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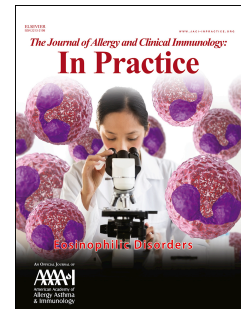
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Choosing a Biologic For Patients With Severe Asthma

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Conflicts of interest

In the last 5 years IDP has received speaker's honoraria for speaking at sponsored meetings from Astra Zeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, Teva, Chiesi, Sanofi/Regeneron, Menarini and GSK and payments for organising educational events from AZ, GSK, Sanofi/Regeneron and Teva. He has received honoraria for attending advisory panels with Genentech, Sanofi/Regeneron, Astra Zeneca, Boehringer Ingelheim, GSK, Novartis, Teva, Merck, Circassia, Chiesi and Knopp and payments to support FDA approval meetings from GSK. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, Astra Zeneca, Teva and Chiesi. He has received a grant from Chiesi to support a phase 2 clinical trial in Oxford. He is co-patent holder of the rights to the Leicester Cough Questionnaire and has received payments for its use in clinical trials from Merck, Bayer and Insmed. In 2014-5 he was an expert witness for a patent dispute involving Astra Zeneca and Teva.

NH served on advisory committees for GSK, Sanofi, Mylan. Consultant for Boehringer Ingelheim. Speaker Regeneron, Astra Zeneca. Research Industry Initiated GSK, Boehringer Ingelheim, Sanofi, Genentech, Gossamer Bio.

JC received research funding from AZ, Genentech, Novartis, Optinose, Regeneron, Sanofi, TEVA; Consulting fees from AZ, Novartis, RAPT Pharmaceuticals, Regeneron, Sanofi; payments for advisory boards from AZ, Eli Lilly, Novartis, Optinose, Regeneron, Sanofi; and speakers fees from AZ, Genentech, Novartis, Regeneron, Sanofi

Abstract

The availability of a range of new biological treatments targeting type-2 inflammation has provided new opportunities for patients with more severe asthma. Treatment has a bigger effect on exacerbations than day-to day symptoms and efficacy increases with increasing intensity of type-2 airway inflammation as reflected by the blood eosinophil count and exhaled nitric oxide (FeNO). The similarity of the clinical effects and target populations coupled with the absence of direct head to head comparative data makes it difficult to choose the right biologic for a given patient. In this review we summarise the key efficacy data from phase 3 trials; discuss indirect comparisons; review clinical and laboratory variables that may be associated with a differential response to treatment; outline practical considerations that might be important to individual patients; and suggest an algorithm for choosing the most appropriate biologic to start with and the first choice to switch to.

Introduction

The introduction of biological agents targeting the Type-2 cytokines IL-5, IL-4 and IL-13 has provided exciting new opportunities to manage patients with severe asthma(1, 2). Anti-IL-5 (Mepolizumab and Reslizumab), anti-IL-5 receptor- α (Benralizumab) and anti-IL-4 receptor- α (Dupilumab) are all widely available to treat patients with severe asthma; they reduce type-2 inflammation and in so doing reduce exacerbations, improve lung function and ameliorate symptoms(2-5). Anti-IgE (Omalizumab) is approved to treat severe allergic asthma and there is some evidence that the effects of omalizumab are most strongly related to the presence of type-2 inflammation(6, 7). The profile of effects of these biologics on clinically important outcomes are similar, with a bigger effect on exacerbations than day-to-day symptoms. Moreover, therapeutic effects of these drugs increases with increasing intensity of type-2 airway inflammation as reflected by the blood eosinophil count and exhaled nitric oxide (FeNO).

The similarity of the clinical effects and target populations coupled with the absence of direct head to head comparative data makes it difficult to choose the right biologic for a given patient. Related and equally difficult questions are when to discontinue a biologic in favour of another and which drug to switch to? As new data emerge and as clinical experience with biologics grows, we have the beginnings of a consensus on these important questions. In this review we will address the question ‘which biologic for which patient with severe asthma?’. Our primary focus is on differentiating between biologic classes (i.e. biologics targeting IL-5, IL-4&13 and IgE) and less upon the comparison of specific drug. We summarise the key efficacy data from phase 3 trials; discuss indirect comparisons between these medications; review clinical and laboratory variables that may be associated with a differential response to treatment; and outline practical considerations that might be important to individual patients. We finish with a suggested algorithm for choosing the most appropriate biologic to start with and the first choice to switch to.

Findings from Phase 3 Clinical Trials

A summary of the targets, characteristics and clinical outcomes of biological treatments for asthma are shown in Table 1. Crucial to the understanding of these data is the target population and we discuss this in more detail below.

Targeting IgE

Omalizumab binds to circulating IgE, preventing it from binding to high-affinity IgE receptors (Fc ϵ RI) expressed by mast cells and basophils, leading to reduced cellular activation and mediator release

(Figure 1). It is approved for the treatment of moderate-to-severe atopic asthma in patients ≥ 6 years of age. Criteria for treatment are poor asthma control on usual medications and sensitization to at least one perennial allergen, based either on serum specific-IgE levels or on skin prick testing. Furthermore, the patient should demonstrate levels of total IgE between 30 IU and 1500 IU/L (700 IU/L in the USA), which is used in combination with their weight to calculate the dose and frequency (every 2 or 4 weeks) of subcutaneous injections of the medication. Treatment is well tolerated, with only local skin reactions at the injection site (3%) and very rare (0.2%) hypersensitivity reactions reported(6, 8). In the U.S., a black box warning about anaphylaxis exists for Omalizumab although it is rare.

The efficacy of omalizumab has been extensively studied in this population: it reduces exacerbations by approximately 30% and improves symptoms and lung function modestly and inconsistently(6, 8). Dosing prior to the fall season, at which time there may be increased exposure to important allergens and viral infections, has demonstrated more significant improvements in exacerbations in children(9). Multiple analyses have failed to show any reliable biomarker to predict response to omalizumab therapy; in particular, serum IgE, sensitisation to a perennial allergen and patient weight have not been associated with treatment efficacy. A placebo controlled trial has shown that a raised blood eosinophil count and FeNO are associated with greater efficacy(7) but this finding was not confirmed in an open label real world study(10), although open label studies might not be optimum for identifying a predictive biomarker. Omalizumab has been shown to be efficacious against co-morbid conditions sometimes seen in patients with severe asthma, including chronic spontaneous urticaria(11) and chronic rhinosinusitis and nasal polyposis(12).

Targeting Interleukin-5

Interleukin-5 drives the differentiation of eosinophils in the bone marrow and their survival, acts as a chemoattractant for eosinophils and activates eosinophils causing them to degranulate. This releases a variety of pro-inflammatory mediators including additional proinflammatory cytokines, eosinophilic toxins and galectin-10, which contribute to asthma morbidity by mediating airway smooth muscle contraction, airway remodelling and airway mucus plugging (figure 1)(13).

There are three approved anti-IL-5 therapies for patients with severe eosinophilic asthma: mepolizumab and reslizumab, which bind IL-5 directly; and benralizumab, which inhibits IL-5 activity by binding to the IL-5 receptor- α (figure 1). Accordingly, successful anti-IL-5 trials included patients with higher blood eosinophils (in the range >150 to >400 cells/mcL; table 1) to achieve improvement

in asthma exacerbations, variable improvements in symptoms and reduction in need for oral corticosteroids (~50% decrease of median OCS dose compared to placebo). Finally, it is noteworthy that mepolizumab has shown efficacy for other eosinophilic diseases such as eosinophilic granulomatosis with polyangiitis (EGPA)(14), nasal polyposis(15) and hypereosinophilic syndrome (HES)(16).

The phase 2b (DREAM)(17) and 3 (MENSA)(5) trials of mepolizumab demonstrated a 50% reduction in severe exacerbations and showed that of the many variables assessed, only the blood eosinophil count and the prior frequency of asthma attacks were associated with the beneficial effect of treatment(18). Indeed, efficacy became apparent at a blood eosinophil count >150 cells/mcL and increased progressively with counts above this (Table)(18). The SIRIUS study confirmed a significant OCS sparing effect(19): the median percentage reduction from baseline in the glucocorticoid dose was 50% in the mepolizumab group vs no reduction in the placebo group. Mepolizumab is approved for adults and children down to age 6, although efficacy data in patients aged <18 is limited.

Reslizumab, which also binds to IL-5, had similar effects upon clinical outcomes, although comparison between studies is made difficult by different entry criteria (table 1). The phase 3 studies of reslizumab showed efficacy in patients with an eosinophil cut off of 400 cells/mcL. There was a 50-60% reduction in exacerbation frequency, a 115-160ml improvement in FEV1 and a clinically significant improvement in symptoms(3), although no studies to date have demonstrated an OCS-sparing effect. Reslizumab is only available by intravenous infusion. Reslizumab is approved for adults 18 years of age and older and has a US FDA black box warning for anaphylaxis.

Benralizumab targets the IL-5R α receptor on the surface of eosinophils and certain basophils. It also differs from mepolizumab and reslizumab insofar as it triggers antibody-dependent cell-mediated cytotoxicity, apoptosis of eosinophils and has been shown to cause more profound and acute onset eosinopenia than mepolizumab(20). Benralizumab has been evaluated in patients with asthma and a blood eosinophil count >300 cells/mcL and a history of 2 or more exacerbations in the last year. The phase 3 trials (SIROCCO and CALIMA) largely confirmed the effects seen in earlier phase studies, with a decrease in annualized exacerbation rates of 30-50% and an increase in FEV1 of 110-160 mL; efficacy is strongly associated with the blood eosinophil count(21, 22). The ZONDA study investigated the effects of 28 weeks treatment with benralizumab on oral corticosteroid requirements in patients with oral corticosteroid dependent asthma. It showed a 75% reduction in OCS-dosage vs 25% with placebo(23). Benralizumab has a safety profile similar to other anti-IL-5 blockers (table 1). Finally, there is some evidence to suggest that the acute biological effects of benralizumab may translate into

clinical efficacy in the setting of acute asthma attacks(24). Whether the drug can be used as an alternative to systemic corticosteroids in the acute setting in severe eosinophilic airways disease is currently under investigation (NCT04098718). Benralizumab is approved for patients with severe asthma who are 12 years and older.

Targeting Interleukin-4 and 13

The cytokines IL-4 and IL-13 are complementary in their roles in the Type 2 inflammatory pathway (figure 1). They act via the IL-4 receptor 1&2, both of which contain the alpha subunit of the IL-4 receptor. Dupilumab prevents this by binding to the IL-4 receptor- α whilst leaving the IL-13 receptor (which is inhibitory in its soluble form) unaffected. Interleukin-4 promotes T helper 2 lymphocyte populations. Both IL-4 and IL-13 have roles in tissue-specific trafficking of Type 2 inflammatory cells and in promoting isotype class switching of B cells to produce IgE. Lastly, IL 13 has pathological effects such as mucus secretion and increasing smooth muscle contractility and hyperplasia (Figure 1).

The phase 3 ASTHMA LIBERTY QUEST trials(2) compared two Dupilumab doses (200 and 300 mg) subcutaneously every two weeks with placebo in an unselected population of patients with moderate to severe asthma and a history of 1 or more asthma exacerbations in the last year. It confirmed that efficacy was only seen in patients with raised FeNO and/or blood eosinophil counts (table 1). Specifically, in the intention-to-treat all-comer population, asthma exacerbations decreased by 46-48% and FEV1 increased by 130-140 mL compared with placebo. In patients with blood eosinophil cell counts of 0.3×10^9 per L or higher, the overall effect size was larger, with an exacerbation reduction of 66-67% and FEV1 improvement of 210-240 mL. As with mepolizumab and benralizumab, dupilumab has also been shown in the ASTHMA LIBERTY VENTURE study(25) to enable patients on maintenance OCS to decrease their steroid dose, with a 70% reduction of OCS maintenance dose in patients treated with dupilumab compared with a 42% decrease in patients treated with placebo. The main safety and tolerability aspect observed in the clinical trials were rare cases of hypereosinophilia of unknown clinical significance. Finally, it is noteworthy that dupilumab has been found efficacious and is a licenced treatment for two other type 2 high diseases which can coexist with severe asthma: atopic dermatitis(26) and chronic rhinosinusitis with nasal polyposis(27). Dupilumab is approved for patients with severe asthma who are 6 years of age and older.

Indirect treatment comparisons

One approach to comparing efficacy of the different biologics has been to do indirect treatment comparisons. A variety of approaches have been used to make a number of different between -

treatment comparisons (table 2). None of these studies have succeeded completely in matching patient characteristics and many of the studies can be criticised because of somewhat arbitrary inclusion and exclusion criteria (table 2). Perhaps the most useful approach is to compare efficacy in patient groups matched by blood eosinophil count, since this is the most influential baseline variable associated with response. Table 1 shows the effect of the approved biologics on asthma exacerbations rates and pre-bronchodilator FEV₁ in patients with a baseline blood eosinophil count >300 cells/mcL. The findings on exacerbations are very similar whereby Dupilumab tends to be associated with a greater improvement in FEV₁, as might be expected given that it blocks more inflammatory pathways potentially linked to airflow limitations than the more selective biologics (figure 1). A bigger impact on FEV₁ was also seen in the phase 3 VENTURE study(25) evaluating the oral corticosteroid sparing effect of Dupilumab compared to SIRIUS(19) and ZONDA(23), which evaluated the oral corticosteroid sparing effect of Mepolizumab and Benralizumab (table 2).

Clinical and laboratory variables potentially associated with a differential response to treatment

The similarity of the clinical effects seen in phase 3 and the lack of a clear consensus on comparative efficacy from the indirect treatment comparison studies means that the decision on which biologic for which patient is often based on the presence or absence of other potentially differentiating variables. One important variable consistently associated with a better response to biologics, but not useful for differentiating the response by biologic class, is prior exacerbation history(18, 28). Patients with a history of prior exacerbations have a better response to treatment and most would regard the presence of a history of asthma exacerbations despite optimised inhaled treatment to be an absolute requirement for biologic treatment.

Biomarkers

Exhaled nitric oxide (FeNO) and the peripheral blood eosinophil count have emerged as the biomarkers most consistently associated with the efficacy of biologics targeting Type-2 inflammation (figure 1). The extent to which the blood eosinophil count increases the probability of a response to treatment is related to the intensity and consistency of the signal with clinically important responses to anti-IL-5 (18,28) and dupilumab (2) becoming apparent and progressively increasing above a blood eosinophil count of 150 cells/mcL. Better responses to treatment for a given blood eosinophil count are also seen when both blood eosinophils and FeNO are raised (30). A recent cross sectional study in severe asthma(29) showed that FeNO is closely associated with increased induced sputum levels of airway Type-2 cytokines (IL-4, IL-5), chemokines (eotaxin-3, TARC), alarmins (IL-33, TSLP) and

eosinophils. In contrast, blood eosinophils correlate with serum IL-5 and not with any assessed measure in sputum. These results imply that FeNO and blood eosinophils relate to different components and compartments of Type-2 inflammation, with FeNO reflecting the chemotactic pull to the airways and blood eosinophils reflecting the systemic pool of available eosinophils (figure 2). It is notable that Dupilumab reduces FeNO whereas the anti-IL-5 and anti-IL-5 receptor- α biologics have no effect. In contrast, the anti-IL-5 and anti-IL-5 receptor- α biologics reduce the blood eosinophil count markedly whereas Dupilumab treatment is associated with a temporary increase in blood eosinophils. Thus, the effects of these different biologics on biomarkers implies that they target Type-2 inflammation in different compartments, raising the possibility that biomarker profiles might be an effective means of stratifying Type-2 asthma and identifying patients best suited for different biologics.

There is some evidence to support this view. The blood eosinophil count has been shown to relate consistently to the efficacy of Mepolizumab(18) and Benralizumab(28) and above a count of 500 cells/mcL, the efficacy of both of these agents is very large. For example, the 32 week phase 3 MENSA study(5) showed that in the 30% of enrolled patients who had a baseline blood eosinophil count >500 cells/mcL, Mepolizumab 100 mg subcutaneously every 4 weeks was associated with a 80% reduction in exacerbations, a 300 ml improvement in pre-bronchodilator FEV₁ and a 12 point improvement in St George's Respiratory Questionnaire score (with the minimally clinically important difference being 4 points). In uncomplicated Type-2 high asthma with blood eosinophil count >500 cells/mcL, we suggest that anti-IL-5 or anti-IL-5 receptor- α are often the agent of choice. This view is influenced by theoretical concerns about the risk of an increase in an already increased blood eosinophil following the introduction of Dupilumab. We acknowledge that as greater safety and blood eosinophil stratified efficacy data emerges, this advice may change. In patients with blood eosinophil counts between 150 and 500 cells/mcL there may be differential efficacy of Dupilumab and anti-IL-5 agents according to whether FeNO is raised, with Dupilumab being more effective in those with a raised FeNO(30).

Although used as a biomarker to identify patients suitable for Omalizumab and to dose treatment, there is no evidence that serum IgE is a useful predictive or prognostic biomarker(7). Airflow limitation, symptom scores, and asthma related quality of life have not proved useful predictive variables and higher bronchodilator reversibility is associated with a less good response to Mepolizumab(31), probably because significant Type-2 airway inflammation tends to be associated with non-reversible airflow limitation.

Long-term oral corticosteroid use

Between 25 and 64% of patients attending severe asthma clinics in Europe are treated with regular oral corticosteroids and in 2010, the introduction of regular oral corticosteroids was the commonest therapeutic intervention in UK severe asthma centres(32). Chronic oral corticosteroid treatment is utilized less frequently in the United States, accounting for approximately 10% of patients with severe asthma(33). Treatment associated morbidity is dose-related and accumulates with time, becoming an important component of the clinical problem in many patients with severe asthma(34). Biologics targeting IL-5 and IL-4 & 13 have proved to be highly effective oral corticosteroid sparing agents (table 1) and it is likely that these treatments will have a big impact on oral corticosteroid use in patients with severe asthma over the next 5-10 years. The baseline blood eosinophil count has not proved to be a useful predictive biomarker of the oral corticosteroid sparing effect of these biologics because of suppression of blood eosinophil counts by oral corticosteroids. Omalizumab is less effective in patients with oral corticosteroid dependent asthma(6) and there are no randomised, double-blind placebo-controlled trials demonstrating an oral corticosteroid sparing effect. For this reason, we do not recommend Omalizumab in this group of patients.

Comorbidities***Chronic rhinosinusitis and nasal polyposis***

Chronic rhinosinusitis and nasal polyposis are common comorbidities in patients with severe asthma, present in up to 60% of patients and particularly common in those with adult-onset disease. When occurring in a patient with severe asthma they are associated with more severe Type-2 airway inflammation, worse asthma associated outcomes, a high rate of recurrence of nasal polyps post-surgery and a better response to all biologic agents. Omalizumab(35), mepolizumab(15) and dupilumab(36) have been demonstrated in published trials to have efficacy against symptoms and objective measures of chronic rhinosinusitis and nasal polyposis (table 3). However, dupilumab has the greatest positive impact across a range of outcome measures (table 3). Therefore, in patients with severe asthma and clinically troublesome chronic rhinosinusitis and nasal polyposis, we recommend Dupilumab as the first choice biologic.

Other comorbidities

Eosinophilic granulomatosis and polyangiitis (EGPA) and hypereosinophilic syndrome can coexist with severe asthma and these conditions, or early subclinical forms, should be considered in patients with suggestive clinical features and a persistent eosinophilia of >1500 cells/mcL. Mepolizumab is a

licensed treatment for both conditions(14, 16) and would be our first choice biologic in this situation. The dose of Mepilizumab in these situation is 300 mg subcutaneous injection every 4 weeks. Omalizumab is a licensed and highly successful treatment for chronic spontaneous urticaria(11) and would be a logical choice in patients with this comorbidity. Finally, Dupilumab is alone amongst the biologics considered here in being effective in atopic dermatitis(26) and would be the first-choice biologic in patients with this comorbidity. Dupilumab is being evaluated in other conditions associated with type-2 inflammation, including eosinophilic oesophagitis.

Pregnancy

There is limited experience with all biologics in pregnancy, but the available data are reassuring and there is an emerging consensus that continuing a biologic to maintain control of maternal asthma is usually the best option in pregnancy. Most clinicians involved in the management of severe asthma would therefore not stop successful therapy or delay the introduction of a biologic if pregnancy is a possibility, nor would this possibility influence the choice of biologic(37).

Age of onset

Reslizumab(38) and benralizumab(28) have been found to be more effective in patients with adult-onset versus childhood onset disease. This probably reflects the higher prevalence of more severe Type-2 airway inflammation in patients with adult-onset disease and we do not regard this as a clinically useful stratification variable. Omalizumab, consistent with its efficacy in allergic asthma, may be more effective in early-onset asthma(39).

Allergy

Serum IgE and the presence of specific IgE to perennial and seasonal allergens has not proved to be related to the efficacy of the anti-IL-5(17) and anti-IL-4/13(2) biologics. However, a subgroup of patients with severe asthma report severe allergen-provoked symptoms and some have seasonal worsening clearly linked to allergen exposure. Clinical trials have done a poor job identifying this important sub-group and we do not have useful data on whether biologics are differentially effective. This is an important omission for Dupilumab in particular, since longer-term treatment reduces serum IgE and allergen specific IgE markedly(40). One important study showed enhanced efficacy of Omalizumab against exacerbations in young patients with 'back to school' asthma(9), likely reflecting a combined suppressive effect on allergen-mediated Type-2 inflammation and enhancing effect on anti-viral immunity. For this reason, we recommend Omalizumab as a treatment of choice in patients

with clear allergen-associated asthma who do not have a biomarker profile suggesting efficacy for the more efficacious, newer generation biologics.

Practical considerations

In many patients the factors above are insufficient to make a confident treatment decision. In this situation a discussion of the practicalities of treatment is perfectly legitimate. The relative importance of these characteristics will differ from patient to patient. Positive attributes include an easy dosing regimen (i.e. subcutaneous injection, monthly or 2 monthly administration), the possibility of home administration via an autoinjector, good long term safety and efficacy data, consistent phase 3 trial data and efficacy against common comorbidities. Table 4 presents our view on how the current biologics perform in these areas. A clear and open discussion with the patients about biologic therapies is imperative as a shared decision is needed especially when the potential choice of more than one biologic exists. A web-based shared decision making tool is available for patients (<https://asthma.chestnet.org/sdm-tool/>).

An algorithm for choosing the best biologic to start and to swap to

A suggested algorithm for selection of the first and second choice biologic in different clinical situations is shown in figure 3. We are unable to make any strong recommendations within the anti-IL-5 class as there is insufficient evidence of differences although the greater experience with Mepolizumab in hyper-eosinophilic conditions means that this agent may be preferred in this subgroup. The algorithm emphasises the blood eosinophil count, regular oral corticosteroid use and presence of comorbid atopic dermatitis and chronic rhinosinusitis and nasal polyposis as predictive variables that have been shown consistently to relate to treatment efficacy and allow differentiation of biologics. These biologic choices are not set in stone and different choices may well be made in individuals who have compelling practical reasons, or less common comorbidities associated with a differential treatment response. The second named biologic represents the best alternative option if the first named biologic is not available and the best option for a swap if the first choice biologic does not achieve treatment goals.

Legends to figures

Figure 1

Type-2 airway inflammation is driven by an adaptive and innate immune response driven by epithelial alarmins (IL-33 and TSLP particularly). Type-2 airway inflammation is detected in clinical practice by assessing exhaled nitric oxide (FeNO, reflecting airway IL-13 activity) and blood eosinophils (reflecting systemic IL-5 activity). The main functional consequence of type-2 inflammation is airflow limitation as a result of airway mucus plugging; airway wall oedema and thickening; airway smooth muscle hyperplasia; and the induction of airway hyperresponsiveness. Key cellular players, cytokines, chemokines, effector mediators and their receptors are shown. Coloured crosses indicate the pathways inhibited by the relevant biologic (shown in same colour).

Figure 2

In severe asthma with documented treatment adherence exhaled nitric oxide (FeNO) is closely associated with increased induced sputum levels of airway type-2 cytokines, chemokines and alarmins. In contrast, blood eosinophils correlate with serum IL-5 and not with any assessed measure in sputum. These results imply that FeNO and blood eosinophils relate to different components and compartments of type-2 inflammation, with FeNO reflecting the chemotactic pull (magnet) to the airways and blood eosinophils reflecting the systemic pool of available eosinophils (bomb). When both occur together the risk of asthma attacks (bomb detonating) is particularly high.

Figure 3

Suggested algorithm for selecting the first (first named in red box) and second (second named in red box) choice biologic in different circumstances. FeNO=exhaled nitric oxide; CRSNP= chronic rhinosinusitis.

	Mepolizumab		Benralizumab			Reslizumab	Dupilumab		Omalizumab
Study	MENSA(5) ⁵	SIRIUS(19)	CALIMA(22)	SIROCCO(21)	ZONDA(23)	Castro et al(3)	QUEST(2)	VENTURE(25)	EXTRA(7)
Dose and duration	100 mg SC*, 4 weekly for 32 weeks	100 mg SC, 4 weekly for 24 weeks	30 mg SC, 8 weekly** for 52 weeks	30 mg SC, 8 weekly** for 52 weeks	30 mg SC, 8 weekly** for 28 weeks	3 mg/kg IV, 4 weekly for 52 weeks [#]	200 and 300 mg SC 2 weekly for 52 weeks	300 mg SC 2 weekly for 24 weeks	0.008 mg/kg per IgE (IU/mL) 2 weekly or 0.016 mg/kg per IgE 4 weekly
Blood eosinophils (cells/mm ³)	>150 and/or >300 in last year	>150 and/or >300 in last year	>300	>300	>150	>400	Unselected	Unselected	Unselected
Number of patients	580	135	881	805	148	953	1902	210	850
Placebo exacerbation rate (/year)	1.75	2.12	0.93	1.33	1.83	1.8-2.1	0.87-0.97	1.60	0.88
% reduction in exacerbations with active treatment	53	38	28	51	55	50-59	46-47.7	59.3	25

% reduction in exacerbations resulting in hospitalisation	61	0 vs 7 patients	-23	63	93	31-34	46.8	NA	NA
Improvement in pre-bd FEV ₁ (ml)	98	114	116	159	112	90-126	130-140	220	NA
Improvement in post-bd FEV ₁ (ml)	138	128	NA	NA	NA	NA	NA	NA	NA
Reduction in ACQ	0.44	0.52	0.1	0.29	0.55	0.2-0.27	0.31-0.34	0.47	0.36
Reduction in SGRQ	7	5.8	NA	NA	NA	NA	NA	NA	NA
Injection site reactions (placebo vs active %)	3 vs 9	NA	2 vs 3	2 vs 3	2 vs 2	NA	7.9 vs 16.8	4 vs 9	3.1 vs 1.2
Oral corticosteroid sparing effect (active vs placebo %)	NA	50 vs 0	NA	NA	75 vs 25	NA	NA	70.1 vs 41.9	NA

Exacerbation reduction (%) in patients with blood eosinophils $>0.3 \times 10^9/L$	61	NA	28	51	NA	NA	66-67	NA	32 ^{##}
Improvement in pre-bd FEV1 (ml) in patients with blood eosinophils $>0.3 \times 10^9/L$	202	NA	116	159	NA	NA	210-240	NA	40 ^{###}

Table 1

Summary of the phase 3 data with licenced biological treatments for severe eosinophilic asthma. Outcomes are relative to placebo. In non-oral corticosteroid sparing studies patients were required to have objective evidence of asthma and 2 or more asthma exacerbations in the year before randomisation despite high intensity inhaled treatment with the exception of EXTRA and QUEST where one or more exacerbations were required. * 75 mg IV also evaluated with broadly similar findings. ** 4 weekly dosing also evaluated with broadly similar findings. # two studies combined. ## above baseline eosinophil count of $0.26 \times 10^9/L$. ### Estimated based on % predicted FEV₁. bd = bronchodilator. ACQ = Asthma Control Questionnaire Score (5 or 6 item). SGRQ = St George's Respiratory Questionnaire Score.

Study	Comparison	Population	Methodology	Findings		Comments
				Exacerbations (rate ratio for first named)	FEV ₁ (L)	
Cockle et al(41)	Mepolizumab vs Omalizumab	RCT in patients with severe asthma and a exacerbation history. Overlap (eligible for both) and trial population. No biomarker matching	Indirect treatment comparison (Bayesian framework)	Overlap: Rate ratio 0.66 (0.37, 1.19) Trial: Rate ratio 0.63 (0.45, 0.89)	Overlap: -0.1 L (-6.35, 4.36) Trial: 0.24 (-3.61, 4.1)	Only trials utilising standard dosing compared
Iftikhar et al(42)	Benralizumab vs Dupilumab vs lebrikizumab vs Mepolizumab vs Reslizumab vs Tralokinumab	Heterogeneous but inclusive, with all placebo controlled RCTs with data on FEV ₁ , ACQ and AQLQ included. No biomarker matching	Systematic review and network meta-analysis	Only Reslizumab (0.64; 0.53, 0.78) and Dupilumab (0.37; 0.17, 0.8) were significant vs placebo	Dupilumab (0.16) > Reslizumab (0.14) > Benralizumab (0.13) > Mepolizumab (0.1) > Lebrikizumab (0.1) > tralokinumab (0.07)	Included studies before and after importance of stratification by type-2 biomarkers was recognised
Bourdin et al(43)	Benralizumab vs other anti-IL-5	Severe asthma with an exacerbation history and selection (and matching) on basis of blood eosinophils (varying criteria)	Systematic review and matching adjusted indirect comparison	0.94 (0.78, 1.13) vs Mepolizumab No comparison possible with reslizumab because populations too different	0.03 (-0.06, 0.12) vs mepolizumab No comparison possible with reslizumab	Included phase 2b DREAM study for Mepolizumab but only phase 3 studies for benralizumab

Busse et al(44)	Mepolizumab vs Benralizumab and Reslizumab	Severe eosinophilic asthma. Matching by baseline blood eosinophils and prior exacerbation history	Eligible studies selected from Cochrane review followed by indirect treatment comparison	Significant benefit vs Benralizumab at all eosinophil thresholds (0.55 to 0.66) Vs Reslizumab 0.55 (0.36, 0.85)	No significant differences vs Benralizumab at all eosinophil thresholds. Benralizumab > Reslizumab in those with eosinophils >400 (0.11; 0.01, 0.2)	Phase 2b DREAM study not included. Matches the two key predictive variables
Bateman et al(45)	Dupilumab vs all other biologics	Patients with moderate to severe eosinophilic asthma and an exacerbation history selected from QUEST phase 3 study to match the populations in comparator trials	Systematic review followed by Bucher indirect treatment comparison	vs Benralizumab 0.46 (0.32, 0.67) vs Mepolizumab 0.72 (0.57, 0.92) vs Reslizumab 0.62 (0.48, 0.79) vs Omalizumab 0.73 (0.38, 1.42)	vs Benralizumab 0.12 (0.02, 0.22) vs Mepolizumab 0.08 (-0.08, 0.24) vs Reslizumab 0.08 (-0.02, 0.18) vs Omalizumab 0.06 (-0.04, 0.17)	Could not be fully matched with Mepolizumab because of historical criteria for Mepolizumab trials. Omalizumab comparison was ITT population, with no type-2 biomarker stratification

Table 2

Summary of the indirect treatment comparisons between biological treatments for severe eosinophilic asthma. ACQ = Asthma Control Questionnaire Score (5 or 6 item); AQLQ = Asthma Quality of Life Questionnaire; RCT=randomised controlled trial.

Clinical trial	Sinus 24(36)	Sinus 52(36)	Polyp1 and Polyp 2(12)	Synapse(15)
Population	Adults with bilateral CRSNP and symptoms despite topical CS. Surgery or systemic CS in last 2 years		Adults with corticosteroid refractory CRSNP	Patients with CRSNP with previous surgery and in need of repeat
Intervention	Dupilumab 300 mg subcutaneously every 2 weeks		Omalizumab by subcutaneous injection every 2-4 weeks, dose based on weight and serum IgE	Mepolizumab 100 mg subcutaneously every 4 weeks
Duration	24 weeks	52 weeks	24 weeks	52 weeks
Reduction in nasal polyp score (0-8)	2.06 (baseline 5.6)	1.8 (baseline 6.1)	0.59 to 1.14 (baseline 6.2 and 6.4)	0.73 (baseline 5.4)
Reduction in congestion score (0-3) *reduction in VAS (0-10)	0.89 (baseline 2.3)	0.87 (baseline 2.5)	0.5 to 0.55 (baseline 2.4 and 2.3)	3.14* (baseline 8.9)
Recovery of sense of smell (USPIT 0-40). *VAS (0-10)	10.6 (baseline 14.7)	10.5 (baseline 13.5)	3.8 to 3.9 (baseline 12.8 and 12.8)	-0.37* (baseline 9.6)
Improvement in SNOT 22 (0-110)	21.1 (baseline 48)	17.4 (baseline 50.2)	15 to 16.1 (baseline 59.8 and 59.2)	16.5 (baseline 63.7)
Reduction in need for OCS	74%		62.5%	25% mepolizumab, 37% placebo

Table 3

Summary of phase 3 studies evaluating the effect of biologics on chronic rhinosinusitis and nasal polyposis (CRSNP). Changes are relative to placebo with baseline value for that treatment group also shown. SNOT=sinonasal outcome test; SNOT-22 is a 22 item questionnaire with higher scores indicating worse symptoms. CS=corticosteroids

Considerations	Benralizumab	Mepolizumab	Reslizumab	Omalizumab	Dupilumab
Non-weight-based dosing	++	++	-	-	++
Monthly dosing	++	++	++	+	-
Subcutaneous administration	++	++	-	++	++
At home self-administration / autoinjector	++	++	-	++	++
Predictive biomarker	++	++	++	-	++
Consistent Phase III data	-	++	+	+	++
Real-World Evidence	+	++	+	++	-
Long-term safety and efficacy data	+	++	-	++	++

Efficacy against common comorbidities	+	+	+	+	++
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Table 4

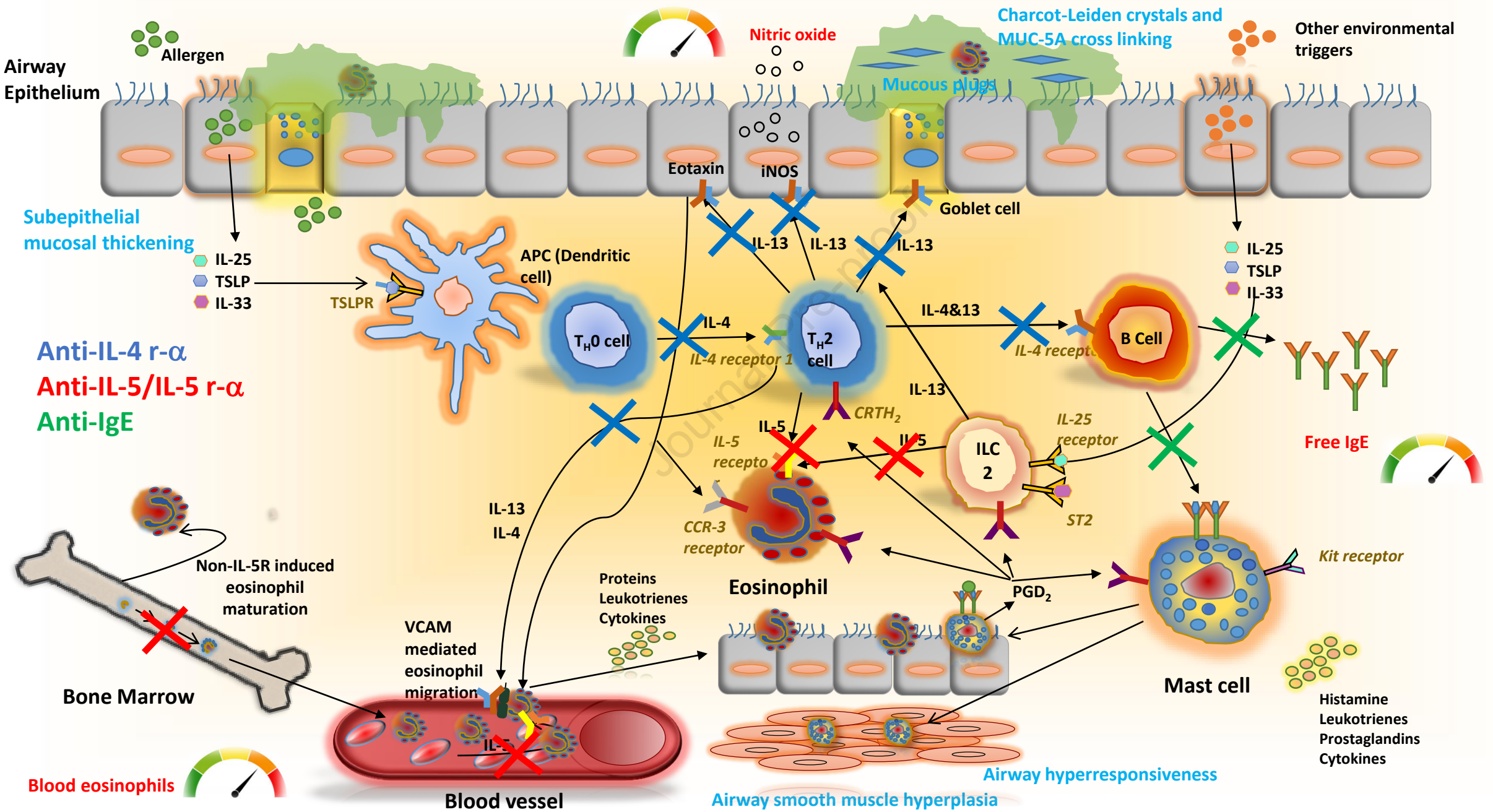
Practical considerations when choosing a biologic to treat moderate-severe type-2 asthma. ++ = succeeds to a large extent; + = some effect; - = no effect

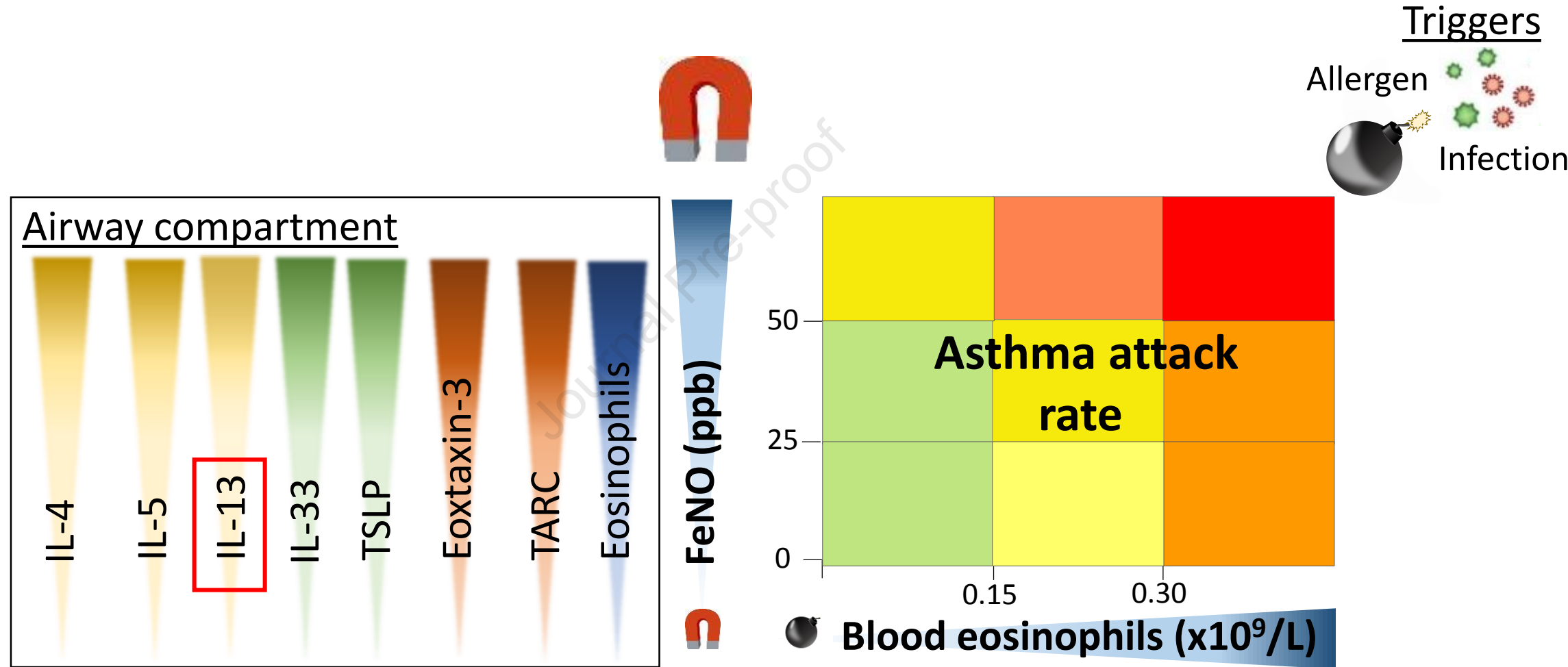
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- Causal mechanism for $\uparrow$ biomarker
- Correlation

Severe asthma with:

- Documented adherence to moderate or high dose or maximum tolerated dose ICS/LABA
- 2 or more exacerbations in the last year and/or regular OCS use

