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Review article

Omalizumab as alternative to chronic use of oral corticosteroids in severe asthma

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ABSTRACT

Systemic/oral corticosteroids (OCS) have been used for decades in the management of acute asthma exacerbations and chronically in patients with uncontrolled severe asthma. However, while OCS are effective at treating acute exacerbations, there is only empirical evidence regarding the efficacy of OCS at reducing the rate of exacerbations. Evidence, although scarce, is suggestive of high exacerbation rates in severe asthma patients even when receiving maintenance treatment with OCS. In addition, use of OCS is associated with undesirable effects. Despite all this, physicians have continued to use OCS for managing severe asthma and acute exacerbation due to the lack of availability of effective alternatives. Fortunately, in the last decade several biologics have been proven safe and effective for patients with uncontrolled severe asthma. This has led to the Global Initiative for Asthma (GINA) recommending the use of biologics, instead of maintenance OCS, in patients with severe asthma (GINA Step 5). These include one biologic targeting immunoglobulin E (IgE) (omalizumab), and different biologics targeting interleukin-5 (IL-5), the IL-5 receptor (IL-5R) or IL-4 receptor α-unit (IL-4R α), including mepolizumab (subcutaneous), reslizumab (intravenous), benralizumab (subcutaneous) and dupilumab (subcutaneous).

Omalizumab for the treatment of severe allergic asthma reduces exacerbations, irrespective of blood eosinophil levels. Anti-IL-5/IL-5R biologics are indicated in patients with severe eosinophilic asthma and repetitive exacerbations, irrespective of the presence or absence of allergy. Recently, an anti-IL4Rα biologic has been approved by the FDA for eosinophilic phenotype or oral corticosteroid-dependent asthma. Finally, physicians should consider using biologics as an alternative to chronic OCS therapy.

1. Introduction

Systemic/oral corticosteroids (OCS) have been a mainstay of severe asthma management. Despite their acknowledged safety risks, the updated Global Initiative for Asthma (GINA 2018) report recommends short-term low-dose OCS for managing exacerbations and as an add-on to maintenance treatment with inhaled corticosteroids (ICS) plus long-acting β_2-agonists (LABA) in severe asthma to prevent exacerbations and for better asthma control [1,2]. However, only empirical data are available to support the efficacy of OCS in exacerbation reduction. Furthermore, a recent 20-year observational study in severe asthma patients showed that those who were OCS-dependent had high mortality (50% of patients died), and had high exacerbation rates [3].

Emerging biologic agents targeting molecular pathways in asthma have shown significant promise in reducing the need for OCS use [4]. Omalizumab, targeting immunoglobulin E (IgE), reduces exacerbations in patients with severe allergic asthma, irrespective of blood eosinophil count [5]. Other biologics targeting specific interleukins (IL), such as anti-IL5 (mepolizumab and reslizumab), anti-IL5 R α (benralizumab) and anti-IL4 Rα (dupilumab) also reduce exacerbations in patients with

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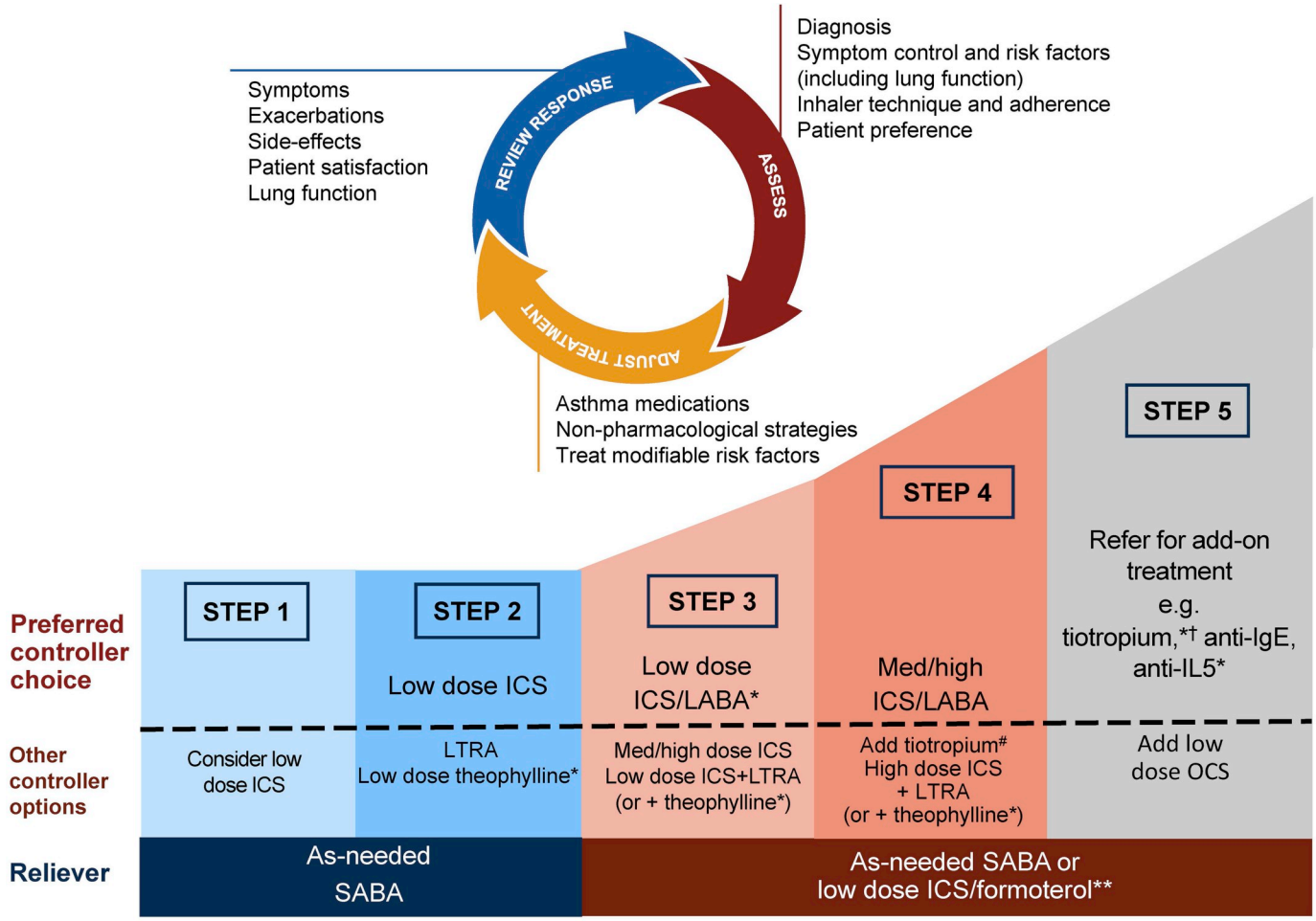

Fig. 1. The Global Initiative for Asthma (GINA) control-based cycle of asthma care and stepwise approach.
*Not for children aged < 12 years; **For children aged 6–11 years, the preferred Step 3 treatment is medium-dose ICS; #For patients prescribed beclomethasone/formoterol or budesonide/formoterol maintenance and reliever therapy; †Tiotropium by mist inhaler is an add-on treatment for patients aged ≥12 years with a history of exacerbations.
Remember to:

- Provide guided self-management education (self-monitoring + written action plan + regular review).
- Treat modifiable risk factors and comorbidities, e.g. smoking, obesity, anxiety, etc.
- Advise about non-pharmacological therapies and strategies, e.g. physical activity, weight loss, avoidance of sensitizers where appropriate.
- Consider stepping up if, uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first.
- Consider SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV_1 is > 70% predicted.
- Consider stepping down if symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.

FEV_1, forced expiratory volume in 1 s; HDM, house dust mite; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL-4, interleukin 5; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroids; SABA, short-acting β_2-agonist; SLIT, sublingual allergy immunotherapy.
Reproduced with permission of the GINA 2018 [1].

severe eosinophilic asthma, without the major safety concerns that overshadow OCS. As the first-line treatment in severe asthma, GINA recommends addition of these biologics and/or long-acting muscarinic antagonists (LAMA) to an ICS and LABA combination [1]. This review focuses on the current treatment approaches to severe asthma, including the burden of systemic corticosteroid-based therapy and the potential role of omalizumab and other biologics in reducing this burden.

2. Management of severe asthma: what guidelines recommend

The primary goal of any asthma treatment is to achieve and maintain overall asthma control through reduction of both symptom severity and risk of future exacerbations [6,7]. GINA [1] advocates a continuous cycle of asthma management (assess – adjust treatment – review response) that incorporates a step-wise approach to pharmacological treatment depending on the level of asthma control and response to treatment (Fig. 1). This step-wise approach aims to control asthma symptoms, minimize future risk of exacerbation, and the use of controller and reliever medications.

In general, ICS is the mainstay of asthma management regardless of the disease severity. Guidelines such as GINA (2018 [1]), National Heart, Lung and Blood Institute (NHLBI, revised 2007 [8]) and the British Thoracic Society (BTS, revised 2016 [9]) recommend the use of OCS in certain circumstances. For example, GINA [1] recommends the use of low-dose OCS for the treatment of severe asthma exacerbations in patients who fail to respond to an increase in reliever and controller medication, deteriorate rapidly or have a history of sudden severe

exacerbations. However, this use is not desirable, as repeated usage of systemic corticosteroid is associated with cumulative systemic adverse events and persistent negative impact on the hypothalamic-pituitary-adrenal (HPA) axis [10]. Nevertheless, it is difficult to avoid systemic corticosteroid use completely as it may be the last option for treatment of acute exacerbations [1,11,12].

Meanwhile, chronic use of OCS as a maintenance therapy should be assessed based on the potential benefits compared to the high risk of adverse events, particularly when safe and effective alternatives are available [13]. If control is not achieved with standard-of–care treatments (high-dose of ICS/LABA and/or LAMA and other controller) for GINA Step 5 patients, four parameters should be assessed before prescribing maintenance OCS or a systemic corticosteroid burst: (i) alternative diagnosis to asthma, (ii) adherence to treatment, (iii) comorbidities, and (iv) continuing exposure to the sensitizing agents [1,14]. Patients with uncontrolled severe asthma should be educated on asthma self-management, and physicians should use action plans and have regular follow-ups with their patients. The patients should also be made aware of the benefits of non-pharmacological management of asthma including exercise, weight loss, avoidance of triggers and smoking cessation, concurrent with pharmacological treatment [1,8,9,15].

Anti-IgE (omalizumab) and IL-5-targeting biologics (mepolizumab, reslizumab and benralizumab) are recommended in the GINA 2018 report as add-on therapy to LABA/ICS for the long-term control of asthma in patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment [1]. Omalizumab and anti-IL-5 biologics may provide an opportunity to reduce the OCS burden in patients with severe allergic asthma and severe eosinophilic asthma, respectively [16–18]. This potential will be discussed in more detail later in this review.

3. Systemic corticosteroid in severe asthma: its use and concerns

Although corticosteroids can be effective at reducing airway inflammation and treating exacerbations, these treatments are associated with numerous adverse reactions (Table 1) [19–22]. In many patients with difficult-to-control asthma (which includes asthma that is uncontrolled due to adherence issues, inappropriate or incorrect use of medicines, environmental triggers or comorbidities), OCS are often prescribed as maintenance therapy [13,23]. Chronic OCS users constitute about 3.5% [24], while intermittent OCS users constitute approximately 40% of the severe asthma population [15]. Hence, chronic and intermittent uses of OCS need to be discussed.

3.1. Chronic use

Chronic use of OCS is not the optimal treatment when safe and effective alternatives are available. Use of OCS suppresses the HPA axis function, with the risk of stress-induced acute adrenal crisis and growth retardation [25]. It inhibits cortisol and corticotropin secretion via the pituitary gland [26,27], increases the risk of cataracts [19,28], and can delay growth and puberty [23]. Although, osteoporosis may be the most concerning adverse effect with OCS use, it can be managed by prophylactic intervention [29–32]. Hypertension, type II diabetes and cataracts are other prominent adverse events [13,33]. Even a small increase in total cumulative OCS dose increases the risk of diabetes [34–36]. OCS use is also associated with renal fluid retention and influences angiotensin II pathways and catecholamine release, which might lead to uncontrolled hypertension and worsening of cardiovascular disease (relative risk found to be 2.56 compared with controls) [37].

Two recent, large, retrospective claims-based analyses found a significant dose–response relationship between long-term use of systemic corticosteroid and the risk of developing related complications in patients with severe asthma [38,39]. In addition, the authors found that this has resulted in increased burden and costs on the healthcare system. Another cross-sectional study of two large UK registries found that 93% of patients with severe asthma had one or more conditions linked to systemic corticosteroid exposure [40] and that regular daily corticosteroid exposure was associated with a measurably greater prevalence of corticosteroid-associated morbidities compared with subjects with severe disease receiving frequent rescue courses [41,42]. High mortality among OCS-treated patients with severe asthma has also been reported [40]. Previous systematic reviews showed that OCS are a common cause of adverse events in heterogeneous patients, even at regular doses; high dose of OCS for a short period, or prolonged use of small dose can have clinical impact. Sullivan et al. [37] showed that intermittent use of OCS (≥4 OCS prescriptions/year was associated with 1.29 times the odds of experiencing a new adverse event within the year. Patients with asthma who were treated with OCS for > 30 days/year have a greater overall risk of possible corticosteroid-related adverse events compared with the patients with no OCS use [43]. Some patients, can develop Cushingoid appearance with chronic administration of prednisone at 5 mg/day dose [44]. It was also observed that the dose response relationship of oral corticosteroids, particularly in relation to fractures showed that of all forms of OCS treatment, the highest doses (approximately > 7 mg/day prednisolone equivalent) were universally found to be associated with the largest incidence of fractures [19].

Table 1
Reported adverse reactions associated with long-term systemic corticosteroid use.

Common (≥1/100[c])	Less common (1/100–1/1000[c])
Adrenal suppression (high doses for prolonged periods)[b]	Aggravation of epilepsy
Anxiety	Aggravation of schizophrenia
Bruising	Corneal or scleral thinning
Behavioral changes (hyperactivity, irritability, and aggression)	Ecchymosis
Candidiasis	Facial erythema
Cataracts	Hypersensitivity reactions (including anaphylaxis)
Cushing's syndrome	Hypokalemia[a]
Depression	Impaired healing
Diabetes[a]	Malaise
Dyspepsia	Menstrual irregularities and amenorrhea
Exacerbation of ophthalmic viral or fungal disease	Muscle weakness
Growth retardation[b]	Papilledema
Headache	Peptic ulceration
Hyperglycemia	Petechia
Hypertension[a]	Sodium and water retention
Increased susceptibility to and severity of infection[a]	Vertebral and long-bone fractures
Leukocytosis	Vertigo
Nausea	
Neutrophilia	
Reduced bone mineral density/ osteoporosis[a]	
Skin atrophy	
Skin thinning[a]	
Suppression of skin test reactions	
Weight gain	

[a] Particularly common adverse effects in elderly patients.
[b] Particularly common in children.
[c] Frequency of cases in corticosteroid-exposed individuals.

3.2. Intermittent use

In severe asthma, intermittent systemic corticosteroid use is generally recommended for managing acute asthma exacerbations [1]. Asthma control and exacerbation reduction are the aims of treatment with all biologics. If we reduce exacerbations, we decrease the

intermittent systemic corticosteroid use. Studies on all biologics have generated solid data in controlling the disease and decreasing its exacerbations. Omalizumab significantly reduced the rate of clinically significant severe asthma exacerbations (26% in the INNOVATE study) in severe allergic asthma [46]. The eXpeRience registry also revealed substantial reductions in clinically significant severe asthma exacerbations after 1 (80.5%) and 2 years (89.9%) of omalizumab treatment [47]. The recently published GINA pocket guide for severe asthma is still recommending omalizumab for severe allergic asthma with positive skin prick testing per specific IgE and total serum IgE and weight within dosage range. It additionally adds as positive predictive factors childhood onset asthma, FeNO ≥20 ppb, allergen driven symptoms and blood eosinophils ≥260 cells/μL. It does not consider separately the overlap group of allergic and eosinophilic severe asthmatic patients, but implies starting first with anti-IL5/anti-IL5R treatment in patients with blood eosinophils ≥300 cells/μL, nasal polyposis, adult onset asthma, more exacerbations in the previous year [48].

4. Corticosteroids: a focus on children

4.1. ICS use

ICS are the cornerstone of care for asthma of all severities; however, use of high-dose ICS in children warrants caution. Pre-pubertal high-dose ICS exposure during the first 1–2 years of treatment has been associated with negative growth outcomes such as decreased adult height, although this is not progressive or cumulative [49]. Indeed, the use of high-dose ICS may be avoided by adding-on an alternative treatment like registered biologics, as recommended by GINA [1] and as shown in some studies [50]. We will not assess the benefits and risks of high-dose ICS in this review.

4.2. OCS use

Recent reviews of asthma prescribing patterns show that OCS are widely prescribed in children [51]. In a 2015, US-based study of 69,056 children with asthma, 42.1% children had ≥1 OCS prescription, 9.9% had ≥2 OCS prescriptions, and 3.3% had ≥3 OCS prescriptions [52]. A separate study in US children reported that patients with non-severe (N = 624,219) and severe asthma (N = 34,950), 23% and 64% of patients, respectively, were prescribed OCS [41]. A Dutch study found a higher OCS prescription incidence rate in early childhood (0–5 years) compared with school age children (6–10 years) [51]. In addition, socioeconomic status is a factor: poor children seem to receive up to 2.55 times more systemic corticosteroid prescriptions than urban children who are not poor [53].

5. Benefits of OCS in the pediatric asthma population is controversial

Few studies have examined the therapeutic benefit of using systemic corticosteroid and the findings are conflicting. A recent review (2016) of 11 studies examined the use of OCS in the treatment of recurrent wheezing in infants, toddlers, and preschool children. When the analysis was stratified by trial setting, differences in benefits and risks of OCS use were identified; among the emergency department studies, children who received OCS had a 42% lower risk of hospitalization, indicating a therapeutic benefit for OCS. However, among the outpatient studies, children who received OCS had a > 2-fold higher risk of hospitalization compared with those who received placebo [54]. Even parent-initiated OCS use in an asthma exacerbation failed to improve outcomes such as emergency department visits, hospital admissions, unscheduled medical reviews, symptom scores, bronchodilator use, parent and patient impressions, physician assessment, or days lost from work or school; rather, it increased hospitalizations among those receiving OCS [55].

Among preschool children, OCS use for acute exacerbations in asthma is well documented [37,56–60], but as explained above, there is a related cumulative negative burden on both the current and future health of patients with asthma from OCS exposure that is independent of the dose and duration of treatment [37]. As such, so-called OCS-sparing strategies that reduce the burden of OCS use in patients with asthma are likely to improve patient outcomes by reducing the risks associated with OCS use [37].

6. Biologics: an alternative to systemic corticosteroids in severe asthma

A few biologics are currently licensed for use in severe asthma but are often indicated for use in specific asthma phenotypes. The GINA report recommends use of biologics (anti-IgE, anti-IL-5) as preferred controller options for Step 5 patients before the use of OCS [1]. Anti-IgE therapy (omalizumab) is recommended for adult patients and children aged ≥6 years with moderate or severe *allergic* asthma that is uncontrolled on GINA Step 4 treatments before the use of OCS (Fig. 1) [1,47]. This recommendation is given in accordance with the GINA 'Evidence A' category, which reflects the large amount of data available [1]. In severe allergic asthma, omalizumab has been studied for more than 15 years in both randomized controlled and observational clinical trials that showed that omalizumab provides clinical benefits and reduces OCS use in patients with severe allergic asthma [1,18].

In addition to anti-IgE treatment, treatments targeting the IL-5 pathway, such as mepolizumab, reslizumab and benralizumab, are included in the latest GINA update and dupilumab was recently approved by the FDA. These biologics are recommended as add-on therapy for patients with severe eosinophilic asthma that is uncontrolled on Step 4 therapy (Evidence B – based on the results of randomized clinical trials [RCTs] and meta-analyses) [48]. Omalizumab, mepolizumab, benralizumab and dupilumab have demonstrated OCS-sparing capacity. Omalizumab [17,60–65] demonstrated its OCS sparing effectiveness in severe allergic asthma, mostly in real-world evidence (RWE) observational studies across various patient population spanning more than 15 years and some RCTs [46,66–69]. Whereas, relatively newer mepolizumab [16], benralizumab [70] and new dupilumab [71] demonstrated OCS sparing effect in RCTs in order to include OCS sparing effect in their label. Outcomes from key clinical trials involving omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab are summarized in Table 2. Current evidence suggests that these anti-IL-5 treatments are safe and effective in the treatment of severe eosinophilic asthma [1,72–81]. However, further prospective studies are warranted to evaluate efficacy (mainly related to eosinophil reduction and depletion) and safety of these biologics in children [8 1]. Table 3 summarizes, within the limitations of existing label information at the time of writing this paper, the attributes of the biologics currently licensed for use in patients with severe asthma.

7. Omalizumab in pediatric asthma

Among biologics, omalizumab is registered for use in children aged ≥6 years with severe allergic asthma [1]. Deschildre et al. and Rottem et al. demonstrated an OCS-sparing effect of omalizumab, an improvement in lung function and health status and reduced exacerbations, while showing a good safety profile [61,62]. Hence, chronic and intermittent (related to exacerbations) OCS exposure is reduced. In addition to control of exacerbations in patients with severe asthma, the PROSE study showed that omalizumab prevents seasonal autumn viral-induced exacerbations (needing systemic corticosteroid) by blocking the dendritic cell (DC) IgE, the secretion of interferons by DC, which is key against viral infection. When giving a short course of omalizumab to children before school entry, we observed > 80% reduction in exacerbations in children who previously exacerbated [82].

A number of RWE studies have observed steroid-sparing effects with

Table 2
Main findings from key studies that aimed to reduce the use of oral corticosteroids (OCS).

Citation	Design	Main findings
Omalizumab		
Berger et al. [91]	28-week, double-blind, RCT with a 24-week open-label extension in children (N = 225) with moderate-to-severe allergic asthma requiring ICS	There was a substantial reduction in ICS use in the double-blind period that was maintained in the open-label phase Almost all patients who withdrew ICS at the end of the core study remained ICS-free at the end of the extension period
Teach et al. [82]	Three-arm, randomized, double-blind, double placebo controlled, multicenter clinical trial in asthmatic children aged ≥6 years with ≥1 recent exacerbation	A subgroup analysis from the PROSE study showed that omalizumab was significantly more efficacious than both placebo and ICS burst in patients with an exacerbation during the run-in phase
Deschildre et al. [61]	One-year observational survey of atopic children and adolescents (N = 104) with severe allergic asthma who were given omalizumab as an add-on therapy to high level maintenance treatment	Over the year on treatment, a 30% reduction in ICS dose was reported ($P < 0.0001$).
Brodlie et al. [17]	Interventional study in 34 children with severe asthma receiving maintenance oral prednisolone	There was a median daily prednisolone dose reduction from 20 mg to 5 mg ($P < 0.0001$), including 7 children who stopped taking prednisolone completely
Rodrigo et al. [100]	Systematic review examined 8 RCTs (3429 participants), which compared subcutaneous omalizumab with placebo as an add-on to corticosteroids (inhaled or oral) in patients with allergic asthma. Six studies were in adults and adolescents (aged ≥12 years) and two were in children (aged < 12 years)	Compared with placebo, omalizumab resulted in significantly fewer asthma exacerbations (RR 0.57, 95% CI 0.48 to 0.66, NNTB = 10, 95% CI 7 to 13). Omalizumab significantly reduced asthma exacerbations per patient (WMD −0.19, 95% CI −0.23 to −0.14; eight RCTs), hospitalization rates (RR 0.44, 95% CI 0.23 to 0.83; 5 RCTs), inhaled or OCS dose (more than 50% dose reduction RR 1.34, 95% CI 1.23 to 1.46; 4 RCTs) and steroid use (complete withdrawal RR 1.80, 95% CI 1.42 to 2.28; 4 RCTs)
Molimard et al. [65]	Real-world evidence study assessing prescriptions of omalizumab for > 16 weeks by French and German clinicians to patients with severe persistent allergic asthma (N = 346)	Following omalizumab therapy, 50.6% patients on OCS at baseline reduced/stopped OCS dose at the time of data collection; 20.5% stopped and 30.1% reduced OCS. In all patients receiving maintenance OCS at baseline, mean reduction from baseline in daily OCS dose was 29.6% (7.1 mg prednisolone). In patients who reduced/stopped maintenance OCS, mean reduction from baseline in daily OCS dose was 74.3% (15.4 mg prednisolone).
Siergiejko et al. [63]	Randomized, open-label, placebo-controlled trial of omalizumab added to optimized asthma therapy, compared with standard therapy alone over 34 weeks (N = 82)	Change from baseline in mean maintenance OCS dose at the end of the study was significantly greater in the omalizumab-treated group compared with the standard therapy group (mean OCS dose at baseline [13.1 mg] vs at Week 32 [8.4 mg]; change from baseline, −45%; $P = 0.002$). Significantly more patients (n = 59) treated with omalizumab reduced or stopped OCS use at Week 32
Rottern et al. [62]	Small study in a real-life setting in Israel that compared use of OCS in patients taking omalizumab with those taking placebo (N = 33)	The number of patients who used OCS significantly decreased for those receiving omalizumab therapy (84.8% vs 57.6%, $P < 0.003$), as did the median dosage of OCS for 33 patients (753 mg vs 662 mg; $P < 0.002$)
Lafeuille et al. [64]	Retrospective cohort study of patients (N = 644) with uncontrolled asthma based on a US health insurance claims database	Data showed 53.3% of those who initiated omalizumab therapy were able to reduce their OCS use
Braunstahl et al.– the eXpeRience registry [47]	2-year multinational, observational study of 943 patients with uncontrolled allergic asthma who were taking omalizumab, 263 of whom were also receiving maintenance OCS therapy	The proportion of patients (n = 131) who had maintenance OCS therapy was lower at Month 24 (14.2%) compared with Month 12 (16.1%) and baseline (28.6%). The mean total daily OCS dose (prednisolone equivalent) decreased between baseline (15.5 mg) and Month 12 (7.7 mg), and continued to decrease between Months 12 and 24 (5.8 mg)
Mepolizumab		
Nair et al. [101]	Randomized, double-blind 26-week trial involving 20 patients with persistent airway eosinophilia and symptoms despite prednisone treatment. Patients received monthly intravenous infusions of either mepolizumab (750 mg) or placebo	Patients receiving mepolizumab were able to reduce their prednisone dose by a mean (± SD) of 83.8 ± 33.4% of their maximum possible dose, as compared with 47.7 ± 40.5% in the placebo group ($P = 0.04$). The mean dose of prednisone was reduced from 11.9 to 3.9 mg in the mepolizumab group and from 10.7 to 6.4 mg in the placebo group (median reduction in the two groups, from 10 to 5 mg) ($P = 0.11$)
Bel et al. [16]	Placebo-controlled, double-blind, randomized study of patients (N = 135) with severe eosinophilic asthma who had at least a 6-month history of systemic corticosteroid maintenance treatment prior to study initiation	In the pre-specified primary outcome, more patients in the mepolizumab group than in the placebo group had a reduction of 90–100% in the OCS dose (23% vs 11%) and a reduction of 70 to less than 90% (17% vs 8%) during Weeks 20–24 of the study In the placebo group, 56% patients had no reduction in OCS dose, had a lack of asthma control, or withdrew from the study, than patients in the mepolizumab group (36%). Further analyses of these data show an overall odds ratio for a reduction in the OCS dose in the mepolizumab group was 2.39 (95% CI, 1.25 to 4.56; $P = 0.008$)
Benralizumab		
Nair et al. [71]	28-week randomized, double-blind, parallel-group, placebo-controlled trial in severe asthmatic patients (N = 220) who had been treated continuously with oral glucocorticoids for 6 months or more before enrollment and were receiving oral prednisone or prednisolone at the trial entry	The two benralizumab dosing regimens significantly reduced the median final OCS dose from baseline by 75%, compared with a reduction of 25% in the OCS doses in the placebo group ($P < 0.001$ for both comparisons). The odds of a reduction in the oral glucocorticoid dose were more than 4 times as high with benralizumab as with placebo. Benralizumab administered every 4 and 8 weeks resulted in an annual asthma exacerbation rate by 55% and 70%, respectively, lower than the rate with placebo.
Dupilumab		

(*continued on next page*)

Table 2 (*continued*)

Citation	Design	Main findings
Rabe et al. [72]	24-week randomized, double-blind, parallel-group, placebo-controlled trial in patients with steroid-dependent severe asthma (N = 210)	Compared with placebo, dupilumab reduced 70% OCS dose while decreasing the rate of severe exacerbations and increasing the FEV_1

CI, confidence interval; ICS, inhaled corticosteroid; OCS, oral corticosteroid; NNTB, number needed to treat for benefit; RR, risk ratio; WMD, weighted mean difference.

omalizumab in severe allergic asthma (up to 25 mg/day reduction) [16,17,47,61–64,83–97]. Also, RCTs like EXALT [62], Study 011 [68], INNOVATE [46], and ETOPA [69] evaluated OCS sparing effect of omalizumab. If at 4 months of treatment there is no response (global evaluation of treatment effectiveness [GETE] score) [98], omalizumab should be stopped following the early stopping rule. If the blood eosinophils are high (the new GINA pocket guide suggests blood eosinophils $\geq$300/μL) in adolescents older than 12 years, anti-IL-5 biologics (mepolizumab, benralizumab) targeting eosinophilic asthma should be initiated [45,98] and the response should be assessed after four months [48]. Nevertheless, treatment with any biologics are subjected to patients' allergic phenotype, in terms of IgE and/or blood eosinophil levels and cannot be distinguished as first-line or second-line therapies [99].

8. Other alternatives to systemic corticosteroid

Apart from anti-IgE, anti-IL-5, anti-IL5 R and recently approved anti-IL-4Rα [102] therapies and several other treatments that may also represent OCS-sparing options for patients with severe asthma are in development. Those that have successfully reached Phase II and Phase III clinical trials include biologic agent targeting anti-thymic stromal lymphopoietin (TSLP, tezepelumab) [103], and non-biologic agents, such as the prostaglandin receptor D_2 (DP2) antagonist, fevipiprant [104] Fig. 2 shows the key immunological pathways of asthma together with the targets for existing and new treatments.

9. Severe asthma management: the CARE pathway

For patients who are already receiving OCS, use of biologics may allow the OCS dose to be gradually reduced and eventually withdrawn [11]. In severe allergic asthma, following the integrated care pathway guidance on the choice of biologics proposed by Bousquet et al. [45] treatment could start with omalizumab and response must be assessed at 4 months of treatment (Fig. 3). This guidance in the integrated care pathway is not based on effectiveness, since the other biologics are also proven effective, but in 15 years of safety data, age (could be given in children) and data that in case of [45] unresponsiveness to omalizumab, anti-IL5 treatment could also be initiated directly [105]. However, the new GINA pocket guide suggests to also considering starting first with anti-IL5/anti-IL5R treatment if blood eosinophils $\geq$300/μL, having in mind that nasal polyposis, adult onset asthma, more exacerbations the previous year and higher blood eosinophils could predict responsiveness which should be assessed in four months [48,106]. Our goal should be to minimize OCS misuse in patients with severe uncontrolled asthma and help assist physicians in determining the most appropriate biologic to help the patient control their asthma.

10. What if biologics are not effective?

For patients who do not respond to biologics, high-dose and/or long-term corticosteroid treatment will be required to effectively control their asthma, as per guidelines. Although, OCS is widely used in T2 inflammation, effectiveness of OCS in non-type2 asthma is unclear. A recent study in children difficult asthma showed comparable efficacy of OCS in terms of improvement in lung function, irrespective of sputum eosinophils levels [107]. In these instances, physicians will need to consider the potential for unwanted adverse effects and attempt to minimize exposure to steroids, especially in female, children, adolescent and elderly patients who are more at risk of adverse effects. To minimize the potential for unwanted adverse effects, the lowest effective dose of OCS should be administered for the minimum amount of time to achieve control [23,108]. Therefore after avoiding exposures (i.e. tobacco smoke) and adding tiotropium or macrolide (if not already tried), we should consider add-on low dose OCS, but implement strategies to minimize side-effects [48]. Bronchial thermoplasty (BT) may also be an option, but is recommended only in the context of a systematic registry or a clinical study [15]. Previous findings showed that BT was associated with long-term blood eosinophil suppression [109] and reduction in OCS dose [110] in patients with uncontrolled asthma. Hence, BT may be an option for asthmatics inadequately controlled by biologic therapy [110].

If all treatments are unsuccessful, where possible, patients could be included in ongoing clinical studies of new severe asthma medications, like anti-TSLP (tezepelumab [103], Phase II completed; ClinicalTrials.gov Identifier: NCT03347279), anti-IL-33 [111], anti-IL-4 and or fevipiprant (Phase III ongoing), a DP_2 antagonist [104].

11. Conclusions

Although OCS therapy is an option in the treatment guidelines for patients with severe asthma, the consequences of chronic use, or even systemic corticosteroid bursts, should be considered and balanced with the therapeutic efficacy of these drugs. Indeed, as a lot is already known about the adverse effects of OCS, their use in patients with severe asthma may be considered inappropriate. Biologics offer a well-tolerated and effective solution to the problems observed with systemic corticosteroid use in specific phenotypes of severe asthma and offer many benefits. Hence, biologics such as omalizumab, and anti-IL-5 targeting biologics should be considered as alternatives to OCS in well-selected patients with uncontrolled severe asthma.

Omalizumab has 15 years of clinical experience and safety data in severe allergic asthma, and more than 800,000 patient-years of exposure [18], with a clear allergic indication in terms of positive skin test or in vitro reactivity to a perennial aeroallergen and in addition the serum total IgE levels in the range of 30–700 IU/mL (in the US) or $\geq$30 to $\leq$1500 IU/mL (Europe) in adults and children $\geq$12 years and < 1300 IU/mL for children $\geq$6 years. It can reduce exacerbations, control the disease and reduce the OCS burden Therefore, it may be offered as the first choice in patients with severe allergic asthma, as shown by the integrated clinical pathway guidance [45]. Omalizumab also has a well-defined early stopping rule in four months if the response to treatment is not good according to GETE. Our approach is not based on effectiveness, as IL-5 targeting biologics have been also proved effective in reducing exacerbations.

Physicians rightly are very conscious of the danger of systemic corticosteroid overuse in patients with severe asthma. Considering the existing data on efficacy, real-life effectiveness and safety of several biologics in severe asthma, physicians should consider these treatments, and either prescribe the appropriate biologic therapy or alternatively, refer patients with corticosteroid-dependent severe asthma to a specialist.

Table 3
Attributes of biologics currently licensed for the treatment of severe asthma.

Attributes for novel treatment	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Mechanism of action known	IgE	IL-5	IL-5	IL-5Rα	IL-4Rα
Biomarker mechanistic relevance	IgE in allergic and viral inflammation	IL-5 and eosinophil levels in eosinophilic asthma	IL-5 and eosinophil levels in eosinophilic asthma	IL-5 and eosinophil levels in eosinophilic asthma	IL-4 and IL13 signaling and eosinophil levels in eosinophilic asthma
Personalized dosing	YES; Level of serum total IgE and body weight	NO	YES; body weight	NO	NO
Dose[†]	75–375 mg s.c. every 2–4 weeks	100 mg s.c. every 4 weeks	3 mg/kg i.v. every 4 weeks over 20–50 min	30 mg every 4 weeks or every 8 weeks; first three doses every 4 week	400/600 mg s.c. (initial dose). Followed by 200/300 mg every 2 weeks
Indication	Severe allergic asthma adult patients and children aged 6 years and older	Severe asthma patients aged 12 years and older, and with an eosinophilic phenotype	Severe asthma patients aged 18 years and older, and with an eosinophilic phenotype	Severe asthma patients with an eosinophilic phenotype, age group not decided yet[b]	Moderate-to-severe asthma patients aged 12 years and older, and with an eosinophilic phenotype
Large RCTs[a] (Based on the number of patients)	+ + +	+ +	–	+	+
Real-life studies confirming RCTs[a]	+ + +	+ +	–	–	–
Pharmacoeconomic evaluation[a]	+ + +	+ +	–	N/A	N/A
Early stopping rule	Yes (16 weeks)	NO	NO	N/A	N/A
Commonly reported adverse reactions	Adult patients and children aged ≥6 years: arthralgia (8%), pain (general [7%]), leg pain (4%), fatigue (3%), dizziness (3%), fracture (2%), arm pain (2%), pruritus (2%), dermatitis (2%), earache (2%) Children aged 6 to < 12 years: nasopharyngitis, headache, pyrexia, upper abdominal pain, pharyngitis streptococcal, otitis media, viral gastroenteritis, arthropod bite, epistaxis	Adult patients and children aged ≥12 years: headache (19%), injection site reaction (8%), back pain (5%), fatigue (5%), influenza (3%), urinary tract infection (3%), abdominal pain upper (3%), pruritus (3%), eczema (3%), muscle spasms (3%)	Adult patients aged ≥18 years: oropharyngeal pain (2.6%), musculoskeletal reactions on day of infusion, including musculoskeletal chest pain, neck pain, muscle spasm, extremity pain, muscle fatigue, and musculoskeletal pain (2.2%), myalgia (1%)	Patients aged 12–75 years who weighed at least 40 kg:[c] Worsening asthma (13%), nasopharyngitis (12%), upper respiratory tract infection (10%), headache (8%) injection-site reactions (4%), hypersensitivity adverse events (3%)	Patients aged ≥12 years:[c] oropharyngeal pain, eosinophilia, eye problem, viral upper respiratory tract infection (18%), Injection-site reaction (17%), upper respiratory tract infection (12%), bronchitis (11%), headache (7%), influenza (6%), back pain (4%), urinary tract infection (3%)

IgE,immunoglobulin E; IL-5, Interleukin 5, s.c., subcutaneous; i.v., intravenous; LABA, long-acting β2-agonist; ICS, inhaled corticosteroid.

[a] A positive (+) or negative (−) symbol indicates either studies on this drug or a lack of studies on this treatment.

[b] Dosage and administration scheme used in Phase III clinical trials.

[c] Benralizumab and dupilumab safety profile based on clinical trials data.

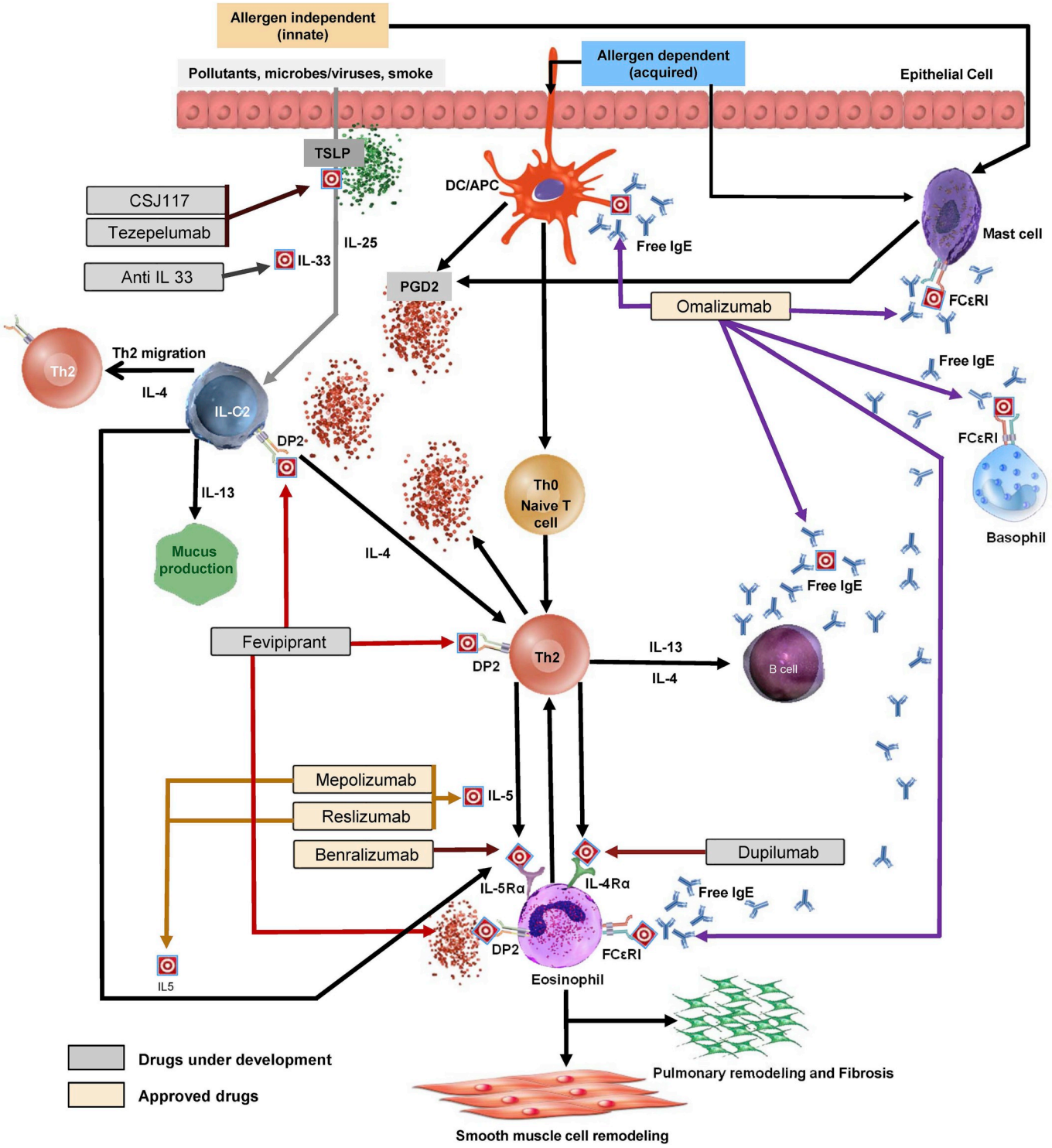

Fig. 2. Targets for key therapeutics in immunological pathways of severe asthma
APC, antigen presenting cell; DC, dendritic cell; DP_2,prostaglandin D receptor 2; FCεRII, FCε receptor II; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cells; PGD2, prostaglandin D2; TH, T-helper cell; TSLP, thymic stromal lymphopoietin.

Authors contributions

All authors designed the concept, collected, assembled, and interpreted the data, drafted the manuscript, revised and approved its final version.

Declaration of interest

PK has completed an ERS fellowship with Novartis Pharma AG and has received honoraria for lectures and consultancies from GSK, Chiesi, Boehringer Ingelheim, Menari, Pfizer. **RB** reports personal fees from AstraZeneca, Chiesi, GSK and Teva, and grants and personal fees from Boehringer Ingelheim, Novartis and Roche. **GB** has within the last 5 years received honoraria for lectures or advisory boards from

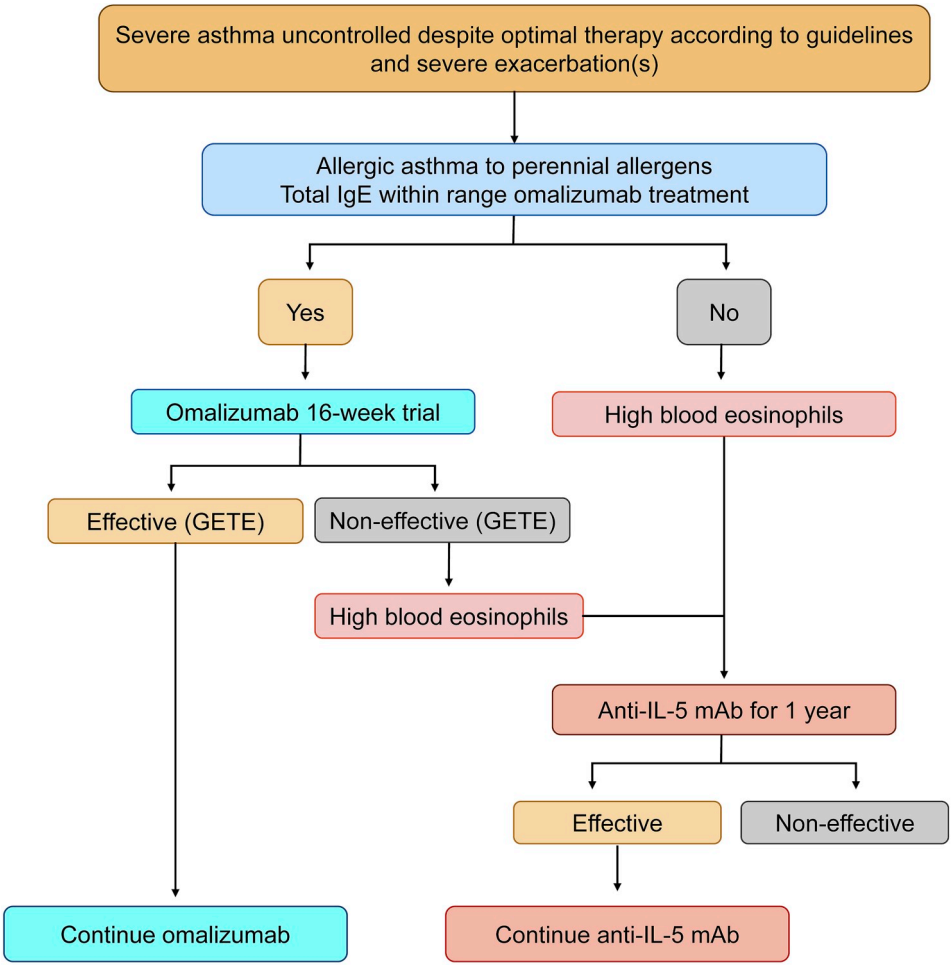

Fig. 3. Care pathways for biologics in severe asthma.
GETE, global evaluation of treatment effectiveness; Ig, immunoglobulin; IL: interleukin; mAb: monoclonal antibody. Reproduced with permission of the © ERS 2018 [45].

AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Sanofi, Teva, and Zambon. **PP** and **RM** are employees and shareholders of Novartis. **UW** has received honoraria for lectures and consultancies from GSK, AstraZeneca, Merck, Novartis, Schering-Plough Corporation, Allergopharma, Stallergenes, Phadia AB and Hitachi. **JB** has received personal fees for being on the scientific and advisory board for Almirall, Meda, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach; and has received lecture fees from Almirall, AstraZeneca, Chiesi, GSK, Meda, Menarini, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach.

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