REVIEW ARTICLE

Targeted anti-inflammatory therapeutics in asthma and chronic obstructive lung disease

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Asthma and chronic obstructive pulmonary disease (COPD) are chronic inflammatory diseases of the airway, although the drivers and site of the inflammation differ between diseases. Asthmatics with a neutrophilic airway inflammation are associated with a poor response to corticosteroids, whereas asthmatics with eosinophilic inflammation respond better to corticosteroids. Biologicals targeting the Th2-eosinophil nexus such as anti–interleukin (IL)-4, anti–IL-5, and anti–IL-13 are ineffective in asthma as a whole but are more effective if patients are selected using cellular (eg, eosinophils) or molecular (eg, periostin) biomarkers. This highlights the key role of individual inflammatory mediators in driving the inflammatory response and for accurate disease phenotyping to allow greater understanding of disease and development of patient-oriented antiasthma therapies. In contrast to asthmatic patients, corticosteroids are relatively ineffective in COPD patients. Despite stratification of COPD patients, the results of targeted therapy have proved disappointing with the exception of recent studies using CXC chemokine receptor (CXCR)2 antagonists. Currently, several other novel mediator-targeted drugs are undergoing clinical trials. As with asthma specifically targeted treatments may be of most benefit in specific COPD patient endotypes. The use of novel inflammatory mediator-targeted therapeutic agents in selected patients with asthma or COPD and the detection of markers of responsiveness or nonresponsiveness will allow a link between clinical phenotypes and pathophysiological mechanisms to be delineated reaching the goal of endotyping patients. (Translational Research 2015;■:1–12)

Abbreviations: AHR = airway hyperresponsiveness; ACQ = Asthma Control Questionnaire; ACOS = asthma-COPD overlap syndrome; BAL = bronchoalveolar lavage; CLCA1 = chloride channel regulator 1; COPD = chronic obstructive lung disease; CS = corticosteroids; CXCR = CXC chemokine receptor; EGF = epidermal growth factor; EGFR = epidermal growth factor receptor; FKBP51 = FK506-binding protein 51; FP = fluticasone propionate; FEV_1 = Forced expiratory volume in 1 second; FeNO = fraction of exhaled nitric oxide; GR = glucocorticoid receptor; GM-CSF = Granulocyte-macrophage colony-stimulating factor; HDACs = histone deacetylases; HNE = Human neutrophil elastase; IgE = Immunoglobulin E; ICS = inhaled corticosteroids; LABAs = Long-acting beta-adrenoceptor agonists; mRNA = messenger RNA; MAbs = mono-

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Submitted for publication May 13, 2015; revision submitted August 11, 2015; accepted for publication August 12, 2015.

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1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2015.08.004

clonal antibodies; PDE = phosphodiesterase; PI3K = phosphoinositide-3-kinase; RT-qPCR = Real time quantative polymerase chain reaction; SAL = salmeterol; SERPINB2 = serpin peptidase inhibitor; clade B = member 2; sIL-4R = soluble IL-4 receptor; GOLD = The Global Initiative for Chronic Obstructive Lung Disease; TSLP = Thymic stromal lymphopoietin; TORCH = Towards a Revolution in COPD Health

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) affect more than 500 million people worldwide representing the 2 most common chronic inflammatory diseases of the lower airways.[1,2] This review summarizes some of the recent evidence indicating how the use of therapeutics targeting specific inflammatory mediators has indicated their role in disease pathophysiology and also highlighted the importance of subphenotyping these diseases to optimize the response to these targeted drugs.

The current consensus definition of asthma is "an (sic) heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable airflow obstruction."[1] Patients with asthma have variable airflow obstruction and airway hyper-responsiveness (AHR).[3] Asthma affects 10%–12% of the adult population in Europe and most high (€20.65 billion) annual costs of asthma in Europe are because of patients with severe disease who do not respond well to conventional anti-inflammatory corticosteroids that is the mainstay treatment of mild-moderate asthma.[4]

The analysis of airway biopsies after bronchoscopy and the introduction of induced sputum analysis allowed the inflammatory nature of the asthmatic airways to be confirmed.[5-7] These analyses revealed the presence of eosinophils and Th2 cytokines particularly interleukin (IL)-2 and IL-4,[8] which emphasized the Th2-driven nature of asthmatic inflammation. As a result asthma was, for a long time, considered as a single Th2-driven eosinophilic disease whose diagnosis is based on the patient presenting with an intermittent wheeze, dyspnea, and cough. However, it was clear that the presentation and natural history of the disease differ between patients; some asthmatics undergo clinical remission during adolescence, some patients have more severe disease, some asthmatics are nonallergic or atopic, whereas others have exercise-induced asthma.[9,10]

Later studies showed that although eosinophils were present in many asthmatic biopsies, some subjects, particularly those with more severe disease, also demonstrated increased levels of neutrophils.[11] Similarly, Gibson et al have shown different types of sputum cellular composition in asthma with some subjects having predominant eosinophilia, others more neutrophilic or with a mixed cell composition, and another group with paucicellular sputum.[12,13] This has led to the idea of asthma being a complex disease or even a group of "diseases" caused by different pathophysiological mechanisms.[9,10]

The Global Initiative for Chronic Obstructive Lung Disease guidelines define COPD as "a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients."[14] COPD is expected to rise from the 4th to the 3rd leading cause of morbidity and mortality worldwide within the next 5 years.[14] According to the World Health Organization, approximately 3 million people in the world die as a consequence of COPD every year.[15] The estimated annual costs of COPD are $24 billion and 70% are related to exacerbations requiring hospitalization.[2] In developed countries, the leading risk factor for COPD is cigarette smoking with smokers constituting more than 90% of COPD patients.[14] In less-well developed countries, biomass fuel used in cooking and other environmental pollutants are major factors.[16,17]

The pathologic features of COPD are lung parenchymal destruction (pulmonary emphysema), inflammation of the small (peripheral) airways (respiratory bronchiolitis), and inflammation of the central airways. Inflammation occurs within all these compartments (central and peripheral airways and lung parenchyma).[18] The major sites of airflow obstruction are the small airways and lung parenchyma in COPD.[19,20]

CORTICOSTEROID RESPONSIVENESS IN ASTHMA

Asthma was implicated as a chronic inflammatory disease, and this was confirmed when the potent anti-inflammatory prednisolone was shown to be of benefit in patients with asthma. Some of the original studies with oral prednisolone highlighted that blood levels of eosinophils were not altered in patients who were more refractory to treatment. This provided early evidence for the concept of relatively corticosteroid-resistant asthma.[21] However, the introduction of inhaled corticosteroids (ICSs) resulted in such a dramatic improvement in the asthma symptoms of most asthmatics[22,23] that these earlier studies indicating that