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Therapeutic approaches to asthma–chronic obstructive pulmonary disease overlap syndromes

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The recognition that there are some patients with features of asthma and chronic obstructive pulmonary disease (COPD) has highlighted the need to develop more specific treatments for these clinical phenotypes. Some patients with COPD have predominantly eosinophilic inflammation and might respond to high doses of inhaled corticosteroids and newly developed specific antieosinophil therapies, including blocking antibodies against IL-5, IL-13, IL-33, and thymic stromal lymphopoietin, as well as oral chemoattractant receptor-homologous molecule expressed on T_H2 cells antagonists. Other patients have severe asthma or are asthmatic patients who smoke with features of COPD-induced inflammation and might benefit from treatments targeting neutrophils, including macrolides, CXCR2 antagonists, phosphodiesterase 4 inhibitors, p38 mitogen-activating protein kinase inhibitors, and antibodies against IL-1 and IL-17. Other patients appear to have largely fixed obstruction with little inflammation and might respond to long-acting bronchodilators, including long-acting muscarinic antagonists, to reduce hyperinflation. Highly selected patients with severe asthma might benefit from bronchial thermoplasty. Some patients with overlap syndromes can be conveniently treated with triple fixed-dose combination inhaler therapy with an inhaled corticosteroid, long-acting β_2-agonist, and long-acting muscarinic antagonist, several of which are now in development. Corticosteroid resistance is a feature of asthma-COPD overlap syndrome, and understanding the various molecular mechanisms of this resistance has identified novel therapeutic targets and presented the prospect of therapies that can restore corticosteroid responsiveness. (J Allergy Clin Immunol 2015;136:531-45.)

Key words: *Corticosteroids, bronchodilator, cytokine, chemokine, IgE, kinase, p38 mitogen-activated protein kinase, bronchial thermoplasty, corticosteroid resistance, macrolide*

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Asthma and chronic obstructive pulmonary disease (COPD) are distinct clinical entities with different management strategies, although in clinical practice they are often treated with the same medications. However, some patients appear to have features of both diseases, which is termed asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS).[1,2] ACOS is poorly defined and understood and includes several phenotypes that might necessitate different therapeutic approaches: (1) patients with COPD who have increased eosinophil counts that might respond to corticosteroids or specific antieosinophil therapy, (2) asthmatic patients with severe disease or who are current smokers who have predominantly neutrophilic inflammation, and (3) asthmatic patients who have had largely irreversible airflow obstruction and might or might not have increased inflammation. Examination of sputum cellularity can identify patients with airway disease with eosinophil-predominant, neutrophil-predominant, mixed-pattern, and no inflammation (paucigranulocytic).[3] The different therapeutic options are shown in Fig 1 and Table I.

TREATING EOSINOPHILIC COPD

The presence of increased eosinophil counts in sputum (>3%) or blood (>400/dL) might predict a clinical response to inhaled corticosteroids (ICSs), and these patients can have increased airway reversibility.[4-7] These patients can have both asthma and COPD (because these are both common diseases), or they might represent a variant of COPD. It is appropriate to treat these patients with bronchodilators and ICSs. However, even high doses of oral corticosteroids might not suppress eosinophils and eosinophil activation markers in patients with COPD.[8] This suggests that more specific antieosinophilic therapy might be more effective in the face of such corticosteroid resistance (Fig 2).

Anti–IL-5

Patients with eosinophilic COPD have increased ***IL-5*** concentrations in sputum, suggesting that targeting IL-5 might be beneficial in these selected patients with COPD.[9] IL-5 can be targeted by blocking antibodies (mepolizumab and reslizumab) or its

From the National Heart and Lung Institute, Imperial College.

Supported by the NIHR Respiratory Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London, United Kingdom.

Disclosure of potential conflict of interest: P. J. Barnes has received research support from GlaxoSmithKline, AstraZeneca, Pfizer, Chiesi, Takeda, Nycomed/Takeda, Novartis, and Aquinox; has received consulting fees or honoraria from AstraZeneca, Chiesi, Novartis, Zambon, and Boehringer Ingelheim; has received fees for participation in review activities from GlaxoSmithKline; is on Scientific Advisory Boards for Boehringer Ingelheim and Pfizer; has consultant arrangements with Glenmark and Sun Pharma; has provided expert testimony on behalf of Boehringer Ingelheim and Teva; and has received payment for lectures from AstraZeneca, Nycomed, Chiesi, Novartis, and Pfizer.

Received for publication May 7, 2015; revised May 21, 2015; accepted for publication May 22, 2015.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2015.05.052

Terms in boldface and italics are defined in the glossary on page 532.

Abbreviations used

ACOS: Asthma–chronic obstructive pulmonary disease overlap syndrome
COPD: Chronic obstructive pulmonary disease
CRTH2: Chemoattractant receptor-homologous molecule expressed on T_H2 cells
ERK: Extracellular signal-regulated kinase
GR: Glucocorticoid receptor
HDAC2: Histone deacetylase 2
ICS: Inhaled corticosteroid
IKK2: IκB kinase
ILC2: Type 2 innate lymphoid cell
JAK: Janus-activated kinase
JNK: c-Jun N-terminal kinase
LABA: Long-acting β_2-agonist
LAMA: Long-acting muscarinic antagonist
MAPK: Mitogen-activated protein kinase
MKP: Mitogen-activated protein kinase phosphatase
NF-κB: Nuclear factor κB
Nrf2: Nuclear factor erythroid-derived 2 like 2
PDE: Phosphodiesterase
PGD_2: Prostaglandin D_2
PI3K: Phosphoinositide 3-kinase
RORγt: Retinoic acid–related orphan receptor γt
Treg: Regulatory T
TSLP: Thymic stromal lymphopoietin

receptor (IL-5 receptor α; benralizumab). Mepolizumab and reslizumab are effective in reducing exacerbations in patients with severe asthma with increased sputum eosinophil counts not suppressed by high-dose ICSs or oral corticosteroids.[10-13] In patients with eosinophilic COPD, benralizumab did not significantly reduce exacerbations or improve symptoms or lung function, and therefore patients with even higher degrees of eosinophilia might be selected in future studies.[14]

Anti–IL-13

IL-13 also drives eosinophilia in patients with severe asthma, and anti–IL-13 therapies have shown some benefit in reducing exacerbations in these patients.[15] The role of IL-13 in patients with COPD is uncertain, despite the fact that it can stimulate mucus hypersecretion and airway fibrosis, as well as induction of corticosteroid resistance. In unselected patients with COPD, there was no increase in sputum IL-13 concentrations, but this did not specifically include patients with eosinophilia.[16] Bronchoalveolar lavage studies have demonstrated that patients with COPD have a population of ***$CD8^+$ T cells*** (T_C2 cells) that secrete T_H2 cytokines, such as ***IL-4*** and IL-13.[17] Plasma ***periostin*** levels might reflect stimulation of airway epithelial cells by IL-13, and high periostin concentrations have been described in patients with severe asthma who have rhinosinusitis with fixed airway narrowing that can be regarded as a subtype of ACOS.[18] There is a correlation between annual decrease in FEV_1 and periostin expression in bronchial biopsy specimens of asthmatic patients, supporting the idea that IL-13 is linked to structural remodeling in the airways and therefore might be relevant to the development of fixed obstruction in asthmatic patients.[19]

GLOSSARY

APOPTOSIS SIGNAL-REGULATING KINASE (ASK1): A kinase that activates c-Jun N-terminal kinase and p38 mitogen-activated protein kinases in response to an array of stresses, such as oxidative stress, endoplasmic reticulum stress, and calcium influx.

BARDOXELONE METHYL: An experimental and orally available semisynthetic molecule related to sulforaphane that has been reported to have antioxidative and anti-inflammatory properties.

CASPASE-1: An enzyme that proteolytically cleaves other proteins, such as the precursor forms of the inflammatory cytokines IL-1β and IL-18, into active mature peptides.

$CD8^+$ T CELLS: Cytotoxic T lymphocytes that kill cancer cells, infected cells (particularly those infected with viruses), or damaged cells. CD8 T cells often express T-cell receptors that can recognize a specific antigen bound to the class I MHC molecule of infected cells and ultimately kill the cell through release of granzymes and perforin.

c-JUN N-TERMINAL KINASE (JNK): A kinase responsive to stress stimuli, such as cytokines, UV irradiation, heat shock, and osmotic shock. It also plays a role in T-cell differentiation and the cellular apoptosis pathway.

CYCLIC NUCLEOTIDES: Cyclic AMP and cyclic GMP have been recognized as important signaling molecules within cells. Under normal physiologic conditions, cyclic nucleotides regulate a myriad of biological processes, acting as second messengers between an extracellular signal, such as a hormone, neurotransmitter, or cytokine, and the elicited intracellular response.

CYSTEINYL LEUKOTRIENES (cys-LTs): A family of inflammatory lipid mediators synthesized from arachidonic acid by a variety of cells, including mast cells, eosinophils, basophils, and macrophages.

DIMETHYL FUMARATE (BG12): The methyl ester of fumaric acid thought to have immunomodulatory properties without significant immunosuppression. It also works on Nrf2.

DNAzymes: DNA molecules that are catalytically active and can cleave complementary RNA molecules after appropriate binding, directly exerting RNA endonuclease activity.

EXTRACELLULAR SIGNAL-REGULATED KINASE (ERK): A widely expressed protein kinase intracellular signaling molecule that transmits signals from many extracellular agents to regulate cellular processes, such as proliferation, differentiation, and cell-cycle progression.

GATA3: A transcription factor that is an important regulator of T-cell development and plays a significant role in endothelial cell biology. GATA3 is required for the T_H2 differentiation process and secretion after immune and inflammatory responses.

GLUCOCORTICOID-INDUCED LEUCINE ZIPPER (GILZ): A protein that plays a key role in the anti-inflammatory action of glucocorticoids.

HISTONE DEACETYLASE 2 (HDAC2): An enzyme responsible for the deacetylation of lysine residues on the N-terminal part of the core histones (H2A, H2B, H3, and H4). Histone deacetylation produces a tag for epigenetic repression, plays an important role in regulation of inflammatory genes, and mediates the anti-inflammatory effects of glucocorticoids.

IκB KINASE (IKK2): An enzyme that serves as a protein subunit of IκB kinase and leads to the activation of nuclear factor κB.

IL-1β: A member of the IL-1 cytokine family that is produced by activated macrophages as a proprotein and is proteolytically processed to its active form by caspase 1 by the inflammasome. IL-1β is an important mediator of the inflammatory response and is involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis.

IL-2: A cytokine produced by T cells in response to antigenic or mitogenic stimulation, which is required for T-cell proliferation and other activities crucial to regulation of the immune response.