Exacerbations of severe asthma while on Anti-IL5 biologicals

Running title: Asthma exacerbations on anti-IL5 biologics

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Abstract

Anti-interleukin 5 (IL5) and anti-IL5 receptor alpha monoclonal antibodies markedly decrease airway and peripheral blood eosinophil numbers; thus, they are highly effective in reducing asthma exacerbations. Nonetheless, flare-ups are not completely ameliorated on these biologics. There is modest evidence regarding the nature of these exacerbations, where severe asthmatics on these therapies could still have serious exacerbations that are non-eosinophilic. Using illustrative clinical case scenarios, we highlight the importance of carefully characterizing asthmatics at the time of exacerbation and recognizing neutrophilic causes of exacerbations. This is important to manage these exacerbations. While an eosinophilic exacerbation may benefit with more glucocorticosteroids or by switching to another anti-IL5 mAb, a non-eosinophilic exacerbation will likely not. An infective exacerbation needs to be recognized, the pathogen identified and treated with the appropriate anti-microbial agent.

Key words: Severe asthma. Exacerbations. Anti-IL5 biologics. Sputum cell counts. Airway infections. Eosinophils.

Resumen

Los anticuerpos monoclonales anti-interleucina 5 (IL5) y anti-receptor de IL5 son altamente efectivos en reducir las exacerbaciones del asma al disminuir notablemente el número de eosinófilos en las vías respiratorias y en sangre periférica. Sin embargo, aun estando bajo el tratamiento con estos biológicos, las descompensaciones asmáticas no desaparecen por completo. Disponemos de una modesta evidencia que señala la naturaleza de estas exacerbaciones, y los pacientes afectos de asma grave en estas terapias podrían tener exacerbaciones graves no eosinofílicas. Utilizando como escenarios ilustrativos varios casos clínicos, destacamos la importancia de caracterizar cuidadosamente al paciente asmático en el momento de la exacerbación y reconocer las causas neutrofílicas de las exacerbaciones, lo cual es de importancia a la hora de manejar estas exacerbaciones. Si bien una exacerbación eosinofílica puede beneficiarse con más glucocorticosteroides o al cambiar a otro mAb anti-IL5, una exacerbación no eosinofílica probablemente no lo hará. Es necesario reconocer una exacerbación infecciosa, identificar el patógeno y tratarlo con el agente antimicrobiano más apropiado.

Palabras clave: Anti-IL5. Biológicos. Exacerbación. Eosinófilos. Asma grave.

Introduction

Anti-eosinophilic biologics are changing the landscape of severe asthma treatment. Particularly in severe asthmatics with a type 2 high inflammatory signature, these monoclonal antibodies (mAbs) have demonstrated significant improvement in symptoms, quality of life, lung function, exacerbation frequency and corticosteroid dependence [1,2]. Long-term monitoring shows that these therapies that deplete circulating and tissue eosinophils are well-tolerated with minimal adverse effects [3-5]. Traditionally, eosinophils have been considered to be key effector cells against helminth infections and in propagating allergic diseases. However, there is surmounting evidence that eosinophils are also intimately involved in innate host defense [6,7]. The Local Immunity And/or Remodeling/Repair (LIAR) hypothesis also suggests that resident tissue eosinophils can provide local homeostasis and remodelling in areas where there are complex and dynamic immune reactions [8]. This is especially true for tissues with a high degree of cell proliferation or where there is significant interface with environment, such as the gastrointestinal tract, the uterus and, to some degree, the respiratory tract [8]. As such, eosinophilic depletion may potentially lead to immune dysregulation in susceptible individuals and infections may occur as a collateral consequence of eosinophil suppression. In this review, we present a series of four patients who developed atypical or serious airway infections (many leading to exacerbations) while being treated with anti-eosinophil biologics. We discuss potential mechanisms that may lead to susceptibility to infections, including the possible role that eosinophils may play in host defence. These cases also highlight the importance of considering non-eosinophilic exacerbations in patients on anti-IL5 therapies before switching between biologics.

Anti-IL-5 biologics and asthma exacerbations

Although most patients with asthma may have eosinophils either in their circulation or in their airway at some time during their disease course, we do not have a precise estimate. In approximately 40% of asthmatics, the eosinophils may play a predominant role in pathobiology of the disease, with a higher prevalence in severe asthmatics.[9] Under inflammatory conditions, including allergen and irritant exposures, eosinophils mature and differentiate in the bone marrow, egress into blood, and move to target organs including the lung. IL-5, IL-4 and IL-13, derived from classic CD4 cells, play pivotal roles in this process.[10] Notably, Il-5 along with IL-3 and GM-CSF are critical cytokines involved in eosinophil development and survival, whereas complement C5a, platelet activating factor (PAF), eicosanoids (leukotriene B4 and prostaglandin D2) and ligands for CC-chemokine receptor 3 (RANTES, MCP-4, eotaxin 1, 2, 3) are major chemoattractant for eosinophils.[11] Recently, non-classic immune cells, including innate lymphoid cells 2 (ILC2), have also been shown to be a potent source of type 2 cytokines, prompting a shift in terminology from Th2 to T2 inflammation. [12] Thus, newer biological agents have been developed to target key pathways involved in type 2 inflammation, namely blocking IgE, IL-5 and IL-4/13 signaling. [2] Moreover, given the crucial role IL-5 plays in eosinophilopoiesis and trafficking, currently there are three monoclonal agents that target IL-5 (mepolizumab, reslizumab) or IL-5 receptor alpha (benralizumab). These agents are currently recommended for severe uncontrolled asthmatics who have evidence of eosinophilic inflammation despite high dose inhaled corticosteroids (ICS) or oral corticosteroids (OCS), require chronic OCS to maintain asthma control, or in asthmatics who experience significant adverse effects from high-dose corticosteroids. [13-15] All three anti-IL-5 biologics, namely mepolizumab (humanized IgG$_1$ mAb, dosed 100 mg subcutaneously every 4 weeks), reslizumab

(humanized IgG4 mAb, dosed 3 mg/kg intravenously) and benralizumab (humanized afucosalated IgG_{1kappa} mAb) have been shown to reduce asthma exacerbations by approximately, 32-53%, 50-55% and 28-70%, respectively, in addition to improving symptoms and quality of life, and decreasing corticosteroid dependence. [13-19] An OCS-sparing clinical trial has not been conducted with reslizumab. However, in clinical trials, despite specifically targeting asthmatics with eosinophilic endotype, anti-IL-5 biologics were unable to completely ameliorate all asthma exacerbations.

There is modest evidence in clinical trials and long-term follow-up data regarding the nature of these exacerbations, whether they are eosinophilic or non-eosinophilic (neutrophilic or paucigranulocytic). In a small sub-study of a mepolizumab clinical trial, patients who remained uncontrolled despite mepolizumab demonstrated persistent sputum eosinophilia (>3%) despite normalization of blood eosinophils.[20] This may be due to *in situ* eosinophilopoiesis orchestrated by ILC_2s, where low dose mepolizumab is inadequate to control intensity of eosinophilia,[21] or due to autoimmune mechanisms,[22] as reviewed previously. [23] In the initial trial of mepolizumab, patients treated with higher dose (750 mg intravenously), experienced no eosinophilic exacerbations; however, there was one exacerbation in the treatment group, which was neutrophilic in nature.[24] Moreover, a review of 250 patients clinically prescribed anti-IL-5 mAbs (mepolizumab and reslizumab), 68.8% showed persistent sputum eosinophils (>3%), despite normalization of blood eosinophils. This was associated with elevated sputum anti-EPX IgG, a marker of localized autoimmune response associated with increased eosinophil activity and sub-optimal response to biologics.[25] Benralizumab, being an afucosylated mAb, enhances binding to FcγRIIIa expressed on immune cells such as natural killer (NK) cells and facilitates antibody-dependent cell-mediated cytotoxicity (ADCC). Thus, in

addition to blocking the IL-5/IL-5R interaction and subsequent downstream signaling, it depletes IL-5R+ cells via ADCC (including eosinophils, eosinophil progenitors, basophils, and ILC2s).[26] In a sub-study of benralizumab clinical trial, patients treated with this drug had significant attenuation of sputum and blood eosinophils. [26] However, inflammatory endyotypes are not stable during an exacerbation, where asthmatics with eosinophilic bronchitis can develop neutrophilic bronchitis or paucigranulocytic worsening. [9] Thus, it is critical that patients on these biologics undergo through investigations, including sputum differential cell counts, to determine nature of exacerbation.

Illustrative clinical examples

Case 1

A 61-year-old female was being followed since 2015 for severe eosinophilic asthma, bronchiectasis and previously treated allergic bronchopulmonary aspergillosis (ABPA). She also had peptic ulcer disease causing chronic dyspepsia despite partial gastrectomy. Given ongoing prednisone (15mg) requirements in addition to fluticasone propionate 1000mcg and salmeterol 200 mcg, she was initiated on mepolizumab in May 2018, when her peak blood eosinophil count was 0.2×10^9/L and her sputum eosinophil proportion was 3.5% With treatment, she was able to reduce prednisone to 5mg (necessary to prevent adrenal insufficiency). In November 2018, she noticed significant weight loss with vomiting and increasing cough and sputum. This was initially attributed to her on-going gastrointestinal disorder, but no abnormalities were detected on endoscopy. Sputum differential cell counts revealed neutrophilic bronchitis (total cell count of 182×10^6 cells/g with 98.8% neutrophils) without evidence of eosinophilia. Computed tomography (CT) scan of the chest demonstrated a 3.5 cm right upper lobe cavity containing a

shaggy opacity (figure 1A). Bronchoscopy was macroscopically unremarkable but the bronchoalveolar lavage (BAL) fluid grew *Hemophilus influenzae*. There was only modest improvement in her symptoms with an appropriate antibiotic course. CT-guided biopsy of the cavity showed necrotizing granulomatous inflammation with fungal organism consistent with a diagnosis of semi-invasive aspergillosis. Since she was intolerant of voriconazole and itraconazole, she was treated for 6 weeks with isavuconazole with significant clinical and radiological improvements. Mepolizumab is currently discontinued.

Case 2

A 62-year-old male was followed since 2013 for eosinophilic asthma. CT scans in 2014 had shown several millimetric, upper lobe predominant nodules. Investigations, including a BAL, did not yield pathogenic microbial growth or evidence for vasculitis. Due to persistent sputum eosinophilia (58.8%) despite prednisone 10mg, fluticasone propionate 3000mcg, salmeterol 200mcg daily, he was treated with anti-IL5 MAbs between 2014 and 2018. He had suboptimal responses to both mepolizumab and reslizumab marked by exacerbations associated with sputum eosinophilia requiring higher doses of OCS. He was then switched to benralizumab. Over eight months of treatment, prednisone was reduced only modestly (to 7.5 mg), and he continued to have cough and sputum. Therefore, benralizumab was discontinued, leading to an increase in sputum eosinophils (42%). Shortly after, in order to evaluate him for another biologic, a CT chest done in August of 2019, and this demonstrated several new and larger pulmonary nodules (figure 1B). Biopsy of the largest lesion (2.7 cm in left upper lobe) showed necrotizing granulomatous inflammation with PCR positive for *Mycobacterium avium-intracellulare*. He is

currently on azithromycin, rifampin, and ethambutol. His prednisone dose has been increased to 25mg daily to control ongoing airway eosinophilia.

Case 3

A 61-year-old male was first seen in 2015 for evaluation of persistent blood eosinophilia (peak 4.2×10^9/L) and sputum eosinophilia (16.5%) associated with severe asthma. Work-up lead to a diagnosis of CD20+ Hodgkin's lymphoma in a cervical lymph node, which was initially thought to be the likely cause of eosinophilia. Treatment with adriamycin, bleomycin, vinblastine and dacarbazine lead to lymphoma remission and resolution of the eosinophilia. However, eosinophilia recurred two-years later associated with recurrent airway infections possibly related to acquired hypogammaglobinemia. He was initiated on monthly intravenous immunoglobulin, which effectively controlled airway infections. Given persistence of eosinophilia and asthma symptoms despite prednisone 10mg, fluticasone propionate 2000mcg and salmeterol 200mcg daily, he was started on mepolizumab in 2017. On this therapy, he had an eosinophilic exacerbation (BAL demonstrating 20% eosinophils) and therefore was switched to benralizumab in August 2018. After six months of treatment, he developed dyspnea, purulent cough and weight loss. Blood work demonstrated leukocytes of 7.9×10^9/L with eosinophils of 0.1×10^9/L. Sputum differential cell counts demonstrated intense neutrophilic inflammation (total cell count of 169.1 $\times 10^6$cells/g, 96.8% neutrophils) with no eosinophilia. CT chest demonstrated extensive bilateral patchy upper lobe predominant peripheral consolidations (figure 1C). Initial bronchoscopy did not reveal any causative organisms, alveolar hemorrhage or malignant cells. He further underwent surgical lung biopsy which showed bronchocentric lymphocytes and neutrophils, and occasional giant cells. Shortly after, he had an ICU admission for septic shock,

where a repeat BAL demonstrated *Streptococcus pneumonia* and *Pseudomonas aeruginosa*. He is now recovering on intravenous antibiotics and is on a tapering dose of prednisone, currently 15mg daily. Benralizumab has been discontinued and he is waiting for reslizumab to be approved by his insurance company to facilitate further prednisone tapering.

Case 4

An 82-year-old female, diagnosed with severe eosinophilic asthma (one severe exacerbation in the prior six months) despite being treated with deflazacort 30mg, fluticasone furoate 200mcg, vilanterol 25mcg, tiotropium and chronic azithromycin. Given the severity, she was started on benralizumab in August 2019. Despite this, the patient suffered two severe exacerbations, both associated with normal blood eosinophils, one requiring hospital admission in March 2020. Due to lack of improvement despite high doses of salbutamol and methylprednisolone, a CT chest was performed, which demonstrated peripheral ground glass opacities (figure 1D). Subsequent BAL showed normal eosinophil count but elevated neutrophils (1% eosinophils, 67% neutrophils) and grew *Pneumocystis jiroveci* in culture. The patient was not on any immunosuppression and CD4 lymphocyte count was normal. The patient was treated with trimethoprim/sulfamethoxazole, and this was associated with significant improvement in his clinical condition.

Eosinophils, IL-5 and host defense

These cases highlight four severe eosinophilic asthmatics who developed atypical airway infections while being treated with biologics targeting the IL-5 pathway, with three of the four patients having asthma exacerbations that were not associated with eosinophilia. The second

patient's exacerbation was eosinophilic as was off all anti-IL5 therapies and the infection was picked up on CT imaging. It is possible that this was gradual progression of a non-tubercular mycobacterial infection that he had for the previous few years. All patients were well-characterized as eosinophilic endotype, and given that post-treatment there was no evidence of eosinophilic inflammation, we hypothesized that an increase susceptibility to infections may be mediated by depletion of eosinophils or alteration of immunological pathways in vulnerable hosts. All patients were on oral and high doses of inhaled corticosteroids that may have additionally contributed to the risk of airway infections.

The role of eosinophils against helminths is well known, but eosinophils may also play a role against viral, bacterial or fungal organisms [6,7,27,28]. Eosinophils may participate in host defense against other organisms and are capable of phagocytosing bacteria, yeasts [29], and parasites [30]. Increased eosinophil migration and activation is observed with both gram-positive and gram-negative bacteria. When activated, eosinophils degranulate and release cationic proteins, such as eosinophilic cationic protein (ECP), which can permeabilize bacterial cell membranes [31]. Other killing mechanisms observed include release of RNase [32], DNA traps [33], and production of superoxide species [34]. Eosinophils can also cause a dose-dependent reduction in infectivity of respiratory syncytial virus by releasing eosinophil derived neurotoxin [27]. Moreover, eosinophils may act as scavengers with the ability to capture and reduce infectivity of viruses. However, eosinophils derived from severe asthmatics are noted to be defective and have a reduced capacity to bind viruses, which may lead to an increase viral load. [35] In murine models, eosinophil deficiency was associated with decreased *Aspergillus*

fumigatus clearance and increased detection of germinating organisms in the lung, independent of neutrophils [36]. How this relates to the eosinophilia seen in ABPA is still unclear.

IL-5 is a key cytokine that plays a role in eosinophils differentiation, proliferation and trafficking. IL-5 receptor is expressed on eosinophils, basophils and type 2 innate lymphoid cells (ILC2). [12] Under inflammatory conditions, IL-5 receptor can also be expressed on other inflammatory cells, particularly neutrophils. Indeed, Gorski and colleagues demonstrated in mouse models that IL-5 receptor expression on neutrophils was increased post-influenza A infection. In this study, ILC_2 derived IL-5 was involved in optimal recovery of influenza A virus by dampening the inflammatory effector function of neutrophils in the inflamed lungs [37]. Airway epithelial cells are also recently reported to express functional IL-5 receptor [38]. Thus, blocking IL-5 pathways (by all three anti-IL-5 MAbs) or apoptosis of cells that express IL-5R by antibody-dependent cytotoxicity (by benralizumab) may potentially impair innate immune response. Moreover, the IL-5 pathway is also important in adaptive immune responses as well. The IL-5/IL-5R interaction contributes to the maturation of B cells undergo class switch recombination that results in IgG1 production [39]. In mice models, IL-5 overexpression significantly increase antibody production [40] while IL-5R-alpha chain deficient mice have reduced immunoglobulins level overall – in particular IgG and IgA – which are crucial for mucosal immunity [41-43].

While there is evidence supporting the role of eosinophils in host defense against all types of microbes in laboratory and mice studies, there is insufficient evidence in humans. Complete lack of eosinophils in humans does not appear to be associated with significant adverse events [44]. Moreover, eosinophil count poorly correlated with infection and sepsis among critically ill patients [45]. Furthermore, in all clinical trials evaluating anti-eosinophil biologics in asthmatics,

suppression of eosinophils did not correlate with an increased risk for infection [3-5,46]. But randomized controlled clinical trials are underpowered to detect rare events. Thus, while the airway infections that we report may be coincidental, it is important to consider them as potential causes in patients who have non-eosinophilic exacerbations. It is intriguing that three of the four patients were on benralizumab. It is possible that the mechanistic and structural differences between benralizumab and the other anti-IL-5 mAbs may contribute to this phenomenon, as elaborated on in the next section.

Benralizumab and airway infections

Although mepolizumab, reslizumab and benralizumab all target the IL-5 pathway, benralizumab does so by binding the IL-5 receptor (IL-5R) alpha chain located on the surface of eosinophils as opposed to IL-5 itself [47]. This mAb, unlike mepolizumab or reslizumab, is an afucosylated humanized $IgG_{1\kappa}$ and facilitates interaction with CD16 (FcγRIII) on natural killer (NK) cells, causing downstream antibody-dependent cell-mediated cytotoxicity (ADCC) and thus, the destruction of $IL-5R^{+}$ cells [26,47] and the eradication of both mature eosinophil and eosinophil progenitors [26]. Mepolizumab can also decrease eosinophil progenitors in local tissues by 30% but not completely abolish them [48], unlike benralizumab [26]. Moreover, this was only achieved with the 750mg intravenous regimen and the effect was not seen on the approved clinical dose and route (100mg, subcutaneous) [21]. While direct comparisons between biologics have not been done, there are differences in the magnitudes of treatment effects of the three biologics [49]. In OCS-dependent patients, benralizumab was associated with a 70% reduction in exacerbations [13] compared to 50-60% [14] for other anti-IL-5 mAbs. Regardless, 20% of

patients in the benralizumab clinical trials still remain OCS dependent or require higher doses to maintain asthma control [13].

In the multicenter Severe Asthma Research Program, patients with severe asthma were found to have relatively reduced NK numbers in BAL fluid and they were less effective at killing myeloid target cells, compared to those isolated from healthy controls. The presence of corticosteroids further reduces the cytotoxic mediator release from NK cells [50]. Thus, ineffective ADCC in the context of NK cell reduction or dysfunction or an associated macrophage phagocytosis may contribute to persistent eosinophilia and sub-optimal response to benralizumab. However, this was not the case in a recent single center study that demonstrated infections, and not eosinophils, as the main cause of exacerbations while on benralizumab [51]. While the sub-optimal responders had reduced circulating NK cell numbers and low CD16 expression on $CD56^{dm}$ NK cells, only 2 out of 20 sub-optimal responders had evidence of persistent airway eosinophilia, suggesting that even the reduced number and function of NK cells are sufficient for benralizumab mediated eosinophil depletion. As a matter of fact, all other patients, responders and sub-optimal responders alike, had complete suppression of their sputum and blood eosinophils. This is in direct contrast with the other anti-IL-5 biologics, where the main cause of treatment failure can be attributed to sub-optimal eosinophil suppression as witnessed in this study as well as other mechanistic studies of anti-IL-5 biologic failures [25,52]. More importantly the study indicates the increase in infective exacerbations while on benralizumab when compared to a similar subset of patients treated with mepolizumab and reslizumab.

The use of sputum cytology is crucial in understanding the nature of the exacerbation and directing the optimal subsequent management. This may have contributed to inadvertent underreporting of infection adverse events in large clinical trials. Post-hoc analysis of the BORA extension trial, reports respiratory infections (including both upper and lower respiratory tract infections) in 22% of patients over the 1 year follow up period (351 out of 1576) [3]. Nevertheless, this may still be underestimated in the BORA extension study as, asthma exacerbations were reported in 823 (52%) patients without further information regarding the characteristics of these exacerbations by sputum measurements. As illustrated by the cases in this review, infective exacerbations may be completely indistinguishable from eosinophilic exacerbations without sputum analysis and it is possible that a portion of these "asthma" exacerbations in the clinical trials were mislabelled and are actually infectious in nature.

Mechanistically, it is still unclear how benralizumab contributes to infectious exacerbations, how potentiates infections in a susceptible host, and how it affects the NK cell number and function. Perhaps benralizumab induced ADCC is not specific to the eosinophil cell lineage. Whether the ADCC of other the cells that express IL-5 (basophils, neutrophils [37], B-lymphocytes [39] and epithelial cells [38]) have a role to play in the benralizumab associated airway infections requires to be investigated.

Advances on sputum measurement for identifying exacerbations

Assessing the nature of exacerbation in severe asthmatics, particularly in those on daily oral corticosteroid and/or anti-eosinophil targeted biologics, using blood counts is not very helpful. There is adequate evidence that shows (i) discordance in blood and sputum eosinophils in uncontrolled asthma [53,54], particularly those OCS-dependent [55], and (ii) blood being a poor

surrogate for monitoring response to anti-IL-5 biologics and associated exacerbations [22,56,57]. In fact, sputum cytology to assess airway inflammation has been a pivotal part of clinical management of patients with complex airways disease. The method of sputum collection is well described and standardized [58,59]. Changes in sputum cellular indices are reproducible, reliable [58] and responsive to change in anti-inflammatory treatments [60]. Using sputum strategy to guide treatment has been shown to have lowered risk ratio of asthma exacerbations by 49% compared to clinical guidelines [61]. It helps to increase corticosteroids in exacerbations associated with an eosinophilic bronchitis (presence of sputum eosinophils >3% or evidence of free eosinophil granules [62]). More importantly, it limits the use of corticosteroids in exacerbations associated with a non-eosinophilic bronchitis and prescribe antibiotics instead when exacerbations are associated with a neutrophilic bronchitis [9,63]. An increased total cell count and neutrophils >65% in sputum [62] is indicative of an airway infection. Furthermore, deep sequencing and extended culture of the sputum plugs allows for identification of bacterial species, otherwise not seen in routine cultures. Assessment of sputum also identifies those with a paucigranulocytic differential i.e, absence of airway inflammation, indicating other factors such as airway hyperresponsiveness underlying increase in asthma symptoms.

Of recent, sputum measurements have been pursued beyond simple cell counts. Reports from different laboratories globally have successfully measured a number of fluid-phase mediators that include but not limited to cytokines, growth factors, chemokines (comprehensive list reviewed by Kelly et al., 2002 [64]), inflammatory mediators such as eosinophil peroxidase [65] and myeloperoxidase [66], immunoglobulins [67] and exosomes [68] in the processed cell-free supernatants. Sputum cells have been further used to assess *ex vivo* inflammatory events, identify rare cell populations (such as ILC2s and progenitors [69]). Microbiome [70] and gene signatures

[71] associated with different disease population and indices of severity. Cellular and molecular assessment of sputum therefore can increase understanding of the nature of exacerbation, the underlying mechanisms and thereby aid in optimal clinical management.

Our recommendation to manage exacerbations while on anti-IL-5 biologicals

Blood eosinophil count is commonly used to initiate therapy with anti-IL5 mAb, however, currently there are no recommendations for monitoring response to therapy. [72] If a patient develops an exacerbation while on a biological, it is critical to assess the nature of exacerbation and to determine the underlying pathophysiology that may have contributed to the worsening of symptoms. We recommend spirometry (pre and post-bronchodilator) and sputum differential cell counts along with a blood count. Persistent sputum eosinophilia (often with a normal blood eosinophil count) constitutes an inadequate response to an anti-eosinophilic biologic, and thus these exacerbations are treated with a short burst of prednisone and it is reasonable to consider switching to another biologic. There is evidence demonstrating effectiveness of reslizumab [52] and benralizumab [73] in severe eosinophilic asthmatics who have suboptimal response to mepolizumab. Of course, there may be some patients on benralizumab who may show better response to one of the other anti-IL5 mabs. There are anecdotal reports to this effect but we do not have randomized controlled clinical trials to support this. Neutrophilic bronchitis represents underlying infections and patients are treated with the appropriate antibiotics. We do not discontinue or switch a biologic after the first neutrophilic exacerbation. However, if a patient continues to have recurrent neutrophilic exacerbations or a persistent airway infection, we suggest further work-up for susceptibility to infections including high resolution CT chest to look for bronchiectasis, or pulmonary fibrosis, sputum extended bacterial cultures, CFTR genetic

mutation panel and quantitative immunoglobulins. We do not generally recommend azithromycin in all patients with neutrophilic bronchitis, rather we recommend the appropriate antimicrobial therapy guided by culture reports. Bronchoscopy may be performed in patients with radiological abnormalities who are unable to provide a sputum sample. Currently the relationship between the use of benralizumab and airway infections is an association and does not imply causality. However, it may be prudent to discontinue the biologic (any biologic not just benralizumab) and observe if the frequency of infections decreases. In a patient who is on high doses of prednisone (>12.5 mg/day) and who has recurrent airway infections and associated sputum eosinophilia (these are patients who are prone to have an autoimmune response in the airway [22]), it is probably best not to initiate therapy with mepolizumab (because of a risk of autoimmune worsening of asthma [25]) . If therapy is initiated with benralizumab, we recommend very careful monitoring for any indication of worsening of airway infections [51]. In the absence of airway inflammation (normal sputum), the likely mechanism of worsening is smooth muscle hyperresponsiveness, which can be confirmed with either a post-bronchodilator reversibility or bronchoprovocation challenge. These patients are treated with additional bronchodilators, weight loss or bronchial thermoplasty (if severe airway hyperresponsiveness with PC20 <0.25 mg/ml), with continuation of current biologic therapy. An approach to management of non-T2 asthma has been previously reviewed. [74] An algorithm regarding management of exacerbation in patients on anti-IL-5 biologics is shown in Figure 2.

Conclusion

In summary, while anti-IL5 mAbs have bolstered our pharmacological arsenal to treat patients with severe asthma, they are not silver bullets. Not only are these therapies indicated only in

patients whose severity and exacerbations are primarily driven by eosinophils, they may not abolish all eosinophilic exacerbations particularly when airway eosinophilia is not controlled. Moreover, they would be ineffective for infective exacerbations of asthma. We have highlighted this with four clinical case scenarios of infective exacerbations while eosinophilic asthma was being treated with anti-IL-5 mAbs. This is particularly evident the with the anti-IL-5R mAb, benralizumab. Quantitative sputum cytometry is helpful to identify eosinophilic vs non-eosinophilic exacerbations. The majority of exacerbations while on treatment with mepolizumab or reslizumab are likely to be eosinophilic. In contrast, the majority of exacerbations while on treatment with benralizumab are likely to neutrophilic (Table 3). Monitoring of blood eosinophil count is not very helpful to identify the nature of exacerbation. It is important to identify the cellularity of airway secretions (with sputum cytometry when available, or by bronchoscopy if necessary) during exacerbations before considering switching biologics. An eosinophilic exacerbation may respond to an alternate anti-IL5 biologic, while a neutrophilic exacerbation will not.

Disclosure statement

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Table 1. Baseline characteristics of cases described.

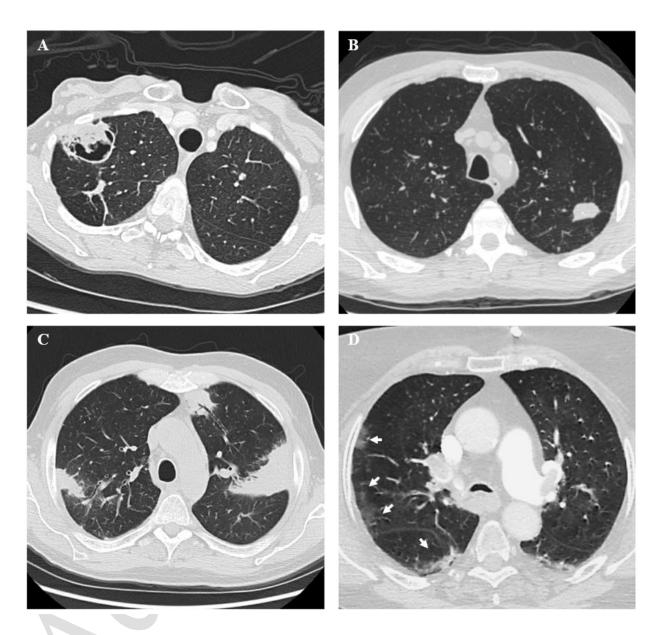|	Case 1	Case 2	Case 3	Case 4
Age	61	62	61	82
Gender	Female	Male	Male	Female
ICS dose[*, §]	1000mcg	3000mcg	2000mcg	1000mcg
OCS dose[*, ±]	15mg	10mg	10mg	25mg
FEV1 (%pred)[*]	56%	28%	51%	75%
FVC (%pred)[*]	67%	59%	64%	91%
FEV1/FVC%[*]	64%	33%	60%	56.8%
Blood eos (10^9/L)[*, £]	0.2	0.3	0.2	0.1
Sputum total cell count (x10^6/g)[*]	17.4	1.5	78.7	3.8
Sputum eos (%) [*, £]	3.5%	58.8%	16.5%	5.5%
Biologic(s) treatment	Mepolizumab	Mepolizumab, reslizumab, benralizumab	Mepolizumab, Benralizumab	Benralizumab

ICS: inhaled corticosteroid, OCS: oral corticosteroid, [*]before initiating biologics, [§] fluticasone propionate equivalent, [±] prednisone equivalent, [£] peak values

Table 2. Characteristics at time of infectious exacerbation while on biologics.

	Case 1	Case 2	Case 3	Case 4
ICS dose [§]	1000mcg	2000mcg	2000mcg	1000mcg
OCS dose[±]	5mg	15mg	0mg	25mg
FEV1 (%pred)	53%	27%	77%	67%
FVC (%pred)	68%	55%	84%	85%
FEV1/FVC%	60%	38%	64%	55%
Blood eos (10^9/L)	0.0	0.3	0.0	0.0
Sputum total cell count (x10^6/g)	55.5	11.1	148.5	n.a.
Sputum neut (%)	93.3	36.8	97.8	n.a.
Sputum eos (%)	0.3%	42.0%	0%	n.a.
Biologic during exacerbation	Mepolizumab	Benralizumab	Benralizumab	Benralizumab
Causative organism(s)	*Aspergillus fumigatus*	*Mycobacterium avium-intracellulare*	*Streptococcus pneumoniae, Pseudomonas aeruginosa*	*Pneumocystis jiroveci*
Time to infection in months[¶]	6	60 (8)	18 (6)	6

ICS: inhaled corticosteroid, OCS: oral corticosteroid, [§] fluticasone propionate equivalent, [±] prednisone equivalent, [¶] from first biologic initiation; if multiple biologics were used, time to infection from initiation of the last biologic is listed in brackets.

Figure 1. Representative computed tomography (CT) scan images of the cases presented.

Panel A: case 1's 3.5cm right upper cavity. Panel B: case 2's 2.7cm left upper lobe nodule. Panel

C: case 3's bilateral, patchy upper lobe consolidations. Panel D: case 4's peripheral ground glass

opacities (arrows)

Table 3. Differences in sputum cellularity during exacerbations on mepolizumab, reslizumab and benralizumab.

Nature of exacerbation	Intervention		Potential reasons
	Mepolizumab/ Reslizumab	Benralizumab	
Eosinophilic	90%	10%	Inadequate dosing/dosing frequency, anti-drug antibodies, auto-immune phenomena
Non-eosinophilic	10%	90%	Susceptibility to infections due to ADCC on innate immunity cells, increased airway hyperresponsiveness

Figure 2. Management of exacerbations on anti-IL-5 biologics.