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Clinical Practice

Workup of difficult-to-treat asthma: implications from treatable traits

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Abstract

Traditional stepwise approach usually adjusts the treatment regimen based on changes in asthma symptoms and severity to achieve good asthma control. However, due to the generalized heterogeneity and complexity of asthma, its therapeutic efficacy in difficult-to-treat asthma is limited. Recently, a precision medicine approach based on the identification and intervention of treatable traits of chronic airway disease has been proposed and appears to be of greater benefit to asthmatics. We reported a 71-year-old male with uncontrolled asthma and multiple exacerbations over the past year. He complained of persistent dyspnea despite high-dose of inhaled corticosteroids plus other controllers. Does this patient have some potential treatable traits contributing to difficult-to-treat asthma? Through a multidimensional assessment of three domains including pulmonary, extrapulmonary, and behavioral/risk factors, 15 treatable traits were identified in the patient, mainly including airflow limitation, eosinophilic airway inflammation, small airway dysfunction, exacerbation prone, dilated cardiomyopathy, diabetes mellitus, inhaler device polypharmacy, smoking, and the absence of an asthma action plan. After targeted treatment for these treatable traits, the patient experienced significant improvement in dyspnea and he could maintain good asthma control with low-dose inhaled corticosteroids and long-acting β_2-agonist. This study shows that, in response to the limitation of a stepwise approach to therapy, treatable traits is a new strategy where patients are individually assessed for a specified set of treatable problems, and an individualized treatment program is developed and implemented based on this multidimensional assessment, especially for difficult-to-treat asthma.

Keywords: difficult-to-treat asthma, treatable traits, multidimensional assessment, comorbidity, stepwise approach

Introduction

Difficult-to-treat asthma (DA) affects only 5%–10% of the asthma population,[1] but its care accounts for >60% of asthma-related medical expenses due to the complexity and heterogeneity of the disease,[2] which brings significant challenges to current asthma management. The traditional stepwise approach recommended in asthma management guidelines is mainly effective for patients like mild or moderate asthmatics, while it is of much less clear value in patients with DA or severe asthma. Individualized multidimensional assessment and treatment for complex asthma was proposed in 2010[3] and then further developed and named "treatable traits" (TTs) by Agusti *et al.*[4] in 2016 as a new taxonomy for precision medicine of chronic airway diseases. The aim of this "label-free" strategy based on the identification of "TTs" is to provide individualized assessment for patients and develop a more precise treatment program. This novel therapeutic approach was also supported by the Lancet commission on asthma and the European Respiratory Society's annual meeting as a favored strategy toward precision medicine in airway diseases.[5]

TTs represent "potentially modifiable elements" based on genetic, biomarker, phenotypic, psychosocial characteristics, and environmental or behavioral factors that impact disease control or prognosis. They can be assessed and identified in three domains including pulmonary, extra-pulmonary, and behavioral/risk factors. A trait must meet three conditions: (1) clinically relevant, (2) measurable, and (3) modifiable.[6,7] A randomized controlled trial carried out by McDonald *et al.*[8] demonstrated that targeted intervention based on TTs could significantly improve symptom control, health-related quality of life and reduce the risk of acute exacerbations in severe asthma.

Identification of TTs as therapeutic targets can lead to a greater likelihood of asthma control, especially in patients with DA, as this strategy can effectively identify the heterogeneity of existing diseases and provide more inclusive, individualized treatment. Therefore, this case study aimed to demonstrate the benefit from TTs in improving asthma symptoms and clinical outcomes through a case of DA management based on the TTs approach, and to provide additional evidence to support its application in clinical practice.

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Methods

Patient

On 14 July 2021, a 71-year-old male with asthma visited the asthma clinic of West China hospital to seek specialist treatment. He had a 2-year history of asthma and had experienced four exacerbations in the past 12 months despite treatment with 100/200 μg/day of salmeterol/fluticasone and 10 mg/day of montelukast. In May 2021, he underwent 7 days of anti-infective and nebulized inhaled corticosteroids therapy at the local clinic due to acute asthma attack and respiratory tract infection triggered by a cold. Then his cold symptoms improved; however, his dyspnea was not relieved under an escalated anti-asthma treatment of salmeterol/fluticasone (50/250 μg, one inhalation twice daily).

Initial assessment and stepwise approach

We reviewed the patient's medical history. First, his diagnosis of asthma was confirmed based on recurrent respiratory symptoms, including dyspnea and wheezing, and the documented evidence of a positive bronchodilator test (230 ml, 15.3%). Second, we assessed his asthma control level through clinical symptoms, lung function, and asthma exacerbation history. The respiratory symptom control assessed by the Asthma Control Questionnaire (ACQ)[9] showed a total score of 2.5, and dyspnea quantified by the revised Borg scale scored 4, which indicated uncontrolled asthma. Within the last year, the patient experienced four exacerbations, three of which required systemic corticosteroid treatment. To summarize, this patient not only had poor asthma symptom control and obvious airway obstruction but was also at increased risk of future exacerbations.

According to the patient's preference and inhaler device technique ability, we replaced salmeterol/fluticasone with budesonide/formoterol. By reviewing the patient's response during the follow-up in the outpatient department, we gradually increased budesonide/formoterol from 640/18 to 1280/36 μg/day, and finally, added tiotropium bromide and low-dose oral prednisone (10 mg, once daily) based on the step 5 therapy recommended by the Global Initiative for Asthma (GINA).[10] After 2 weeks of short-term oral corticosteroids (OCS) treatment, the asthma symptoms in this patient finally improved with ACQ scores of 0.75, indicating a well-controlled level. However, his respiratory symptoms worsened again while stepping down the asthma treatment.

Multidimensional assessment

According to GINA guidelines,[10] this patient's asthma control remained poor despite treatment with high-dose inhaled corticosteroids (ICS) and long-acting β_2-agonist (LABA) combined with additional therapies, which indicated that he had DA and did not respond well to the stepwise approach. In order to find and identify the potential factors that contributed to his refractory asthma, we performed a multidimensional assessment of the patient based on evidence of asthma-related TTs that had been identified and validated from existing studies including our previous research.[8,11–13] As a result, a total of 27 TTs involving 8 pulmonary traits, 13 extra-pulmonary traits, and 6 behavioral traits/risk factors were eventually assessed in this patient (Table 1).

Pulmonary domain

Following the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines,[14] airflow limitation was assessed using a standardized spirometer (MedGraphics CPES/D USB, MN, USA) to measure baseline (pre) and post-salbutamol (post) forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and FEV_1/FVC. The forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75}$), the forced expiratory flow at 50% of FVC (FEF50%), and the forced expiratory flow at 75% of FVC (FEF75%) were also recorded as percentages of predicted values. All the predicted values were calculated using data from the Chinese population.[15] Bronchodilator reversibility was defined as a ≥12% or 200 ml improvement in FEV_1 at 15 min after inhaled 400 μg salbutamol (GSK, Madrid, Spain).[16] Small airway disease (SAD) was defined when at least two of the three indicators ($FEF_{25–75}$, FEF50%, and FEF75%) were <65% of predicted values.[17]

Airway inflammation was identified by induced sputum differential cell counts. Sputum induction and analysis were performed as described previously.[18] Sputum was induced using 4.5% saline atomized with an ultrasonic nebulizer (Cumulus, HEYER Medical AG, German), with 400 μg salbutamol pre-treatment. If pre- or post-FEV_1 was ≤40% of predicted, sputum was induced with 0.9% saline after it was deemed safe by the supervising physician. Selected sputum plugs were dispersed using dithiothreitol, a total cell count performed, and differential cell counts were performed by well-trained researchers from Australia and China after preparation of cytospins. Airway inflammatory phenotypes were classified as eosinophilic (eosinophils ≥ 3%), neutrophilic (neutrophils ≥ 61%), mixed granulocytic (eosinophils ≥ 3% and neutrophils ≥ 61%), and paucigranulocytic (eosinophils < 3% and neutrophils < 61%).[19]

Fractional exhaled nitric oxide (FeNO) was measured by a NIOX analyzer (Aerocrine, Solna, Sweden) as a surrogate biomarker for evaluating eosinophilic airway inflammation when sputum is not available.

Extrapulmonary domain

In addition to patient self-report of medical history and symptoms, the patient was screened for the following conditions: diabetes mellitus (fasting and random blood glucose levels, hemoglobin A1c), hypertension (blood pressure levels), heart disease (myocardial injury markers, echocardiography), and psychological dysfunction (Hospital Anxiety and Depression Scale, HADS).[20] Height and weight were measured to calculate body mass index (BMI).

Peripheral venous blood was collected either in ethylenediamine tetra acetic acid-treated tubes for total blood cell counts or Vacutainer tubes (BD Biosciences, San Jose, CA, USA) to obtain serum for determining C-reactive protein (CRP) and immunoglobulin E (IgE), which were quantified via enzyme-linked immunosorbent assay following the manufacturer's instructions.

Risk factors/behavioral domain

Medication adherence was assessed using medication possession ratio and pharmacy prescription records. Inhalation technique was assessed using a standardized inhaler technique checklist[21] and inhalation-device polypharmacy was defined as using three or more types of inhaler to deliver asthma medication.[22] Both smoking and written asthma action plan (AAP) were assessed by patient self-report.

Allergen sensitization was assessed by skin prick testing (SPT) with allergen extracts for house dust mites (Dermatophagoides pteronyssinus, Dermatophagoides farinae), mold (Alternaria tenuis, Aspergillus species), dog hair, cat hair, pollen (ragweed, birch, London plane), and cockroach, together with positive (histamine) and negative (saline) controls.

Table 1. Treatable traits assessment and identification in the patient.

Treatable traits		Assessment method	Defining criteria	Assessment results
Pulmonary traits				
Airflow limitation	Variable airflow limitation	Spirometry	Postbronchodilator increase in $FEV_1 \geq 12\%$ and ≥ 200 ml	FEV_1 increased by 15.3% and 230 ml after bronchodilator inhalation
	Persistent airflow limitation	Spirometry	Postbronchodilator $FEV_1/FVC < 0.7$	$FEV_1/FVC = 68.21\%$ after bronchodilator inhalation
Eosinophilic airway inflammation		Induced sputum, FBC, FeNO	Meet one or more of the following: sputum eosinophils $\geq 3\%$, blood eosinophil count $\geq 0.3 \times 10^9$/l, FeNO ≥ 30 ppb[13]	FeNO = 45 ppb, blood eosinophil count = 770 cells/μl
Pulmonary infection		Self-report, chest CT, microbiologic testing	Typical clinical symptoms and infiltrates on chest imaging and/or positive etiological detection	Patient had symptoms of cough, sputum production, and dyspnea, and his chest CT revealed bilateral pneumonia
Small airway dysfunction		Spirometry	Spirometry: ≥ 2 indicators <65% pred: FEF_{25-75}, FEF50% and FEF75%[17]	FEF_{25-75} pred = 25.1%, FEF50% pred = 21.6%, FEF75% pred = 22.7%
Exacerbation prone		Self-report	≥ 3 courses of systemic corticosteroids in the last 12 months[12]	The patient experienced four asthma exacerbations in the past 12 months, three of which required oral corticosteroids
Emphysema		Chest HRCT	Doctor and/or radiologist diagnosis	The patient's chest HRCT showed no obvious signs of emphysema
Bronchiectasis		Chest HRCT	Doctor and/or radiologist diagnosis	The patient's chest HRCT showed no significant signs of bronchiectasis
Extrapulmonary traits				
Upper airway disease: allergic rhinitis, rhinosinusitis, nasal polyps, and vocal cord dysfunction		Self-report	Doctor and/or radiologist diagnosis	Denied previous history of upper airway disease, no symptoms such as nasal obstruction, sneezing, nasal itch, and hoarseness
Obstructive sleep apnea		Self-report	Doctor's diagnosis	Denied symptoms such as daytime somnolence, excessive snoring, and fragmented night sleep
Gastroesophageal reflux disease		Self-report	Doctor's diagnosis	Denied symptoms such as heartburn, regurgitation, nausea, belching, and angina-like retrosternal chest pain
Cardiovascular disease	Hypertension	Self-report, blood pressure	Doctor's diagnosis	Blood pressure up to 140/100 mmHg
	Dilated cardiomyopathy	ECG, echocardiogram, cardiac MRI	Doctor's diagnosis	Left ventricular dilatation and systolic dysfunction, LVEF = 25%
	Heart failure	NT-proBNP, echocardiogram	Doctor's diagnosis	Nocturnal dyspnea, NT-proBNP = 2892 pg/ml
	Pulmonary hypertension	mPAP, echocardiogram	Doctor's diagnosis	PAP = 68 mmHg, moderate
Diabetes		Fasting and random blood glucose, HbA1c	Fasting blood glucose ≥ 7.0 mmol/l or random blood glucose ≥ 11.1 mmol/l or HbA1c $\geq 6.5\%$	Fasting blood glucose = 7.21 mmol/l, HbA1c = 6.4%
Anemia		Hemoglobin	Hb < 130 g/l in males	Hemoglobin = 161 g/l
Systemic inflammation		hs-CRP	hs-CRP ≥ 3 mg/l[8]	CRP = 2.18 mg/l
Underweight/obesity		BMI	Underweight: BMI < 18.5 kg/m^2 Obesity: BMI > 30 kg/m^2	BMI = 27.43 kg/m^2
Psychological dysfunction	Anxiety	HADS-A	Anxiety domain score ≥ 8	Both anxiety and depression scores were 0
	Depression	HADS-D	Depression domain score ≥ 8	
Eczema		Self-report	Doctor's diagnosis	Denied symptoms such as severe itching, erythema, and dry skin
Behavioral traits/risk factors				
Medication adherence		Self-report or drug prescription records	Reported use of < 70% of prescribed treatment	The patient's adherence to asthma medications was more than 95% of the prescribed dose.

Table 1. (*Continued*)

Treatable traits		Assessment method	Defining criteria	Assessment results
Inhalation technique	Poor inhalation technique Inhaler device polypharmacy	Questionnaire, standard inhaler checklists Medication review	Inhaler technique rated as inadequate With ≥3 different inhaler devices	The patient had a qualified inhalation technique and no critical errors occurred Maintain asthma control with Symbicort + Spiriva and relieve asthma exacerbations with Ventolin
Smoking		Self-report, questionnaire	Admit to smoking	Smoking for >40 years and six to seven cigarettes per day
Allergen sensitization		Skin prick test or allergen-specific IgE	≥ 1 positive skin response to tested allergens or increased allergen-specific IgE	He denied previous allergies and had negative skin prick tests on 11 common allergens
Absence of asthma action plan		Self-report, questionnaire	Absence of written action plan or not using the plan during exacerbations	The patient did not have a written asthma action plan

NT-proBNP, N-terminal pro-B-type natriuretic peptide; BMI, body mass index; CT, computed tomography; ECG, electrocardiographic; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FBC, full blood count; FeNO, fractional exhaled nitric oxide; FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEF50%, forced expiratory flow at 50% of forced vital capacity; FEF75%, forced expiratory flow at 75% of forced vital capacity; HRCT, high-resolution computed tomography; Hb, hemoglobin; HADS, Hospital Anxiety and Depression Scale; HbA1c, Hemoglobin A1c; hs-CRP, high-sensitivity-c reactive protein; IgE, immunoglobulin E; LVEF, left ventricular ejective fraction; mPAP, mean pulmonary arterial pressure; pred, predicted.

Results

Identification of TTs

Following the multidimensional assessment, a total of 15 TTs were identified in this patient, including 6 pulmonary traits, 6 extra-pulmonary traits, and 3 behavioral traits/risk factors. The results of this TTs-related assessment are shown in Table 1.

Pulmonary traits

Asthma specialists in our multidisciplinary team (MDT) identified the pulmonary traits based on the patient's asthma diagnosis, lung function, and history of recent acute attacks. This patient's FEV_1 increased by 15.3% and 230 ml from baseline after bronchodilator inhalation, confirming the diagnosis of asthma and demonstrating that he had variable airflow limitation. In the meantime, he also had persistent airflow limitation, as seen by the post-bronchodilator FEV_1/FVC ratio of 68.21%, which contributed to his poor response to ICS-LABA therapy.[23] Further evidence for the presence of SAD in this patient came from the fact that his FEF_{25-75}, FEF50%, and FEF75% were all <65% of the predicted values. In order to identify and distinguish different types of airway inflammation, we attempted sputum induction on this patient but failed due to his poor cooperation. He was ultimately defined as having an eosinophilic phenotype of asthma[13] with a peripheral eosinophil count of 770 cells/μl and a FeNO level of 45 ppb.

Additionally, the patient in this case had a distinct exacerbation-prone asthma phenotype,[24] as evidenced by the four exacerbations he experienced in the previous 12 months, three of which required oral corticosteroids. His most recent exacerbation was brought on by an acute respiratory infection, which mainly manifested as cough, sputum production, and dyspnea; a radiologist was invited to evaluate the patient's chest high-resolution computed tomography (HRCT) and there were no obvious signs of emphysema or bronchiectasis. After receiving the anti-infective treatment of piperacillin-tazobactam for 4 days and amoxicillin for 10 days at a local hospital, his cough and expectoration symptoms were significantly resolved.

Extrapulmonary traits

No evidence supported the diagnosis of upper airway illness, obstructive sleep apnea, gastroesophageal reflux disease, or eczema based on the patient's present symptoms and self-report. He also did not have systemic inflammation or anemia since his CRP was 2.18 mg/l and his hemoglobin level was 161 g/l.[8,25] According to the results of both HADS-A and HADS-D scores of 0, we concluded that this patient had no psychological dysfunction and did not require specialized psychological intervention. However, he needed to pay attention to weight management because he was already overweight with a BMI of 27.43 kg/m^2.

In this case, this patient's fasting blood glucose level briefly increased 5 years ago, but he failed to monitor it constantly. Under the guidance of the endocrinologist in our MDT, we determined that the patient had diabetes based on his fasting blood glucose level of 7.21 mmol/l.[26] Subsequent dietary or pharmacological interventions may be considered to reduce the possible impact of glycemic fluctuations on asthma control.[12,27]

Furthermore, the initial evaluation of cardiovascular disease in this patient showed that, in addition to a 5-year history of hypertension, he also had heart failure (HF) and myocardial damage with a serum myoglobin of 126.20 ng/ml, serum creatine kinase isoenzyme of 10.73ng/ml, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) of 2892 pg/ml. Echocardiography further indicated a decrease in left ventricular systolic function [left ventricular ejective fraction (LVEF) of 25%] and moderate pulmonary hypertension (Fig. 1A). To look for the cause of the decreased cardiac function, the patient underwent cardiac magnetic resonance imaging (MRI) and the results revealed that he had dilated cardiomyopathy (DCM) (Fig. 1B–E). Given the patient's poor cardiopulmonary function and relative contraindications to endomyocardial biopsy,[28] a myocardial biopsy was not performed to identify the etiology of his DCM. The decreased ventricular ejection fraction presented in DCM caused systemic circulatory hypovolemia and further aggravated his airway damage, which eventually developed into cardiogenic pulmonary edema with nocturnal dyspnea as the main symptom. That is to say, the patient had both asthmatic dyspnea and cardiogenic dyspnea, which explains why his dyspnea could not be completely relieved by high-dose ICS-LABA treatment.

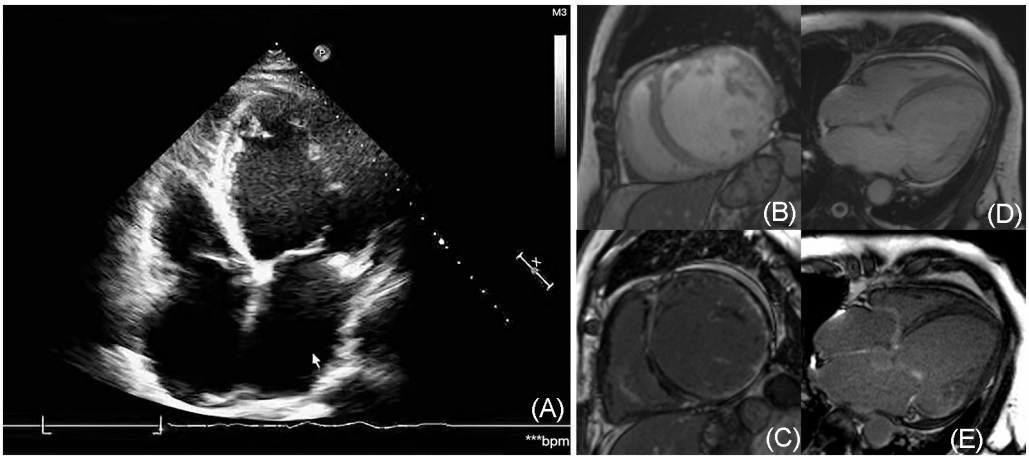

Figure 1. Echocardiography and cardiac MRI. (**A**) shows the decreased left ventricular systolic function (LVEF = 25%) and moderate pulmonary hypertension (pulmonary arterial pressure = 68 mmHg). (**B**–**E**) show the whole heart was enlarged mainly with left ventricular enlargement, decreased systolic function, and the left ventricular wall shows thinning and diffuse fibrosis.

Behavioral traits/risk factors

The patient showed good medication adherence and qualified inhalation technique during our multidimensional assessment, both of which are essential for achieving maximum therapeutic benefit in asthma management. Due to the use of three distinct inhaled medications, this patient was identified as having inhalation-device polypharmacy, which increased his medication burden and exposed him to greater risk of adverse drug reactions.[29] In terms of risk factors, this asthma patient's SPT results were negative and there were no signs of allergen sensitization. However, he smoked 6–7 cigarettes per day and had been a smoker for 40 years. Long-term active smoking may have contributed to his increased risk of respiratory infections and asthma exacerbations, and it is never too late to quit smoking.[30] Moreover, the asthma patient in this case had not received any advice about AAP from the initial diagnosis until this acute attack, and his lack of awareness of the warning symptoms might partly explain his recurrent exacerbations over the past year.[31]

Targeted Interventions for TTs

We gave targeted interventions for each TT identified in this asthma patient. Based on their clinical impact, dyspnea symptoms, airflow limitation, eosinophilic airway inflammation, and DCM are thought to be the more important TTs that should be prioritized in targeted treatment (Fig. 2). As a consequence, the modified diagnosis for this patient was: (1) DA, (2) DCM, (3) HF, (4) pulmonary hypertension, (5) hypertension, (6) diabetes, (7) overweight.

Considering that the patient's symptom of dyspnea was still poorly controlled, high-dose ICS with LABA and long acting muscarinic antagonist (LAMA) should be continued for the treatment of airflow limitation and eosinophilic airway inflammation, and low-dose OCS was tapered to discontinuation in the presence of effective interventions for other TTs. Furthermore, we replaced salmeterol/fluticasone with budesonide/formoterol for treating SAD since the latter had a higher deposition rate in the distal airways.[32] Under the 2019 European Society of Cardiology recommendations for the treatment of DCM with HF,[33] the cardiologists in our MDT treated this patient with drugs such as diuretics and angiotensin-converting enzyme receptor inhibitors. In addition, the patient would use low-dose metoprolol tartrate to maintain good blood pressure control, which was also recommended to improve the prognosis of HF with reduced ejection fraction while had little impact on bronchial asthma.

Afterwards, we successfully discontinued OCS and de-escalated the patient's asthma treatment to a low dose of ICS-LABA, with the use of a single inhalation device that also avoided the risk of unnecessary adverse drug reactions. We also advised the patient to stop smoking, keep a healthy diet, and appropriately increase his physical activity in order to intervene in other TTs. Finally, we developed a written AAP for the patient at the follow-up to help him achieve better asthma management (supplementary Fig. 1, see online supplementary material). We also asked him to attend the cardiology clinic after discharge for DCM-specific evaluation and follow-up.

Follow-up

The DCM-related cardiac dysfunction in this patient, which was the most important TT that influences asthma management, had significantly improved after targeted treatment, with NT-proBNP falling from 2892 to 728 pg/ml. After another echocardiography was performed 2 months later, his LVEF had increased to 36%. In addition, the patient's dyspnea symptom had also been relieved with the revised Borg score declining from 4 to 0 points and his ACQ score decreased to 0.5 at the same time.

Long-term outpatient follow-up showed that the patient could maintain good asthma control with low-dose inhaled corticosteroids and a long-acting β_2-agonist. More importantly, he had not experienced any acute attacks thereafter and his quality of life also greatly improved.

Discussion

Precision medicine in airway diseases now urgently needs to move to clinical practice, and the TTs strategy is thought to be the best alternative to achieve this goal.[34] As seen in this case, the identification of TTs through multidimensional assessment has allowed for real-world targeted therapy, especially for the important TTs, to improve clinical outcomes for an individual. To our knowledge, this is the first case study to test a multidimensional and targeted approach to DA. We carefully assessed and characterized 27 relevant TTs, 15 of which were ultimately identified in this asthma patient, and individualized treatment for

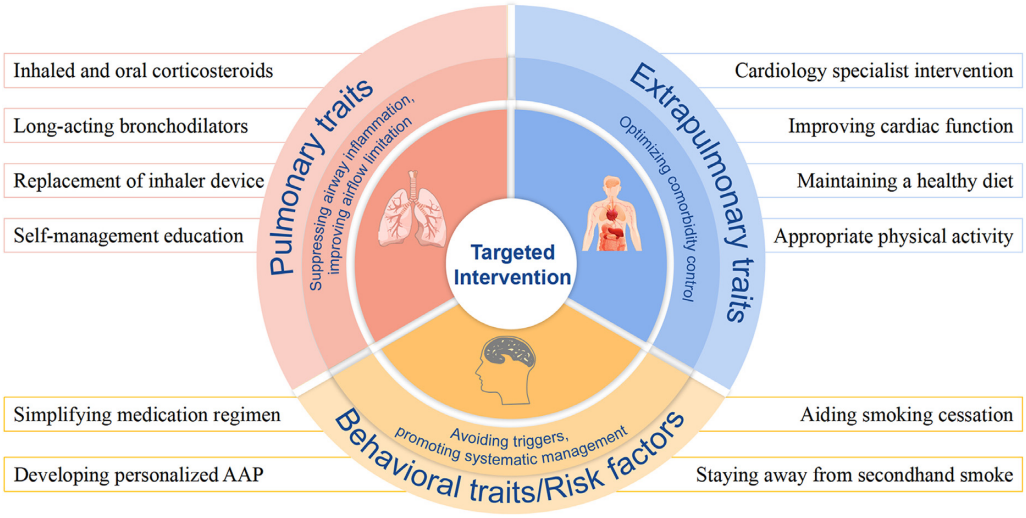

Figure 2. Targeted intervention for TTs.

these traits resulted in satisfactory asthma control. This study advances knowledge of the precision medicine approach based on a TTs strategy for DA, a challenging airway disease, and provides complementary evidence to support the new treatment paradigm.

Unlike traditional diagnostic labels, the TTs approach often extends beyond the disease itself to find more treatment opportunities for people with asthma, especially in the setting of suboptimal response to high-dose corticosteroids. We identified multiple TTs from pulmonary, extrapulmonary, and risk factor/behavioral domains, with DCM being the most important trait affecting asthma control and requiring additional specialist evaluation. After targeted interventions for DCM, this patient experienced a significant improvement in DCM-related cardiac dysfunction, which would facilitate the de-escalation of his asthma treatment from high-dose ICS-LABA and OCS. In addition, other identified TTs may also affect the patient's symptom control and future risk of exacerbations. Ensuring treatment results of multiple traits had additional stacked effects leading to the optimal improvement in asthma outcomes.[34]

According to GINA recommendations,[10] DA usually refers to asthma that is uncontrolled despite treatment with medium- or high-dose ICS-LABA or requires high-dose ICS-LABA to maintain symptom control and reduce exacerbations. Most patients with DA have modifiable factors, such as allergen exposure, poor adherence, or untreated comorbidities, and their asthma will be well-controlled if these issues are addressed. In contrast, severe asthma remains uncontrolled despite adherence to optimized high-dose ICS-LABA therapy and management of contributory factors, or requires these high-dose treatments to achieve control. It is important to distinguish between DA and severe asthma, but the two are frequently confused in clinical practice due to the limited objective evidence for diagnosing severe asthma and the complexity and time-consuming nature of assessment.[35] Our case study provides good evidence that the application of the TTs strategy can help to distinguish patients with DA from "true severe asthma".

There are several key issues related to TTs in clinical practice that should be considered. First, international consensus on the criteria for candidate TTs and associated evidence-based treatment recommendations need to be established. Second, there is a lack of criteria to determine the importance of specific TTs that require greater priority in patient assessment and management. In our case study, DCM was given priority for specialist treatment because, in the context of clinical expertise and extensive medical experience, we believe that it had a greater impact on the patient's dyspnea symptom than other identified TTs. Third, how do we apply the TTs approach to clinical practice in primary care or other environments with poor health care?

Conclusions

The TTs-oriented precision medicine approach provides the possibility of individualized assessment and treatment for patients with chronic airway diseases. Our study shows the ability to apply the concept of TTs to the complex population of patients with DA and provides strong support for the feasibility and validity of this new treatment paradigm. By using this targeted TTs framework, we can focus on specific treatment that improves clinical outcomes for patients while reducing excess medication and side effects. Meanwhile, this strategy can also help to distinguish patients with DA from those with "true severe asthma".

Supplementary data

Supplementary data is available at *PCMEDI* online.

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Ethics statement

Informed consent has been obtained from the patient himself, who was from the Australasian Severe Asthma Network (ASAN) (https://www.severeasthma.org.au) reviewed and approved by the

Institutional Review Board at West China Hospital, Sichuan University, Chengdu, China (No. 2014-30).

Conflict of interest

None declared.

Author contributions

Q.Z. and L.L. collected the original medical records and drafted the initial manuscript. Q.Z., W.W.W., and L.L. participated in the design of the article framework and critically reviewed the manuscript. G.W. and P.G.G. conceived the research question and contributed to the preparation and critical review of the manuscript. V.M.M. and P.G.G. critically reviewed the manuscript. Y.C.C. provided the evaluation and management of cardiovascular disease, especially dilated cardiomyopathy. All authors have read and approved the final version of the manuscript.

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