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Current concepts in targeting COPD pharmacotherapy: making progress towards personalized management

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Abstract

Chronic obstructive pulmonary disease (COPD) is a common, complex and heterogeneous condition which is responsible for considerable and growing morbidity, mortality and healthcare expense worldwide. In order to decipher the complexity of COPD, it is imperative that we identify groups of patients with similar clinical characteristics, prognosis and/or therapeutic needs, so called *clinical phenotypes*. This strategy is logical for research but it may be of limited clinical value because clinical phenotypes may overlap in the same patient and the same clinical phenotype could result from different biological mechanisms. With the goal of matching assessment to treatment choices, the most recent iteration of GOLD reorganized treatment objectives into two categories (improving symptoms, i.e., dyspnoea and health status, and decreasing future risk, as predicted by FEV_1 level and exacerbations history), thus moving closer to individualized medicine using currently available bronchodilators and anti-inflammatory medications. Yet, future therapeutic options are likely to include targeting *endotypes* which reflect subtypes of patients defined by a distinct pathophysiological mechanism. Specific *biomarkers* of these endotypes would be particularly useful for clinical practice, especially when clinical

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phenotype alone is insufficient to identify the underlying endotype. Currently, a limited series of potential COPD endotypes and biomarkers have been suggested. We will gain empiric knowledge from proof of concept trials in COPD with emerging drugs that target specific inflammatory pathways. In each instance, specific endotyping and biomarker efforts will likely be required for success of these trials, since the pathways are likely to be operative in only a subset of patients. Network analysis of human diseases offers the possibility of a better understanding of disease patho-biologic complexity while facilitating the development of new therapeutic alternatives and, importantly, a reclassification of complex diseases. All these development should pave the way towards personalized treatment of COPD in the clinic.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, complex and heterogeneous condition which is responsible for considerable and growing morbidity, mortality and healthcare expenses worldwide (1). Within this context *complexity* relates to many different components with non-linear dynamic interactions, whereas *heterogeneity* implies that not all of these components are present in all patients at any given time point and/or at different time points in the same patient (2). To address this complexity and heterogeneity it is imperative to identify groups of patients with similar clinical characteristics, prognosis and/or therapeutic needs, so called *clinical phenotypes* (3). This strategy is logical for research as it may facilitate a more homogeneous selection of patients in whom to decipher the complexity of COPD. On the other hand, it may be of limited clinical value because, first, clinical phenotypes may overlap in the same patient and, second, the same clinical phenotype could result from different biological mechanisms (i.e. there can be “etiologic heterogeneity”). Although the evolution of therapeutic approaches has increasingly attempted to address these complexities, to date the majority of therapeutic options belong to a limited number of pharmacological classes, i.e. bronchodilators (short-acting and long-acting β2 agonists (SABA and LABA) and corresponding antimuscarinic agents (SAMA and LAMA)) and inhaled corticosteroids (ICS).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) was established in 1998 to improve the diagnosis, management and prevention of COPD. A challenge for GOLD has been to provide recommendations for the correct use of the available therapies while positioning recommendations flexibly to allow the use of future, innovative therapeutic approaches that have the potential to target a personalized medicine approach. Another challenge faced by GOLD and other guideline or strategy documents, is the current paucity of evidence on how clinicians can identify patients who are more likely to benefit from available COPD treatments. This underlines the need for new treatment approaches in conjunction with refining the way treatment indications are determined. Finally, in most patients COPD is associated with other chronic diseases as part of a chronic comorbid condition that should be addressed globally. This may decrease the likelihood that treatments targeting only the COPD component will change the natural history of the patient’s disease.

The current review addresses the strengths and limitations, including gaps in the evidence, of the approaches taken by GOLD to move towards personalized medicine. We also address

potential future approaches to position emerging therapies that will likely target specific biological pathways. As such, we also review the concept of an *endotype*, "a subtype of a (clinical) condition defined by a distinct pathophysiological mechanism, " (4) as it may relate to future COPD therapy, and the role of biomarkers in marking endotypes and directing therapy.

Search strategy and selection criteria

To inform this brief review of endotypes and targeted therapies in COPD, we utilized several approaches. We searched the Cochrane Library, MEDLINE, and EMBASE. Search terms included "COPD AND (clinical trial OR effectiveness OR systematic review), one year. For the preceding years of this search we used the bibliography cited in the GOLD document (GOLD search strategy is COPD, filters: human, all adult, items with abstracts, clinical trial or systematic review. In addition we used a search strategy of "COPD" OR "Chronic Obstructive Pulmonary Disease" OR "Emphysema" OR "Chronic Bronchitis" AND "LABA" OR "LAMA" OR "LABA/LAMA" or "ICS" OR "ICS/LABA." Finally we used the search "COPD" OR "Chronic Obstructive Pulmonary Disease" OR "Emphysema" OR "Chronic Bronchitis" AND "Endotype" OR "Molecular Phenotype" OR "Biomarker-directed" OR "Biomarker-driven" OR "Targeted Therapy." Since some of these terms have only recently entered the medical vocabulary, we then supplemented this search strategy by pursuing relevant references in the associated bibliographies.

Positioning current therapeutic options – the GOLD (r)evolution

The GOLD 2001 and 2006 reports used the degree of airflow limitation alone (as assessed by the FEV_1 value) to assess disease severity. Bronchodilators were recommended as treatments to improve lung function and reduce symptoms in all patients, with ICS reserved for patients with severe and very severe airflow limitation suffering with repeated exacerbations. In 2011, the GOLD document acknowledged that using FEV_1 alone to assess disease severity was an overly simplistic approach (1), as FEV_1 is often a poor predictor of the degree of symptoms, health status impairment and risk of exacerbations (5). Treatment objectives were re-organized into two categories: relieving current symptoms and reducing the risk of future adverse health events. A well-known 4-quadrant assessment system that characterizes patients into broad phenotypic categories, based on symptoms and risk of exacerbations (as assessed by FEV_1 and the history of exacerbations in the last year) was introduced with the goal of matching assessment to treatment choices, thus moving *"COPD treatment towards individualized medicine – matching the patient's therapy more closely to his or her needs."* This evolution was a major step forward in the strategy for COPD management, and other groups have proposed conceptually similar approaches, although with several variations (6, 7).

Current GOLD treatment propositions

For all GOLD groups, short acting bronchodilators are recommended for symptom relief. These drugs may be sufficient in GOLD A patients. When patients exhibit more symptomatic limitation (GOLD B) long acting bronchodilators are recommended as maintenance. In patients at greater risk of an exacerbation (GOLD C and D) the first choice

pharmacotherapy includes ICS/LABA combinations or LAMA, as both of these drug classes reduce exacerbation rates and improve lung function and health status (1). LABA/LAMA combinations are suggested as an option for GOLD B, C and D patients, as there is evidence that these drugs are more effective than long acting bronchodilator monotherapy, although most of these studies were not designed to capture effects on exacerbations (8) or were performed in patients who do not have a history of frequent exacerbations (9). Roflumilast, a phosphodiesterase 4 inhibitor, is positioned to prevent exacerbations in GOLD C and D patients with a chronic bronchitic phenotype, a novel example of phenotypically driven therapy (3, 10).

Strengths and weaknesses of GOLD propositions

The overall concept of matching more closely the clinical assessment of an individual patient to specific treatment options is attractive and a first step towards personalized therapy: “high symptom” patients (groups B and D) require more bronchodilators, while “high risk” patients (groups C and D) may require anti-inflammatory therapy. However, some GOLD treatment propositions may be criticized for not being strictly evidence-based (11), which is largely due to the paucity of evidence on treatment effects in different subgroups of patients. For example, more studies are required to investigate the effects of LABA/LAMA combinations in patients with a history of exacerbations (12). Additionally, triple therapy (ICS/LABA plus LAMA) is a treatment option for group D patients, and is frequently prescribed in clinical practice, but the evidence for this regime preventing exacerbations is limited (13). Group C and D patients are heterogeneous regarding the future risk, depending on the way they qualified for these categories (low FEV_1, history of exacerbations, or both). It would thus be logical to restrict the use of ICS/LABA to those who have a history of exacerbations with or without severe airflow limitation, long-acting bronchodilator(s) being preferred for those with low FEV_1 and no exacerbation history (14). Furthermore, while results of the ECLIPSE study identified a stable clinical phenotype of patients with ≥ 2 exacerbations each year (supporting GOLD’s threshold defining patients at risk) (15), ICS/LABA combinations have been studied predominantly in populations with an annual exacerbation rate nearer 1; thus, the corresponding GOLD treatment positioning does not quite match the evidence generated by randomized clinical trials (RCTs). Indeed, no therapeutic trial published before the 2011 GOLD document and only a few published after used selection criteria strictly matching the current GOLD classification (16).

Recent evidence from clinical trials: supporting, enriching or challenging current treatment propositions?

How should inhaled corticosteroids be used in COPD?—Studies have demonstrated inconsistent effects of ICS on the rate of FEV_1 decline (17), so the main focus of use for these drugs is to prevent exacerbations. ICS are generally used as part of fixed-dose combinations (FDCs) with LABAs in order to maximize the clinical benefits. Historically, many clinical trials assessing these FDC have included patients with FEV1<50% predicted and a history of exacerbations (18, 19). In contrast, the TORCH study included patients with FEV<60% predicted (pre-BD) to study fluticasone propionate/salmeterol (20), and patients with FEV1<70% predicted (post-BD) were used to study the effect of fluticasone furoate/vilanterol (21); in both cases these ICS/LABA combinations had

a greater effect than the LABA alone on exacerbation rates. This suggests that for patients with a history of exacerbations, the level of airflow limitation is less important in predicting benefit from ICS. Furthermore, fluticasone furoate/vilanterol was studied using ICS doses of 50, 100 and 200 μg, addressing for the first time the lack of evidence on dose-response relations regarding long-term ICS effects (21). The dose-response curve was relatively flat in terms of exacerbations, suggesting that high ICS doses are not required to achieve optimal benefit in COPD. However, it must be noted that the number of side effects of interest (i.e., pneumonia and bone fractures) was not decreased at the lower dosages.

ICS withdrawal in patients receiving long-acting bronchodilators—In 2011, a systematic review concluded that ICS withdrawal was not associated with important deterioration in overall patient outcomes, but that this result could be influenced by the definition of exacerbations and concomitant treatments (22). In 2014, results of the WISDOM trial were reported (23). This randomized controlled trial included patients with severe airflow limitation and a history of exacerbations despite often being on ICS treatment (70% were taking ICS treatment at screening), who received triple therapy during a run in period before being randomized into the ICS withdrawal and control (ICS maintained) groups. In the withdrawal group, the dose of fluticasone propionate was progressively reduced (1000 μg/day, 500 μg/day, 200 μg/day) every 6 weeks before the drug was eventually stopped. There was no difference in the occurrence of exacerbations between the two groups, but there was a difference between groups of 40 ml loss of FEV_1 over the 40 weeks following complete withdrawal. Despite extensive subgroup analyses (24) the study did not identify patients at increased withdrawal-associated risk of exacerbations, but it should be noted that the overall exacerbation rate in both arms was relatively low (approximately 0.5 exacerbations / patient / year), which probably made it difficult to detect a treatment difference in the context of a low rate of events and, as occurs in many clinical trials, WISDOM was not powered for such subgroup analysis. Nevertheless, the loss of lung function after ICS withdrawal, also reported by two other previous studies (25, 26), suggests some benefit for ICS in these patients. Likewise, these results also suggest that low-dose ICS may be sufficient in some patients.

When to use combination treatments—Comparisons between ICS/LABA FDCs and LAMAs did not reveal any consistent difference in terms of exacerbation rate (27). In general, combination treatments including ICS/LABA, LABA/LAMA and ICS/LABA +LAMA have been found to be superior to bronchodilator monotherapy treatments at least for some clinical endpoints (27–32). However, the magnitude of the overall difference between combination treatments and monotherapy is often limited and less than the expected additive effect of the components of the combination. Furthermore, most studies of LABA/LAMA combination inhalers have included patients that were previously treated with at least one long acting bronchodilator monotherapy. Thus, it would seem logical to restrict the use of combination treatments to patients with dyspnoea and/or exacerbations persisting despite previous long acting bronchodilator monotherapy. GOLD does not include such a step-by-step approach, but this may be what many clinicians expect from therapeutic guidance, provided that the rules and criteria guiding choices are simple enough and

evidence-based. Combining precision and simplicity, as a prerequisite for successful guidelines implementation, remains a major challenge for personalized medicine (33).

Future therapeutic directions

Disappointingly, the overall magnitude of clinical benefit of the different pharmacological treatment options in COPD patients remains somewhat limited. Although symptomatic benefits and reductions in exacerbation rates can be achieved with currently available treatments, the effects on the lung function decline and mortality in long term studies have been disappointing (20, 34). This can be at least in part explained by the presence of some degree of irreversible morphological abnormalities including emphysema and loss of small airways (35). Various inflammatory mechanisms involved in COPD do not respond well to corticosteroids, thus also limiting treatment effects (36). Furthermore, the response to corticosteroids appears to differ based on inflammatory cells involved, the presence of eosinophils suggesting greater likelihood of response (37). Since morphological changes and biological features are markedly heterogeneous among COPD populations (38, 39), the sensitivity to pharmacological treatments will vary between patients. These observations suggest that (i) individualizing the currently available treatments based on more in depth individual characterization of pathophysiology may optimize efficacy, and (ii) developing new treatments targeting specific mechanisms involved in subgroups of patients may be an effective strategy. Additionally, we need to adopt a benefit-risk approach for therapeutics (33) rather than a purely efficacy-based reasoning (Figure 1). Regarding long-acting bronchodilators, the risk of cardio-vascular events has been the topic of several studies with somehow contradictory results depending on study designs and populations' characteristics (40–43). Regarding inhaled corticosteroids (ICS), there are growing concerns related to the risk of pneumonia and systemic side-effects (44). Yet, these risks should be balanced with an apparent reduction of a composite outcome of death and COPD hospitalization recently described in patients received LABA and ICS *vs.* those receiving LABA alone (45). Since these data come from an observational database study, they warrant further confirmation.

Identification of responders or patients at increased risk of side effects

While some patient characteristics clearly influence treatment choice for invasive approaches such as lung volume reduction surgery (46), most large trials investigating COPD pharmacological treatments have not crisply identified predictors of responders or non-responders, or patients at increased risk of side-effects. Importantly, the usual way of analysing data from randomized, controlled, clinical trials (RCTs) is to compare mean effects between treatment arms, which may lead to miss patient who go in a direction opposite to the majority. An example of this is the identification of a subgroup of COPD patients with persistent systemic inflammation using network analysis that was not identified using the more conventional group mean comparison (47). Furthermore, most RCTs do not fully reflect real-life populations and contexts (48), and sample sizes are too limited for extensive and powerful subgroup analyses. An exception isroflumilast, which was shown to be especially effective when used with long-acting bronchodilators in patients with symptoms of chronic bronchitis, FEV_1<50% predicted and a history of exacerbations (49). Similarly, azithromycin was found to be more effective at reducing exacerbations in older patients with milder disease who have stopped smoking (50). In terms of side-effects, a

greater increase in the risk of pneumonia related to ICS was found in current smokers, and patients with prior pneumonia, body mass index <25 kg/m^2 and severe airflow limitation (51). Beyond intrinsic patients' characteristics, environmental factors may also influence the benefit-risk ratio of ICS, as recently suggested for the ICS-associated risk of tuberculosis, which is greater in countries with high incidence of tuberculosis (52).

Further progress in the identification of specific characteristics associated with response or adverse effects from treatment can be provided by several approaches: (i) post-hoc exploratory analyses of available therapeutic trials; (ii) observational cohort studies (retrospective, e.g., using databases, or prospective), especially with a comparative effectiveness design; (iii) pragmatic randomized controlled trials; and (iv) novel analytical strategies, such as cluster and network analysis (48); and, (v) large, long-term, "classical" RCTs. All these studies should be performed in carefully selected and extensively characterized patients. In addition to precise clinical characterization (including physiology and imaging), biomarkers will most likely be of major interest both to identify target patients and to assess treatment effects. Given the complex relationships between different biological levels (genomics, epigenetics, proteomics, metabolomics, cell physiology, inflammation, and repair mechanisms, among others), their identification is likely to come from multi-level, dynamic network analyses (47, 53). In fact, studies of gene signatures that used this analytical approach have already generated attractive hypotheses regarding mechanisms and predictors of steroid response independent of the clinical phenotype (54, 55). All these avenues of research have been very recently highlighted in an ATS/ERS statement on "research questions in COPD".

The potential impact of endotyping and biomarker-directed approaches to future therapeutic decision making

Current thinking with respect to COPD endotypes

As discussed above, an *endotype* is a subtype of a (clinical) condition defined by a distinct pathophysiological mechanism, while a *clinical phenotype* is a "single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death) (3)" (Figure 2). Historically, studies aiming at identifying and characterizing sub-populations of COPD patients have been directed at (clinical) phenotyping. Using various statistical techniques to explore cohorts and link cross-sectional characteristics together and to longitudinal outcomes, some phenotypes have been reproducibly identified: they include patients with metabolic and cardio-vascular comorbidities, patients with severe airflow limitation occurring at an early age, frequent exacerbators, patients with predominant emphysema versus predominant airways disease (56, 57). Some but not all these phenotypes have been linked to specific biological mechanisms (endotypes), while many can actually correspond to several endotypes (e.g., frequent exacerbators, patients with cardiovascular comorbidities). As noted previously, linking endotypes to clinical phenotypes and to endotype-specific biomarkers will be crucial, since phenotypes and biomarkers are more accessible to clinicians than endotypes. Therefore, the formal identification of an endotype implies the recognition of several shared

features including clinical characteristics, biomarkers, physiology, genetics, histopathology, epidemiology, and treatment response (4). One well-recognized subset of COPD, alpha-1 antitrypsin deficiency (see below), already meets all of these criteria for an endotype. Other potential COPD endotypes that we identify below only partially fulfil these criteria, although we believe that they are worthy of further investigation as "potential" endotypes. Three of the potential endotypes of COPD that we refer to below are based on markers of inflammation or airway colonization with pathogenic bacteria. Both of these processes can contribute to disease progression in COPD through persistent activation of the immune response (e.g. neutrophilic inflammation in response to bacterial colonization), the production of factors that injure lung cells or the extracellular matrix (ECM) (e.g. neutrophil elastase), structural changes that are a consequence of cellular and ECM injury (e.g. emphysema) and the physiological dysfunction that we recognize as COPD (e.g. loss of elastic recoil and consequent airflow obstruction) (Figure 3).

Alpha-1 antitrypsin deficiency—Alpha-1 antitrypsin (A1AT) deficiency meets all of the criteria for an endotype of COPD. It has known genetic underpinnings, distinct clinical characteristics, characteristic histopathology, distinct epidemiology, and a mechanism-directed treatment approach that is guided by biomarkers (serum A1AT level, A1AT protein phenotyping and A1AT genotyping) (58). However, alpha-1 antitrypsin deficiency is a relatively unique endotype of COPD in that it is a Mendelian disorder. Other endotypes of COPD, as they are identified, are likely to be complex diseases in which predisposition depends on a number of genes and in which developmental and environmental influences are more prominent.

COPD with persistent systemic inflammation—A subgroup of COPD patients with persistently elevated inflammatory biomarker levels in the blood (white blood cells (WBC) count, C-reactive protein (CRP), interleukin (IL)-6 and fibrinogen) has significantly increased all-cause mortality and exacerbation frequency (59). However, it is not yet clear whether this persistent systemic inflammation can be treated pharmacologically and which biomarkers would be most relevant to targeting of specific treatment(s).

Eosinophilic/Th2-high COPD—There is accumulating evidence that this subgroup of patients with COPD who are marked by sputum and/or blood eosinophilia may respond to corticosteroids and possibly to blockers of cytokines produced by T-helper type 2 (Th2) cells. (60). For example, the presence of elevated sputum eosinophils in stable COPD was associated with improvement in symptoms, post-bronchodilator FEV_1 and shuttle walk (a test of functional capacity) in a crossover, randomized trial of systemic corticosteroids (61). Another study confirmed that sputum eosinophilia predicts benefit with systemic corticosteroids (62), and other studies showed that this predictive relationship extends to inhaled corticosteroids as well (62–64). Thus, sputum eosinophils are a biomarker that may be useful in future decision-making relevant to the targeted use of inhaled corticosteroid in COPD. It is possible that blood eosinophils could be a useful surrogate for sputum eosinophils, especially if the blood eosinophilia is persistent. Persistent blood eosinophilia (>2%) was present in 37% of COPD subjects in the ECLIPSE study (65), a longitudinal observational study of COPD. In addition, post-hoc analyses of a recent randomized trial of

benralizumab (an anti-interleukin-5 [IL-5] receptor alpha monoclonal antibody) in COPD patients with sputum eosinophilia, suggested a response in a subgroup with elevated blood eosinophil levels (defined as either ≥200 cells/μl or ≥300 cells/μl) (66). As in asthma, several Th2 cytokines could drive inflammation in eosinophilic/Th2 high COPD. Since these Th2 cytokines (IL-5, IL-4 and IL-13) are difficult to measure directly, specific biomarkers of these cytokines could be valuable. Recently, Christenson *et al* identified molecular biomarkers of ACOS that may be useful in distinguishing the effects of Th2 cytokines and could point to blood biomarkers that might be clinically useful in addition to or as an alternative to eosinophilia (54).

COPD with bacterial colonization—Bacterial colonization is common in COPD, is thought to drive inflammation and risk for exacerbation (67), and characterizes an important subset of patients with stable COPD. Thus COPD with bacterial colonization represents a clinical phenotype and, insofar as this colonization contributes to the biological mechanisms that perpetuate COPD, could be considered an endotype. One new therapy that reduces the risk for exacerbation in COPD is an antibiotic, azithromycin (50, 68). Whether this benefit is due to the antibacterial effect of azithromycin on bacterial colonization or more direct anti-inflammatory effects is uncertain, but biomarkers of bacterial colonization in COPD could be valuable for targeting azithromycin or other emerging antibacterial approaches. While procalcitonin has been mostly assessed as a marker of bacterial infection rather than colonization (69, 70), the “E-nose”, a method for measurement of volatile organic compounds (VOC) in exhaled breath, could help identify colonized patients (71). The beneficial effect of azithromycin (reduction in risk for exacerbation) is accompanied by a reduction in plasma sTNFrII levels which also suggests a possible surrogate outcome measure (72). Ultimately, since different bacteria can elicit different host responses (73–75), optimal endotyping of COPD based on bacterial colonization may depend on methods that are specific for pathogenic species.

Biological sub-types of COPD exacerbations—Exacerbations of COPD are associated with a clinically relevant negative impact in both the short term (morbidity, mortality and increased cost) and the long term (by accelerating decline in lung function) (76, 77). Optimized strategies to prevent and treat them better are therefore an important medical need. To maximize the benefit of corticosteroids and antibiotics in COPD exacerbations, and to develop new therapeutic alternatives, it would be valuable to have biomarkers that identify subtypes of exacerbations that respond to specific therapies. Bafadel *et al* recently described 4 subtypes of exacerbations defined by distinct biomarker profiles (sputum IL-1β, serum CXCL10 and blood eosinophils) which they postulated reflect distinct underlying biology (bacterial, viral, eosinophilic and pauci-inflammatory, respectively) (78). Randomized trial data and a meta-analysis suggest that blood eosinophil levels could be used to target use of oral corticosteroids for the acute treatment of exacerbations (79, 80). Somewhat weaker data suggest that procalcitonin and CRP could guide antibiotic use (70, 81).

Comorbidities—Comorbidities such as cardiovascular disease or sarcopenia (muscle wasting) are highly prevalent in COPD and impact negatively its clinical course and

prognosis (82). Yet, not all COPD patients suffer them or, if they do, present the same pattern. Recent analysis indicates that certain comorbidities share molecular pathways and may constitute shared therapeutic targets (83, 84). Therefore, efforts to understand the biology of clinical phenotypes of COPD characterized by specific constellations of comorbidities may ultimately lead to the identification of specific endotypes of COPD characterized by specific biomarkers and treatment responses.

Lung cancer—Lung cancer is highly prevalent among COPD patients and constitutes one of the main causes of death in this population, especially in patients with mild to moderate airflow limitation (85). Smoking is the main risk factor for both COPD and lung cancer, but not all smokers develop COPD or cancer (1, 86). Yet, those who develop COPD, particularly if emphysema is present, have a much higher risk of developing lung cancer than those without COPD (87, 88), suggesting a synergistic effect between COPD (and emphysema) and lung cancer. The molecular mechanisms linking COPD and lung cancer are unclear, but accumulating evidence suggests that the chronic inflammatory response that characterizes COPD is likely to play a key pathogenic role (89). It follows that a better understanding of the complex molecular networks that characterize such response is essential to design effective chemopreventive and immune-therapeutic strategies.

Future directions

We will gain empiric knowledge from proof of concept trials in COPD with emerging drugs that target specific inflammatory pathways (monoclonal antibodies against IL-5, 4, 6, 13, 17 and IL1β for example) (90). Yet, there are at least two reasons for caution as we approach these clinical trials. First, it is possible that a given endotype might be relevant for only a small subset of the population. If so, these trials will have to consider either enrolling only subjects who are likely to respond to the therapy based on a given biomarker, or enrolling “all-comers” with stratification based on biomarker levels. The latter approach has the advantage that it allows assessment of response in the “biomarker negative” group. Second, an endotype or biomarker-directed therapy could be relatively weak if it targets a pathway that only represents one of several contributing pathways to COPD in a given patient. However, current experience in other respiratory diseases, such as lung cancer (EGFR), asthma (Th2 high, based on periostin) and even in COPD (steroids for eosinophilic COPD and augmentation therapy for A1AT) argue that the benefits of targeted therapy can be of sufficient magnitude to make them clinically relevant. Another important future direction is the longitudinal study of biomarker-defined subgroups to better understand the stability of these subgroupings. Finally, it is important to consider that the subgroups of COPD patients defined by these biomarkers may themselves be extremely complex since they include non-linear, dynamic epigenetic interactions between multiple spatial and time scales mediated by nonlinear biological networks that enable, filter, condition and buffer them (91). Systems biology and Network medicine offer an integrative, multi-level, dynamic approach for the understanding and eventual therapeutic modification of these complex molecular, functional, clinical and environmental networks (47, 92, 93). Recent studies have used this strategy (39, 94, 95). Network analysis of human diseases not only offers the possibility of a better understanding of disease patho-biologic complexity of different disease subtypes (endotypes), but facilitates also the development of new therapeutic alternatives and,

importantly, a reclassification of complex diseases (33, 96, 97). In essence, all these development should pave the way towards personalized medicine, also known as P4 medicine or precision medicine (2, 98, 99). In this context, the precision medicine initiative launched very recently by President Barak Obama indicates how to progress towards better health (100). In the meantime, the concept of a “control panel” for COPD (101) that identifies “treatable clinical traits” could represent an appropriate way forward to facilitate the implementation of a more personalized treatment of COPD in the clinic (2).

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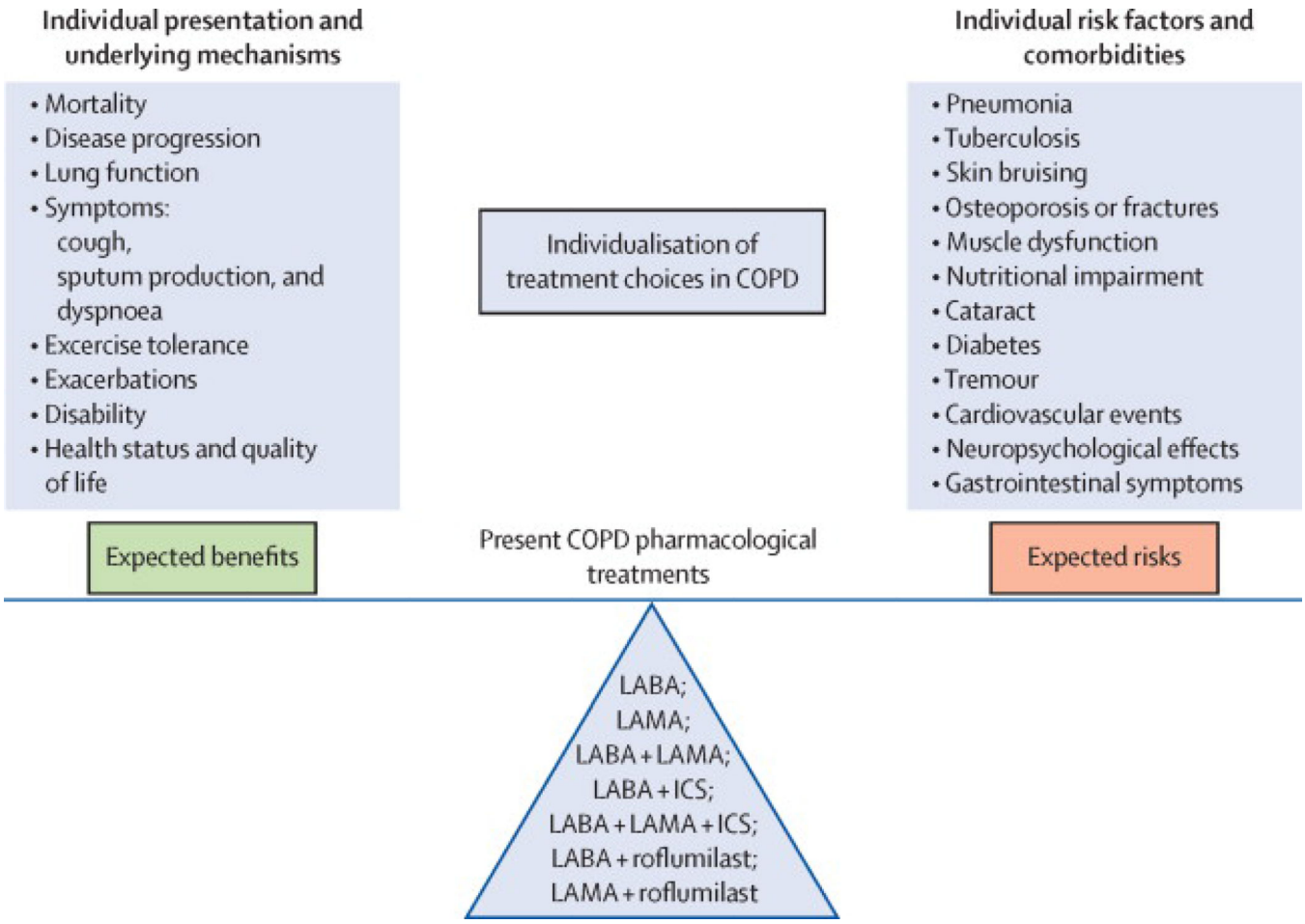

Figure 1.

Considering the benefit-risk balance and its individual determinants when personalizing COPD treatment choices. When deciding which pharmacological treatment option the clinician will prescribe to a given patient, he/she has to consider (i) expected benefits (left), which are determined by individual presentation and underlying mechanisms and (ii) possible risks (right), which depend on individual risk factors and comorbidities.

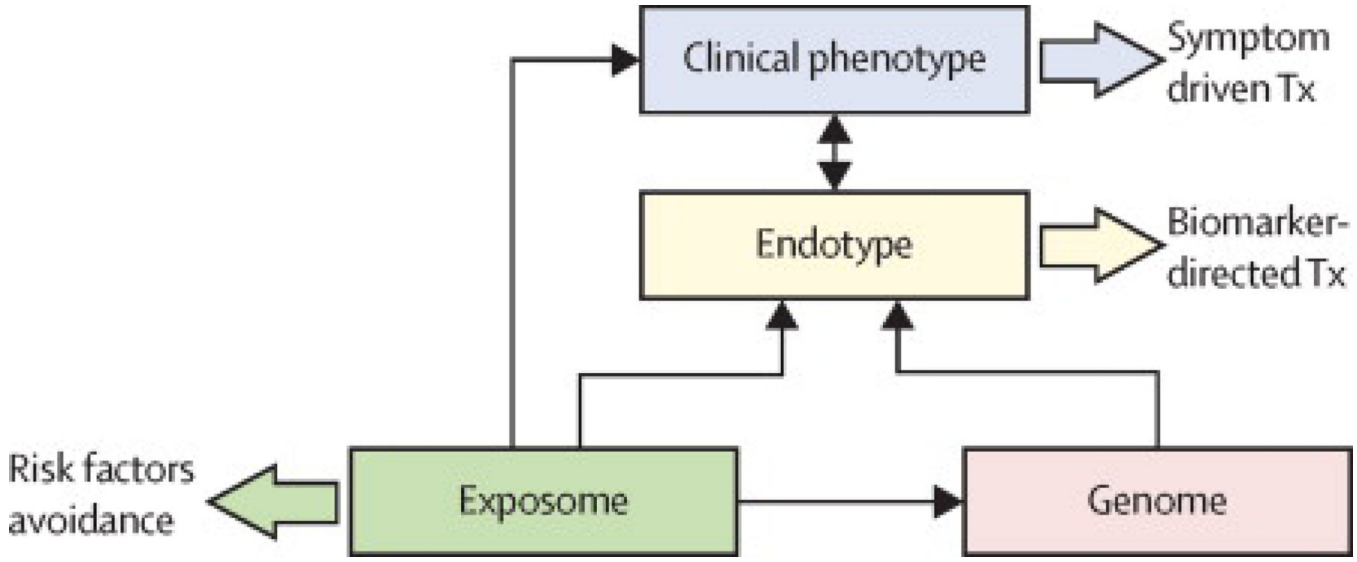

Figure 2.

Diagram depicting the inter-relationships (small arrows) between the ‘exposome’ (a term that describes the “totality of human environmental exposures, from conception onwards” (102)), the genetic background of the individual (Genome), the Endotype (biological networks that enable and restrict reactions) and the final clinical expression of the disease (Clinical Phenotype). Large arrows indicate different therapeutic strategies. For further explanation, see text.

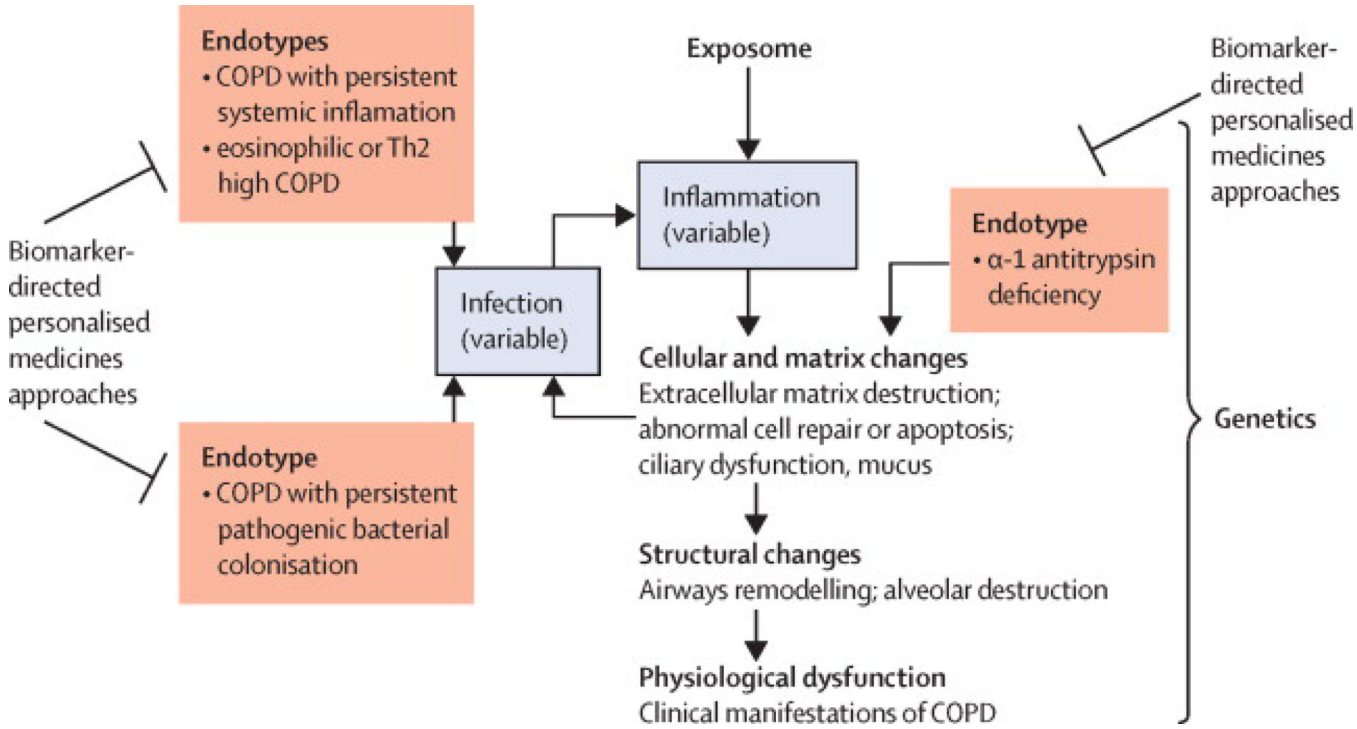

Figure 3.

Our current understanding of potential endotypes of COPD. Depicted are the relationships between inflammation, cellular changes, structural changes and physiological dysfunction in COPD, and the role that chronic infection can play in perpetuating inflammation. Superimposed are potential endotypes of COPD (in red text) that relate to subtypes of inflammation, the presence of colonization with pathogenic bacteria and the absence of a mechanism protective against extracellular matrix destruction (alpha-1 antitrypsin deficiency).