Asia Pac Allergy. 2019 Jan;9(1):e7
https://doi.org/10.5415/apallergy.2019.9.e7
pISSN 2233-8276·eISSN 2233-8268

Asia Pacific allergy

Educational & Teaching Material
Review

Check for updates

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

Sankei Nishima [1,*], **Masanari Kozawa**[2], **Ki Lee Milligan**[2], **and Nikolaos G. Papadopoulos**[3]

[1]National Hospital Organization, Fukuoka National Hospital, Fukuoka, Japan
[2]Medical Division, Novartis Pharma K.K., Tokyo, Japan
[3]University of Manchester, Manchester, UK

OPEN ACCESS

Received: Dec 24, 2018
Accepted: Jan 17, 2019

***Correspondence to**
Sankei Nishima
National Hospital Organization, Fukuoka National Hospital, Fukuoka National Hospital, 4-39-1 Yakatabaru, Minami-ku, Fukuoka 811-1394, Japan.
Tel: +81-92-565-5534
Fax: +81-92-566-0702
E-mail: nishima.sankei.ac@mail.hosp.go.jp

Copyright © 2019. Asia Pacific Association of Allergy, Asthma and Clinical Immunology. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs
Sankei Nishima
https://orcid.org/0000-0001-5349-5519

Conflict of Interest
Dr. Sankei Nishima has received personal fees from AstraZeneca, Kyorin Pharmaceutical Co Ltd., Maruho, MSD, Novartis, Otsuka Pharmaceutical Co Ltd., Pfizer, Teijin Pharma, and Torii Pharmaceutical Co Ltd. Prof. Nikolaos G. Papadopoulos has received personal fees from Novartis, Faes Farma, Biomay, Nutrica Research, Menarini, Alk Abello, Mylan, MSD, Omega Pharma and Danone. Masanari Kozawa and Ki Lee Milligan are employees of Novartis.

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

Generated by KAMIE PRESS

PETITIONER EXHIBIT 1047
Page 1 of 13

Author Contributions

Conceptualization: Sankei Nishima, Masanari Kozawa, Ki Lee Milligan, Nikolaos G. Papadopoulos. Data curation: Sankei Nishima, Masanari Kozawa, Ki Lee Milligan, Nikolaos G. Papadopoulos. Funding acquisition: Masanari Kozawa, Ki Lee Milligan. Investigation: Sankei Nishima, Masanari Kozawa, Ki Lee Milligan, Nikolaos G. Papadopoulos. Project administration: Sankei Nishima, Masanari Kozawa, Ki Lee Milligan, Nikolaos G. Papadopoulos. Resources: Sankei Nishima, Masanari Kozawa, Ki Lee Milligan, Nikolaos G. Papadopoulos. Supervision: Sankei Nishima, Masanari Kozawa, Ki Lee Milligan, Nikolaos G. Papadopoulos. Validation: Sankei Nishima, Masanari Kozawa, Ki Lee Milligan, Nikolaos G. Papadopoulos. Writing - original draft: Sankei Nishima, Masanari Kozawa, Ki Lee Milligan, Nikolaos G. Papadopoulos. Writing - review & editing: Sankei Nishima, Masanari Kozawa, Ki Lee Milligan, Nikolaos G. Papadopoulos.

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

PETITIONER EXHIBIT 1047
Page 2 of 13

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].

PETITIONER EXHIBIT 1047
Page 3 of 13

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

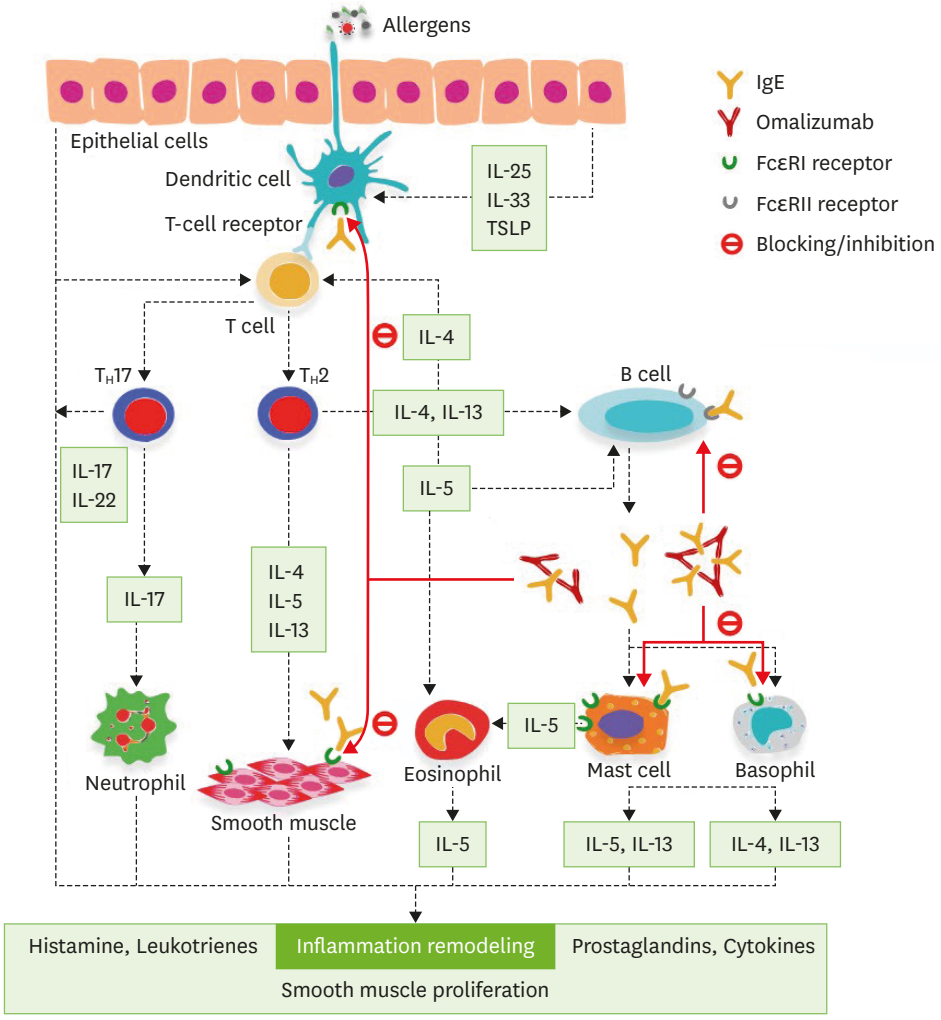

Fig. 1. IgE in allergic asthma inflammation and the role of omalizumab in therapy. IL, interleukin; T_H, T-helper; TSLP, thymic stromal lymphopoietin.

PETITIONER EXHIBIT 1047
Page 4 of 13

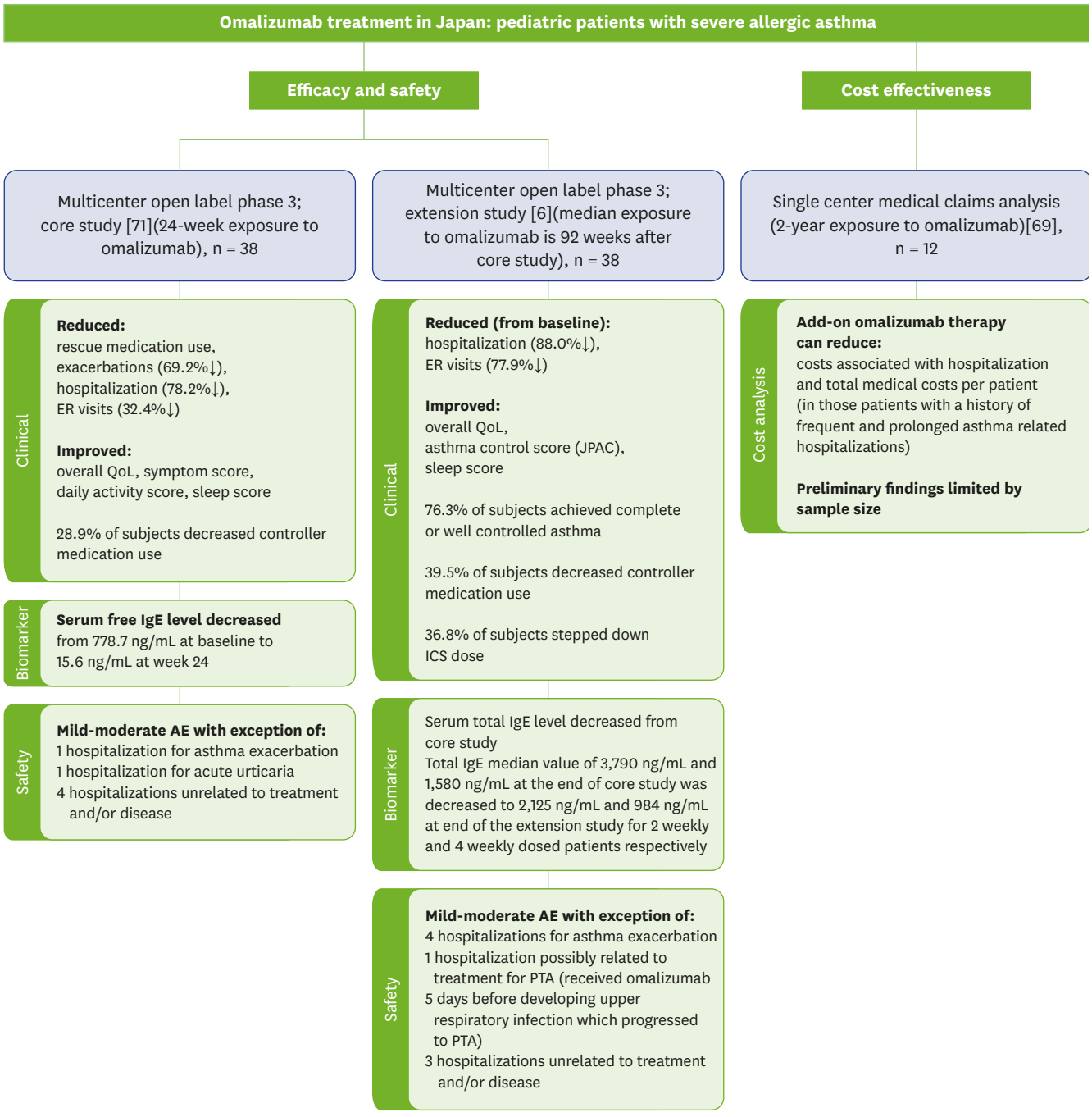

Fig. 2. Studies of omalizumab in Japanese pediatric patients with asthma. AE, adverse events; ER, emergency room; ICS, inhaled corticosteroids; JPAC, Japanese pediatric asthma control test; PTA, peritonsillar abscess; QoL, quality of life.

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

PETITIONER EXHIBIT 1047
Page 5 of 13

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

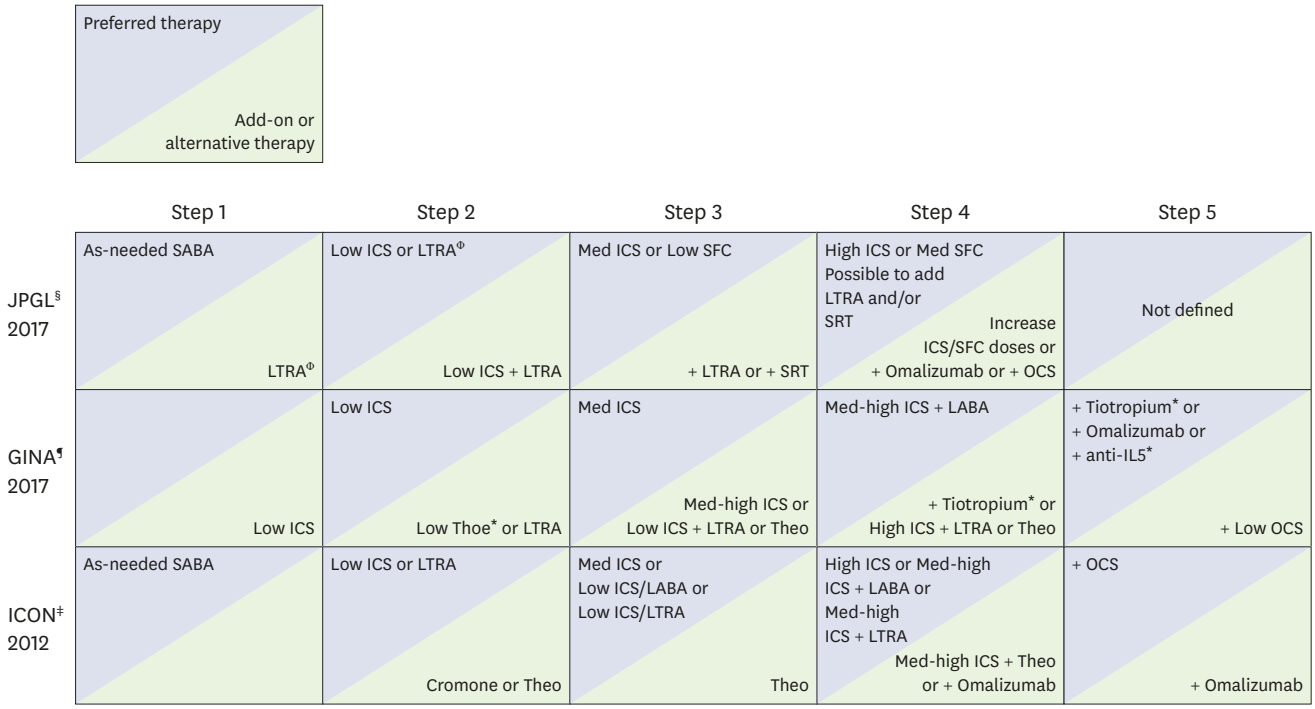

Fig. 3. Comparison of Japanese Pediatric asthma guidelines with GINA and ICON treatment guidelines for pediatric asthma. SABA, short-acting beta agonists; DSCG, disodium cromoglycate; GINA, Global Initiative for Asthma; High, high dose; ICON, International Consensus on Pediatric Asthma; ICS, inhaled corticosteroid; JPGL, Japanese Pediatric Guideline for the Treatment and Management of Asthma; LABA, long-acting β_2-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. [Φ]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.

PETITIONER EXHIBIT 1047
Page 6 of 13

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]

PETITIONER EXHIBIT 1047
Page 7 of 13

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.

ACKNOWLEDGEMENTS

Medical writing and editorial support for this manuscript was provided by Geetika Kainthla M.Sc, M. Fahad Haroon PhD and Rahul Lad PhD (Novartis Healthcare Private Limited, India), which was funded by Novartis in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59:469-78.
   PUBMED | CROSSREF
2. Asthma. WHO Fact sheet no 307 [Internet]. Geneva (Switzerland): World Health Organization; 2017 Aug [cited 2017 Nov 14]. Available from: http://www.who.int/mediacentre/factsheets/fs307/en/#
3. Nishima S, Chisaka H, Fujiwara T, Furusho K, Hayashi S, Hiraba K, Kanaya M, Kobayashi N, Kuda N, Kumamoto T, Maeda T, Murayama A, Nagata Y, Narukami H, Nishikawa K, Nishio K, Odajima H, Oka S, Okabe T, Okazaki K, Okazaki T, Okuma M, Ota K, Satomi K, Shimomura M, Suda M, Sunagawa I, Tanaka O; Allergy Prevalence Survey Group, West Japan Pediatric Allergy Association. Surveys on the prevalence of pediatric bronchial asthma in Japan: a comparison between the 1982, 1992, and 2002 surveys conducted in the same region using the same methodology. Allergol Int 2009;58:37-53.
   PUBMED | CROSSREF
4. Akasawa A, Yoshida K, Adachi Y, Odajima H, Sasaki M, Furukawa M. Time trends in the prevalence of asthma in japanese children. J Allergy Clin Immunol 2015;135 (2 Suppl):AB229.
   CROSSREF
5. Arakawa H, Hamasaki Y, Kohno Y, Ebisawa M, Kondo N, Nishima S, Nishimuta T, Morikawa A; Japanese Society of Pediatric Allergy and Clinical Immunology, The Japanese Society of Allergology. Japanese guidelines for childhood asthma 2017. Allergol Int 2017;66:190-204.
   PUBMED | CROSSREF
6. Odajima H, Akasawa N, Arakawa K. Zensoku Juushoudo Bunpu Keinen Suii ni kansuru Tashisetsu Kento (Japanese). Jap J Pediatr Allergy Clin Immunol 2016;30:590-9.
   CROSSREF
7. Bronchial Asthma. WHO Fact sheet no 206 [Internet]. Geneva (Switzerland): World Health Organization; 2017 Aug [cited 2017 Nov 14]. Available from: http://www.who.int/mediacentre/factsheets/fs206/en/
8. The Global Asthma Report 2018 [Internet]. Auckland (New Zealand): Global Asthma Network; 2018 [cited 2018 Nov 14]. Available from: http://globalasthmareport.org/
9. Sasaki M, Yoshida K, Adachi Y, Furukawa M, Itazawa T, Odajima H, Saito H, Akasawa A. Factors associated with asthma control in children: findings from a national Web-based survey. Pediatr Allergy Immunol 2014;25:804-9.
   PUBMED | CROSSREF
10. Demographics survey in Japan in 2015. Tokyo: Ministry of Health, Labour and Welfare; 2016.
11. de Nijs SB, Venekamp LN, Bel EH. Adult-onset asthma: is it really different? Eur Respir Rev 2013;22:44-52.
   PUBMED | CROSSREF

PETITIONER EXHIBIT 1047
Page 8 of 13

12. Schatz M, Rosenwasser L. The allergic asthma phenotype. J Allergy Clin Immunol Pract 2014;2:645-8.
PUBMED | CROSSREF

13. Porsbjerg C, von Linstow ML, Ulrik CS, Nepper-Christensen S, Backer V. Risk factors for onset of asthma: a 12-year prospective follow-up study. Chest 2006;129:309-16.
PUBMED | CROSSREF

14. Kemeny ME, Rosenwasser LJ, Panettieri RA, Rose RM, Berg-Smith SM, Kline JN. Placebo response in asthma: a robust and objective phenomenon. J Allergy Clin Immunol 2007;119:1375-81.
PUBMED | CROSSREF

15. Milligan KL, Matsui E, Sharma H. Asthma in urban children: epidemiology, environmental risk factors, and the public health domain. Curr Allergy Asthma Rep 2016;16:33.
PUBMED | CROSSREF

16. Lynch SV, Wood RA, Boushey H, Bacharier LB, Bloomberg GR, Kattan M, O'Connor GT, Sandel MT, Calatroni A, Matsui E, Johnson CC, Lynn H, Visness CM, Jaffee KF, Gergen PJ, Gold DR, Wright RJ, Fujimura K, Rauch M, Busse WW, Gern JE. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. J Allergy Clin Immunol 2014;134:593-601.e12.
PUBMED | CROSSREF

17. Andersson M, Hedman L, Bjerg A, Forsberg B, Lundbäck B, Rönmark E. Remission and persistence of asthma followed from 7 to 19 years of age. Pediatrics 2013;132:e435-42.
PUBMED | CROSSREF

18. Covar RA, Strunk R, Zeiger RS, Wilson LA, Liu AH, Weiss S, Tonascia J, Spahn JD, Szefler SJ; Childhood Asthma Management Program Research Group. Predictors of remitting, periodic, and persistent childhood asthma. J Allergy Clin Immunol 2010;125:359-66.e3.
PUBMED | CROSSREF

19. Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964-1999. J Allergy Clin Immunol 2002;109:189-94.
PUBMED | CROSSREF

20. Fitzpatrick AM, Gaston BM, Erzurum SC, Teague WG; National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. Features of severe asthma in school-age children: Atopy and increased exhaled nitric oxide. J Allergy Clin Immunol 2006;118:1218-25.
PUBMED | CROSSREF

21. Fleming L, Murray C, Bansal AT, Hashimoto S, Bisgaard H, Bush A, Frey U, Hedlin G, Singer F, van Aalderen WM, Vissing NH, Zolkipli Z, Selby A, Fowler S, Shaw D, Chung KF, Sousa AR, Wagers S, Corfield J, Pandis I, Rowe A, Formaggio E, Sterk PJ, Roberts G; U-BIOPRED Study Group. The burden of severe asthma in childhood and adolescence: results from the paediatric U-BIOPRED cohorts. Eur Respir J 2015;46:1322-33.
PUBMED | CROSSREF

22. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, Wenzel SE, Aujla S, Castro M, Bacharier LB, Gaston BM, Bleecker ER, Moore WC; National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. J Allergy Clin Immunol 2011;127:382-389.e1-13.
PUBMED | CROSSREF

23. de Groot EP, Kreggemeijer WJ, Brand PL. Getting the basics right resolves most cases of uncontrolled and problematic asthma. Acta Paediatr 2015;104:916-21.
PUBMED | CROSSREF

24. Lang A, Carlsen KH, Haaland G, Devulapalli CS, Munthe-Kaas M, Mowinckel P, Carlsen K. Severe asthma in childhood: assessed in 10 year olds in a birth cohort study. Allergy 2008;63:1054-60.
PUBMED | CROSSREF

25. Loke YK, Blanco P, Thavarajah M, Wilson AM. Impact of inhaled corticosteroids on growth in children with asthma: systematic review and meta-analysis. PLoS One 2015;10:e0133428.
PUBMED | CROSSREF

26. Kapadia CR, Nebesio TD, Myers SE, Willi S, Miller BS, Allen DB, Jacobson-Dickman E; Drugs and Therapeutics Committee of the Pediatric Endocrine Society. Endocrine effects of inhaled corticosteroids in children. JAMA Pediatr 2016;170:163-70.
PUBMED | CROSSREF

27. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. N Engl J Med 2000;343:1064-9.
PUBMED | CROSSREF

28. Guilbert TW, Mauger DT, Allen DB, Zeiger RS, Lemanske RF Jr, Szefler SJ, Strunk RC, Bacharier LB, Covar R, Sorkness CA, Taussig LM, Martinez FD; Childhood Asthma Research and Education Network of the

PETITIONER EXHIBIT 1047
Page 9 of 13

National Heart, Lung, and Blood Institute. Growth of preschool children at high risk for asthma 2 years after discontinuation of fluticasone. J Allergy Clin Immunol 2011;128:956-63.e1.
PUBMED | CROSSREF

29. Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. Pediatrics 2000;106:E8.
PUBMED | CROSSREF

30. Braido F. Failure in asthma control: reasons and consequences. Scientifica (Cairo) 2013;2013:549252.
PUBMED | CROSSREF

31. O'Byrne PM, Pedersen S, Schatz M, Thoren A, Ekholm E, Carlsson LG, Busse WW. The poorly explored impact of uncontrolled asthma. Chest 2013;143:511-23.
PUBMED | CROSSREF

32. Dolan CM, Fraher KE, Bleecker ER, Borish L, Chipps B, Hayden ML, Weiss S, Zheng B, Johnson C, Wenzel S; TENOR Study Group. Design and baseline characteristics of the epidemiology and natural history of asthma: Outcomes and Treatment Regimens (TENOR) study: a large cohort of patients with severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol 2004;92:32-9.
PUBMED | CROSSREF

33. Boulay ME, Morin A, Laprise C, Boulet LP. Asthma and rhinitis: what is the relationship? Curr Opin Allergy Clin Immunol 2012;12:449-54.
PUBMED | CROSSREF

34. Deliu M, Belgrave D, Simpson A, Murray CS, Kerry G, Custovic A. Impact of rhinitis on asthma severity in school-age children. Allergy 2014;69:1515-21.
PUBMED | CROSSREF

35. Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. J Allergy Clin Immunol 2000;106 (5 Suppl):S201-5.
PUBMED | CROSSREF

36. Kou W, Li X, Yao H, Wei P. Meta-analysis of the comorbidity rate of allergic rhinitis and asthma in Chinese children. Int J Pediatr Otorhinolaryngol 2018;107:131-4.
PUBMED | CROSSREF

37. Gough H, Grabenhenrich L, Reich A, Eckers N, Nitsche O, Schramm D, Beschorner J, Hoffmann U, Schuster A, Bauer CP, Forster J, Zepp F, Lee YA, Bergmann RL, Bergmann KE, Wahn U, Lau S, Keil T; MAS study group. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. Pediatr Allergy Immunol 2015;26:431-7.
PUBMED | CROSSREF

38. Liu W, Huang C, Wang X, Cai J, Hu Y, Zou Z, Weschler LB, Shen L, Sundell J. Multimorbidities of asthma, allergies, and airway illnesses in childhood: Chance or not chance? J Asthma 2017;54:687-98.
PUBMED | CROSSREF

39. Kim HY, Kwon EB, Baek JH, Shin YH, Yum HY, Jee HM, Yoon JW, Han MY. Prevalence and comorbidity of allergic diseases in preschool children. Korean J Pediatr 2013;56:338-42.
PUBMED | CROSSREF

40. de Groot EP, Duiverman EJ, Brand PL. Comorbidities of asthma during childhood: possibly important, yet poorly studied. Eur Respir J 2010;36:671-8.
PUBMED | CROSSREF

41. Gibson PG, Reddel H, McDonald VM, Marks G, Jenkins C, Gillman A, Upham J, Sutherland M, Rimmer J, Thien F, Katsoulotos GP, Cook M, Yang I, Katelaris C, Bowler S, Langton D, Robinson P, Wright C, Yozghatlian V, Burgess S, Sivakumaran P, Jaffe A, Bowden J, Wark PA, Yan KY, Kritikos V, Peters M, Hew M, Aminazad A, Bint M, Guo M. Effectiveness and response predictors of omalizumab in a severe allergic asthma population with a high prevalence of comorbidities: the Australian Xolair Registry. Intern Med J 2016;46:1054-62.
PUBMED | CROSSREF

42. Durrani SR, Mukkada VA, Guilbert TW. Eosinophilic esophagitis: an important comorbid condition of asthma? Clin Rev Allergy Immunol 2018;55:56-64.
PUBMED | CROSSREF

43. Mirabelli MC, Hsu J, Gower WA. Comorbidities of asthma in U.S. children. Respir Med 2016;116:34-40.
PUBMED | CROSSREF

44. Jacob L, Keil T, Kostev K. Comorbid disorders associated with asthma in children in Germany - National analysis of pediatric primary care data. Pediatr Allergy Immunol 2016;27:861-6.
PUBMED | CROSSREF

45. Heck S, Al-Shobash S, Rapp D, Le DD, Omlor A, Bekhit A, Flaig M, Al-Kadah B, Herian W, Bals R, Wagenpfeil S, Dinh QT. High probability of comorbidities in bronchial asthma in Germany. NPJ Prim Care Respir Med 2017;27:28.
PUBMED | CROSSREF

PETITIONER EXHIBIT 1047
Page 10 of 13

46. Pénard-Morand C, Raherison C, Kopferschmitt C, Caillaud D, Lavaud F, Charpin D, Bousquet J, Annesi-Maesano I. Prevalence of food allergy and its relationship to asthma and allergic rhinitis in schoolchildren. Allergy 2005;60:1165-71.
PUBMED | CROSSREF

47. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, Castro M, Peters SP, Phipatanakul W, Aujla S, Bacharier LB, Bleecker ER, Comhair SA, Coverstone A, DeBoer M, Erzurum SC, Fain SB, Fajt M, Fitzpatrick AM, Gaffin J, Gaston B, Hastie AT, Hawkins GA, Holguin F, Irani AM, Israel E, Levy BD, Ly N, Meyers DA, Moore WC, Myers R, Opina MT, Peters MC, Schiebler ML, Sorkness RL, Teague WG, Wenzel SE, Woodruff PG, Mauger DT, Fahy JV, Jarjour NN; National Heart, Lung, and Blood Institute's Severe Asthma Research Program-3 Investigators. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. Am J Respir Crit Care Med 2017;195:302-13.
PUBMED | CROSSREF

48. Pinart M, Benet M, Annesi-Maesano I, von Berg A, Berdel D, Carlsen KC, Carlsen KH, Bindslev-Jensen C, Eller E, Fantini MP, Lenzi J, Gehring U, Heinrich J, Hohmann C, Just J, Keil T, Kerkhof M, Kogevinas M, Koletzko S, Koppelman GH, Kull I, Lau S, Melén E, Momas I, Porta D, Postma DS, Rancière F, Smit HA, Stein RT, Tischer CG, Torrent M, Wickman M, Wijga AH, Bousquet J, Sunyer J, Basagaña X, Guerra S, Garcia-Aymerich J, Antó JM. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitised and non-IgE-sensitised children in MeDALL: a population-based cohort study. Lancet Respir Med 2014;2:131-40.
PUBMED | CROSSREF

49. Pijnenburg MW, Baraldi E, Brand PL, Carlsen KH, Eber E, Frischer T, Hedlin G, Kulkarni N, Lex C, Mäkelä MJ, Mantzouranis E, Moeller A, Pavord I, Piacentini G, Price D, Rottier BL, Saglani S, Sly PD, Szefler SJ, Tonia T, Turner S, Wooler E, Lødrup Carlsen KC. Monitoring asthma in children. Eur Respir J 2015;45:906-25.
PUBMED | CROSSREF

50. Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, Taylor AF, Rohane P. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics 2001;108:E36.
PUBMED | CROSSREF

51. Mirra V, Montella S, Santamaria F. Pediatric severe asthma: a case series report and perspectives on anti-IgE treatment. BMC Pediatr 2018;18:73.
PUBMED | CROSSREF

52. Ramratnam SK, Bacharier LB, Guilbert TW. Severe asthma in children. J Allergy Clin Immunol Pract 2017;5:889-98.
PUBMED | CROSSREF

53. Chang TW, Chen JB, Chu CY. The pharmacological mechanisms of omalizumab in patients with very high IgE levels—clues from studies on atopic dermatitis. Dermatol Sinica 2012;30:147-53.
CROSSREF

54. Gill MA, Liu AH, Calatroni A, Krouse RZ, Shao B, Schiltz A, Gern JE, Togias A, Busse WW. Enhanced plasmacytoid dendritic cell antiviral responses after omalizumab. J Allergy Clin Immunol 2018;141:1735-43.e9.
PUBMED | CROSSREF

55. Chanez P, Contin-Bordes C, Garcia G, Verkindre C, Didier A, De Blay F, de Lara MT, Blanco P, Moreau JF, Robinson P, Bourdeix I, Trunet P, Le Gros V, Humbert M, Molimard M. Omalizumab-induced decrease of FcξRI expression in patients with severe allergic asthma. Respir Med 2010;104:1608-17.
PUBMED | CROSSREF

56. Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell FcepsilonRI expression. J Allergy Clin Immunol 2003;112:1147-54.
PUBMED | CROSSREF

57. Zaidi AK, Saini SS, Macglashan DW Jr. Regulation of Syk kinase and FcRbeta expression in human basophils during treatment with omalizumab. J Allergy Clin Immunol 2010;125:902-8.e7.
PUBMED | CROSSREF

58. Holgate S, Smith N, Massanari M, Jimenez P. Effects of omalizumab on markers of inflammation in patients with allergic asthma. Allergy 2009;64:1728-36.
PUBMED | CROSSREF

59. Oliver JM, Tarleton CA, Gilmartin L, Archibeque T, Qualls CR, Diehl L, Wilson BS, Schuyler M. Reduced FcepsilonRI-mediated release of asthma-promoting cytokines and chemokines from human basophils during omalizumab therapy. Int Arch Allergy Immunol 2010;151:275-84.
PUBMED | CROSSREF

60. Roth M, Tamm M. The effects of omalizumab on IgE-induced cytokine synthesis by asthmatic airway smooth muscle cells. Ann Allergy Asthma Immunol 2010;104:152-60.
PUBMED | CROSSREF

PETITIONER EXHIBIT 1047
Page 11 of 13

61. Humbert M, Grant JA, Taborda-Barata L, Durham SR, Pfister R, Menz G, Barkans J, Ying S, Kay AB. High-affinity IgE receptor (FcepsilonRI)-bearing cells in bronchial biopsies from atopic and nonatopic asthma. Am J Respir Crit Care Med 1996;153 (6 Pt 1):1931-7.
PUBMED | CROSSREF

62. Garcia G, Magnan A, Chiron R, Contin-Bordes C, Berger P, Taillé C, Devouassoux G, de Blay F, Couderc LJ, Didier A, O'Callaghan DS, Girodet PO, Bourdeix I, Le Gros V, Humbert M. A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma. Chest 2013;144:411-9.
PUBMED | CROSSREF

63. Marone G, Spadaro G, Palumbo C, Condorelli G. The anti-IgE/anti-FcepsilonRIalpha autoantibody network in allergic and autoimmune diseases. Clin Exp Allergy 1999;29:17-27.
PUBMED | CROSSREF

64. Ong YE, Menzies-Gow A, Barkans J, Benyahia F, Ou TT, Ying S, Kay AB. Anti-IgE (omalizumab) inhibits late-phase reactions and inflammatory cells after repeat skin allergen challenge. J Allergy Clin Immunol 2005;116:558-64.
PUBMED | CROSSREF

65. Trischler J, Lieb A, Arnold M, Schulze J, Rosewich M, Schubert R, Bottoli I, Zielen S. Omalizumab effectively protects against early and late allergic responses in asthma after 4 weeks. Allergy 2017;72:1912-5.
PUBMED | CROSSREF

66. Milgrom H, Fick RB Jr, Su JQ, Reimann JD, Bush RK, Watrous ML, Metzger WJ. Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb-E25 Study Group. N Engl J Med 1999;341:1966-73.
PUBMED | CROSSREF

67. Fahy JV, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, Fick RB Jr, Boushey HA. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. Am J Respir Crit Care Med 1997;155:1828-34.
PUBMED | CROSSREF

68. Belliveau PP. Omalizumab: a monoclonal anti-IgE antibody. MedGenMed 2005;7:27.
PUBMED

69. Yoshikawa H, Iwata M, Matsuzaki H, Ono R, Murakami Y, Taba N, Honjo S, Motomura C, Odajima H. Impact of omalizumab on medical cost of childhood asthma in Japan. Pediatr Int 2016;58:425-8.
PUBMED | CROSSREF

70. Odajima H, Ebisawa M, Nagakura T, Fujisawa T, Akasawa A, Ito K, Doi S, Yamaguchi K, Katsunuma T, Kurihara K, Teramoto T, Sugai K, Nambu M, Hoshioka A, Yoshihara S, Sato N, Seko N, Nishima S. Long-term safety, efficacy, pharmacokinetics and pharmacodynamics of omalizumab in children with severe uncontrolled asthma. Allergol Int 2017;66:106-15.
PUBMED | CROSSREF

71. Odajima H, Ebisawa M, Nagakura T, Fujisawa T, Akasawa A, Ito K, Doi S, Yamaguchi K, Katsunuma T, Kurihara K, Kondo N, Sugai K, Nambu M, Hoshioka A, Yoshihara S, Sato N, Seko N, Nishima S. Omalizumab in Japanese children with severe allergic asthma uncontrolled with standard therapy. Allergol Int 2015;64:364-70.
PUBMED | CROSSREF

72. Chipps BE, Lanier B, Milgrom H, Deschildre A, Hedlin G, Szefler SJ, Kattan M, Kianifard F, Ortiz B, Haselkorn T, Iqbal A, Rosén K, Trzaskoma B, Busse WW. Omalizumab in children with uncontrolled allergic asthma: Review of clinical trial and real-world experience. J Allergy Clin Immunol 2017;139:1431-44.
PUBMED | CROSSREF

73. Deschildre A, Marguet C, Salleron J, Pin I, Rittié JL, Derelle J, Taam RA, Fayon M, Brouard J, Dubus JC, Siret D, Weiss L, Pouessel G, Beghin L, Just J. Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey. Eur Respir J 2013;42:1224-33.
PUBMED | CROSSREF

74. Walker S, Monteil M, Phelan K, Lasserson TJ, Walters EH. Anti-IgE for chronic asthma in adults and children. Cochrane Database Syst Rev 2006;(2):CD003559.
PUBMED

75. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ Jr, Calatroni A, Wildfire JJ, Gergen PJ, Cohen RT, Pongracic JA, Kercsmar CM, Khurana Hershey GK, Gruchalla RS, Liu AH, Zoratti EM, Kattan M, Grindle KA, Gern JE, Busse WW, Szefler SJ. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. J Allergy Clin Immunol 2015;136:1476-85.
PUBMED | CROSSREF

76. Fahy JV. Type 2 inflammation in asthma--present in most, absent in many. Nat Rev Immunol 2015;15:57-65.
PUBMED | CROSSREF

PETITIONER EXHIBIT 1047
Page 12 of 13

77. Wilson SJ, Rigden HM, Ward JA, Laviolette M, Jarjour NN, Djukanović R. The relationship between eosinophilia and airway remodelling in mild asthma. Clin Exp Allergy 2013;43:1342-50.
PUBMED | CROSSREF

78. Roth M, Zhao F, Zhong J, Lardinois D, Tamm M. Serum IgE induced airway smooth muscle cell remodeling is independent of allergens and is prevented by omalizumab. PLoS One 2015;10:e0136549.
PUBMED | CROSSREF

79. Mauri P, Riccio AM, Rossi R, Di Silvestre D, Benazzi L, De Ferrari L, Dal Negro RW, Holgate ST, Canonica GW. Proteomics of bronchial biopsies: galectin-3 as a predictive biomarker of airway remodelling modulation in omalizumab-treated severe asthma patients. Immunol Lett 2014;162 (1 Pt A):2-10.
PUBMED | CROSSREF

80. Riccio AM, Dal Negro RW, De Ferrari L, Micheletto C, Canonica GW, Folli C, Chiappori A. Anti-IgE and airway remodelling: omalizumab affects reticular basement membrane thickness in severe persistent atopic asthma. Eur Respir J 2011;38 Suppl 55:p3846.

81. Lowe PJ, Renard D. Omalizumab decreases IgE production in patients with allergic (IgE-mediated) asthma; PKPD analysis of a biomarker, total IgE. Br J Clin Pharmacol 2011;72:306-20.
PUBMED | CROSSREF

82. Chan MA, Gigliotti NM, Dotson AL, Rosenwasser LJ. Omalizumab may decrease IgE synthesis by targeting membrane IgE+ human B cells. Clin Transl Allergy 2013;3:29.
PUBMED | CROSSREF

83. Hoshino M, Ohtawa J. Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma. Respiration 2012;83:520-8.
PUBMED | CROSSREF

84. Riccio AM, Dal Negro RW, Micheletto C, De Ferrari L, Folli C, Chiappori A, Canonica GW. Omalizumab modulates bronchial reticular basement membrane thickness and eosinophil infiltration in severe persistent allergic asthma patients. Int J Immunopathol Pharmacol 2012;25:475-84.
PUBMED | CROSSREF

85. Namazy J, Cabana MD, Scheuerle AE, Thorp JM Jr, Chen H, Carrigan G, Wang Y, Veith J, Andrews EB. The Xolair Pregnancy Registry (EXPECT): the safety of omalizumab use during pregnancy. J Allergy Clin Immunol 2015;135:407-12.
PUBMED | CROSSREF

86. Vashisht P, Casale T. Omalizumab for treatment of allergic rhinitis. Expert Opin Biol Ther 2013;13:933-45.
PUBMED | CROSSREF

87. Tsabouri S, Tseretopoulou X, Priftis K, Ntzani EE. Omalizumab for the treatment of inadequately controlled allergic rhinitis: a systematic review and meta-analysis of randomized clinical trials. J Allergy Clin Immunol Pract 2014;2:332-40.e1.
PUBMED | CROSSREF

88. Casale TB, Condemi J, LaForce C, Nayak A, Rowe M, Watrous M, McAlary M, Fowler-Taylor A, Racine A, Gupta N, Fick R, Della Cioppa G; Omalizumab Seasonal Allergic Rhinitis Trail Group. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. JAMA 2001;286:2956-67.
PUBMED | CROSSREF

89. Labrosse R, Graham F, Des Roches A, Bégin P. The use of omalizumab in food oral immunotherapy. Arch Immunol Ther Exp (Warsz) 2017;65:189-99.
PUBMED | CROSSREF

90. Abdel-Gadir A, Schneider L, Casini A, Charbonnier LM, Little SV, Harrington T, Umetsu DT, Rachid R, Chatila TA. Oral immunotherapy with omalizumab reverses the Th2 cell-like programme of regulatory T cells and restores their function. Clin Exp Allergy 2018;48:825-36.
PUBMED | CROSSREF

91. Dantzer JA, Wood RA. The use of omalizumab in allergen immunotherapy. Clin Exp Allergy 2018;48:232-40.
PUBMED | CROSSREF

PETITIONER EXHIBIT 1047
Page 13 of 13