Allergy Asthma Immunol Res. 2018 Sep;10(5):428-447
https://doi.org/10.4168/aair.2018.10.5.428
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Review

Autoimmune Responses in Severe Asthma

Manali Mukherjee, Parameswaran Nair*

Division of Respirology, Department of Medicine, St. Joseph's Healthcare Hamilton, McMaster University, Hamilton, Canada

Received: Jan 2, 2018
Revised: Jan 29, 2018
Accepted: Feb 13, 2018

Correspondence to
Parameswaran Nair, MD, PhD, FRCP, FRCPC
Division of Respirology, Department of Medicine, St Joseph's Healthcare Hamilton, McMaster University, 50 Charlton Avenue East, Hamilton, Ontario L8N 4A6, Canada.
Tel: +1-905-522-1155 (ext 35044)
Fax: +1-905-521-6183
E-mail: parames@mcmaster.ca

Funding
PN is supported by the Frederick E. Hargreave Teva Innovation Chair in Airway Diseases. In the past 2 years, he has received consultancy and lecture fees from AstraZeneca, Sanofi, Teva, Novartis, Theravance, Knopp, Merck, GlaxoSmithKline and Roche; research support from GlaxoSmithKline, AstraZeneca, and Novartis; and his institution has received research support from Roche, Teva, Sanofi, Boehringer Ingelheim, AstraZeneca, and Novartis.

ABSTRACT

Asthma and autoimmune diseases both result from a dysregulated immune system, and have been conventionally considered to have mutually exclusive pathogenesis. Autoimmunity is believed to be an exaggerated Th1 response, while asthma with a Th2 underpinning is congruent with the well-accepted Th1/Th2 paradigm. The hypothesis of autoimmune involvement in asthma has received much recent interest, particularly in the adult late-onset non-atopic patients (the "intrinsic asthma"). Over the past decades, circulating autoantibodies against diverse self-targets (beta-2-adrenergic receptors, epithelial antigens, nuclear antigens, etc.) have been reported and subsequently dismissed to be epiphenomena resulting from a chronic inflammatory condition, primarily due to lack of evidence of causality/pathomechanism. Recent evidence of 'granulomas' in the lung biopsies of severe asthmatics, detection of pathogenic sputum autoantibodies against autologous eosinophil proteins (*e.g.*, eosinophil peroxidase) and inadequate response to monoclonal antibody therapies (*e.g.*, subcutaneous mepolizumab) in patients with evidence of airway autoantibodies suggest that the role of autoimmune mechanisms be revisited. In this review, we have gathered available reports of autoimmune responses in the lungs, reviewed the evidence in the context of immunogenic tissue-response and danger-associated molecular patterns, and constructed the possibility of an autoimmune-associated pathomechanism that may contribute to the severity of asthma.

Keywords: Autoantibodies; autoimmunity; severe asthma; sputum eosinophils; neutrophils; degranulation; danger associated molecular patterns; sputum; immunoglobulin G

INTRODUCTION

A concomitant global increase in the incidences of asthma and autoimmune diseases, along with the discovery of novel pathogenic effector cells, has led to theories of common underlying pathophysiological pathways.[1-3] A review focussing on 2 such disease types, conventionally thought to be exclusive of each other, requires 'definition.' The nominalist definition of 'asthma' describes it as a disease characterized by abnormal airway function with episodic variable airflow limitation. It is now unanimously considered a heterogeneous respiratory condition clinically characterised by airway inflammation, reversible airflow obstruction and airway hyperresponsiveness.[4] Autoimmune diseases are the consequence of autoantibodies

Disclosure

There are no financial or other issues that might lead to conflict of interest.

against self-structures generated by self-reactive lymphocytes to an extent that causes sustained self-reactivity and tissue damage.[5] Autoimmunity includes a spectrum of diseases with varying morbidity and mortality ranging from the potentially fatal systemic lupus erythematosus (SLE), granulomatosis and polyangiitis (GPA) to tissue-specific morbidities such as Hashimoto's thyroiditis, rheumatoid arthritis (RA), Crohn's disease, etc.[5] In essence, clinical manifestations of asthma are mostly the result of a dysregulated immune system, similar to autoimmune diseases. Until recently, both were considered to have mutually exclusive pathogenesis with contrasting and counter-regulatory effector mechanisms.

SHIFT FROM PARADIGM

General theory implies an impaired Th1 pattern that promotes autoimmunity, while a Th2 axis supports allergic respiratory diseases, and that both effector pathomechanisms are counteractive. In fact, epidemiological studies have reported a lower incidence of asthma and allergy in patients with severe autoimmune diseases such as multiple sclerosis (MS)[6] and RA.[7] Evidence for the Th1/Th2 paradigm was originally hypothesized and accepted based on the observations in both humans and animal models of disease, that associated signature cytokines and transcription factors were reciprocally regulated and adequate for their respective polarization.[8] For instance, interleukin (IL)-12 and interferon-gamma dominated the Th1 response, while cytokines such as IL-4, IL-5 and IL-13 were responsible for the effector mechanisms in allergy and asthma. Of recent, there has been a paradigm shift in this school of thought. A Swedish study in 2010 reported increase in standardised incidence ratios of common autoimmune diseases (such as RA, Crohn's and polyarteritis nodosa) diagnosed at least 5 years after an asthma exacerbation that required hospitalisation (n=4,006).[9] Again, in a large Taiwanese cohort study over a period of 11 years, the incidence rate of asthma was computed to be 2.61-fold greater in the SLE cohort (n=13,072) compared to the non-SLE cohort (n=52,288) (22.9 vs 8.00/10,000 person-years).[10] The possible co-existence of a Th1/Th2 pathology has also been reported in pediatric populations. The cumulative incidences of asthma within the first 7 years of life, according to a Finnish Medical Birth Register data on the whole 1987 birth cohort (n=60,254), was significantly higher in children with RA and coeliac disease.[11] Evidences from epidemiological studies that report shared incidences of diverse autoimmune diseases and atopic manifestations including allergic asthma have recently been reviewed.[1,2,12] The current review will focus on evidences from immunological studies and re-visit concepts of immunology and molecular breakthroughs in asthma, to ascertain merit (and provide a working hypothesis) to this paradigm shift.

AUTOIMMUNE PHENOMENA IN ASTHMA: EVIDENCE FROM IMMUNOLOGICAL STUDIES

Autoantibodies are a hallmark of autoimmunity. However, the mere presence of autoantibodies does not clinically justify the presence of an autoimmune disease. Autoimmune involvement in the pathogenesis of asthma has been proposed based on the numerous studies that report the presence of 'circulating' autoantibodies against diverse self-antigens/structures (**Table 1**).

Antibodies against beta-2-adrenergic receptors

As early as 1980, circulating autoantibodies against beta-2-adrenergic receptors were reported.[13] These autoantibodies indeed correlated with abnormal autonomic responsiveness

https://doi.org/10.4168/aair.2018.10.5.428

Table 1. Studies reporting circulating autoantibodies in asthma: 1980-2017 (a comprehensive list)

Year	Diversity in autoantibody targets	Molecular methods	Clinical significance
1980[13] 1981[14] 1982[17] 1984[16] 1991[15]	· Against beta-2-adrenergic receptors · IgG · Detected in serum	· Competitive inhibition of binding of I125-labelled HBP to beta-receptors on tissue) · IgG was assessed indirectly by co-IP	· Patients with autoantibodies had impaired sensitivity to adrenergic agents · Detectable in a small proportion of allergic asthmatics
1993[18]	· Against 55 kDa platelet/endothelial · Circulating IgG autoantibodies · Specific target not confirmed	Immunoblot analysis of sera and T cell reactivity against same autoantigen	· Non-atopic corticosteroid dependent asthmatics · Significant correlation of T cell reactivity with FEV_1 (r=0.544, *P*=0.003) · Same aAb found in few SLE (3/30) and RA (2/36) patients
1995[26]	· Circulating IgGs · ANAs · Speckled pattern · Not dsDNA or ANCA · Target antigen not confirmed	· Hep-2 substrate slides (IIF) · Titer >1:40	· In 55% of aspirin-sensitive asthma, 41% with intrinsic asthma, 39% extrinsic asthma · Titers correlated with CIC, complement activation and RF · Some patients with autoantibodies had signs of clinical signs of autoimmunity (rheumatic symptoms, cold sensitivity, and Raynaud's phenomenon)
2001[116] 2002[19] 2006[20] 2008[21] 2009[22]	· Circulating autoantibodies against bronchial epithelial antigens · Targets confirmed to be cytokeratin-18 and alpha-enolase · Subtype IgG1 · Cytotoxicity to epithelial cells	Cell-based ELISA, immunoblot analysis, mass-spectrometry, cell lysis *in vitro* assays	· Predominantly in patients with severe non-atopic asthma with reduced lung function (FEV_1) and at least one annual exacerbation · Same autoantibodies found in up to 10% SLE patients
2009[28]	· Circulating ANAs (IgG) · 21/95 (22%) patients positive for ANAs (3.3% in healthy) · speckled pattern (15), homogenous (4), nucleolar (2) – indicative diverse autoantigen targets · ANCA sero-positive patients and those with ANAs specific for mixed tissue connective disease excluded	· Third generation ELISA and confirmed by Hep-2 IIF patterns · Mean titers up to 48.6	· One-year observational study with n=95 (26 were severe) · ANA incidence was not different between atopic (20.59%) and non-atopic (22.73%) · ANAs: independent risk factor for mortality (*P*=0.037), severe exacerbations requiring hospitalization (*P*=0.01), and rapid FEV_1 · Decline (>100 mL/yr) (*P*=0.006) · Presence of ANA associated with decreased responsiveness to ICS · No associated signs of clinical autoimmunity in the 22 sero-ANA positive patients
2012[23]	· autoantibodies against Collagen V · Circulating · Predominantly IgG subtype, though IgA and IgM present · IgE reactivity was absent · Other targets: EGFr, activin A type 1 receptor, alpha-catenin	· In-house developed ELISA and Proto-Array from Invitrogen · 1:200 titer	· Presence of anti-Collagen V antibodies in mild, moderate, and severe asthmatics (n=99) compared to 60 healthy controls (*P*=0.002). · Significantly higher in severe asthmatics · Titers correlate with asthma severity and corticosteroid use
2014[92]	· Anti-IgE IgGs · No significant variation between tested population (atopic/non-atopic asthma and healthy) · Circulating · Free and bound to Fc-epsilon-receptors were detected	· IgE-specific ELISA · ANA (IgG) ELISA	· Naturally occurring autoantibodies · Increased titers in some asthmatics, irrespective of atopy status · Inhibits allergen-induced basophil activation · No significant variation in serum ANAs · No correlation between auto-IgE IgGs and ANAs
2016[24]	· Circulating autoantibodies against PPL · Titers not mentioned · IgG subtype in 18% patients, IgE subtype in 8.7% patients	· Western blot using both human placental extract and recombinant PPL · Band at 195 kDA	· Anti-PPL IgG frequency similar between severe (17.6%) and mild-to-moderate (19.4%) · No correlation with disease activity · Anti-PPL IgE associated with nasal polyposis
2017[27]	· Circulating ANAs · Clinically relevant titer of ANA >1:160 present in 11/110 asthmatics (10%) · ANCA undetectable in asthma sera	· ELISA and IIF for ANAs, ANCA (both MPO and PR3, rheumatoid factor, anti-citrullinated peptide-3 · Titer >1:160	· No correlation with clinical indices of asthma severity · No patient with ANAs showed any clinical symptoms of autoimmunity (dry eyes, dry mouth, Raynaud's)

ANCA, anti-neutrophil cytoplasmic antibody; aAb, autoantibody; CIC, circulating immune complex; dsDNA, double stranded deoxyribonucleic acid; EPX, eosinophil peroxidase; FEV1, forced expiratory volume in one second, HBP, hydroxybenzylpindolol; ICS, inhaled corticosteroid; IP, immunoprecipitation; IIF, immunofluorescence; MPO, myeloperoxidase; PR3, proteinase 3; RF, rheumatoid factor; Ig, immunoglobulin; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; ELISA, enzyme-linked immunosorbent assay; EGFr, epidermal group factor receptor; PPL, periplakin; ANA, anti-nuclear antibody.

characterized by alpha-adrenergic and cholinergic hypersensitivity and beta-adrenergic hyposensitivity.[14] By 1982, the group confirmed that the circulating immunoglobulins (Igs) inhibited the specific binding of ^{125}iodine-labelled hydroxybenzylpindolol to beta-receptors on mammalian lung membrane. By 1991, Wallukat and Wollenberger[15] demonstrated that the inhibitory effect of the gamma-globulin serum fraction on the positive chronotropic response

https://doi.org/10.4168/aair.2018.10.5.428

of cultured neonatal rat heart myocytes to 2 μmol/L of clenbuterol was pronounced in severe asthmatics (83%) compared to moderate (58%) and mild patients (23%). The group also confirmed the previous observations that the autoantibodies were of the IgG isotype. Though this brought about the first working concept of autoimmunity in context to bronchial asthma, the clinical relevance was doubtful since the incidences of these autoantibodies were low[16] and unremarkable between the asthmatics (4/17) and normal healthy controls (3/19).[17]

Antibodies against common endothelial/platelet antigens

Circulating IgGs against 55 kDa antigens (platelet/endothelial in origin) were detected in 34/97 asthmatics, with corresponding T/B cell reactivity confirmed *in vitro*. The autoantibodies were mostly restricted to asthmatics who were non-allergic, *i.e.*, skin-prick test negative (P=0.001) and who were maintained on oral corticosteroids (P=0.004).[18]

Antibodies against bronchial epithelial cells

In the following years, circulating IgG autoantibodies to cytokeratin 18 were more frequently detected in patients with non-atopic asthma compared to those with atopic asthma or healthy controls.[19,20,116] IgG autoantibodies to alpha enolase were more frequently detected in patients with severe asthma compared with those with mild-to-moderate asthma or healthy controls.[20] The subclass was confirmed to be predominantly IgG,[1] indicating a possible complement-mediated cytotoxicity.[21] Though the cytotoxicity of the detected IgGs against the bronchial antigens were confirmed *in vitro*, involvement of the complement cascade was not determined.[22] Although a clinical correlation was reported with a decline in lung function, the use of immortalised cell-lines (A549 and BEAS-2B) might have restricted the translational merit of these studies.

Antibodies against extracellular matrix protein and cellular junctions

Collagen V, an extracellular matrix protein, was demonstrated to be a self-antigen in asthma, where the isotype of autoantibodies detected was predominantly IgG. At 1:200 titer, the levels correlated with severe asthma (P<0.01) and corticosteroid use (P=0.03). In addition, the study also showed circulating antibodies reactive to other epithelial proteins such as epidermal group factor receptor (EGFr), activin A type 1 receptor and alpha-catenin.[23] A major limitation of the study was the lack of mechanistic data or any follow-up on the pathogenesis of the detected autoantibodies.

More recently, in a French cohort study (Cohorte Obstruction Bronchique et Asthme [COBRA]), periplakin (PPL), a component of desmosomes involved in epithelial cohesion, intracellular signal transduction and antigen presentation, was proposed to be a target for autoimmunity in asthma. Based on a 195 kDA band on Western blot analysis, 47 patients out of 260 (18%) were concluded to have anti-PPL IgG reactivity and 12/138 (8.7%) with anti-PPL IgE reactivity. The IgG autoantibodies were present irrespective of the disease severity, while the latter was prevalent more in patients with nasal polyps.[24] The data did not provide means to determine any causal relationship with asthma pathogenesis, but an earlier study showed anti-PPL autoantibodies to inhibit epithelial repair *in vitro*.[25]

Antinuclear antibodies (ANAs)

Using Hep-2 cells as substrate, ANAs were determined by immunofluorescence (IIF) staining. ANAs were assessed to be prevalent at serum titers of 1:40 or above, in 55% of the asthmatics with aspirin-sensitivity, 41% with intrinsic asthma, and 39% extrinsic asthma compared to 11% in healthy controls.[26] Another study showed 21 out of 95 (22%) asthmatics with

https://doi.org/10.4168/aair.2018.10.5.428

demonstrable bronchodilator reversibility had circulating ANAs (mean titer of 48), confirmed by Hep-2 IIF and enzyme-linked immunosorbent assay (ELISA). However, another study reported that clinically significant high ANA titers ≥1:160 was detected in 10% of patients with asthma but there was no significant association between ANA positivity and clinical indices of asthma severity.[27] There were conflicting reports of clinical signs of ANAs between these studies. While signs of autoimmune manifestations such as rheumatic symptoms, cold sensitivity and Raynaud's phenomenon were reported in patients with low titer 1:40,[26] while the study with patients with higher ANA titers (>1:100) reported otherwise.[28] The latter study, however, showed that ANAs were predictors of asthma exacerbations, mortality and decrease in lung function. In contrast, the study by Tamai and co-workers[27] reported no correlation with clinical indices of severe asthma in patients who showed ANAs at clinically relevant titers of 1:160.

Taken together, evidence over the past few decades suggest that an association between asthma and circulating autoantibodies against antigens derived from diverse tissues, in addition to the classic nuclear antigens (**Table 1**). The disparities in the clinical significances reported in the different studies question the contribution of these autoimmune markers to disease severity and therefore, the pathological relevance of these circulating autoantibodies. However, there are 3 striking features that are common to these observations. First, all reported autoantibodies were predominantly of the IgG subclass. Secondly, the incidence of autoantibodies though variable between the studies, was significantly higher in non-atopic patients with noted severity (reported either as annual exacerbations requiring hospitalisation, or dependence on oral corticosteroid). Therefore, though autoantibodies of IgE subclass have been suggested at driving atopic asthma, it will not be the focus henceforth, and has been extensively reviewed elsewhere.12 Thirdly, reported prevalence (percentage of seropositive patients) of circulating autoantibodies within the study cohorts showed a decline with sophistication of immunoassay techniques (improved specificity).

AUTOIMMUNE PHENOMENA IN ASTHMA–EVIDENCE FROM MOLECULAR STUDIES

Cutting-age molecular techniques, including Genome Wide Association Studies (GWAS), microarray platforms, 'omics' data from large cohort studies, *etc.*, have revealed common genetic variants between asthma, allergy and the wide spectrum of autoimmune diseases. In 2001, polymorphisms within IL-4 receptor alpha (associated with asthma and allergy) were reported to be relevant in autoimmune diseases such as SLE and Crohn's disease.[29] In the asthma-related GWAS studies such as the GABRIEL and AUGOSA, genes such as *SLC22A5/A4* located on chromosome 5q31.1 were identified to be asthma susceptibility genes,[30,31] with known pathomechanism in progression of Crohn's disease and inflammatory bowel syndrome.[32] Recent meta-analysis of 2 GWAS studies (n=62,330) examined 290 genes commonly associated with autoimmune diseases. Twenty-nine genes were significantly associated with allergic diseases at a false discovery rate of <0.05. Common loci such as HLA-B, Smad3, Myc, IKZF1 and IL2R/IL15R (with previous known associations with asthma susceptibility) were shown to be on the same direction of the effect, suggesting increasing risk of both autoimmune and allergic diseases.[33]

Cellular and molecular assessment of airway inflammation have shed light on the diversity of underlying pathways in asthma that ultimately lead to clinical manifestations/symptoms

https://doi.org/10.4168/aair.2018.10.5.428

represented as 'phenotypes,'[34] and molecular signatures to determine 'endotypes.'[35] In fact, asthma is no longer considered a typical Th2-mediated disease with allergy-driven pathomechanism. Detailed molecular studies have revealed asthmatics with a Th2-high, Th17-high and Th2/Th17-low molecular signature.[36] Of interest, autoimmune diseases are in general thought to act through the Th1/Th17-driven cell-mediated pathway,[37] generally associated with an infection-derived pathomechanism. That being said, there is increasing evidence of eosinophils, most exclusively viewed as a Th2 effector cell, to have contributing role in certain autoimmune diseases (extensively reviewed[38]). In addition, there is an increase in autoimmune diseases in eosinophil-mediated diseases such as eosinophilic esophagitis and hypereosinophilic syndrome (HES).[38]

ARRIVING AT A HYPOTHESIS FOR AUTOIMMUNE PATHOMECHANISM IN ASTHMA

Introduction to immunological theories

Before constructing a working hypothesis, it is pertinent that we review the concepts of immunology with context to autoimmunity. The concept of 'self/non-self' when introduced by MacFarlene Burnet in 1949, was neither a theory nor a metaphor, but an analogy for descriptive host-defence that failed to explain the phenomenon of autoimmunity. This remained true even for Charles Janeway's 'Infectious non-self model' (1989) that introduced the concept of antigen presenting cells (APCs) recognising evolutionarily conserved consensus patterns on infectious agents termed pathogen-associated molecular patterns (PAMPs) to be triggers for an immune response. 'Autoimmunity' is defined as an anomaly within the body's immune response where the immune cells generate antibodies that attack self, leading to injury, falls outside the realm of both theories. A fresh perspective was offered by Matzinger's 'Danger model' around early 2000s,[39,40] based on Paul Ehrlich's forethought on '*horror autotoxicus.*'[41] Autoimmune responses were described to stem from deficiencies in normal physiological processes and specific tissue response to danger-associated molecular patterns (DAMPs) released as a result of inflammation, continual tissue-injury and impaired repair.

As discussed in previous section, the disparity in the reported studies with questionable causal relationship between the detected circulating autoantibodies and the clinical indices of asthma severity may be resolved by implicating the concept of tissue-specific response to danger signals.[42] Indeed, in an interview, Dr. Matzinger[43] hints that underlying immunology of asthma and allergy could be explained by the Danger model if one considers tissue-specific response compartmentalized in the lungs.

Studies supporting localized lung autoimmunity: evidence from other diseases

Breach of immune tolerance in the lungs is not uncommon. Chronic 'unresolved' inflammation is considered an acute trigger for inducible bronchus associated lymphoid tissue (iBALT) formation,[44] which are essentially ectopic clusters of B cells in different stages of differentiation sparsed with T cells, and APCs like macrophages/dendritic cells (DCs), capable of *de novo* antibody production on local stimuli and antigen exposure.[45] Additionally, iBALTs have been shown to be centres for localized autoantibody production in organ-specific specific autoimmune disorders like Sjogren's disease[46] and RA[47,48] presenting with pulmonary complications. Of particular interest is a recent study where anticyclic

https://doi.org/10.4168/aair.2018.10.5.428

citrullinated peptide.3 antibody (anti-CCP3), a diagnostic marker for RA, was detected in the induced sputum of at-risk seronegative patients, in addition to those with seropositive 'early' and 'active' disease.[49] In fact, in RA there is growing interest in proposing breach in lung mucosal immunology to be the seat of autoimmune development.[50] With regard to the respiratory tract, IgG autoantibodies against several self-antigens (such as dsDNA and thyroid peroxidase [TPO]) were detected in the nasal polyp tissues, extracted from 44 patients with chronic rhinosinusitis (CRS), out of which 24 had concurrent asthma.[51] Ectopic lymphoid clusters triggered by cigarette smoke and chronic inflammation have been observed in lung tissue specimens from patients with chronic obstructive pulmonary disorder (COPD). ANAs were present in the induced sputum from COPD patients, otherwise absent in the serum.[52] However, we need to exercise caution with the interpretation of the human data, since the sputum ANAs reported were detected using a horse radish peroxidase-based ELISA platform, which might not be ideally suited for sputum samples.[53] Nevertheless, the possible presence of luminal ANAs in COPD patients' refractory to steroid treatment further highlights the importance of identifying tissue-specific autoimmune mechanisms latent in obstructed airways.

Evidence of localized autoimmune responses in asthmatic lungs

Two recent studies suggest the possibility of a localized autoimmune phenomenon in an asthmatic lung with persistent eosinophils, despite maintenance oral steroid therapy. First, 'asthmatic granulomatosis' based on the immunohistological evidence of cellular aggregates or 'granulomas' in the lung parenchyma of prednisone-dependent severe asthmatics was described in 2012 by Wenzel and colleagues.[54] Though the study did not include autoantibody detection, the steroid-sparing response to drugs like methotrexate and azathioprine, classically prescribed for autoimmune diseases, provided evidence of a possible autoimmune-type anomaly.[54] More direct evidence was reported recently. Antieosinophil peroxidase (EPX) IgGs were reported in the sputa (and not sera) of 24/65 of eosinophilic asthmatics (37%), levels of which correlated positively with the sputum ANAs (detectable in 25/56 asthmatics).[55] Similar to some aforementioned studies in section 3 (**Table 1**), there were diverse IIF patterns observed ranging from speckled to homogenous. Further similarity can be drawn from the fact that only 4/15 severe asthmatics had circulating ANAs and was comparable to be the healthy controls (3/15). It is to be noted that this data was collected from 15 severe eosinophilic asthmatics who had high titers of sputum autoantibodies (both ANA and anti-EPX IgG). Taken together, the authors suggest the presence of a polyclonal autoimmune event localized to the airways.[55] More importantly, the airway autoantibodies were pathogenic to naïve eosinophils triggering degranulation *in vitro*, which in turn significantly correlated with the clinical indices of airway eosinophil activity (EPX and free eosinophil granules)[56] documented clinically. Both free eosinophil granules and EPX are significantly pathogenic[57] and are indicative of 'active' disease.[56] The study was limited in terms of determining the mechanism/source of *in situ* autoantibody generation in the lungs, though an increased B cell activity was evident in patients with the sputum autoantibodies.[55] Intriguingly, patients who were determined to have 'asthmatic granulomatosis' ('granulomas' consisting of eosinophils and plasmacytoid lymphocytes in lung biopsies) had similar clinical characteristics to the autoantibody-positive subset described by Mukherjee *et al.*,[55] with adult-onset asthma, persistent eosinophilia despite prednisone use, unremarkable total serum IgE and sinus disease.[54] The presence of such 'granulomas' or even ectopic lymphoid structures with higher organisation iBALT enclosing follicular T cells, APCs and B cells at different stages of development, in patients with sputum autoantibodies is justifiable. The presence of such structured clusters will support local production of autoantibodies as detectable in the induced sputum.

https://doi.org/10.4168/aair.2018.10.5.428

WORKING HYPOTHESIS OF AUTOIMMUNE-ASSOCIATED ASTHMA PATHOGENESIS

There is a growing body of evidence that cumulatively indicates the presence of autoimmune mechanisms underpinning disease severity in a subset of asthmatics, in particular, the late-onset non-atopic severe asthmatics. In fact, the underlying pathomechanism in this subset till date remains obscure and uncertain. Based on available evidence (discussed in the following sections) a plausible theory of breach of tolerance and localized autoantibody production has been schematically represented in **Fig. 1**.

Chronic Inflammation and tissue injury in asthmatic airways

Persistent airway inflammation is pivotal to the pathophysiology of asthma. Epithelial damage from airway inflammation may result in exposure of self-antigens or their determinants resulting in immune response which may contribute to disease pathology. There is evidence of autoantibodies against epithelial antigens such as cytokeratin and PPL (**Table 1**) that are further equipped to cause cellular damage.[19] Epithelial and parenchymal damage may result directly due to environmental/extraneous insults, infection or by cytotoxicity induced by granule proteins released by degranulation of innate cells such as eosinophils, mast cells, neutrophils, *etc.*, (recruited to the lungs in response to inflammatory stimuli). Increased frequency of immune cell degranulation over time leads to peroxidase release that has known immunogenic properties.[58] Myeloperoxidase and TPO are known autoantigens, antibodies (IgGs) against which have established pathomechanism in autoimmune diseases such as eosinophilic granulomatosis and polyangiitis (eGPA)[59] and Hashimoto's thyroiditis,[60] respectively. Intranasal IgGs against TPO was detected in nasal polyp extracts from patients with CRS.[51] Pathogenic antibodies against EPX have recently been described in a small subset of eosinophilic asthmatics with increased frequency of eosinophilic degranulation and EPX.[55] Therefore, with progression of disease and persistence of inflammation, the airways are constantly exposed to immunogenic entities such as a EPX, and subsequent markers of tissue injury (DAMPs), capable of triggering the adaptive immune response (**Fig. 1**). We speculate that with recruitment of the diverse lymphocyte subsets due to ongoing inflammation (allergen/infection/damage), the host micro-environment starts accumulating a cocktail of chemokines such as B cell activating factor (BAFF), B cell chemoattractant (BCA-1/CXCL13), that would support ectopic lymphoid neogenesis (or initial B cell clusters), *in situ* autoantibody generation,[61] cytokines that induce/facilitate class switch recombination to IgG, *etc.*, events critical for a localized autoimmune response (**Fig. 1**). Indeed, BAFF and CXCL13[62,63] have been suggested to be important in asthma pathogenesis, and increased levels were reported in the airways of asthmatic children[64] and adults with sputum autoantibodies.[55]

Extensive degranulation and extra-cellular DNA traps

Ig-induced eosinophil degranulation was demonstrated by Gleich and co-workers[65] as early as 1991 to be to be unresponsive to dexamethasone. In addition to piecemeal degranulation by activated intact eosinophils,[66] there has been recent evidence of extracellular histone-coated DNA traps (eosinophil extracellular traps [EETs]) released by eosinophil cytolysis *in vitro*.67 In fact, evidence of EETs was recently demonstrated in nasal polyps from patients with CRS.[68] The authors commented on a plausible association between the EETs and the pathogenesis of CRS, in context to the recently described localized autoimmune responses.[51] *In vitro* evidence of EETs triggered by sputum autoantibodies (from eosinophilic asthmatics) was provided recently.[55] The event was quantified by the evaluating the release of dsDNA (a known DAMP), and

https://doi.org/10.4168/aair.2018.10.5.428

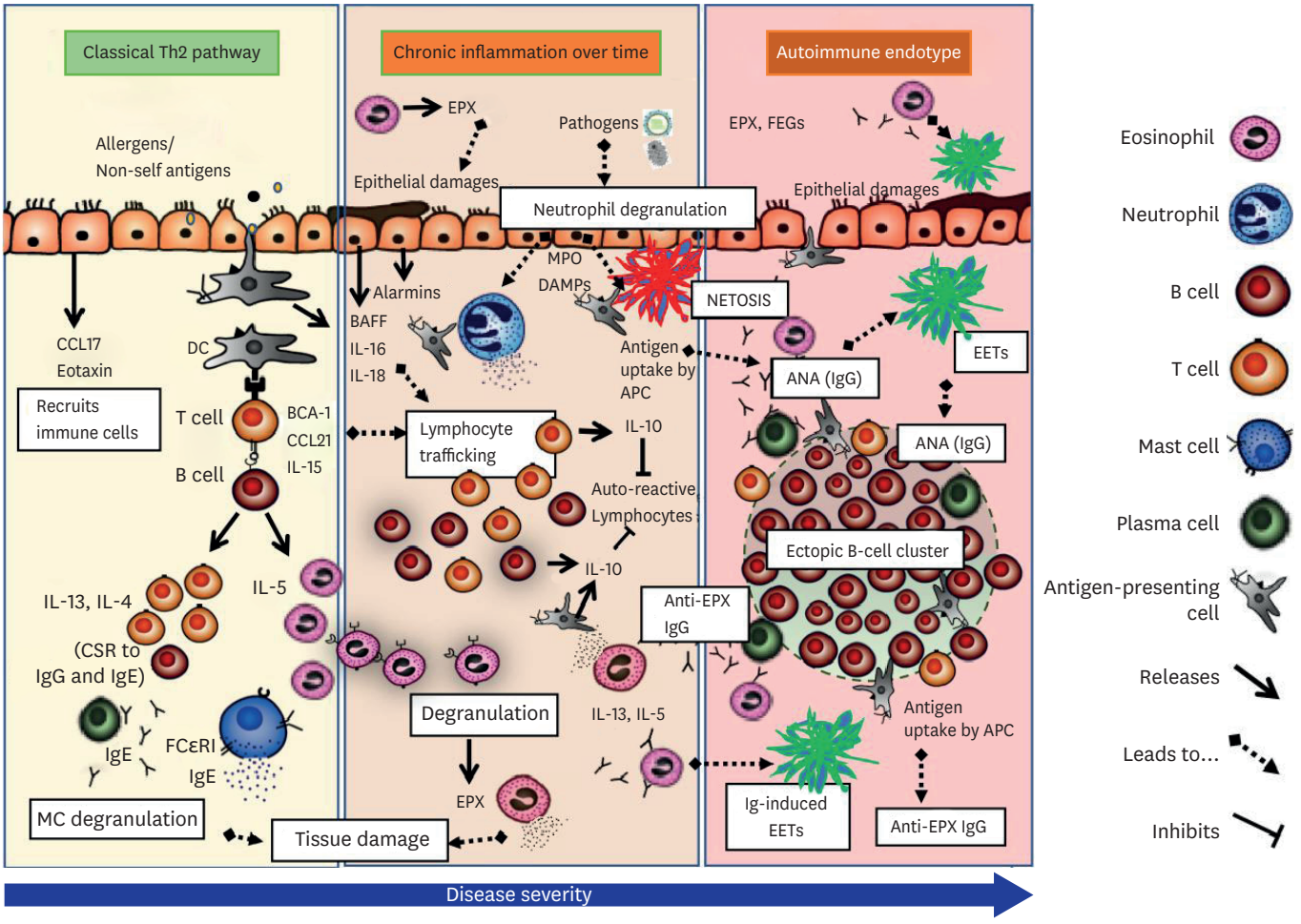

Fig. 1. Working hypothesis for localized autoimmune phenomenon in asthmatic lung. Classical Th2 pathway leads to IL-5, IL-4, IL-13 release, recruitment of eosinophils (eotaxin) and lymphocytes (CCL17), and favors class-switch to IgE. Eosinophil activation and degranulation releases EPX and mediators of tissue damage. With disease progression and chronic inflammation over time, increased localized expression of BCA-1, BAFF, IL-15, IL-16 and CCL17 will allow homing of lymphocytes into the submucosa. Reduced number of regulatory lymphocytes with possible lower IL-10 production will allow activation of the autoreactive lymphocytes (present as a small percentage of the total lymphocyte pool) in the vicinity of their cognate antigens (products of degranulation and tissue damage). Over time, B cell clusters with interspersed APCs and T cells in near proximity are formed. BAFF, CXCL13, CCL21, IL-15 and IL-16 released by different sources including B cells themselves support ectopic B cell clusters, its organization and autoantibody formation. Low levels of anti-EPX IgG and ANAs (polyclonal IgG autoantibodies) formed initially during earlier episodes of degranulation, trigger Ig-induced cytolysis (EETs) on recruited eosinophils (increased eotaxin), thereby increasing self-antigen exposure. The extracellular traps allow efficient antigen priming by APCs and B cells that further leads to increase in *in situ* ANA and anti-EPX IgG production. In some patients, pulmonary infection triggers release of pro-inflammatory mediators like IL-18 which along with neutrophil degranulation 'NETosis' (with possible NET formation) supports further tissue damage, accumulation of self-autoantigens and autoantibody production. Drawing is not to scale.
APC, antigen presenting cell; ANA, anti-nuclear antibodies; BAFF, B cell activating factor; BCA-1, B cell attracting chemokine; CSR, class switch recombination; DAMP, danger-associated molecular pattern; EET, eosinophil extracellular trap; EPX, eosinophil peroxidase; Ig, immunoglobulin; IL, interleukin; NET, neutrophil extracellular trap; MC, mast cell; MPO, myeloperoxidase.

lactose dehydrogenase (indicator of loss of membrane integrity). The autoantibody-induced eosinophil cytolysis releasing EET could not be effectively curbed by physiologically relevant concentrations of dexamethasone(10^{-6} M). Though at a nascent stage, it can be said that sputum autoantibodies are pathogenic in nature and can lead to extensive airway degranulation, an event that remains possibly uncurbed by the maintenance dose of corticosteroid.

One of the phenotypes of asthma is characterized by mixed granulocytic sputum, *i.e.*, increased sputum cell count indicative of infection, increased neutrophil content, and evidence of underlying eosinophilia[69] and poor lung function.[70] These patients have recurrent

https://doi.org/10.4168/aair.2018.10.5.428

incidences of chest infection, and have been shown to have detectable sputum ANAs and anti-EPX IgGs.[55] In addition to EETs, we speculate the presence of bacterial induced neutrophil-derived extracellular DNA traps (neutrophil extracellular traps [NETs]) in the underlying pathomechanism. Indeed, NETs released due to NETosis, a novel neutrophil degranulation machinery, has established pathomechanism including development of specific autoantibodies against neutrophil-targets in autoimmune diseases such as eGPA.[71,72] Choi and co-workers[73] demonstrated that NETs formed (*in vitro*) by neutrophils extracted from severe asthmatics have the ability to induce secretion of cytokeratin-18 autoantibodies from airway epithelial cells. Furthermore, peripheral blood neutrophils from severe asthmatics (n=30) demonstrated greater ability of NET production and neutrophil autophagy compared to neutrophils from non-severe asthma (n=38). In fact, IL-8-induced NET production levels negatively correlated with lung function (r=-0.700, P=0.016).[74] More recently, release of NETs by neutrophils recruited as an immune response to rhinovirus infection has been demonstrated in mice models of type-2 allergic asthma.[75,76] The study suggests the release of cellular dsDNA content as a consequence of NETosis is pathogenic and might be central to asthma exacerbations due to rhinovirus infections. Though dsDNA is a known DAMP, investigating autoantibodies to dsDNA was not included in the study design. Therefore, a possible localized autoimmune pathology leading to exacerbation of a type-2 inflammation cannot be dismissed.

The trigger for inducing NETosis is mostly infectious agents such as bacteria and viruses, while EETs seems to be triggered by autoantibodies as demonstrated *in vitro* by Mukherjee and co-workers.[55] Increased IgG-load in the eosinophilic airways could lead to extensive EETs, in addition to formation of NETs in an infective environment, thereby allowing a less-conservative presentation of autoantigens like histone and dsDNA to the plausible submucosal B cell clusters (T-cell independent mechanism) or the follicular T cells/DCs allowing T-cell: B-cell interactions in an organized iBALT (**Fig. 1**).

Peripheral tolerance and lymphopenia

The fact that not all severe asthmatics show airway autoantibodies indicates the presence of regulatory mechanisms that maintain local immune tolerance. During development, the B and T cells with self-reactive antigen receptors (also called autoreactive lymphocytes) are generally deleted from the repertoire of lymphocytes released into the peripheral circulation to avoid autoimmune events. However, a small percentage of self-reactive clones do exist in the circulation, which are thereafter regulated by $Foxp3^+$-regulatory T cells (Tregs), a key mechanism for peripheral tolerance.[77] To counter the development of autoimmunity due to recognition of self-antigens during tissue injury, Tregs and B cells present in the pool of lymphocytes 'homed' from the circulation, act as sentinels that induce apoptosis in the activated lymphocytes with autoreactive receptors.[77,78] Concepts of regulatory B cells are being investigated for their role in suppressing T cell-independent activation of B cells with self-reactive B cell receptors (BCRs)[79] and IL-10-mediated regulation of autoimmune responses.[80] In context to asthma, there is evidence of both compromised peripheral tolerance in severe asthmatics with significant low levels of $Foxp3^+$-Treg cells[81,82] and reduced IL-10 expression.[81,83] Furthermore, $CD25^+$ $CTLA4^+$ $Foxp3^+$-T cells with regulatory functions were enumerated to be significantly reduced in induced sputum from atopic asthmatics compared to healthy volunteers.[84] Again, none of these studies investigated autoantibodies and therefore neither association nor causality can be derived. However, it can be speculated that transient lymphopenia could lead to dysregulation of regulatory lymphocytes[85] and reduce the numbers 'homed' to the airways, and consequently the IL-10 expression (**Fig. 1**). Animal models with

https://doi.org/10.4168/aair.2018.10.5.428

T-cell lymphopenia have been shown to spontaneously develop organ-specific autoimmune diseases with an array of autoantibodies, due to compensatory homeostatic expansion of autoreactive T cells.[86,87] In fact, lymphopenia is not uncommon in human autoimmune disorders. In patients with both systemic autoimmune disorders like SLE and organ-specific autoimmune disorder like RA, a strong association with lymphopenia and thereby, reduced regulatory cells has been established to be accountable for the inability to suppress self-reactive T cells, leading to loss of peripheral tolerance.[88] Patients with a history of transient lymphopenia in addition to a history of intense airway eosinophil degranulation were seen to be have higher detection of sputum autoantibodies.[55] In this context, the triad of variables, *viz.*, lymphopenia, long-term corticosteroid use and development of autoantibodies, leads to the classic situation of which came first, the chicken or the egg?

CLINICAL IMPLICATIONS

Clinical implications of the presence of autoimmunity in asthma are manifold. Most of the clinical implications of the putative autoimmune endotype is circumstantial and speculative, because a direct measurement of autoantibodies or associated autoimmune end-points were not included as a part of clinical trials nor reported for clinical follow-ups during routine asthma management.

Response to maintenance therapy

Presence of autoantibodies in the lungs could be one of the mechanisms that contribute to the observed steroid subsensitivity in severe asthmatics (reviewed recently[89]). The prednisone-sparing effect of classical autoimmune drugs (such as azathioprine, methotrexate and cyclosporine) in severe eosinophilic prednisone-dependent patients with biopsy evidence of granulomas is indicative of the same, even though airway autoantibody titers were not investigated.[54] One of the potential mechanisms may be attributed to the increase in autoantibody titers in an eosinophil-rich tissue, and the consequent autoantibody-induced eosinophil degranulation with EETs. As discussed earlier in previous section, the event was shown to be a steroid-unresponsive *ex vivo*,[55] and therefore could explain the concurrent presence of high eosinophil activity and sputum autoantibodies despite intake of daily prednisone in those patients. In an autoimmune tissue, increased doses of corticosteroid will be able to reduce the lymphocytic infiltration and eosinophils, but will not be efficient in reducing the number of autoantibodies or suppressing their immediate mechanism of action on effector cells (*e.g.*, eosinophils). Again, in the same microenvironment of increased IgG load, the cross-linking of Fc-gamma receptors on eosinophils can negatively affect glucocorticosteroid-induced apoptosis, promoting survival.[90,91] Furthermore, earlier studies (**Table 1**) could address impaired response to bronchodilators in patients who showed circulating autoantibodies to beta-2-adrenergic receptors.[13,17]

Response to novel biologics

Autoantibodies to IgE reported in asthmatic patients[92] could interfere with omalizumab (IgG1 monoclonal antibody, mAb targeting IgE) and compromise clinical response. The possible involvement of anti-IgE IgG competitively inhibiting the therapeutic antibody requires to be investigated since the effectiveness of omalizumab in severe prednisone-dependent asthmatics is not as marked as its effects in decreasing exacerbations in poorly-controlled asthmatics on inhaled corticosteroids.[93] Unlike omalizumab, there is circumstantial proof of asthma-worsening in a prototype severe eosinophilic patient after mepolizumab therapy

https://doi.org/10.4168/aair.2018.10.5.428

(anti-IL-5 mAb, 100 mg subcutaneous [SC]) associated with a localized airway autoimmune response.[94] The said patient showed IL-5 complexed to Igs post treatment, associated with drop in lung function and increase in autoantibody titers. Indeed, we have demonstrated that patients who showed less than optimal response to 100 mg SC mepolizumab had increased sputum IL-5 (along with Ig-bound IL-5) and anti-EPX IgG in their titers post treatment.[95] Reslizumab treatment (anti-IL-5 mAb, intravenous [IV], 3 mg/kg) effectively reduced autoantibody titers in the airways of the same ten eosinophilic prednisone-dependent asthmatics who were assessed for mepolizumab therapy previously. When the receptor was targeted instead of the ligand with benralizumab (anti-IL-5R alpha IgG1, SC), 20% of the study population were reported to have suboptimal clinical response,[96] although the overall study population showed a 75% reduction in their maintenance dose of prednisone. In the Canadian sub-study of the ZONDA trial, despite reducing both blood and sputum eosinophils, benralizumab was inefficient in ameliorating sputum anti-EPX IgGs[97] unlike reslizumab (3 mg/kg IV)[95] and mepolizumab (750 mg/kg, IV).[117] We have tabulated our observations in **Table 2**, and it is interesting to note that greater amelioration of eosinophils and EPX is associated with greater reduction in anti-EPX IgGs. In fact, sputum anti-EPX IgGs was one of the predictors of response to anti-IL-5 mAb therapy.[95]

The difference in the treatment response to anti-IL-5 mAb therapies may be contributed to 1) route of administration (IV vs SC) that allows an adequate dose to reach the target tissue; 2) administered dose itself (fixed dose vs weight-adjusted dose), ensuring the mAb is in excess to the target antigen and formation of aggregates (immune complexes) are avoided; and 3) difference in Fc backbone where mepolizumab is an IgG1 molecular capable of binding complement C1q,[98] and reslizumab, an IgG4 which does not bind complement and inhibits complement-associated lysis.[99] All 3 factors have a common denominator, that they can have a deleterious effect in a scenario when the patient has an ongoing localized autoimmune response. In the instance where the target mAb is in equivalent proportion to the target antigen in the tissue, it may form aggregates. Though large immune complexes are unlikely to form with IL-5 and mepolizumab based on the stoichiometric design of the molecule;[100] nevertheless, the molecule being an IgG1 mAb can potentially bind complement C1q.[98] In the tissue, with additional IgG autoantibodies, a complement-mediated tissue injury can occur with heightened inflammation.[101] Secondly, reslizumab being an IgG4 molecule holds the ability of not only avoiding C1q binding but also inhibiting complement-mediated lysis.[99] Therefore, in an autoimmune-prone tissue, any increase in IgG4 load (in this instance, reslizumab) can potentially reduce complement-mediated inflammation in addition to neutralising IL-5.

Table 2. Autoimmune responses to the different anti-eosinophil monoclonal antibody therapies

Variable	Mepolizumzb 750 mg IV[117]	Mepolizumab 100 mg SC[95]	Reslizumab 3 mg/kg IV[95]	Benralizumab 30 mg SC[97]
Blood eos	↓↓↓	↓↓↓	↓↓↓	↓↓↓
Sputum eos	↓↓↓	↓	↓↓↓	↓↓↓
Sputum EPX	↓↓↓	↓	↓↓↓	n/d
Anti-EPX IgG	↓↓↓*	↑↑	↓↓↓	↑↓
Clinical response†	+++	+	++‡	+++

Down arrows indicate reduction in levels, and the number of symbols correlate tot the degree of amelioration. Up arrows indicate increase.
IV, intravenous; SC, subcutaneous; eos, eosinophils; n/d, not done, was not one of the exploratory outcomes in the study protocol; EPX, eosinophil peroxidase; Ig, immunoglobulin. *Unpublished data; †Exacerbation reduction/steroid sparing/anti-eosinophilic effect in the severe prednisone-dependent patients; ‡Prednisone-sparing effect not evaluated.

https://doi.org/10.4168/aair.2018.10.5.428

This concept might be relevant for all novel biologics currently approved or under development for severe asthma. Effectiveness of therapies such as benralizumab that include an extra variable *i.e.*, the component of antibody-mediated cytotoxicity (ADCC) might be implicated if there are autoantibodies present against CD16 (Fc-gamma-receptor IIIa) epitopes, crucial for initiating ADCC or autoantibody-associated macrophage dysfunction and apoptotic cell clearance. This is speculative for asthma, but evidence for autoantibodies against CD16[102] and scavenger receptors on macrophages[103] have been reported.

Revisiting intravenous immunoglobulin (IVIG) clinical trials

Before the availability of mAb therapies, IVIG trials in asthma were conducted on the rationale that they will effectively reduce recurrent airway infections in asthmatic patients with associated immunodeficiency syndromes.[104] In addition, where infection was not apparent, IVIG could work by inhibiting mononuclear cell proliferation, B-cell differentiation (anti-BAFF activity), IgG-Fc-receptor blockage, modification of complement activation and reduction of IgE synthesis by anti-idiotype antibodies.[105] An open label trial of IVIG (2 g/kg every 4 weeks) conducted by Mazer and Gelfand,[106] in 8 severe atopic prednisone-dependent children resulted in improvements of symptoms including spirometry, and reduction in daily corticosteroid use. In fact, the authors suggested IVIG as a steroid-sparing treatment option in asthma and atopic dermatitis.[107] However, subsequent double-blind placebo-controlled trials in severe asthma could not confirm the beneficial effect of IVIG.[108,109] This could be explained by injudicious patient selection. For example, in the Kishiyama *et al.*[108] trial, patients recruited ranged between 6 and 68 years. Most of the mentioned trials were in children and adolescents, and as evident from the ongoing discussion, autoimmune mechanisms in asthma might be more prevalent in the adult-onset patient group. IVIG could potentially be an effective therapy in patients whose asthma severity is driven by autoantibodies. In fact, autoantibodies to cytokeratin 18 in serum samples from patients with bronchial asthma and CRS was suggested as a biomarker for monitoring response to IVIG therapy (United State Patent Application Publication #US20050208583; Page 9, **Table 4**, paragraph [0103]). In addition, a case study was recently reported where IVIG was effective in improving FEV1, and ameliorating airways autoantibodies in a patient with severe eosinophilic refractory asthma.[94] In the current light of evidence, it is perhaps prudent that we re-visit the idea of IVIG as a therapeutic option for those asthmatics who show evidence of autoantibodies in conjunction with other indices of severity (such as high airway eosinophil activity and corticosteroid sub-sensitivity).

Systemic autoimmune diseases with pulmonary manifestations

Numerous systemic autoimmune diseases such as eGPA, Sjogren's syndrome, RA, mixed connective tissue disease and SLE present with pulmonary complications.[110] In RA, the pulmonary complications can be addressed by the presence of iBALT and airways anti-CCP3 antibodies.[47] In fact, as previously discussed, anti-CCP3 autoantibodies were detectable in the sputum of at-risk RA patients, and therefore exhibited immediate prognostic value.[49] Though the presence of circulating autoantibodies are considered biomarkers and associated with specific disease severity, the sensitivity and specificity can often be a problem. This is apparent for patients with eGPA, only 40% of whom show the characteristic circulating anti-neutrophil cytoplasmic antibody (ANCA).[111] In brief, eGPA is a distinct form of autoimmune systemic vasculitis, diagnosed as the presence of 4 or more of the following 6 criteria (American College of Rheumatology guideline): peripheral blood eosinophilia, paranasal sinus abnormality, neuropathy, extravascular evidence of eosinophils, asthma (often severe enough to require daily maintenance corticosteroids) and transient pulmonary infiltrates.[112] Again, eGPA evolves through an initial pro-dermic allergic phase characterized by asthma

and/or rhinosinusitis, followed by an eosinophilic phase with increased blood eosinophil levels and organ-involvement, and finally a 'vasculitis' phase showing clinical manifestations of small-vessel vasculitis.[113] If the progression of the disease is to be followed, then there is an indication of the early allergic/inflammatory events giving rise to the autoimmune conditions. This natural course of eGPA suggests that asthma can be a prodromal condition of this systemic autoimmune eosinophilic vasculitis (eGPA) and that an autoimmune mechanism can be involved in both severe asthma and eGPA. However, it is likely that the seat of autoimmunity is localized to the lungs since most patients who are serum-ANCA negative present with severe pulmonary complications, while the sero-positive population have a prominent vasculitis component.[113,114] In fact, we have recently shown sputum ANCA in 16/22 (72%) eGPA patients irrespective of their serum ANCA status.[115] Localized autoimmune phenomenon may be more relevant in understanding the severity of asthma and CRS observed in these eGPA patients and choosing the optimal treatment strategy.

Caution needs to be exercised in ascertaining the dose of anti-IL5 mAb therapies in patients presenting with severe asthma and a known systemic autoimmune pathomechanism such as eGPA. If the mAb dose is not adequate, these severe patients with increased IgG load (ongoing autoimmunity), and increased levels of IL-5 molecules present with a higher probability of falling into the 'zone of antibody-antigen equivalence' leading to heightened inflammation/immune-complex mediated complications. Investigating target specificities of sputum autoantibodies against disease-specific autoantigens or adopting an 'omics' approach can provide a tool for prognosis, diagnosis and monitoring response to biologics for several systemic autoimmune diseases that present with pulmonary complications.

DISCUSSION

Presence of autoantibodies (auto-inflammation) and development of autoimmunity (clinical manifestations caused by the autoantibodies) are part of a spectrum of immunological diseases, in the same way that innate and adaptive immune responses constitute the immunological continuum. It is likely that the definition and significance of autoimmunity in context to asthma severity and treatment responses will evolve over the next decade as we continue to investigate immune pathways in asthma using "omics" platforms. These may have particular relevance to the use of biologics in the treatment of patients with severe asthma.

REFERENCES

1. Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. Clin Exp Immunol 2010;160:1-9.
PUBMED | CROSSREF
2. Rabin RL, Levinson AI. The nexus between atopic disease and autoimmunity: a review of the epidemiological and mechanistic literature. Clin Exp Immunol 2008;153:19-30.
PUBMED | CROSSREF
3. Rottem M, Shoenfeld Y. Asthma as a paradigm for autoimmune disease. Int Arch Allergy Immunol 2003;132:210-4.
PUBMED | CROSSREF
4. Hargreave FE, Nair P. The definition and diagnosis of asthma. Clin Exp Allergy 2009;39:1652-8.
PUBMED | CROSSREF
5. Davidson A, Diamond B. General features of autoimmune disease. In: Rose NR, Mackay IR, editors. The autoimmune diseases. 5th ed. San Diego (CA): Elsevier; 2014. 25-36.

6. Bergamaschi R, Villani S, Crabbio M, Ponzio M, Romani A, Verri A, et al. Inverse relationship between multiple sclerosis and allergic respiratory diseases. Neurol Sci 2009;30:115-8.
PUBMED | CROSSREF
7. Rudwaleit M, Andermann B, Alten R, Sörensen H, Listing J, Zink A, et al. Atopic disorders in ankylosing spondylitis and rheumatoid arthritis. Ann Rheum Dis 2002;61:968-74.
PUBMED | CROSSREF
8. Singh VK, Mehrotra S, Agarwal SS. The paradigm of Th1 and Th2 cytokines: its relevance to autoimmunity and allergy. Immunol Res 1999;20:147-61.
PUBMED | CROSSREF
9. Hemminki K, Li X, Sundquist J, Sundquist K. Subsequent autoimmune or related disease in asthma patients: clustering of diseases or medical care? Ann Epidemiol 2010;20:217-22.
PUBMED | CROSSREF
10. Shen TC, Tu CY, Lin CL, Wei CC, Li YF. Increased risk of asthma in patients with systemic lupus erythematosus. Am J Respir Crit Care Med 2014;189:496-9.
PUBMED | CROSSREF
11. Kero J, Gissler M, Hemminki E, Isolauri E. Could TH1 and TH2 diseases coexist? Evaluation of asthma incidence in children with coeliac disease, type 1 diabetes, or rheumatoid arthritis: a register study. J Allergy Clin Immunol 2001;108:781-3.
PUBMED | CROSSREF
12. Tedeschi A, Asero R. Asthma and autoimmunity: a complex but intriguing relation. Expert Rev Clin Immunol 2008;4:767-76.
PUBMED | CROSSREF
13. Venter JC, Fraser CM, Harrison LC. Autoantibodies to beta 2-adrenergic receptors: a possible cause of adrenergic hyporesponsiveness in allergic rhinitis and asthma. Science 1980;207:1361-3.
PUBMED | CROSSREF
14. Fraser CM, Venter JC, Kaliner M. Autonomic abnormalities and autoantibodies to beta-adrenergic receptors. N Engl J Med 1981;305:1165-70.
PUBMED | CROSSREF
15. Wallukat G, Wollenberger A. Autoantibodies to β2-adrenergic receptors with antiadrenergic activity from patients with allergic asthma. J Allergy Clin Immunol 1991;88:581-7.
PUBMED | CROSSREF
16. Blecher M, Lewis S, Hicks JM, Josephs S. Beta-blocking autoantibodies in pediatric bronchial asthma. J Allergy Clin Immunol 1984;74:246-51.
PUBMED | CROSSREF
17. Harrison LC, Callaghan J, Venter JC, Fraser CM, Kaliner ML. Atopy, autonomic function and beta-adrenergic receptor autoantibodies. Ciba Found Symp 1982:248-62.
PUBMED
18. Lassalle P, Delneste Y, Gosset P, Gras-Masse H, Wallaert B, Tonnel AB. T and B cell immune response to a 55-kDa endothelial cell-derived antigen in severe asthma. Eur J Immunol 1993;23:796-803.
PUBMED | CROSSREF
19. Nahm DH, Lee YE, Yim EJ, Park HS, Yim H, Kang Y, et al. Identification of cytokeratin 18 as a bronchial epithelial autoantigen associated with nonallergic asthma. Am J Respir Crit Care Med 2002;165:1536-9.
PUBMED | CROSSREF
20. Nahm DH, Lee KH, Shin JY, Ye YM, Kang Y, Park HS. Identification of alpha-enolase as an autoantigen associated with severe asthma. J Allergy Clin Immunol 2006;118:376-81.
PUBMED | CROSSREF
21. Lee HA, Kwon B, Hur GY, Choi SJ, Nahm DH, Park HS. Isotype and IgG subclass distribution of autoantibody response to alpha-enolase protein in adult patients with severe asthma. Yonsei Med J 2008;49:923-30.
PUBMED | CROSSREF
22. Kwon B, Lee HA, Choi GS, Ye YM, Nahm DH, Park HS. Increased IgG antibody-induced cytotoxicity against airway epithelial cells in patients with nonallergic asthma. J Clin Immunol 2009;29:517-23.
PUBMED | CROSSREF
23. Liu M, Subramanian V, Christie C, Castro M, Mohanakumar T. Immune responses to self-antigens in asthma patients: clinical and immunopathological implications. Hum Immunol 2012;73:511-6.
PUBMED | CROSSREF
24. Taillé C, Grootenboer-Mignot S, Estellat C, Roy C, Ly Ka So S, Pretolani M, et al. Periplakin is a target for autoimmunity in asthma. Respir Res 2016;17:126.
PUBMED | CROSSREF

25. Taillé C, Grootenboer-Mignot S, Boursier C, Michel L, Debray MP, Fagart J, et al. Identification of periplakin as a new target for autoreactivity in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;183:759-66.
PUBMED | CROSSREF

26. Szczeklik A, Nizankowska E, Serafin A, Dyczek A, Duplaga M, Musial J. Autoimmune phenomena in bronchial asthma with special reference to aspirin intolerance. Am J Respir Crit Care Med 1995;152:1753-6.
PUBMED | CROSSREF

27. Tamai K, Yoshimatsu H, Saito T, Matsuoka H, Okada N, Koma Y, et al. Autoantibody profiles and their association with blood eosinophils in asthma and COPD. Allergol Int 2017;66:332-7.
PUBMED | CROSSREF

28. Agache I, Duca L, Anghel M, Pamfil G. Antinuclear antibodies in asthma patients- a special asthma phenotype? Iran J Allergy Asthma Immunol 2009:49-52.
PUBMED

29. Heinzmann A, Deichmann KA. Genes for atopy and asthma. Curr Opin Allergy Clin Immunol 2001;1:387-92.
PUBMED | CROSSREF

30. Wan YI, Shrine NR, Soler Artigas M, Wain LV, Blakey JD, Moffatt MF, et al. Genome-wide association study to identify genetic determinants of severe asthma. Thorax 2012;67:762-8.
PUBMED | CROSSREF

31. Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, et al. A large-scale, consortium-based genomewide association study of asthma. N Engl J Med 2010;363:1211-21.
PUBMED | CROSSREF

32. Pochini L, Scalise M, Galluccio M, Indiveri C. OCTN cation transporters in health and disease: role as drug targets and assay development. J Biomol Screen 2013;18:851-67.
PUBMED | CROSSREF

33. Kreiner E, Waage J, Standl M, Brix S, Pers TH, Couto Alves A, et al. Shared genetic variants suggest common pathways in allergy and autoimmune diseases. J Allergy Clin Immunol 2017;140:771-81.
PUBMED | CROSSREF

34. Nair P, Dasgupta A, Brightling CE, Chung KF. How to diagnose and phenotype asthma. Clin Chest Med 2012;33:445-57.
PUBMED | CROSSREF

35. Svenningsen S, Nair P. Asthma endotypes and an overview of targeted therapy for asthma. Front Med (Lausanne) 2017;4:158.
PUBMED | CROSSREF

36. Choy DF, Hart KM, Borthwick LA, Shikotra A, Nagarkar DR, Siddiqui S, et al. TH2 and TH17 inflammatory pathways are reciprocally regulated in asthma. Sci Transl Med 2015;7:301ra129.
PUBMED | CROSSREF

37. Sallusto F, Lanzavecchia A. Human Th17 cells in infection and autoimmunity. Microbes Infect 2009;11:620-4.
PUBMED | CROSSREF

38. Diny NL, Rose NR, Čiháková D. Eosinophils in autoimmune diseases. Front Immunol 2017;8:484.
PUBMED | CROSSREF

39. Matzinger P. Tolerance, danger, and the extended family. Annu Rev Immunol 1994;12:991-1045.
PUBMED | CROSSREF

40. Matzinger P. The danger model: a renewed sense of self. Science 2002;296:301-5.
PUBMED | CROSSREF

41. Ehrlich P, Morgenroth J. On haemolysins: third and fifth communications. In: Ehrlich P, Himmelweit F, Marquandt M, Dale HH Sir, editors. The collected papers on Paul Ehrlich. London: Pergamon; 1957. 205-55.

42. Matzinger P, Kamala T. Tissue-based class control: the other side of tolerance. Nat Rev Immunol 2011;11:221-30.
PUBMED | CROSSREF

43. Matzinger P. The evolution of the danger theory. Expert Rev Clin Immunol 2012;8:311-7.
PUBMED | CROSSREF

44. Bienenstock J, Johnston N, Perey DY. Bronchial lymphoid tissue. I. Morphologic characteristics. Lab Invest 1973;28:686-92.
PUBMED

45. Randall TD. Bronchus-associated lymphoid tissue (BALT) structure and function. Adv Immunol 2010;107:187-241.
PUBMED | CROSSREF

46. Salomonsson S, Larsson P, Tengnér P, Mellquist E, Hjelmström P, Wahren-Herlenius M. Expression of the B cell-attracting chemokine CXCL13 in the target organ and autoantibody production in ectopic lymphoid tissue in the chronic inflammatory disease Sjögren's syndrome. Scand J Immunol 2002;55:336-42.
PUBMED | CROSSREF

47. Rangel-Moreno J, Hartson L, Navarro C, Gaxiola M, Selman M, Randall TD. Inducible bronchus-associated lymphoid tissue (iBALT) in patients with pulmonary complications of rheumatoid arthritis. J Clin Invest 2006;116:3183-94.
PUBMED | CROSSREF

48. Sato A, Hayakawa H, Uchiyama H, Chida K. Cellular distribution of bronchus-associated lymphoid tissue in rheumatoid arthritis. Am J Respir Crit Care Med 1996;154:1903-7.
PUBMED | CROSSREF

49. Willis VC, Demoruelle MK, Derber LA, Chartier-Logan CJ, Parish MC, Pedraza IF, et al. Sputum autoantibodies in patients with established rheumatoid arthritis and subjects at risk of future clinically apparent disease. Arthritis Rheum 2013;65:2545-54.
PUBMED

50. Mikuls TR, Payne JB, Deane KD, Thiele GM. Autoimmunity of the lung and oral mucosa in a multisystem inflammatory disease: the spark that lights the fire in rheumatoid arthritis? J Allergy Clin Immunol 2016;137:28-34.
PUBMED | CROSSREF

51. Tan BK, Li QZ, Suh L, Kato A, Conley DB, Chandra RK, et al. Evidence for intranasal antinuclear autoantibodies in patients with chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol 2011;128:1198-1206.e1.
PUBMED | CROSSREF

52. Morissette MC, Jobse BN, Thayaparan D, Nikota JK, Shen P, Labiris NR, et al. Persistence of pulmonary tertiary lymphoid tissues and anti-nuclear antibodies following cessation of cigarette smoke exposure. Respir Res 2014;15:49.
PUBMED | CROSSREF

53. Kim LH, Plaza K, Thomas SR, Draijer C, Radford K, Peters-Golden M, et al. Endogenous peroxidases in sputum interfere with horse-radish peroxidase-based ELISAs. J Immunol Methods 2018;454:76-9.
PUBMED | CROSSREF

54. Wenzel SE, Vitari CA, Shende M, Strollo DC, Larkin A, Yousem SA. Asthmatic granulomatosis. Am J Respir Crit Care Med 2012;186:501-7.
PUBMED | CROSSREF

55. Mukherjee M, Bulir DC, Radford K, Kjarsgaard M, Huang CM, Jacobsen EA, et al. Sputum autoantibodies in severe eosinophilic asthma. J Allergy Clin Immunol. Forthcoming 2017.
PUBMED | CROSSREF

56. Nair P, Ochkur SI, Protheroe C, Radford K, Efthimiadis A, Lee NA, et al. Eosinophil peroxidase in sputum represents a unique biomarker of airway eosinophilia. Allergy 2013;68:1177-84.
PUBMED | CROSSREF

57. Persson C, Uller L. Theirs but to die and do: primary lysis of eosinophils and free eosinophil granules in asthma. Am J Respir Crit Care Med 2014;189:628-33.
PUBMED | CROSSREF

58. Wang J, Slungaard A. Role of eosinophil peroxidase in host defense and disease pathology. Arch Biochem Biophys 2006;445:256-60.
PUBMED | CROSSREF

59. Gueirard P, Delpech A, Gilbert D, Godin M, Loet XL, Tron F. Anti-myeloperoxidase antibodies: immunological characteristics and clinical associations. J Autoimmun 1991;4:517-27.
PUBMED | CROSSREF

60. McLachlan SM, Rapoport B. Thyroid peroxidase as an autoantigen. Thyroid 2007;17:939-48.
PUBMED | CROSSREF

61. Aloisi F, Pujol-Borrell R. Lymphoid neogenesis in chronic inflammatory diseases. Nat Rev Immunol 2006;6:205.
PUBMED | CROSSREF

62. Baay-Guzman GJ, Huerta-Yepez S, Vega MI, Aguilar-Leon D, Campillos M, Blake J, et al. Role of cxcl13 in asthma: novel therapeutic target. Chest 2012;141:886-94.
PUBMED | CROSSREF

63. Kang JS, Yoon YD, Ahn JH, Kim SC, Kim KH, Kim HM, et al. B Cell-activating factor is a novel diagnosis parameter for asthma. Int Arch Allergy Immunol 2006;141:181-8.
PUBMED | CROSSREF

64. Jee HM, Choi BS, Kim KW, Sohn MH, Han MY, Kim KE. Increased B cell-activating factor (BAFF) level in the sputum of children with asthma. Korean J Pediatr 2010;53:795-800.
PUBMED | CROSSREF

65. Kita H, Abu-Ghazaleh R, Sanderson CJ, Gleich GJ. Effect of steroids on immunoglobulin-induced eosinophil degranulation. J Allergy Clin Immunol 1991;87:70-7.
PUBMED | CROSSREF

66. Lacy P, Moqbel R. Immune effector functions of eosinophils in allergic airway inflammation. Curr Opin Allergy Clin Immunol 2001;1:79-84.
PUBMED | CROSSREF

67. Ueki S, Melo RC, Ghiran I, Spencer LA, Dvorak AM, Weller PF. Eosinophil extracellular DNA trap cell death mediates lytic release of free secretion-competent eosinophil granules in humans. Blood 2013;121:2074-83.
PUBMED | CROSSREF

68. Ueki S, Konno Y, Takeda M, Moritoki Y, Hirokawa M, Matsuwaki Y, et al. Eosinophil extracellular trap cell death-derived DNA traps: their presence in secretions and functional attributes. J Allergy Clin Immunol 2016;137:258-67.
PUBMED | CROSSREF

69. D'silva L, Hassan N, Wang HY, Kjarsgaard M, Efthimiadis A, Hargreave FE, et al. Heterogeneity of bronchitis in airway diseases in tertiary care clinical practice. Can Respir J 2011;18:144-8.
PUBMED

70. Chu DK, Al-Garawi A, Llop-Guevara A, Pillai RA, Radford K, Shen P, et al. Therapeutic potential of anti-IL-6 therapies for granulocytic airway inflammation in asthma. Allergy Asthma Clin Immunol 2015;11:14.
PUBMED | CROSSREF

71. Panda R, Krieger T, Hopf L, Renné T, Haag F, Röber N, et al. Neutrophil extracellular traps contain selected antigens of anti-neutrophil cytoplasmic antibodies. Front Immunol 2017;8:439.
PUBMED | CROSSREF

72. Vaglio A, Buzio C, Zwerina J. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): state of the art. Allergy 2013;68:261-73.
PUBMED | CROSSREF

73. Choi Y, Pham LD, Lee DH, Ban GY, Lee JH, Kim SH, et al. Neutrophil extracellular DNA traps induce autoantigen production by airway epithelial cells. Mediators Inflamm 2017;2017:5675029.
PUBMED | CROSSREF

74. Pham DL, Ban GY, Kim SH, Shin YS, Ye YM, Chwae YJ, et al. Neutrophil autophagy and extracellular DNA traps contribute to airway inflammation in severe asthma. Clin Exp Allergy 2017;47:57-70.
PUBMED | CROSSREF

75. Busse WW. A role for neutrophils in asthma exacerbations. Nat Med 2017;23:658.
PUBMED | CROSSREF

76. Toussaint M, Jackson DJ, Swieboda D, Guedán A, Tsourouktsoglou TD, Ching YM, et al. Host DNA released by NETosis promotes rhinovirus-induced type-2 allergic asthma exacerbation. Nat Med 2017;23:681.
PUBMED | CROSSREF

77. Hori S, Takahashi T, Sakaguchi S. Control of autoimmunity by naturally arising regulatory CD4+ T cells. Adv Immunol 2003;81:331-71.
PUBMED | CROSSREF

78. Mauri C, Blair PA. The incognito journey of a regulatory B cell. Immunity 2014;41:878-80.
PUBMED | CROSSREF

79. Mauri C, Blair PA. Regulatory B cells in autoimmunity: developments and controversies. Nat Rev Rheumatol 2010;6:636-43.
PUBMED | CROSSREF

80. Fillatreau S, Sweenie CH, McGeachy MJ, Gray D, Anderton SM. B cells regulate autoimmunity by provision of IL-10. Nat Immunol 2002;3:944-50.
PUBMED | CROSSREF

81. Donma M, Karasu E, Ozdilek B, Turgut B, Topcu B, Nalbantoglu B, et al. $CD4^+$, $CD25^+$, $FOXP3^+$ T regulatory cell levels in obese, asthmatic, asthmatic obese, and healthy children. Inflammation 2015;38:1473-8.
PUBMED | CROSSREF

82. Eusebio M, Kuna P, Kraszula L, Kupczyk M, Pietruczuk M. The relative values of $CD8^+CD25^+Foxp3$brigh Treg cells correlate with selected lung function parameters in asthma. Int J Immunopathol Pharmacol 2015;28:218-26.
PUBMED | CROSSREF

83. Takanashi S, Hasegawa Y, Kanehira Y, Yamamoto K, Fujimoto K, Satoh K, et al. Interleukin-10 level in sputum is reduced in bronchial asthma, COPD and in smokers. Eur Respir J 1999;14:309-14.
PUBMED | CROSSREF

84. Kawayama T, Matsunaga K, Kaku Y, Yamaguchi K, Kinoshita T, O'Byrne PM, et al. Decreased CTLA4^{+} and Foxp3^{+} CD25^{high}CD4^{+} cells in induced sputum from patients with mild atopic asthma. Allergol Int 2013;62:203-13.
PUBMED | CROSSREF

85. Merayo-Chalico J, Rajme-Lopez S, Barrera-Vargas A, Alcocer-Varela J, Diaz-Zamudio M, Gomez-Martin D. Lymphopenia and autoimmunity: a double-edged sword. Hum Immunol 2016;77:921-9.
PUBMED | CROSSREF

86. Barrett SP, Toh BH, Alderuccio F, van Driel IR, Gleeson PA. Organ-specific autoimmunity induced by adult thymectomy and cyclophosphamide-induced lymphopenia. Eur J Immunol 1995;25:238-44.
PUBMED | CROSSREF

87. Gleeson PA, Toh BH, van Driel IR. Organ-specific autoimmunity induced by lymphopenia. Immunol Rev 1996;149:97-125.
PUBMED | CROSSREF

88. Schulze-Koops H. Lymphopenia and autoimmune diseases. Arthritis Res Ther 2004;6:178-80.
PUBMED | CROSSREF

89. Mukherjee M, Svenningsen S, Nair P. Glucocortiosteroid subsensitivity and asthma severity. Curr Opin Pulm Med 2017;23:78-88.
PUBMED | CROSSREF

90. Kim JT, Schimming AW, Kita H. Ligation of FcγRII (CD32) pivotally regulates survival of human eosinophils. J Immunol 1999;162:4253-9.
PUBMED

91. Druilhe A, Letuve S, Pretolani M. Glucocorticoid-induced apoptosis in human eosinophils: mechanisms of action. Apoptosis 2003;8:481-95.
PUBMED | CROSSREF

92. Chan YC, Ramadani F, Santos AF, Pillai P, Ohm-Laursen L, Harper CE, et al. "Auto-anti-IgE": naturally occurring IgG anti-IgE antibodies may inhibit allergen-induced basophil activation. J Allergy Clin Immunol 2014;134:1394-1401.e4.
PUBMED | CROSSREF

93. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 2014:CD003559.
PUBMED | CROSSREF

94. Mukherjee M, Lim HF, Thomas S, Miller D, Kjarsgaard M, Tan B, et al. Airway autoimmune responses in severe eosinophilic asthma following low-dose Mepolizumab therapy. Allergy Asthma Clin Immunol 2017;13:2.
PUBMED | CROSSREF

95. Mukherjee M, Aleman Paramo F, Kjarsgaard M, Salter B, Nair G, LaVigne N, et al. Weight-adjusted intravenous reslizumab in severe asthma with inadequate response to fixed-dose subcutaneous mepolizumab. Am J Respir Crit Care Med 2018;197:38-46.
PUBMED | CROSSREF

96. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med 2017;376:2448-58.
PUBMED | CROSSREF

97. Sehmi R, Lim HF, Mukherjee M, Huang C, Radford K, Newbold P, et al. Benralizumab attenuates airway eosinophilia in prednisone-dependent asthma. J Allergy Clin Immunol. Forthcoming 2018.
PUBMED | CROSSREF

98. Duncan AR, Winter G. The binding site for C1q on IgG. Nature 1988;332:738-40.
PUBMED | CROSSREF

99. van der Zee JS, van Swieten P, Aalberse RC. Inhibition of complement activation by IgG4 antibodies. Clin Exp Immunol 1986;64:415-22.
PUBMED

100. Pouliquen IJ, Howarth P, Austin D, Gunn G, Meyer E, Price RG, et al. Response to case report: Airway autoimmune responses in severe eosinophilic asthma following low-dose Mepolizumab therapy. Allergy Asthma Clin Immunol 2017;13:45.
PUBMED | CROSSREF

101. Stokol T, O'Donnell P, Xiao L, Knight S, Stavrakis G, Botto M, et al. C1q governs deposition of circulating immune complexes and leukocyte Fcγ receptors mediate subsequent neutrophil recruitment. J Exp Med 2004;200:835-46.
PUBMED | CROSSREF

102. Durand V, Pers JO, Renaudineau Y, Saraux A, Youinou P, Jamin C. Differential effects of anti-FcγRIIIb autoantibodies on polymorphonuclear neutrophil apoptosis and function. J Leukoc Biol 2001;69:233-40.
PUBMED

103. Wermeling F, Chen Y, Pikkarainen T, Scheynius A, Winqvist O, Izui S, et al. Class A scavenger receptors regulate tolerance against apoptotic cells, and autoantibodies against these receptors are predictive of systemic lupus. J Exp Med 2007;204:2259-65.
PUBMED | CROSSREF

104. Page R, Friday G, Stillwagon P, Skoner D, Caliguiri L, Fireman P. Asthma and selective immunoglobulin subclass deficiency: improvement of asthma after immunoglobulin replacement therapy. J Pediatr 1988;112:127-31.
PUBMED | CROSSREF

105. Smiley JD, Talbert MG. High-dose intravenous gamma globulin therapy: how does it work? Am J Med Sci 1995;309:295-303.
PUBMED

106. Mazer BD, Gelfand EW. An open-label study of high-dose intravenous immunoglobulin in severe childhood asthma. J Allergy Clin Immunol 1991;87:976-83.
PUBMED | CROSSREF

107. Gelfand EW, Landwehr LP, Esterl B, Mazer B. Intravenous immune globulin: an alternative therapy in steroid-dependent allergic diseases. Clin Exp Immunol 1996;104 Suppl 1:61-6.
PUBMED

108. Kishiyama JL, Valacer D, Cunningham-Rundles C, Sperber K, Richmond GW, Abramson S, et al. A multicenter, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma. Clin Immunol 1999;91:126-33.
PUBMED | CROSSREF

109. Niggemann B, Leupold W, Schuster A, Schuster R, v Berg A, Grübl A, et al. Prospective, double-blind, placebo-controlled, multicentre study on the effect of high-dose, intravenous immunoglobulin in children and adolescents with severe bronchial asthma. Clin Exp Allergy 1998;28:205-10.
PUBMED | CROSSREF

110. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD. Pulmonary manifestations of systemic autoimmune diseases. Maedica (Buchar) 2011;6:224-9.
PUBMED

111. Sinico RA, Di Toma L, Maggiore U, Bottero P, Radice A, Tosoni C, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum 2005;52:2926-35.
PUBMED | CROSSREF

112. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094-100.
PUBMED | CROSSREF

113. Pagnoux C, Guillevin L. Churg-Strauss syndrome: evidence for disease subtypes? Curr Opin Rheumatol 2010;22:21-8.
PUBMED | CROSSREF

114. Cottin V, Bel E, Bottero P, Dalhoff K, Humbert M, Lazor R, et al. Respiratory manifestations of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Eur Respir J 2016;48:1429-41.
PUBMED | CROSSREF

115. Mukherjee M, Thomas SR, Davychenko S, Lim HF, Kjarsgaard M, Radford K, et al. Sputum anti-neutrophil cytoplasmic antibodies in eosinophilic granulomatosis and polyangiitis patients with respiratory involvement. Allergy 2017;72:756.

116. Nahm DH, Shin MJ, Yim H, Kang Y, Choi DC, Kim JK, et al. Increased levels of circulating autoantibodies to cultured human bronchial epithelial cell in adult patients with nonatopic asthma. J Korean Med Sci 2001;16:407-10.
PUBMED | CROSSREF

117. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med 2009;360:985-93.
PUBMED | CROSSREF