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Conflict of Interest

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Omalizumab and unmet needs in severe asthma and allergic comorbidities in Japanese children

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ABSTRACT

Childhood asthma is one condition within a family of allergic diseases, which includes allergic rhinitis, atopic dermatitis, and food allergy, among others. Omalizumab is an anti-IgE antibody therapy that was approved in Japan for children with asthma and added to the Japanese pediatric asthma guidelines in 2017. This review highlights the Japanese clinical perspectives in pediatric allergic asthma, and consideration for allergic comorbidities, and reflects on omalizumab clinical trials in progress to present comprehensive future opportunities.

Keywords: Biologicals; Therapeutic guidelines; Japan; Omalizumab; Pediatric asthma

INTRODUCTION

Epidemiology of childhood asthma in Japan

Asthma is the most common noncommunicable disease in children worldwide [1, 2]. The prevalence of pediatric asthma in Japan after the year 2000 has ranged from 3.6% to 19.9%, depending on the age group and region studied [3-5]. Of all children with asthma in Japan, nearly 50% have persistent disease, and 20%–30% have moderate to severe asthma [6]. From the perspective of wheezing, almost 20% of preadolescent children in Japan had wheezing symptoms, among whom 17% had severe wheezing [7, 8]. A Japanese survey found that 14.6% of children aged 6–11 years had uncontrolled asthma [9]. Pediatric asthma mortality (in patients younger than 19 years) in Japan remains below 10 cases per year on average, and has improved since the 1980s [5, 10]. In 2017, asthma deaths in Japanese children reached a record low, with zero cases for the year.

Clinical perspectives in pediatric asthma

Early onset allergic asthma is the most commonly observed phenotype in children. ‘Early onset’ refers to the initial presentation of asthma before age 12 years, although typically 95% of childhood cases will occur before 6 years of age [11]. Diagnosing allergy is of high clinical importance, because aeroallergens are one of the most common (and potentially preventable) precipitants for asthma symptoms in susceptible children. More than 90% of children with asthma have underlying allergies confirmed by immunoglobulin E (IgE) mediated aeroallergen sensitivity [12]. Predictors of childhood asthma include intrinsic (genetic) and

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extrinsic (environmental) risk factors. The intrinsic factors are male gender, race, ethnicity, personal and parental history of atopy, airway hyper-reactivity and recently identified polymorphisms in various genes (for example, those encoding epithelial membrane barriers and oxidative stress proteins) [13, 14]. Extrinsic influences on asthma risk occur through direct insults and/or epigenetic changes, and these include environmental tobacco smoke, air pollution, and early life exposures to microbes and aeroallergens [15, 16]. The likelihood that a child may outgrow asthma varies from 14%–75% [17, 18] and childhood variables associated with persistent asthma into adulthood include female gender, diminished lung function, severe disease at onset, and atopy (indoor allergen exposure increased the risk of persistent asthma by 3 fold) [18, 19].

Managing trigger avoidance is fundamental to asthma care, though in some cases causal relationships between asthma and its triggers may be challenging to confirm [11]. Viral respiratory infections, irrespective of phenotype, are another frequent trigger for asthma exacerbation and partly explain seasonal variations in asthma flares.

Regarding the severe asthma phenotype, atopy is a central factor in childhood asthma pathology according to the Severe Asthma Research Program (SARP) and Unbiased BIOMarkers in PREDiction of respiratory disease outcomes (U-BIOPRED) studies [20-22]. In the SARP pediatric cohort, 4 distinct clusters were identified, and evidence of allergic sensitivity was shared by all clusters. The vast majority of children with severe preschool wheeze or severe asthma in U-BIOPRED were also atopic. The phenotypic complexity seen in adults with severe asthma is not appreciable in children, simply childhood asthma regardless of disease severity appears to be allergic in nature.

Another relevant consideration in children with severe asthma relates to corticosteroid exposure. Approximately 1%–3% of Japanese children with physician diagnosed asthma receive oral corticosteroids (OCS) [6] and 3%–5% of children internationally have steroid-resistant asthma [23, 24]. Adverse effects are dose dependent and children using high-dose ICS and OCS suffer the most [25]. Chronic steroid exposure for asthma increases risk (in a dose-dependent manner) for adrenal insufficiency [26], although rare, and growth deceleration uniquely more in children than adults [27-29].

Poorly controlled childhood asthma manifests as deficits in daily activities, sleeping patterns, academic performance, social development, family dynamics, and longitudinal lung health; and also imposes substantial socioeconomic burden [30, 31]. Children with asthma were higher utilizers of medications and unplanned health care (emergency visits, hospitalizations, oral steroid bursts, and intubation) compared proportionally to adults with asthma [32]. Unmet needs in childhood asthma are evident for those suffering from persistent and/or poorly controlled disease.

Comorbidities in pediatric allergic asthma

Allergic rhinitis and asthma are the most common inflammatory conditions of the airways and occur concomitantly in most children. Asthma and rhinitis are strongly associated, such that rhinitis has become a predictor of asthma among young patients [33-35]. Few large-scale studies have investigated the comorbidity of asthma and allergic rhinitis in children [36]. A systematic review by Boulay et al. [33], suggested that asthma control in children is affected by allergic rhinitis and the intensity and duration of rhinitis is correlated with the development and remission of asthma. Comorbid allergic rhinitis was a significant risk for

uncontrolled asthma in Japanese children of age 6 to 11 years [9]. International Study of Asthma and Allergies in Childhood worldwide study (1994–1997) found that 15%–40% of asthmatic children had a lifetime diagnosis of allergic rhinitis [37]. In Asian studies, between 36.0%–64.3% of asthmatic children were diagnosed allergic rhinitis [38, 39]. Broadly, childhood asthma worldwide has been associated with comorbidities such as allergic and vasomotor rhinitis, conjunctivitis, sinusitis, pneumonia, atopic dermatitis, eosinophilic esophagitis, obesity, vocal cord dysfunction, gastro-esophageal reflux, food allergy, cardiovascular disease, and depressive disorders [40–44]. Allergic conjunctivitis is also found to be closely associated with asthma and allergic rhinitis [39]. In a study by Heck et al. [45], high probability of allergic comorbidities such as allergic rhinitis and allergic conjunctivitis coexisted with allergic asthma in patients of age <18 years in Germany with higher prevalence in males. Food allergy is another comorbidity with prevalence of 20.7 and 32.7% in children with asthma from French and Chinese cohorts, respectively [46]. In the U-BIOPRED study, the majority of school-aged children with asthma had a diagnosis of hay fever, eczema, and allergic rhinitis [21]. Sinusitis and gastroesophageal reflux disease were significantly associated with exacerbation frequency of asthma across age groups in the SARP-3 cohort [47]. A prospective cohort study in children from 12 European birth cohort studies participating in MeDALL (Mechanisms of the Development of ALLergy) reported an absolute excess of specified comorbidities such as eczema, rhinitis, and asthma as 1.6% and 2.2% in children of age 4 years and 8 years, respectively. Children with comorbidities (eczema, rhinitis, and asthma) at 4 years had an increased risk of having sustained comorbidities at 8 years, suggesting a strong relationship between these diseases [48].

These results indicate a high burden of allergic comorbidities among children with asthma. In adults, rhinitis, sinusitis, food allergy and reflux are risk factors for poor asthma control [43, 49]. However, the influence of comorbidities on asthma control has received less attention in children than in adults [40] and the exact role comorbidities play in pediatric asthma control is still in debate [23]. Also the premise for improving pediatric severe asthma by treating comorbidities has yet to be confirmed [50].

As evidence continues to emerge on the impact of comorbidities on childhood asthma, the likelihood that comorbidities may impact asthma's clinical expression and contribute to poor asthma control [51, 52] is gaining support. Asthma comorbidities are becoming an important consideration in selecting comprehensive allergic treatment strategies.

Omalizumab for severe pediatric allergic asthma

Omalizumab is an anti-IgE monoclonal antibody that disrupts the inflammatory allergic cascade by preventing allergen-specific IgE from associating with its high affinity FcεRI receptors on mast cells and basophils [53]. Omalizumab improves clinical outcomes for allergic asthma through multiple mechanisms by: reducing the levels of free IgE thereby minimizing receptor stimulation, reducing the expression of FcεRI on effector cells thereby dampening the activation of cellular targets of allergy, and also by restoring plasmacytoid dendritic cell (DC) interferon activity (by preventing IgE crosslinking of plasmacytoid DC FcεRI) and thereby restoring antiviral protection of airway mucosa [54–57]. Omalizumab also reduced production of type 2 inflammatory cytokines by Th2 cells, basophils, and airway smooth muscle cells [58–60]. Interestingly, when compared with the airways of healthy controls, the airways of asthma patients, with or without allergy, showed increased expression of the high affinity IgE receptor [61] and omalizumab treatment in nonatopic patients also effectively suppressed IgE receptor expression [62].

The allergic response is orchestrated by the mediators shown in Fig. 1 [63]. Omalizumab protects against the early and late phases of the allergic reaction [58, 64-67]. The majority of omalizumab-IgE complexes exist as trimers, although the largest complexes are hexamers, and this bulky immune complex size hinders IgE clearance and explains the observed rise in total IgE levels seen during omalizumab therapy [68]. The omalizumab-IgE complexes have long half-lives and can successfully out-compete receptor-bound IgE for allergens, and thus may ameliorate the allergic response for sustained periods of time.

Omalizumab's drug mechanism does not predict an increased risk for anaphylaxis; the drug does not contribute to degranulation of mast cells or basophils because omalizumab neutralizes only free IgE and does not crosslink receptor-bound IgE.

In Japan, three studies (Fig. 2) in children 6 years and older receiving omalizumab for severe allergic asthma demonstrated safety, efficacy, reduced ICS needs, and reduced healthcare costs [69-71]. Omalizumab treatment reduced corticosteroid use across pediatric populations worldwide, lowering the mean dose of ICS and OCS, and occasionally allowing for complete

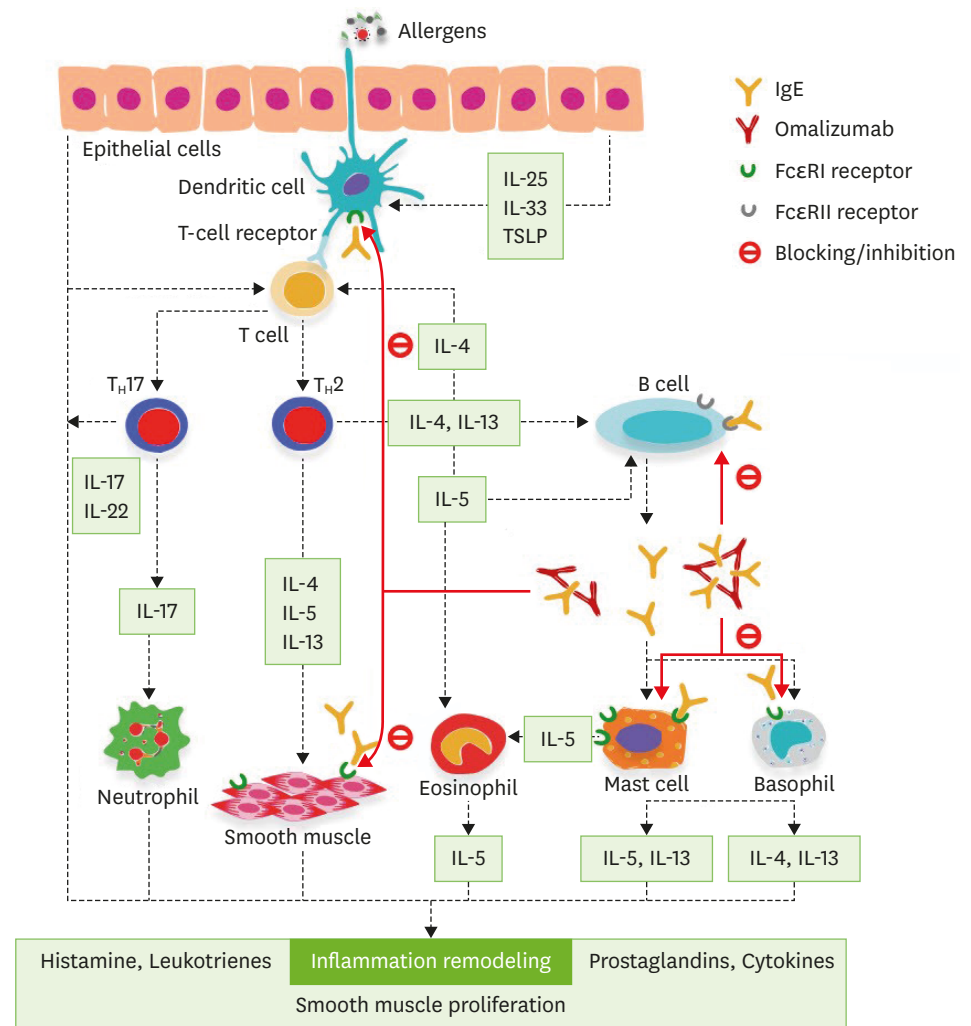


Fig. 1. IgE in allergic asthma inflammation and the role of omalizumab in therapy. IL, interleukin; T_H, T-helper; TSLP, thymic stromal lymphopoietin.

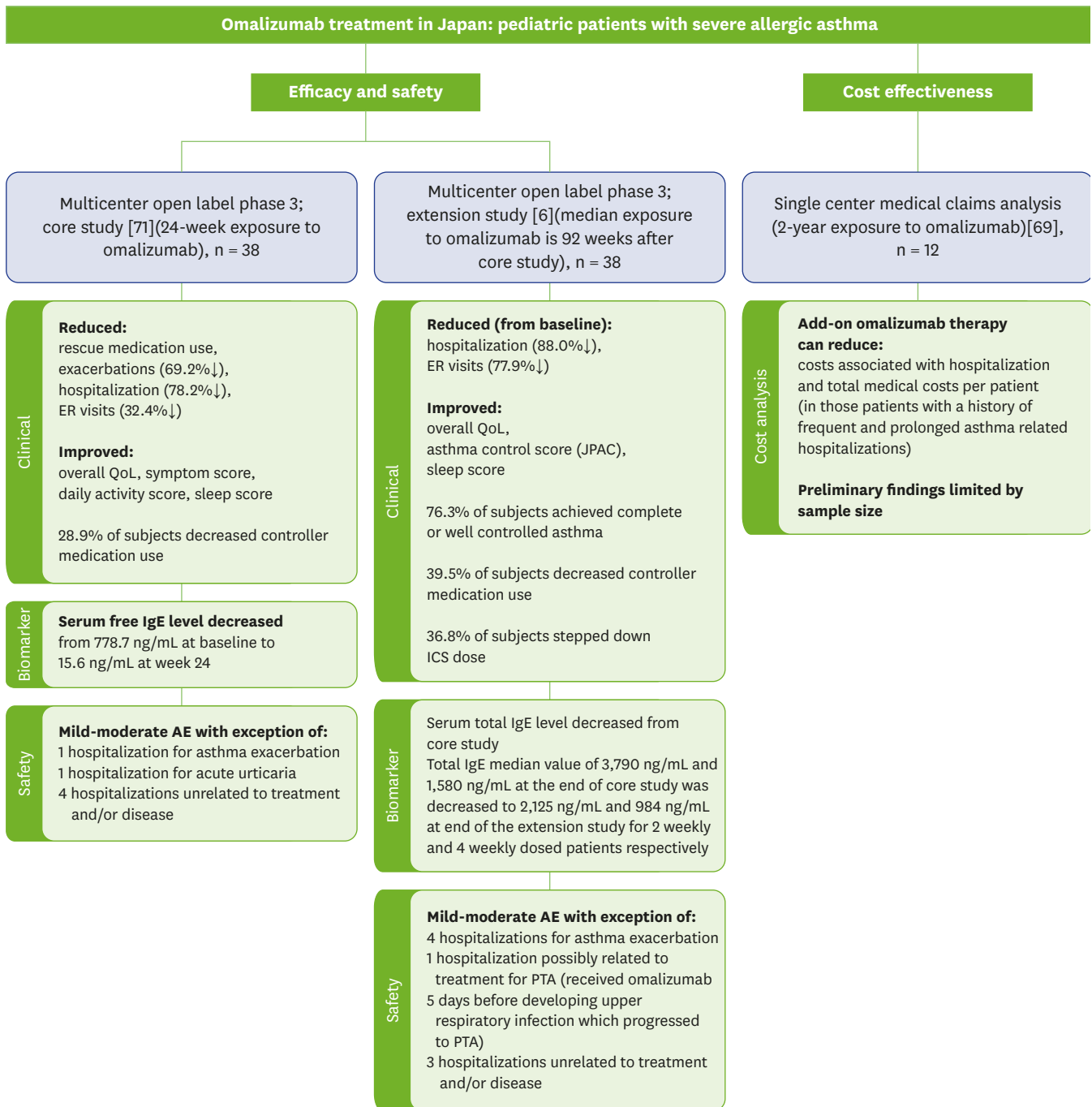


Fig. 2. Studies of omalizumab in Japanese pediatric patients with asthma. AE, adverse events; ER, emergency room; ICS, inhaled corticosteroids; JPAC, Japanese pediatric asthma control test; PTA, peritonsillar abscess; QoL, quality of life.

withdrawal from maintenance OCS [72]. In one study, more than 85% of children treated with omalizumab were able to reduce OCS use, and over 20% completely stopped taking OCS. Additionally, omalizumab treatment for one year or more has resulted in less reliance on ICS up-dosing and rescue medication use [70, 73, 74].

Preventative Omalizumab or Step-up Therapy for Fall Exacerbations (PROSE), a multicenter study including 513 urban children in the United States, showed that omalizumab, in a

prespecified subgroup of children who experienced at least one exacerbation during the run-in period, was more effective than stepping up of ICS dose in preventing exacerbations related to seasonal triggers (allergen-induced and viral respiratory infections) when given preseasonally, 4–6 weeks before return to school [75]. *Ex vivo*, peripheral blood mono-nuclear cells from PROSE study patients receiving omalizumab demonstrated robust interferon-alpha responses to rhinovirus, which correlated directly with fewer seasonal exacerbations [75].

The Japanese pediatric asthma guidelines were revised in November 2017, and omalizumab was added as a recommendation for Japanese children 6 years and older in Step 4 (Global Initiative for Asthma Step 5) with intended use before OCS. The newest guidelines also issued a consensus statement to minimize cumulative corticosteroid exposure in children. Comparison of asthma guidelines is presented in Fig. 3.

Emerging evidence in pediatric asthma: what's new for omalizumab?

Studies exploring omalizumab's impact in disease modification for asthma, prevention of allergic asthma in children, safety in pregnant mothers (indirectly measuring effects of in utero exposure through birth outcomes), efficacy in allergic rhinitis, and development for food allergy are detailed next.

Airway inflammation related to repeated allergic events leads to pathologic airway remodeling, a distinctive feature of chronic asthma. Morphological tissue changes include thickening of the reticular basement membrane, goblet cell hyperplasia, submucosal

	Step 1	Step 2	Step 3	Step 4	Step 5
JPGL [§] 2017	As-needed SABA LTRA [Ⓟ]	Low ICS or LTRA [Ⓟ] Low ICS + LTRA	Med ICS or Low SFC + LTRA or + SRT	High ICS or Med SFC Possible to add LTRA and/or SRT Increase ICS/SFC doses or + Omalizumab or + OCS	Not defined
GINA [¶] 2017	Low ICS	Low ICS Low Thee* or LTRA	Med ICS Med-high ICS or Low ICS + LTRA or Theo	Med-high ICS + LABA + Tiotropium* or High ICS + LTRA or Theo	+ Tiotropium* or + Omalizumab or + anti-IL5* + Low OCS
ICON [‡] 2012	As-needed SABA	Low ICS or LTRA Cromone or Theo	Med ICS or Low ICS/LABA or Low ICS/LTRA Theo	High ICS or Med-high ICS + LABA or Med-high ICS + LTRA Med-high ICS + Theo or + Omalizumab	+ OCS + Omalizumab

Fig. 3. Comparison of Japanese Pediatric asthma guidelines with GINA and ICON treatment guidelines for pediatric asthma. SABA, short-acting beta agonists; DSCG, disodium cromoglycate; GINA, Global Initiative for Asthma; High, high dose; ICON, International Consensus on Pediatric Asthma; ICS, inhaled corticosteroid; JPGL, Japanese Pediatric Guideline for the Treatment and Management of Asthma; LABA, long-acting β₂-agonist; Low, low dose; LTRA, leukotriene receptor antagonist; Med, medium dose; IL, interleukin; OCS, oral corticosteroid; SFC, salmeterol/fluticasone fixed-dose combination; SRT, slow-released theophylline; Theo, theophylline. [Ⓟ]Including DSCG inhalation and other oral anti-allergic drugs (Th2 cytokine inhibitors, etc.) ^{*}Not indicated for children below 12 years of age. [¶]Treatment recommendations for age 6 to 15 years; [‡]Treatment recommendations for ages ≥6 years; [†]Treatment recommendations for ages 5 to 12 years.

fibrosis with increase in number and volume of submucosal glands, and hypertrophy of the airway smooth muscle cells [76]. In addition to bronchoconstriction during an asthma attack, airway smooth muscle cells also release pro-inflammatory cytokines in response to IgE, and play a major role in airway remodeling [77]. Omalizumab responders showed downregulation of structural smooth muscle proteins and a significant decrease of reticular basement membrane thickening in biopsies [78-80]. Some omalizumab-treated patients also produced less total IgE over time [81]. Clinical observations and growing evidence suggest that omalizumab interrupts airway remodeling, and exact mechanisms are currently under study [78, 82-84]

Disease modulation is especially relevant to children, and in particular to children with high risk of progressing to lifetime asthma. The Preventing Asthma in High Risk Kids (PARK) study (formerly the Controlling and Preventing Asthma Progression and Severity in Kids study) is a multicenter Phase III prevention study examining omalizumab therapy in preschool children (as young as 24 months of age) recognized to be at high risk for progressing to childhood asthma. The PARK study explores the effects of omalizumab compared with placebo on asthma prevalence, asthma severity, and allergic sensitization (NCT02570984; clinicaltrials.gov).

The omalizumab registry “EXPECT” was one of the largest pregnancy registries available for an asthma drug and offered both the opportunity to: (1) directly examine safety in pregnant women exposed to omalizumab and (2) indirectly examine effects of in utero exposure by measuring pregnancy outcomes following omalizumab exposure. Safety evidence from EXPECT showed that pregnancy outcomes in the registry were similar for mothers taking omalizumab as well as for unexposed mothers. Omalizumab was assigned pregnancy category B by the U.S. Food and Drug Administration (FDA). In the absence of clinical study outcomes in pregnant women, category B implies that omalizumab use does not appear to increase risks to the fetus compared with the inherent risks of uncontrolled asthma [85].

Following asthma rates in prenatally exposed infants from the EXPECT registry (infants with presumably elevated risk for asthma given maternal history) could inform future prevention strategies in asthma.

Omalizumab's experience in allergic rhinitis is favorable and data showing treatment benefit is growing, both through clinical studies and published observational insights [86, 87]. Omalizumab's proof of concept in allergic rhinitis is well established with the first studies dating back almost 2 decades [88]; however, concerns for cost of therapy and uncertainty around optimal positioning have presented limitations in licensing omalizumab for patients. A Phase III registration study for cedar sensitized allergic rhinitis patients is underway (NCT03369704) in Japan, and expected to form basis for regulatory approval in Japan.

Food allergy is a potentially life-threatening allergic disease, and remains without suitable therapies apart from strict avoidance of triggers, and emergent epinephrine in case of accidental exposure. The FDA recently granted omalizumab a breakthrough designation for expedited development for food allergy. A collaborative study including the Consortium of Food Allergy Research, Genentech, and Novartis Pharmaceuticals is ongoing. A number of international studies have also shown omalizumab to be an effective adjunct for oral immunotherapy (OIT), omalizumab accelerated the course of OIT and limited the number and severity of adverse OIT reactions in food allergic children [89-91]

CONCLUSION

Pediatric asthma is allergic and frequently coexists with allergic rhinitis and other allergic comorbidities. Omalizumab is a steroid-sparing, mechanistically intuitive biological therapy for children with severe allergic asthma. The rationale for omalizumab therapy in childhood asthma is affirmed by safety and clinical efficacy in children globally, corticosteroid reduction effects, and scientific alignment with disease pathology. Finally, disease-modifying potential with long-term omalizumab use as well as a future role for omalizumab in children with allergic comorbidities continue to be areas of ongoing research.

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