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Review Article

Severe Neutrophilic Asthma: Pathogenesis and Treatment

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Abstract

Asthma is a common chronic airway disease affecting about 358 million people worldwide, and an estimated 7 million children globally. Approximately 10% of patients with asthma have severe refractory disease, which is difficult to control on high doses of inhaled corticosteroids and other modifiers. Among these, are patients with severe neutrophilic asthma. Neutrophilic asthma is a severe phenotype of asthma, characterized by frequent exacerbations, persistent airway obstruction, and poor lung function. Immunopathologically, it is characterized by the presence of high levels of neutrophils in the airways and lungs. Interleukin-17 produced by Th17 cells, plays a key role in the pathogenesis of neutrophilic asthma by expressing the secretion of chemoattractant cytokines and chemokines for the recruitment, and activation of neutrophils. Interleukin-8 is a powerful chemoattractant and activator of neutrophils. Activated neutrophils produce an oxidative burst, releasing multiple reactive oxygen species, proteinases, cytokines, which cause airway epithelial cell injury, inflammation, airway hyperresponsiveness, and remodeling. Furthermore, exasperated neutrophils due to viral, bacterial or fungal infections, and chemical irritants can release extracellular nucleic acids (DNA), designated as NETs (neutrophil extracellular traps), which are more toxic to the airway epithelial cells, and orchestrate airway inflammation, and release alarmin cytokines. Dysregulated NETs formation is associated with severe asthma. Most patients with neutrophilic asthma are unresponsive to the standard of care, including high dose inhaled corticosteroids, and to targeted biologics, such as mepolizumab, and dupilumab, which are very effective in treating eosinophilic asthma. There is unmet need to explore for novel biologics for the treatment of neutrophilic asthma, and in refining therapies, such as bronchial thermoplasty.

Key words: neutrophilic asthma; cytokines; interleukin-17; monoclonal antibodies; bronchial thermoplasty

Introduction

Asthma is a significant public health problem, affecting more than 358 million people worldwide [1], and its prevalence has been increasing during the last 40 years [2,3]. It is the most common childhood chronic respiratory disease affecting about 7 million children [4].

Asthma is a complex heterogenous chronic airway disease with several distinct phenotypes characterized by different immunopathological pathways, clinical presentation, physiology, comorbidities, biomarker of allergic inflammation, and response to treatment. It has now become clinical practice to phenotype asthma for precision and targeted treatment, because asthmatic patients respond to the standard of care (SoC) treatment differently [5,6].

Asthma is classified into four distinct phenotypes based on quantitative induced sputum cytology [7-9]. The four phenotypes of asthma include eosinophilic asthma, neutrophilic asthma, paucigranulocytic asthma, and mixed cellularity asthma [9,10]. Patients with eosinophilic asthma have an eosinophil count of 2% to 3% [11-13], whereas patients with neutrophilic asthma have elevated sputum neutrophil count between ≥61% [11] and ≥65% [12-14], depending on the study. Mixed cellularity phenotype is characterized by increase in both eosinophils (>3%), and neutrophils (>61% or ≥65%) [14-16]. Paucigranuocytic phenotype embraces patients with very low eosinophil numbers (<3%), and low neutrophils count (<61% or <65%) in induced sputum [14,17]. Non-eosinophilic asthma is the term designated to classify patients with low eosinophil counts (<3%), which include neutrophilic asthma, and paucigranulocytic phenotype [17,18]. Asthma can also be classified as type 2-high and type 2-low, depending on biomarkers of eosinophilic inflammation, and instigating cytokines. Type 2-high is associated with eosinophilic Th2-driven asthma, whereas type 2-low represents non-eosinophilic asthma [15,19].

The pathogenesis of neutrophilic asthma is multifaceted and is not fully understood; however, approximately 30%-50% of the patients with symptomatic asthma have the neutrophilic phenotype [5]. Neutrophilic asthma is characterized by very severe refractory disease [20-24], and persistent airway obstruction [8,25-27], frequent exacerbations, hospitalizations, emergency room visits [20], and status astmaticus [21]. Furthermore patients with neutrophilic asthma have poor response to SoC

treatment, such as inhaled corticosteroids (ICSs), long-acting β2-agonists (LABA), and leukotriene receptor antagonists (LTRA) [28-33]. Furthermore, neutrophilic asthma is frequently associated with steroid-resistant asthma. Several cytokines incriminated in the pathogenesis of neutrophilic asthma, such as interleukin-17 (IL-17) [32,34], IL-8 [35], and tumour necrosis factor-α (TNF-α) [36] play an important role in the induction of steroid resistance.

Interleukin-17 plays a key role in the pathogenesis of neutrophilic asthma, by expressing the induction of cytokines, chemokines, and adhesion molecules which are responsible for the recruitment, and activation of neutrophils. Interleukin 8 is a very potent chemoattractant and activator of neutrophils, signaling via its receptors, CXCR1, and CXCR2. Activated neutrophils degranulate and secrete reactive oxygen species (ROS), proteases, matrix metalloproteinases, metaloperoxidases, and cytokines, which cause epithelial cells injury, inflammation, and airway hyperresponsiveness (AHR). Airway epithelial injury, and dysfunction release alarmin cytokines, such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP); and chemokines, which further orchestrates airway inflammation, AHR, and airway remodeling.

Airway remodeling in asthma is a complex progressive process involving structural changes, leading to airway narrowing, increased airflow resistance, and severe asthma. Airway remodeling includes epithelial-mesenchymal transition (EMT), fibroblast and myofibloblast proliferation, deposition of extracellular matrix protein, subepithelial fibrosis, goblet cells metaplasia, airway smooth muscle (ASM) cells hyperplasia and hypertrophy, and angiogenesis [37]. Such structural changes require innovative therapies such as bronchial thermoplasty to trim the hypertrophied ASM mass, and subepithelial fibrosis.

Neutrophils in Neutrophilic Asthma

Neutrophils are polymorphonuclear leukocytes that have a fundamental role to play in innate immune response [38,39]. Neutrophils act as the first line of defense against pathogens, such as bacteria, fungi and perhaps viruses, and participate in the resolution of inflammation [40]. However, neutrophils also contribute to immunopathology of many diseases, including respiratory diseases, such as cystic fibrosis, bronchiectasis, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), and neutrophilic asthma [38,41].

Activated neutrophils produce an NADPH oxidative burst, releasing multiple reactive oxygen species, proteases, matrix metalloproteases, myeloperoxidases, cytokines, chemokines, and lipid mediators which lead to airway inflammation, AHR, and airway remodeling. Additionally, the inflammatory mediators are responsible for airway epithelial injury, which result in the release of alarmin cytokines by epithelial cells; and mucus hypersecretion [41]. The chemoattractant mediators, such as CXCL1, CXCL6, CXCL8 (IL-8), LTB4, PAF, and thromboxanes further enhances neutrophil recruitment, migration and activation, thus amplifying the neutrophilic airway inflammation [42].

Neutrophils produce reactive oxygen species (ROS), such as superoxide anion (superoxide radical $O2^{-}$), hydrogen peroxide (H2O2), and Hypochlorous acid (HOCl), which lead to an increase in transcription of IL-8 by epithelial cells, further propagating the chemoattractant neutrophilic response [43,44]. Additionally, ROS synergize with neutrophil proteases to cause severe tissue damage by inactivating the actions of antiproteases [44].

Several studies have reported increased concentrations of neutrophil active mediators, such as IL-8, neutrophil elastase, matrix metalloproteinase-9 (MMP-9), leukotriene B4 (LTB4), IL-17A, GM-CSF, and TNF-α in plasma, BAL fluid, and bronchial epithelial-conditioned media derived from patients with severe neutrophilic asthma [45-49]. Grunell et al. [49] have demonstrated that children with neutrophil-predominant asthma have proinflammatory neutrophils with enhanced survival. The BAL fluid from these children demonstrates quantitatively increased levels of cytokines (IL-1β, IL-6, IL-8); chemokines (CXCL2, CXCL3, and CXCL4); myeloperoxidase; and neutrophil elastase.

The most important proteases secreted by neutrophils during neutrophilic airway inflammation include neutrophil elastase, cathepsin G, and metalloproteases (MMP), especially MMP-9.

Metalloproteases

Metalloprotease-9 is one of the most studies inflammatory mediators in asthma. Elevated levels of MMP-9 have been found in sputum and BAL fluid from patients with asthma, and the levels correlated with neutrophil numbers [50], and the severity of asthma [51]. Wenzel et al, [52] have suggested that localized tissue MMP-9 deposition in the lungs may lead to subepithelial basement membrane thickening, fixed airflow obstruction, and severe asthma.

Neutrophil Elastase

Neutrophil elastase is one of the most cytotoxic proteins produced by activated neutrophils form the primary granules. It has been implicated in all the pathophysiological aspects of severe neutrophilic asthma. The immunopathological roles of elastase include airway epithelial injury, increased vascular permeability, hyperplasia of bronchial submucosal glands and mucus hypersecretion, bronchoconstriction, and airway hyperresponsiveness [53]. Neutrophil elastase can induce goblet cell metaplasia, mucus secretion a hallmark of severe asthma [54]. It can also induce airway smooth muscle proliferation [55], and has been implicated in airway remodeling, leading to severe airway narrowing, and progressive decline in lung function [56].

Neutrophil proteases, such as elastase, cathepsin G, and proteanase-3 may induce airway inflammation through activation of eosinophils to produce cytotoxic cationic proteins, ROS, lipid mediators, cytokines, and chemokines [57], thus aggravating neutrophilic asthma [58]. Thus, during neutrophilic asthma, there is collaborative cross-talk between neutrophils and eosinophils, leading to severe neutrophilic airway inflammation.

Neutrophil elastase levels have been reported to be elevated in bronchial secretions, and in induced sputum in asthmatic patients compared to healthy controls, especially during exacerbations [59,60].

Myeloperoxidase

Myeloperoxidase (MPO) released from neutrophil primary granules can react with hydrogen peroxide generated during a respiratory burst, and produce hypochlorous acid, and other reactive oxygen species [60]. The ROS are crucial for microbial activity and antigen presentation, but play deleterious role in causing injury to lung tissue during neutrophilic inflammatory process [1]. MPO levels have been shown to be elevated in the BAL fluid of patients with asthma compared to normal subjects [60]

Lipid Mediators

Neutrophils can synthesize lipid mediators such as and leukotrienes (LTB4) and platelet activating factor (PAF). They are also able to produce prostaglandins (PGE2) and thomboxanes (TBXA2) via cyclooxygenase

enzyme systems [61,62]. Lipid mediators play an important role in neutrophil migration, and activation in the airway inflammation process.

Reactive Oxygen Species

Activated neutrophils are the major source of reactive oxygen species (ROS), such as hydrogen peroxide, hypochlorous acid, and superoxide radical ($O2^-$) in allergic inflammation. ROS act synergistically with neutrophil proteases to cause lung tissue damage, submucosal glands hyperplasia and mucus secretion, and airway hyperreactivity [56,63,64].

In vitro stimulation of neutrophils from atopic asthmatic patients with inophore A2318, and the chemoattractant fMLP have been shown to produce higher level of ROS compared to non-atopic subjects [65,66]. Tanazawa et al. [66] have reported that the production of free oxygen radicals was inversely proportional to measures of airway obstruction, e.g., FEV1. Furthermore, higher levels of $O2^-$ have been reported during asthma attacks and exacerbations compared to levels in stable asthma [64]. Thus implicating ROS in the pathogenesis of severe neutrophilic asthma, and in promoting exacerbations. Loukides and colleagues have reported an increase in hydrogen peroxide in expired breath condensate from patients with asthma, which correlated with airway inflammation, and asthma severity [67].

Table 1 shows neutrophil-derived antimicrobials and inflammatory mediators, including cytoplasts, and Table 2 lists mediators associated with neutrophilic airway inflammation.

Neutrophil Extracellular Traps

Neutrophils play a sentinel role by safeguarding the host immune homeostasis through maintaining a strict equilibrium of the innate immunity, and acute inflammatory responses [68]. Neutrophils' defense against invading microbes include phagocytosis, degranulation, and NADPH oxidative burst [69]. However, neutrophils can extrude cytosolic, and nuclear material via a conservative cell death process distinct from apoptosis and necrosis, which can be more lethal to the invading microbes. Chemical-induced neutrophil autotoxicity has been known for over 2 decades, although its clinical significance was less clear [70,71]. Exasperated neutrophils due to viral, bacterial or fungal infections, and chemical irritants can release extracellular nucleic acids (DNA), designated as NETS (neutrophil extracellular traps) [72]. The term NET was first coined by Brinkmann and colleagues in 2004, as a novel antimicrobial defense system [73]. NETs are web-like scaffolds of extracellular DNA complex with histones, and antimicrobial neutrophil granular proteins, such as neutrophil elastase, and myeloperoxidase. NETosis can generate enucluated ‘’’ghost’’ neutrophils with chemokinesis, termed cytoplasts which are also toxic to the airway epithelial cells, and exogenous bacteria [74]. Furthemore, nefarious neutrophil cytoplast formation in asthmatic lung inflammation is linked to Th17-mediated neutrophilic inflammation in severe asthma [75].

NETosis or neutrophil suicide was first described following chemical stimulation with phorbol 12-myristate 13-acetate (PMA) [71]. NETosis was further elucidated by Takei et al. [72], who demonstrated that PMA-induced suicide resulted in the release of a novel defense structure, named NET [72].

NETs release or NETosis is an NADPH oxidative-dependent cellular death requiring chromatin decondensation [76]. It is an orderly suicide, which involves nucleus envelop fragmentation, and mixing of nucleic acids and granule proteins with in a large vacuole. Finally, after intracellular assembly NETs are release via perforations in the cell membrane, and cell lysis. Once released, the DNA structures entrap both gram-negative and gram-positive [72,73]. This form of cell death is different from apoptosis, because it a novel host defense form of beneficial suicide [77]. Entrapment of microorganisms by NETs restrict potential pathogen dissemination from the initial site of infection [78]. Eosinophils can also undergo NETosis, but eosinophil extracellular traps contain significantly less proteases than neutrophil extracellular traps, and may therefore be very stable, and cause less tissue injury [79]

Although NETs are considered an essential part of neutrophil-mediated immunity, they have also been incriminated in NET-based immunopathology [80,81]. NETosis may represent a “double-edged sword” in innate immunity [82]. Abnormal NET production in the circulation and tissues have been demonstrated in patients with cystic fibrosis, and ARDS [83-85]. These are airways diseases characterized by mucosal neutrophilic inflammation. Additionally, NETs can directly trigger epithelial cell death [86], or may impair lung epithelial barrier function during respiratory viral infection in vivo [87]. Furthermore, murine studied have shown an important role for NETs in inducing airway mucus hypersecretion [88].

Dysregulation of NETs formation may play a critical role in the pathogenesis of chronic airways diseases, such as chronic obstructive pulmonary disease (COPD) [89-92], and asthma [23]. Furthermore, neutrophil autophagy and extracellular DNA traps contribute to airway inflammation, and severe asthma [93]. Similarly, Dicker and colleagues have reported that NET formation in the airways of patients with COPD was associated with disease severity [94].

There is concrete evidence that respiratory virus infection (Rhinovirus) [95,96], bacterial infection (Staphylococcus aureus) [97], and pulmonary fungal infection (Aspergillus fumigatus) [98,99], can induce NETs production. Furthermore, Toussaint et al. [95] have hypothesized that the release of NETs containing DNA may exacerbate airway inflammation, indicating that NETs may be responsible for severe asthma exacerbations. Similarly, Lachowicz-Scroggins and colleagues have shown that patients with severe asthma have significantly higher levels of extracellular DNA compared with healthy controls [100].

INTERLEUKIN-17

Interleukin-17A (thereafter, synonymously called IL-17) was initially identified as cytotoxic T-lymphocyte-associated antigen 8 (CTLA-8) in 1993 by Rouvier and colleagues [101]. Subsequent characterization revealed that IL-17 was produced by a special type of T helper cells known as Th17 cells, and thus renamed as IL-17 [102-104]. Latter genomic sequencing led to the discovery of additional IL-17 family members totaling six, namely IL-17A (IL-17), IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F [105-109]. Unlike its siblings, IL-25 is an epithelial cell-secreted cytokine, mediating Th2 eosinophilic airway inflammation, via induction of Th2 cytokines, such as IL-5, IL-4, and IL-13 [110]. The immunology of the less tweedy, orphan cytokine IL-17D is poorly understood.

IL-17 is disulfide-linked homodimeric glycoprotein consisting of 155 amino acids with a molecular weight of 35 kDa; but heterodimers composed of IL-17A and IL-17F, as well as IL-17F homodimers exist [110,111]. IL-17A homodimer produce more pathophysiologic responses that the heterodimer or the IL-17F homodimer [108,111,112]. Among the IL-17 family members, IL-17F has the highest homology (55%) with IL-17A [108,113], and IL-17E (IL-25), is the most knotty, divergent cytokine in the IL-17 family, sharing 16-20% sequence homology with its cousins

[108]. IL-17A and IL-17F have similar pathophysiological roles, although IL-17 is about 10-30 times as potent as IL-17F [11]. IL-17 is the founding and most studied family member [5,8], especially in the pathogenesis of rheumatoid arthritis [114-117], psoriasis [118-120], and currently in the pathogenesis of neutrophilic asthma [121,122].

Interleukin-17 is secreted mainly by a distinct CD4+ T helper 17 (Th17) cells [123-125], characterized by expression of the master transcription factor retinoic acid-related orphan-receptor-γt (RORγt) [126]. IL-17 is also secreted by other activated immune cells, such as dendritic cells, CD8+ T cells, δγ T cells, natural killer cells, invariant natural killer T cells, lymphoid tissue inducer cells, and type 3 innate lymphoid cells [127-132].

Several studies have reported increased levels of IL-17 in sputum and BAL fluid [133-135], and a positive correlation between IL-17 concentration and severity of asthma [134,135]. Similarly, Bullens et al. [136] have shown an increase in IL-17 mRNA in sputum of asthmatic patients, which was linked with airway influx of granulocytes including neutrophils. Furthermore, increased IL-17 and IL-17F levels [137-139], Th17 cells [140-143], and IL-17-producing innate type 3 lymphoid cells (ILC3) [144], have been demonstrated to be increased in BAL fluid, lung biopsies, and peripheral blood in patients with severe asthma. The levels of these biomarkers of neutrophilic airway inflammation have been shown to correlate with the severity of asthma in both adults [137-141,143,144], and children [142].

Interleukin-17 engenders tissue inflammation mainly by stimulating expression of several proinflammatory cytokine, such as IL-6, IL-8, and TNF-α [145,146], and chemokines, including CXCL1, CXCL2, CXCL5, CXCL8, and CXCL20 [145,147,148]. IL-17 also induces secretion of growth factors, such as G-CSF, and GM-CSF [145,149,150], which play very important roles in neutrophil airway immunopathology.

Interleukin-17, Airway Hyperresponsiveness and Remodeling

Interleukin-17 directly or indirectly contributes to airway hyperresponsivess, and remodeling in patients with neutrophilic asthma [151]. IL-17 contributes to the development of subepithelial fibrosis by enhancing the production of profibrotic cytokines, and activation of fibroblasts, which produces collagen [152-155]. Increased airway smooth muscle (ASM) mass is a hallmark of airway remodeling in severe asthma. IL-17 and the cytokines it induces, such as IL-6, IL-1β, and chemokines including CXCL8/IL-8, and eotaxin, promote airway smooth muscle (ASM) cell proliferation and migration [156-158]. IL-17 also promotes ASM cell survival by inhibiting apoptosis [156-158]. Blockade of IL-17 receptors (IL-17A or IL-17C) prevents the ability of ASM cells to proliferate and migrate [158]. Additionally, IL-17 enhances ASM cell contraction. This effect is mediated by the IL-17-induced activation of the RhoA-ROCK pathway in ASM cells. This pathway is an important regulator of myosin light chain phosphorylation involved in smooth muscle contractility [159]. Increase in ASM cell mass and contractility can result into airway hyperresponsiveness, bronchoconstriction, and severe airflow limitation. Furthermore, IL-17 promotes angiogenesis, which is a hallmark of remodeling in severe asthma [160]

Airway mucus hypersecretion and mucus plugging is one of the serious complication of severe neutrophilic asthma. IL-17 is a potent secretagogue which stimulates submucosal glands and goblet cell hyperplasia, and hypersecretion of mucus. Increased mucus secretion results from increased gene expression. It has been reported to stimulate MUC5A and MUC5B gene expression in monkey and mouse tracheobronchial epithelial cells 161,162]. Noteworthy, IL-17 contributes to the development of steroid-insensitive asthma [163,164]. The pathophysiological mechanisms for severe neutrophilic asthma are outlined in Table 3.

Treatment of Severe Neutrophilic Asthma

Most patients with stable asthma respond to treatment with standard therapies, such as long-acting β-agonists (LABA), low dose inhaled corticosteriods (ICS), and leukotriene receptor antagonists (LTRA), using the stepwise guidelines. However, treatment of severe neutrophilic asthma is challenging. Unlike eosinophilic asthma, there are no specific biomarkers, such as fractional exhaled nitric oxide (FeNO), periostin, and DDP-4 to select patients who are more likely to benefit from biologics. Currently, there are also no effective biologics specifically targeting airway neutrophilic inflammation. The approved biologics by the FDA, and their dosages for the treatment of eosinophilic asthma are portrayed in Table 4.

Several clinical trials investigating the efficacy and safety of biologics targeting the incriminated cytokines and their receptors in the pathogenesis of neutrophilic asthma, such as IL-8 (CXCR1/2), and IL-17 (IL-17AR) have not been successful. Biologics targeting the IL-8/CXCR1/2 axis did not meet the endpoints for the treatment of severe uncontrolled neutrophilic asthma. In a small clinical trial, the CXCR1/2 inhibitor SCH527123 significantly reduced sputum neutrophil count, but only led to a modest improvement in asthma control [165]. Similarly, in a larger multicenter study in patients with uncontrolled persistent asthma, and high blood neutrophil count, the CXCR2 antagonist AZ5069 did not reduce severe asthma exacerbations [166]. Currently, none of the IL-8/CXCR1/2 axis antagonists has achieved the endpoints in the treatment of severe neutrophilic asthma

Biologics targeting IL-17 signaling, such as brodalumab [167], and secukinumab [168], have also not been successful in clinical trials. Busse at al. [167] in a randomized, placebo-controlled phase IIa trial of brodalumab, a monoclonal antibody against IL-17 receptor, in patients with moderate-to-severe asthma, reported that, brodalumab did not result in any statistically significant benefit in terms of ACQ scores, FEV1, or use of rescue short-acting β-agonists (SABA). Similarly, secukinumab failed to suppress ozone-induced airway neutrophilic inflammation in healthy volunteers [168]. The good news is that, both brodalumab (Siliq) [169], and secukinumab (Consentyx) [170], have been approved by the Food and Drug Administration for the treatment of plaque psoriasis, and ankylosing spondylitis.

Macrolide Antibiotics

Macrolide antibiotics, such as erythromycin (ERM), azithromycin (AZM), clarithromycin (CAM), and roxithromycin (RXM), and the 16-membered lactone ring (spiromycin, josamycin, midecamycin), or the new ketolide antibiotic telithromycin have antiviral, antibacterial [171-174], anti-inflammatory, and immunomodulatory effects [175-178].

Several studies have reported that treatment with AZM, CAM, and RXM decrease eosinophil and neutrophil counts, inhibit neutrophil migration, and oxidative burst activity and mediator release. Consequently, there is a decrease in the concentrations of neutrophil elastase, metalloproteinase-9, IL-8, IL-6, IL-1β, TNF-α, and eosinophilic cationic protein (ECP) [178-183].

Long-term, low-dose macrolides plays an important role in the treatment of chronic inflammatory airway diseases [184,185], such as panbronchiolitis [186], cystic fibrosis [187], noncystic fibrosis bronchiectasis [188], bronchiolitis obliterans syndrome [189], post-lung transplantation bronchiolitis obliterans syndrome [190], and COPD [191]. Macrolide antibiotics have been used for the treatment of asthma since

1970 [192], and currently, they have become very popular for the treatment of severe, uncontrolled neutrophilic asthma [193,194]. The British Thoracic Society has outlined very valuable guidelines for the use of long-term macrolides in adults with respiratory diseases, including asthma [195].

Several clinical trials have documented the efficacy and safety of long-term, low-dose macrolides in the treatment of severe asthma. Simpson, et al. [196] have shown that clarithromycin in patients with severe refractory asthma reduced neutrophil count, and sputum IL-8 levels, although they did not observe any change in lung function or asthma control [196]. The Azithromycin for prevention of exacerbations in severe asthma (AZISAST) randomized, placebo-controlled trial investigated the efficacy of azithromycin in patients with severe asthma with history of severe exacerbations, despite receiving high-dose ICS and LABA [197]. There was no effect of AZM on the primary outcome in the total population when assessed without inflammatory phenotype. However, AZM (250 mg daily three times per week) as add-on treatment in patients with nonesonophilic asthma, defined by normal blood eosinophil count, and normal FeNO, resulted in significantly fewer severe exacerbations during 26-week period compared with controls [197]. Azithromycin significantly reduced both severe exacerbations, and lower respiratory tract infection in non-eosinophilic asthma phenotype by approximately 67% compared to 38% in placebo group. Azithromycin was ineffective in eosinophilic asthma, and in fact, the eosinophilic subgroup had more exacerbations when taking AZM [26]. This underpins the importance of phenotyping in selecting patients for targeted precision therapies [193,197].

The second well conducted, randomized double-blinded, placebo-controlled trial (AMAZES) compared add-on azithromycin (500 mg three times per week) with placebo for 48 weeks in patients with symptomatic asthma despite medium-to high dose ICS and LABA [198]. Treatment with add-on azithromycin significantly reduced the incidence of medium and severe exacerbation by 1.07 versus 1.86 per person-year, for AZM and placebo, respectively. AZM treatment was also associated with an improvement in Asthma Quality of life Questionnaire (AQLQ) scores in both groups of patients with eosinophilic and noneosinophilic asthma phenotypes [198].

Similarly, the Telithromycin, Chlamydophila, and Asthma (TELICAST) multicenter, randomized, double-blind, placebo-controlled study in 278 patients with moderate-to severe asthma reported significantly greater improvement in symptoms, and lung function in patients receiving telithromycin, 800 mg once daily, for 10 days compared with placebo [199]. Patients receiving telithromycin showed improvement in exacerbation symptoms at the end of treatment of 51% versus 29% in the placebo treated patients. There was also a significant improvement in FEV1 of 0.63 L in telithromycin-treated patients versus 0.29 L in placebo-treated [199].

The Azithromycin Against Placebo in Exacerbations of Asthma (AZALEA) study investigated the effectiveness of azithromycin treatment as add-on to standard therapy for adult patients with exacerbation [200]. In the AZALEA clinical trial, addition of azithromycin 500 mg daily for 3 days to the standard treatment resulted in no statistically significant clinical improvement, including symptoms and quality of life scores, and FEV1 [200]. This large trial in the United Kingdom had challenges in the recruitment of subjects, because there was widespread use of antibiotics in the 31 centers enrolled for the study. The study was therefore underpowered because a large number of patients (2044) were excluded, because they were already taking antibiotics for their exacerbations [200]. It is possible that the population randomized was not representative of the larger population, because more than 2000 other patients were excluded from the study for other reasons [200]. However, long-term, low-dose macrolide antibiotic therapy does clinically, and significantly reduce severe exacerbations, improve lung function, and health-related quality of life (HLQoL) in patients with neutrophilic asthma.

The outcomes of the above clinical trials, indicate that different macrolides including the dosages of the specific drugs may influence the immunomodulatory effects, and efficacy of macrolide antibiotics in patients with severe neutrophilic asthma. Phenotyping of patients, and treatment of comorbid diseases with neutrophilic asthma, such as allergic rhinitis, chronic rhinosinusitis with nasal polyps, gastroesophageal reflux disease, and obesity influence the effectiveness of macrolides [193]. Therefore, before patients are administered long-term macrolide therapy, the patients should be carefully selected; and comorbid disorders should be treated, in order to prevent unnecessary cardiotoxicities, and community-wide macrolide resistance.

Bronchial Thermoplasty

Bronchial thermoplasty (BT) is a novel bronchoscopic therapy aimed at reducing the hypertrophied ASM mass in patients with severe refractory asthma [201-203]. BT is approved for subjects aged 18 and above with severe persistent asthma not responding to high-dose ICS, LABA, and eosinophilic interleukin antagonists. It is suitable for all the phenotypes of asthma characterized by ASM hypertrophy, and severe airway remodeling [204-209], insensitive to eosinophilic biologics, such as neutrophilic, and paucigranulocytic asthma [208,209].

Bronchial thermoplasty is a complex procedure, and should be performed in highly specialized centers. Performance of BT requires bronchoscopic meticulousness, dexterity, and good knowledge of the airway anatomy [210]. The selection and preparation of patients for BT is rigorous, and the procedure should be performed by experienced pulmonologists or bronchoscopists [205,206,210]. Patients for bronchial thermoplasty should be in an optimal stable condition, and selection of patients for BT is critical. In addition to their standard medical treatment for severe asthma, patients should be pre-treated with prednisolone 50 mg/day for 3 days before BT, one day before BT, on the day of BT, and the day after bronchial thermoplasty [206]. Before the procedure, patients should be pre-treated with nebulized salbutamol and/or ipratropium bromide [206].

Bronchial thermoplasty is performed under moderate-to-deep sedation or general anesthesia [205-210]. At bronchoscopy a special disposable Alair™ catheter (Boston Scientific, Marlborough, MA, USA) with a distal diameter of 1.4 mm, and a basket-like array of expandable electrodes is inserted through the instrument channel [211]. Optimal thermoplasty of all subsegment bronchi is successful with ultrathin, rotatable bronchoscopes with increased ease of use and higher degree of flexibility [206]. BT trims excessive hypertrophied ASM mass, submucosal glands [201-203,208,212,213], collagen deposition [2013], epithelial cells, and neuroendocrine cells [214], and hyperreactive cholinergic nerves [215]. Thus, reducing all the structural changes involved in AHR, airway remodeling, and severe neutrophilic asthma. Noteworthy, BT promotes regeneration of epithelial cells [214], and persistently reduces mucin production after bronchial thermoplasty [216]. Bronchial thermoplasty also reduces regeneration of ASM cells, and decreases (Ki67+) subepithelial cells proliferation [17]. Furthermore, BT increases the expression and activation of glucocorticoid receptors (GR) in airway epithelial cells, and subepithelial mesenchymal cells [218], and probably restores steroid-sensitivity.

Post-bronchial thermoplasty care should be optimized, because BT-associated adverse effects usually occur during the first 30 days after the procedure. Post-BT adverse events (Table 4) should not scare anyone, because bronchial thermoplasty has been demonstrated to be safe and well tolerated in experienced hands.

Several clinical trials have reported the efficacy and safety of bronchial thermoplasty. Most studies have reported that BT improves asthma symptoms, reduces exacerbations, hospitalizations, and emergency department visits [201,208-213]. Additionally, BT improves asthma quality of life questionnaire (AQLQ) scores, lung function [201,219,220], and allows patients to wean or discontinue corticosteroids [219].

The beneficial effects of BT are durable and can last up to 3-5 years [207,221-224]. At 5 years patients still have stable lung function, and lack of increase in hospital admission, and emergence department visits [220-223]. Furthermore, BT has been reported to be still effective after 10 years of the procedure. The preliminary findings were that the AQLQ scores, and severe exacerbation rates were comparable to those recorded 1 year after bronchial thermoplasty [225]. Refinement in the technique is in progress, and more patients with severe refractory asthma will cherish thermoplasty.

Conclusion

Neutrohilic asthma is a severe phenotype of asthma characterized by persistent airway obstruction, and poor lung function. Interleukin-17, and its subordinate cytokine IL-8 play a key role in the pathogenesis of neutrophilic asthma, The dual cytokines promote trafficking, activation, and degranulation of neutrophil in the airways, which result in secretions of reactive oxygen species, proteases, cytokine, chemokines, and growth factors. These pro-inflammatory mediators propagate airway inflammation, AHR, and airway remodeling. Treatment of severe neutrophilic asthma is challenging, because it does not respond to Th2 eosininophilic biologics, such as mepolizumab, and dupilumab; and targeting IL-17, IL-8 and their receptors has been unsuccessful, and fruitless. Macrolide antibiotics have immunomodulatory effects, and some patients with neutrophilic asthma respond to long-term, low-dose macrolide therapy. Bronchial thermoplasty is an innovative bronchoscopy procedure aimed at reducing the hypertrophied ASM mass. BT has been shown to improves asthma symptoms, reduce exacerbations, hospitalizations, and emergency department visits. Additionally, BT improves AQLQ scores, lung function, and allows patients to taper or discontinue corticosteroids. The therapeutic effects of BT can last for more than 5 years.

Conflict of interest

The author declares that the publication was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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