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Ryan K. Nelson, MD, Andrew Bush, MD, Jeffrey Stokes, MD, Parameswaran Nair, MD, PhD, FRCP, FRCPC, Praveen Akuthota, MD



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Clinical Management Review

Eosinophilic Asthma

Ryan K. Nelson, MD¹, Andrew Bush, MD², Jeffrey Stokes, MD³, Parameswaran Nair, MD, PhD, FRCP, FRCPC^{4,5}, and Praveen Akuthota, MD¹

¹ Division of Pulmonary, Critical Care, and Sleep Medicine; Department of Medicine; University of California San Diego; La Jolla, CA, USA.

² Department of Paediatric Respiratory Medicine; Royal Brompton Hospital, and National Heart and Lung Institute; Imperial School of Medicine; London, UK.

³ Division of Allergy, Immunology and Pulmonary Medicine; Department of Pediatrics; Washington University School of Medicine in St. Louis; St. Louis, MO, USA.

⁴ Division of Respiriology; Department of Medicine; McMaster University; Hamilton, ON, Canada.

⁵ Firestone Institute for Respiratory Health; St Joseph's Healthcare; Hamilton, ON, Canada.

Corresponding Author:

Praveen Akuthota, MD

9500 Gilman Dr., MC 7381

La Jolla, CA 92037

Telephone: 858-822-4106

Fax: 858-657-5021

Email: pakuthota@ucsd.edu

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ABSTRACT

Asthma endotypes are constantly evolving. Currently, there are no universally accepted criteria to define endotypes. The T-helper Type 2 (T2)-high endotype can have either allergic or nonallergic underpinnings and is typically characterized by some degree of eosinophilic airway inflammation. Unbiased clustering analyses have led to the identification of pediatric and adult phenotypes characterized by T2 inflammation and associated endotypes with eosinophilic inflammation. Aspirin-exacerbated respiratory disease (AERD) has also long been recognized as a unique asthma phenotype. An approach to identify these groups with biomarkers and subsequently choose a targeted therapeutic modality, particularly in severe disease requiring biologic agents, is outlined.

KEY Words:

Asthma; Eosinophils; Aspirin-exacerbated respiratory disease; Endotypes

INTRODUCTION

Asthma is a chronic disorder of the airways estimated to affect more than 300 million people worldwide [1]. Within this large cohort of affected individuals, significant disease heterogeneity has been recognized. Severe asthma contributes substantially to asthma related health care expenditures, particularly when exacerbations are considered [2-3]. Though our understanding of asthma pathophysiology and our arsenal of therapeutics to address these shortcomings and reduce exacerbation rates has grown significantly over the past decade, precisely matching patients with an optimal treatment regimen remains a constant clinical challenge. To assist in efforts to better understand the subgroups of asthma which make it such a heterogeneous disease, and therefore to better match patients with treatment, recent attention has been placed towards identifying asthma phenotypes and endotypes. Biostatistical techniques have allowed for an unbiased approach in identifying clusters of similar patients, and as a result, large cohorts of patients with asthma have been partitioned into groups defined by a shared set of observable characteristics, or “phenotypes” [4-8]. These cluster-defined phenotypes incorporate a wide range of variables including clinical features, physiologic lung function measurements and response to therapies. While asthma phenotypes may be practical in that they are readily identified in clinical practice, they do not consistently associate with an underlying pathophysiology, and thus do not fully inform targeted therapeutic approaches. As such, many have supported the need to identify asthma “endotypes” (groups sharing a similar pathophysiological mechanism) in guiding therapeutic choices in this emerging era of precision medicine [9]. The Severe Asthma Research Program and U-BIOPRED group have incorporated biomarkers into their cluster analyses to define endotypes of asthma. While valuable information

has been gleaned in exploring commonality of mechanisms from these substantial multicenter, multinational efforts, the resulting endotypes have not been readily applicable to clinical practice, and do not yet fully inform changes over time in an individual patient, although they may do so in the future as more longitudinal data is collected [5,6,10]. Given the rapid expansion of targeted therapeutic options in asthma, this is going to be ever more important as more novel biologicals become licensed.

Asthma endotypes are constantly evolving. Currently, there are no universally accepted criteria to define endotypes. As transcriptomic, proteomic, and metabolomic studies expand our understanding of asthma pathophysiology, it is foreseeable that endotypes will become more refined and that more targeted therapies will become available to treat the most difficult to control asthmatics. At this time endotyping on the basis of inflammation is most practical. The first proponent of this was Harry Morrow Brown in the 1950s, who used his medical student microscope to show that only patients with sputum eosinophilia responded to oral and then inhaled corticosteroids [11]. Wenzel *et al* extended this concept in classifying severe asthmatics based on the presence of eosinophilia on endobronchial biopsy, finding that those with airway eosinophilia had increased numbers of lymphocytes, mast cell and macrophages, thicker subbasement membrane on histology and a greater number of intubations [12]. This dichotomy has evolved into T-helper type 2 (T2)-high and T2-low asthma endotypes and has become a popular branch point to conceptualize airway inflammation. The T2-high endotype can have either allergic or nonallergic underpinnings and is typically characterized by some degree of eosinophilic airway inflammation, while the neutrophilic or paucigranulocytic airway inflammation is associated with the T2-low endotype [13]. Gene set variation analysis of the sputum transcriptome obtained from the U-BIOPRED study suggest that genes related to the

ILC2 cell biology (IL5, IL13, TSLP and IL33) may account for the majority of eosinophil recruitment into the airway in patients with severe asthma [14]. However, it should also be noted that in both pediatric and adult asthma, airway eosinophilia is not necessarily synonymous with T2 driven inflammation [14-16].

Identifying patients with the T2-high endotype has been facilitated by the use of several non-invasive biomarkers, though deficiencies in precision remain. Peripheral blood eosinophils and serum IgE are commonly used in practice today due to their widespread availability and association with targeted biologic therapies [17-18]. Sputum eosinophil measurement has been widely studied and validated as a biomarker, though requires further incorporation into clinical practice, which has favored the current convenience of blood eosinophils. However, it is important to note that blood eosinophils may not always accurately represent the cellular state of the asthmatic airway. Although demonstrated to be effective for disease monitoring to reduce exacerbations and for predicting response to anti-IL-5 biologics, direct measurement of airway eosinophilia by sputum cytometry has been slow to implement due to barriers associated with cost and infrastructure [19-21]. Fractional exhaled nitric oxide ($F_{E}NO$) (a reflection of epithelial cell activation from IL-5 and IL-13) and periostin (an extracellular matrix protein upregulated by IL-13) have both been linked to T2-high inflammation; however, their clinical use has not yet become strongly advocated given sparse literature support focused on outcome measures [22-23]. It has become increasingly clear that better markers of the T2-high endotype are desperately needed [24].

In the following text, how unbiased clustering analyses have led to the identification of pediatric and adult phenotypes characterized by type 2 inflammation will be reviewed. An

approach to identify these groups with biomarkers and subsequently choose a targeted therapeutic modality, particularly in severe disease requiring biologic agents, will be outlined.

ASTHMA PHENOTYPES ASSOCIATED WITH EOSINOPHILIC INFLAMMATION

Childhood-Onset Atopic Asthma

As our understanding of asthma heterogeneity has advanced, childhood-onset asthma has clearly emerged as distinct from that arising in adulthood. By and large, children are much more likely to be atopic [25-26]. Even within the realm of pediatric asthma, however, individual phenotypes have been identified as the result of clustering analyses. The Severe Asthma Research Program (SARP) analysis revealed four such pediatric clusters, with separation largely determined by asthma duration, the number of required controller medications, and baseline lung function. These three variables could be used in isolation to correctly assign over 90% of patients to their respective cluster in the original SARP cohort [7]. While the degree of atopy (measured by serum IgE levels and the number of positive skin prick responses) accounted for part of the remaining group variability, some degree of atopy was notably present across all four clusters [7]. Similarly, in separate cluster analyses performed by both the Childhood Asthma Management Program and the Inner-City Asthma Consortium, five pediatric clusters were identified, with allergic sensitization as an important distinguishing characteristic [27-28]. Given this high prevalence of atopy in the pediatric population, in addition to limitations of phenotype-derived clusters to inform targeted therapy, many have recognized childhood-onset atopic asthma as an individual phenotype [26,29].

The childhood-onset atopic asthma phenotype is linked to T2-high allergic inflammation and associated biomarkers [30]. The pathobiology of T2 inflammation has been well delineated by animal studies and is corroborated by evidence in human asthma, both in children and adults. In a patient predisposed to an allergic immune response based on their genetic and environmental background, inhalation of an aeroallergen triggers epithelial cells to release cytokines (IL-25, IL-33, TSLP) and initiate a series of downstream events differentiating naïve T cells into mature Th2 lymphocytes, which ultimately produce the classic Th2 cytokines IL-4, IL-5, and IL-13. Release of the Th2 cytokine IL-4 triggers B-cell isotype switching and synthesis of IgE, a hallmark of allergic inflammation that is readily identified by serum assays [31]. Upon re-exposure of an allergen to a sensitized individual, IgE becomes crosslinked, activating mast cells and basophils to release preformed histamines, prostaglandins, and leukotrienes. Through their effects on airway smooth muscle, these mediators are responsible for the clinical asthma syndrome that characterizes the early-phase response to allergen exposure [13]. Through their effects on other end-organs, these mediators also explain why patients with atopic asthma are more likely to harbor other signs of allergic disease such as rhinitis and dermatitis. While not uniformly detected, sputum and/or peripheral blood eosinophilia often manifests as a consequence of IL-5 stimulation, which is key to the development and maturation of eosinophils [31].

Adult Late-Onset Eosinophilic Asthma

Given the lack of a standardized method in defining adult asthma phenotypes, Wenzel proposed a three-category approach to classification (one of which accounted for the type of

cellular inflammation) but found precise phenotype characterization challenging due to the lack of large datasets with immunological and pathological information [4]. Later, the Leicester, Severe Asthma Research Program (SARP), and Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) cohorts were developed, providing unbiased statistical clustering analyses of adult patients with asthma [5-6,8,32]. Despite using different algorithms and having variations in the number of traits included for cluster analysis, each identified unique clusters of asthmatic patients, some of which shared considerable overlap across all cohorts. One such cluster identified across all three cohorts included patients with late-onset, severe asthma and significant eosinophilic inflammation. A schematic of adult and pediatric clusters in SARP, including late-onset severe asthma, is depicted in **Figure 1** [26].

Late-onset, severe asthma with eosinophilic inflammation is now a well-recognized adult asthma phenotype and thought to be driven by different pathophysiological mechanisms than childhood-onset allergic asthma. It typically presents in the fourth or fifth decade of life and is characterized by T2-high eosinophilic inflammation of the airway that persists despite inhaled corticosteroid therapy [6,32-33]. Patients often have difficult to control asthma from disease onset and tend to develop fixed airways obstruction early in the disease course [34-35]. Exacerbations occur frequently, and patients may be dependent on oral corticosteroids. Concomitant chronic rhinosinusitis and nasal polyposis are typical of this eosinophilic inflammation and may present with or without aspirin sensitivity [36-37].

Though late-onset eosinophilic asthma is similar to childhood-onset atopic asthma in that it is characterized by T2-high inflammation, elevated IgE and/or symptoms related to allergic mediators are not prominent. Evidence suggests the eosinophilic asthma endotype may arise from allergen-independent signaling processes that involve activation of innate lymphoid cells to

produce IL-5 and IL-13 [38-39]. Therefore, the allergic signaling cascade through T cells is bypassed, and IL-4 production to induce B-cell isotype switching is less robust.

Aspirin Exacerbated Respiratory Disease (AERD)

Aspirin exacerbated respiratory disease (AERD) has long been described as an independent asthma phenotype classically in adult patients. While not identified as an exclusive cluster in unbiased statistical analyses (likely due to a combination of relatively low disease prevalence and imperfect variable lists used in such analyses), AERD is well established as a unique chronic inflammatory airways disease in the clinical realm [40]. Invariably, patients exhibit upper and/or lower respiratory symptoms within minutes to hours following oral ingestion of aspirin or a nonsteroidal anti-inflammatory (NSAID) with cyclooxygenase 1 (COX-1) inhibition. The presence of asthma and nasal polyposis completes the traditional description of “Samter’s Triad” but additional upper respiratory symptoms such as nasal congestion, rhinorrhea, and anosmia are not uncommon. Nasal polyps are often aggressive and rapidly recurring after surgical intervention and asthma symptoms are typically severe and difficult to control [41].

Identifying the AERD phenotype relies heavily on patient history, linking NSAID ingestion to respiratory symptoms. In some cases, an observed aspirin challenge may be required to confirm this association. Sinus CT scans have an added diagnostic benefit in that they carry a strong negative predictive value when normal [42]. Unlike other asthma phenotypes/endotypes, AERD identification is less dependent on biomarker utilization. Due to COX-1 inhibition and shunting of arachidonic acid metabolism down the 5-lipoxygenase arm, elevations of the pro-

inflammatory cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) and decreased levels of anti-inflammatory PGE₂ are expected. LTE₄ levels, measured from either a spot or 24-hour urine collection, are elevated at baseline in patients with AERD relative to those with aspirin-tolerant asthma but have not proved useful in predicting AERD when used alone, independent of other clinical parameters [43-45]. Given their strong negative predictive value, however, normal urinary LTE₄ levels may be an alternative adjunct to help exclude AERD [44]. Blood eosinophils are frequently elevated in patients with AERD and often localize to sites of inflammation as a consequence of the chemoattractant effects of cysteinyl leukotrienes [46-47]. While atopy is often associated with AERD, AERD is not a true allergic disease and elevations in aspirin-specific IgE are not expected.

TREATMENT

Eosinophilic Asthma

Management of nonallergic T2-high asthma begins with guideline driven inhaled corticosteroid and bronchodilator therapy. For patients labeled with severe eosinophilic asthma, escalation to a biologic is often required to reduce exacerbation frequency and/or the use of chronic oral corticosteroids. In recent years, some have argued for a “treatable trait” approach, which would identify eosinophilia as such a trait, potentially influencing in future treatment algorithms when biologics might be considered. Such concepts may further evolve with increasing understanding of the mechanisms of eosinophilia and eosinophil activation refining the choice of personalized therapy.

Several biologics have shown benefit for severe eosinophilic asthma in placebo-controlled clinical trials, but no controlled head-to-head comparisons have been completed. Clinicians are therefore left to incorporate clinical characteristics, biomarker testing, and other considerations for the patient (such as route and frequency of administration) when choosing a biologic to prescribe. The use of blood and/or sputum eosinophilia is critical in establishing that a patient has eosinophilic asthma. In general, we advise measuring blood (and sputum) eosinophils while a patient remains on their established controller therapy, though in corticosteroid-dependent patients, circulating eosinophils may be suppressed while sputum eosinophilia might persist.

At the present time, the United States Food and Drug Administration (FDA) has approved biologics with two distinct cytokine targets and one antibody target for use in severe eosinophilic asthma (**Figure 2**). Three disrupt IL-5 signaling (benralizumab, mepolizumab, and reslizumab) by blocking a key cytokine responsible for the activation and survival of eosinophils. A recent American Thoracic Society (ATS) and European Respiratory Society (ERS) joint task force report on the management of severe asthma suggests the use of these IL-5 disrupting therapies as add-on therapy for adults with severe, uncontrolled eosinophilic asthma and for adults with severe, corticosteroid-dependent asthma [48]. This document also suggests the use of blood eosinophils as a predictive biomarker, with the use of a cut-point of 150 cells/ μ l to guide the initiation of anti-IL-5 therapy [48]. This cut-point may be useful in patients on high dose inhaled corticosteroids, though does not necessarily account for the complexity of eosinophil biology and activation, nor for differences amongst the IL-5 therapies, all of which would support a more tailored approach. Specific considerations of the use of blood and sputum eosinophils as predictive biomarkers for the individual anti-IL-5 agents will be discussed below.

Another of the approved biologics, dupilumab, blocks both IL-4 and IL-13 signaling and therefore has an effect on airway goblet and smooth muscle cells in addition to theoretical downstream effects on eosinophilia. Omalizumab, the asthma biologic that has been available for longest period of time, blocks the effects of immunoglobulin E [49].

Mepolizumab

The presence of blood or sputum eosinophilia predicts treatment success with mepolizumab. Administered as fixed-dose 100 mg subcutaneous injection every four weeks, its use is approved for patients ≥ 12 years old with severe eosinophilic asthma (≥ 6 years in UK). At a higher dose of 300 mg every four weeks, its use is extended for treatment of eosinophilic granulomatosis with polyangiitis [50]. Mepolizumab administration is generally safe with an on-treatment serious adverse event rate similar to that of placebo [51]. In rare circumstances, hypersensitivity reactions or reactivation of herpes zoster can occur [52]. In patients with increased blood eosinophils, randomized control trials have demonstrated that mepolizumab reduces asthma exacerbations, reduces oral corticosteroid use, and improves asthma control scores [53-55]. A modest improvement in lung function, as assessed by FEV₁ measurements, has been reported in some [55] but not all of these trials [53-54]. Even when oral corticosteroid use is reduced in patients on mepolizumab, the reduction in exacerbation rates is preserved [54].

Early clinical trials of mepolizumab, which did not select for patients with severe eosinophilic asthma, failed to show drug efficacy [56]. However, when mepolizumab was specifically evaluated in the subgroup of patients with sputum eosinophilia and airway symptoms despite prednisone and high-dose inhaled corticosteroids [57-58], it reduced exacerbations, and

also improved FEV1 (on average by 300 ml, Δ from placebo 200 ml) even when prednisone dosage was reduced on average by 87% [58]. These observations prompted further investigations to identify predictors of a favorable treatment response to mepolizumab. The DREAM study, designed to identify the lowest effective dose of mepolizumab as well as identify variables predictive of mepolizumab success (defined as a reduction in clinically significant exacerbation rates), identified peripheral blood eosinophil levels as a predictive biomarker for treatment response to mepolizumab [53]. An additional post-hoc analysis of the data from the DREAM and MENSA studies defined a blood eosinophil count ≥ 150 cells/ μ L at the start of treatment or ≥ 300 cells/ μ L any time in the past year as a threshold to predict a clinically relevant reduction in asthma exacerbations, with the reduction in exacerbation rate appearing more pronounced the higher the baseline blood eosinophil count [59-60].

It has been suggested that blood eosinophils are more predictive of treatment success than sputum eosinophils [61]. However, this inference was drawn from an under-powered subgroup analysis of 14% of patients in the DREAM study who had both sputum and blood eosinophils enumerated at baseline. Mepolizumab does not consistently suppress airway eosinophilia at the approved 100 mg subcutaneous monthly dose [49,53,60]. For patients on mepolizumab, increased sputum eosinophil counts seem to correlate with asthma exacerbations and may serve an indicator of unsuppressed local eosinophilopoietic activity [62]. This may be the reason for a gradual decline in FEV1 over 5 year of treatment at this dose following participation in the clinical trial where all patients received mepolizumab intravenously [52]. Of more concern is the lack of efficacy in the more severe prednisone-dependent patients in whom approximately 60% of patients do not respond to the 100 mg dose and, very worryingly, a third could get worse [63]. This is likely due to the inadequate neutralization of airway IL-5 and consequent IL-5 anti-IL5

immune complexes that activate complement [63-64]. F_ENO has not been demonstrated to have a predictive role for mepolizumab in studies completed to date [53,60].

Reslizumab

Similar to mepolizumab, reslizumab is a monoclonal antibody that directly binds IL-5. It is administered as a weight-based (3 mg/kg) IV infusion every four weeks and is approved only for adults ≥ 18 years old with severe eosinophilic asthma [65]. Though the incidence was low, anaphylaxis was observed in clinical trials and has led to a black box warning. In controlled trials, reslizumab improved lung function [66-67] and decreased exacerbation frequency relative to placebo [68]. Its effect on chronic oral corticosteroid use has not been directly assessed in a placebo-controlled large steroid-reduction clinical trial. However, it has been shown to be effective in improving asthma control and FEV₁ in the prednisone-dependent patients who had participated in the phase 3 pivotal trial (Nair et al JACI: In Practice, under revision). In a small clinical trial, weight-based reslizumab dosing demonstrated a superior reduction in sputum eosinophils and an associated improvement in asthma control scores in prednisone-dependent patients with an inadequate response to fixed-dose mepolizumab [69].

Peripheral blood eosinophilia or sputum eosinophilia is also a necessary prerequisite for the use of reslizumab. Patients with a blood eosinophil count of < 400 cells/ μ L had no significant improvement in lung function when receiving reslizumab rather than placebo [70]. Patients with nasal polyps had a superior improvement in asthma control scores in the earliest clinical trial [66], and additional evidence has been developed to support improved lung function and exacerbation rates in patients with chronic sinusitis with nasal polyposis [71].

Benralizumab

Benralizumab is a monoclonal antibody against the IL-5 receptor on eosinophils. In addition to blocking IL-5 binding and subsequent eosinophil activation, benralizumab has the distinct advantage of further depleting eosinophils through a natural killer cell mediated apoptosis. It is approved for patients ≥ 12 years old. Administered as a 30 mg subcutaneous injection every four weeks for the first three doses, subsequent maintenance injections can be spaced to eight-week intervals. Phase three randomized trials support a role for benralizumab to reduce exacerbation frequency and improve lung function in patients with uncontrolled eosinophilic asthma [72-74]. In the more recent ZONDA trial, benralizumab was shown to have a strong effect on reducing oral corticosteroid use and exacerbation frequency [74].

The effects of benralizumab are also most favorable when baseline peripheral blood eosinophils and exacerbation frequency are high [75]. Blood eosinophil counts ≥ 300 cells/ μ L have predicted a favorable reduction in annual exacerbation rates. For the same endpoint, patients with eosinophil levels < 300 cells/ μ L have responded favorably to benralizumab when they have baseline oral corticosteroid use, nasal polyps, and a prebronchodilator forced vital capacity less than 65% predicted [76].

Dupilumab

Dupilumab is a monoclonal antibody against the IL-4 α receptor, blocking signaling of both IL-4 and IL-13. It is FDA approved for patients ≥ 12 years old with eosinophilic asthma,

corticosteroid-dependent asthma regardless of phenotype/endotype and for atopic dermatitis. After an initial 400 mg subcutaneous loading dose, dupilumab is followed by one 200 mg subcutaneous injection every other week. For patients dependent on oral corticosteroids, 600 mg as the initial loading dose, followed by 300 mg every other week may be given. The pre-filled syringe allows for the ease of home self-administration after proper teaching. Administration is safe but carries a small risk of a local injection site reaction. In randomized control trials, dupilumab reduced asthma exacerbations and oral corticosteroid use while improving lung function and asthma control [77-78].

Dupilumab (and omalizumab, discussed below) are different from the three other biologics used in eosinophilic asthma in that it does not directly block the cytokine traditionally associated with eosinophil activation. Nevertheless, patients with higher blood eosinophil counts had a greater reduction in exacerbations when treated with dupilumab, with the subgroup of patients having ≥ 300 cells/ μ L of eosinophils demonstrating the greatest reduction. The ATS/ERS task force report on severe asthma recommends consideration of dupilumab as add-on therapy in severe, uncontrolled asthma regardless of eosinophil levels [48]. While not seen with the anti-IL-5 biologics, elevated $F_E\text{NO}$ levels predicted a favorable response to dupilumab in reducing exacerbations [77]. Finally, patients with nasal polyposis have been shown to lower their endoscopic polyp burden when dupilumab is added to intranasal corticosteroids [79]. Dupilumab is now approved by the FDA for chronic rhinosinusitis with nasal polyposis.

Omalizumab

In the United States, omalizumab, a monoclonal antibody against IgE, is approved for the treatment of moderate to severe allergic asthma uncontrolled despite inhaled steroids in adults and children 6 years of age or older. It is administered subcutaneously according to weight and IgE level. Omalizumab has been commercially available for severe asthma for almost two decades. However, recent refinement of the understanding of asthma endotypes, including improved recognition of the eosinophilic phenotype, has allowed for advancement in understanding of patients who would be predicted to best respond to omalizumab. Hanania et al in a *post hoc* analysis of the EXTRA study, which itself demonstrated that omalizumab reduced exacerbations in patients with severe allergic asthma inadequately controlled by standard therapy, showed that patients with peripheral eosinophilia greater than 260 cells/ μ l had a substantially improved exacerbation rate when compared to those with less than 260 cells/ μ l [80-81]. Based on these data, the ATS/ERS task force suggests using this cut-point of blood eosinophils to help guide initiation of omalizumab therapy [48]. Like dupilumab, omalizumab is an effective therapy for the eosinophilic asthma endotype via a mechanism that does not directly affect blood and tissue eosinophils. These findings highlight the importance of interpreting biomarkers in context and suggest that a hierarchy of biomarkers, with sputum and blood eosinophils at the first branchpoint, may be appropriate with the current array of asthma biologics and biomarkers.

Aspirin Exacerbated Respiratory Disease

Therapy for AERD, as for other phenotypes of asthma, centers around a guideline-driven stepwise approach to inhaled corticosteroids and bronchodilators. Additional attention must be

given towards managing concurrent rhinosinusitis and nasal polyposis, for which topical nasal corticosteroids and antihistamines are first line. Given the refractory nature of nasal polyposis in AERD, systemic corticosteroids and surgical debulking are often required and it is not uncommon for multiple surgical procedures to be needed throughout the disease course [82].

To address the unique role of dysregulated arachidonic acid metabolism in AERD, the avoidance of aspirin and COX-1 inhibiting NSAIDs should be reviewed with patients. Selective COX-2 inhibitors (e.g. celecoxib) may be used as a safe alternative if needed for control of pain or inflammation. Leukotriene-modifying agents should be utilized for control of asthma and rhinosinusitis in all patients with AERD. Leukotriene receptor antagonists (e.g. montelukast) have demonstrated the ability to improve lung function and asthma quality of life scores, as well as reduce asthma exacerbation frequency, in randomized control trials [83]. While they are often prescribed first due their safety profile, ease of once daily administration and cost, some argue the direct inhibition of 5-lipoxygenase with zileuton is superior in that it directly reduces production of the cysteinyl leukotrienes. Compared to leukotriene receptor antagonists, zileuton has performed more favorably in patients with AERD in a patient survey study, but no head-to-head clinical study has objectively demonstrated this superiority [84]. Combination therapy of zileuton with a leukotriene receptor antagonist has been met with success in several case reports [85].

Aspirin desensitization is a therapy unique to AERD and is indicated for refractory nasal polyposis or when aspirin/NSAIDs are needed to manage another disease process. When done correctly and followed by an appropriate maintenance regimen, aspirin desensitization can have a dramatic effect both on symptoms related to rhinosinusitis and asthma [86-87]. This has

translated into reduced patient morbidity as well as reduced health care costs associated with medical and surgical care.

With the rise in biologic use for other asthma phenotypes, recent studies have investigated the use of biologics in AERD. Omalizumab, a monoclonal antibody against IgE often used in severe allergic asthma, has been reported to reduce leukotriene levels [88-89] and improve asthma control [90] in small trials. Both mepolizumab and dupilumab have also successfully been used as adjunct therapies in AERD, showing improved asthma control and sino-nasal outcome test scores [91-92]. How such biologics should be used in AERD remains in early investigation and the optimal patient subpopulation for these therapies is yet to be defined.

CONCLUSION

Severe asthma remains challenging to manage due to significant clinical heterogeneity. Progress in identifying asthma phenotypes and endotypes has improved our ability to manage many patients with severe asthma, particularly those characterized by T2-high eosinophilic inflammation. Nevertheless, our understanding of asthma pathophysiology is far from complete and work must be done to provide optimal precision medicine for all.

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FIGURE LEGENDS

Figure 1: Adult and Pediatric Severe Asthma Phenotypes in the Severe Asthma Research Program. The median FEV1 and median age are represented by the horizontal and median axes of the diamonds, respectively. Reprinted with permission from: Fitzpatrick AM, Moore WC. J Allergy Clin Immunol Pract 2017 [Reference 30].

Figure 2: Targets of Currently Approved Biologics in Asthma.



