EDITORIAL

Precision Medicine in Respiratory Care: Where do We Stand Now?

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Abstract

Precision medicine also known as "personalized medicine" is a healthcare delivery system based on identifying biomarkers using genomics to link endotypes with phenotypes. Significant overlap exists between different phenotypes. Endotyping helps in giving a more precise definition of the phenotypes. However, it has proved to be most helpful in the development of therapeutics in oncology. Precision medicine has been brought to much more common use with COVID-19 with various drugs developed targeting interleukins. Precision medicine is now being actively developed for the management of infectious diseases and chronic and lifestyle diseases. Various challenges still exist in the path of future development of precision medicine such as cost, ethics, incorporation of machine learning, and availability of trained manpower to manage the data and algorithms. In this review, we will discuss the growth and challenges precision medicine faces in the field of respiratory care.

Keywords: Acute respiratory distress syndromes, Asthma, Biomarkers, Phenotypes, Precision medicine.

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Introduction

Precision medicine provides personalized or individualized treatments targeted to the individual patient based on their genetic makeup and phenotypic or endotype features. Genomics, proteomics, and similar technologies are used to identify and analyze biomarkers in large groups of patients with specific diseases. Precision medicine helps minimize iatrogenic damage, reduce medical expenses, and reach an optimal therapeutic effect.[1] The current practice of medicine is to provide evidence-based care. Evidence-based medicine has been defined initially as the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.[2] This evidence is mainly derived from large multicenter randomized controlled trials. The main area for improvement of such evidence-based medicine is the need for more consideration given to heterogeneity in the population concerning any illness because of different molecular processes and pathophysiology.[3] On the contrary, precision medicine means providing specific medical treatment to a specific patient according to the individual susceptibility to respond to the specific treatment and risk.[4] Management is optimized based on genetic, pathophysiological, environmental, and psychosocial presentation. It is said to be "precise" as it is based on the endotypic features of individual patients. Individuals with a specific are classified according to certain characteristics and biomarkers that determine differences in their response to a specific treatment.[1] Respiratory diseases ranging from respiratory tract infection, chronic obstructive lung diseases, and lung cancer have a significant global impact with a high disease burden and mortality. In this article, we review the development and challenges of precision medicine concerning various respiratory illnesses.

Lung Cancer

Lung cancer is one of the most common causes of malignancy in the world.[5] It has the highest morbidity and mortality among malignant tumors.[6] According to statistics, new lung cancer cases account for 12.9% of all tumor types yearly. Many studies have shown that treating advanced epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK)—rearranged lung cancers with tyrosine kinase inhibitors is superior to chemotherapy.[7,8] Molecular alterations in nonsmall cell lung cancers with a good therapeutic response have not yet been identified, unlike EGFR or ALK alterations in lung adenocarcinoma. Deep convolutional neural networking, has been used to identify cytological images of three major types of lung cancer with up to 70% accuracy, with the highest classification accuracy for adenocarcinoma and the lowest for small cell carcinoma.[9] Another area of rapidly developing research is biomarkers of response to drugs targeting the immune system. Expression of the ligand on the surface of immune checkpoint molecules like programmed cell death protein 1 (PD1) on T-cells and programmed cell death ligand 1 (PDL1) on cancer cells and antigen-presenting cells are being explored as a marker predictive of response to immunotherapies. Immune checkpoint inhibitors like nivolumab, pembrolizumab acting against PD1, and atezolizumab acting against PDL1 are Food and Drug Administration (FDA)—approved for nonsmall cell lung cancer.[10] Patients responding to

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anti-PD1 therapy have a higher mutational load. It remains unclear which biomarker will be most predictive for a specific type of lung cancer.[11] Several major trials to evaluate the role of genomic screening and assess therapy targeting various biomarkers of response are ongoing like the Lung-MAP trial (NCT02154490).[12]

Bronchial Asthma

Asthma is a heterogeneous disorder with complex treatment. Multiple phenotypes of bronchial asthma have been identified on cluster analysis.[13] The phenotypes identified on the basis of the history of allergy, eosinophilic inflammation, and airflow limitation are early-onset atopic asthma, obese female asthma without eosinophilic airway inflammation, and benign asthma with minimal active disease. Other classifications based on symptom and eosinophilia are patients with high symptom expression, early onset, and minimal eosinophilic inflammation and patients with predominant eosinophilic inflammation, few symptoms, late-onset, and male preponderance.[14] However, the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes study described four phenotypes—(1) well-controlled moderate-to-severe asthma, (2) late-onset smoking history with chronic airflow obstruction and predominantly eosinophilic inflammation, (3) nonsmoking severe asthma with chronic airflow obstruction and increased use of oral corticosteroid therapy, and (4) obese female, multiple exacerbations and normal lung function.[15] The biologics approved by FDA for bronchial asthma have been discussed in Table 1.

Allergic Phenotype

This phenotype is characterized by increased total immunoglobulin E (IgE) levels and exhaled nitric oxide fraction levels. Omalizumab is an anti-IgE monoclonal antibody that forms complexes with circulating IgE. It also downregulates IgE receptors on mast cells and basophils. However, in a meta-analysis, it has been found helpful only in nonsmokers and severe asthma.[16]

Eosinophilic Phenotype

In patients with sputum or blood eosinophilia, interleukin-5 (IL-5) is considered a primary therapeutic target as it acts as a maturation and differentiation factor for eosinophils. The FDA approved mepolizumab for severe eosinophilic asthma in 2015. The following year reslizumab was approved for the same indication. These monoclonal antibodies bind to IL-5 and prevent the binding between IL-5 and eosinophils and basophils. Benralizumab is another recently FDA-approved anti-IL-5 drug. Benralizumab directly binds the IL-5-α receptor on the surface of eosinophils and basophils. This prevents IL-5 from binding to eosinophils and basophils.[13] Another target of therapy in eosinophilic asthma is IL-4. Dupilumab is an anti-IL-4 receptor antibody that reduces exacerbations by 87% in moderate-to-severe asthma with blood eosinophil counts >300 cells/mL or with >3% sputum eosinophils.[17]

Phenotype Specific Biomarkers

Previously, T helper 2 (Th2) cell activation, causing chronic eosinophilic inflammation, was thought to be the primary pathophysiology of bronchial asthma. However, increasing evidence suggests that neutrophils can predominate in some cases, while some cases can be paucigranulocytic.[18,19] Th2 asthma is more responsive to corticosteroid therapy and other target therapies against Th2 activation molecules like IgE, IL-4, IL-5, etc. However, recent studies have found drugs like tezepelumab to be helpful in both Th2 and non-T2 asthma. Tezepelumab blocks thymic stromal lymphopoietin (TSLP). TSLP is released from airway epithelium on exposure to various allergens. It potentiates T2 and non-T2-related processes by increasing the inflammatory effects through IL-4, IL-5, IL-13, and mast cells.[20]

Chronic Obstructive Pulmonary Disease (COPD)

The management of patients with chronic obstructive pulmonary disease (COPD) has moved over the past many years from generalized to individual-specific management. However, it has been based mainly on the clinical profile of individuals. Identification of the phenotypes of COPD patients by the inflammatory profile will help use more individualized treatment approaches. Patients with eosinophilia have high sputum eosinophil and Th2 inflammation. However, Th2 inflammation in eosinophilic COPD differs from Th2 inflammation in asthma. In the past 20 years, though biologics development has significantly progressed for asthma, no biologics have been approved for COPD. Therapy targeting IL-5 has shown disappointing results in COPD.[21] High IL-13 levels in COPD patients with high eosinophil count indicate airway remodeling and mucus secretion as pathology.[22] A recent phase 3 trial assessed the effect of dupilumab, which acts against IL-4 and IL-13. The COPD patients with Th2 inflammation and elevated blood eosinophil counts had fewer episodes of exacerbations with dupilumab compared to placebo.[23]

Cystic Fibrosis

It is an autosomal recessive disorder characterized by a mutation in the *cystic fibrosis transmembrane regulator (CFTR)* gene. Drugs have been developed to target *CFTR* genotypes using *CFTR* modulation. Ivacaftor is a potentiator drug that increases *CFTR* function in patients with G551 mutations. A lumacaftor is a corrector that moves *CFTR* protein near the cell membrane. It has been approved for individuals with δF508.[24]

Table 1: FDA-approved monoclonal antibodies for bronchial asthma

Drugs	*Year*	*Receptor*	*Action*
Omalizumab	2003	IgE	Decreases circulating total IgE
Mepolizumab	2015	IL-5	Blockage of IL-5/IL-5-receptor binding on eosinophils decreases blood and sputum eosinophils
Benralizumab	2017	IL-5-receptor-α	Decreases eosinophils and basophils by antibody-dependent cell-mediated cytotoxicity
Dupilumab	2017	IL-4-receptor-α	Blocks binding of IL-4-receptor-α–IL-4 and IL-13
Reslizumab	2016	IL-5	Blockage of IL-5/IL-5-receptor binding on eosinophils decreases blood and sputum eosinophils
Tezepelumab	2021	TSLP	Blockage of TSLP/TSLP-receptor binding

Acute Respiratory Distress Syndrome (ARDS)

Despite extensive research, it has been challenging to identify potential sources of heterogeneity in acute respiratory distress syndrome (ARDS). Phenotypic variations have been noticed after the COVID-19 pandemic. Clinical and molecular phenotyping of such patients has revealed differential responses to treatment, which is ineffective in other ARDS patients.[25–27] Two subphenotypes for ARDS have been identified. A hyperinflammatory subphenotype associated with high levels of inflammatory biomarkers like IL-6, protein C, soluble tumor necrosis factor receptors-1 (sTNFR-1), high vasopressor use, low serum bicarbonate levels, high-risk of sepsis, higher mortality, and less ventilator-free days compared to hypoinflammatory phenotype.[27] Genetic predisposition to specific infectious and noninfectious proinflammatory stimuli can cause ARDS.[28] Elevated plasma levels of soluble receptors for advanced glycation end products (sRAGE) and angiopoietin 2 (induces endothelial activation) are associated independently with ARDS during sepsis.[29,30] High levels of sRAGE are not dependent on clinical features like the driving pressure of the ventilator and tidal volume generated. ARDS patients with elevated plasma concentration of surfactant protein-D, von Willebrand factor, sTNFR-1 and 2, soluble intercellular adhesion molecule-1, and plasminogen activator inhibitor-1 have poor prognosis.[31] Other causes of genetic variations in ARDS are cell-matrix proteins and vascular endothelial growth factor receptor 1.[32] Genetic variation can be a source of significant heterogeneity in cases of ARDS and can be targeted as future treatment goals.

Precision medicine, especially for conditions like COPD and ARDS can help in respiratory care and respiratory therapy by assisting in determining the ventilator strategies and humidification and aerosol therapy best suited and individualized for every patient.

Conclusion

Precision medicine, while progressing steadily concerning illnesses like lung cancer and bronchial asthma, is still in its experimental stages for conditions like COPD and ARDS. The main challenge remains to harness the knowledge of the pathogenesis of these conditions and use it to direct further development of biologics and targeted therapies for precise and individualized treatment.

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