Severe T2-high asthma in the biologics era: European experts' opinion

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This review provides a summary of the discussions and highlights important concerns identified by the participants of the European Respiratory Biologics Forum on the current management of severe asthma. http://bit.ly/2YhpP1k

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ABSTRACT The European Respiratory Biologics Forum gathered participants from 21 countries in Madrid, Spain, to discuss the management and treatment of severe asthma in the era of biologics. The current insights on the pathophysiology of severe asthma were discussed, as well as the role of respiratory biologics in clinical practice and strategies for eliminating chronic use of oral corticosteroids. The participants also highlighted the key challenges in identifying patients with severe asthma based on phenotypes, biomarkers and treatable traits, and the existing problems in patient referral to specialist care. The monitoring of treatment was debated and the need for a change towards precision medicine and personalised care was emphasised throughout the meeting. This review provides a summary of the discussions and highlights important concerns identified by the participants regarding the current management of severe asthma.

The era of biologics for airways disease: where are we now?

On February 23 and 24, 2018, the European Respiratory Biologics Forum, sponsored by AstraZeneca and held in Madrid, Spain, brought together experts in respiratory disease and those who specialise in the management of severe asthma from 21 different countries across Europe. During the forum, the current status of the pathophysiology of severe asthma, the role of respiratory biologics in clinical practice, key challenges related to the identification of the right patient based on phenotypes, biomarkers and treatable traits, and the best ways of monitoring treatment response were discussed.

The scientific faculty of the meeting included Marc Humbert (chair), Thomas Bahmer, Fulvio Braido, Borja G. Cosío, Marco Idzko and Ian Pavord. Among the faculty members and participants, there was broad consensus on the importance of biomarkers and the characterisation of treatable traits for the identification of appropriate patients for biological therapies. Throughout the meeting, it was highlighted that a precision medicine approach needs to be established for the management of severe asthma.

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TABLE 1 Important concerns in the management of severe asthma identified at the European Respiratory Biologics Forum

How can biomarkers and phenotypes be best identified and utilised in daily clinical practice?
Is the ACQ the right tool for monitoring the response to biologics?
Is treatment response assessed using the ACQ related to the effect of treatment on exacerbations?
How can awareness be raised among patients and non-specialists regarding the burden of oral corticosteroids and the potential of new treatments available?
Are oral steroids effective in patients having exacerbations while on biological therapies?
When should patients start and stop taking a biologic?
When should patients be switched from one biologic to another?

ACQ: Asthma Control Questionnaire.

Based on the input of the participants and the faculty (table 1), three key areas of interest were identified: 1) the importance of appropriate patient referral to specialist care; 2) the potential of treatable traits, biomarkers and phenotypes for improving the management of patients with severe asthma; and 3) the potential of biological therapies and strategies for eliminating the use of oral corticosteroids (OCSs).

Throughout this review, examples from several European countries are used to highlight aspects of everyday clinical practice, ongoing national research projects, and successful national healthcare interventions in the management of asthma. During the meeting, participants and faculty members interactively discussed these topics based on their personal experience and their national healthcare environment. In Europe, large differences in the referral structure, reimbursement policy, and general patient management practices were noted. These differences were related to the general healthcare policies in the respective European countries. Here, we share some particular examples and discuss these in the context of the identified key areas of interest.

Patient referral to specialist care

One of the major challenges in current clinical practice is the appropriate referral of patients with severe asthma to specialist centres. Specialist centres should aim to set up a multidisciplinary team of physicians and/or nurse practitioners focused on asthma and with the availability to perform tests other than lung function tests (*e.g.* fractional exhaled nitric oxide (*F*ENO) test, induced sputum analysis, *etc.*). Asthma is highly complex and heterogeneous in terms of its manifestation and clinical course, which creates a barrier to the efficient management of the disease [1]. Due to the complexity of the disease, patients with severe asthma should be treated in specialist care; however, the referral systems are not always effective. The referral guidelines used in primary care for asthma vary across the different European countries. For instance, in Italy, the Global Initiative for Asthma (GINA) guidelines are followed, whereas countries such as the Netherlands, Portugal and Sweden have produced local guidelines developed by general practitioners (GPs) and used by physicians and nurses in general practice. A consensus guideline developed by respiratory specialists, allergy specialists and GPs is used in other countries such as Spain, although referral procedures vary between regions. A standardised approach is needed in order to provide the best treatment at the right time [2].

An additional problem that still exists in some countries is the lack of appropriate referral for patients who have been discharged from hospital after an acute exacerbation episode. In particular, it was noted that patients who were admitted to the emergency department were often put on a short course of OCSs, without detailed assessment of the cause of their current deterioration, demonstrating evidence for the lack of an individualised strategy for the patient during the high-risk period after an emergency room or hospital visit. Therapy with systemic steroids may improve a patient's symptoms but does not necessarily treat the underlying causes of the disease, which results in further hospitalisations and a vicious cycle of exacerbations and OCS dependence. To move beyond this model, it is important to ensure that patients with severe asthma are identified and promptly referred to a specialist. As reported by some participants, the inappropriate referral process in the emergency department setting is still an unmet clinical need.

Phenotypes, treatable traits and biomarkers

Based on discussions held during the forum, the respiratory experts recognised the role of phenotypes, biomarkers and treatable traits in guiding treatment decisions and patient identification. However, there is a discrepancy between the scientific recognition and the implementation of the biomarkers and treatable traits in daily practice, which probably relates to the need for additional evidence on how they can be implemented and combined. The majority of experts stated that they use two to three biomarkers

TABLE 2 Current status of biologics in severe asthma management

Further understanding is needed on how and when to switch from one biological therapy to another
There is still no consensus on the appropriate length of waiting time before a patient is classified as a non-responder
The efficacy of biologics in severe asthma has been demonstrated in a number of trials in recent years, but further research is needed to understand the long-term effects of biological therapy
Several clinical studies have demonstrated the oral corticosteroid-sparing effect of biologics

routinely in their clinical practice; blood eosinophils and *F*ENO were identified as the most practical or pragmatic biomarkers in use for the diagnosis and management of severe asthma and there was broad agreement that the combination of these biomarkers provides the best overall assessment of type 2 (T2) airway inflammation.

The potential of biological therapies and strategies for eliminating the use of OCSs

When discussing real-life patient case studies, the efficacy of biologics and their OCS-sparing benefits were emphasised as reasons why specialists consider them as an option for treating severe T2-high asthma. If a patient is not responsive to the first biological therapy prescribed, it was suggested that a different one should be considered.

Although biologics have had an impact in the treatment of severe asthma, there are still some aspects that warrant further research and evidence generation (table 2). Aspects such as how and when to switch from one biological therapy to another, or the appropriate length of treatment after which a patient can be classified as a non-responder have not been elucidated.

The need to reduce OCS use, especially in light of recent OCS-sparing evidence with biologics [3–6], was highlighted at the meeting. However, it is not fully understood why physicians delay stopping OCS therapy. Resistance from some patients, who may feel that their symptoms are controlled with OCSs, was noted as one of the issues.

Management of severe asthma with currently available biological therapies

A number of clinical phase III trials have in recent years demonstrated the efficacy of biologics in severe asthma. In particular, trials with anti-interleukin (IL)-5 (mepolizumab and reslizumab), anti-IL-5 receptor antagonist (RA) (benralizumab), anti-IL-4/IL-13 RA (dupilumab) and anti-immunoglobulin E (IgE) (omalizumab) have reported reductions in asthma exacerbations varying from 25% to more than 60%, as well as a decrease in hospitalisation events [7–11]. Nonetheless, results on lung function have varied across trials. Most trials have reported improvements in lung function [12–15]; however, this attribute is variable and appears to depend on the level of currently active airway inflammation and the modality [16], suggesting that further research is required to better understand the direct effects of biological therapies on lung function.

The first biological therapy approved for the treatment of asthma was omalizumab in 2003, followed by mepolizumab in 2014, reslizumab and benralizumab in 2017, and most recently dupilumab, which was approved in the USA in October 2018.

Moreover, a number of trials evaluating the efficacy of biologics in reducing OCS dosage have demonstrated significant improvements in asthma control alongside reductions in OCS use. In the ZONDA trial, benralizumab was shown to reduce OCS use by 75%, compared with 25% with placebo [4]. Similarly, the SIRIUS trial demonstrated an OCS-sparing effect associated with mepolizumab, with a median reduction in daily OCS dose of 50%, compared with no reduction in the placebo arm [3]. Dupilumab was also found to reduce OCS use by 70% in patients with blood eosinophil count $\geqslant$300 cells·μL^{-1} at baseline, compared with 42% with placebo [5]. A similar effect was observed with omalizumab in a trial comparing omalizumab as an add-on to optimised asthma therapy *versus* optimised asthma therapy alone, although this was not a placebo-controlled study [6]. Biologics may therefore offer a new avenue for the reduction of chronic OCS use in patients with severe asthma.

Is it possible to recognise severe asthma earlier?

Optimisation of referral networks and severe asthma management

The bottleneck of recognising and treating severe asthma early is, as highlighted before, related to the lack of appropriate referral of patients to specialist care. Across the regional working groups, it became apparent that there is an unmet need for standardisation of the referral pathway leading to early

TABLE 3 Core principles from the charter to improve patient care in severe asthma

1	I deserve a timely, straightforward referral when my uncontrolled asthma cannot be managed in primary care
2	I deserve a timely, formal diagnosis of my severe asthma by an expert team
3	I deserve support to understand my type of severe asthma
4	I deserve care that reduces the impact of severe asthma on my daily life and improves my overall quality of care
5	I deserve not to be reliant on oral corticosteroids
6	I deserve to access consistent quality care, regardless of where I live or where I choose to access it

identification of patients with severe or difficult-to-treat asthma. In most healthcare systems, it could be several years before a patient who suffers multiple asthma attacks is referred to specialist care. In 2018, a group of severe asthma specialists and patient advocacy group representatives, concerned with the current patient care, published a patient charter for severe asthma [17]. This document consists of six core principles (table 3) with the aim of mobilising national governments, payer policymakers, industry partners, healthcare providers and patients or caregivers to address the unmet need in severe asthma and ultimately improve patient care.

In Spain, Germany and Italy, action plans for the management of asthma have been relatively common. Throughout Europe, in countries where coordinated asthma management programmes have been initiated, clear improvements in patient care have been reported [18]. Successful programmes tend to incorporate measures to facilitate early diagnosis and introduction of first-line treatments, establish long-term disease control, promote self-management and improve education and awareness among health providers.

Identification and use of biomarkers and phenotypes in daily clinical practice

The participants of this forum were in broad agreement that phenotype identification will have a major impact on the management of severe asthma in the next 20 years. GINA guidelines already refer to phenotype-guided add-on treatment in their step 4 of treatment with biological therapies [19]. Early identification of patients through phenotyping could provide further benefits and improve asthma control earlier in the referral pathway. In general, biomarkers, exacerbation history and age of asthma onset were highlighted as the most important factors in the identification of asthma phenotypes. Indeed, the distinction between early and late onset of the disease (childhood *versus* adulthood) and the incorporation of biomarkers into the phenotyping process have been key in the phenotypic characterisation of asthma [15, 20]. In terms of clinical practice, blood eosinophils and *F*ENO were identified as commonly used biomarkers. Eosinophil-guided therapy has been shown to improve clinical outcomes, as demonstrated by the reduction in the number of severe exacerbations compared with therapy that is guided by symptoms and lung function [21].

The need for biomarkers that can be used to predict and define endotypes was also discussed during the forum. The phenotyping process needs to be refined in order to better measure or make inferences about the underlying biological endotypes [22]. The long-term stability and reproducibility of biomarkers were discussed as one of the key challenges in their identification; for instance, the stability of eosinophils should be established both over time and during exacerbations. Furthermore, the impact of current inhaled or oral steroid therapy has to be taken into account. Crucially, there is a need to determine when eosinophils are acting as the driver of the disease and when they are not. A recent study has shown that blood eosinophil count was a good predictor for the likelihood of exacerbations; it was observed that patients with a blood eosinophil count >400 cells·μL^{-1} are 1.4-fold more likely to have two or more exacerbations [23].

Interestingly, profiling of volatile organic compounds (VOCs) was selected by the experts at the forum as one of the most important potential biomarkers for the future. VOC profiling has been shown to have diagnostic performance in asthma similar to that of *F*ENO and lung function measures [24]. It has also been shown to be effective in enabling discrimination between early- and late-onset asthma and between asthma with fixed airways obstruction and chronic obstructive pulmonary disease (COPD) [25]. The potential of VOC profiling as a biomarker goes beyond diagnosis and patient identification; it could potentially be used to predict treatment response, as it has been shown that VOC profiling adequately predicted responsiveness to steroid therapy [26].

Several studies addressing the use of biomarkers with efficacy in severe asthma are ongoing or have been completed in recent years [27–30]. Focusing on the biology of the four clinical independently validated easy-to-access Airways Disease Endotyping for Personalized Therapeutics (ADEPT) asthma phenotypes

may provide the foundation for including the right biomarkers in clinical practice [29]. However, single or at times clustered biomarkers have had limited success in predicting the disease course and the therapeutic efficacy of medication in children [28]. This suggests that further research on how biomarkers shape respiratory disease outcomes in younger populations is needed [31, 32].

In summary, there is an emerging need to better understand the clinical relevance of phenotypes and biomarkers, and how biomarkers identified in the laboratory could best be utilised to drive patient identification, early asthma recognition and, ultimately, treatment decisions. Composite phenotypes may be more accurate and reproducible than individual phenotypes; for instance, the treatment responsiveness phenotype model is based on a number of clinically relevant characteristics, such as symptoms, lung function, airway responsiveness, visits to the emergency department and hospitalisations, and OCS bursts [33].

Treatable traits

The use of treatable traits to guide treatment decisions and monitor treatment response is becoming increasingly important. Experts at the forum identified eosinophilic airway inflammation as the currently most important treatable trait, although it was noted that patients have many other potential pulmonary and non-pulmonary treatable traits, and it is not always obvious which one is driving disease-associated morbidity. Treatable traits are intrinsically linked with predictive biomarkers, endotypes and phenotypes, and constitute traits that are modifiable with resulting patient benefits [34, 35]. The vast majority of experts at the forum agreed that eosinophilic airway inflammation and airflow limitation will continue to be the most relevant treatable traits for the next 20 years. For example, blood eosinophil count (a biomarker that is one of the predictors of the response to benralizumab [36] or omalizumab [37]) can be considered a treatable trait that is identifiable, modifiable and able to predict response to treatment. Similarly, F_{ENO} has also been shown to be useful in supporting the diagnosis of asthma and predicting the response to inhaled steroids [38] and to dupilumab [39]. Treatable traits were introduced in the literature as a potential label-free precision medicine approach to the management of chronic airway diseases, including severe asthma [34]. Agusti *et al.* [34] highlighted that treatable traits take into account the complexity of severe asthma and COPD, which consequently provides an adaptable option for all levels of care as opposed to the rigid diagnostic label approach. Nevertheless, treatable traits remain far from being effectively incorporated into clinical practice, and the key challenges in this context were identified (table 4). The definition and identification of treatable traits need to be refined, which will rely on new trial designs that prioritise this goal. Ultimately, changes in the guidelines would need to be implemented, with a focus on effectively identifying and using treatable traits.

Monitoring treatment response and addressing the lack of adherence to medication

Overcoming the asthma paradoxes and poor adherence to medication in patients with severe asthma

Asthma paradoxes and poor adherence to medication [40] were identified by attendees at the forum as key challenges in the management of severe asthma. Based on the number of prescription refills, non-adherence in patients with severe asthma has been estimated to be close to 50% [41–43]. This ongoing problem of patients not taking their medications as prescribed contributes to the difficulty in treating asthma. In fact, adherence to medication should always be investigated, particularly before patients are diagnosed with severe asthma. In addition, non-adherence to medication should be addressed differently according to the disease severity. Studies have shown that a high degree of adherence is associated with a lower risk of severe asthma exacerbations, suggesting that adherence is a major contributor to asthma control [44]. In fact, it has been suggested that monitoring adherence with electronic smart inhalers may be of great value [45, 46]. More recently, the ASCONA study demonstrated that testing adherence to inhalers may be useful for identifying poor adherence as a potential reason for

TABLE 4 Key challenges in incorporating the use of treatable traits in the management of severe asthma

Education of non-specialists and patients
Better identification of patients with severe asthma
Regional standardisation of the referral pathway
Real-life identification and application of phenotypes and biomarkers in clinical practice
Further evidence on treatable traits
Understanding the clinical relevance of biomarkers and phenotypes
Understanding the value of combining different biomarkers and establishing criteria for their combination

poor asthma control. The study also highlighted that physicians may be overestimating adherence among their patients [47]. Education and increasing the awareness of patients and primary care physicians through initiatives, the media and online resources were suggested as important measures for addressing poor adherence. Early initiation of treatment with biologics was also suggested as a way to improve adherence to medication. Also highlighted was the significant proportion of patients who feel that their asthma is well controlled when in reality this is not the case, as measured by objective parameters and according to the specialists. A recent study in difficult-to-treat patients who were eligible for biologics reported non-adherence levels close to 60%, in line with previous studies [48].

Guided self-management has been identified as an element of strategies included in successful national asthma management initiatives in Europe [18]. It was the opinion of some of the participants at the forum that home administration of biologics could also be important for improving medication adherence. More generally, a systematic analysis of 18 studies including 800 000 people across six countries demonstrated that interventions that adopted processes involving self-management that directly simultaneously target patients, healthcare professionals and organisations resulted in improvements in clinical outcomes [49].

The need to improve awareness of asthma among the general population, GPs and specialist asthma centres was highlighted, particularly by participants from Italy. As part of the Global Alliance against Chronic Respiratory Diseases, Italy has committed to prioritising respiratory disease prevention through the prevention of risk factors by involving healthcare professionals, patients and policymakers [50].

An example of a successful systematic asthma strategy in Europe is Finland's comprehensive nationwide asthma programme. Undertaken between 1994 and 2004, the programme involved raising awareness of asthma and its management among patients and physicians, which resulted in estimated asthma-related cost savings of EUR 300–600 million per year by 2010 [51].

Individualisation of treatment response monitoring

Several working groups at the forum highlighted that there is (or should be) a shift away from the one-size-fits-all approach in the monitoring of treatment responses. Instead, an approach based on the individual patient's characteristics should be adopted, taking into account age, clinical presentation, disease severity and different comorbidities. Therefore, it may be preferable to consider treatment responses on a case-by-case basis rather than using general criteria for all patients. Identifying the right biomarkers that enable the prediction of patients who are (or are likely to be) non-responders would be an important step towards refining how treatment response is monitored.

In the PRACTALL consensus document prepared by the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology, the utmost importance of adopting a precision medicine approach in the management of allergic diseases was highlighted [52]. According to this document, establishing a rich framework of recognised biomarkers, disease pathogens and well-defined endotypes will allow for better monitoring of treatment response and management through pathway-specific approaches [52].

The time required to assess treatment efficacy in a patient with severe asthma also needs to be defined. Throughout the forum, the experts suggested that 3 months should be the minimum, although some of the participants recommended allowing up to 6–12 months for assessing whether or not a patient's severe asthma is controlled with a given treatment. After the introduction of a biological therapy, it was suggested that the patient should be monitored every 3 months. However, patient follow-up as well as time to monitor treatment response are closely related to the national healthcare system, referral network and reimbursement policies of the respective countries. Therefore, the design of observational studies that address the topic of treatment response may differ between countries due to different practices.

Moreover, the attending experts highlighted that it is necessary to better understand and define the goal of therapy for each patient and to ensure that the targets of the treatment are correctly chosen on an individual basis. Exacerbations remain the cornerstone for evaluating the efficacy of response to a biological therapy, but an increasing number of specialists acknowledge the importance of tailoring the monitoring of treatment response to individual requirements and specific objectives set for each patient. Although a number of patient-reported outcome measures are increasingly being used worldwide, a systematic review covering studies from 1990 to 2013 demonstrated that additional work is required to define appropriate patient-reported outcome measures that can be used in both research and clinical practice [53].

While asthma control has typically been evaluated on the basis of symptoms, lung function and exacerbations, it was noted that measures beyond forced expiratory volume in the first second (FEV_1), such as airway inflammatory markers, immune monitoring, clinical and functional assessments, quality of life and the association between sputum cell counts and exacerbations, may provide a more comprehensive evaluation of the response to treatment [54–56].

What is a good tool for monitoring treatment response to biologics?

The Asthma Control Questionnaire (ACQ) measures the quality of asthma control by including questions on symptoms, reliever medication use and lung function, and may be used to assess the efficacy of asthma treatments. The use of the ACQ is recommended in international guidelines and it is a well-established tool in clinical trials. Assessments based on the full ACQ and on shortened versions have been carried out in different patient populations and have been validated as predominantly robust and effective [57–59], even in children [60]. The advantages of the ACQ over a daily asthma control diary have also been supported in a study that directly compared the two; it was observed that the ACQ demonstrated better discriminative and evaluative measurement properties than the diary [61]. However, a systematic meta-analysis of 21 studies with 11 141 participants, published in 2013, suggested that using the Asthma Control Test (ACT) may be preferable to the ACQ in clinical practice. This study suggested that despite having demonstrated good diagnostic performance in assessing asthma control, the applicability of the ACQ and the ACT is different in clinical research and in clinical practice [62]. Therefore, it is important to re-assess the potential and applicability of currently available tools, particularly in terms of capturing improvements driven by new treatments such as biologics.

Furthermore, it will be imperative in the future to identify the right additional measures for evaluating treatment response, especially as more therapeutic options become available and the understanding of how biomarkers, phenotypes and treatable traits define disease progression evolves. Overall, although the right tools may be available from a technical perspective, there is still a need to better understand how to use these more effectively to improve clinical practice. For instance, the possibility of developing a standardised approach on the basis of a detailed algorithm was put forward as a future option for improving the monitoring of treatment responses. Lastly, the monitoring of patient-specific adverse events and other comorbidities should also be considered; this will require close communication between different healthcare providers (*i.e.* GPs, respiratory specialists and hospitals).

Initiating biological therapies

Strategies for eliminating the use of OCSs

Throughout the forum, the participants emphasised that biologics are currently often introduced too late, especially when discussed in the context of oral steroids. The dependence on oral steroids experienced by many patients with severe asthma was identified as a key challenge in the current management of the disease. Chronic OCSs are prescribed to a large proportion of patients; data from the UK show that 57% of patients on the British Thoracic Society Difficult Asthma Registry were reported to be on daily OCSs [63]. Similarly, OCSs are also widely used in children with asthma. A retrospective study between 2011 and 2015 involving more than 60 000 children demonstrated that more than 40% of them had at least one occurrence of OCS dispensing [64].

In line with this, the faculty members agreed that it is time for wider adoption of OCS-sparing strategies by physicians. Patients treated with OCSs experience a higher rate of comorbidities [65, 66] and are at a higher risk of all-cause mortality [67], with 93% of patients with severe asthma experiencing at least one OCS-related comorbidity [65]. During a panel discussion on OCS use, the experts highlighted that it is a realistic goal to eliminate chronic use of OCSs in the treatment of severe asthma in the future. The forum participants were in agreement that, given the opportunity, they would switch an OCS-dependent patient to a biologic, and the vast majority agreed that they would taper OCS doses in a patient on a biologic. However, an interesting question raised at the meeting was whether burst therapies of oral steroids are safe and effective for treating exacerbations occurring in a patient who is already receiving treatment with biologics; this is an area in need of further study.

Nevertheless, the potential of biologics to reduce OCS use while providing adequate asthma control has been demonstrated in trials [3, 4, 6], supporting the idea that treatment with biologics could alleviate the adverse impact of OCSs on patients with severe asthma. In the ZONDA trial, the reduction in the final OCS daily dose was four times greater with benralizumab compared with placebo [4]. Although it is a common perception that use of OCS therapies may be necessary to treat hospitalised patients, the rates of asthma exacerbations requiring hospitalisation or emergency department visits were decreased with benralizumab treatment compared with placebo, without the need for OCS use in previously OCS-dependent patients [4].

Participants highlighted the need for a structured study to evaluate the effect of biologics on OCS use in both acute and chronic settings, and it was recommended that, in these contexts, patients should be followed up for at least 1 year.

The lack of evidence regarding the use of biologics during pregnancy was also noted during the forum. Corticosteroids are associated with multiple comorbidities and adverse events [65–67] and linked to increased non-asthma-related medication costs [68], but they are routinely used in pregnant women.

However, there is currently no justification for avoiding the use of biologics in these patients. Nonetheless, throughout the discussion, there was a broad agreement that more data are required to establish the use of biologics in pregnant women.

Precision medicine

The precision medicine approach based on using biomarkers and treatable traits to develop and select disease-modifying strategies that are tailored to individual patients has great potential. However, the specificity required to allow for early identification and targeted treatment in airways disease is still lacking. For instance, eosinophil measurements predict responses to anti-IL-4/IL-13, anti-IL-5 and anti-IgE antibodies without giving a clear indication of which antibodies may be the best option for different patients [52, 69]. A composite approach incorporating targeted biomarkers, treatable traits and phenotypes may be a way to overcome such barriers. The utilisation of large population datasets to identify the right endotypes and biomarkers may be another option for enabling early diagnosis, improved management and monitoring of response to treatment in patients with severe asthma [70]. Similarly, a marked improvement in health status and quality of life has been reported following a multidimensional intervention based on a number of treatable traits and biomarkers, such as levels of eosinophils, neutrophils and C-reactive protein in different subgroups of patients, and which included a respiratory questionnaire [71]. Additionally, a personalised care plan in this study was associated with improved quality of life in 82.3% of patients, illustrating the benefit that a precision, composite approach could have in patients with severe asthma.

The participants of the forum were in agreement that a precision medicine approach driven by treatable traits may be the new standard approach in the near future. However, there is still room for more evidence on treatable traits, in terms of their identification and how they can be utilised to guide severe asthma management. Several trials are currently ongoing, which focus on more accurate identification of severe asthma phenotypes (ClinicalTrials.gov, identifier NCT01623089), the clinical and molecular phenotypes in adult asthmatics (ClinicalTrials.gov, NCT01718197 and NCT02419274) and in children with wheeze and asthma (ClinicalTrials.gov, NCT02496468) [32], precision medicine interventions based on patient phenotypes, endotypes and biomarkers [22], and the identification of phenotypes in COPD (ClinicalTrials.gov, NCT02760329). A study assessing potential real-life factors that distinguish responders to biologics from non-responders was also recommended.

The potential of biologics as disease modifiers

Asthma pathogenesis includes structural changes of the airways that are characterised by increased thickness of the subepithelial reticular basement membrane, increased mass of airway smooth muscle, angiogenesis and goblet cell hyperplasia, which contribute to irreversible loss of lung function [72] as a result of airway remodelling. It is thought that biological therapies could act as disease modifiers by preventing airway remodelling, as it has been shown that treatment with an anti-IL-5 resulted in the reduction of the incorporation of proteoglycans in a human airway wall [73]. Moreover, it has also been shown that treatment of a murine model of asthma with an anti-IL-5 prevented the development of subepithelial fibrosis [74]. These results are encouraging; however, more research is warranted.

During the forum, the participants discussed the potential of a study designed to determine the effects of long-term treatment with biologics on airway remodelling in severe asthma. The study would also be informative in relation to the identification of biomarkers reflective of airway remodelling and clinically relevant in the monitoring of treatment response. It is thought that such a study would show whether biologics are acting as disease modifiers, which is still yet to be proven. In order to progress towards remission of asthma, it is imperative that airway remodelling is addressed.

TABLE 5 The future of asthma management: scientific questions that need to be addressed

How are acute and chronic oral corticosteroids managed once biologics are initiated in a real-life setting?
How should a second-line biological treatment be chosen if a patient fails with first-line respiratory biological therapy?
What are the different sub-phenotypes of non-eosinophilic asthma?
Can the natural course of the disease be modified by early intervention with anti-interleukin-5?
What is the effect of biological therapies on airway remodelling?
Could there be a beneficial impact of biologics on the cost of treatment through home care delivery in the severe asthma population?
What real-life factors could be used to distinguish between high and low responders to biologics?
What is the effect of using biologics in an acute asthma setting?

The era of biologics is shaping the management of severe asthma in new ways; however, more research is needed to better understand how patient identification, asthma management, treatment responses and reduction of OCS use can be achieved in the future. A number of key areas requiring further investigation were identified at the forum (table 5), such as the use of biomarkers and phenotypes in the management of acute asthma and the selection of biologics for the right patients at the appropriate time.

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