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Precision medicine and treatable traits in chronic airway diseases - where do we stand?

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Nicola A. Hanania^e, and Zuzana Diamant^{f,g,h}

Purpose of review

To provide an update on the implementation of precision medicine, based on treatable traits and mechanisms, in the daily clinical management of chronic airways diseases.

Recent findings

Recent insights into the complex and heterogeneous nature of chronic airway diseases including chronic obstructive pulmonary disease (COPD) and asthma identified several clinical and inflammatory phenotypes. This shifted the management focus of these diseases away from the prototypic disease labels and paved the way for developing novel targeted therapies.

The concept of precision medicine aims to link the right patient to the right treatment, while minimizing the risk of adverse effects. Several treatable features ('treatable traits') have now been identified for these chronic airway diseases, including pulmonary, extra-pulmonary, and psychological/lifestyle/environmental traits. As the next step, innovative detection techniques should clarify underlying mechanisms and molecular pathways of these treatable traits and novel reliable point-of-care (composite) biomarkers to help predict responders to targeted therapies must be developed.

Summary

Precision medicine links the right patient to the right treatment. Identification of treatable traits in asthma and COPD will help optimize the treatment approach in these heterogeneous diseases. Furthermore, in-depth identification of underlying molecular pathways and reliable biomarkers in chronic airways diseases to guide targeted treatment in individual patients is in progress.

Keywords

asthma, biologics, biomarkers, COPD, small molecules

INTRODUCTION

The paradigm of our understanding of chronic inflammatory airways diseases has gradually shifted away from prototypic disease labels, e.g., asthma and chronic obstructive pulmonary disease (COPD), as introduced by Dr William Osler at the end of the 19th century, to differentiated disease subsets [1,2]. Toward the end of the past century, asthma was regarded as an allergen-driven, T-helper-2-driven disease with mast cells and eosinophils as key effector cells. This concept was primarily tested in experimental mice models and all asthma treatment options were initially tested in humans in the allergen challenge model, reinforced by its good responsiveness to corticosteroids, fair positive predictive value, and excellent negative predictive value for the likely clinical effectiveness of novel antiasthma therapies (albeit based on a highly selected patient population) [3]. Hence, by the end of the 20th century, guidelines advocated a one-size-fits-all

management that included a step-wise treatment approach for chronic airway diseases. However, in the case of asthma, after an initial improvement in

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KEY POINTS

- Chronic airway diseases have a significant impact on the patient and healthcare system and comprise highly complex, and heterogeneous diseases.
- Many patients with chronic airway diseases continue to have symptoms and exacerbations despite current best possible therapy.
- Novel insights and exploration of these diseases have provided a better understanding of underlying mechanisms, the validation of reliable and sensitive biomarkers, as well as the identification of targeted therapies that focus on the underlying airway inflammatory mechanisms and/or treatable traits.
- This approach has now been well adopted in severe asthma in which trials identified innovative therapies has led to improving patient outcomes.
- Multiple unmet needs exist to further refining the above approach to chronic airway diseases.

disease control and outcomes, convincing evidence showed a clear association between high doses of inhaled corticosteroids and clinically important adverse effects [4]. Furthermore, in both asthma and COPD in spite of optimal maintenance therapy and adequate treatment adherence, too many patients still remain symptomatic and sub-optimally controlled [5,6]. Clearly, this called for a more personalized strategy for disease management of both asthma and COPD.

In recent years, tissue sampling methods combined with innovative omics-technologies and systems biology approaches have helped to increase our understanding and insights into the mechanisms and molecular pathways underlying chronic airway diseases [7,8]. Indeed, novel discoveries

showed a vast complexity, i.e., comprising several components, and heterogeneity, i.e., indicating that not all components are present in individual patients over time, within and across different disease subsets, especially in the case of severe asthma [9,10], revealing various clinical and/or inflammatory phenotypes and endotypes [2]. In this context, a 'phenotype' reflects an individual's observable features, including clinical, functional, imaging, physiological, and biological characteristics, while 'endotype' refers to the cellular and molecular components and pathways underlying the pathogenesis of a disease [11] (Fig. 1) Reliable (composite) point-of-care biomarkers are being explored to help linking individual phenotypes to underlying pathways to aid identification and monitoring of responders to targeted treatment options [12,13]. These new discoveries and insights have driven the translational concept of precision medicine, aimed at providing adequate management and therapy to individual patients based on treatable traits and treatable mechanisms [14,15¹⁶].

In this review, we will discuss recent developments and current status of precision medicine in chronic airways diseases with special focus on severe asthma.

TOWARD PRECISION MEDICINE AND TREATABLE TRAITS

Novel insights into the pathogenesis, helped to shape the concept of precision medicine for chronic airway diseases [16]. In 2016, an expert panel proposed a precision medicine strategy based on the presence of 'treatable traits' [11]. This pragmatic approach, advocating active identification, assessment, and treatment of, label-free, disease traits, has been applied to patient data within the unbiased biomarkers in prediction of respiratory disease

FIGURE 1. Association between endotypes, phenotypes, and treatable traits.

outcomes (U-BIOPRED) project. 23 treatable traits were identified in the U-BIOPRED mild to moderate and severe asthma cohorts, consisting of several pulmonary trait (including bronchoconstriction, nonspecific airway hyperresponsiveness, cough, sputum production, concomitant bronchiectasis, and bacterial colonization), extra-pulmonary traits (including comorbidities such as allergy, rhinosinusitis, nasal polyps, NSAID-exacerbated respiratory disease, obesity, gastro-esophageal reflux disease (GERD), and obstructive sleep apnea), and behavioral/psychological/lifestyle/environmental traits, and risk factors (including nonadherence, poor inhalation technique, depression, anxiety, stress, smoking, (occupational) exposure to irritants, poverty, and side-effects of treatments [14,17]. The presence of (multiple) treatable traits was associated with poor clinical outcome and was generally higher in patients with severe asthma compared to mild/moderate asthma [17]. In line with the updated guidelines, comorbidities and other triggers, and factors potentially interfering with disease control, should be pro-actively addressed and treated [18,19].

MECHANISMS UNDERLYING TREATABLE TRAITS

Apart from ‘treatable traits’, validated biomarkers, such as serum IgE, eosinophil count in peripheral blood or sputum, and the fraction of exhaled nitric oxide (FeNO), can guide the implementation of precision medicine as they may predict treatment response to therapeutic options, including not only inhaled corticosteroids, but also some biologics and small molecules [12,20,21]. However, given the redundancy in the underlying pathways, these biomarkers can partly overlap, e.g., IL13 signaling can increase serum IgE, eosinophils, and FeNO. On the other hand, absence of these biomarkers can help to identify individual patients likely to be nonresponders to such therapies and protect them from potential side-effects associated with (long-term use of) these therapies [12]. Following the strategy of precision medicine, the right patient will receive the right treatment, with the ultimate goal to improve clinical outcomes for individual patients and minimize risk of side-effects in nonresponders. Currently, “treatable traits” are explicitly being implemented in clinical practice guidelines [18,19].

However, additional knowledge about the mechanisms underlying these treatable traits is needed to guide targeted-treatment based on identified traits in the individual patient. Results of the U-BIOPRED consortium demonstrated that the use of systems biology might provide novel insights on these treatable mechanisms, linking pathways to

clinical and physiological characteristics [15^{***}]. Transcriptomic analysis of bronchial biopsies and epithelial cells identified type2-high molecular endotypes associated with corticosteroid insensitivity. A tree-based inference scheme based on sputum eosinophilia, FeNO, and oral corticosteroids (OCS) use could predict these endotypes [22]. More recently, another U-BIOPRED study identified novel sub-phenotypes of eosinophilic and neutrophilic asthma using unbiased proteomic profiling of sputum [23^{***}]. The application of machine learning techniques combined with the integration of omics layers [24^{*}] may lead to new clinically applicable tools to guide treatment.

PRECISION MEDICINE CURRENT STATUS AND FUTURE NEEDS

Is precision medicine ready for prime time in daily clinical practice?

Based on gene-profiling, so far, two different endotypes have been identified in severe asthma: i.e., the type2-high endotype (underlying both the allergic and the nonallergic eosinophilic phenotypes, sometimes overlapping, and propagated through the T helper-2 and innate lymphoid cells (ILC)2-immune pathways), and the type2-low endotype (presenting as noneosinophilic, often neutrophilic, pauci-granulocytic, and/or airway smooth muscle predominant disease) [25]. In addition, coexistence of both type2-high and type2-low endotypes has also been reported in individual patients [2,26].

Currently, type2-high is the best characterized endotype and several type2-targeted treatment options (i.e., biologics and small molecule antagonists) have been developed or are in late stages of development [27]. Targeted treatments block specific inflammatory pathways or single mediators. Currently, there are several type2-targeted therapeutic options, consisting of three groups of biologics, including anti-IgE (omalizumab) for patients with allergy-driven uncontrolled disease, anti-IL5 strategies (mepolizumab, reslizumab, and benralizumab – all inhibiting IL-5 signaling although by slightly different mechanism) for severe eosinophilic asthma, anti-IL4/13 (dupilumab) for both allergic and nonallergic type2-driven (eosinophilic) asthma and two different small molecules. The latter comprise the leukotriene modifying agents such as montelukast (recommended as an alternative to ICS in milder or allergic asthma or as add-on in more severe asthma [18] and the Chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTH2)/prostaglandin D2 (DP2 receptor) antagonists (e.g., fevipiprant, timapiprant) currently in

phase three development for the same indications [28].

Consequently, discriminating biomarkers for pheno/endotyping are increasingly being integrated into the guidelines [18]. Single and composite biomarkers help identify patients who may benefit from these targeted therapeutic options. However, so far, only a few point-of-care inflammatory biomarkers have been validated for clinical application: i.e., to predict and/or to monitor treatment response [12].

For type2-low asthma, both discriminating biomarkers and targeted treatment options are still largely lacking, although recent advances with omics technology revealed two transcriptome-associated clusters (TAC2 and TAC3) underlying this endotype, in contrast to TAC1 which associates with type2-high severe asthma phenotype/endotype [29]. In this study, the TAC2 cluster was characterized by interferon-tumor necrosis factor- α and inflammasome-associated genes, and presented with the highest sputum neutrophil counts, serum C-reactive protein levels, and eczema. In contrast, the TAC3 cluster was characterized by genes of the metabolic pathways, ubiquitination and mitochondrial function, and patients in this cluster presented with normal to moderately increased sputum eosinophils and overall less severe disease with higher forced expiratory volume in 1 [29]. As type2-low asthma often shows, at best, an incomplete responsiveness to standard therapy with corticosteroids, there is an urgent unmet need for alternative pharmaceutical options. Patients with clear sputum neutrophilia (defined by differing cut-offs, as blood neutrophils do not qualify as discriminating biomarker), in some studies interpreted as reflecting underlying infection, and in this subgroup, macrolides have been shown to be a rational treatment choice [30]. For those with bronchoconstriction lacking underlying inflammation, combinations with longacting beta2-agonists, long-acting antimuscarinic agent, mast-cell-directed therapies or bronchial thermoplasty have been shown to have beneficial effects [31–33].

In our recently published European Academy of Allergy and Clinical Immunology (EAACI) position article, our task force aimed to define clinically applicable biomarkers reflecting the immune/inflammatory pathways underlying the severe asthma phenotypes and to establish the links to existing and upcoming (targeted) treatment options [12].

TARGETED TREATMENT OPTIONS AND ALGORITHMS BASED ON PRECISION MEDICINE

In the early 2000s, two types of targeted therapies became available for the treatment of mainly

allergic asthma: the small molecule cysteinyl leukotriene receptor1 antagonists (LTRA), exemplified by montelukast, and the biologic, omalizumab, which binds free serum IgE [1].

Increasing insight into the underlying mechanisms of especially more severe asthma phenotypes have paved the way for defining several new potential targets and novel treatment options during the past decade. As a result, a growing number of biologics targeting the eosinophil/type2 inflammatory pathways have recently been included into the global initiative for asthma (GINA) treatment strategy [18]. In addition, several others are currently in different stages of drug development with both upstream targets (e.g., the alarmins: (Thymic stromal lymphopoietin) TSLP, IL-33, and IL-25) and (more) downstream targets (e.g., IL-17, CRTH2/DP2, MMPs, GATA3, ST2, IL-6, phosphatidylinositol 3-kinase [PI3K], TSLP, JAK) [27,28]. Currently available and some of the emerging targeted therapies are summarized in Table 1.

To aid precision medicine based on the underlying immune/inflammatory pathways and available biomarkers, a number of treatment algorithms for uncontrolled severe asthma have been proposed [34,35]. Based on novel developments, linking inflammatory phenotypes, validated biomarkers, and novel targeted treatment options, a recent task force of the EAACI also proposed a treatment algorithm [12].

The use of maintenance therapy with OCS in asthma varies from country to country, but nevertheless is used for a substantial number of patients with uncontrolled and/or severe asthma. Long-term exposure to OCS (either if taken as frequent bursts or as maintenance therapy) is associated with severe adverse effects, and in asthma, maintenance therapy with OCS is not evidence-based, although recommended as a treatment option by many guidelines [18]. As also pointed out in the most recently updated version of the GINA Strategy: the goals of asthma therapy are not only to prevent acute exacerbations and improve disease outcome, but also to reduce as much as possible the risk of adverse effects of treatments [18]. Therefore, asthma management strategies aimed at reducing exposure to systemic corticosteroids are important, not in the least in patients with more severe disease [36]. After confirming the diagnosis of severe asthma based on systematic assessment [37] and optimized management, including treatment of co-morbidities [18] the main target in a patient on maintenance therapy with OCS should be tapering to reduce systemic steroid exposure. In patients on maintenance OCS, probably not least patients with evidence of type-2 inflammation and/or small airways disease, a trial of (add-on) high-dose inhaled steroid such as

Table 1. Currently available and emerging targeted therapies for chronic inflammatory airway disease

Currently available			
Target	Medication	Administration route/frequency	Indication + asthma phenotype
Small molecule			
CysLT1R	Montelukast	Oral, once daily	CysLT-driven: e.g., EIA, CARAS; as add-on to low-moderate doses ICS
Biologic			
IgE	Omalizumab	Subcutaneous, 2–4 week	(Moderate)-severe allergic
IL-5	Mepolizumab	Subcutaneous, 4 week	Severe eosinophilic
IL-5	Reslizumab	Intravenous, 4 week	Severe eosinophilic
IL-5Ralpha	Benralizumab	Subcutaneous, 4 week (then 8 week)	Severe eosinophilic
IL-4Ralpha (IL-4/ IL-13 pathway)	Dupilumab	Subcutaneous, 2 week	Moderate-severe eosinophilic steroid-dependent Asthma
Under clinical development			
Target	Medication	Indication	
Small molecule			
FLAP	GSK2190915	Asthma/COPD	
CRTH2/DP2R	Timapiprant, oral	(allergic/severe eosinophilic) asthma	
CRTH2/DP2R	Fevipiprant, oral	(allergic/severe eosinophilic) asthma	
PDE3/4	RPL554/Ensifentrine	COPD/(asthma)	
PI3Kδ	GSK2269557; orally inhaled	Asthma/COPD	
PI3Kδ /γ	RV-1729	Asthma/COPD	
PI3Kδ	AQX-1125	Asthma (‡)/COPD	
GATA3	DNAzyme	type2-disease	
TLR9	AZD1419, inhaled	Asthma	
TLR7	GSK2245035, intranasal	Asthma/ allergic rhinitis	
Dopamine receptor	Dexpramipexole	(severe eosinophilic) asthma	
Biologic			
TSLP	CSJ117, Tezepelumab	Asthma	
IL-33	RGN3500, Etokimab	Asthma	
IL1-1RL1/ST2	MSTT1041A, GSK3772847	Asthma	
IL-25	ABM125	Asthma	
IL-17A	CJM112	Asthma	

CARAS, concomitant allergic rhinitis and asthma syndrome; CRTH2, Chemoattractant receptor-homologous molecule expressed on T_H2 cells; CysLT1R, cysteinyl leukotriene receptor; DP2R, prostaglandin D2 receptor; EIA, exercise-induced asthma; FLAP, 5-lipoxygenase activating protein; IL, interleukin; PDE3/4, phosphodiesterase three and 4; PI3K, Phosphoinositide-3-Kinase; ST2 (receptor for IL-33), also known as IL-1 receptor like one (IL-1RL1); TSLP, Thymic stromal lymphopoietin.

ciclesonide may be considered, as previous studies have shown low potential for systemic effect [36] together with successful tapering of OCS in 63% of enrolled patients (OCS discontinued in 28% of patients) [38]. Provided it is available, the next step is to consider add-on type-2 targeted biologic therapy with choosing between available therapies primarily based on predictors of response [12,18], including evidence for allergen-driven disease, blood-eosinophil count, and concomitant nasal polypsis. In addition, the choice of a biologic therapy should include a shared decision with the patient or

his/her care giver. If the response to the type-2 targeted therapy is favorable, the next step is to consider decreasing/stopping maintenance OCS therapy, as several controlled clinical trials have shown that such therapies in this subgroup of patients reduce the daily dose of systemic steroids [39]. In patients with severe non-Type two asthma, as well as patients with type-2 asthma not responding to targeted biologic therapy, on maintenance OCS, overall reassessment is needed together with implementation of strategies to minimize OCS side-effects (if tapering is not possible).

CONCLUSION

Multiple unmet needs exist in our understanding chronic airway diseases including severe asthma (Box 1). Our understanding of the underlying heterogeneity of this disease has allowed us to ‘think differently’ in approaching its diagnosis and treatment. This has also influenced us to examine the heterogeneity of other chronic airway diseases such as COPD. So far, targeted treatment options with biologics in severe asthma have shown a substantial improvement in disease outcome while enabling reduction of corticosteroids load in selected patients with severe eosinophilic and allergic asthma. Validated (composite) biomarkers are recommended by guidelines to predict and monitor treatment response to such targeted treatments.

However, not all patients respond equally well, despite apparently similar clinical, functional, and/or inflammatory characteristics, while some patients seem “late-responders” or show a variable response over time.

Omics studies have also provided insights in the variability and heterogeneity of pathways underlying chronic inflammatory airway disease. Given this complexity and redundancy, it seems unlikely that targeting a single pathway could successfully act on all treatable mechanisms and successful lead to optimal disease control. Studies are required to assess the effect of combination therapy (e.g., ≥ 1 biologics, small molecules, or combinations), as well as safety and long-term effectiveness. In addition, the question remains whether targeting a treatable mechanism could ultimately modify the course of disease on the long run. Furthermore, studies with biologics in children have been scarce (also see review by Vijverberg *et al.* in this issue 77–83). As pediatric asthma phenotypes do not necessarily overlap with phenotypes in adults, caution is needed when extrapolating results to the pediatric population [40]. Finally, it is unknown whether the use of targeted therapy in patients with mild disease or in those at risk of the disease can alter the natural history of the disease or have disease modifying effects.

Box 1. Unmet needs

- Exploration of molecular pathways underlying (severe) chronic inflammatory airway disease.
- Identification of point-of care predictive, prognostic, and pharmacodynamics biomarkers to improve the personalized approach to asthma and monitor treatment response.
- Examination of long-term efficacy and safety of existing and future targeted therapies (consistency, variability, and heterogeneity of treatment response, disease modifying effect).

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Conflicts of interest

CSU is head of the Respiratory Research Unit Hvidovre that conducts clinical trials sponsored by the pharmaceutical industry. In the past three years, CSU has received consultancy fees/speakers honoraria from Sanofi, GSK, AstraZeneca, Boehringer-Ingelheim, ALK-Abello, Roche, Actelion, Novartis, TEVA, Chiesi, Mundipharma and Sandoz. No conflicts of interests in relationship to this manuscript.

SV has no conflict of interest to report regarding this manuscript.

NAH received honoraria for serving on advisory boards or as consultant for Novartis, Sanofi Genzyme, Regeneron, GSK, Boehringer Ingelheim, Astra Zeneca, Gossamer Bio, Genentech and Roche. His institution has received research grant support on his behalf from Astra Zeneca, GSK and Boehringer Ingelheim, and Sanofi Genzyme.

ZD acts as Director Respiratory & Allergy at QPS-NL, a CRO that conducts clinical studies sponsored by pharmaceutical companies. In the past 3 years, ZD has received consultancy fees and/or speaker's honoraria from: ALK, Aquilon, Acucort, Boehringer-Ingelheim, HAL Allergy, MSD, and Sanofi-Genzyme. No conflicts of interests in relationship to this manuscript.

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