LITERATURE REVIEW

Emerging Role of Precision Medicine in the Diagnosis and Treatment of Chronic Respiratory Disease

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ABSTRACT

Precision medicine is the current approach to managing chronic respiratory diseases, especially asthma and chronic obstructive pulmonary disease (COPD). It involves the evaluation of genetic, environmental, and lifestyle variations for each patient. It requires valid and specific biomarkers obtained through genetic studies, biomolecular technology, and omics-based technology to determine targeted therapies. Asthma and COPD have heterogeneous clinical phenotype variations, and giving one standard treatment for asthma and COPD may not necessarily provide the same effectiveness to other patients. The endotype, a specific molecular mechanism in disease pathogenesis, is essential in phenotype variation. The role of precision medicine in asthma and COPD is to determine endotypes through specific biomarkers and to provide specific targeted therapy for achieving personalized treatment in each patient. The application of precision medicine not only provides precise diagnosis and treatment but also enables early detection in individuals at risk and prevention of progression and exacerbation in asthma and COPD.

INTRODUCTION

Giving one standard treatment to a disease does not necessarily provide the same effectiveness for all patients. The difference in efficacy in standard therapy is often found, especially in chronic respiratory diseases, due to variations in clinical phenotype and differences in the molecular mechanisms underlying the disease in each patient. Chronic respiratory diseases, especially asthma and chronic obstructive pulmonary disease (COPD), can have morbidity and mortality, which have a high impact on health costs and cause a decrease in work productivity. Because of the variation in disease presentation, treatment, treatment response in each patient, and optimal management can be achieved by increasing the accuracy of diagnosis based on disease endotypes through precision medicine.[1]

Precision medicine is a treatment that results from in-depth research and is specifically designed by including the variations in genes, environment, and lifestyle of each patient.[2] It is a new paradigm and concept to address the limitations of one-size-fits-all treatment.[3] The development of precision medicine knowledge by doctors, health systems, the pharmaceutical industry, patients, and policymakers reflects the acceleration and renewal of medical practice, resulting in progress that can benefit patients and doctors now and in the future. One of the visible benefits of precision medicine is in the field of oncology. Technological developments can help evaluate genetic material quickly and efficiently to design specific therapies according to the cancer genotype. Over several decades, genomic research has succeeded in identifying specific genetic variants that play a role in susceptibility

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to several diseases, including asthma, COPD, tuberculosis, interstitial lung disease, and others.[2]

The main goal of precision medicine is to provide rational therapy, including the right drug, the right patient, the correct dose, and the right time to reduce the risk of side effects and costs. Through developments in the fields of genetics, molecular biology, and biochemistry, the scope has also become more exhaustive, including diagnostics, therapy, and prognostics. During the COVID-19 pandemic, there was a rapid development of therapies and vaccines to fight the coronavirus, which became the basis of a good platform for developing precision medicine in the future.[4]

Through detailed knowledge and understanding of disease endotypes, precision medicine can be used in respiratory diseases, thereby changing the treatment paradigm based on disease names and population-based prevention approaches to personalized medicine that take into account the variation factors of each individual.[5] This new era of medicine will be a significant step towards a better future for pulmonology and respiratory medicine. This literature review discussed precision medicine for chronic respiratory diseases, especially asthma and COPD, and its challenges and implementation.

THE BASIC CONCEPT OF PRECISION MEDICINE

The central concept of precision medicine is the identification and implementation of biomarkers that can explain specific molecular mechanisms that are useful in stratifying the diagnosis, prognosis, and treatment of a disease. Precision medicine is an approach for treating and preventing disease by considering individual variability, namely genes, environment, and lifestyle. The focus in precision medicine is the biological mechanisms underlying disease. The precision medicine approach can identify the natural course of disease and specific interventions and provide accurate predictions of treatment and prevention strategies for certain diseases.[1,6]

Precision medicine is a healthcare approach that uses genetic evaluation, biomarkers, and environmental or lifestyle factors to classify patients with similar clinical characteristics into different endotypes according to disease mechanisms and treatment response.[2] Through specific endotype characteristics in chronic respiratory disease, precision medicine can provide specific and diverse treatment and prevention strategies to improve clinical outcomes and patient safety.[7]

The development of precision medicine for managing asthma and COPD is needed because the ability to determine heterogeneity and specific endotypes remains limited. New techniques are needed to identify asthma and COPD to determine therapeutic approaches, prognosis, diagnosis, genetic or therapeutic biomarkers, and specific pathophysiological mechanisms. The recent classification system of pulmonology and respiratory disease based on molecular mechanisms can overcome the challenges of precision medicine in the context of respiratory disease by adjusting treatment according to the molecular biological mechanisms underlying the disease.[8]

COMPONENTS OF PRECISION MEDICINE IN CHRONIC RESPIRATORY DISEASE

Biological connections in organ systems and disease require new analytical techniques to integrate the multilevel complexity of the exposome, genome, endotype, and phenotype to discover and understand the pathobiology of disease. With a better understanding of pathobiological components, biomarkers can be identified and validated adequately. These biomarkers include biological and functional, imaging, and clinical characteristics that are objectively measured and evaluated as indicators of standard processes, pathological processes, or biological responses to therapy.[2] Specific and valid biomarkers are needed for progress in the development treatment of chronic respiratory diseases through precision medicine.

In the clinical application of precision medicine in chronic respiratory diseases, an understanding of the components that play a role in precision medicine is needed, namely exposome, genome, endotype, phenotype, biomarker, and treatable traits. Similar to other diseases, chronic respiratory diseases are the result of continuous and dynamic interactions of genetic and environmental factors that are regulated by multilevel biological factors.[8] Better understanding and classification of phenotype and genotype in chronic respiratory diseases can help develop treatments such as the newest personalized and targeted therapies.

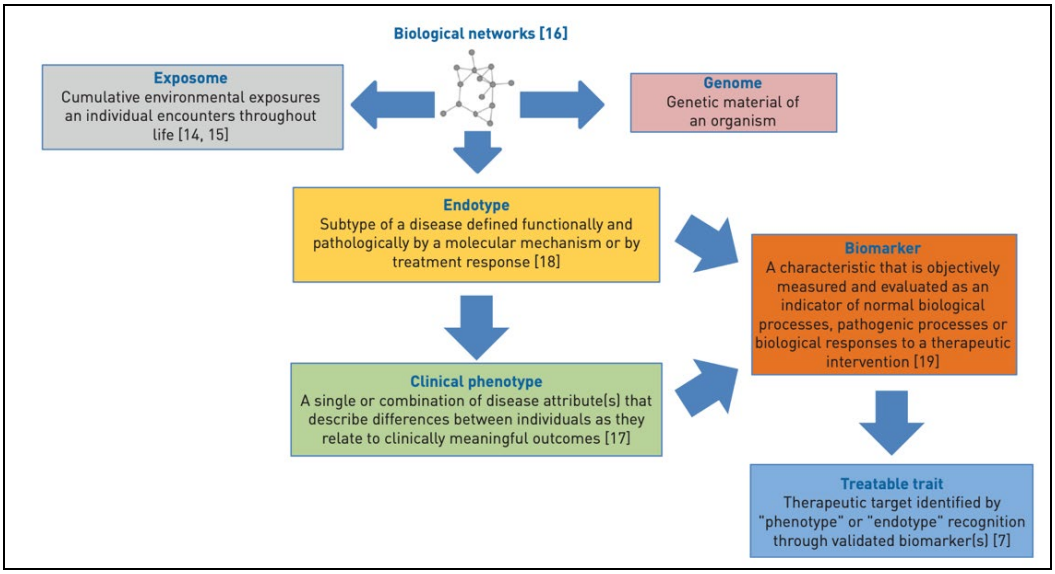

Figure 1. Scheme of the relationship and interaction of the exposome and genome, which results in endotypes and phenotypes and the use of biomarkers and treatable traits.[6]

Exposome and genome

The results of complex interactions between the exposome and the genome in humans can produce certain disease endotypes that vary in each patient. Exposome is the cumulative environmental exposure that occurs in an individual during his or her lifetime. Exposome in chronic respiratory disease refers to exposure to tobacco smoke, air pollution, occupational, respiratory infection, diet, and lifestyle. The genome is the genetic structure that forms each patient. The interaction of the exposome and genome includes various molecular mechanisms that cause disease and disease subtypes, which can have different clinical character manifestations.[6]

Phenotype and endotype

Treatment strategies are still largely one-size-fits-all, based on disease severity and symptoms, and not on the biomolecular disease mechanisms in the individual patient. Precision medicine targets the specific molecular mechanisms of each patient to find the most effective treatment, which aims to avoid ineffective therapy.[9] Phenotype is a characteristic of an organism that can be observed and modified for a clinical framework. Clinical phenotypes are disease attributes, either singly or in combination, that explain differences between individuals. Asthma and COPD are widely known to have varied and heterogeneous clinical phenotypes. Complex molecular biological mechanisms that play a role in pathogenesis can be the basis for variations of phenotypes. Endotypes are groups of diseases that are functionally or pathologically characterized by specific molecular mechanisms or therapeutic responses. An endotype is a dynamic molecular composition in response to individual genetic factors and environmental factors to which exposure occurs from birth. Asthma endotypes, especially severe asthma, have been widely identified, but for COPD, there are only a few biomarkers that have been identified. The majority of endotypes underlying the phenotypes of asthma and COPD still need to be understood better. The implementation of precision medicine requires the identification of phenotypes and endotypes in asthma and COPD.[10,11]

Biomarker

Endotypes in respiratory diseases can be well-detected using validated biomarkers. Biomarkers are an essential component in precision medicine and are measured and evaluated objectively as indicators of normal or pathological biological processes or pharmacological responses to therapeutic interventions.[3] Valid and specific biomarkers can provide a clear picture of the main determinants of morbidity, timely treatment selection, indications, and the right patient. Biomarkers are classified into diagnostic biomarkers, response biomarkers, prognostic biomarkers, and predictive biomarkers.[12] Predictive biomarkers are used to predict the response to treatment given to provide treatment targets for specific individuals. Prognostic biomarkers are used to accurately determine the risk of clinical events, including disease progression, acute exacerbations, hospitalization, and mortality. Response biomarkers are biomarkers whose values change because of the therapy given. They can be further divided into pharmacodynamic biomarkers, which help measure the biological effects of therapy, and surrogate endpoint biomarkers, which help estimate the potential clinical impact of therapy. The available biomarkers in chronic respiratory diseases include blood eosinophils, exhaled nitric oxide fraction, immunoglobulin E (IgE), and C reactive protein (CRP).

Apart from biomarkers, other components that play an essential role in realizing precision medicine are pharmacogenomics and targeted therapy based on disease endotypes.[3,12]

Treatable traits

Treatable traits are therapeutic components identified by recognizing a phenotype or endotype through validated biomarkers. The treatable traits approach is a precision medicine approach developed to apply personalized medicine to chronic airway diseases. The division of treatable traits in chronic respiratory diseases is based on three main components, namely, pulmonary-related treatable traits (airflow limitation, eosinophilic airway inflammation, airway bacterial colonization), extrapulmonary treatable traits (obesity, obstructive sleep apnea, cardiovascular disease), and lifestyle risk factors (smoking, symptom perception, adherence to treatment).[6,10,13]

Treatable traits include specific clinical features, biomarkers, and certain factors that lead to a therapy that is appropriate for each individual. Patients may have several treatable traits that lead to holistic treatment. Several aspects regarding treatable traits are that they are independent of the syndrome currently used. For example, certain cases have characteristics of asthma and COPD. Treatable traits can appear in the same patient. They can change over time, and the approach to treatable traits requires prospective validation.[6] The treatable trait is a new strategy that individually assesses specific component problems that can be treated and therapy based on multidimensional assessment. It is also necessary to identify non-treatable traits because they can influence specific research for a comprehensive evaluation of existing gaps.[1,6] Because the treatable traits in patients with chronic respiratory disease can change over time, regular assessment is required to evaluate the response to personalized therapy.[14]

Omics-based technology

Omics-based technology has been widely developed to identify genes and molecules associated with respiratory diseases and includes genomics, transcriptomics, proteomics, and metabolomics.[15,16] Genomics studies genetic characteristics and their relationship to disorders in cells or tissues. Transcriptomics studies the structure and function of ribonucleic acid (RNA) molecules, which include mRNA, rRNA, microRNA, and others, while proteins or peptides in cells can be studied through proteomics. Metabolite molecules, which are the result of cell metabolism, can also be studied using metabolomics.[17] Omics technology can help clinicians determine endotypes for chronic respiratory diseases, which are currently developing in asthma. Using omics technology will improve understanding of the function of the lung microbiome. In the future, omics technology will be essential in developing precision medicine. By combining information from various omics, we can learn more specifically about disease characteristics, molecular mechanisms of disease processes, and possible interactions between diseases and comorbidities. Challenges in utilizing omics technology are related to validating the blood samples, bronchial tissue, sputum, or metabolites used.[17,18]

Human microbiome

The microbes that play a role in the human microbiome are ecologically and immunologically integrated with the human body. Their numbers exceed the cells of the body and their genetic complexity. This microbial interaction relationship consists of bacteria, fungi, viruses, bacteriophages, archaea, and eukaryotes, as well as the colonization of niches throughout the body. The human microbiome is very dynamic, meaning it changes with growth and age and varies from one location to another throughout the body. It has an acute response to specific drivers, including diet, pharmaceuticals, exercise, and immunity.[19]

Interactions between hosts and microbes, especially on mucosal surfaces, play an essential role in the development and regulation of adaptive and natural immunity, maintaining metabolic homeostasis and neurophysiological function.[20] Abnormalities in these interactions can disrupt human health due to disturbances in the commensal microbiota called dysbiosis. The microbiome has an essential role in human physiology and must be a consideration in precision medicine models. Microbiome analysis provides an opportunity to develop novel prognostic markers in airway disease, clarify the definition of clinical phenotypes, guide treatment selection, and improve more accurate indicators of therapeutic effect. The respiratory microbiome as a guide in treatment includes prognosis, risk of infection, exacerbation therapy, and treatment efficacy. Changes in lung microbiota may play a role in the pathogenesis of chronic respiratory diseases. An increase in specific microbes in chronic respiratory diseases can play a role in immune dysregulation and changes in lung structure, such as asthma and COPD and their exacerbations. Variations in disease phenotype, changes in lung physiology due to disease progression, antibiotic and corticosteroid treatment, and exacerbating conditions can influence the dynamics of the pulmonary bacterial microbiome.[21]

ROLE OF PRECISION MEDICINE IN CHRONIC RESPIRATORY DISEASE

Understanding genetics and molecules in pathogenesis

A critical aspect of precision medicine is understanding the genetic and molecular factors that play a role in the pathogenesis of chronic respiratory diseases. The development of precision medicine has had a significant impact on asthma and COPD therapy. Recent genetic and molecular studies have been conducted that can act as biomarkers for asthma and COPD. Currently, the known COPD endotypes are related to alpha-1 antitrypsin deficiency and eosinophilic COPD.[22] Other types of endotypes are related to the molecular mechanisms of type 2 inflammation, namely interleukin-17 (IL-17), bacterial colonization, airway mucus disorders, and other mechanisms that still need to be studied. Furthermore, determining biomarkers is essential to determine the COPD endotype.[23,24]

Inflammatory biomarkers, including CRP and fibrinogen, club cell protein 16 (CC16), and soluble receptor for advanced glycation end products (sRAGE), have a role as prognostic or predictive biomarkers. CRP and fibrinogen are biomarkers associated with increased risk of death and severe COPD exacerbations, while CC16 and sRAGE are biomarkers associated with decreased lung function and progression of emphysema.[25] Levels of miR-320c in serum, which is an inhibitor of SERPINA1 expression, are associated with lung disease in patients with high levels of alpha-1-antitrypsin. There is a decrease in the expression of SOD3 and fibulin-5 in COPD patients and an increase in methylated miR-7 levels in emphysema patients.[23] Other studies showed that levels of CC16, CRP, fibrinogen, and sRAGE are not associated with decreased lung function, exacerbation, or hospitalization in COPD patients.[26] Fibrinogen and CRP have a higher risk of mortality in patients with COPD. Hence, they can be used as predictive biomarkers.[26]

The pathogenesis of asthma based on the degree of inflammation is divided into type 2 asthma and non-type 2 asthma. The cell activity causes airway inflammation in asthma through the production of IL-4 (produces IgE), IL-5 (produces eosinophil activation), and IL-13 (mucus secretion and IgE production). The recent discovery of innate lymphoid cells type 2, which is a strong producer of IL-5 and IL-13, is classified as a T2 high endotype. Meanwhile, the T2 low-endotype has characteristics of IL-1 and IL-17 secretion.[18,27] Each of these endotypes has different biological mechanisms, which result in differences in clinical characteristics and molecular pathways. Asthma endotypes are based on omics data, namely transcriptomics through gene expression in bronchial epithelial cells and sputum cells, proteomics through protein expression in bronchoalveolar lavage (BAL) specimens, bronchial biopsies and sputum supernatants, and metabolomics through exploration of biological molecules originating from biological processes.[15,28] In the future, with complete knowledge and understanding of genetics and biomarkers related to asthma and COPD endotypes, efforts can be made for early detection and prevention of asthma and COPD, especially in individuals at risk.[29]

Development of targeted therapy

In precision medicine, the selection of effective target therapy according to the asthma phenotype can be determined based on endotype identification. Treatment of asthma, especially severe asthma, requires a precision medicine approach with endotype identification to provide specific therapeutic targets based on the inflammatory pathway.[29] Through precision medicine, specific therapy can be identified according to the endotype, such as refractory T2 high asthma, namely by administering monoclonal antibodies. Monoclonal antibodies include omalizumab, which can bind IgE, mepolizumab and reslizumab, which block IL-5, benralizumab blocks the IL 5 receptor, and the IL-4RA antagonist dupilumab, which blocks IL-4 and IL-13 signals.[30] In T2 low or neutrophilic asthma endotypes, specific therapy options include chemokine receptor (CXCR2) antagonists and dual CXCR1/CXCR2 antagonists.[4]

COPD is a disease with high morbidity and mortality that has heterogeneous characteristics, which can cause difficulties in predicting response to therapy and prognosis if based only on clinical data and lung function. Therefore, COPD-specific biomarkers are needed to determine an accurate diagnosis, target therapy, and prognosis.[25] Biomarkers in COPD are being widely studied, but there are difficulties in interpreting research data due to weak association relationships and lack of reproducibility between cohorts. Blood eosinophil biomarkers of more than 300 cells/μL are widely used to determine the risk of exacerbations and assess the response to inhaled corticosteroid (ICS) therapy. Indications for administering ICS at eosinophil count values above 300 cells/mm^3 can reduce the risk of COPD exacerbation. This biomarker is the beginning of the application of precision medicine in COPD.[31] This targeted therapy in asthma and COPD is expected to provide earlier treatment and prevent exacerbations.

Personalised treatment planning

Precision medicine and treatable trait components can help in providing personalized treatment. Through a comprehensive and multidimensional assessment of

asthma and COPD patients, which includes airway assessment, inflammatory biomarkers, comorbidities, risk factors, and lifestyle, can have a significant impact on the response to therapy and the clinical outcome of patients.[6]

Research and innovation in management

Precision medicine can trigger the development of research related to biomarkers and targeted therapy to find the latest interventions and treatments. The latest developments in predictive biomarkers for COPD therapy include serum immunoglobulin, sputum microbiome, and computed tomography (CT) scan imaging. COPD patients can experience impaired humoral immunity, namely immunoglobulin deficiency, which can play a role in susceptibility to exacerbations in COPD patients. The MACRO and Simvastatin for the Prevention of Exacerbation in COPD Exacerbation (STATCOPE) cohort studies showed that serum IgG levels can identify patients at high risk of exacerbation and hospitalization.[3] Examination of sputum samples for microbial evaluation can be a prognostic biomarker in acute exacerbations of COPD and serve as a guide in antibiotic selection. CT scan examination with emphysema findings using a semiquantitative scoring system, mapping of small airway disease, and a decrease in the total number of airways are associated with a decrease in forced expiratory volume (FEV1) in patients at high risk of COPD or mild COPD. The use of CT scan imaging can be a prognostic biomarker for mild COPD or early COPD and predict individuals who are susceptible to COPD progression.[3]

New management strategies, namely those based on treatable traits, can help manage heterogeneous and complex diseases, such as asthma and COPD. Determination of treatable traits is identified based on phenotype and endotype through validated biomarkers. Treatable traits in COPD include persistent symptoms and exacerbations, which are involved in determining pharmacological therapy. On the other hand, there are also pulmonary and extrapulmonary trait components, including risk factors related to social, habitual, and lifestyle.[31] In the future, precision medicine in chronic respiratory disease does not need to be limited to severe or refractory disease but can also be helpful in mild disease.

CHALLENGES IN THE IMPLEMENTATION OF PRECISION MEDICINE

Precision medicine, apart from having the potential to improve the effectiveness and quality of treatment, also has many challenges. These include costs, ethics, security of big data, the integration of data science application platforms, and the availability of skilled human resources to manage data and algorithms. Creating an efficient database for storing patient data, high costs, increasing the competence of health workers in the fields of molecular genetics and biochemistry, increasingly strict informed consent, and standardizing data collection from clinics and hospitals are challenges that must be faced in efforts to adopt the concept of precision medicine.[6,32]

The main challenge in implementing precision medicine lies in determining the type of molecule used for examination and the type of sample used, whether blood, sputum, cytology, or tissue samples. Sampling as a biomarker should ideally be performed using non-invasive methods, namely through potential sources, including peripheral blood, urine, and exhaled breath condensate. However, the weakness of peripheral blood samples and clinical evaluations, such as pulmonary function tests, is that they cannot accurately describe pathobiological processes in the lung. Meanwhile, taking biomarker samples directly from the airways or lung parenchyma requires invasive techniques, including BAL or surgical lung biopsy. Thus, their use is limited to certain conditions. Likewise, the risk of radiation exposure, such as the use of radiology imaging, is a challenge in selecting biomarker samples. The challenge lies in selecting suitable biomarkers for each individual because data on specific biomarkers are as yet unavailable for different races and ethnicities.[4,6,33] Extensive genomic research involving all races and ethnicities is needed. Therefore, a genomic database can be created. Moreover, the sensitivity and specificity of biomarkers are still a challenge in applying them to chronic respiratory diseases.

STRATEGY IN THE IMPLEMENTATION OF PRECISION MEDICINE

Implementation strategy is needed to overcome the challenges in the application of precision medicine. Utilization of the latest biomolecular technology and artificial intelligence (AI), as well as a bedside-to-bench approach to identify endotypes and treatable traits, can play a role in precision medicine and personalized therapy. Doctors must be more tenacious, thorough, and empathetic with patient complaints and increase their knowledge of omics. They can use big data, AI, and machine learning to provide the best capabilities and analyze complex disease information. Efforts are needed to build an intelligent big data platform, uniformly collect structured data, train health workers in genomics, build infrastructure, and involve patients and the community to participate.[32,34]

Research methods are needed, especially in the validation of biomarkers, integration of big data, and international cooperation related to genomic data. Therefore, an organization that regulates the development of genomic research and the security of patient data is needed.[17] Through the precision medicine research program currently known as the Precision Medicine Initiative's (PMI) All of Us Research Program (PMI-AURP), cohort studies to collect patient databases related to precision medicine can be performed.[35] This program aims to anticipate problems related to ethics, legality, and social issues in implementing cohort studies.[35] A research protocol with a master protocol that includes a specially designed umbrella, basket, and trial platform can be applied to answer various questions related to various interventions that target populations based on specific biomarkers or disease subtypes.[2]

SUMMARY

Precision medicine in chronic respiratory diseases, especially asthma and COPD, not only increases the ability to identify disease phenotypes but also determines specific molecular disorders in each patient. It is essential to understand the underlying pathobiology to define endotypes and tailor targeted therapy to each patient. The latest developments in biomarkers, omics-based technology, and evaluation of treatable traits in patients with asthma and COPD are needed through multicenter and multicomponent interventional research with formal, prospective, and controlled validation techniques to provide precision and personalized therapy.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

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