Unmet Needs in Severe Asthma Subtyping and Precision Medicine Trials Bridging Clinical and Patient Perspectives

Salman Siddiqui¹, Loren C. Denlinger², Stephen J. Fowler³, Praveen Akuthota⁴, Dominick E. Shaw⁵, Liam G. Heaney⁶, Louise Brown⁷, Mario Castro⁸, Tonya A. Winders⁹, Monica Kraft¹⁰, Scott Wagers¹¹, Michael C. Peters¹², Ian D. Pavord¹³, Samantha Walker¹⁴, and Nizar N. Jarjour²

¹National Institute for Health Research (NIHR) Respiratory Biomedical Research Centre, College of Life Sciences, University of Leicester, Leicester, United Kingdom; ²Allergy, Pulmonary, and Critical Care Division, Department of Medicine, University of Wisconsin–Madison, Madison, Wisconsin; ³Division of Infection, Immunity, and Respiratory Medicine, School of Biological Sciences, The University of Manchester and NIHR Biomedical Research Centre, Manchester University National Health Service Foundation Trust, Manchester, United Kingdom; ⁴Pulmonary Division, Department of Medicine, University of California–San Diego, La Jolla, California; ⁵NIHR Biomedical Research Centre, Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, United Kingdom; ⁶Centre for Experimental Medicine, Queens University Belfast, Belfast, United Kingdom; ⁷Medical Research Council Clinical Trials Unit at University College London, Institute of Clinical Trials and Methodology, London, United Kingdom; ⁸Division of Pulmonary and Critical Care Medicine, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri; ⁹Allergy and Asthma Network, Global Allergy and Asthma Patient Platform, Vienna, Austria; ¹⁰Department of Medicine, University of Arizona College of Medicine, Tucson, Arizona; ¹¹BioSci Consulting, Rijksweg, Belgium; ¹²Division of Pulmonary and Critical Care Medicine, Department of Medicine and the Cardiovascular Research Institute, University of California San Francisco, San Francisco, California; ¹³Respiratory Medicine Unit, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom; and ¹⁴Asthma UK and Edinburgh University, Edinburgh, United Kingdom

ORCID ID: 0000-0003-3770-7870 (S.S.).

Understanding Asthma Subtypes: Unmet Need and Research and Innovation Priority

Asthma affects 300 million people worldwide. Most patients with chronic asthma respond well to currently available therapy. However, approximately 3–5% of patients have severe asthma (although the exact prevalence varies significantly between reported studies), with persistent symptoms and/or reduced lung function despite maximum inhaler therapy leading to significant personal and societal morbidity (1). Severe asthma presentation is variable because of the heterogeneity in underlying mechanisms (2); therefore, there are broad priorities in severe asthma ranging from preventing exacerbations to improving lung function, exercise capacity, and quality of life.

The NHLBI held an Asthma Research Strategic Planning workshop in 2014 to help accelerate the translation of new discoveries to the care of patients with severe asthma. The workshop called on investigators to

build on recent advances in technology and asthma pathobiology to improve severe asthma management, using precision interventions to optimize patient outcomes and reduce the public health burden of asthma (3). More recently, the European Asthma Research and Innovation Partnership Program evaluated the research priorities for asthma through a process of multistakeholder (including patients and patient advocacy groups) consensus workshops (4). Fifteen priorities were identified for asthma research, of which the top priority was to “identify, understand and better classify the different forms of asthma.” The workshops highlighted several critical barriers to personalized medicine in asthma, including the development of better companion diagnostics of asthma subtypes, as well as structural barriers to effectiveness trials, including lack of data integration across primary and specialty care providers, as well the need for real world effectiveness trials and large-scale data registries.

In this Perspective, we discuss the critical gaps in understanding asthma

subtypes and outline our perspective on both current and potential future research in severe asthma. Furthermore, we will discuss the value of, and barriers to, large-scale pragmatic effectiveness trials. Finally, we highlight the importance of collaboration in interdisciplinary large-scale consortia to enable precision medicine trials.

Bridging Critical Gaps in Understanding of Asthma Subtypes

The Definition of Severe Asthma

Current definitions of severe asthma are based on the requirement for high-dose inhaled corticosteroid treatment and concurrent long acting β_2 -agonists (ICS/LABA), which may or may not accomplish disease control (1). These definitions emphasize treatment failure with ICS/LABA, the causes of which can vary widely and are influenced by patient perception, adherence to inhaler therapy, the type of airway inflammation, and comorbidities. Although current guidelines

(Received in original form September 30, 2018; accepted in final form February 6, 2019)

Correspondence and requests for reprints should be addressed to Salman Siddiqui, M.R.C.P., Ph.D., NIHR Biomedical Research Centre (Respiratory Theme), Respiratory BRU Building, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK. E-mail: ss338@le.ac.uk.

Am J Respir Crit Care Med Vol 199, Iss 7, pp 823–829, Apr 1, 2019

Copyright © 2019 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201809-1817PP on February 6, 2019

Internet address: www.atsjournals.org

endorse attempts to optimize comorbidities before making a severe asthma diagnosis, comorbidities may not be easy to address or can recur after they have been treated effectively. In addition, ICS/LABA failure is based on an historical precedent of existing therapy, which will no doubt change with the advent of newer therapies, such as oral (or inhaled) small-molecule inhibitors (targeted modulators).

Current therapeutic strategies in severe asthma target biological traits in the context of disease expression (e.g., monoclonal therapies for patients with eosinophilia and frequent exacerbations). Further complexity arises when recognizing that a single phenotype (e.g., the presence of eosinophilia) may be driven by multiple biological mechanisms (e.g., upstream type 2 driver cytokines, such as thymic stromal lymphopoietin [TSLP], or downstream effectors, such as IL-5, or both, promoting dysregulated type 2 immunity [endotypes]) (2). In addition, a single endotype (e.g., airway remodeling) may be associated with multiple phenotypes (variable symptoms

and, ultimately, impaired lung function and reduced exercise capacity).

Targeting Type 2 Inflammatory Pathways

Eosinophilic airway inflammation is associated with up-regulation in any or all of the classic type 2 cytokines (IL-4, -5, and -13), which may in themselves be associated with allergic IgE-driven disease and can therefore be targeted by monoclonal antibodies against any of these components, most commonly IgE or eosinophils (5, 6).

Several biomarkers have been used to define type 2 disease, but in the absence of head-to-head trials, how can we choose the specific feature to target? For example, in an atopic individual with elevated IgE, fractional exhaled nitric oxide, and eosinophilia, who does not improve on treatment with one anti-IL-5 antibody, should we try IL-5R (IL-5 receptor) inhibitor therapy, switch to an IL-4/13 inhibitor, or use anti-IgE? Or should we combine biologics? An additional challenge is the suppression of some of

the biomarkers by high-dose inhaled (or systemic) corticosteroid therapy masking the phenotype of interest (Figure 1).

The development of monoclonal antibodies against upstream targets of type 2 immunity such as TSLP and IL-33/ST2 receptor may paradoxically challenge the concept of personalized medicine, as early evidence with these compounds suggests that patients both with and without clinically detectable type 2 disease respond to treatment (6, 7).

There are drugs in development that can regulate bone marrow eosinophil differentiation via non-IL-5 receptor-dependent mechanisms such as dexampipexole, (8) and tyrosine kinase inhibitors such as imatinib, JAK-STAT (Janus kinase-signal transducer and activator of transcription) inhibitors (9, 10) that may have benefits in asthma independent of targeting type 2 cytokines. Consequently, basic research to fully elucidate type 2 pathways in severe asthma, combined with the development of more precise companion diagnostics that dissect these pathways, are urgently required.

Figure 1. Existing and emerging therapeutic approaches to target type 2-high severe asthma. Specific therapies are outlined in the context of commonly rehearsed paradigms of type 2 disease in the airway mucosa of patients with severe asthma. The proliferation of licensed therapeutic approaches alongside a thriving pipeline of earlier-phase therapies will require a number of approaches to bridge evidence gaps that extend beyond conventional randomized controlled trials. These include large pragmatic trials and real-world severe asthma multinational registries embedded within multinational research consortia. APC = antigen-presenting cell; ILC2 = group-2 innate lymphoid cell; JAK/STAT = Janus kinase-signal transducer and activator of transcription; KIT = proto-oncogene c-kit; PGD₂ = prostaglandin D₂; TH = T-helper cell; TSLP = thymic stromal lymphopoietin; TSLPR = thymic stromal lymphopoietin receptor.

Non-type 2–driven disease is currently defined by the absence of clinically measurable type 2 inflammation. Given the lack of specific biomarkers and heterogeneity of patient populations, targeting non-type 2 severe asthma remains problematic (11).

Potential Approaches to Targeting Non-Type 2 Severe Asthma

Potential mechanisms leading to non-type 2 severe asthma include T-helper cell type 17 (Th17) immunity with production of IL-17 family cytokines (IL-17A, IL-17F, and IL-22) that play an important role at mucosal barriers in antimicrobial defense (12). Clinical trials of IL-17 inhibition demonstrated disappointing results (13); however, monoclonal antibodies targeting key cytokines (IL-6, IL-21, and IL-23) that contribute to Th17 cell formation are being evaluated as treatment for neutrophilic diseases (e.g., Crohn's disease and psoriasis) (14).

Recent evidence suggests that type 2 and Th17-dependent immunity may be reciprocally related in asthma. In particular, treatment with corticosteroids for asthma may promote the emergence of Th17 immunity (15). Neutrophils are key effector cells in non-type 2 asthma, because of the potent induction of neutrophil chemoattractant CXCL8 (chemokine [C-X-C motif] ligand 8) produced by a range of cells that express the IL-17 receptor (e.g., eosinophils, fibroblasts, and epithelial cells). However, a recent trial of the oral neutrophil CXCR2 (C-X-C motif chemokine receptor 2) antagonist in patients with a blood neutrophilia did not demonstrate an impact on exacerbations despite its clear biological effect demonstrated by a clear dose-dependent reduction in circulating neutrophil counts (16). Therefore, therapeutic approaches that extend beyond modifying inflammation may be required.

There is a well-recognized association between microbes and asthma, with several bacterial species (e.g., *Haemophilus influenzae* and *Moraxella catarrhalis*) cultured from the airways of stable patients with asthma (17).

However, in recent years, 16S ribosomal RNA gene sequencing, a culture-independent technique, has revolutionized the field of microbiology with the identification of a resident lung microbiome. Enrichment of members of the Proteobacteria phylum have been described as consistent features in

sputum samples of patients with mild to moderately severe asthma (reviewed in Reference 18) with a dominance of the genera *Haemophilus*, and *Streptococcus* and *Moraxella catarrhalis* in severe asthma (17, 18). More recently, patients with severe asthma with a neutrophilic phenotype were found to have an abundance of Proteobacteria (*Haemophilus* and *Moraxella*), loss of microbial diversity, and a distinct airway ecology when compared with patients who had eosinophilic asthma (19). Furthermore, Th17 epithelial gene expression was associated with Proteobacteria dysbiosis (20). These observations suggest that dysbiosis of Proteobacteria in the asthmatic airway may promote Th17, neutrophilic, corticosteroid-insensitive inflammation.

A recent placebo-controlled clinical trial of azithromycin in moderate to severe asthma demonstrated the largest impact on exacerbations in patients who had frequent exacerbations or a sputum culture that was positive for bacteria. The effect on exacerbations was seen in patients across the spectrum of blood eosinophilia, implicating pathogenic bacteria and airways dysbiosis as a driver of asthma exacerbations independently of inflammatory phenotype (21). Interestingly, bacterial diversity of the microbiome in sputum samples was not a predictor of response to azithromycin, highlighting the need for robust biomarkers of airways dysbiosis in asthma trials that attempt to target the microbiome. Furthermore, azithromycin has well-recognized antiviral and antiinflammatory properties, rendering it difficult to dissect the precise mechanism of its effect on exacerbations.

As a consequence, further trials are required to identify whether modification of specific patterns of airway dysbiosis (e.g., Proteobacteria dysbiosis), with antibiotics that do not have well-recognized antiviral or antiinflammatory properties, reduces asthma exacerbations in patients with severe asthma. Furthermore, the relationship between dysbiosis and the host (e.g., impact on structural lung damage over time and inflammatory response) needs to be further characterized in longitudinal clinical studies.

Several novel approaches beyond antibiotics that may modify dysbiosis, including phage therapies, prebiotic nutrients, microbe-derived products (bacterial extracts, immune stimulants), and specific live microbial species (probiotics)

may represent novel therapeutic avenues in the future.

Targeting the Airway Smooth Muscle

Airway smooth muscle (ASM) expansion and dysfunction are important aspects of the asthma paradigm and drivers for airway hyperresponsiveness and symptoms. However, there are few therapies beyond bronchodilators that target this aspect of disease. Bronchial thermoplasty (BT) offers the potential opportunity to treat this aspect of disease, as clinical trials have reported reduction in exacerbations with acceptable safety (22). A recent global registry across 19 centers has demonstrated real-world evidence of BT efficacy, with reductions in healthcare utilization and improved clinical outcomes 1 year post procedure that were comparable to controlled trials (23). From a mechanistic perspective, imaging studies have demonstrated that BT significantly reduces airway wall thickness (without a change in airway luminal or total airway diameter) and reduces gas trapping (24). Interestingly, a recent computational modeling study suggests that the thermal energy delivered by the thermoplasty catheter does not fully penetrate the ASM bundle with an impact on epithelial wound healing (25), raising the intriguing possibility that the ASM effects seen in biopsy studies of BT may also include non-smooth muscle target cells, such as airway epithelial cells. An alternative hypothesis supported by histological data from bronchial biopsies is that the effect of BT is mediated by its impact on cholinergic nerves within the airway epithelium (26).

Currently, the place of bronchial thermoplasty in the treatment pathway for severe asthma needs better definition. Furthermore, newer approaches, such as targeted bronchial thermoplasty to remodeled airways and using BT paired with monoclonal therapy, offer potentially intriguing possibilities, but their outcome is unknown at this point.

Targeting Mucus Hypersecretion

An alternative target in asthma that may occur in both the presence and absence of type 2 inflammation is mucus hypersecretion. Recently, quantitative imaging has been applied using computed tomography to develop validated mucus plugging scores in severe asthma (27); with advent of novel inhaled and oral mucolytics (28) and biologics that target IL-13–driven

goblet cell metaplasia, it will be interesting to see whether stratified approaches targeting mucus become more prevalent in severe asthma over the coming years.

Targeting the Systemic Inflammation of Obesity

Obesity is a key risk factor for developing severe asthma, and patients with severe asthma are frequently characterized by high body mass index and other obesity-associated comorbidities. Because obesity induces a state of low-grade systemic inflammation, it is intriguing to consider the possibility that obesity-associated inflammation may cause airway pathology in asthma. In support of this hypothesis, recent work demonstrated that systemic increases in plasma IL-6 levels are associated with poor outcomes of asthma control, including worse asthma symptom scores, lower lung function, and increased asthma exacerbation rates (29). Furthermore, a recent randomized sham controlled clinical trial conducted over 3 months comparing a structured weight loss intervention program with or without exercise (aerobic and resistance training) (30) demonstrated broad benefits (compared with sham) with improvements in asthma control and greater weight loss in the exercise group. The exercise group also demonstrated a reduction in a range of proinflammatory chemokines (e.g., IL-6, IL-10) and adipokines (e.g., leptin and adiponectin). Thus, treatments (both pharmacological and nonpharmacological) that inhibit this systemic inflammation of obesity are potential targets for severe asthma.

Proliferation of Therapeutic Choice: Impact on Clinical Trial Design

The recognition of the severe eosinophilic asthma phenotype (5) and the proliferation of monoclonal antibody-based therapeutics to target this inflammatory phenotype (Figure 1) pose several challenges. Several antibody-based therapeutics targeting IgE (31) and IL-5/IL-5 receptor are licensed (32), with therapeutics targeting IL-4/13 (33), oral prostanoid DP2 receptor, Chemoattractant Receptor-homologous molecule expressed on TH2 cells antagonists (34), and proximal targeting of type 2 pathways with Anti-TSLP (7) either having completed phase III trials and

awaiting licensing or undergoing phase III trials.

In addition, the increasing pharmacopeia in severe eosinophilic asthma, promise of early-phase antibody-based therapeutics, biosimilars, and non-antibody-based oral small molecule kinase inhibitors (9, 10), coupled with the need for cognate testing of these agents in clinical trials, may complicate the design and treatment choice in future clinical trials. An early exemplar of competing choice in severe eosinophilic asthma is that approximately 50% of patients with severe asthma are typically eligible for both omalizumab and IL-5–targeting biologics (35). In the absence of prospective comparative trials of omalizumab in eosinophilic patients or anti-IL-5 in patients with allergic sensitization, large registry studies and *post hoc* evaluations of existing phase III trials have been performed to determine the optimal of choice of therapy and biomarker(s) in these patients (36, 37). However, these studies have produced conflicting results, with a recent indirect treatment comparison of anti-IL-5 with anti-IL-5R biologics reporting superiority of anti-IL-5 therapy (38). Given the heterogeneity in patient characteristics and study design in these trials, we call for prospective pragmatic clinical trials (including treatment switching trials) with head-to-head comparisons. One such trial currently registered on clinicaltrials.gov (PREDICTUMAB [39])—evaluating the comparative efficacy of omalizumab and mepolizumab in patients eligible for both drugs) is currently underway in the Belgian severe asthma network, with the potential to adapt the trial protocol for other countries according to local licensing criteria. A more formal adaptive trial design has been called for in the National Institutes of Health recently funded study PrecISE (Precision Interventions for Severe and/or Exacerbation-prone Asthma), which is expected to start enrolling patients in 2019. However, such sequential treatment trials are inherently difficult to use for comparing multiple biologics because of the potential for incomplete washout of the first biological agent.

Future challenges in the delivery of severe asthma clinical trials may be predicted by drawing analogies to cancer therapeutics, where pharmacopeia has outstripped the capacity to test new drugs

(40). This issue, when coupled with two additional factors, 1) the proliferation of competing compounds targeting the same biological pathways (e.g., immunotherapies targeting PD-1 (programmed cell death protein 1) in a range of solid organ cancers [41]), and 2) the limited number of patients seen at clinical centers that can conduct such sophisticated trials, are likely to make testing the next generation of severe asthma therapies far more complex without novel approaches to study design and collaborations.

Potential Solutions: Next-Generation Severe Asthma Trials

A potential response to these challenges is the implementation of standardized international severe asthma registries (42) that systematically capture clinical care in severe asthma, to better understand the implications of regional/national variations in care. Such registries would ideally require alignment of data capture to allow curation of data across countries. Additional coupling of disease registries with capability cluster information of individual severe asthma centers and networks within countries would facilitate the conduct of pragmatic clinical trials.

In addition, development of a standardized clinical care pathway framework for severe asthma (43), outlining the key baseline assessment for accurate diagnosis, evaluation of adherence, optimization of comorbidities, and ultimately the position of monoclonal therapies, would facilitate the development of a “standard-of-care arm” in pragmatic severe asthma trials. An ideal care pathway would be a live and iterative document with periodic revisions as evidence becomes available from clinical trials and disease registries. The severe asthma international community has taken steps to develop such a pathway framework, having published several joint guidelines for definition and evidence-based management of severe asthma (1). Furthermore, the European Respiratory Society has established a number of clinical research collaborations across Europe (44) to facilitate pragmatic clinical trials, including a clinical research collaboration in severe heterogeneous asthma.

The delivery of pragmatic trials requires the development of robust early stopping rules when biologics are deemed to be failing. Cognate with this ambition is the requirement to develop theragnostic

biomarkers of treatment response or failure. Promising advances in the field include the development of composite endpoints of asthma deterioration (45) using daily diary data with the potential for digital integration of real-time data on treatment adherence from smart inhalers and connected devices. The potential advantage of such systems is earlier recognition of exacerbation events that fail to meet the international consensus criteria for a moderate to severe exacerbation. The concurrent quantification of controller medication adherence would allow determination of whether apparent lack of efficacy was due to lack of adherence. The development of reproducible biomarkers requires considerable efforts to harmonize protocols across severe asthma trials. One successful example in this area was the Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes–Innovative Medicines Initiative–funded consortium that sought to develop fingerprints and handprints of severe asthma using multiomics approaches (46). Standardization of operating procedures for sample collection across participating

centers for multiplatform omics was an enabler of precision medicine and led to the successful development and “pull through” of a urinary prostanoid (2-3-dinor-prostaglandin F-2 α) for the stratification of omalizumab response or failure in a pragmatic clinical trial delivered in severe asthma centers in the United Kingdom (47). Efforts to allow sample sharing across consortia with appropriate ethics committees’ approval are required at the inception stage of clinical protocols. This is particularly important considering new European general data protection regulations and trans-Atlantic efforts for data sharing and compliance.

The Patients’ Goal(s): “Which Type of Asthma Do I Have and How Can It Be Treated Best with the Fewest Side Effects”?

The final and most important triangulation (beyond addressing trial design methods and structural delivery barriers) factor for successful next-generation severe asthma

trials is the participation of patients. Setting the research agenda in severe asthma must be patient centered, such that the key goals of the scientific community are aligned with those of the patients. In the development of this Perspective article, a workshop with patient advocacy from the Allergy and Asthma Network in the United States identified the critical need to develop therapies for asthma that allow withdrawal of maintenance oral steroids, because of their intolerable and often toxic side-effect profile. Furthermore, the advent of monoclonal therapies highlighted that maintenance oral steroid use should be regarded as a “treatment failure” in severe asthma.

Historically, patient participation in trials has been relatively low (3–5% in cancer) (48), an experience that has been borne out in severe asthma in the authors’ opinion. The development of severe asthma trial networks focusing on pragmatic platform trials should enable patients with severe asthma to receive therapies under a clinical trial indication even when they do not meet the criteria for a licensed monoclonal or enter trials of sequential monoclonal antibodies. An optimal model of care would be to embed

Figure 2. Visual schematic of the potential barriers (challenges of collaboration) and key enablers (process of good collaboration) that drive successful collaboration (result) in research consortia. Many of the potential barriers have been encountered within successful respiratory consortia in severe asthma, such as the Severe Asthma Research Program (29) and Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes–Innovative Medicines Initiative (46) consortia, and in each case key enabling approaches and methods (e.g., developing a shared common vision, task orientation, creating a “safe space” for participation, and frequent communication) led to successful long-term consortium outcomes. We propose that similar approaches that harness diversity with a view to developing a common shared vision are key to delivery of the next generation of pragmatic severe asthma clinical trials within public–private partnerships.

clinical trials within the severe asthma treatment pathway with seamless integration, such that all patients are offered participation in a clinical trial. Such trials may include personalized approaches to treatment selection, nonpharmacological measures such as dietary modifications, interventions to optimize patient adherence, and systematic approaches to addressing comorbid factors before considering biologics. The clinical trials being planned as part of the PrecISE network include such an adaptive platform design that will allow identification of novel therapies that are effective in biomarker-defined patients with severe asthma.

The Need for and the Sociology of Collaboration

In recognition of the growing societal challenges, the complexity of health care, and the need for more precision medicine approaches, the American Academy of Arts and Sciences called for more multidisciplinary research in contrast to “siloed” approaches (49). Future advances in novel therapeutics will necessitate larger collaborations that are best developed by academic, foundation, and industry collaborations (50). There are now approximately 500 life sciences research

consortia (51). There has also been a call for the development of more research and better understanding of “consortium science” (52).

It is somewhat intuitive that multidisciplinary teams have more knowledge, skills, abilities, and access to resources and thereby should perform better. However, just getting multiple disciplines together is not enough. Multidisciplinary teams produce higher-quality innovation only when the team follows a set of processes such as having a shared vision, frequent interactions, encouraged participation, and task orientation (53). Larger teams also produce higher quality innovation, but only when they follow a set of processes (Figure 2). Experience bears this out to be true. The Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes–Innovative Medicines Initiative and Severe Asthma Research Program projects have been deemed as highly successful collaborative projects (54).

Therefore, future joint efforts in severe asthma clinical trials will reach their full potential only if they follow established principles for collaboration in a consortium.

Conclusions

In summary, patients with severe asthma comprise a small proportion of patients

with asthma who have failed the standard treatments with high-dose ICSs and a second controller. The past 3 decades have seen significant strides in improved understanding of the disease pathobiology and development of a number of biologics targeting type 2 inflammation. Despite these major strides, half the patients continue to experience asthma exacerbations and suboptimal control. Therefore, there remain significant major unmet needs in treating patients with severe asthma. Future advances are likely to require parallel advances in biomarker identification and defining endotypes and partnership with patients, the pharmaceutical industry, and payers. The recognition of the important clinical needs and commitment of the funding agencies to support research in this area have opened the doors for exciting potential opportunities for transatlantic collaborations on future clinical trials to optimize care of severe asthma. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Dr. Sushila Natarajan from the University of Leicester, UK, for generating the graphic and image for Figure 1 and Aleksandra Draper from BioSci Consulting for generating Figure 2.

References

- Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, *et al*. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343–373. [Published erratum appears in *Eur Respir J* 52:1352020.]
- Lötvall J, Akdis CA, Bacharier LB, Bjerner L, Casale TB, Custovic A, *et al*. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011;127:355–360.
- Levy BD, Noel PJ, Freemer MM, Cloutier MM, Georas SN, Jarjour NN, *et al*. Future research directions in asthma: an NHLBI working group report. *Am J Respir Crit Care Med* 2015;192:1366–1372.
- Masefield S, Edwards J, Hansen K, Hamerlijnck D, Lisspers K, van der Schee M, *et al*. The future of asthma research and development: a roadmap from the European Asthma Research and Innovation Partnership (EARIP). *Eur Respir J* 2017;49:1602295.
- Buhl R, Humbert M, Bjerner L, Chanez P, Heaney LG, Pavord I, *et al*. Expert Group of the European Consensus Meeting for Severe Eosinophilic Asthma. Severe eosinophilic asthma: a roadmap to consensus. *Eur Respir J* 2017;49:1700634.
- Lloyd CM, Snelgrove RJ. Type 2 immunity: expanding our view. *Sci Immunol* 2018;3:eaat1604.
- Corren J, Parnes JR, Wang L, Mo M, Roseti SL, Griffiths JM, *et al*. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med* 2017; 377:936–946.
- Panch SR, Bozik ME, Brown T, Makiya M, Prussin C, Archibald DG, *et al*. Dexamipexole as an oral steroid-sparing agent in hypereosinophilic syndromes. *Blood* 2018;132:501–509. [Published erratum appears in *Blood* 132:1461.]
- Cahill KN, Katz HR, Cui J, Lai J, Kazani S, Crosby-Thompson A, *et al*. KIT inhibition by imatinib in patients with severe refractory asthma. *N Engl J Med* 2017;376:1911–1920.
- Vale K. Targeting the JAK-STAT pathway in the treatment of ‘Th2-high’ severe asthma. *Future Med Chem* 2016;8:405–419.
- Thomson NC. Novel approaches to the management of noneosinophilic asthma. *Ther Adv Respir Dis* 2016;10:211–234.
- Isailovic N, Daigo K, Mantovani A, Selmi C. Interleukin-17 and innate immunity in infections and chronic inflammation. *J Autoimmun* 2015; 60:1–11.
- Busse WW, Holgate S, Kerwin E, Chon Y, Feng J, Lin J, *et al*. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. *Am J Respir Crit Care Med* 2013;188:1294–1302.
- Clinicaltrials.gov [accessed 2018 Sep 30]. Available from: <https://clinicaltrials.gov/>.
- Choy DF, Hart KM, Borthwick LA, Shikotra A, Nagarkar DR, Siddiqui S, *et al*. TH2 and TH17 inflammatory pathways are reciprocally regulated in asthma. *Sci Transl Med* 2015;7:301ra129.
- O’Byrne PM, Metev H, Puu M, Richter K, Keen C, Uddin M, *et al*. Efficacy and safety of a CXCR2 antagonist, AZD5069, in patients with uncontrolled persistent asthma: a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2016;4:797–806.
- Wood LG, Simpson JL, Hansbro PM, Gibson PG. Potentially pathogenic bacteria cultured from the sputum of stable asthmatics are associated with increased 8-isoprostane and airway neutrophilia. *Free Radic Res* 2010;44:146–154.
- Chung KF. Airway microbial dysbiosis in asthmatic patients: a target for prevention and treatment? *J Allergy Clin Immunol* 2017;139:1071–1081.

19. Green BJ, Wiriyaichai P, Grainge C, Rogers GB, Kehagia V, Lau L, *et al.* Potentially pathogenic airway bacteria and neutrophilic inflammation in treatment resistant severe asthma. *PLoS One* 2014; 9:e100645.
20. Huang YJ, Nariya S, Harris JM, Lynch SV, Choy DF, Arron JR, *et al.* The airway microbiome in patients with severe asthma: associations with disease features and severity. *J Allergy Clin Immunol* 2015;136: 874–884.
21. Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, *et al.* Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;390: 659–668.
22. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL, *et al.*; AIR2 Trial Study Group. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med* 2010;181:116–124.
23. Torrego A, Herth F, Munoz AM, Puente L, Facciolo N, Bicknell S, *et al.* Bronchial thermoplasty global registry: one year results. *Eur Respir J* 2018;52:OA1921.
24. Konietzke P, Weinheimer O, Wielpütz MO, Wagner WL, Kaukel P, Eberhardt R, *et al.* Quantitative CT detects changes in airway dimensions and air-trapping after bronchial thermoplasty for severe asthma. *Eur J Radiol* 2018;107:33–38.
25. Chernyavsky IL, Russell RJ, Saunders RM, Morris GE, Berair R, Singapuri A, *et al.* *In vitro*, *in silico* and *in vivo* study challenges the impact of bronchial thermoplasty on acute airway smooth muscle mass loss. *Eur Respir J* 2018;51:1701680.
26. Pretolani M, Bergqvist A, Thabut G, Dombret MC, Knapp D, Hamidi F, *et al.* Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: clinical and histopathologic correlations. *J Allergy Clin Immunol* 2017;139:1176–1185.
27. Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, *et al.*; National Heart Lung and Blood Institute (NHLBI) Severe Asthma Research Program (SARP). Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest* 2018;128:997–1009.
28. Ehre C, Rushton ZL, Wang B, Hothem LN, Morrison CB, Fontana NC, *et al.* An improved inhaled mucolytic to treat airway mucous obstructive diseases. *Am J Respir Crit Care Med* 2019;199:171–180.
29. Peters MC, McGrath KW, Hawkins GA, Hastie AT, Levy BD, Israel E, *et al.*; National Heart, Lung, and Blood Institute Severe Asthma Research Program. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. *Lancet Respir Med* 2016;4:574–584. [Published erratum appears in *Lancet Respir Med* 6:e10.]
30. Freitas PD, Ferreira PG, Silva AG, Stelmach R, Carvalho-Pinto RM, Fernandes FL, *et al.* The role of exercise in a weight-loss program on clinical control in obese adults with asthma: a randomized controlled trial. *Am J Respir Crit Care Med* 2017;195:32–42.
31. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev* 2014;(1): CD003559.
32. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev* 2017;9:CD010834.
33. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, *et al.* Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018;378:2486–2496.
34. Gøtzsche S, Berair R, Singapuri A, Hartley R, Laurencin MFM, Bacher G, *et al.* Fevipiprant, a prostaglandin D2 receptor 2 antagonist, in patients with persistent eosinophilic asthma: a single-centre, randomised, double-blind, parallel-group, placebo-controlled trial. *Lancet Respir Med* 2016;4:699–707.
35. Schleif F, Brusselle G, Louis R, Vandenplas O, Michils A, Pilette C, *et al.* Heterogeneity of phenotypes in severe asthmatics: the Belgian Severe Asthma Registry (BSAR). *Respir Med* 2014;108:1723–1732.
36. Humbert M, Taillé C, Mala L, Le Gros V, Just J, Molimard M; STELLAIR Investigators. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. *Eur Respir J* 2018;51:1702523.
37. Casale TB, Chipps BE, Rosén K, Trzaskoma B, Haselkorn T, Omachi TA, *et al.* Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. *Allergy* 2018;73: 490–497.
38. Busse W, Chupp G, Nagase H, Albers FC, Doyle S, Shen Q, *et al.* Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: indirect treatment comparison. *J Allergy Clin Immunol* 2019;143:190–200, e20.
39. ClinicalTrials.gov. Study of magnitude and prediction of response to omalizumab and mepolizumab in adult severe asthma (PREDICTUMAB). 2018 Mar 23 [updated 2018 Mar 27; accessed 2018 Sep 30]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03476109?term=predictumab&rank=1>.
40. Kolata G. A cancer conundrum: too many drug trials, too few patients. *New York Times* 2017 Aug 12 [accessed 2018 Jan 8]. Available from: <https://www.nytimes.com/2017/08/12/health/cancer-drug-trials-encounter-a-problem-too-few-patients.html>.
41. Alsaab HO, Sau S, Alzhrani R, Tatiparti K, Bhise K, Kashaw SK, *et al.* PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. *Front Pharmacol* 2017;8:561.
42. Bulathsinghala L, Eleangovan N, Heaney LG, Menzies-Gow A, Gibson PG, Peters M, *et al.* Development of the International Severe Asthma Registry (ISAR): a modified Delphi study. *J Allergy Clin Immunol Pract* 2019;7:578–588, e2.
43. Bousquet J, Brusselle G, Buhl R, Busse WW, Cruz AA, Djukanovic R, *et al.* Care pathways for the selection of a biologic in severe asthma. *Eur Respir J* 2017;50:1701782.
44. Brightling C, Genton C, Bill W, Welte T, Gaga M, Heuvelin E, *et al.* ERS clinical research collaborations: underpinning research excellence. *Eur Respir J* 2018;52:1801534.
45. Fuhlbrigge AL, Bengtsson T, Peterson S, Jauhiainen A, Eriksson G, Da Silva CA, *et al.* A novel endpoint for exacerbations in asthma to accelerate clinical development: a post-hoc analysis of randomised controlled trials. *Lancet Respir Med* 2017;5:577–590.
46. Riley JH, Erpenbeck VJ, Matthews JG, Holweg CTJ, Compton C, Seibold W, *et al.*; Industry Representatives of the U-BIOPRED Study Group. U-BIOPRED: evaluation of the value of a public-private partnership to industry. *Drug Discov Today* 2018;23:1622–1634.
47. Heaney LG, Djukanovic R, Woodcock A, Walker S, Matthews JG, Pavord ID, *et al.* Research in progress: medical research council United Kingdom Refractory Asthma Stratification Programme (RASP-UK). *Thorax* 2016;71:187–189.
48. Bell JA, Balneaves LG. Cancer patient decision making related to clinical trial participation: an integrative review with implications for patients' relational autonomy. *Support Care Cancer* 2015;23: 1169–1196.
49. American Academy of Arts and Sciences. ARISE II: unleashing America's research & innovation enterprise. Cambridge, MA: American Academy of Arts and Sciences; 2013.
50. Ramsey BW, Nepom GT, Lonial S. Academic, foundation, and industry collaboration in finding new therapies. *N Engl J Med* 2017;376: 1762–1769.
51. Consortiopedia [accessed 2018 Sep 30]. Available from: <http://consortiopedia.fastercures.org/>.
52. Papadakis M, Hirsch G. Curing consortium fatigue. *Sci Transl Med* 2013; 5:200f35.
53. Fay D, Borrill C, Amir Z, Haward R, West MA. Getting the most out of multidisciplinary teams: a multi-sample study of team innovation in health care. *J Occup Organ Psychol* 2006;79:553–567.
54. Lancet Respiratory Medicine. A new identity for asthma. *Lancet Respir Med* 2015;3:735.