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COMMENTARY

Can Treatable Traits Be the Approach to Addressing the Complexity and Heterogeneity of COPD?

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Abstract: The complexity of COPD implies the need to identify groups of patients with similar clinical characteristics and prognosis or treatment requirements. This is why much attention has been paid to identifying the different clinical phenotypes by investigating the clinical expression of the disease, and endotypes by studying the biological networks that enable and limit reactions. However, this approach is complicated because one endotype gives rise to one or more clinical characteristics, and clinical phenotypes can be derived from several endotypes. To simplify the approach, a new taxonomic classification of COPD based on the different causes (or etiotypes) has been proposed, but these etiotypes have not yet been validated. A simpler method is the so-called tractable traits approach, which is free from any designation of the disorder to be treated and does not present the criticality of using etiotypes. A large randomised controlled trial on using the treatable traits approach in COPD is still lacking. Nevertheless, this approach is already applied by following the GOLD strategy. However, its application is complicated because several potentially treatable traits have been identified within the pulmonary domain, the extrapulmonary domain, and the behavioural/risk factor domain. In addition, the hierarchy of the dominant treatable traits has not yet been established, and they change over time both spontaneously and because of treatment. This means that the patients being treated according to the tractable traits approach must be constantly followed over time so that the therapy is focused on their temporal needs.

Keywords: chronic obstructive pulmonary disease, phenotypes, endotypes, etiotypes, treatable traits

Introduction

COPD is a complex syndrome.[1] Chronic airflow limitation, a combination of parenchymal destruction and small airway damage that varies from patient to patient, often coexists with other diseases, leading to completely different presentations and prognoses.[2] COPD is also a heterogeneous disease.[1] Heterogeneity means that not all intrapulmonary and extrapulmonary components characterising COPD are present in all individuals at any given time.[3] This is further complicated by the observation that the dynamic interactions of the different components over time are not linear. Therefore, when treating an individual with COPD, the complexity and heterogeneity of the disease must be addressed.[4]

Identifying groups of patients with similar clinical characteristics and prognoses or treatment needs is imperative.[4] This implies the necessity to identify groups of patients with similar clinical features and similar prognosis or treatment needs. Unfortunately, there are substantial differences between the available studies on categorising patient groups mainly because sub-types are still generally grouped arbitrarily.[5] This leads to a lack of reproducibility of the subtypes, which does not allow their clinical application.

Clinical Phenotypes and Endotypes

The substantial differences in the classification of subtypes also depend on the need to use a highly complex approach that has to take into account the interrelationships between the exposome (the totality of human environmental exposures from conception onwards), the genome (the genetic background of the individual), the endotype (the biological networks that enable and constrain reactions) and the clinical phenotype (the clinical expression of the disease; eg, symptoms,

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exacerbations, response to treatment, rate of disease progression or death).[4] Moreover, some, but not all, clinical phenotypes have been associated with specific biological mechanisms. At the same time, many may correspond to different endotypes (eg, frequent exacerbators or patients with cardiovascular comorbidities).[6] The endotype expresses the underlying biological pattern acting through cellular and molecular inflammatory mechanisms. The current understanding of COPD endotypes is still relatively imprecise because of the complexity of their interactions with other aspects of the disease, such as risk factors, disease activity, and stage of progression. Furthermore, accurate classification of COPD endotypes is still lacking because one endotype gives rise to one or more clinical features, and clinical phenotypes may be derived from several different endotypes.[6]

To overcome or at least limit these difficulties, an attempt can be made to link endotypes to clinical phenotypes and endotype-specific biomarkers.[4] Phenotypes and biomarkers are easier for clinicians to understand than endotypes, making identifying and validating new biomarkers for transitioning to a personalised approach increasingly urgent. However, despite the considerable advances in omics technology and the role of omics in respiratory medicine, several methodological, practical, and ethical issues must be resolved before laboratory data can be translated into therapeutic applications.[7]

Although obstructive airway diseases, and thus also COPD, are heterogeneous, meaning that all patients are different and can present with a wide range of symptoms and underlying factors, the pivotal randomised controlled trials (RCTs) used to approve each new drug do not take heterogeneity into account.[8] The evidence supporting the use of currently available therapies is based on the results of major Phase III RCTs, which tend to be large, involving thousands of COPD patients selected solely based on the degree of obstruction, smoking history, and a symptom questionnaire or history of exacerbations.[9] This approach does not allow the personalisation of COPD treatment, which must still be considered empirical despite attempts to move towards a more individualised treatment. Few patients are responsive to all the drugs available for COPD treatment.[10] The clinical response to the various treatment options available for COPD varies according to the characteristics of the disease. Since the relationship between symptom severity, airflow limitation and severity of exacerbations varies between patients, each treatment regimen must be specific to the individual patient.[10]

Etiotypes

To spread knowledge about non-smoking-related COPD and also to encourage research into possible diagnostic, preventive or therapeutic methods, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 Executive Summary proposed a new taxonomic classification of COPD based on the different causes (or etiotypes) that may contribute to it.[11] Seven etiotypes were recognised based on the predominant risk factors underlying the disease: genetically determined COPD, COPD due to abnormal lung development, COPD induced by cigarette smoking, COPD due to biomass exposure and pollution, COPD due to infection, COPD and asthma, and COPD from an unknown cause. However, the Executive Summary did not comment on treatment differences depending on the different etiotype, but it is likely that there are, although not yet clearly identified.

These etiotypes have not yet been validated.[10] At present, it seems likely that no regulatory authority will accept their inclusion in RCTs. However, ideally, the same therapy should be compared across different etiotypes. Unfortunately, some individuals will have multiple etiotypes and we do not yet know how many patients have overlapping etiotypes, which makes it problematic to calculate study power and duration to document the efficacy of a drug treatment in a specific etiotype.[10]

The use of etiotypes is very complicated because of the many factors that may be involved and the different clinical phenotypes that respond differently to these factors.[12] Furthermore, it has been suggested that some of these COPD etiotypes should be approached with caution because the pathologies underlying them, such as impaired lung growth and development, are unlikely to represent the ongoing inflammatory lung disease that is commonly thought to characterise COPD.[13] This is why we wonder whether the applicability of these etiotypes to routine diagnostic and therapeutic procedures is feasible and, therefore, whether the search for the best is for the patient's good.

Treatable Traits Approach

Heterogeneity in the COPD population calls for a personalised medicine approach that is not based on the stratification of patients into subgroups but rather on individual characteristics.[14] A new paradigm for the management of chronic airway diseases, and thus also of COPD, is the use of the so-called treatable traits approach, which is free from any designation

of the disorder to be addressed[15] and, consequently, it does not present the criticality of using etiotypes. This approach proposes a label-free precision medicine strategy for managing patients with airway disease based on identifying treatable traits in each patient.[16] These traits may be treatable based on phenotypic recognition (and thus probabilistic evidence based on positive and negative predictive values) or an in-depth understanding of critical causal pathways (eg, true endotypes). The tractable traits approach deconstructs COPD and other chronic airway disorders into quantifiable, clinically relevant, and treatable components.[16] They represent a therapeutic strategy free from traditional diagnostic labels that does not require the identification of phenotypes and endotypes.[16]

The current treatment approach for COPD takes the heterogeneity of this disease into account to some extent, but an appropriately consistent and fully patient-centred treatment concept is still lacking.[8] In fact, a gradual approach is recommended, but this means an increase in the time needed to reach the right treatment schedule, and, in any case, some patients remain poorly controlled despite intensive treatment. In general, recommendations are to increase the dose of corticosteroids, but this is not very beneficial and has potential side effects. After all, the treatment is not adequately personalized. The treatable traits approach recommends considering the patient as a whole, identifying the key factors underlying each patient's disease that may require an approach different from standard guidelines or recommendations, and looking beyond "one-size-fits-all" diagnostic labels to create and implement an individualised management plan.[8]

Several potentially treatable traits were identified within the pulmonary domain (such as airway smooth muscle contraction, systemic allergic inflammation, eosinophilic or neutrophilic airway inflammation, dyspnoea, emphysema, mucus hypersecretion, and others), the extrapulmonary domain (such as depression, anxiety, overweight/obesity, gastro-oesophageal reflux disease, obstructive sleep apnoea, systemic inflammation, and others), and also within the behavioural/risk factor domain (suboptimal inhaler technique or adherence, smoking and others including absence of a written action plan).[17]

It has been pointed out that also chronic bronchial bacterial infection is an important treatable trait to address.[18] According to growing data, the airway microbiome is linked to COPD clinical characteristics, severity, and long-term mortality.[19] The respiratory microbiome is an intriguing therapeutic target as a possible treatable trait in efforts to subphenotype patients and offer precision medicine.[20] It is readily modifiable by clinical interventions and represents an untapped opportunity for therapeutic manipulation.[20] However, the airway microbiome is implicated differently in neutrophilic and eosinophilic COPD, with characteristics that define endotypes that need different forms of treatment.[21]

In any case, the hierarchy of dominant tractable traits has not yet been established, and, in any case, some tractable traits, such as mortality, should be assessed ubiquitously.[17]

In the recent NOVEL observational longiTudinal studY (NOVELTY) study, a large, 3-year, real-world, prospective observational study in patients diagnosed with "asthma", "COPD" or "asthma + COPD" in primary care and specialised centres around the globe, patients with COPD had on average five tractable traits, indicating the need to address multiple traits simultaneously.[22] The most frequent tractable traits in COPD included non-reversible airflow limitation, emphysema, frequent productive cough, environmental exposures (including smoking), susceptibility to exacerbations and frequent use of medication as needed.[22]

To transfer the theory of treatable traits into practice, it has been recommended to prioritise those treatable traits that relate to specific outcomes, such as disease exacerbations or frequent use of oral corticosteroids.[23] This involves targeting an outcome with a high impact and reducing the number of traits to be assessed to 11. The three pulmonary treatable traits are eosinophilic airway inflammation, airflow limitation and frequent chest infection. Four extrapulmonary traits are to be considered, vocal cord dysfunction, rhinitis, dysfunctional breathing, and smoking. Similarly, there are four traits in the area of behavioural/risk factors, suboptimal adherence, inadequate inhaler technique, inhaler device polypharmacy, and absence of a written action plan. These traits are recognised by a specific trait identification marker and are then targeted for treatment.[23] They generally respond to a combination of specific pharmacotherapy and behavioural interventions.

However, crucial aspects that may complicate the use of the treatable traits approach are that COPD patients may change their treatable traits over time, and this indicates that regular assessments to deliver goal-targeted personalised treatments are needed,[24] and sex-related differences were found, with most traits more prevalent and severe among women.[25] Furthermore, the concept of the presence of supertraits is emerging.[23] These traits should always be identified and treated because they improve seemingly unrelated traits. Inhalation device adherence/technique, type (T)2 inflammation, high body mass index/obesity, and smoking are the main supertraits to consider.[23]

A large RCT on using the treatable traits approach in COPD is still lacking. However, a systematic review and meta-analysis have evaluated the effectiveness of treatable traits-targeted interventions for managing obstructive airway disease. Eleven studies were identified.[26] The tracts treated within each study ranged from 13 to 36. Seven controlled trials were included in meta-analyses. Treatable traits interventions effectively improved health-related quality of life, hospitalisations, all-cause mortality at one year, dyspnoea score, anxiety, and depression. These findings suggest that the characterisation of treatable traits and targeted interventions on them may improve outcomes of obstructive airway disease and represent a promising treatment model.

Although the NOVELTY study showed that the prevalence of treatable traits varies whether they are identified in primary care or a specialist setting,[22] it was proposed that treatable traits should be used for all COPD patients, regardless of disease severity or treatment setting.[22] It has been suggested that the general practitioner focuses on the dominant traits in the first instance rather than a broad approach, for example, identifying high T2 inflammation and airflow limitation and treating these traits with ICS and bronchodilators.[23] If the patient does not respond, the remaining characteristics are identified. The presence of an increasing number of treatable traits or resistance to customised trait therapies should, however, prompt the general practitioner to refer the patient to an experienced physician for a more comprehensive examination and management strategy. A multidimensional assessment should therefore evaluate the multitude of interacting traits within the pulmonary, extra-pulmonary and risk/behavioural domains concomitantly or sequentially and then develop a personalised management plan.[23]

However, it was pointed out that implementing a treatable trait strategy adds several new criteria to the standard procedure, increasing the complexity, expense, and time of consultations.[22] Furthermore, this strategy's interdisciplinary character necessitates forming larger and stronger teams of specialised healthcare experts capable of intervening and managing recognised treatable traits. All these factors may produce opposition to its widespread deployment. Nevertheless, since customised treatment options are often more successful and provide a superior risk/benefit ratio, the benefits are expected to surpass the expenses of the early phase quickly.

It is becoming widely accepted among specialists that the treatable traits approach is an essential step toward precision medicine in treating chronic airway diseases. For this reason, it is recommended that new clinical trials focus on prevalent treatable traits.[9] Obviously, if this happens, the outcomes and parameters to be considered will be influenced by the choice of treatable traits. These studies can be a way to provide needed information on treatment efficacy in a personalised medicine context.

Anyway, when following the recommendations of the GOLD strategy, the treatable traits approach is already applied, at least partially. According to these recommendations, follow-up treatment is based on two key treatable traits: dyspnoea and the occurrence of exacerbations.[11] Other treatable traits can be identified based on clinical recognition (phenotypes) and/or an in-depth understanding of critical causal pathways (endotypes) through validated biomarkers (eg, circulating eosinophils to guide treatment with ICS in COPD patients with evidence of T2 inflammation). However, since treatable traits can coexist in the same patient and change over time (spontaneously or due to treatment), the patient treated following the treatable traits approach must be constantly followed over time so that therapy is focused on his or her temporal needs.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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