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Review

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Evolving Concept of Severe Asthma: Transition From Diagnosis to Treatable Traits

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ABSTRACT

In recent decades, the concept of severe asthma has evolved from an umbrella term encompassing patients with high-intensity treatment needs to a clinical syndrome with heterogeneous, albeit distinct, pathophysiological processes. Biased and unbiased cluster approaches have been used to identify several clinical phenotypes. In parallel, cellular and molecular approaches allow for the development of biological therapies, especially targeting type 2 (T2) cytokine pathways. Although T2-biologics have significantly improved clinical outcomes for patients with severe asthma in real-world practice, questions on the proper use of biologics remain open. Furthermore, a subset of severe asthma patients remains poorly controlled. The unmet needs require a new approach. The "treatable traits" concept has been suggested to address a diversity of pathophysiological factors in severe asthma and overcome the limitations of existing treatment strategies. With a tailored therapy that targets the treatable traits in individual patients, better personalized medical care and outcomes should be achieved.

Keywords: Asthma; biological products; endophenotypes; precision medicine; cytokines; outcomes; biologics; omics

INTRODUCTION

Asthma management has evolved to address the unmet clinical needs of patients. The introduction of inhaled corticosteroids (ICSs) was the first breakthrough, which greatly reduced asthma-related morbidity and mortality.[1] The subsequent developments of long-acting beta agonists and muscarinic antagonists (LAMAs) and their combined use with ICSs further reduced the severity of asthma symptoms and the number of exacerbations as well as improved lung function.[2,3] However, 5% to 10% of asthma patients remain treatment-refractory or insufficiently controlled and thus are classified as severe asthma.[4]

Novel biological therapies targeting type 2 (T2) cytokines are recent breakthroughs in the management of severe asthma. Paradoxically, the early failure of mepolizumab, the first-in-class anti-interleukin (IL)-5 monoclonal antibody, in a clinical trial with patients with poorly controlled asthma advanced our understanding of asthma heterogeneity.[5] Now, it is accepted

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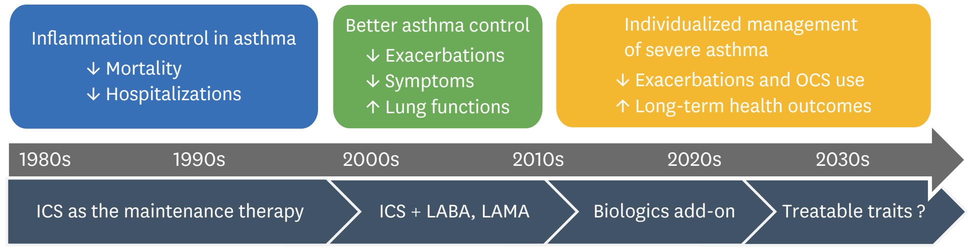

Fig. 1. Evolving concept in asthma management during the last few decades. The concept has evolved to address major unmet needs. The introduction of ICS as the maintenance therapy was the first breakthrough in asthma management, which considerably reduced asthma-related hospitalization and mortality. The subsequent development of LABAs and LAMAs further reduced asthma symptoms and exacerbation as well as improved lung functions. T2-associated biological therapies are the most recent breakthrough in the management of severe asthma. However, several clinical needs remain unmet. Treatable traits are emerging as a concept to further address patient heterogeneity in severe asthma.
ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroid; T2, type 2.

that asthma, particularly severe asthma, is not a single disease entity, but a heterogeneous clinical syndrome encompassing various phenotypes and endotypes.[4,5] Five T2-related biologics, including omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab, are now being used in the management of patients with T2-high severe asthma phenotype. They can help improve asthma control and quality of life (QoL) as well as mitigate the severity of asthma symptoms and exacerbations while reducing the need for oral corticosteroids (OCSs).[6]

However, clinical needs remain unmet. Although T2 biologics help reduce the incidence of asthma exacerbation and OCS use, the risk of exacerbation is not completely eliminated.[6-8] Additionally, there is a fraction of patients with no evidence of T2-related inflammation (non-T2 severe asthma), and biologics in current use do not show better outcomes than placebos in these patients.[9] Furthermore, the conditions of patients in the real world are more complicated than those of participants in randomized controlled trials (RCTs); several factors may modify or confound treatment responses in clinical practice and be significant parts of disease pathophysiology, such as age, socioeconomic status, adherence, smoking history, airway irreversibility, or comorbidities.[10,11] Thus, more comprehensive clinical approaches are warranted that extend beyond diagnosis- or phenotype-based pharmacological treatments to achieve better asthma control in real-world patients (**Fig. 1**).

In this review, we summarize the evolving concept of severe asthma, discuss recent advances in asthma management, including biological therapies and treatable traits-based approaches, and suggest research directions to address the unmet needs for patients in real world.

PHENOTYPES AND ENDOTYPES OF SEVERE ASTHMA

In the literature, the heterogeneity of asthma phenotypes has been recognized for more than 100 years. In 1918, Dr. Francis Rackemann coined the term "intrinsic asthma" for a group of late-onset asthmatic patients who showed no evidence of environmental allergens in skin prick tests.[12] Later, with the development of induced sputum cell count techniques in the 1990s, patients could be further characterized by their inflammatory phenotypes such as eosinophilic, neutrophilic, mixed granulocytic, or paucigranulocytic.[13] Moreover, some difficult-to-treat asthmatic patients show no eosinophilic inflammation[14] or are characterized by nonallergic, albeit eosinophilic airway inflammation, raising questions regarding the

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origin of their disease.[15] The classification was based on a single or small number of clinical traits or biomarkers that were largely chosen on the basis of clinical observation or *a priori* knowledge, such as age at asthma onset, atopy, eosinophilic inflammation, fixed airflow obstruction (FAO), or nonsteroidal anti-inflammatory drug hypersensitivity.

As statistical methods have evolved,[16] unbiased or hypothesis-free approaches, such as clustering analyses, have been used to phenotype patients using a large number of clinical and physiological parameters collected from several severe asthma cohorts, such as the Severe Asthma Research Program (SARP) network in the United States,[17] the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) project in the European Union,[18] the International Severe Asthma Registry (ISAR),[19] and other national severe asthma registries, including the UK Severe Asthma Registry (UKSAR),[20] the Cohort for Reality and Evolution of Adult Asthma (COREA),[21] and the elderly asthma cohort in Korea.[22] Although a firm consensus regarding the eligibility criteria and findings is lacking, the identified clinical phenotypes shared generally similar characteristics across the registry studies, which suggested approximately 4 or 5 common phenotypes of asthma. However, while some distinct phenotypes were revealed, phenotypes had limitations in explaining the detailed pathophysiology and discovering novel therapeutic targets beyond T2 cytokines.

Using sophisticated experimental or omics technology, clinical phenotypes were translated into endotypes (molecular phenotypes).[23] Integration with translational research revealed novel key molecules or cells underlying severe asthma phenotypes, such as innate lymphoid cells, IL-33, IL-25, or thymic stromal lymphopoietin (TSLP).[5] Some of them, such as tezepelumab (anti-TSLP), have recently been translated into clinical practice in the form of biological therapy.[24] Now multiple-omics analyses are gaining more attention, and the integration of omics data with clinical outcomes is expected to bring an advanced understanding of severe asthma endotypes and to identify novel treatments and biomarkers.[25]

IMPACT OF T2 BIOLOGIC THERAPIES AND REMAINING QUESTIONS IN REAL-WORLD PATIENTS

During the last 10 years, the phenotype approach has greatly changed clinical practice of severe asthma. Biologics targeting IgE, IL-5, or IL-4/IL-13 have shown favorable outcomes in pivotal clinical trials in patients with severe asthma,[26-34] and they are increasingly utilized as safe and effective treatment in previously uncontrolled patients. These biologics have also contributed to further understanding different endotypes underlying a single phenomenon (*i.e.*, different mechanisms of regulation between eosinophilic inflammation and fractional exhaled nitric oxide [FeNO] elevation), and such knowledge will help identify biomarkers to pair with targeting treatments.[35,36]

Now the extent of evidence with T2 biologics is rapidly expanding. Recent reports from RCT extension phase studies for up to 2–5 years showed the long-term benefits of continued treatments with T2-biologics, *i.e.*, reducing asthma exacerbations and OCS doses as well as improving asthma symptom control, lung function, and health-related QoL.[37-41] In addition, real-world longitudinal evidence of outcomes, including effectiveness and safety, complemented RCTs and validated their findings in broader populations and clinical settings (**Table 1**).[42-45] Due to the complexity of patient profiles, more attention is now being paid to real-world evidence generation.

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Table 1. Summary of pivotal studies and long-term extension studies for biologics

Biologics	Omalizumab		Mepolizumab				Reslizumab		Benralizumab					Dupilumab		
	EXTRA[26]	Bousquet et al.[42]	MENSA[27]	SIRIUS[28]	COSMEX[37]	REALITI-A[45]	Castro et al[29]	Murphy at al.[38]	CALIMA[30]	SIROCCO[31]	ZONDA[32]	BORA[39]	MELTEMI[40]	QUEST[33]	VENTURE[34]	TRAVERSE[41]
Type of the study	RCT	Real-world effectiveness study	RCT	Open-label, extension study	Observational cohort study	RCT	RCT	Open-label, extension study	RCT	RCT	RCT	Phase 3 extension study	Open-label, extension study	RCT	RCT	Open-label, extension study
Subjects or publication	850	86 publications	576	135	339	368	953	1,051	1,306	1,205	220	1,576	447	1,902	210	2,282
Study duration	48 wk	16 wk to 12 mon	32 wk	24 wk	≥ 172 wk	24 mon	48 wk	≥ 24 mon	56 wk	48 wk	28 wk	68 wk	≥ 5 yr	52 wk	24 wk	96 wk
Outcomes																
Symptoms changes	Asthma symptom scores, −0.26	ACQ at 12 mon, −1.13	ACQ-5, −0.42 to −0.44	ACQ-5, −0.52	ACQ-5 at 168 wk, −0.33	N/A	ACQ-7, −0.251	ACQ at 16 wk, −0.36	ACQ-6, −0.12 to −0.23	ACQ-6, −0.25	ACQ-6, −0.55	ACQ-6 at 56 wk, −0.09 to −0.12 at EOS ≥ 300 −0.10 to −0.14 at EOS < 300	N/A	ACQ-5, −0.39 to −0.22	N/A	ACQ-5 at 48 wk, −1.69 to −1.33
QoL	AQLQ, 0.29	AQLQ at 12 mon, 1.44	SGRQ, −6.4 to −7.0	SGRQ, −5.8	N/A	N/A	AQLQ, 0.23	AQLQ-12 at 96 wk, 0.540	AQLQ-12, 0.16 to 0.24	AQLQ-12, 0.18 to 0.30	AQLQ-12, 0.45	AQLQ-12 at 56 wk, 0.08 to 0.15 at EOS ≥ 300 0.09 to 0.11 at EOS < 300	N/A	AQLQ, 0.26 to 0.29	N/A	AQLQ at 48 wk, 1.07 to 1.40
Lung function (FEV1 changes)	N/A	250 mL at 12 mon	98 to 100 mL	114 mL	100 mL at 168 wk	N/A	110 mL	90 mL at 16 wk	116 to 125 mL	106 to 159 mL	222 to 256 mL	38 to 40 mL at EOS ≥ 300 −1 to 17 mL at EOS < 300	N/A	130 to 140 mL	220 mL	220 to 330 mL
Exacerbation reduction or rate	25%	59% at 12 mon	47% to 53%	32%	0.93 event per year	69%	54%	N/A	36% to 40%	45% to 51%	55% to 70%	0.49 to 0.50 event per year at EOS ≥ 300 0.64 to 0.76 event per year at EOS < 300	0.5 event per year	46.6% to 47.7%	59.0%	0.227 to 0.310 event per year
OCS reduction	N/A	41%	N/A	50%	88%	52%	N/A	N/A	N/A	N/A	75%	N/A	N/A	N/A	28.2%	N/A

ACQ, Asthma Control Questionnaire (5 or 6 item); AQLQ, Asthma Quality of Life Questionnaire; EOS, eosinophils; FEV1, forced expiratory volume in 1 second; N/A, not applicable/available; OCS, oral corticosteroid; RCT, randomized controlled trial; SGRQ, St. George's Respiratory Questionnaire; QoL, quality of life.

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Among various clinical outcomes of severe asthma, the frequency of asthma exacerbation and OCS doses may be the most measurable and clinically relevant ones in the real-world practice. Exacerbation is a major factor that directly affects patient life and health-related QoL.[46] The cumulative dose of OCS is significantly associated with future risks of adverse health outcomes including mortality and treatment complications.[47] Before the era of biologics, OCS administration was inevitable in many cases because there was no alternative for controlling exacerbations and preventing emergency room visits.[46,48] In real-world studies, treatments with T2 biologics (*vs.* pre-treatment) remarkably reduced the rates of asthma exacerbations in patients with severe allergic or eosinophilic asthma.[42,49] The benefits of T2 biologics in reducing exacerbations and OCS use were also demonstrated in the healthcare claims database studies.[50]

Then a pertinent question would be how to better use biologics, along with biomarkers, because they are significantly associated with the treatment responses. Higher blood eosinophil counts are associated with better treatment responses to T2 biologics such as mepolizumab, reslizumab, benralizumab, or dupilumab.[49] However, the cutoff values for blood eosinophil counts are neither sensitive nor specific enough to predict airway eosinophilia.[51] In addition, interpretation of blood eosinophil counts is often confounded by diurnal variation or OCS use.

Biomarker identification is more challenging in treatment with omalizumab. In the *post hoc* analysis from the EXTRA study, baseline T2 markers, such as FeNO, blood eosinophils, or serum periostin levels, have been suggested to predict favorable omalizumab treatment responses in terms of reducing exacerbation.[52] For example, reduction in the incidence of asthma exacerbation was significantly greater in high FeNO (≥ 19.5 ppb) (53% reduction; 95% confidence interval [CI], 37%–70%; $P = 0.001$) than in low FeNO subgroups (< 19.5 ppb) (16% reduction; 95% CI, −32%–46%; $P = 0.450$); in patients with high blood eosinophils (≥ 260/μL) (32% reduction; 95% CI, 11%–48%; $P = 0.005$) than in those with low blood eosinophils (< 260/μL) (9% reduction; 95% CI, −24%–34%; $P = 0.540$); and in patients with high blood periostin (≥ 50 ng/mL) (30% reduction; 95% CI, −2%–51%; $P = 0.070$) than in those with low periostin (< 50 ng/mL) (3% reduction; 95% CI, −43%–32%; $P = 0.940$). However, the utility of T2 biomarkers was not proven in real-world studies. In the STELLAIR study, 872 patients with severe allergic asthma were retrospectively observed after treatment with omalizumab. They found that the treatment responses did not significantly differ by pre-treatment blood eosinophil counts.[53] In the PROSPERO study, a prospective observational study with 806 patients with allergic asthma treated with omalizumab, the reduction of exacerbation did not differ by blood eosinophil counts (< 300/μL *vs.* ≥ 300/μL) or FeNO levels (< 25 ppb *vs.* ≥ 25 ppb).[54] In addition, omalizumab treatment responses did not differ by the number or types of inhalant allergen sensitization in the PROSPERO cohort,[55] suggesting the need to revisit the indication of omalizumab treatment and biomarkers that will guide the treatment decision in the real world. Furthermore, the lack or imprecision of the biomarkers indicates that more thorough endotype research is needed in patients receiving the biological treatment.

There is one major issue that confounds the interpretation of treatment responses in the real world, regression to the mean effects, which may be one of the reasons that make it difficult to determine biomarkers in real-world observations of patients receiving treatments.[56] Regression to the mean is a statistical phenomenon that may bias longitudinal studies with repeated outcome measures.[56] Patients are likely to have more severe disease at the time of initiation of treatment with biologics and to spontaneously improve over time, thus partly accounting

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for larger treatment benefits observed in real-world studies than in RCTs.[57] Thus, it is difficult to differentiate true therapeutic benefits of biologics in the real-world. Consequently, it is clinically and academically useful to identify patient subgroups with exceptionally large treatment effects or "super-responders" as a guide for use in real-world practice.

Several studies have attempted to explore the characteristics of super-responders to T2 biologics. Mepolizumab super-responders were first studied in the Australian Mepolizumab Registry.[58] Super-responders were defined as patients with the top 25% of Asthma Control Questionnaire (ACQ)-5 scores after 6 months of treatments. Compared to poor responders (bottom 25% of ACQ-5 scores), mepolizumab super-responders were significantly different in their baseline characteristics, including female sex, lower body mass index (BMI), shorter asthma duration, higher blood eosinophils and FeNO, higher ACQ-5 scores, less OCS maintenance dose, more nasal polyps, and lower number of non-pulmonary comorbidities such as gastroesophageal reflux disease (GERD), obstructive sleep apnea, psychiatric disorders, or cardiovascular diseases. Similar characteristics of super-responders, such as nasal polyps, lower BMI, and lower OCS maintenance dose, were reported in a retrospective analysis of 96 severe eosinophilic asthmatic patients in the UK.[43]

In a real-world study of 130 severe eosinophilic asthmatic patients treated with benralizumab in the UK, treatment response was defined as ≥ 50% reduction in annualized exacerbation rate or OCS maintenance dose after 48 weeks of treatment; super response was defined as zero exacerbation and without needs for OCS maintenance to control asthma.[59] Responders were not significantly different from non-responders in the baseline characteristics, except for sex and baseline FeNO levels. However, super-responders were distinct from usual responders in several ways; super responders were more likely to have adult-onset asthma, nasal polyps, higher blood eosinophil counts, and lower baseline ACQ6 scores. Similar super responder characteristics were observed in one RCT, although the definition was not identical.[60]

Predictive factors for super-responders to dupilumab—defined as those who reached exacerbation-free status after dupilumab administration (for at least 6 months), discontinuation of maintenance OCS, and major improvement in asthma control—included blood eosinophil counts ≥ 300 cells/μL before the use of any biologics and blood eosinophil counts ≥ 150 cells/μL in patients who switched to dupilumab from other biologics.[61]

However, as described above, the definition of super-responders varied across studies, making it difficult to integrate the findings and translate them into clinical guidance. Recently, Upham and colleagues proposed a consensus definition for super-responders, through a Delphi process.[62] The consensus is that the super-responder definition should be based on improvement across 3 or more domains assessed over 12 months (and 2 of the domains should meet major criteria); major criteria are (1) loss of exacerbation, (2) significant improvement in asthma control (≥ 2× of the minimal clinically important difference), and (3) cessation of OCS maintenance (or weaning to adrenal insufficiency); and minor criteria are (1) 75% exacerbation reduction, (2) well-controlled asthma (ACQ < 1.0 or ACT > 19), and (3) ≥ 500 mL improvement in forced expiratory volume in 1 second (FEV1).[62] The consensus definition may help to build up more robust real-world evidence to guide the use of T2 biologics.

In addition to the success of T2 biologics, more novel biological drugs are being developed or undergoing trials with optimism. Tezepelumab, an anti-TSLP monoclonal antibody, was the first biological agent that showed significant benefits over placebo in reducing exacerbations

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in patients with severe uncontrolled asthma, irrespective of baseline blood eosinophil counts or T2 biomarker status.[24] However, given the complexity of pathophysiological processes in individuals with severe asthma, any single magic bullet is unlikely to address all challenges. Another unsolved problem is the high cost of novel biologics.

THE CONCEPT OF TREATABLE TRAITS IN SEVERE ASTHMA

Although the impact of T2 biological therapies is substantial, treatments are not indicated, or the effects are suboptimal in a sizeable proportion of patients. Phenotype studies identified different asthma phenotypes, but their clinical impacts, except for targeting T2 inflammation, are still limited. Endotype studies have suggested a number of novel biomarkers or treatment target candidates, but they have not been clinically translated. A key challenge in these typing approaches is that they remain just hypothetical unless clinical benefits are proven by specific targeting.

"Treatable traits" is a recently introduced concept that proposes a multidisciplinary and personalized approach to managing patients with more complex chronic obstructive airway diseases.[63] It moves away from traditional diagnostic labeling, such as asthma or chronic obstructive pulmonary disease (COPD), but toward identifying phenotypic "treatable traits" that vary across individual patients with obstructive airway disease. It is an advanced phenotyping approach to identify and treat "clinically relevant" patient traits.

In current asthma guidelines, a unified stepwise approach is advocated, which is usually based on patient symptoms.[64] Thus, this approach may lead to overtreatment in symptomatic patients without evidence of eosinophilic inflammation; moreover, OCS over-use may be problematic. Conversely, patients with less severe symptoms may be undertreated. As shown in cluster analyses, there is a discordance between symptoms and airway inflammation, particularly in males with late-onset eosinophilic asthma or in females with late-onset non-eosinophilic asthma with obesity.[17] Thus, the treatable traits-based approach may reduce the risk of over- or undertreatment, and improve clinical outcomes in patients who remain uncontrolled with currently available therapies.

In real-world registry studies, such as the Australia Severe Asthma Registry or U-BIOPRED, treatable traits were found to be more frequent in patients with severe asthma than in non-severe asthmatic patients.[65,66] Traits, such as proneness to exacerbations, depression, inhaler device polypharmacy, vocal cord dysfunction, and obstructive sleep apnea, were associated with future risk of asthma exacerbation.[65,66] In a small pragmatic RCT of patients with severe asthma, multidimensional management based on treatable traits was significantly better than usual care (in the severe asthma clinic) in improving asthma control and health-related QoL.[67] Although the number of reports is limited, a systematic review found several successful attempts of treatable traits-based or multidimensional management in patients with chronic airway diseases.[68]

Conceptually, 3 minimum criteria should be met for a particular disease characteristic to be considered a "treatable trait."[69] First, it should predict or be associated with clinically relevant outcomes, prognosis, or mortality. Secondly, it should be quantifiable using validated objective or subjective tools. Thirdly, it should be related to specific treatment responses, ideally confirmed in RCTs. The list of treatable traits may differ between regions or clinics,

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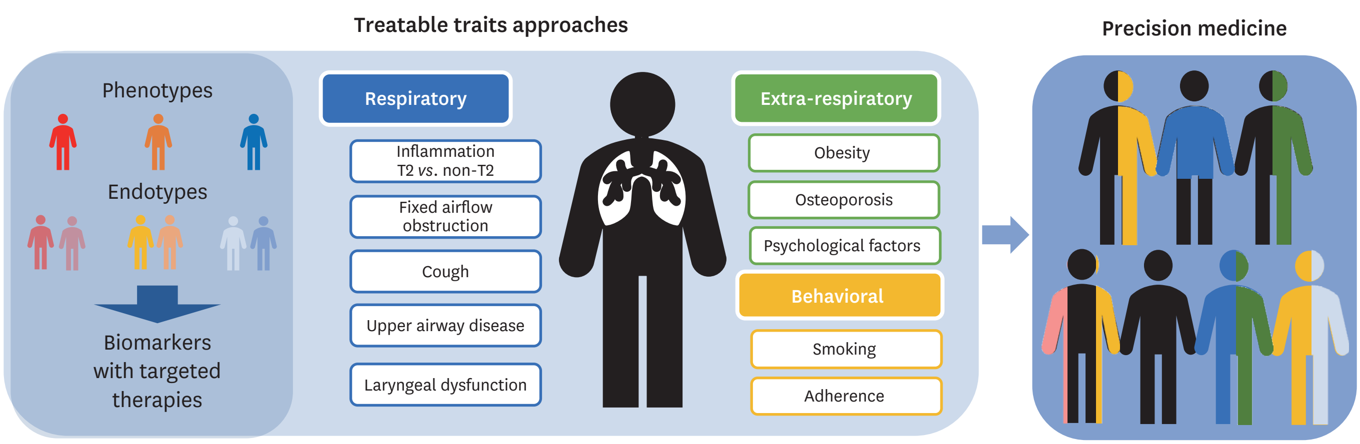

Fig. 2. Endotype, phenotype, and significant treatable traits from respiratory, extra-respiratory, and behavioral domains in severe asthma. Specific investigations and treatments are undertaken for each trait in individuals, allowing for precision medicine in patients with severe asthma.
T2, type 2.

although there are some well-characterized experiences from specialist centers.[68] The list of traits is usually chosen based on prevalence, clinical relevance, and resource availability, including measurement and treatment tools. In Australian cohorts, approximately 20–30 potentially treatable traits were evaluated.[66,67,70] Based on anatomic locations, treatable traits can be classified into 3 domains, including respiratory, extra-respiratory and behavioral domains; each domain is composed of several traits (**Fig. 2**).[65,71] Below, we discuss potentially significant treatable traits regarding their clinical relevance, measurability, and treatability.

Respiratory traits

T2- inflammation is one of the best studied treatable traits in chronic respiratory diseases. As previously discussed, it is associated with the risk of asthma exacerbation and measurable using T2 markers such as blood eosinophil counts or FeNO. The presence of T2-related inflammation indicates favorable treatment responses to T2 biologics in severe asthma.[15] In addition, eosinophilic inflammation is observed in 30% to 40% in COPD.[72] The pathogenetic role of eosinophils is less clear in COPD than in asthma, but eosinophilic inflammation in COPD is associated with an increased risk of exacerbation, and a strategy to mitigate eosinophilic inflammation in patients with COPD reduces severe exacerbation. Although RCTs of T2 biologics in COPD have not demonstrated efficacy, mepolizumab reduces the rate of exacerbations in the subgroup of COPD patients with an elevated blood eosinophil level,[73] suggesting that eosinophilic airway inflammation is considered the most influential treatable trait of chronic airway diseases.

T2-low or neutrophilic severe asthma remains poorly understood and the treatment is frequently challenging. In fact, it is unclear whether T2-low or neutrophilic inflammation could eventually guide treatment decision.[74] Phenotypically, it presents with sputum neutrophilia or paucigranulocytes and steroid resistance. Potential mechanisms include neutrophil abnormalities, activation of the inflammasome pathway, and the IL-17 pathway. However, therapies targeting neutrophilic asthma were not successful in clinical trials.[9] According to the latest Global Initiative for Asthma guidelines, if there is no evidence of T2-related inflammation, add-on therapies without specific inflammatory targets, such as LAMAs or azithromycin, were suggested as treatment options.[75] Treatment with the anti-TSLP monoclonal antibody tezepelumab might also be considered in these patient subgroups[24]; however, it is unclear whether the T2-low phenotype is a treatable trait on its own.

Airflow obstruction is common in asthma, but not fully reversible in some patients. Particularly, FAO, usually defined as postbronchodilator FEV1/forced vital capacity less than 70%, is frequent in severe asthmatic patients and associated with old age, late onset, smoking, long duration of illness, more significant inflammation, and frequent exacerbations.[76] Patients with FAO often have overlapping features with COPD, especially smokers; therefore, the term asthma-COPD overlap has previously been proposed.[77] However, FAO is present even in nonsmoking asthmatic patients and may be related to persistent airway eosinophilic inflammation, mucus plugging, or repeated bronchial smooth muscle contraction.[17,18] Studies using chest computed tomography (CT) scans suggested that parenchymal destruction or hyperinflation may evoke FAO and accelerate lung function declines, regardless of smoking status.[78,79] This finding suggests that patients with prominent FAO have a distinct subtype of severe asthma. Thus, further studies can reveal the potential utility of CT scanning in discovering different pathophysiological mechanisms underlying FAO in severe asthma patients.

Cough is a major symptom during asthma exacerbation causing severe distress, but has not been well investigated for its clinical relevance in the context of severe asthma.[46,80,81] Cough is more frequent in severe asthma than in non-severe asthma and associated with worse health-related QoL and asthma control.[81] Mechanisms underlying cough may overlap with, but are distinct from those of wheezing or breathlessness. However, as cough is not included in current asthma assessment tools, such as ACT or ACQ, poorly controlled cough often misguides clinicians to step up in asthma therapy. Three major pathophysiological processes are thought to underlie cough in asthma: (1) peripheral triggers of airway sensory nerves (*i.e.*, the presence of active airway inflammation, mucus, or acid reflux triggering sensory nerves), (2) hyper-excitability in the cough reflex circuit, and (3) impaired cough inhibition.[82] Control of peripheral triggers may be achieved with optimal treatments according to current asthma guidelines. Treatment of patients with severe eosinophilic asthma, treatments with anti-IL-5 monoclonal antibody or OCS may help to relieve cough.[83] However, in patients with persistent symptoms including cough, other treatable traits such as cough reflex hypersensitivity or undiscovered comorbidity should be considered. Cough can be measured using subjective tools such as cough severity scores or cough-specific QoL questionnaire, although no tool has been specifically developed to measure cough in asthma. Drugs modulating cough reflex sensitivity such as P2X3 antagonists, codeine, or gabapentin[84] may be tested, but clinical evidence is lacking in patients with severe asthma.

Control of upper airway diseases is associated with asthma control. Chronic rhinosinusitis (CRS) with or without nasal polyposis is a major comorbidity, particularly in adults with late-onset asthma. CRS with nasal polyps (CRSwNP) is frequently associated with T2 -associated inflammation in the lower airways and with asthma severity.[85] CRSwNP should be objectively assessed using nasal endoscopy or CT scanning, but in asthma clinics, loss of smell may be used as a proxy that indicates the presence of nasal polyps with relatively high specificity.[86] As the inflammation is frequently common in nature between the upper and lower airways in severe asthmatic patients with CRSwNP, T2-related biologics can be helpful in controlling both conditions.

Laryngeal dysfunction may not only mimic asthma, but also frequently presents as a comorbidity in severe asthma. It is defined as paradoxical supraglottic or glottic movements in response to trivial triggers such as exercise, talking, breathing, stress, or perfume.[87] It is frequently misdiagnosed as exacerbation-prone or difficult-to-treat asthma; thus, the proper

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diagnosis is helpful in avoiding overtreatments. Challenge laryngoscopy (using external triggers such as exercise or other environmental triggers) is recommended as the standard diagnostic tool over simple laryngoscopy, because patients usually remain normal without trigger provocation.[88] Treatments have not been established, but speech pathology therapy is considered effective.

Extra-respiratory traits

Obesity is a common condition in severe asthmatic patients. Severe asthma cluster analyses have consistently identified late-onset asthma in patients with obesity as a phenotype, and asthma in individuals with obesity is associated with lower exercise capacity, reduced lung function, increased asthma exacerbations, and poorer health-related QoL when compared to asthma in individuals without obesity.[89] Asthmatic patients with obesity often have other comorbid conditions, including GERD, hypertension, obstructive sleep apnea, insulin resistance, and dyslipidemia. In addition, steroid resistance is common in severe asthmatic patients with obesity, and chronic OCS use aggravates weight gain. Weight reduction by diet and exercise or by surgical intervention may improve lung function, asthma control, and QoL in some patients with severe asthma and morbid obesity; however, further high-quality studies on severe asthma patients with obesity are required.

Osteoporosis is frequent comorbidity closely related to steroid administration. The risk of osteoporosis increases even with low-dose systemic corticosteroid use, especially in older individuals.[90] Osteoporosis increases the risk of fracture, and subsequent deconditioning complicates asthma management. Bone mineral density or trabecular bone scores based on dual-energy X-ray absorptiometry imaging are used to assess osteoporosis. Current guidelines recommend that patients expected to be treated for ≥3 months with OCS should be assessed to determine the presence of osteoporosis. The need for appropriate preventive medications, including bisphosphonates, should be reviewed.[4]

Psychological factors, such as anxiety and depression, are important causes of morbidity in asthma patients. The mental health of asthmatic patients can deteriorate because of uncontrolled asthma symptoms, recurrent asthma attacks, or the adverse effects of systemic corticosteroid therapy. In the SARP cohort, patients with insomnia, anxiety, and depression had a 2.4-fold increased risk of poor asthma control and a 1.5-fold higher risk of using healthcare resources, which suggested a significant impact of these conditions on asthma-related outcomes.[91] Conversely, when depression or anxiety improved in these asthma patients, asthma control and lung function improved.[92] The Hospital Anxiety and Depression Scale is a commonly used tool to assess psychiatric problems, in addition to the Asthma Quality of Life Questionnaire for health status and the St. George's Respiratory Questionnaire. Individuals with asthma and comorbid anxiety and depression are currently treated using the same standard approaches, such as behavior interventions, psychotherapy, and pharmacotherapies, as those used for the general population. However, the number of studies on the impact of controlling anxiety on severe asthma outcomes is limited.

Behavioral traits

Smoking is associated with more severe asthma symptoms, increased incidence of exacerbation, accelerated decline in lung function, and reduced responses to corticosteroids.[93] Smoking status is generally assessed through interviews or the use of exhaled carbon monoxide. As smoking cessation was shown to mitigate the decline in lung function and the risk of recurrent exacerbations, the importance of smoking cessation

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strategies should be highlighted in the management of severe asthma. Nonpharmacological interventions and pharmacotherapies, such as nicotine replacement therapy, bupropion, and varenicline, are used to assist smokers in their attempts to quit smoking. However, there are few prospective studies on changes in the clinical courses and inflammation patterns of smoking patients with severe asthma, which needs to be addressed in the future, and research should be conducted on the recent increase in the use of e-cigarettes.

Treatment adherence is problematic even in severe asthmatic patients, with reports of suboptimal adherence in >50% of the patients.[94] Suboptimal treatment adherence was associated with poor control, increased risk of exacerbation and healthcare utilization, and frequently resulted in an unnecessary treatment escalation.[95] There is no standardized method to measure adherence. Although questionnaires, self-reports, or prescription refill rates are commonly used, they often overestimate adherence or lack of reliability. Electronic device monitoring, such as chipped inhalers, could be an alternative tool to objectively assess adherence. Recent RCTs with patient self-monitoring via an electronic device and smartphone application plus remote clinician feedback on inhaler use helped maintain baseline adherence to ICS-containing controller medications and decrease the number of days with SABA use.[96]

Implementation of a treatable trait-based approach

Given the complexity of pathophysiological processes underlying severe asthma in individual patients, a treatable trait-based approach is reasonable. However, it may be too ideal and rather lead to overutilization of healthcare resources, in the absence of confirmative evidence. Substantial resources will be required to assess and control 20–30 potential respiratory, extra-respiratory, and behavioral traits.

For proper implementation, the prevalence and clinical relevance of potentially relevant treatable traits should be investigated first. Large-scale patient registries may serve as databases.[65,71] In the Korean Severe Asthma Registry phase 2 (KoSAR-2) study,[97] we have added a module for systematic assessment of potentially treatable traits and expect to generate the data on major treatable traits in terms of the frequency and impact on longitudinal outcomes in Korean patients with severe asthma (**Table 2**). Given the future potential risks of mortality and treatment-related morbidity,[47] long-term outcomes should be investigated in relation to specific traits and treatments. Furthermore, it is important to address patients' needs and to consider resource availability and cost effectiveness in developing treatable trait-based healthcare models in each region. However, based on previous studies, a number of traits are expected to be associated with clinical outcomes such as exacerbations or OCS use[66,68,70]; subsequently, the demonstration of treatment potential (or RCTs confirming targeted treatments) will be a critical determining step. Currently, only a few traits have robust clinical evidence: T2-related inflammation (corticosteroids and T2 biologics), airflow obstruction (bronchodilators), and smoking (smoking cessation).[4,98] Thus, further evidence is required to prove whether the treatable trait-based approaches are more beneficial than current uniform stepwise therapy in patients with severe asthma.

CONCLUSION

The concept of severe asthma has evolved to address unmet clinical needs. With the heterogeneity and complexity of severe asthma, a novel approach is required for effective

Table 2. List of potential treatable traits and their assessment tools in KoSAR-2

Treatable traits	Assessment
Respiratory traits	
Airway inflammation	T2: blood eosinophil count, FeNO
	Non-T2: induced sputum
Fixed airflow limitation	Spirometry (FEV1/FVC < 0.7)
	Chest CT
Cough	Cough severity score
Small airway dysfunction	Spirometry (MMEF)
	Chest CT
Bronchodilator reversibility	Spirometry (bronchodilator response)
Bronchial hyperresponsiveness	Bronchial provocation challenge test (PC20)
Extra-respiratory traits	
Allergic rhinitis	Questionnaire - Doctor's diagnosis
Rhinosinusitis ± nasal polyps	Questionnaire - Doctor's diagnosis
	OMU CT
	Rhinoscopy
GERD	Questionnaire - Doctor's diagnosis
Obesity	BMI
Cardiovascular disease	Questionnaire - Doctor's diagnosis
Diabetes	Questionnaire - Doctor's diagnosis
Osteoporosis	Questionnaire - Doctor's diagnosis
	Bone mineral density
Behavioral/Psychosocial traits	
Smoking	Questionnaire
Depression/Anxiety	Questionnaire - Doctor's diagnosis
Medication adherence	Questionnaire
	Prescription refill rate
Medication side-effects	Questionnaire
Quality of life	Questionnaire (EQ-VAS, SAQ)
Allergen sensitization	Skin prick test, ImmunoCAP assay

KoSAR-2, Korean Severe Asthma Registry phase 2; BMI, body mass index; CT, computed tomography; FeNO, exhaled nitric oxide fraction; EQ-VAS, EuroQol Visual Analogue Scale; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; PC20: provocative concentration causing a 20% fall in forced expiratory volume in 1 second; MMEF, maximum mid-expiratory flow; OMU, ostiomeatal unit; SAQ, severe asthma questionnaire; T2, type 2.

management and improvement in long-term health outcomes. Clinical phenotyping and molecular endotyping of severe asthma have accelerated the development and clinical application of novel biologics targeting key cytokines and have significantly alleviated the burden of severe asthma. Despite these advances, a subset of severe asthmatic patients remains uncontrolled. To improve the management and prognosis of these patients, new biological knowledge and novel therapeutic strategies should be incorporated into clinical management. The treatable traits approach, which includes the systematic assessment of specific characteristics within respiratory, extra-respiratory, and behavioral domains as well as targeting traits in each domain at the individual level, is an emerging paradigm for severe asthma management. Although further evidence is required, we expect that treatable traits-based approaches will overcome the limitations of previous stepwise approaches and improve long-term health status in severe asthmatic patients.

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