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HETEROGENEITY IN THE USE OF BIOLOGICS FOR SEVERE ASTHMA IN EUROPE: A SHARP ERS STUDY

Authors

Anne-Noelle Frix[1], Liam G Heaney[2], Barbro Dahlén[3], Florin Mihaltan[4], Svetlana Sergejeva[5], Sanja Popović-Grle[6], Vratislav Sedlak[7], Lauri Lehtimäki[8], Arnaud Bourdin[9], Stephanie Korn[10], Eleftherios Zervas[11], Zsuzsanna Csoma[12], Dora Lúðvíksdóttir[13], Marcus Butler[14], Giorgio Walter Canonica[15], Ineta Grisle[16], Kristina Bieksiene[17], Anneke Ten Brinke[18], Piotr Kuna[19], Claudia Chaves Loureiro[20], Natalia M Nenasheva[21], Zorica Lazic[22], Sabina Škrgat[23], David Ramos-Barbon[24], Joerg Leuppi[25], Bilun Gemicioglu[26], Apostolos Bossios[27], Celeste M Porsbjerg[28], Elisabeth H Bel[29], Ratko Djukanovic[30], Renaud Louis[31].

1. Department of Respiratory Medicine, University Hospital of Liège, Liège, Belgium

2. Centre for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK

3. Respiratory Medicine Unit, Department of Medicine, Solna Campus, and Center for Molecular Medicine, Karolinska Institute, Stockholm, Sweden

4. National Institute of Pneumology M Nasta, Bucharest, Romania

5. Institute of Technology, University of Tartu, Tartu, Estonia

6. The Clinic for Lung Diseases Jordanovac, University Hospital Centre Zagreb, Jordanovac 104, 10 000 Zagreb, Croatia

7. Department of Pneumology, University Hospital and Charles University Faculty of Medicine, Hradec Kralove, Czech Republic

8. Allergy Centre, Tampere University Hospital, and Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

9. PhyMedExp, Univ Montpellier, CNRS, INSERM, CHU Montpellier, Montpellier, France

10. Universitätsmedizin Mainz, Langenbeckstr, Mainz, Germany

11. Respiratory Medicine Department and Asthma Center, Athens Chest Hospital "Sotiria", Athens, Greece

12. National Korányi Institute of Pulmonology, Budapest, Hungary

13. Dept. of Allergy, Respiratory Medicine and Sleep Landspitali University Hospital Reykjavik Iceland, University of Iceland, Reykjavik, Iceland

14. St Vincent's University Hospital, University College Dublin, Dublin, Ireland; School of Medicine, University College Dublin, Dublin, Ireland

15. Personalized Medicine, Asthma and Allergy, Humanitas Clinical and Research Center IRCCS, Rozzano, Milan, Italy

16. Latvian Association of Allergists Center of Tuberculosis and Lung Diseases Riga Latvi

17. Dept of Pulmonology, Lithuanian University of Health Sciences, Kaunas, Lithuania

18. Department of Respiratory Medicine, Medical Center Leeuwarden, Leeuwarden, the Netherlands

19. Division of Internal Medicine, Asthma and Allergy Barlicki University Hospital Medical University of Lodz Poland

20. Pulmonology Department, Hospitais da Universidade de Coimbra, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

21. Department of Allergology and Immunology, Russian Medical Academy of Continuous Professional Education, Moscow, Russia

22. Faculty of Medical Sciences, University of Kragujevac, and Clinic for Pulmonology, Clinical Centre, Kragujevac, Serbia

23. University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

24. Respiratory Research Unit, Complexo Hospitalario Universitario & Instituto de Investigación Biomédica de A Coruña (INIBIC), Spain

25. University Clinic of Medicine, Cantonal Hospital Basel and, Liestal; and University of Basel, Basel, Switzerland

26. Department of Pulmonary Diseases, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Istanbul, Turkey

27. Department of Respiratory Medicine and Allergy, Karolinska University Hospital, Stockholm, Sweden

28. Respiratory Research Unit, Bispebjerg University Hospital, Copenhagen, Denmark

29. Department of Respiratory Medicine, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands

30. Faculty of Medicine, University of Southampton, Southampton, UK ; NIHR Southampton Biomedical Research Centre, Southampton, UK

31. Department of Respiratory Medicine, Liège University Hospital, Liège, Belgium

Keywords

Severe asthma, Biologics, Usual clinical practice, Exacerbations, Asthma management

Abbreviations

ERS: European Respiratory Society

ATS: American Thoracic Society

ICS: Inhaled Corticosteroids

OCS: Oral Corticosteroids

LABA: Long-Acting Beta Agonist

IL: Interleukin

SHARP: Severe Heterogeneous Asthma Research collaboration, Patient-centered

CRC: Clinical Research Collaboration

EMA: European Medicines Agency

NICE: National Institute for Health and Care Excellence

FDA: Food and Drug Administration

GDP: Gross Domestic Product

ENT: Ear-Nose-Throat (otorhinolaryngologist)

FEV1: Forced Expiratory Volume in 1 second

FeNO: Fractional Exhaled Nitric Oxide

GETE: Global Evaluation of Treatment Effectiveness

ACQ: Asthma Control Questionnaire

GINA: Global Initiative for Asthma

GTI: Glucocorticoid Toxicity Index

SC: Subcutaneous

IV: Intraveinous

QOL: Quality of Life

Abstract

Introduction. Treatment with biologics for severe asthma is informed by international and national guidelines and defined by national regulating bodies, but how these drugs are used in real-life is unknown.

Materials and methods. The ERS SHARP clinical research collaboration conducted a 3-step survey collecting information on asthma biologics use in Europe. Five geographically distant countries defined the survey questions, focusing on 7 endpoints: biologics availability and financial issues, prescription and administration modalities, inclusion criteria, continuation criteria, switching biologics, combining biologics, and evaluation of corticosteroid toxicity. The survey was then sent to SHARP National Leads of 28 European countries. Finally, selected questions were submitted to a broad group of 263 asthma experts identified by national societies.

Results. Availability of biologics varied between countries, with 17/28 countries having all 5 existing biologics. Authorized prescribers (pulmonologists and other specialists) also differed. In-hospital administration was the preferred deliverance modality. While exacerbation rate was used as an inclusion criterion in all countries, FEV_1 was used in 46%. Blood eosinophils were an inclusion criterion in all countries for IL5- and IL4/IL13- targeted biologics, with varying thresholds. There were no formally established criteria for continuing biologics. Reduction in exacerbations represented the most important benchmark, followed by improvement in asthma control and quality of life. Only 73% (191/263) of surveyed clinicians assessed their patients for corticosteroid-induced toxicity.

Conclusion. Our study reveals important heterogeneity in the use of asthma biologics across Europe. To what extent this impacts on clinical outcomes relevant to patients and healthcare services needs further investigation.

Introduction

Asthma is a chronic disease characterized by variable airway obstruction, underpinned by airway inflammation and bronchial hyperresponsiveness, and occasional acute exacerbations. It affects 1-18% of the world population (1), with 3.5% to 5% of patients having severe disease (2), displaying higher morbidity and representing more than 50% of the direct total cost of asthma management (1) due to increased use of medications, emergency department visits and hospitalizations. The ERS/ATS consensus (European Respiratory Society / American Thoracic Society) defines severe asthma as a pattern of disease requiring high-dose inhaled corticosteroids (ICS) and a second controller, such as oral corticosteroids (OCS) or long-acting beta-agonists (LABA), to prevent it from being uncontrolled, or that remains uncontrolled despite well-applied therapy (1,3).

The main aims of asthma treatment are reduction in exacerbations, improvement in quality of life and lung function, and minimization of long-term adverse events from corticosteroids (1). Improved characterization of severe asthma pathophysiology (4,5) has led to development of biological therapies aiming to modulate the airway inflammatory processes driven by IgE and Type-2 interleukins (IL) 4, 5 and 13 (6). Five biologics are currently available: omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab (Table 1).

The “Severe Heterogeneous Asthma Research collaboration, Patient-centered” (SHARP), is a Clinical Research Collaboration (CRC) of the European Respiratory Society (ERS) with an overall ambition to improve asthma care and wellbeing of patients with severe asthma across Europe, through a patient-centered approach (7). Discussions between four stakeholders (patients, clinicians, scientists and pharmaceutical companies) have identified the use of biologics as an important issue to study so as to inform best practice and ensure that the right patient is given the most effective biological treatment.

Whilst evidence-based guidance on treatment with biologics are provided by international (European Medicines Agency, EMA) or national agencies (e.g. National Institute for Health and Care Excellence (NICE) in the UK), pricing and reimbursement criteria are defined at national level in each country, potentially leading to heterogeneity in their use. A previous study performed by the SHARP/ERS research group indicated that the severe asthmatic population in Europe is heterogeneous and differs in both clinical characteristics and treatment regimen before initiation of any biologics (8). Harmonizing the use of biologics in Europe is of interest for reproducible clinical practice and effective comparison of treatments in longitudinal and multicentric real-life studies. In order to understand current and influence future practice, we conducted a survey in 28 European nations to

investigate how biologics are currently employed, focusing on key treatment indicators: availability, inclusion criteria, administration modalities, and continuation criteria.

Materials and methods

We applied a 3-steps survey (figure 1) to describe the use of biologics in across Europe between June 2020 and April 2021. In the first step (June 2020 - November 2020), 5 geographically distant countries (Belgium, Estonia, Romania, Sweden, UK) were selected to define the survey questions during virtual meetings, assisted by the SHARP support team, focusing on availability of biologics, their administration and criteria for inclusion or continuation of treatment. In the second step (November 2020 - April 2021), the survey was extended (by email correspondence) to all SHARP National Leads in 28 European countries (SHARP National Leads Survey, table 2). In the third step (January 2021 - April 2021), a selection of questions was submitted to a larger audience of 263 asthma experts across Europe, identified by their national societies (Experts Broad Survey).

The survey involving SHARP National Leads covered 7 endpoints. 1) *Availability and financial issues.* Lists of biologics available in individual countries and financial issues (patient contribution or fixed hospital budget dedicated to biologics) were requested. We analyzed the number of available biotherapies related to per capita Gross Domestic Product (GDP), comparing countries with ≤3 and those with >3 biologics. 2) *Prescription and administration modalities.* Information on prescribers (pulmonologist, allergologist, ENTs (Ear-Nose-Throat, otorhinolaryngologist), pediatrician, team of experts) was collected, together with prescription and administration modalities (home or hospital administration). 3) *Inclusion criteria.* Participants provided the criteria for prescribing biologics, focusing on each biologic individually, singling out common basic criteria among nations, together with additional criteria specifically required in some countries. 4) *Continuation criteria.* Details were requested for how and when effectiveness of biologics was evaluated and how decisions were made whether to continue treatment. After the initial survey returned multiple and diverse criteria, a second survey, containing 10 objective criteria commonly used to assess efficacy in severe asthma clinical trials, was undertaken. National Leads were asked to rank those criteria in order of importance. We separated 2 groups of patients to apply those criteria: those on and those not on maintenance OCS. The survey participants ranked criteria between 1 and 10 (from most to least important). The mean value was calculated for each criterion's rank in order to obtain a complete ranking of objective criteria. 5) *Switching biologics.* SHARP National Leads were asked to describe how easy it was to switch from one biotherapy to another. 6) *Combining biologics.* SHARP National Leads were asked whether combining biologics was possible in their country. 7) *Evaluation of*

corticosteroids toxicity. Participants were asked whether and how they evaluated corticosteroid toxicity in patients with severe asthma.

After completing the National Leads survey, the broad panel of European asthma experts (Experts Broad Survey) were surveyed to validate the following endpoints: (4) Continuation criteria, (5) Switching biologics, (6) Combining biologics, (7) Evaluation of corticosteroids toxicity.

Statistics

Parametric unpaired T tests compared GPD per capita and number of available biologics. Objective continuation criteria were ranked by calculating the mean value for each criterion's rank: the lower the mean item score, the higher the importance of the criterion.

Results

Availability and financial issues

The details of biologics available in the surveyed countries are shown in table 2. Availability was related to per capita GDP, which was significantly (p=0.0072) lower in countries with ≤3 biologics (n=7) than in those with ≥3 biologics (n=21) ($16,831 ± $9102 vs. $41302 ± $21327) (Figure 2). Patient financial contribution was required in 9 countries: patients had to pay a percentage of total cost in 6 countries, whereas those from the 3 others had a fixed amount to pay. Six countries worked with a fixed hospital budget dedicated to biologics.

Prescription and administration modalities

Biologics could be prescribed by a single prescriber in all but 3 countries, where decisions were taken by a team/panel of experts (including pulmonologists, allergologists, pediatricians and ENTs). Pulmonologists were sole prescribers in 4 countries, whereas allergologists, and pediatricians could also prescribe biologics for severe asthma in the other countries. Initial administration was performed in hospitals in all countries, with subsequent home administration possible in 20.

Inclusion criteria

Exacerbation rates were inclusion criterion in all (n = 28) countries, with a threshold of ≥2/year, except in 2 countries for which cut-off was 1/year (table 3). Forced Expiratory Volume in 1 second (FEV_1) was used in 46% of countries, mainly for omalizumab, with a threshold at FEV1 <80% of predicted value, except for one country with a threshold <50% of predicted. Blood eosinophil counts

were used in all countries for IL5- and IL4- targeted medications, but threshold values differed between biologics and countries, ranging from 150 to 500/uL. To prescribe omalizumab, serum IgE levels were used in all countries with an inclusion threshold varying from 30 to 148 IU/mL, and evidence of sensitization to ≥1 aero-allergen, as judged by serum specific IgE or prick tests, was required in 21 countries (75%). Additional criteria had to be met for certain biologics, such as asthma control and quality of life questionnaires, good adherence to existing treatment, evidence of non-smoking status (eg. saliva cotinine levels), fractional exhaled nitric oxide (FeNO), sputum eosinophil levels, expert consensus meeting prior to initiation of treatment.

Assessment of effectiveness and criteria for continuation

Recommendations for treatment duration before first evaluation after starting therapy and modalities to assess treatment effectiveness differed between countries and biologics. In 13 countries, clinicians were required to perform an assessment at 4-6 months and continue medication only if effectiveness was proven, whereas in 3 countries this was done at 1 year. However, in 12 countries, unlimited initial reimbursement was directly granted.

Although effectiveness evaluation was mandatory in most countries, assessment criteria were not strictly defined. Some countries had few objective criteria and mainly assessed patients' subjective responses, whereas others needed demonstration of improvement in objective benchmarks, such as reduction in exacerbation rate and/or maintenance OCS dose or positive change in the Global Evaluation of Treatment Effectiveness (GETE) score (for omalizumab).

After analyzing these preliminary results, a predefined ranking questionnaire was sent back to National Leads and to the wider group of 263 asthma experts (table 4). For patients on maintenance OCS, the four most important criteria were similar in the SHARP National Leads survey and the Experts Broad survey. For participants, the most meaningful criteria of effectiveness were the reductions in exacerbation rate by 75% and 50% and reduction in maintenance OCS dose. For patients not on maintenance OCS, the 4 most important criteria were identical between the 2 groups, represented by reduction in exacerbation rate (by 75%, 50% then 25%) then improvement of Asthma Control Questionnaire ACQ (by 1 on 1 year). Overall, the reduction in exacerbations was the most important criterion, followed by improvements in asthma control and quality of life scores. The least important criterion was 5% improvement in FEV_1 both for patients on and those not on OCS.

Switching biologics

The survey in SHARP National Leads revealed that it is easy to switch between biologics, although one country (1/28) reported difficulties and one had no experience. The Experts Broad survey showed that 202/263 participants (77%) found it easy to switch between biologics. For those who faced difficulties in switching, the main reasons were lack of experience, formal prohibition, need for a wash-out period, health insurance issues and cost.

Combining biologics

The SHARP National Leads survey revealed that combining biologics was not authorized in 16 countries, while there were no formal restrictions in the other 12, but experience was lacking. This was verified by the Experts Broad survey, which showed that combining biologics was not allowed or not tested for 81% of participants.

Evaluation of corticosteroids toxicity

The SHARP National Leads survey revealed that corticosteroid-induced toxicity was assessed in 20 countries (mainly by clinical evaluation and cortisol blood levels). This was supported by data extracted from the Experts Broad survey, which showed evaluation by 70% of experts. Cortisol blood level and clinical evaluation were also the most commonly used assessment modalities.

Discussion

Our study shows that availability of biologics, especially those most recently licensed, varies across Europe. This was also recently observed in the International Severe Asthma Registry (9). In our survey, the wealthier countries (by GDP per capita) offer a greater choice of biologics. Large variation was observed in medical criteria for reimbursing the patients. Although any financial contributions imposed on the patient vary greatly between countries, it was encouraging to see that health insurance covers the majority of the cost in all countries. Our survey also demonstrated differences in prescription and administration modalities, albeit without negative impact on initiation of treatment. Three countries required an expert panel to initiate treatment; whether or not this impacts on clinical outcomes is unclear, but we speculate that expert panels discussing each case individually, especially during multi-disciplinary meetings, may be more likely to pick up other unmet needs for which alternative treatment modalities could be offered. We also speculate that this could reduce unnecessary premature introduction of biologics. We also noticed differences in prescribers (pulmonologist, allergologist, pediatrician). Furthermore, while hospital administration of biologics is standard in every country, home administration was possible in 71% of countries, making it easier for patients living at distance from the hospital to access those medications in some but not all European countries.

Surprisingly, our survey revealed marked differences in treatment inclusion criteria. Remarkably, some countries have established reimbursement criteria that do not strictly follow the clinical or laboratory criteria used in monoclonal antibodies RCTs. While all countries agreed on the need to meet the strict definition of severe asthma, the required minimal exacerbation rate in the past year was highly variable, ranging from 1 to 4, the greatest proportion of countries choosing 2. Arguably, doctors should strive to prevent all exacerbations, but the financial realities make this a difficult objective to achieve. We would argue that duration and severity of an exacerbation should also be included in the decision-making process. Omalizumab and anti-IL5 or anti-IL4/IL13 biologics all required specific laboratory biomarkers, namely total serum IgE concentration and blood eosinophil counts, respectively. While these biomarkers are used in most European countries, there were marked differences in threshold values, for unclear reasons that need elucidation. Of note, in two countries, it was possible to bypass the blood eosinophil threshold and offer anti-IL5 therapy if sputum eosinophil counts were high. In three countries, dupilumab was offered to patients on OCS for >50% of the year irrespective of immunological T2 profile. Lung function has long been a measure of treatment efficacy but has often been considered as secondary endpoint in severe asthma clinical trials studying biologics. In keeping with this established concept, FEV_1 was mostly used as an inclusion criterion for omalizumab (in 50% of countries) but was only used in 9% of countries for dupilumab. This is paradoxical given that dupilumab was found to be more effective than other biologics at improving FEV_1 (10). Furthermore, considerable improvement in FEV_1 has been reported with benralizumab in severe eosinophilic asthma and nasal polyposis (11). Arguably, requiring an already altered FEV1 as inclusion criteria might not be suitable as it may limit access to the medication in patients who might have benefited from prevention of remodeling and subsequent decrease in lung function. Indeed, there are some data on long-term follow-up suggesting that biologics may prevent decline in lung function (12–14). Finally, there was an obligation in some countries to prove non-smoking status or treatment adherence, or completion of a questionnaire of quality of life. Concerning exposure to tobacco, there is an exclusion of smokers or sometimes significant ex-smokers in severe asthma clinical trials, which may explain why some countries also apply this restriction when prescribing biologics. While there are no RCTs including smokers, a recent work focusing on ex-smokers suggested that a significant smoking history did not preclude effectiveness of anti-IL5/anti-IL5R therapy regarding exacerbations and asthma control (15). In addition, a recent real-life study has indicated that anti-IL5 was able to attenuate lung function decline in severe eosinophilic asthmatics independently of smoking status (13). Whilst we recognize the need to encourage smoking cessation, we question the morality of withholding treatment in people who are unable to quit. In addition, it is worth highlighting that most countries do not need

strict proof of compliance regarding background ICS treatment, which is surprising as it is known that non-adherence is an important cause of uncontrolled asthma.

An important but very contentious point for treatment with biologics is its effectiveness evaluation. GINA (Global Initiative for Asthma) guidelines recommend a 4-month trial period before assessing effectiveness in respect of asthma control (1). A recent panel of European experts recommended a traffic lights assessment system that offers three decision pathways: 1) continue treatment in super-responders, 2) stop if there is no evidence of response and 3) extend for one year in intermediate responders in case the response is delayed (16). Our survey noted divergence between countries in timing between first administration of biologics and first assessment of effectiveness. While in most countries evaluation was done at 4-6 months (depending on biologic), others only assessed at 1 year, and some allowed immediate access to an unlimited reimbursement without strict evaluation of effectiveness. The most appropriate timing of effectiveness assessment needs to be addressed, as early evaluation might not show clinically relevant reduction in exacerbations, whereas late evaluation might delay any treatment discontinuation or switch between biologics. Similarly, we noted large differences in the benchmarks used to assess effectiveness. Indeed, many countries did not take into account efficacy criteria obtained in severe asthma monoclonal antibodies RCTs. In an attempt to reach a consensus on optimal assessment, we asked asthma experts to rank the clinical efficacy criteria used in those RCTs. Not surprisingly, the reduction in exacerbation rate and the burden of maintenance OCS were rated as the most important, followed by improvements in asthma control and quality of life. Of note, the least important criterion was improvement of 5% predicted in FEV1, although this level of improvement has been achieved in most RCTs and real-life studies with biologics (17,18). Overall, there is yet no general consensus about criteria defining significant response to treatment with biologics, even if this is an active area of discussion (19).

The question of switching or combining biologics emerges when asthma remains uncontrolled despite the biologic. There are reports indicating that switching from anti-IgE to anti-IL5 or anti-IL5R may improve asthma control (20–22). Our survey showed that it is easy in most countries to switch between biologics if standard inclusion criteria for the alternative biologic are met. Combining biologics in cases of uncontrolled asthma is a plausible option since biologics act through different mechanisms. However, combination therapy has not been studied extensively so its efficacy-safety profile is not established. Indeed, relevant data on this subject are mainly derived from case reports (23,24). This is not surprising, as our survey showed that combining biotherapies is not authorized in 16 of 28 countries, while 12 countries have no formal restrictions but also have no experience. A recent study has shown that combining dupilumab with an anti-IL33 did not bring further advantage

(25). Formal studies are necessary to define the benefit-risk balance of combining asthma biologics that target different molecular pathways (26).

Despite known side-effects, OCS treatment remains a cornerstone in the management of a substantial proportion of severe asthmatics. Some biologics have been shown to have a corticosteroid-sparing potential, such as mepolizumab (27), benralizumab (28) or dupilumab (29). Our survey revealed that corticosteroid-related side-effects were assessed in 70% of countries, which is quite considerable, but this leaves almost one third of patients without appropriate assessment. The methods used to evaluate OCS side-effects also varied, with cortisol blood levels and clinical evaluation being most frequently used. There are accurate tools, including the Glucocorticoid Toxicity Index (GTI) (30), that can be used. Standardization is essential for patient-centered care to improve evaluation of corticosteroid-induced toxicity, as it might lead to a more rapid identification of side-effects on the one hand, and a better structured and consistent approach to corticosteroid weaning on the other hand.

This survey has several limitations. Firstly, it did not take into account patient engagement. As a patient-centered CRC, we recognize the importance of patients' perspectives of effectiveness, but patient involvement in SHARP in some countries is still lacking either completely or is sub-optimal. Thus, patient engagement to define the inclusion and exclusion criteria would have been insufficiently representative of all the European countries. To follow-up on this study, an additional European collaborative and patient-centered survey led by SHARP/ERS expert group, involving patient organizations and networks, is needed. Secondly, our study being essentially descriptive, it has not investigated how between-nation differences in inclusion or continuation criteria may result in disparities in real-life effectiveness and patient care. Thirdly, the study has not assessed the impact of corticosteroid monitoring on patient outcomes, particularly on the weaning of steroids, which is one of the fundamental aim when starting biologics in patients receiving maintenance OCS.

Conclusion

Our survey has demonstrated some similarities but also great disparities in the use of biologics for severe asthma, which need to be understood better and remedied to achieve best possible practice for patients. Harmonizing the use of biologics is also of interest for reproducible clinical practice and effective comparison of treatments in longitudinal and multicentric real life studies. While harmonization of practice across Europe requires further analysis, we can already now, as members of a strongly patient-centered clinical research collaboration, appeal to healthcare providers of all

countries where the full complement of biologics is not available to explore ways of improving availability. From a patient and public heath perspective, we also strongly recommend that formal criteria for effectiveness assessment should be established.

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Tables and figures

Biologics	Type	Route and dosing	Mechanism of action	FDA-EMA recommendations
Omalizumab (Xolair)	Anti-IgE	SC (subcutaneous) 0,016 mg/kg per IU/ml of IgE per month, injected every 2 to 4 weeks	- Binds to free IgE, thereby preventing IgE binding to its receptor	***FDA approval: 2002*** • Adults and children > 6 years old • IgE mediated moderate-to-severe allergic asthma • Uncontrolled despite a well-applied GINA step 4 treatment • High IgE blood levels • Sensitization to at least one perennial allergen (31,32)
Mepolizumab (Nucala)	Anti-IL5	SC 100mg every 4 weeks	- Bind to IL5-ligand - Prevents IL5 from binding to its receptor	***FDA approval: 2015*** • High blood eosinophil count (≥ 150 cells/µl at first administration or ≥ 300 cells/µl in the past year) • ≥ 2 asthma exacerbations requiring OCS in the previous year (33,34)
Reslizumab (Cinquaero)	Anti-IL5	IV (intravenous) 3mg/kg	- Binds to IL5-ligand - Prevents IL5 from binding to its receptor	***FDA approval: 2016*** • Adult patients • Severe eosinophilic asthma (≥ 400 eosinophils/µl) • ≥ 3 asthma exacerbations in the past 12 months (35,36)
Benralizumab (Fasenra)	Anti-IL5R	SC 30 mg every 4 weeks for the 3 first doses, then 30mg every 8 weeks	- Binds to IL5 receptor subunit alpha on eosinophils and basophils - Causes apoptosis of eosinophils and basophils	***FDA approval: 2017*** • Adults (EMA) or patients aged ≥ 12 years (FDA) • Inadequately controlled severe eosinophilic asthma • High blood eosinophilic count (≥ 300 blood eosinophils/µL) (37,38)
Dupilumab (Dupixent)	Anti-IL4/13	SC 400-600mg for loading dose, then 200-300mg every 2 weeks	- Binds to IL4 receptor subunit alpha - Blocks IL4 and IL13 signaling pathways	***FDA approval: 2018*** • Moderate-to-severe asthma patients aged ≥ 12 years • Eosinophilic phenotype or OCS-dependent asthma (39) (FDA) • Type 2 inflammation with high blood eosinophils and/or elevated FeNO levels (40) (EMA)

Table 1. Biologics available in severe asthma.

SC: Subcutaneous. IV: Intravenous. IL: Interleukin. FDA: Food and Drug Administration. EMA: European Medicines Agency.

Country	Number of available biologics	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Austria	5	1	1	1	1	1
Belgium	4	1	1	1	1	0
Croatia	4	1	1	1	1	0
Czech Republic	5	1	1	1	1	1
Denmark	5	1	1	1	1	1
Estonia	5	1	1	1	1	1
Finland	5	1	1	1	1	1
France	5	1	1	1	1	1
Germany	5	1	1	1	1	1
Greece	2	1	1	0	0	0
Hungary	5	1	1	1	1	1
Iceland	5	1	1	1	1	1
Ireland	4	1	1	1	1	0
Italy	3	1	1	0	1	0
Latvia	5	1	1	1	1	1
Lithuania	3	1	1	0	1	0
Netherlands	5	1	1	1	1	1
Poland	3	1	1	0	1	0
Portugal	5	1	1	1	1	1
Romania	2	1	0	0	1	0
Russia	5	1	1	1	1	1
Serbia	3	1	0	1	1	0
Slovenia	4	1	1	1	1	0
Spain	5	1	1	1	1	0
Sweden	5	1	1	1	1	1
Switzerland	5	1	1	1	1	Off label
Turkey	2	1	1	0	0	0
UK	5	1	1	1	1	1

Table 2. Availability of biologics in Europe (as of April 2021).

Of note, this table summarizes the availability of biologics at the time the survey was conducted (November 2020 – April 2021). Since survey completion, dupilumab has become available in Spain, Switzerland, Croatia and Slovenia.

Biotherapy	Common criteria	Disparities noted between countries	Additional criteria for some countries
Omalizumab (N = 26 countries)	- Severe asthma definition (ATS/ERS) (24/26) - Exacerbation rate (24/26) ❖ 4 countries required >2 exacerbations/ year ❖ 20 countries considered ≤2 exacerbations/ year - IgE levels (25/26), with very variable threshold (majority > 30 or >76 IU/mL)	- Age threshold: adults versus children for some countries - FEV1 levels: used as criterion in 13/26 countries (50%)	- Adherence is an absolute criterion in 2 countries - Non-smoking status is an absolute criterion in 3 countries - Questionnaire for quality of life (QOL) was used as criterion in 1 country
Mepolizumab (N = 24 countries)	- Severe asthma definition (ATS/ERS) (21/24) - Exacerbation rate (24/24) ❖ 5 countries required >2 exacerbations/ year ❖ 19 countries considered ≤2 exacerbations/ year - Blood eosinophils (24/24), with a threshold variable between 150 and 500 cells/µl). Of note, one country separated maintenance OCS patients and not on maintenance OCS patients to define threshold	- Age: adult versus children. This was not clearly defined as criterion in some countries. - FEV1 levels: used as criterion in 5/24 countries (20.8%)	- Adherence is an absolute criterion in 4 countries - Non-smoking status is an absolute criterion in 3 countries - Questionnaire for QOL was used as criterion in 1 country - 2 countries offer the possibility of inclusion if sputum eosinophils are high, even if blood eosinophils are below the fixed threshold - Cotinine levels in saliva is a criterion in 1 country
Benralizumab (N = 24 countries)	- Severe asthma definition (ATS/ERS) (20/24) - Exacerbation rate (22/24) ❖ 5 countries required >2 exacerbations/ year ❖ 17 countries considered ≤2 exacerbations/ year - Blood eosinophils (24/24), with a threshold variable between 150 and 500 cells/µl).	- Age: adult versus children. This was not clearly defined as criterion in some countries. - FEV1 levels: used as criterion in 6/24 countries (25%)	- Adherence is an absolute criterion in 3 countries - Non-smoking status is an absolute criterion in 3 countries - Questionnaire for QOL was used as criterion in 1 country - 2 countries offer the possibility of inclusion if sputum eosinophils are high, even if blood eosinophils are below the fixed threshold - Cotinine levels in saliva is a criterion in 1 country

Reslizumab (N = 16 countries)	- Severe asthma definition (ATS/ERS) (16/16) - Exacerbation rate (16/16) ❖ 7 countries required >2 exacerbations/ year ❖ 9 countries considered ≤2 exacerbations/ year - Blood eosinophils (16/16), with a threshold variable between 150 and 400 cells/µl)	- Age: adult versus children. This was not clearly defined as criterion in some countries. - FEV1 levels: used as criterion in 5/16 countries (31.2%)	- Adherence is an absolute criterion in 3 countries - Non-smoking status is an absolute criterion in 3 countries - Questionnaires for QOL were not used - 2 countries offer the possibility of inclusion if sputum eosinophils are high, even if blood eosinophils are below the fixed threshold - 3 countries granted the biotherapy if patient was on OCS >50% of the year - Cotinine levels in saliva was not used
Dupilumab (N = 11 countries)	- Severe asthma definition (ATS/ERS) (10/11) - Exacerbation rate (10/11) ❖ 1 country required >2 exacerbations/ year ❖ 9 countries considered ≤2 exacerbations/ year ❖ 1 country had no threshold - Blood eosinophils (11/11), with a threshold variable between 150 and 300 cells/µl)	- Age: adult versus children. This was not clearly defined as criterion in some countries. - FEV1 levels: used as criterion in 1/11 countries (9.1%) - FeNO levels: used in 5/11 countries (45.5%), with threshold >25 ppb for all countries	- Adherence is an absolute criterion in 2 countries - Non-smoking status is an absolute criterion in 2 countries - Questionnaires for QOL were not used - 3 countries granted the biotherapy if patient was on OCS >50% of the year (without needing exacerbations or high blood eosinophilic count) - Cotinine levels in saliva is a criterion in 1 country

Table 3. Inclusion criteria for severe asthma biotherapies in Europe.

ATS: American Thoracic Society, ERS: European Respiratory Society, FEV1: Forced Expiratory Volume in 1 second, QOL: Quality of Life, OCS: Oral Corticosteroids.

National Leads' survey (n = 28)				
Ranking	**Patients on maintenance OCS**	Item score	**Patients not on maintenance OCS**	Item score
1	Reduction of exacerbation rate by 75% over 1 year	3.4	Reduction of exacerbation rate by 75% over 1 year	2.5
2	Reduction of chronic dose of OCS by 50%	3.4	Reduction of exacerbation rate by 50% over 1 year	2.8
3	Stopping chronic maintenance OCS	3.5	Reduction of exacerbation rate by 25% over 1 year	4.8
4	Reduction of exacerbation rate by 50% over 1 year	4.1	Reduction in ACQ by 1 at 4/6 months	5
5	Reduction of exacerbation rate by 25% over 1 year	6	Increase in AQLQ by 1 at 4/6 months	5
6	Increase in AQLQ by 1 at 4/6 months	6.1	Reduction in ACQ by 0.5 at 4/6 months	5.5
7	Reduction in ACQ by 1 at 4/6 months	6.2	Increase in AQLQ by 0.5 at 4/6 months	5.7
8	Reduction in ACQ by 0.5 at 4/6 months	6.6	Reduction of chronic dose of ICS by 50%	6.2
9	Increase in AQLQ by 0.5 at 4/6 months	6.9	Improvement of 5% predicted FEV1	7.6
10	Improvement of 5% predicted FEV1	8.5		
Experts Broad survey (n = 263)				
1	Reduction of exacerbation rate by 75% over 1 year	2.6	Reduction of exacerbation rate by 75% over 1 year	1.9
2	Reduction of exacerbation rate by 50% over 1 year	3.1	Reduction of exacerbation rate by 50% over 1 year	3.1
3	Stopping chronic maintenance OCS	3.5	Reduction of exacerbation rate by 25% over 1 year	4.5
4	Reduction of chronic dose of OCS by 50%	4.1	Reduction in ACQ by 1 at 4/6 months	4.6
5	Reduction in ACQ by 1 at 4/6 months	4.8	Reduction in ACQ by 0.5 at 4/6 months	5.2
6	Reduction of exacerbation rate by 25% over 1 year	5.1	Reduction of chronic dose of ICS by 50%	5.6
7	Reduction in ACQ by 0.5 at 4/6 months	6.3	Increase in AQLQ by 1 at 4/6 months	6.3
8	Increase in AQLQ by 1 at 4/6 months	7.3	Increase in AQLQ by 0.5 at 4/6 months	6.8
9	Increase in AQLQ by 0.5 at 4/6 months	8.5	Improvement of 5% predicted FEV1	7.8
10	Improvement of 5% predicted FEV1	8.9		

Table 4. Assessment of effectiveness in biologics: ranking of objective criteria.

Those items are clinical efficacy criteria used in most RCTs to assess effectiveness of biologics in severe asthma. The lower the mean score of the item is, the higher its importance as effectiveness criteria is, according to participants.

OCS: Oral Corticosteroids, ICS: Inhaled Corticosteroids, AQLQ: Asthma Quality of Life Questionnaire, ACQ: Asthma Control Questionnaire.

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HETEROGENEITY IN THE USE OF BIOLOGICS FOR SEVERE ASTHMA IN EUROPE: A SHARP ERS STUDY

Figures

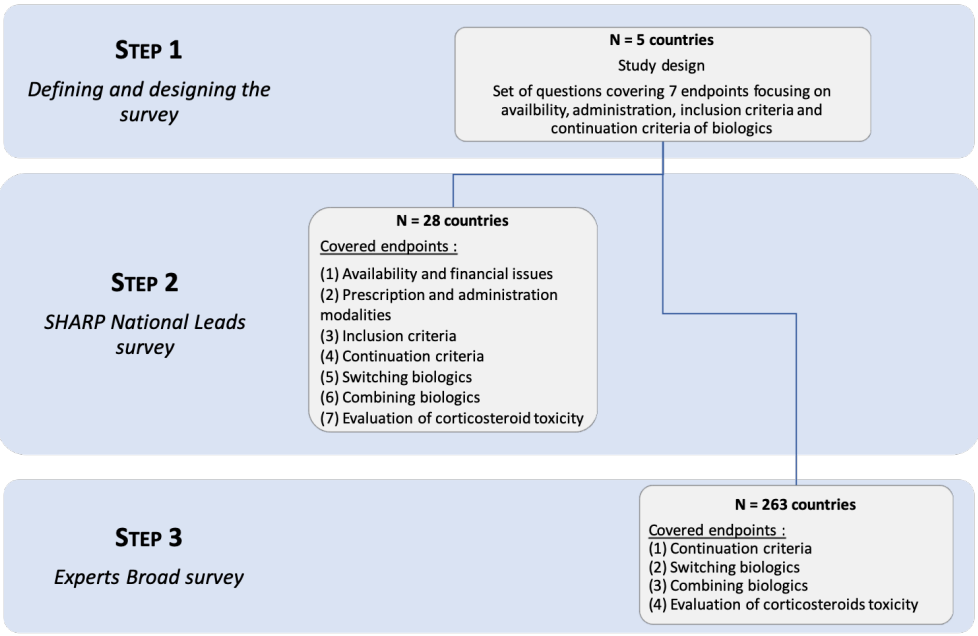

Figure 1. Study flow chart: a 3-steps survey

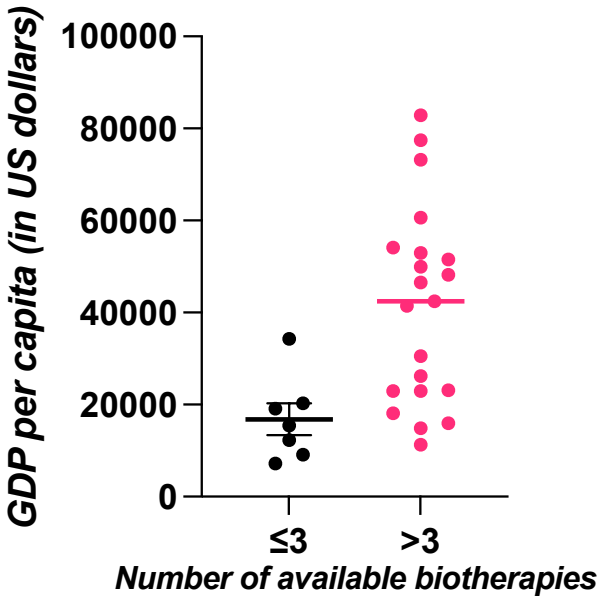

Figure 2. Comparison of the number of available biotherapies according to Gross Domestic Product per capita

Results are expressed in mean ± SEM, data analyzed by parametric impaired T-tests