 28 March 2017 for atopic dermatitis).

‡In Mexico, mepolizumab and benralizumab are partially reimbursed only if indication has been approved by the Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS),), as happened recently, by private medical insurance, by the general social security system Instituto Mexicano del Seguro Social (IMSS) at selected tertiary care centres, and by the social security system Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE) for those employed by the State, at selected tertiary care centres. For asthma, it is from 12 and 18 years onward for mepolizumab and benralizumab respectively.

§In Mexico, dupilumab is partially reimbursed only if indication has been approved by the COFEPRIS (as happened recently) by private medical insurance, and by the IMSS at selected tertiary care centres. For asthma, it is from 12 years onward.

‖In Brazil, omalizumab and mepolizumab are reimbursed by the public and private health system.

¶In Bulgaria, omalizumab, mepolizumab, and benralizumab are fully reimbursed: 75% by the National Health Insurance Fund (NHIF) and 25% by the Marketing Authorization Holder (MAH) according to a patient access scheme (PAS), negotiated on an annual basis between NHIF and MAH.

#In Colombia, omalizumab, mepolizumab, benralizumab, and dupilumab are fully reimbursed by the National Health System through Administrators of the Benefit Plan (insurers) of the System and governmental electronic prescription is required.

**In Ireland, omalizumab is only reimbursed in Ireland's publicly funded acute hospitals designated as severe asthma centres.

††In Mexico, omalizumab is partially reimbursed by the public healthcare system at selected secondary and tertiary care centres. Omalizumab is also partially reimbursed only if indication has been approved by the COFEPRIS by private medical insurance, by the IMSS at selected tertiary care centres, and by the ISSSTE for those employed by the State at selected secondary and tertiary care centres. For asthma, it is from 6 years onward.

‡‡in Brazil, benralizumab is reimbursed only in the private health system.

§§In Finland, there is no reimbursement system for any drugs administered in hospital.

‖‖In Argentina, roughly 50% of patients may get full reimbursement or coverage, while the other half will get 0% reimbursement for benralizumab – this is due to the different policies of the Health Maintenance Organization (HMO) in Argentina. Aside from that, benralizumab is not covered or reimbursed by the public hospitals.

AR: Argentina; AU: Australia; BG: Bulgaria; BR: Brazil; CN: Canada; CO: Colombia; DE: Germany; DK: Denmark; EE: Estonia; ES: Spain; FI: Finland; FR: France; GR: Greece; IE: Ireland; IN: India; IS: Iceland; IT: Italy; JP: Japan; KW: Kuwait; MX: Mexico; NL: Netherlands; PT: Portugal; RU: Russia; SA: Saudi Arabia; SG: Singapore; SK: South Korea; TW: Taiwan; UK: United Kingdom; US: United States of America.

824 **TABLE III.** Percentage of ISAR countries requiring each biologic criterion (April 2021)

	Anti-IgE		**Anti–IL-5/5R**						**Anti–IL4R**	
	Omalizumab		**Mepolizumab**		**Reslizumab**		**Benralizumab**		**Dupilumab**	
	N=28		**N=28**		**N=15**		**N=28**		**N=20**	
	n	%	n	%	n	%	n	%	n	%
Age (years)										
≥6	19.0	67.9	12.0	42.9	0.0	0.0	0.0	0.0	0.0	0.0
≥12	5.0	17.9	5.0	17.9	1.0	6.7	2.0	7.1	15.0	75.0
≥18	0.0	0.0	8.0	28.6	12.0	80.0	23.0	82.1	2.0	10.0
Not required	1.0	3.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Criteria not decided	3.0	10.7	3.0	10.7	2.0	13.3	3.0	10.7	3.0	15.0
Severity and Phenotype										
IgE mediated OR type II driven OR eosinophilic	1.0	3.6	1.0	3.6	1.0	6.7	1.0	3.6	2.0	10.0
Bronchial asthma refractory OR uncontrolled allergic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

	Anti-IgE		Anti–IL-5/5R						Anti–IL4R	
	Omalizumab		**Mepolizumab**		**Reslizumab**		**Benralizumab**		**Dupilumab**	
	N=28		**N=28**		**N=15**		**N=28**		**N=20**	
	n	%	n	%	n	%	n	%	n	%
Moderate to severe (persistent, eosinophilic or OCS dependent)	2.0	7.1	0.0	0.0	0.0	0.0	0.0	0.0	3.0	15.0
Severe (persistent, eosinophilic, with type II inflammation OR allergic)	16.0	57.1	16.0	57.1	11.0	73.3	16.0	57.1	10.0	50.0
Severe (uncontrolled, uncontrolled + eosinophilic, uncontrolled allergic, refractory, refractory + eosinophilic)	5.0	17.9	8.0	28.6	2.0	13.3	8.0	28.6	3.0	15.0
Not required	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Criteria not decided	4.0	14.3	3.0	10.7	1.0	6.7	3.0	10.7	2.0	10.0
Serum IgE (IU/ml)										
≥30, ≥35, or elevated	18.0	64.3								
≥70, ≥75, or ≥76	7.0	25.0								

	Anti-IgE		Anti–IL-5/5R						Anti–IL4R	
	Omalizumab		Mepolizumab		Reslizumab		Benralizumab		Dupilumab	
	N=28		N=28		N=15		N=28		N=20	
	n	%	n	%	n	%	n	%	n	%
≥150	0.0	0.0								
≥400	0.0	0.0								
Not required	1.0	3.6								
Criteria not decided	2.0	7.1								
Allergic Asthma										
SPT or serum specific IgE	27.0	96.4								
SPT and serum specific IgE	0.0	0.0								
Not required	0.0	0.0								
Criteria not decided	1.0	3.6								
Blood Eosinophil Count (cells/µl)										
≥150 or raised			2.0	7.1	0.0	0.0	0.0	0.0	11.0	55.0
≥150 in last 12 months			0.0	0.0	0.0	0.0	1.0	3.6	1.0	5.0
≥150 in last 1 month			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
≥300 or ≥150 on long-term OCS			4.0	14.3	1.0	6.7	9.0	32.1	3.0	15.0

	Anti-IgE		Anti–IL-5/5R						Anti–IL4R	
	Omalizumab		**Mepolizumab**		**Reslizumab**		**Benralizumab**		**Dupilumab**	
	N=28		**N=28**		**N=15**		**N=28**		**N=20**	
	n	%	n	%	n	%	n	%	n	%
≥300 in last 12 months or historical			18.0	64.3	2.0	13.3	12.0	42.9	3.0	15.0
≥300 x2 in last 12 months			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
≥400 or in last 12 months			0.0	0.0	10.0	66.7	1.0	3.6	0.0	0.0
≥500			1.0	3.6	0.0	0.0	1.0	3.6	0.0	0.0
Not required			1.0	3.6	1.0	6.7	1.0	3.6	0.0	0.0
Criteria not decided			2.0	7.1	1.0	6.7	3.0	10.7	2.0	10.0
Fractional exhaled Nitric Oxide (ppb)										
≥20 or ≥25 or raised	2.0	7.1	2.0	7.1	1.0	6.7	2.0	7.1	10.0	50.0
≥50	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Not required	2.0	7.1	2.0	7.1	2.0	13.3	3.0	10.7	7.0	35.0
Criteria not decided	24.0	85.7	24.0	85.7	12.0	80.0	23.0	82.1	3.0	15.0
Adherence										
Required			16.0	57.1	7.0	46.7	13.0	46.4	8.0	40.0

	Anti-IgE		Anti–IL-5/5R						Anti–IL4R	
	Omalizumab		Mepolizumab		Reslizumab		Benralizumab		Dupilumab	
	N=28		N=28		N=15		N=28		N=20	
	n	%	n	%	n	%	n	%	n	%
Not required			1.0	3.6	4.0	26.7	2.0	7.1	1.0	5.0
Criteria not decided			11.0	39.3	4.0	26.7	13.0	46.4	11.0	55.0
Asthma Control										
Required	23.0	82.1	19.0	67.9	10.0	66.7	18.0	64.3	12.0	60.0
Not required	1.0	3.6	0.0	0.0	3.0	20.0	1.0	3.6	1.0	5.0
Criteria not decided	4.0	14.3	9.0	32.1	2.0	13.3	9.0	32.1	7.0	35.0
Lung Function										
FEV_1 ≤80%	13.0	46.4	3.0	10.7	0.0	0.0	2.0	7.1	0.0	0.0
≥12% reversibility +/- > 200 ml FEV_1	1.0	3.6	2.0	7.1	1.0	6.7	1.0	3.6	0.0	0.0
FEV_1 ≤80% & evidence of reversibility	6.0	21.4	3.0	10.7	1.0	6.7	3.0	10.7	3.0	15.0
FEV_1 ≤80% & 12% reversibility & AHR	1.0	3.6	1.0	3.6	0.0	0.0	1.0	3.6	0.0	0.0

	Anti-IgE		Anti–IL-5/5R						Anti–IL4R	
	Omalizumab		Mepolizumab		Reslizumab		Benralizumab		Dupilumab	
	N=28		N=28		N=15		N=28		N=20	
	n	%	n	%	n	%	n	%	n	%
FEV_1 ≤60%	1.0	3.6	1.0	3.6	0.0	0.0	1.0	3.6	0.0	0.0
Not required	2.0	7.1	1.0	3.6	10.0	66.7	2.0	7.1	1.0	5.0
Criteria not decided	4.0	14.3	17.0	60.7	3.0	20.0	18.0	64.3	16.0	80.0
Background Therapy										
ICS	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
High dose ICS (+/- LABA or long-term OCS or xanthine or LTRA)	2.0	7.1	1.0	3.6	1.0	6.7	0.0	0.0	2.0	10.0
Medium dose ICS/LABA (+/- LTRA)	0.0	0.0	2.0	7.1	3.0	20.0	2.0	7.1	2.0	10.0
High dose ICS/LABA (+/- LAMA or LTRA), OR High dose ICS/LABA (+/- long-term OCS)	21.0	75.0	17.0	60.7	8.0	53.3	20.0	71.4	9.0	45.0

	Anti-IgE		Anti–IL-5/5R						Anti–IL4R	
	Omalizumab		Mepolizumab		Reslizumab		Benralizumab		Dupilumab	
	N=28		N=28		N=15		N=28		N=20	
	n	%	n	%	n	%	n	%	n	%
High dose ICS/LABA + ≥ 1 other controller (not OCS)	4.0	14.3	3.0	10.7	2.0	13.3	2.0	7.1	3.0	15.0
High dose ICS/LABA + long term OCS	0.0	0.0	2.0	7.1	0.0	0.0	2.0	7.1	1.0	5.0
Not required	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Criteria not decided	1.0	3.6	3.0	10.7	1.0	6.7	2.0	7.1	3.0	15.0
Long-term OCS										
Long term OCS use	6.0	21.4	5.0	17.9	0.0	0.0	3.0	10.7	3.0	15.0
Not required	4.0	14.3	12.0	42.9	9.0	60.0	14.0	50.0	9.0	45.0
Criteria not decided	18.0	64.3	11.0	39.3	6.0	40.0	11.0	39.3	8.0	40.0
Exacerbations										
≥1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

	Anti-IgE		Anti–IL-5/5R						Anti–IL4R	
	Omalizumab		Mepolizumab		Reslizumab		Benralizumab		Dupilumab	
	N=28		N=28		N=15		N=28		N=20	
	n	%	n	%	n	%	n	%	n	%
≥1 requiring hospitalization, emergency room visit, or rescue OCS	5.0	17.9	4.0	14.3	2.0	13.3	3.0	10.7	3.0	15.0
≥2	6.0	21.4	5.0	17.9	4.0	26.7	4.0	14.3	4.0	20.0
≥2 requiring hospitalization, emergency room visit, or rescue OCS	9.0	32.1	10.0	35.7	3.0	20.0	10.0	35.7	4.0	20.0
≥3	0.0	0.0	2.0	7.1	2.0	13.3	3.0	10.7	1.0	5.0
≥4	1.0	3.6	1.0	3.6	1.0	6.7	1.0	3.6	0.0	0.0
Not required	2.0	7.1	1.0	3.6	2.0	13.3	2.0	7.1	2.0	10.0
Criteria not decided	5.0	17.9	5.0	17.9	1.0	6.7	5.0	17.9	6.0	30.0

825 AHR: Airway hyperresponsiveness; FeNO: Fractional exhaled Nitric Oxide; FEV1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; LABA:
826 long-acting beta agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting beta agonist; SPT: skin prick test

827