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PERSPECTIVES

A Proposed Approach to Chronic Airway Disease (CAD) Using Therapeutic Goals and Treatable Traits: A Look to the Future

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Abstract: Chronic airflow obstruction affects a wide range of airway diseases, the most frequent of which are asthma, COPD, and bronchiectasis; they are clearly identifiable in their extremes, but quite frequently overlap in some of their pathophysiological and clinical characteristics. This has generated the description of new mixed or overlapping disease phenotypes with no clear biological grounds. In this special article, a group of experts provides their perspective and proposes approaching the treatment of chronic airway disease (CAD) through the identification of a series of therapeutic goals (TG) linked to treatable traits (TT) – understood as clinical, physiological, or biological characteristics that are quantifiable using biomarkers. This therapeutic approach needs validating in a clinical trial with the strategy of identification of TG and treatment according to TT for each patient independently of their prior diagnosis.

Keywords: airflow obstruction, biomarker, personalised medicine, COPD asthma overlap

Introduction

Current definitions identify the classical patterns (clinical and biological) of asthma and COPD unequivocally. However, the heterogeneous nature of both processes and their overlap in some cases has given rise to intense research in order to define more homogeneous groups of patients on the basis of phenotypes or endotypes. This problem is not new and was pointed out as far back as 1987 by Burrows et al, who described a group of patients (with what they called "asthmatiform bronchitis") who had a clinical evolution and prognosis that lay between asthma and COPD[1] supporting the view of a common origin of asthma and COPD, the so-called Dutch hypothesis.[2] Recent studies of lung function trajectories in COPD also support the influence of early childhood asthma in early lung development.[3] This is now known as asthma-COPD overlap (ACO).[4] ACO is a theoretical construct with no clear biological grounds and with an imprecise definition that encompasses both long-standing asthmatics who smoke and develop chronic airflow obstruction, and patients with COPD who have blood eosinophilia or greater reversibility after a bronchodilator test,[5] even though they have been shown to be very different from each other.[6]

Some authors have already proposed leaving behind the approach based on phenotypes or endotypes in order to adopt a pragmatic view through the identification of "treatable traits" (TT) for each particular patient.[7,8] However, this novel

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approach contains a few inaccuracies as there is some confusion as to what TT really are, and which ones should be taken into account. The article published by McDonald et al[9] defines them as "therapeutic targets identified by the phenotype or endotype through validated biomarkers". This publication puts forwards lists with different TT that leave out cardinal symptoms such as dyspnoea while including others such as "smooth muscle contraction" or "oedema of the bronchial mucosa", which are of doubtful clinical significance. What is more, contradictorily, blood or sputum eosinophilia is considered a TT, whereas at the same time it is claimed not to be a TT, but rather a "TT biomarker".

With the present document, a group of authors in the areas of asthma and COPD from the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) aims to provide their insight with regard to the therapeutic approach based on TT, by overcoming some inaccuracies so that this may be applicable in clinical practice, and be able to serve as a basis for a clinical trial in order to prove its effectiveness. Further, we argue that the therapeutic goals (TG) set for each patient must be considered separately from the TT upon which action can be taken in order to achieve them.

Operational Definition of Chronic Airway Disease (CAD)

The proposal is to group patients who have Chronic Airflow Obstruction under the common denomination of Chronic Airway Disease (CAD) – defined as an obstructive spirometry pattern with post-bronchodilator FEV_1/FVC below 0.70 – independently of the underlying etiopathogenic mechanism; and to adapt their treatment based on TG and TT that have been previously identified using biomarkers or specific diagnostic tests (Figure 1).

Therapeutic Goals and Treatable Traits in CAD

We argue that it is reasonable to separate clinical needs – what we want to improve in each patient (TG) – from the characteristics (TT) upon which action may be taken in order to achieve this improvement. The definitions proposed for TG and TT are summarised in Table 1. We acknowledge that scientific evidence is still scarce in some cases, but we believe this approach offers practical advantages when it comes to deciding on therapeutic interventions for specific patients. In this article, we will discuss the TG and TT in CAD, and we will show that the different diseases making it

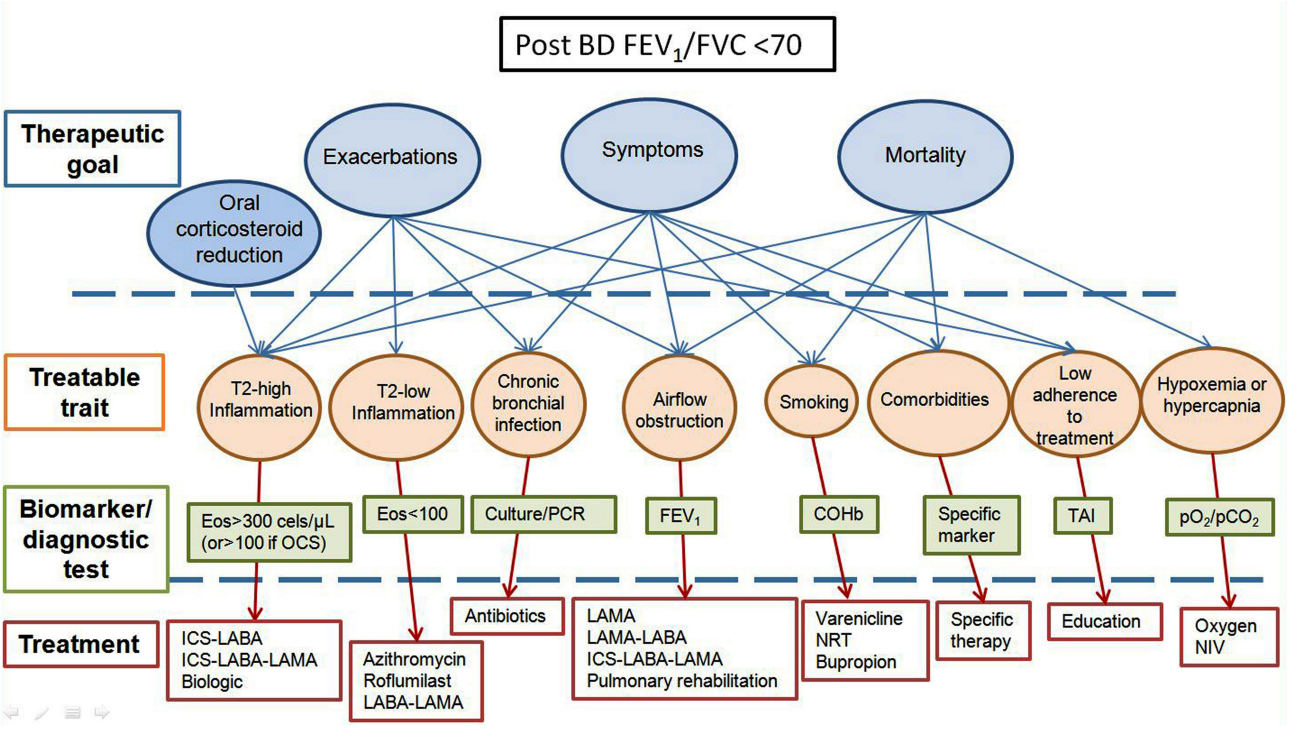

Figure 1 Conceptual approach to treatment of CAD.

Abbreviations: Eos, eosinophils; OCS, oral corticosteroids; PCR, polymerase chain reaction; FEV_1, Forced expiratory volume in 1 second; COHb, carboxyhemoglobin; TAI, test of the adherence to inhalers; pO_2, partial pressure of oxygen; pCO_2, partial pressure of carbon dioxide; ICS, inhaled corticosteroids; LABA, long-acting beta agonists; LAMA, long-acting muscarinic antagonists; NRT, nicotine replacement therapy; NIV, non-invasive ventilation.

Table 1 Definition and Characteristics of Therapeutic Goals and Treatable Traits

	Definition	Characteristics
Therapeutic goals	These are the clinical needs of patients (symptoms, exacerbations, quality of life, physical activity) or aspects of the disease upon which action must be taken to improve their prognosis (progression of the disease, mortality)	-These are not therapeutic targets, but rather clinical problems that must be eliminated or improved -Most patients have several TG -It is possible to improve different TG with a single therapeutic intervention
Treatable traits	These are the clinical, physiological, or biological characteristics present in each individual patient, and they are quantifiable through biomarkers or specific diagnostic tests. They must have effective treatment to improve the value of the variable	-They must themselves have an impact on one of the TG (that is, there must be a clear relationship between the value the characteristic takes and that of the objective in question; eg: more eosinophils, more exacerbations) -Treatment, through the improvement of the value of the treatable trait must, as a result, improve one or more TG

up (asthma, COPD, bronchiectasis . . .) basically coincide in these. Table 2 summarises the TG and TT in CAD.

Therapeutic Goals

Two types of TG can be considered: symptomatic improvement, and reduction of the risks involved in the disease and its treatment. The main TG is a reduction in mortality, something that has already been achieved in asthma with the use of inhaled corticosteroids (ICS);[10] however, even in developed countries, deaths are still recorded, but they are nearly always associated to poor social conditions.[11] COPD is a disease with a high mortality rate, although to date few strategies have been proven to be effective in reducing it (for instance, giving up smoking).

Exacerbations have a high impact on the quality of life of asthmatics,[12] as they are risk factors for mortality,[13] and also for loss of lung function.[14] In COPD and bronchiectasis, control of exacerbations is also an evident TG, as these events worsen the quality of life of patients and their prognosis.[15,16] Lastly, it is of vital importance to avoid the iatrogeny associated with the treatment, which is especially evident in the case of systemic corticosteroids.[17]

Control of symptoms, particularly dyspnoea, is an indisputable TG in CAD, taking into account its relationship to the quality of life of patients. Besides, in the case of asthma, poor symptomatic control represents a greater risk of exacerbations,[18] and in COPD it is independently associated with mortality.[19]

Treatable Traits

* Therapeutic non-adherence (TN). It is well established that TN in asthma is a risk factor for exacerbations.[20] However, different reminder systems (e-mails, telephone . . .) have been shown to improve adherence[21] and, although some doubts still persist concerning their impact on asthma control[22] it seems reasonable to detect and reduce TN. Patients with poor

Table 2 Therapeutic Goals and Treatable Traits in CAD

Therapeutic Goals	Treatable Traits	Biomarker Associated to Therapeutic Trait
Reduction of symptoms:	- Bronchial obstruction	-FEV_1
-Dyspnoea	-Non-adherence	-Questionnaires
-Night awakenings	-Aggravating factors (allergens, environmental pollution, etc.)	-Environmental levels
-Health-related quality of life	-Smoking	-CO-oximetry
Reduction of risk:	-Comorbidities	-Variable in each case
-Reduce mortality	-Eosinophilia	-Eosinophils in blood or airways
-Reduce progression of the disease	- Chronic infection	-Germ isolation
-Prevent exacerbations	- Chronic bronchitis	- Chronic bronchitis
-Reduce adverse effects of medication	- Chronic hypoxemia	-PaO_2/SaO_2
	- Chronic hypercapnia	-$PaCO_2$
	-Deficit of alfa1-AT	-AAT levels
	-Lung hyperinflation	- Inspiratory capacity

adherence to the treatments used in COPD are at greater risk of being hospitalised and even passing away.[23,24] Some interventions may improve therapeutic adherence in this disease.[24]

* Tobacco use. Smoking worsens asthma control in a dose-dependent way.[25] However, giving up the habit improves both the lung function and symptoms of asthmatics.[26] Carrying on smoking bears a strong relationship to morbidity and mortality in COPD, whereas giving it up is associated to clear improvements in survival rates.[27]

* Comorbidities. The presence of certain comorbidities associated with asthma are linked to poorer control of the disease[28] and specific treatment for any of them improves it, as occurs for instance with polyposis and obstructive apnoea syndrome during sleep.[29,30] Patients with COPD and bronchiectasis suffer from numerous comorbidities that aggravate their prognosis.[31–34] Nevertheless, these must be considered independent diseases that require specific treatment which, on most occasions, does not depend on their association with chronic airway disease. Gastroesophageal reflux is associated with a greater risk of exacerbations, but there is no definitive evidence that its treatment reduces its incidence.[35]

* Bronchial obstruction. In asthma, FEV_1 below 80% of the theoretical value is an independent predictor of exacerbations[36] and poor lung function is related (albeit imperfectly) to symptoms of the disease.[37] Further, several clinical trials have demonstrated that tiotropium added to a combination of inhaled corticosteroids and long-acting β-2 agonists (ICS/LABA) in poorly controlled asthmatics with bronchial obstruction achieves significant functional improvement (approximately 100 mL), resulting in a 21% reduction of exacerbations,[38] accompanied by symptomatic improvement independently of blood eosinophils.[39] In COPD, bronchial obstruction is associated with greater mortality, more symptoms, and more exacerbations.[40] Other measurements of airflow obstruction such as air trapping or lung hyperinflation would need to be explored.

* T2 Inflammation. The presence of T2 inflammation, measured by the presence of eosinophils, both local and peripheral is associated with poorer asthma control and more exacerbations.[41] Besides, it has been proven that eosinophilia is a good predictor of the response to corticosteroids,[42] and that adjusting the treatment of severe asthma on the basis of sputum eosinophilia reduces exacerbations.[43] The role of the monoclonal antibodies anti-interleuquina-5 (anti-IL-5) and anti-IL4 and 13 in the treatment of severe eosinophilic asthma has been perfectly established.[44]

Eosinophilia, measured in induced sputum or in peripheral blood, is a good marker of the therapeutic response to ICS also in COPD. Due to the difficulty in using sputum eosinophilia as a biomarker in usual clinical practice, blood eosinophilia is emerging as the most useful TT biomarker in order to decide about the use of ICS as maintenance treatment in COPD.[45–50]

* Chronic bronchial infection. The isolation of potentially pathogenic microorganisms (PPMs) in bronchial secretions of patients with COPD is considered to be a chronic infection, instead of a colonization.[51] Colonization implies no harm to the host, and, by definition, it would not require any type of treatment, but PPMs in stable COPD are associated with increased inflammation, increased frequency and severity of exacerbations and faster decline in pulmonary function; therefore, the term colonization is no longer considered adequate.[52] Regarding the treatment of chronic bronchial infection in chronic airway diseases, there is limited experience in asthma and COPD. The isolation of *Pseudomonas aeruginosa* has been shown to be associated to a greater risk of exacerbation in asthma, and the AMAZES study evidenced that azithromycin at a dose of 500 mg 3 times a week, as a treatment added to the usual medication, is capable of reducing severe exacerbations and improving the quality of life of poorly controlled asthmatics despite a combination of ICS/LABA.[53] Several studies have demonstrated that long-term treatment with macrolides reduces exacerbations in COPD.[54–56]

Clinical trials of intermittent treatment with quinolones in patients with chronic bronchial infection have been shown to decrease exacerbations.[57] However, this treatment is not currently recommended due to the risk of inducing resistance against a first-line drug in the management of exacerbations.

The greatest experience is in bronchiectasis and, therefore, we consider that treatment must follow the recommendations of antibiotic treatment of chronic bronchial infection in bronchiectasis.[58] According to the pathogen, the antimicrobial resistance pattern and the clinical manifestations, treatment may consist of a course of antibiotics, the long-term use of macrolides or inhaled antibiotics.

* Chronic bronchitis. Patients with COPD and chronic bronchitis suffer more exacerbations, have a poorer quality of life, and experience greater loss of lung function than subjects without a production of sputum.[59] Mucolytics

could also have a beneficial effect in patients with emphysema owing to their antioxidising action, but another drug used to reduce exacerbations, roflumilast, is indicated only in patients with chronic bronchitis.[60]

In patients with asthma, mucous hypersecretion is associated with more symptoms, more obstruction, and more exacerbations.[61] Furthermore, in this case, roflumilast has revealed improvement of symptoms and lung function in asthmatics when added to montelukast, in comparison to this drug used in monotherapy.[62]

* Respiratory insufficiency. Severe chronic hypoxemia is a factor associated with a rise in mortality in COPD, and its correction is one of the few interventions known to increase survival in the disease, wherefore it constitutes an evident TT.[63,64] Chronic hypercapnic respiratory insufficiency is associated with greater risk of mortality,[65] which could be modified through the use of non-invasive ventilation (even though there are some discordant studies in this regard),[66–68] in which case it could also be considered a treatable trait.

* In contrast, we do not consider the following to be TT at this time, due to a lack of clear evidence in some of the fundamental aspects (although this is something that could change in the future):

- Exhaled nitric oxide fraction (FeNO). Despite the fact that this is widely used clinically, there is ongoing controversy as to whether adjusting treatment on the basis of its values improves asthma control, and neither is there a well-established cut-off point separating what is normal from pathological; consequently, a recent review in the Cochrane database advises against this indication (except, perhaps, in patients with frequent exacerbations).[69] In COPD, something similar happens: its persistent high levels seem to be associated to a greater risk of exacerbation of COPD,[70,71] but a therapeutic strategy based on this biomarker has not yet been demonstrated to have an impact on clinical results, and neither has the best cut-off points been established as yet.

-Allergy. Immunotherapy is not indicated in severe asthma, which usually presents with non-reversible bronchial obstruction, and allergic avoidance is not well established in this context.

- Bronchial hyperresponsiveness (BHR). Asthma control and degree of BHR do not show a close relationship and a large percentage of patients with good control of the disease exhibit ongoing BHR. Further, bronchoprovocation tests are contraindicated with $FEV_1 < 65\%$ and their relative complexity means they are not routinely carried out, not even in expert consultations. The AMPUL study[72] demonstrated that adjusting medication on the basis of methacholine test results could improve lung function and reduce exacerbations (mild ones), but a single study does not seem to be enough to justify considering BHR a TT.

In COPD, BHR appears to be a biomarker that is able to identify subgroups of patients with greater risk of disease progression and mortality.[73] These subjects could, hypothetically, be the best target group for treatment with ICS, which would confer this variable the character of TT. However, using this trait to indicate treatment with corticosteroids has not yet been demonstrated to produce clinically relevant results.

- Left ventricular diastolic dysfunction associated with lung hyperinflation. Some patients could present an alteration in filling of the left ventricle produced specifically by the hyperinflation associated with COPD. Bronchodilator treatment has been shown to be able to improve left ventricular telediastolic volume in these cases.[71] Thus, it is conceivable that in the future it will emerge as a new TT in COPD; however, for the time being, information is limited to a single study, and its relationship with dyspnoea, mortality, and other clinical outcomes has not yet been proven, whereby it is still premature to consider it as such.

Unified Treatment of CAD and Controversial Points

Figure 1 shows a unified conceptual approach to the treatment of CAD – independently of the "classical" diagnosis – based on TG and TT using their biomarkers or specific diagnostic tests. This conceptual approach poses a series of problems in clinical practice:

The definition of "high T2": It seems evident that blood eosinophils must be included in this definition. Ideally, eosinophilia should be measured in airways, but this is not feasible from a practical point of view at this time. According to the literature, the reasonable cut-off point appears to be 300 cells/μL. It must be taken into account that eosinophil count is affected by treatment with oral corticosteroids (OCS), high doses of inhaled corticosteroids (ICS), and biological drugs, so historical values should be taken into consideration.

The question also arises as to whether FeNO ought to be considered a marker of "high T2", since high values can be recorded in patients with rhinitis or respiratory infection. Besides, there is no clear cut-off point to

separate what is normal from abnormal, and each device offers different values of FeNO. Therefore, although its use is widespread in routine clinical practice and it may be useful in some situations, it does not seem advisable at the current time to classify it as a TT.

Meanwhile, neither is the definition of "low T2" clear enough to make it possible to claim that a patient will not benefit from anti-inflammatory treatment with corticosteroids or biological therapy working on T2 inflammation. In COPD there are already data that suggest that an eosinophil count below 100 cells/μL enables a poor response to ICS to be predicted;[74] and in asthma, data from the SIENNA study point in the same direction in patients with a low sputum eosinophil count.[75]

- According to this approach, patients classically diagnosed as COPD and "high T2" would be treated with ICS, whereas patients with the diagnosis of asthma and "low T2" would not receive them. There is a good number of published reports to support the former statement,[45–50] but the evidence to underpin the latter is more limited. Nevertheless, it has been shown that both sputum and blood eosinophilia predict significant response to corticosteroids in asthma patients.[76–78] Bearing in mind that induced sputum is technically demanding, the number of eosinophils in blood and sputum can be influenced by treatment (particularly systemic and inhaled corticosteroids) and the predictive value of these two biomarkers is far from perfect, it seems risky to leave a patient with bronchial obstruction – a clinical presentation compatible with asthma and a low blood eosinophil count – without ICS. Although blood eosinophil count is universally available, it is an imperfect surrogate for airway eosinophilia and a significant proportion of patients in real life have eosinophil counts between 100 and 300 cells/μL, in which case it would be necessary to draw up a therapeutic approach based on other TT (obstruction, infection, etc.) and/or carry out a therapeutic trial with anti-inflammatory drugs. While novel omics-based signatures have emerged, they have hardly ever been evaluated clinically, although a limited number of investigations have observed that a given gene expression signature in respiratory samples can predict response to corticosteroids.[79,80]

Clinical Trial Proposal

Evidently, this conceptual approach must be validated in a clinical trial. We propose launching a prospective, multicentre, open-label, double-arm clinical trial. Patients with post-bronchodilator FEV1/FVC<0,70 regardless of the previous diagnosis, and with a significant clinical impact (measured by 2 exacerbations requiring oral corticosteroids or antibiotics in the previous year and ACT<19 or CAT>10) would be recruited and randomized. At one arm, patients would be classified according to their prior diagnosis (asthma, COPD or bronchiectasis) and would be treated in accordance with the recommendations in international guidelines (GINA, GOLD, or ERS bronchiectasis guidelines).[81] In the other, patients would be treated in accordance with the TG/TT strategy, independently of their original diagnosis. Patients should be stratified according to their level of airflow obstruction severity (to avoid differences between the two groups) in the initial visit. The follow-up period would be 12 months, and adjustments in medication could be made depending on their evolution. The main response variable ought to be the burden the disease represents for the patient, by grouping specific aspects such as severe exacerbations and health status. The main objective would be to demonstrate that the strategy based on TG/TT achieves a greater proportion of controlled patients (without severe exacerbations, and with ACT $\geq$ 20 and CAT $\leq$10). Variables for secondary objectives would be exacerbations, pneumonias, quality of life, and burden of corticosteroid treatment in both arms. As secondary analysis, other variables are to be explored such as FeNO, BHR, sputum eosinophils and microbiota or lung hyperinflation.

Conclusions

Asthma, COPD, and other obstructive bronchial processes can have similar TG and TT, which enables them to be encompassed in a broader concept: chronic airways disease (CAD). It is possible to develop a therapeutic algorithm that is valid for CAD, based on TG and TT, although the one put forward herein lacks prospective validation (we propose launching a clinical trial) and relies on biomarkers with some limitations in identifying the underlying inflammatory process. We have absolutely no doubt that in the near future we will be able to have more precise tools available in order to decide the treatment for each patient, without the most relevant being the classical clinical diagnosis.

Disclosure

Luis Perez de Llano declares to have received grants and/or fees for consultancy or speeches from Novartis, AstraZeneca, GSK, Teva, Boehringer-Ingelheim, Chiesi, Sanofi, Menarini, Mundipharma, and Esteve, and reports grants,

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