Biologic Therapies for Asthma and Nasal Polyposis

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THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Improving People's Lives
through innovations in personalized health care

ACOI: October 21, 2022

Disclosures

- Consultant: ALK
- Past-president, American College of Allergy, Asthma and Immunology
- President Elect, World Allergy Organization.
- I was a program Director in AI for over 16 years, and have a brother who was also a program director in AI.

Objectives

- Discuss the role of biologic medications in the armamentarium of the practicing allergist
- Identify key patient and disease characteristics to assist in individualizing therapy recommendations
- Characterize key differences between biologics based on their targeted pathways and mechanisms of action
- Understand that anti-TSLP has been FDA approved for asthma, and may provide clinicians with a novel biologic that works in T2 Low asthma.

2021

Biologic Therapy in Allergy Practice: A New Era in Treatment Has Begun

Ann Chen Wu, MD[a], and William W. Busse, MD[b] *Boston, Mass; and Madison, Wis*

The last decade has seen a transformation in approaches to treat allergic diseases with the development, approval, and increasing use of biologics. Asthma was the initial disease targeted by biologics with omalizumab, which binds free IgE to reduce the allergic airway response. The primary clinical effect of reducing circulating IgE and its cell-bound receptor was a prevention of asthma exacerbations, which was a bit of a surprise rather than the expected improvement in lung function. With omalizumab's effects on asthma risk being a vanguard observation, a new concept in asthma management emerged: targeted treatment on a major outcome of asthma—exacerbations. Observations with omalizumab provided guidance and direction for selection of patient populations for subsequent biologics that centered on blocking components of T2-inflammation.

Based on these findings and experiences in asthma, the use of

Corticosteroids are often the primary "last stop" medication for use in recalcitrant allergic diseases. Although effective for many patients, there are frequently immediate risks and, more importantly, an increasing frequency of side effects with long-term systemic corticosteroid use. Moreover, recent data verify that significant side effects also occur even with limited lifetime "bursts" of prednisone. Therefore, the composite benefits that are emerging with the use of biologics include life-changing outcomes in disease control and an elimination of risks for side effects frequently found with needed cotreatment of systemic corticosteroids.

In addition to transforming clinical care, biologics have provided insight into disease mechanisms and identified biomarkers to predict the likelihood for therapeutic responses. Furthermore, insights into mechanisms of action have also

JACI-in Practice. (2021)9:1118-20

2015

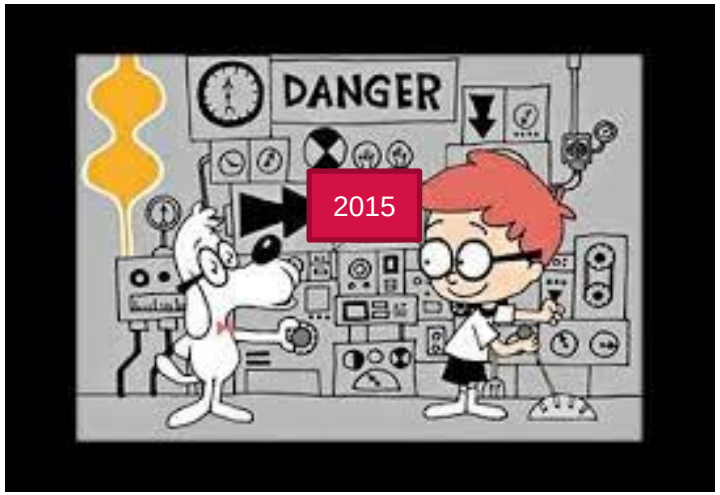
Grand Rounds Review

Biologics in Asthma—The Next Step Toward Personalized Treatment

Jared Darveaux, MD, and William W. Busse, MD *Madison, Wis*

Asthma is a multifaceted disease and is associated with significant impairment and risk, and a therapeutic response that is highly variable. Although current treatments are usually effective for patients with mild-to-moderate disease, patients with more severe asthma are often unresponsive to current efforts, and there remains a need for agents with properties that may achieve control in these individuals. There is ongoing research to identify bioactive molecules that contribute to the pathophysiology of asthma, and many of these have been identified as potential therapeutic targets to improve control of this disease. As a consequence of these efforts, monoclonal antibodies have been developed and tested as to their effectiveness in the treatment of asthma. The assessment of these new treatments has identified particular pathways that, in selected patients, have shown benefit. The following review will discuss the current and future use of biological agents for the treatment of asthma, their efficacy, and how certain patient phenotypes and endotypes may be associated with biomarkers that may be used to select treatments to achieve greatest effectiveness of their use. As knowledge of the effects of these biological agents in asthma emerges, as well as the patients in whom they are most beneficial, the movement toward personalized treatment will follow. **(J Allergy Clin Immunol Pract 2015;3:152-60)**

Key words: *Asthma; Biologics; Therapeutics*



Department of Medicine, Section of Allergy Pulmonary and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wis

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2213-2198

http://dx.doi.org/10.1016/j.jaip.2014.09.014

JACI In Practice. 2015;3:152-60

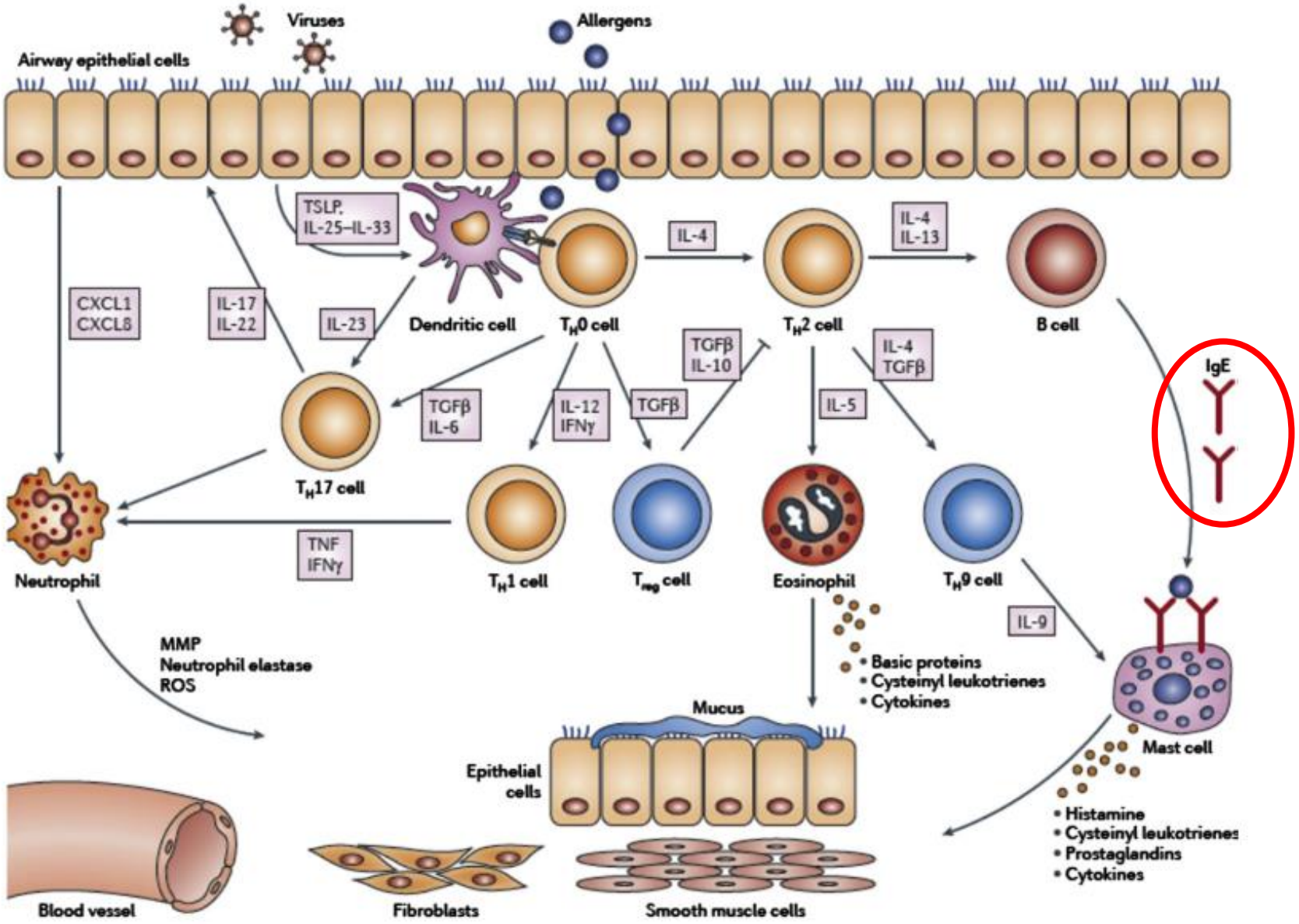
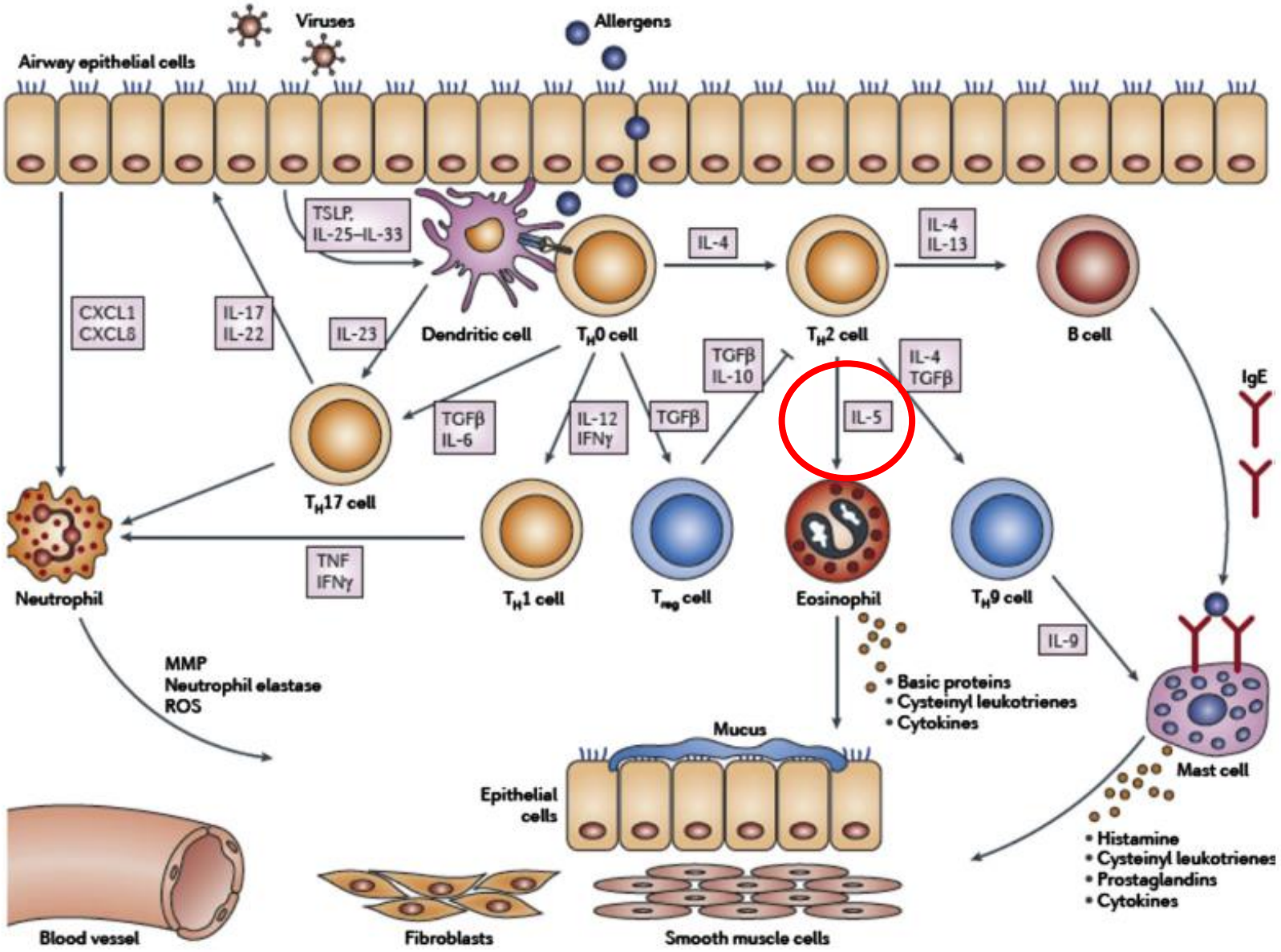


FIGURE 1. Pathobiology of asthma. Asthma originates from complex interactions between genetic factors and environmental agents such as aeroallergens and respiratory viruses. In particular, within the airway lumen, allergens can be taken up by dendritic cells, which process antigenic molecules and present them to naive T-helper (Th0) cells. The consequent activation of allergen-specific Th2 cells is responsible for the production of multiple cytokines and chemokines producing an allergic response. Adapted from Ref. 3.

The only biologic available in 2015 was Omalizumab, anti IgE.

Many pathways were known and were being investigated.

JACI In Practice. 2015;3:152-60



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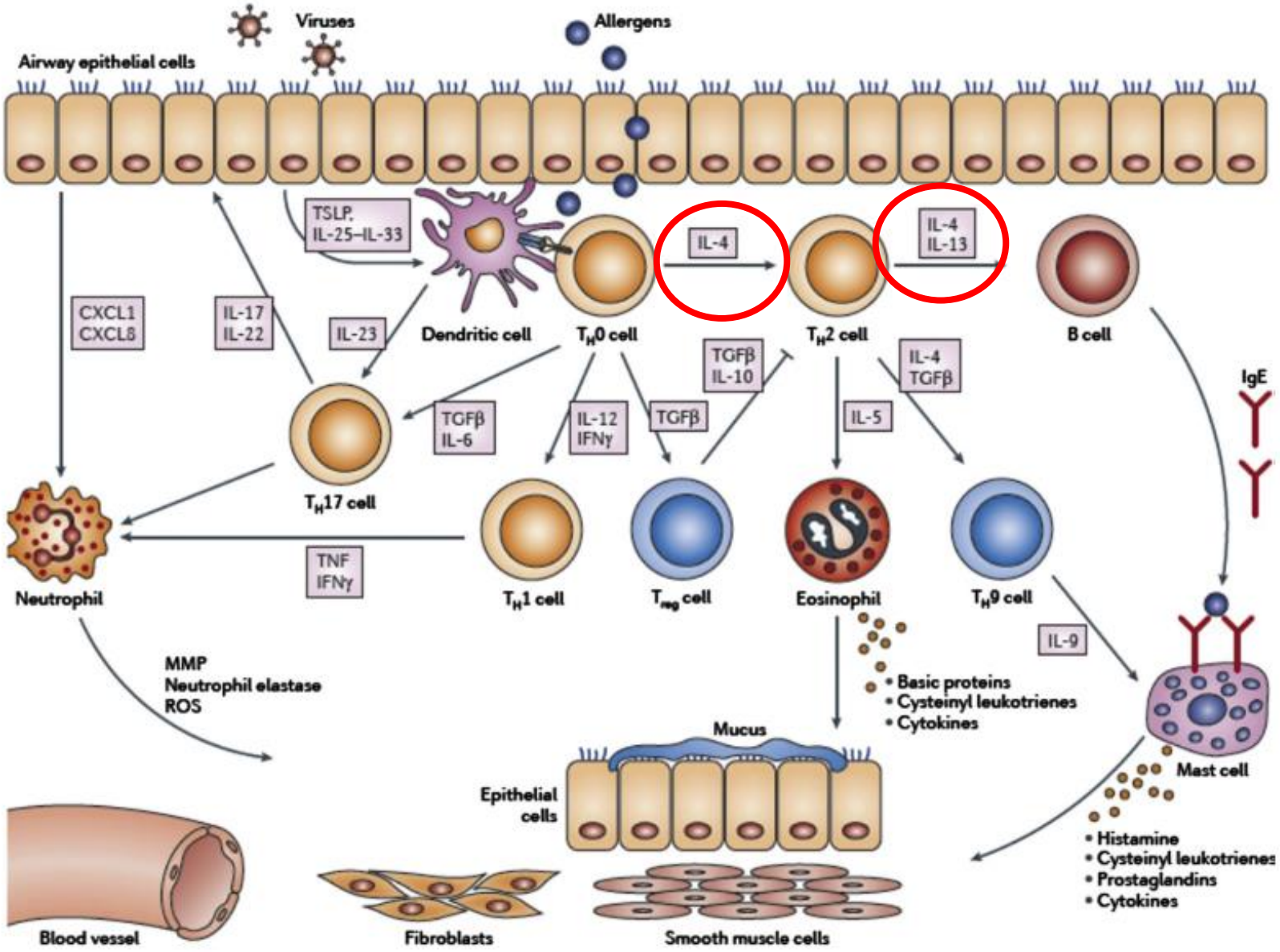
IL-5 was a clear target as it controls production, activation and localization of eosinophils.

Mepolizumab

Reslizumab

benralizumab

JACI In Practice. 2015;3:152-60



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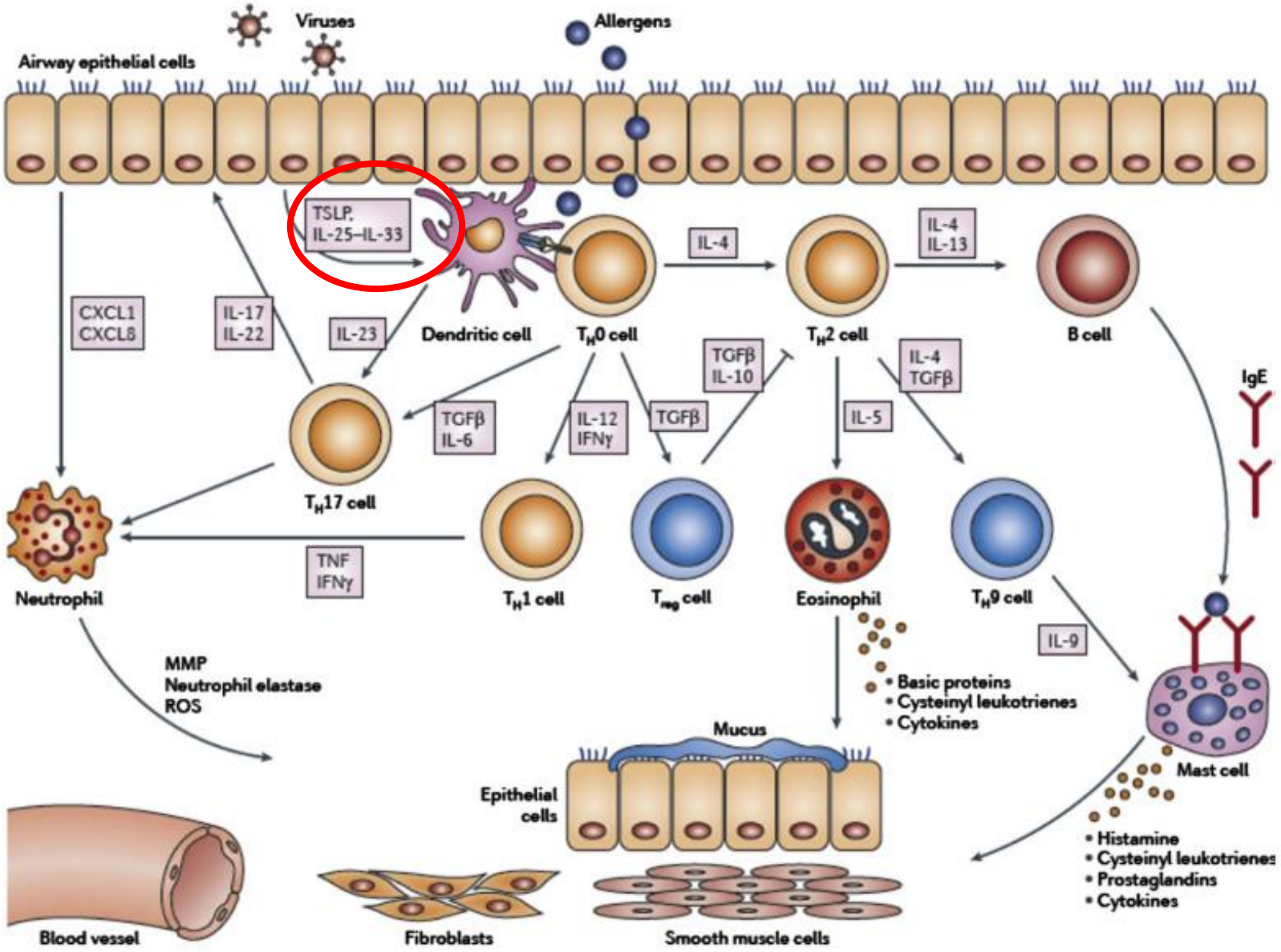
IL-4 and IL-13 were targets

Dupilumab blocks the IL-4R alpha subunit, which also inhibits IL-13 signaling.

JACI In Practice. 2015;3:152-60



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TSLP is a target much earlier in the activation of the inflammatory cascade.

January 2022, anti TSLP was approved by the FDA

JACI In Practice. 2015;3:152-60

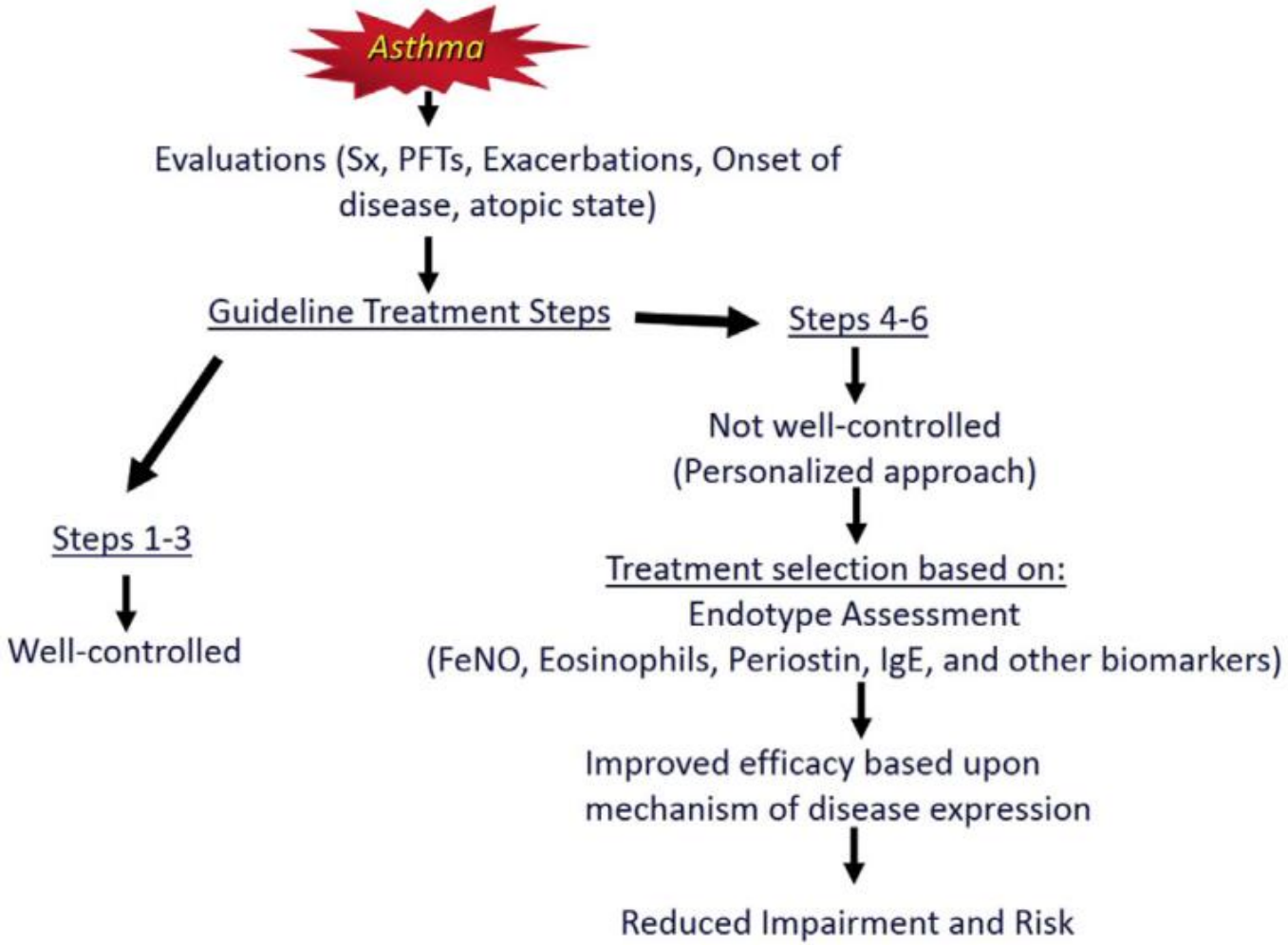


FIGURE 6. Individualized management for asthma. If control is not achieved with ERP3 steps 1-3, the assessment of asthma phenotype should guide selection of the most likely effective biological agent.

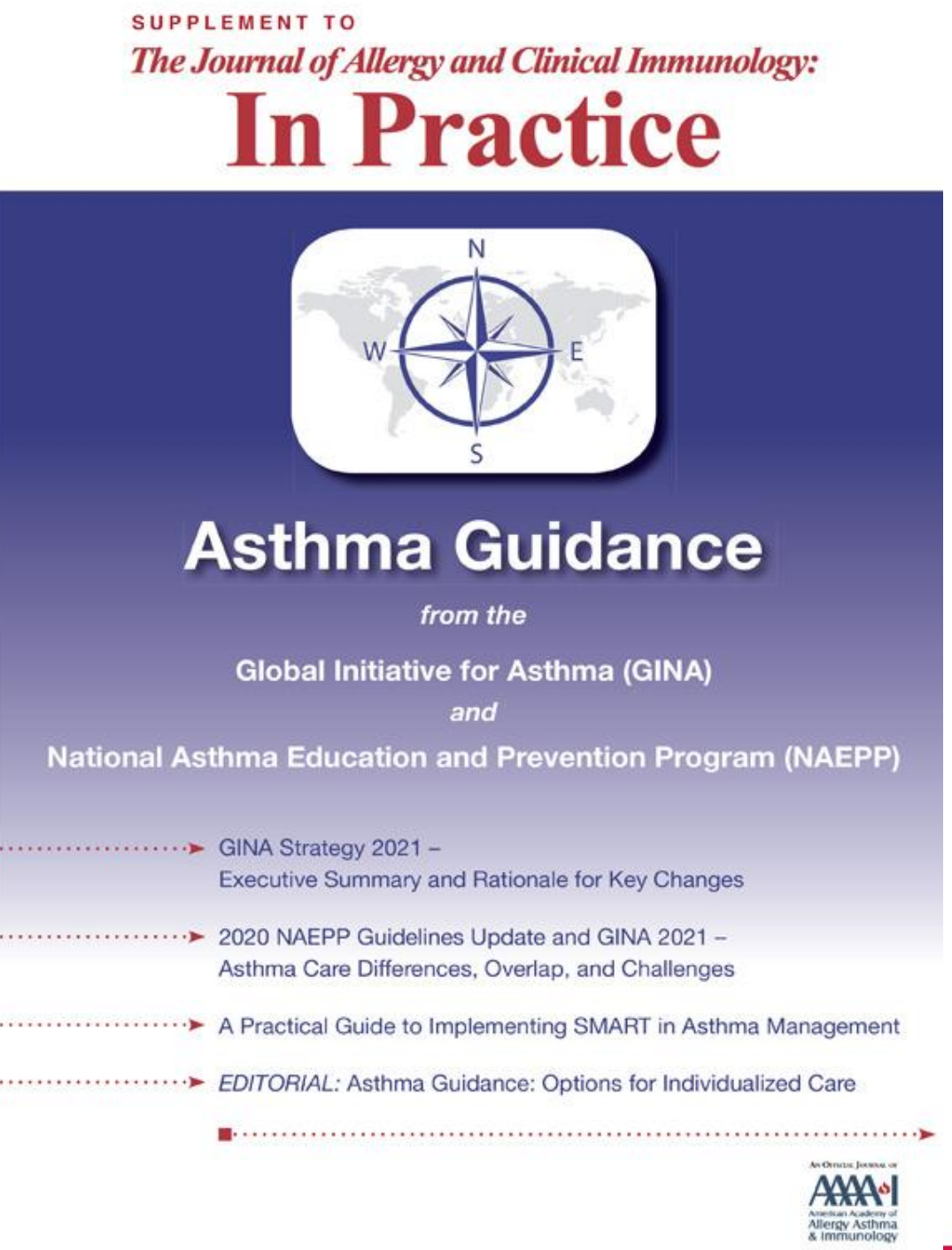
2015: Endotypes

If asthma is not easily controlled, that is using ERP3 guidelines through step 3, then we need to better understand the endotype of the underlying asthma to determine the best therapy.

JACI In Practice. 2015;3:152-60

What has happened since 2015?

- January 2015, our armamentarium of biologics is pretty limited…
- Omalizumab: approved for use in moderate to severe asthma
- Beginning in late 2015, things became more exiting, and biologics had 2 very good years.



January 2022

- Volume 10, Issue 1, Supplement, S1-S40.
- Asthma Guidance
- Challenging condition (umbella term)
  - Endotype: deals with mechanistic pathway
  - Phenotype: clinical presentation, that is the observable characteristics or traits, without implication of a particular mechanism

Allergic Biologics Timeline

Shows when each of the biologics was approved and for what indication Prior to 2022

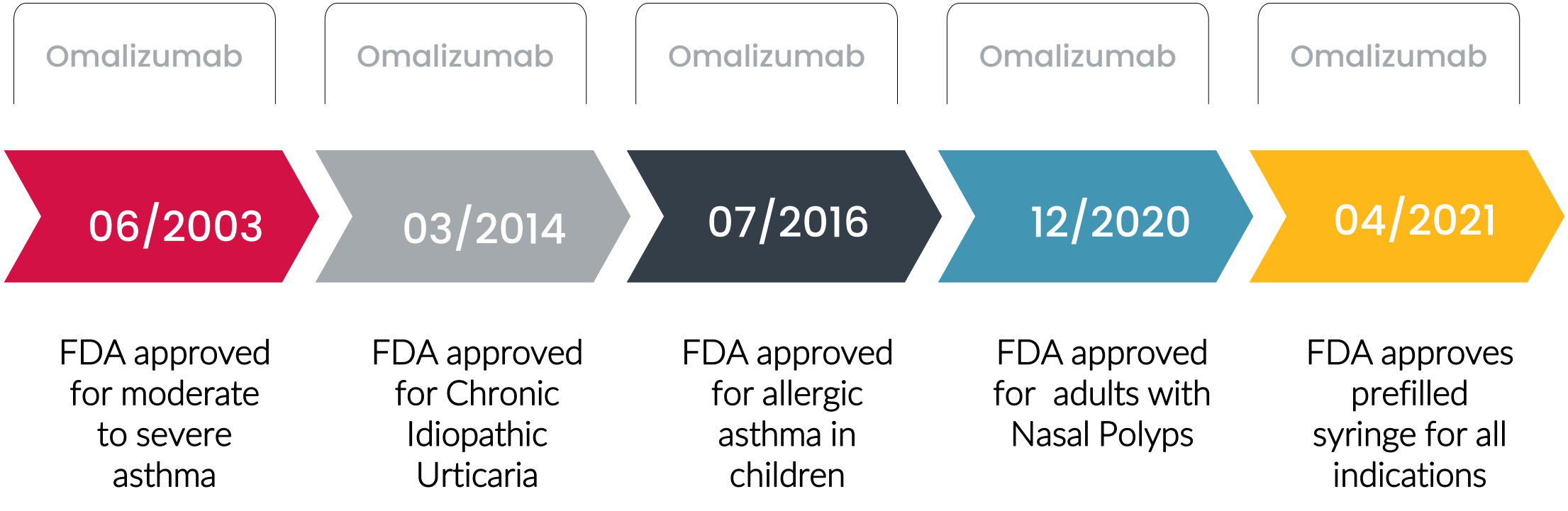
Omalizumab	mepolizumab	reslizumab	Dupilumab	Benralizumab	Tezepelumab
06/2003	11/2015	03/2016	03/2017	04/2017	01/2022
FDA approved for moderate-severe asthma	FDA approved for Severe Asthma.	FDA approved for Severe Asthma	FDA approved for Eczema; Asthma in 2018	FDA approved for severe eosinophilic asthma	FDA approved for severe asthma

Omalizumab Timeline

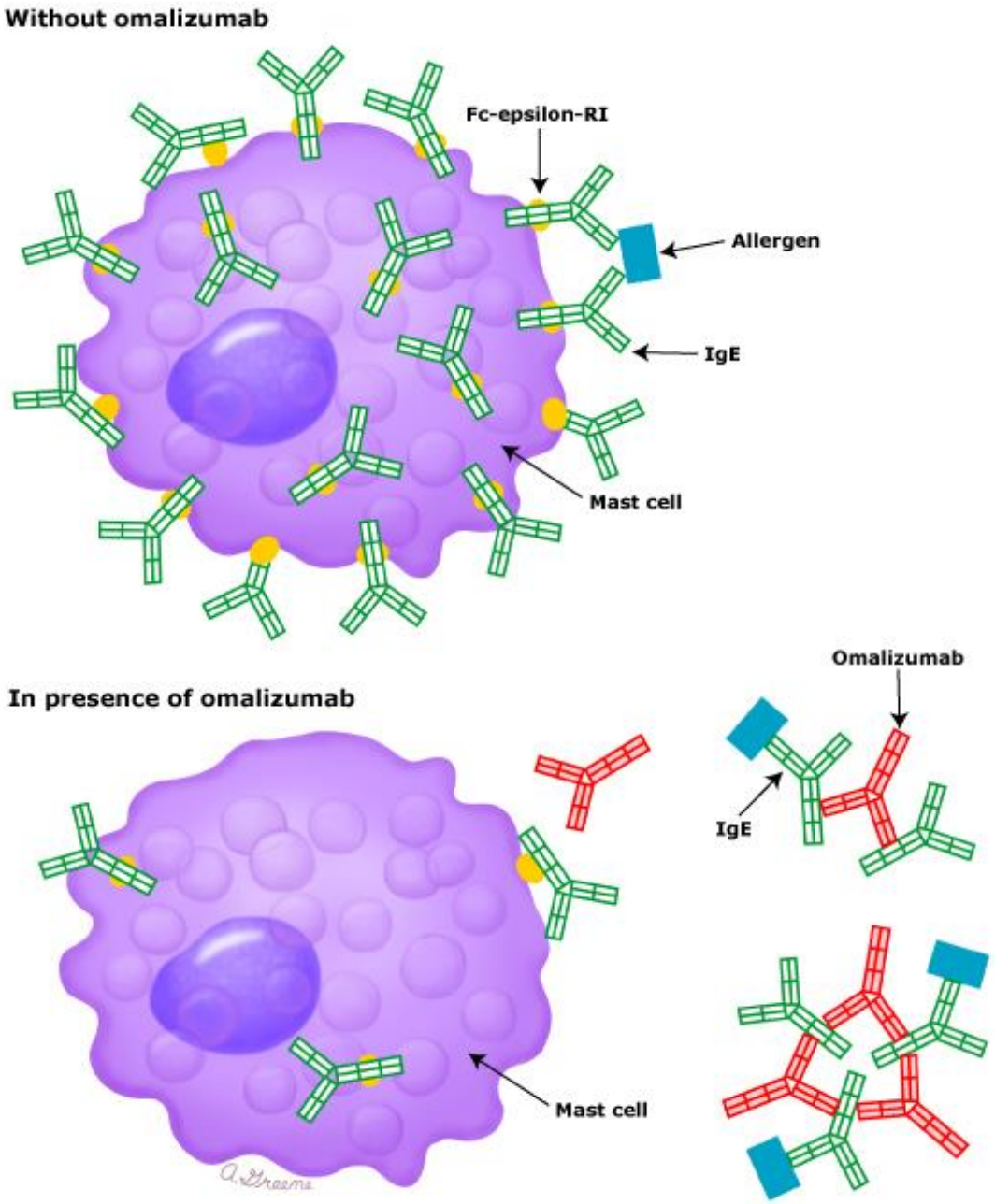
Brand Name: Xolair

Timeline of FDA approvals for various disease states.

Mode of action:



Omalizumab mechanism of action



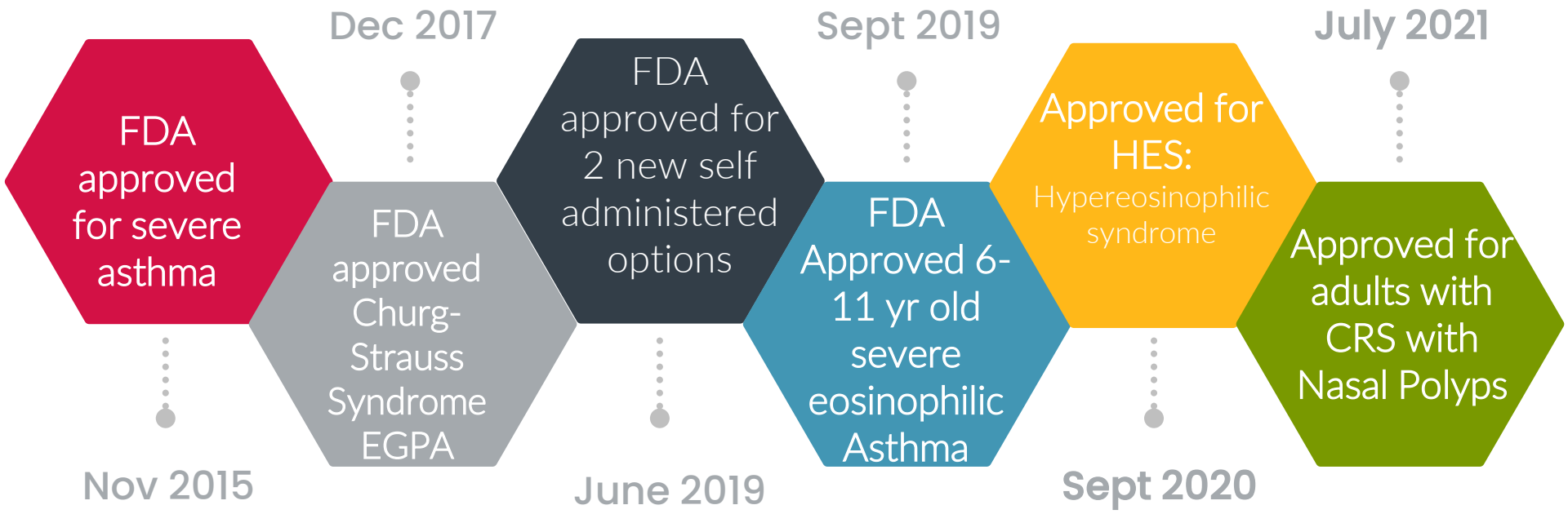
Omalizumab binds free IgE in the serum, forming trimers and hexamers. The drug binds to IgE at the same site that the high-affinity IgE receptor (Fc-epsilon-RI) binds, so IgE bound to drug cannot bind its receptor on mast cells and basophils. Omalizumab does not bind IgE that is already bound to Fc-epsilon-RI and so should not result in cross-linking of receptors. As a result of the binding of free IgE, the number of IgE receptors on the surface of mast cells and basophils declines over time, which is believed to be a critical component of the clinical effect of the drug. Omalizumab also blocks binding of IgE to the low-affinity IgE receptor (Fc-epsilon-RII or CD23, not shown), although the therapeutic relevance of this is not known.

Source of image is UpToDate, 2022

mepolizumab Timeline

Brand Name: Nucala

Timeline of FDA approvals for various disease states humanized 1L-5 antagonist monoclonal antibody

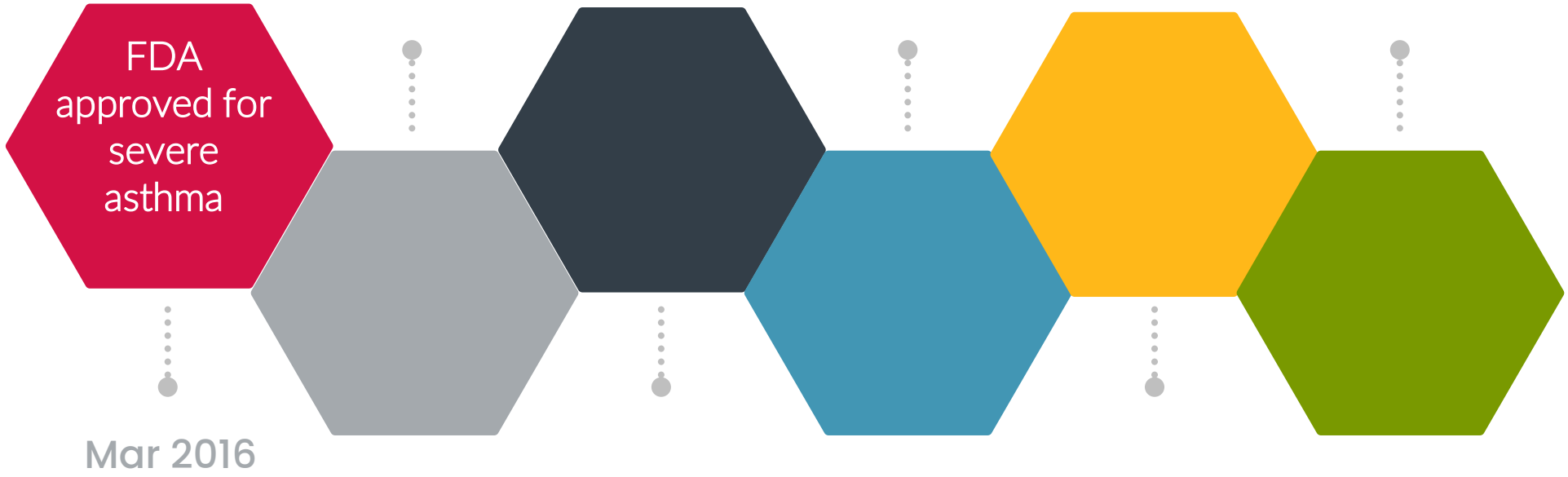


mepolizumab

- Humanized IL-5 antagonist
- SubQ injection 100 mg every 4 weeks
- No loading dose: no weight adjustment

reslizumab Timeline

Brand Name: Cinquair in the US, Cinqaero in Europe
Timeline of FDA approvals for various disease states



Reslizumab

- Humanized IL-5 antagonist
- Given IV once every four weeks over 20-50 minutes: may given at infusion center, in office or at home.
- Weight based dosing: 3mg/kg every four weeks.
- Add on maintenance therapy for adults with severe asthma with an eosinophilic phenotypes

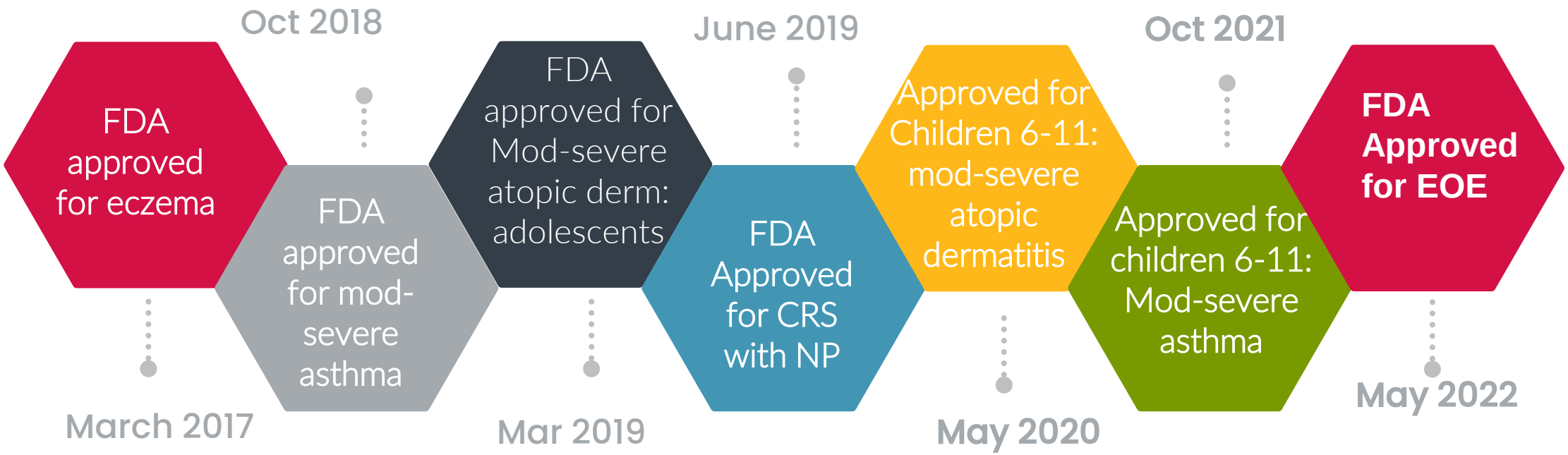
- What is the difference between Reslizumab and mepolizumab?
- **Conclusions**: Mepolizumab and reslizumab provide significant and clinically relevant improvements in exacerbation rate and OCS reduction. Indirect, inter-study comparisons revealed no differences between the anti-IL-5 drugs in efficacy or safety measures.*

*Henriksen DP, et al. Efficacy, adverse events, and inter-drug comparison of mepolizumab and reslizumab anti IL-5 treatments of severe asthma – a systematic review and meta-analysis. Eur Clin Respir J. (2018) 5(1): 1536007

Dupilumab Timeline

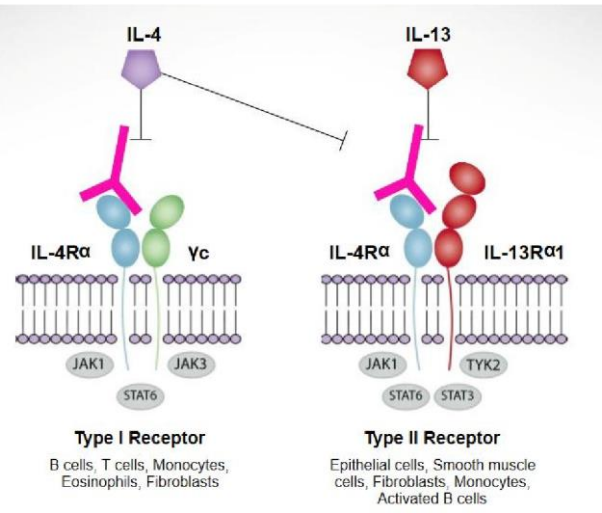
Brand Name: Dupixent

Timeline of FDA approvals for various disease states



Dupilumab:

- By blocking IL-4R alpha subunit, it is a dual inhibitor of IL-4 and IL-13
  - It does not have 2 inhibitors
  - It blocks two pathways that use the same subunit in their receptor.
- Given SubQ: There is some variability in dosing depending on condition.
- Available in 100 mg, 200 mg and 300 mg pre-filled syringe or pen
- Given every 2 weeks to those who weigh over 30 Kg
- 15-30 Kg: give every 4 weeks

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@inproceedings{Roucy2015InnovationTD, title={Innovation th{\'e}rapeutique
dans l'asthme : cas du dupilumab}, author={R{\'e}mi de Roucy}, year={2015} }
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Dupilumab: EOE

- FDA approved May 20 2022 for Eosinophilic Esophagitis (EOE)
- Approved for adults and children over 12 year of age weighing at least 40 kilograms.
- Dosing is unique for EOE: No loading dose
  - 300 mg weekly

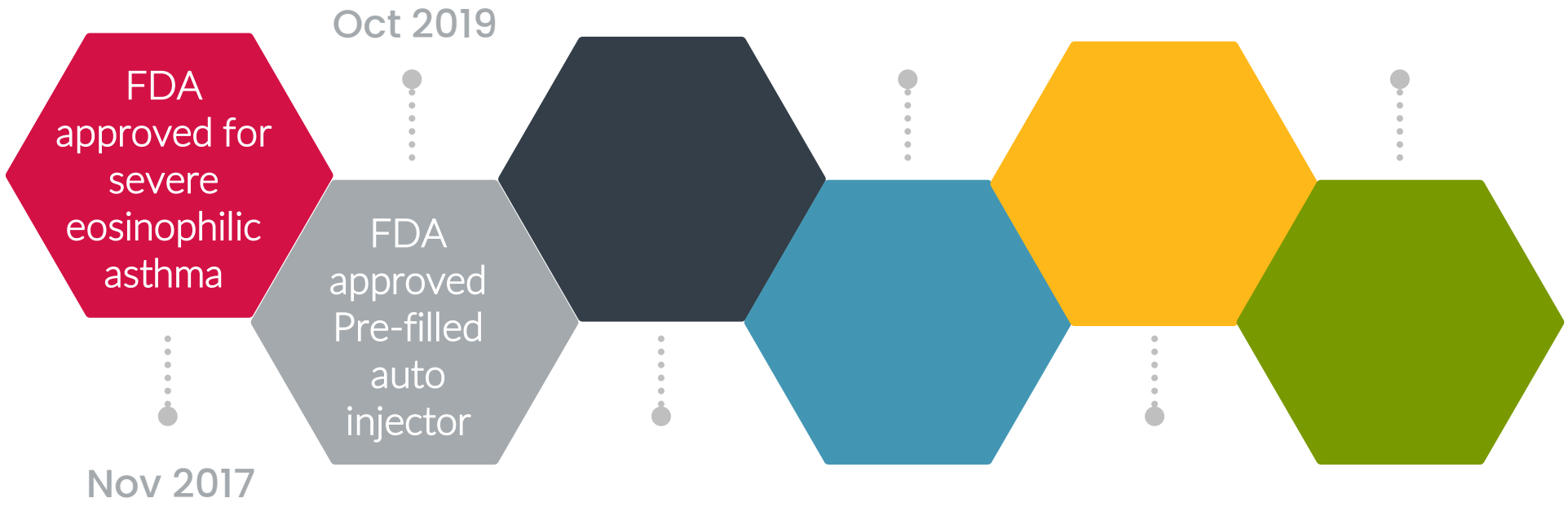
Dupilumab dosing other than EOE

- Asthma
  - 200 to 300 mg every other week
- Chronic Rhinosinusitis with nasal polyposis
  - 300 mg every other week
- Atopic dermatitis
  - Read the package insert carefully for dosing instructions by age and weight
  - Patients over 6 years of age get loading dose, those under 6 do not.

benralizumab Timeline

Brand Name: Fasenra

Timeline of FDA approvals for various disease states



benralizumab

- IL-5 receptor, alpha-directed cytolytic mAb: Reduces eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity (ADCC)

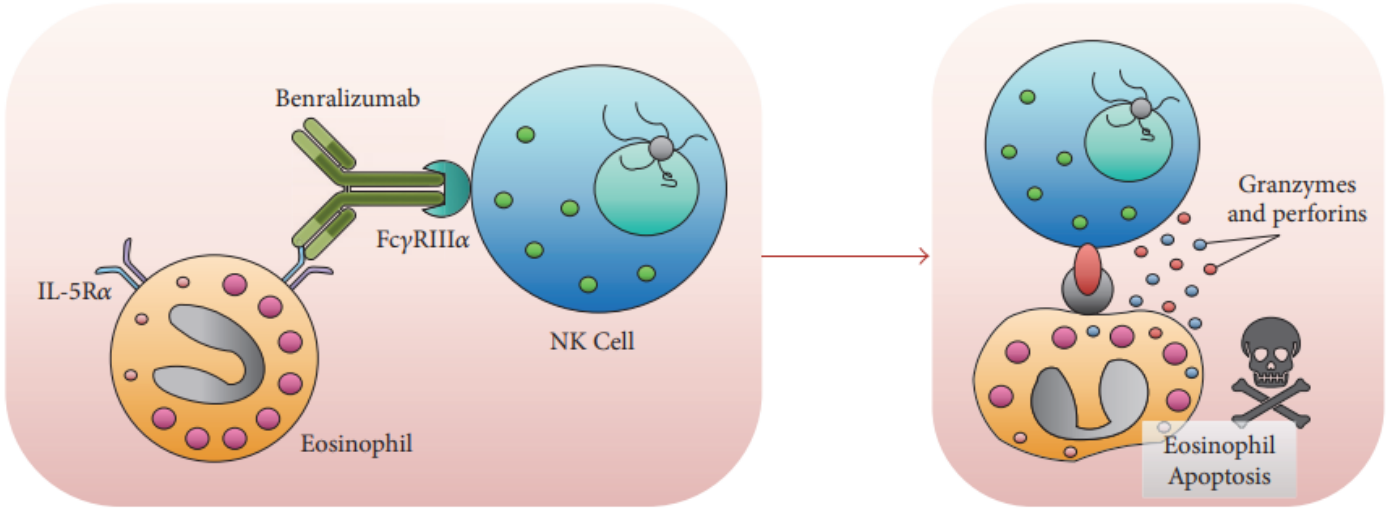
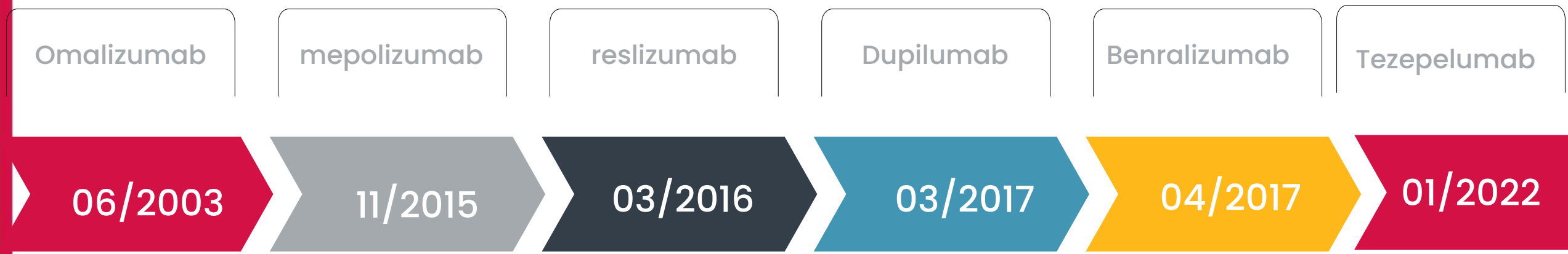


FIGURE 2: Mechanisms of action of benralizumab. Via its Fab fragments, the humanized monoclonal antibody benralizumab specifically binds to IL-5Rα, thereby preventing the interaction between IL-5 and its receptor. In addition, through its Fc constant region, benralizumab binds to the FcγIIIRa receptor expressed by natural killer cells, thus inducing eosinophil apoptosis operated by the release of proapoptotic proteins such as granzymes and perforins.

Pelaia C, et al. Benralizumab: From the Basic Mechanism of Action to the Potential Use in the Biological Therapy of Severe Eosinophilic Asthma. BioMed Research International (2018). Article ID 4839230, 9 pages

Allergic Biologics Timeline

Shows when each of the biologics was approved and for what indication Prior to 2022



FDA approved for moderate-severe asthma

FDA approved for Severe Asthma.

FDA approved for Severe Asthma

FDA approved for Eczema; Asthma in 2018

FDA approved for severe eosinophilic asthma

FDA approved for severe asthma

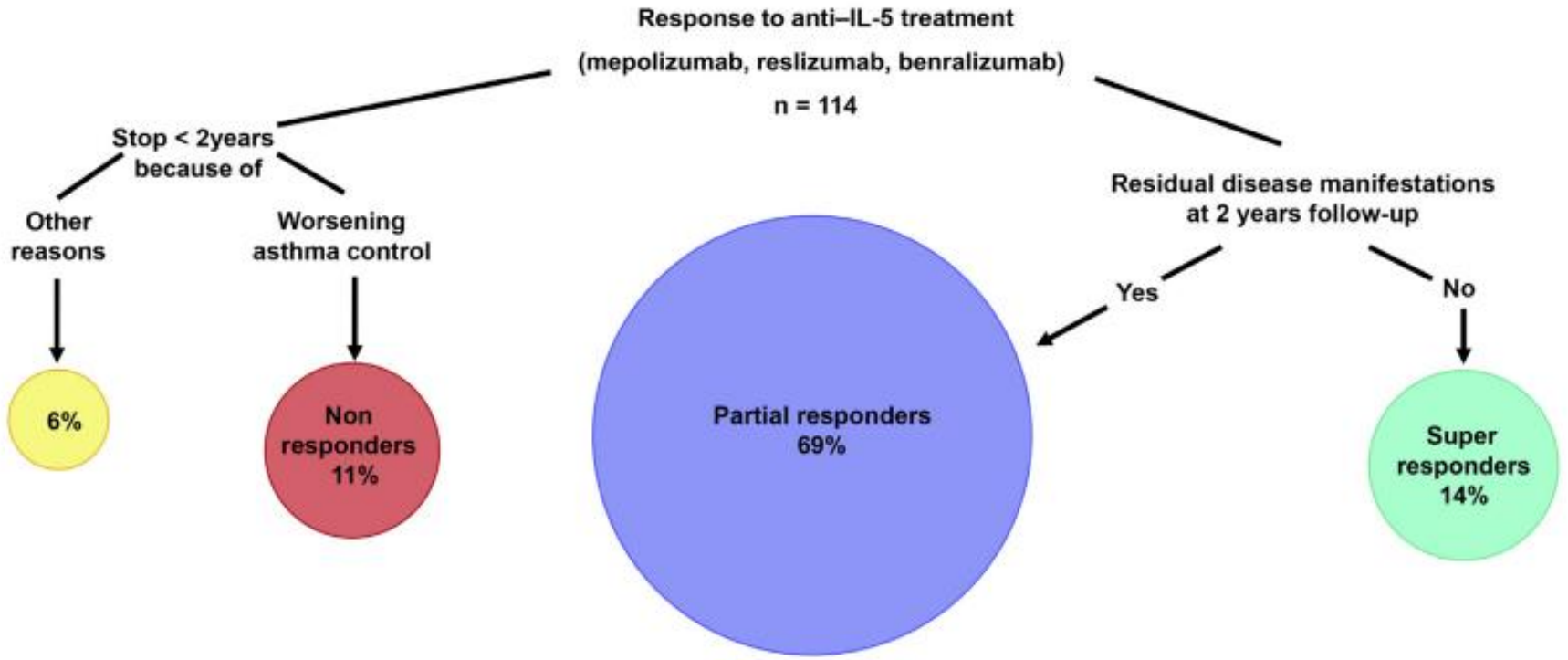


FIGURE 1. Prevalence of super responders, partial responders, and nonresponders after 2 years of treatment with anti–IL-5 biologics for severe eosinophilic asthma. In this observational cohort study, 11% of patients could be labeled as nonresponders, 69% as partial responders, and 14% as super responder after 2 years of anti–IL-5 treatment for severe eosinophilic asthma. Six percent of patients discontinued anti–IL-5 treatment after less than 2 years for other reasons.

Biologics are not miracle drugs.

Eger K, et al. Long-Term Therapy Response to Anti-IL5 Biologics in Severe Asthma – A Real-Life Evaluation. JACI in Practice. 2021;9(3):1194-2000.

nature reviews drug discovery

NEWS IN BRIEF | 13 January 2022

FDA approves first-in-class TSLP-targeted antibody for severe asthma

Asher Mullard

The FDA approved AstraZeneca and Amgen's first-in-class anti-TSLP monoclonal antibody tezepelumab for the treatment of severe asthma. Tezepelumab is the first biologic approved in the US for severe asthma without any phenotype or biomarker limitations.

January 2022:
FDA approves TSLP targeted antibody for severe asthma.

Menzies-Gow et al. Respiratory Research (2020) 21:268
https://doi.org/10.1186/s12931-020-01505-x

Respiratory Research

COMMENTARY Open Access

Unmet need in severe, uncontrolled asthma: can anti-TSLP therapy with tezepelumab provide a valuable new treatment option?

Andrew Menzies-Gow[1*], Michael E. Wechsler[2] and Chris E. Brightling[3]

Abstract

Despite treatment with standard-of-care medications, including currently available biologic therapies, many patients with severe asthma have uncontrolled disease, which is associated with a high risk of hospitalization and high healthcare costs. Biologic therapies approved for severe asthma have indications limited to patients with either eosinophilic or allergic phenotypes; there are currently no approved biologics for patients with eosinophil-low asthma. Furthermore, existing biologic treatments decrease exacerbation rates by approximately 50% only, which may be because they target individual, downstream elements of the asthma inflammatory response, leaving other components untreated. Targeting an upstream mediator of the inflammatory response may have a broader effect on airway inflammation and provide more effective asthma control. One such potential target is thymic stromal lymphopoietin (TSLP), an epithelial-derived cytokine released in response to multiple triggers associated with asthma exacerbations, such as viruses, allergens, pollutants and other airborne irritants. Mechanistic studies indicate that TSLP drives eosinophilic (including allergic) inflammation, neutrophilic inflammation and structural changes to the airway in asthma through actions on a wide variety of adaptive and innate immune cells and structural cells. Tezepelumab is a first-in-class human monoclonal antibody that blocks the activity of TSLP. In the phase 2b PATHWAY study (NCT02054130), tezepelumab reduced asthma exacerbations by up to 71% compared with placebo in patients with severe, uncontrolled asthma across the spectrum of inflammatory phenotypes, and improved lung function and asthma control. Phase 3 trials of tezepelumab are underway. NAVIGATOR (NCT03347279), a pivotal exacerbation study, aims to assess the potential efficacy of tezepelumab further in patients with a broad range of severe asthma phenotypes, including those with low blood eosinophil counts. SOURCE (NCT03406078) aims to evaluate the oral corticosteroid-sparing potential of tezepelumab. DESTINATION (NCT03706079) is a long-term extension study. In addition, an ongoing phase 2 bronchoscopy study, CASCADE (NCT03688074), aims to evaluate the effect of tezepelumab on airway inflammation and airway remodelling in patients across the spectrum of type 2 airway inflammation. Here, we summarize the unmet therapeutic need in severe asthma and the current treatment landscape, discuss the rationale for targeting TSLP in severe asthma therapy and describe the current development status of tezepelumab.

Keyword: Asthma, Biologics, Burden of illness, Phenotype, Tezepelumab, Thymic stromal lymphopoietin

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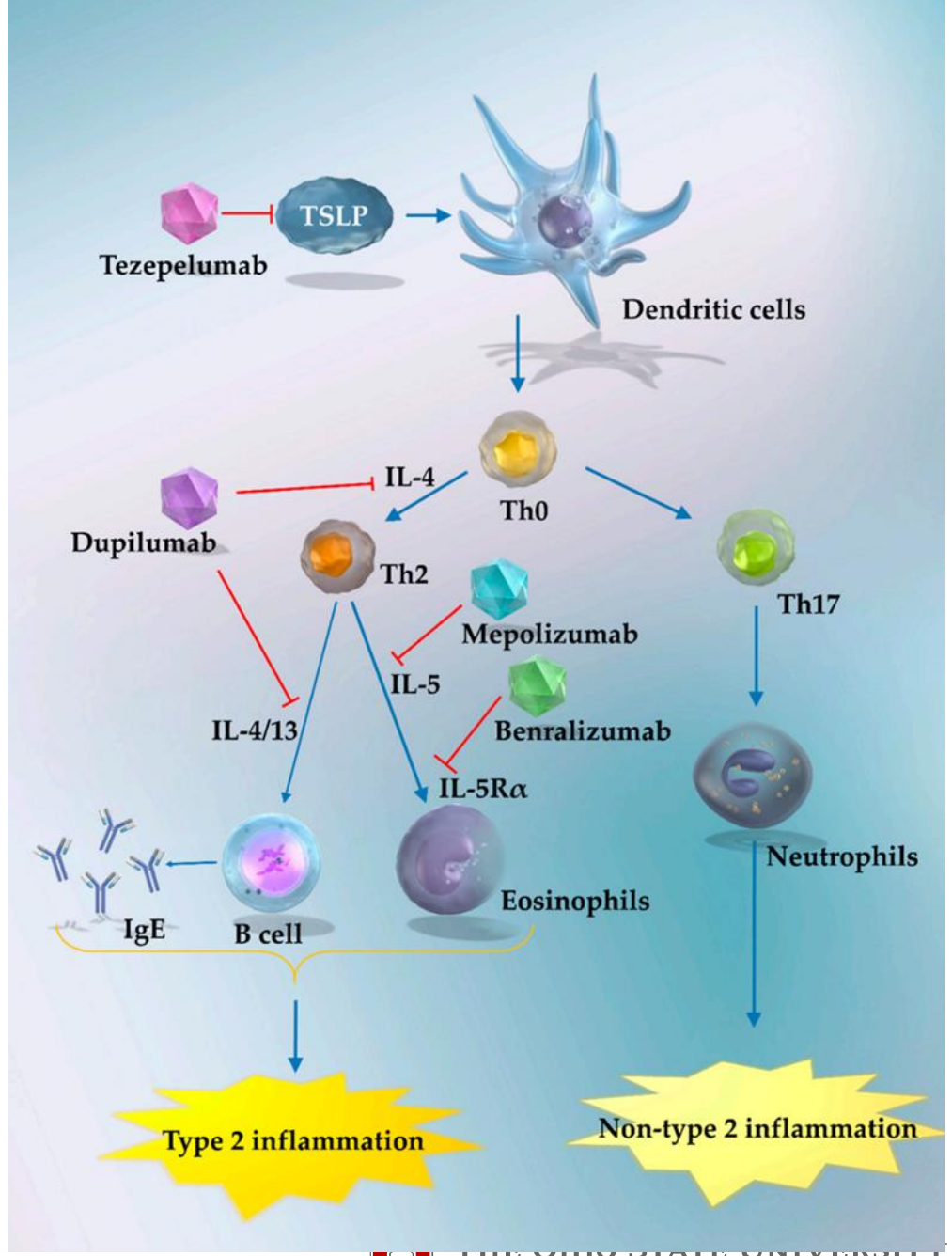
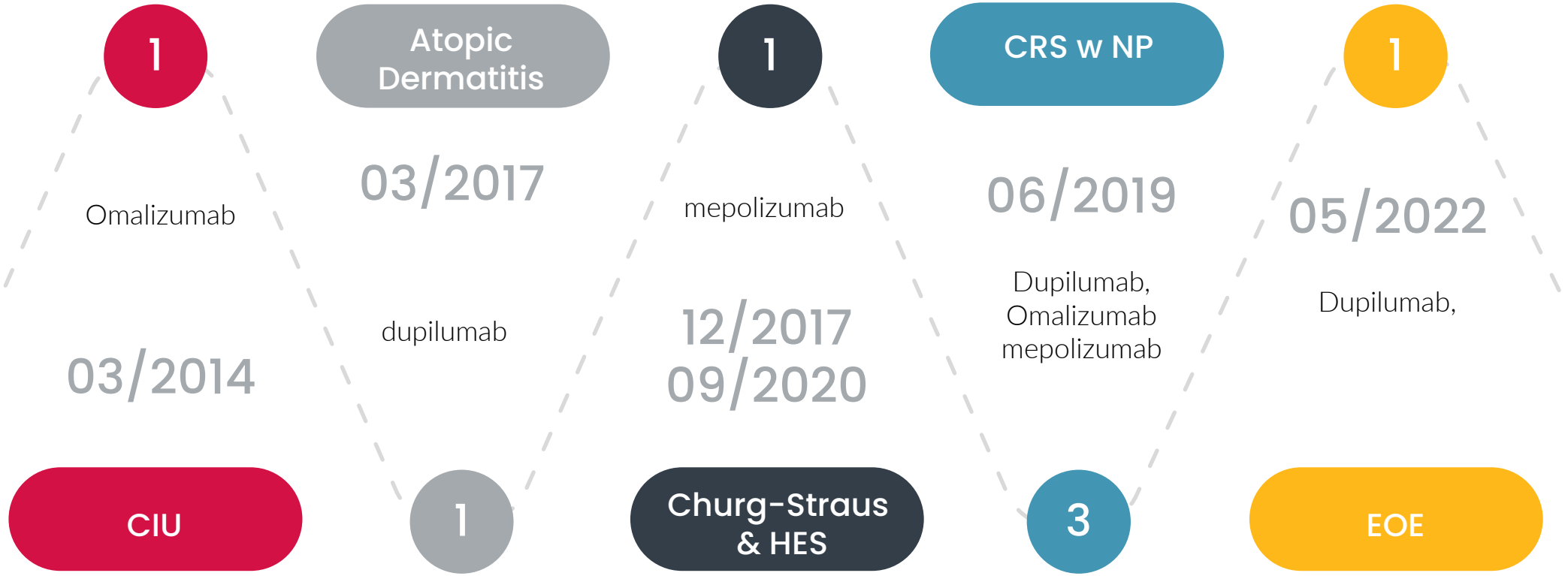
[1]Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK
Full list of author information is available at the end of the article



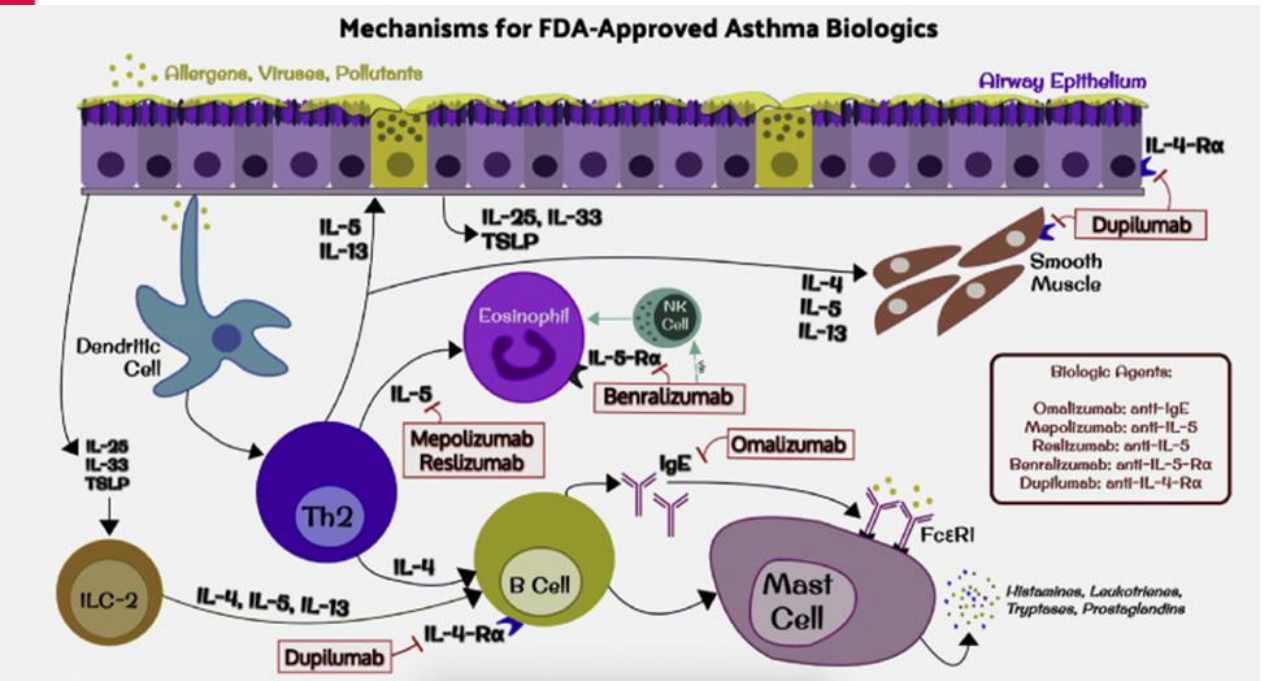
Approved Allergic Conditions for biologics

These conditions are approved indications for biologic use in allergic diseases other than ASTHMA. Date of approval and biologics currently approved are noted. .



Asthma

- Which Biologic should I use?
- This data changes rapidly



- Studies of the biologics have a high degree of variation & are difficult to compare
- Reduce blood eosinophils:
  - Dupilumab, mepolizumab and relizumab have strongest supporting data
- Improve lung function:
  - Dupilumab, benralizumab
- Reduce daily oral steroids:
  - Benralizumab, dupliumab

Doroudchi A. et al. Asthma Biologics. Ann Allergy Asthma Immunol 124 (2020) 44-56

CONCISE CLINICAL REVIEW

Role of Biologics in Asthma

Mary Clare McGregor[1], James G. Krings[1], Parameswaran Nair[2], and Mario Castro[1]

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Abstract

Patients with severe uncontrolled asthma have disproportionally high morbidity and healthcare utilization as compared with their peers with well-controlled disease. Although treatment options for these patients were previously limited, with unacceptable side effects, the emergence of biologic therapies for the treatment of asthma has provided promising targeted therapy for these patients. Biologic therapies target specific inflammatory pathways involved in the pathogenesis of asthma, particularly in patients with an endotype driven by type 2 (T2) inflammation. In addition to anti-IgE therapy that has improved outcomes in allergic asthma for more than a decade, three anti–IL-5 biologics and one anti–IL-4R biologic have recently emerged as promising treatments for T2 asthma. These targeted therapies have been shown to reduce asthma exacerbations, improve lung function, reduce oral corticosteroid use, and improve quality of life in appropriately selected patients. In addition to the currently approved biologic agents, several biologics targeting upstream inflammatory mediators are in clinical trials, with possible approval on the horizon. This article reviews the mechanism of action, indications, expected benefits, and side effects of each of the currently approved biologics for severe uncontrolled asthma and discusses promising therapeutic targets for the future.

Keywords: severe asthma; eosinophils; asthma treatments; biologics; monoclonal antibodies

Am J Respir Crit Care. (2019);199(4): 433-4

Clinical Commentary Review

J Allergy Clin Immunol Pract 2021;9:1107-17

Cost-Effectiveness of Biologics for Allergic Diseases

Ann Chen Wu, MD, MPH[a], Anne L. Fuhlbrigge, MD, MSc[b], Maria Acosta Robayo, BA[a], and Marcus Shaker, MD, MSc[c,d]

Boston, Mass; Aurora, Colo; and Lebanon and Hanover, NH

The introduction of specific humanized monoclonal antibodies over the past 20 years has dramatically changed the treatment of allergic diseases. At present, 5 mAbs are licensed for treating moderate to severe allergic and eosinophilic asthma, atopic dermatitis, chronic spontaneous urticaria, chronic sinusitis with nasal polyps, and eosinophilic granulomatosis with polyangiitis. Given the high costs of biologics, understanding their cost-effectiveness is critical. As new biologics are developed and new indications are approved for existing biologics, the use of biologics for allergic diseases will increase. Conducting cost-effectiveness evaluations in parallel to efficacy and effectiveness trials will help patients, providers, payers, and policymakers in decision making.

and eosinophilic asthma, atopic dermatitis, chronic spontaneous urticaria (CSU), chronic sinusitis with nasal polyps, and eosinophilic granulomatosis with polyangiitis. Additional mAbs are under development, and studies to support additional indications for already approved mAbs are ongoing. Given the high costs of biologics, understanding their cost-effectiveness is critical.

The first mAb to be approved for allergic diseases was omalizumab, approved by the Food and Drug Administration (FDA) in 2003 for moderate to severe asthma.[1,2] The critical role of IgE in the pathogenesis of allergic inflammation was discovered in 1967 and paved the way for the concept introduced in 1986 that anti-IgE treatments could serve as treatment for allergic diseases.[3-5] An initial study found that omalizumab inhibited early- and

REVIEW ARTICLE

WILEY

PAI. 2019;30:159-171

New perspectives of childhood asthma treatment with biologics

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Abstract

Asthma is no longer considered as a single disease but rather as a syndrome corresponding to different entities and pathophysiologic pathways. A targeted strategy is part of personalized medicine which aims to better define each patient's phenotype and endotype so as to prescribe the most suitable treatment at an individual level. Omalizumab and, more recently, mepolizumab are the first biologics approved for children (6-18 years). Omalizumab is now widely used to treat severe allergic asthma in children and is highly effective for asthma exacerbations and asthma control with a good safety profile. Moreover, several other drugs—lebrikizumab, dupilumab, tezepelumab, mepolizumab, reslizumab, benralizumab—are used or are being studied

Biochemical Pharmacology 179 (2020) 114012

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journal homepage: www.elsevier.com/locate/biochempharm

Review

Promises and challenges of biologics for severe asthma

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ARTICLE INFO

Keywords:
Omalizumab

ABSTRACT

Patients with severe asthma that remain uncontrolled incur significant medical burden and healthcare costs. Severe asthma is a heterogeneous airway disorder with complex pathophysiological mechanisms which can be

Clinical Commentary Review

J Allergy Clin Immunol Pract 2015;3:162-6

The Use of Anti-IgE Therapy Beyond Allergic Asthma

Jeffrey R. Stokes, MD[a], and Thomas B. Casale, MD[b] *Omaha, Neb; and Tampa, Fla*

Omalizumab is a monoclonal anti-IgE antibody that has been used to treat allergic asthma for over a decade. The use of omalizumab to treat other diseases has largely been limited to case reports until the recently reported large multicenter studies that have established omalizumab as an effective treatment option for chronic spontaneous urticaria. The utility of omalizumab to treat nonallergic asthma and allergic rhinitis and the added safety and therapeutic benefits in combination with allergen immunotherapy have been demonstrated in placebo-controlled trials. Data supporting the clinical efficacy of omalizumab in treating atopic dermatitis, physical urticarias, mast cell disorders, food allergy, and various other allergic disorders have shown promise in small clinical trials and case studies. More carefully designed, large clinical trials of high quality are needed to fully appreciate the potential of omalizumab in treating various allergic and nonallergic diseases. **(J Allergy Clin Immunol Pract 2015;3:162-6)**

(CSU). H1 antihistamines are effective for 50% to 60% of these patients.[1,2] Several small studies have demonstrated the effectiveness of omalizumab in chronic autoimmune urticaria, nonimmune chronic urticaria, and CSU.[3-5]

A randomized, placebo-controlled study involving 90 patients with antihistamine refractory CSU evaluated a single administration of 3 different doses of omalizumab, 75, 300, or 600 mg, versus placebo. Only the 300- and 600-mg doses demonstrated an improvement in urticaria scores 4 weeks after treatment and there was no significant difference in efficacy between the higher doses.[6] This led to 3 large, phase III, randomized, double-blind, placebo-controlled studies: Asteria I, Asteria II, and Glacial. All the 3 studies evaluated 12- to 75- year-old patients with CSU that was refractory to standard of care with oral H1 antihistamines.[7-9]

Results of the Asteria I trial were published in 2014.[7] In this study, 318 patients were randomized to 1 of 3 different doses of omalizumab (300, 150, 75 mg) or placebo every 4 weeks for 24

ERSITY

Potential therapeutic utility of omalizumab in diseases other than allergic asthma

- **Urticaria**
- Physical urticarias
- Non allergic Asthma
- Allergic Rhinitis
- **Atopic Dermatitis**
- Allergic Bronchopulmonary Aspergillosis
- **Nasal Polyps**
- Food Allergy
- Immunotherapy
- Eosinophilic Esophagitis
- Mast Cell Disorders
- Other Diseases:
  - **Churg-Strauss syndrome**, bullous pemphig geal angioedema, chronic eosinophilic pneumonia

We're back to 2015 with this graphic

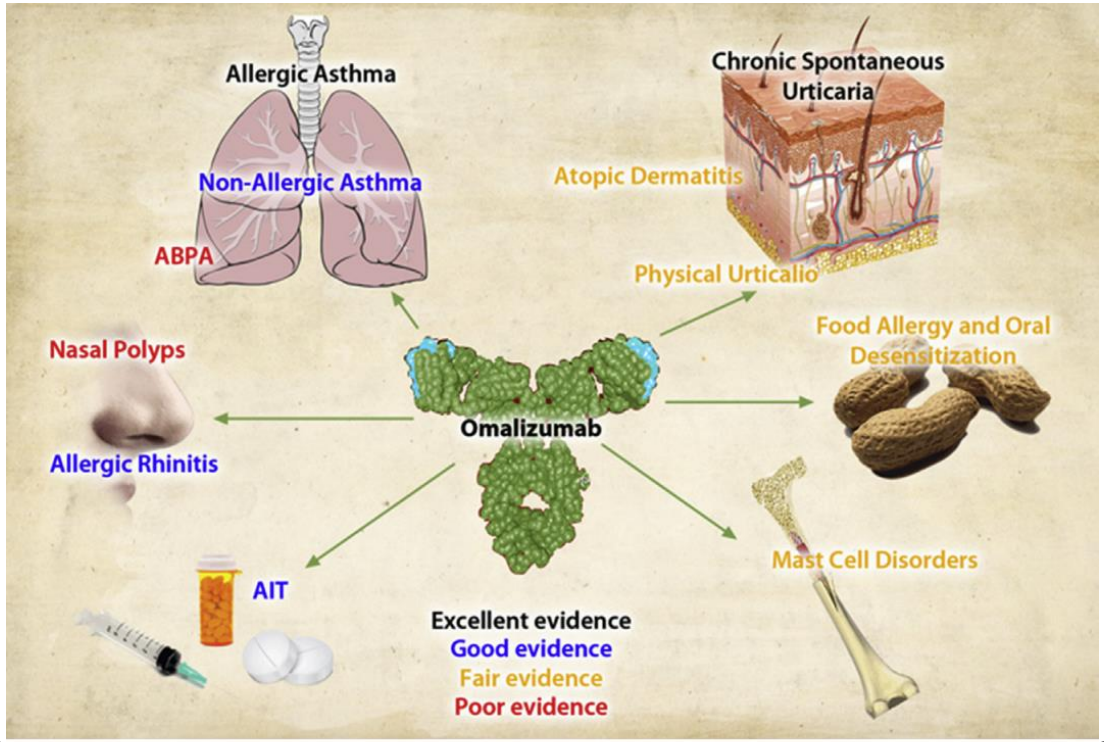


FIGURE 1. Omalizamab: Clinical benefits in published data.

J Allergy Clin Immunol Pract 2015;3:162-6

Atopic Dermatitis

The scratch that itches…

Not just a pediatrics problem

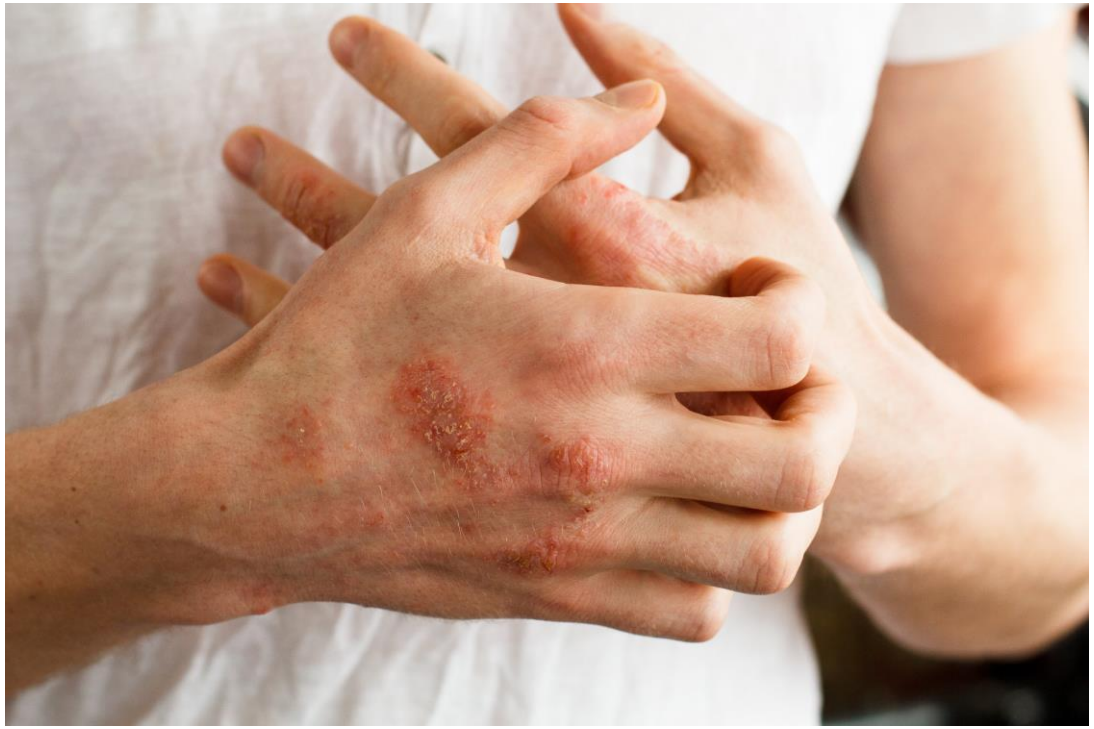
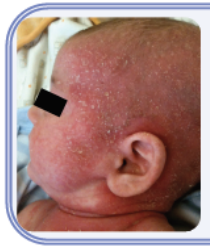


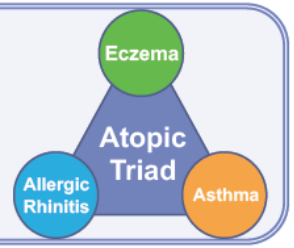
Image from Academic Alliance in Dermatology

ATOPIC DERMATITIS (AD)



Atopic dermatitis (also known as eczema) is a common chronic inflammatory skin condition that begins during infancy or early childhood, characterized by dry, pruritic, erythematous papules and plaques

Pattern of AD



CLINICAL FEATURES

Diagnostic criteria: itchy skin (essential) + ≥ 3 of the following:

1. Hx of relapsing **OR** current visible **flexural dermatitis (> 4 yo)** or dermatitis on **cheeks, forehead, outer limbs (< 4 yo)**
   See pattern of AD above
2. Personal Hx of **asthma** or **allergic rhinitis** (or positive FHx of first-degree relative in children < 4 yo)
3. **Xerosis** within past year
4. Onset < 2 years

DIFFERENTIAL DIAGNOSIS

- **Seborrheic / contact / nummular dermatitis**
- **Infestations** - scabies
- **Infection** - tinea, impetigo
- **Autoimmune** - lupus, dermatomyositis
- **Primary immunodeficiencies** (rare)
- **Mycosis fungoides** (in adolescents)

PATHOPHYSIOLOGY

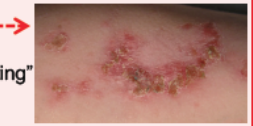
Epidermal Barrier Dysfunction
Genetic Disposition
Immune Dysregulation

QUALITY OF LIFE

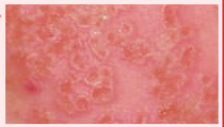
- Psychosocial distress (loss of sleep, intense pruritis, social embarrassment)
- ↑ risk of ADHD, depression, and anxiety

COMPLICATIONS

IMPETIGO
- *S. aureus* infection
- Yellow overlying "honey-crusting"
- Topical/systemic antibiotics



ECZEMA HERPETICUM
- HSV infection
- Monomorphic, punched out erosions
- Immediate antiviral therapy



ECZEMA COXSACKIUM
- Coxsackie virus infection

MANAGEMENT

NON-PHARMALOGICAL (All patients)	MILD TO MODERATE DISEASE	MODERATE TO SEVERE DISEASE
➢ **Patient education** (www.eczemahelp.ca) ➢ **Eliminate exacerbating factors** (e.g. scented products, dry air) ➢ Skin **hydration** (e.g. petroleum jelly, thick unscented creams)	➢ **Topical corticosteroids** (BID) ➢ Face: Hydrocortisone 1% ointment ➢ Body: Betamethasone valerate 0.05% ointment ➢ Topical calcineurin inhibitors ➢ Topical phosphodiesterase-4 inhibitor	➢ **Phototherapy** ➢ **Immunosuppressants** ➢ **Biologics** (dupilumab)

Published July 2021
Selena Osman (MD Student 2023, University of Calgary), Dr. Harry Liu (Dermatology Resident, UBC), and Dr. Michele Ramien (Pediatric Dermatologist, University of Calgary) for www.pedscases.com

Clinical Management Review

Biologics for Treatment of Atopic Dermatitis: Current Status and Future Prospect

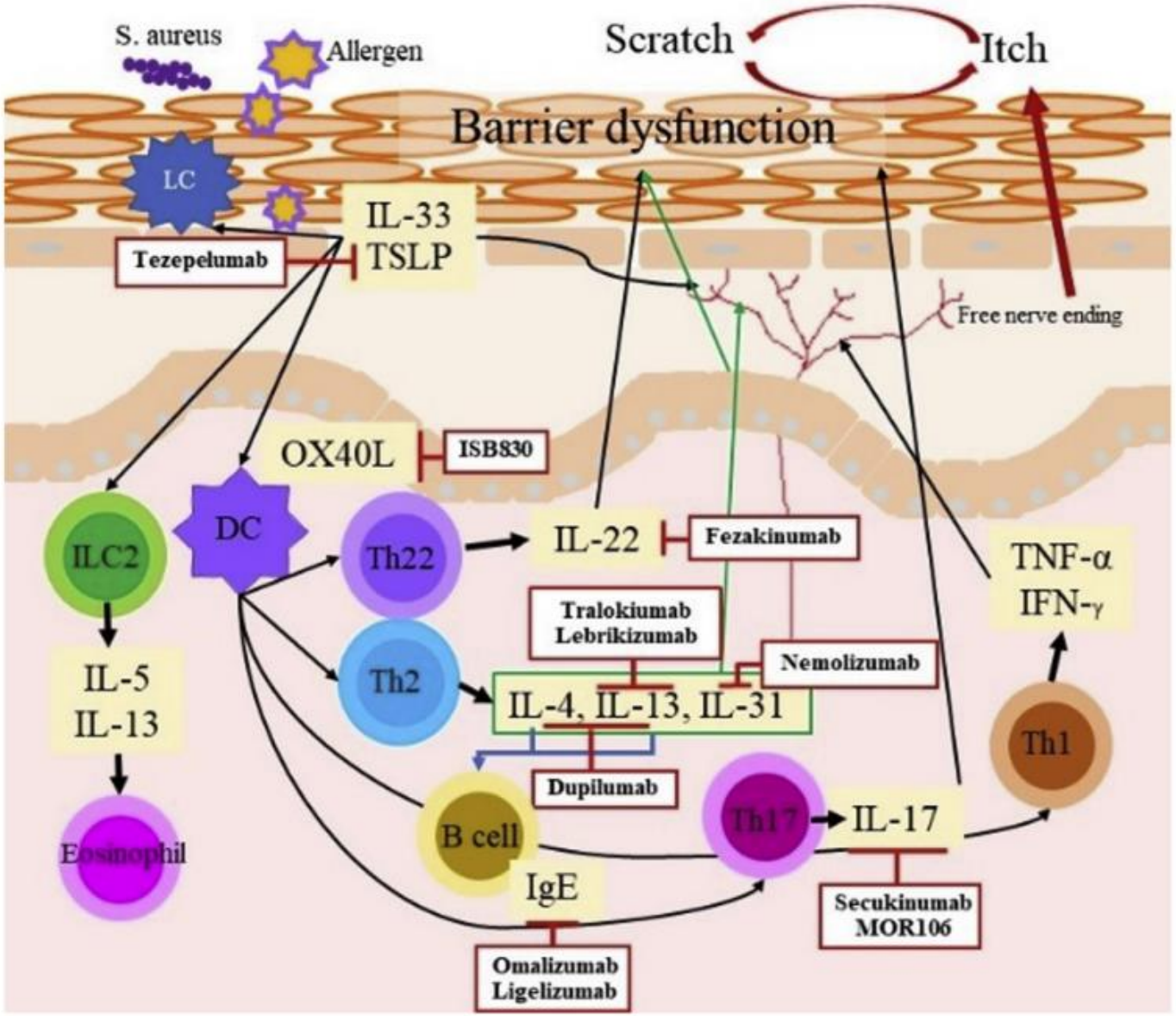
Thanaporn Ratchataswan, MD[a], Tina M. Banzon, MD[a,b], Jacob P. Thyssen, MD, PhD, DmSci[c], Stephan Weidinger, MD, PhD, MaHM[d], Emma Guttman-Yassky, MD, PhD[e], and Wanda Phipatanakul, MD, MS[a,b] *Boston, Mass, Copenhagen, Denmark; Kiel, Germany; and New York, NY*

Atopic dermatitis (AD) is a common inflammatory skin disease characterized by intense pruritus and recurrent eczematous lesions that significantly impair quality of life. It is a heterogeneous disease affecting both children and adults. The treatment of moderate-to-severe forms of AD is challenging, as topical corticosteroids are often insufficient to achieve disease control or inappropriate and off-label use of immunosuppressants may have significant undesirable side effects. The development of targeted biologic therapies specifically for AD is thus highly desirable. Dupilumab is the only biologic therapy that is Food and Drug Administration approved for the treatment of moderate-to-severe AD in patients 6 years and older, with consistent long-term efficacy and safety trial data. In this article, we review the mechanisms, safety, and efficacy of dupilumab from recent clinical trials, and we review the current data, mechanism of action, clinical efficacy, and limitations of new biologics currently in phase 2 and 3 clinical trials (lebrikizumab, tralokinumab, nemolizumab, tezepelumab, and ISB 830).

J Allergy Clin Immunol Pract 2021;9:1053-65

Approved biologics for Atopic Dermatitis

- Dupilumab is the only biologic currently approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for moderate to severe AD.
- Although dupilumab shows good efficacy, only approximately 1/3 patients have complete clearance
- There is a need for further innovation of therapeutics, to include other biologics targeting cytokines involved in the inflammatory pathway of Atopic Dermatitis.



J Allergy Clin Immunol Pract 2021;9:1053-65

FIGURE 1. Atopic dermatitis pathogenesis and targets of biologics approved and in clinical development for atopic dermatitis. *DC*, Dendritic cell; *IFN*, interferon; *IgE*, immunoglobulin E; *IL*, interleukin; *ILC*, innate lymphoid cell; *LC*, langerhans cell; *Th*, T-helper; *TNF*, tumour necrosis factor; *TSLP*, thymic stromal lymphopoietin.

J Allergy Clin Immunol Pract 2021;9:1053-65

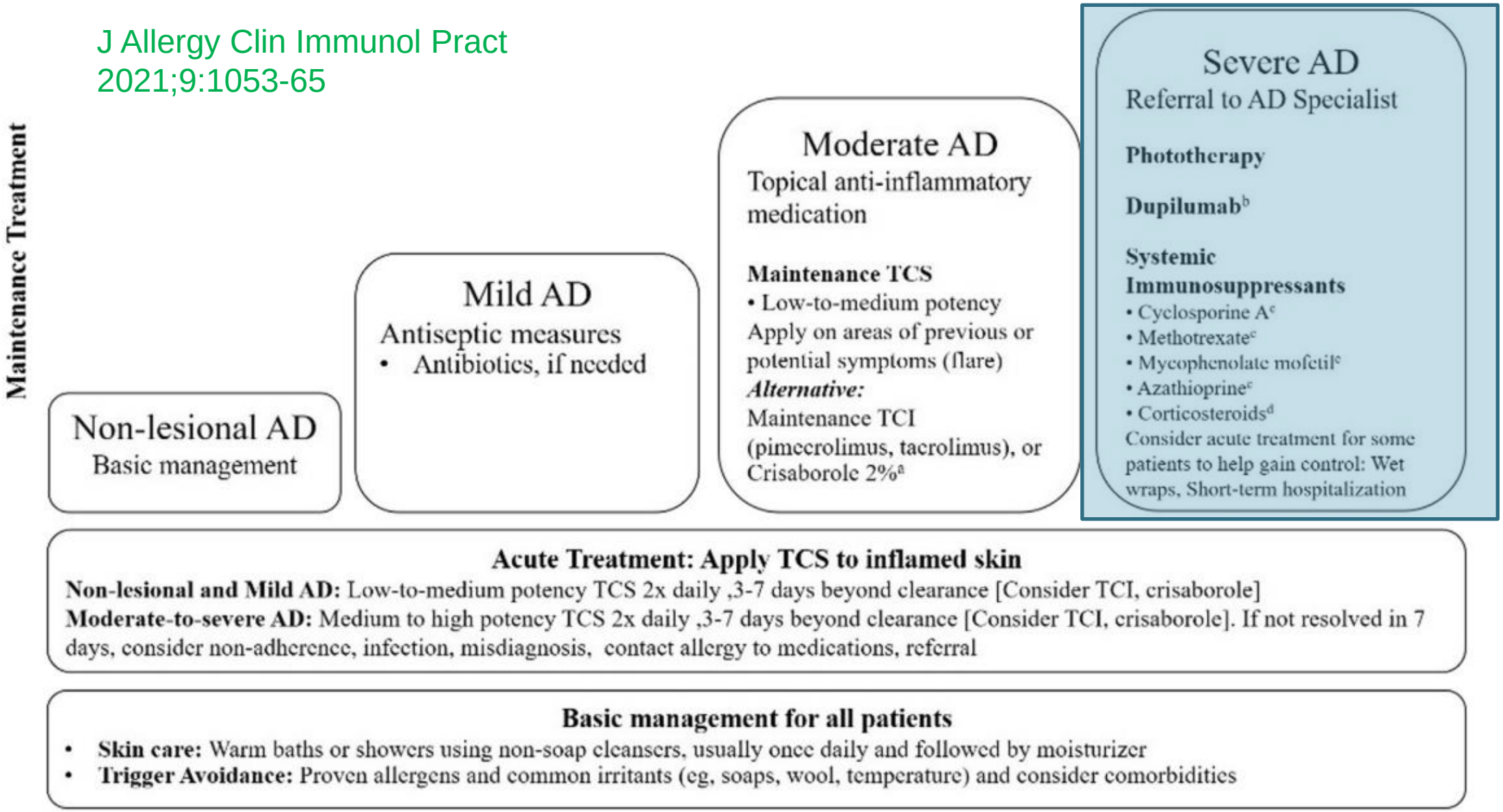


FIGURE 2. Step-care management of atopic dermatitis (AD). Acute and maintenance treatments for AD across the spectrum of disease severity. [a]For patients aged ≥2 years with mild-to-moderate AD. [b]For patients aged ≥6 years with moderate-to-severe AD. [c]Not approved by the Food and Drug Administration to treat AD. [d]Not recommended for long-term maintenance. *TCI*, Topical calcineurin inhibitor; *TCS*, topical corticosteroid. Adapted from Eichbein et al.[81]

ERSITY

ORIGINAL ARTICLE

Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma

Leonard B. Bacharier, M.D., Jorge F. Maspero, M.D., Constance H. Katelaris, M.D., Alessandro G. Fiocchi, M.D., Remi Gagnon, M.D., Ines de Mir, M.D., Neal Jain, M.D
Lawrence D. Sher, M.D., Xuezhou Mao, Ph.D., Dongfang Liu, M.S., Yi Zhang, Ph.D., M.P.H., Asif H. Khan, M.B., B.S., M.P.H., et al., for the Liberty Asthma VOYAGE Investigators*

December 9, 2021
N Engl J Med 2021; 385:2230-2240
DOI: 10.1056/NEJMoa2106567

- 408 children between 6-11 years old with mod-severe asthma
- subQ dupilumab q 2 weeks; continued standard therapy
- Results: Children with uncontrolled mod-severe asthma who received add-on dupilumab had fewer exacerbations, better lung function and asthma control than those who received placebo.

December 9, 2021: Bacharier et al. NEJM (2021); 385; 2230-2240

Biologics for Urticaria

- Urticaria affects approximately 1.6 million people in the US
- Most often occurs between ages of 20 and 40.
- Has large effect on quality of life and leaves people feeling frustrated, anxious and fatigued.
- Omalizumab is currently the only biologic approved for urticaria

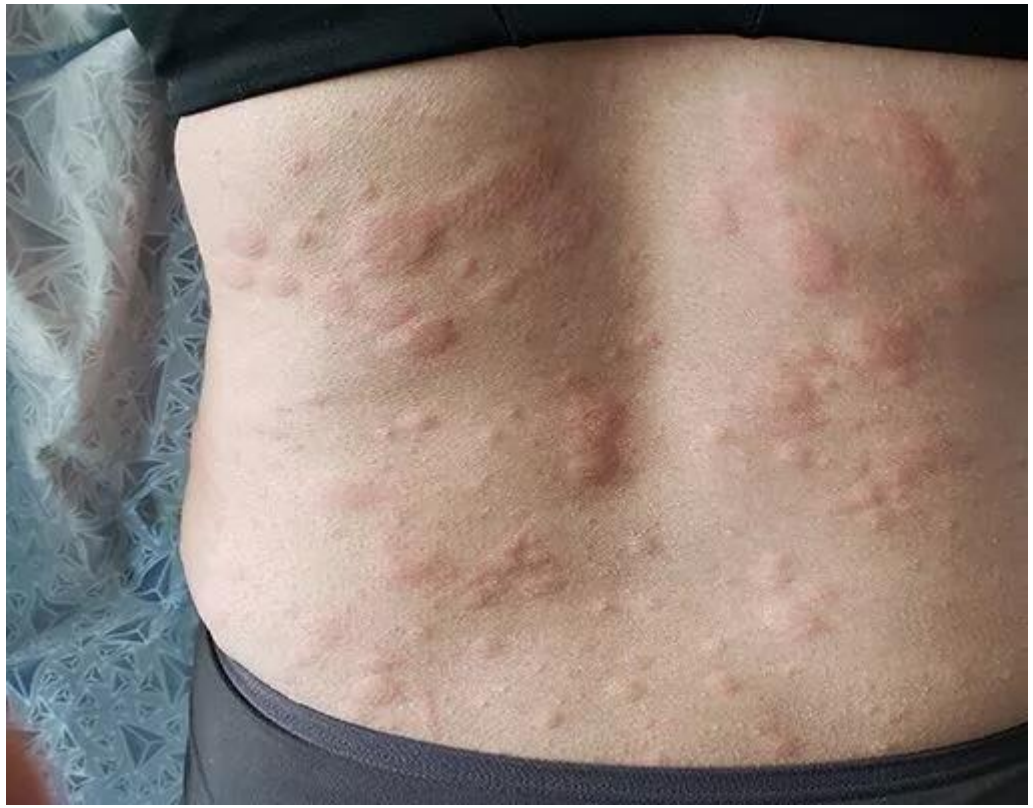


Image from the Allergy & Asthma Network

Clinical Commentary Review

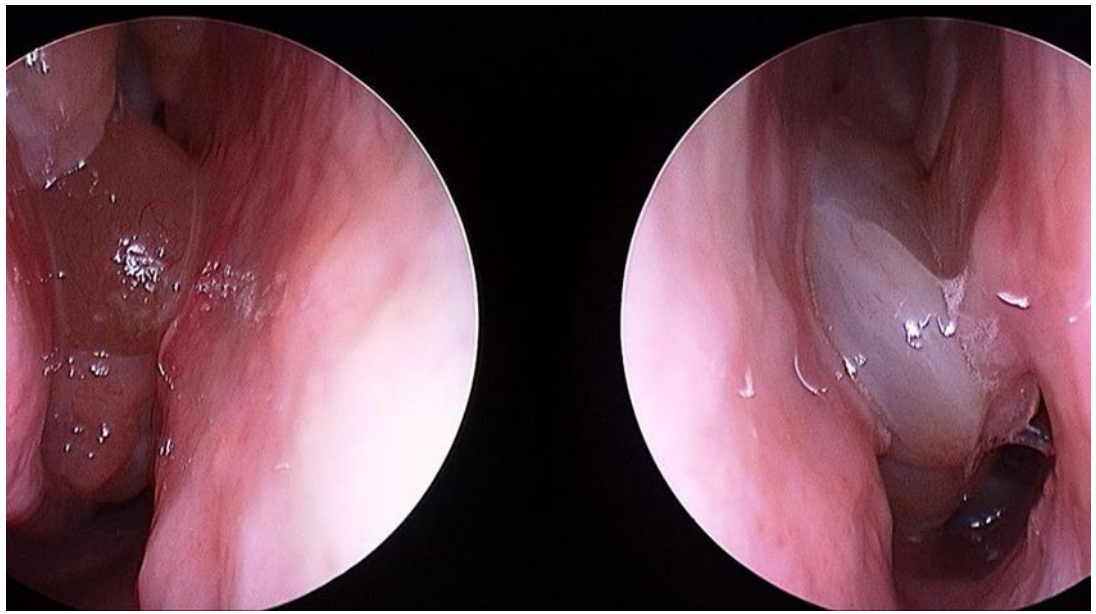
J Allergy Clin Immunol Pract 2021;9:1067-78

Biologics for the Use in Chronic Spontaneous Urticaria: When and Which

Marcus Maurer, MD[a,*], David A. Khan, MD[b,*], Daniel Elieh Ali Komi, MSc[c], and Allen P. Kaplan, MD[d,*] *Berlin, Germany; Dallas, Tex; Urmia, Iran; and Charleston, SC*

Guidelines for the treatment of chronic spontaneous urticaria (CSU) recommend the use of the IgE-targeted biologic omalizumab in patients with antihistamine-refractory disease. The rationale for this is supported by the key role of IgE and its high-affinity receptor, FcεRI, in the degranulation of skin mast cells that drives the development of the signs and symptoms of CSU, itchy wheals, and angioedema. Here, we review the current understanding of the pathogenesis of CSU and its autoimmune endotypes. We describe the mechanisms of action of omalizumab, the only biologic currently approved for CSU, its efficacy and ways to improve it, biomarkers for treatment response, and strategies for its discontinuation. We provide information on the effects of the off-label use, in CSU, of biologics licensed for the treatment of other diseases, including dupilumab, benralizumab, mepolizumab, reslizumab, and secukinumab. Finally, we discuss targets for novel biologics and where we stand with their clinical development. These include IgE/ligelizumab, IgE/GI-310, thymic stromal lymphopoietin/tezepelumab, C5a receptor/avdoralimab, sialic acidebinding Ig-like lectin 8/lirentelimab, CD200R/ LY3454738, and KIT/CDX-0159. Our aim is to provide updated information and guidance on the use of biologics in the treatment of patients with CSU, now and in the near future

Nasal Polyps



- Nasal polyps are benign growths in the nose that are believed to come about due to prolonged inflammation. They may be associated with chronic rhino-sinusitis.

Chronic Rhino-sinusitis with Nasal Polyps (CRS w NP)

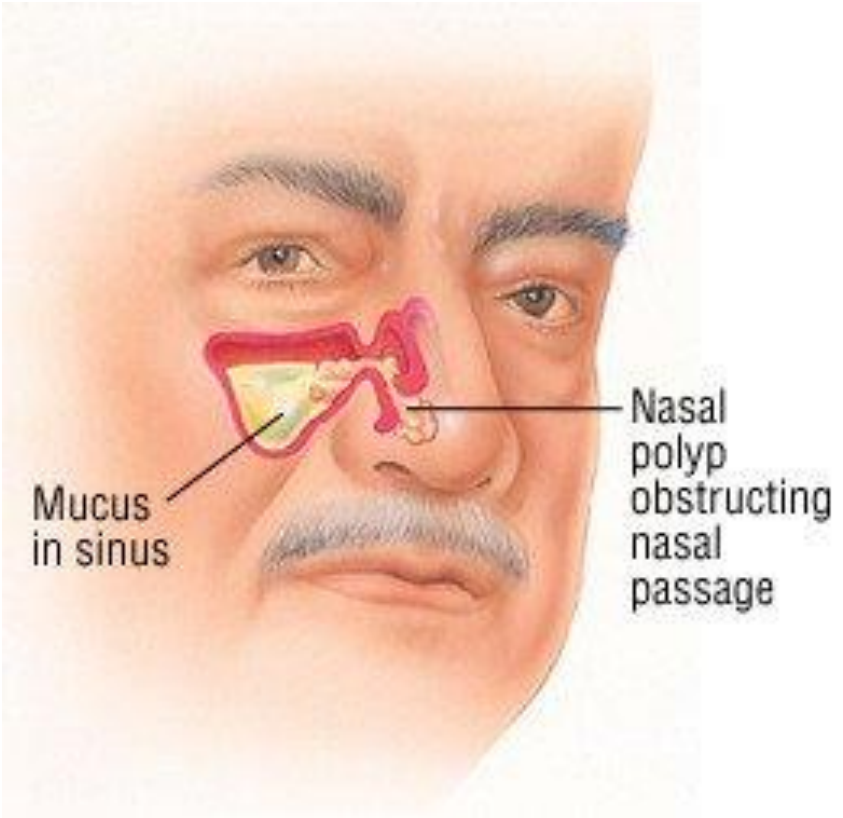
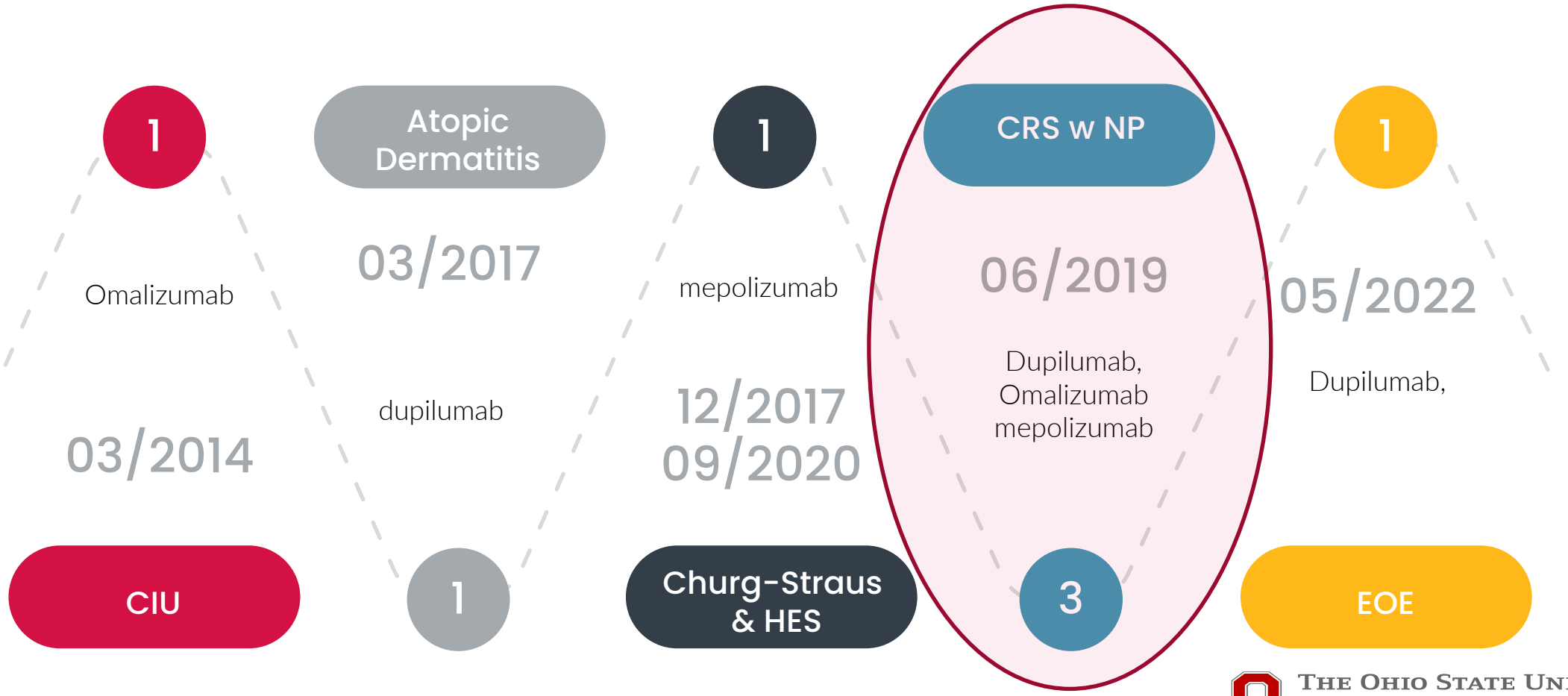


Image from Prof Richard Harvey: sydneyentclinic.com

Image from Drugs.com access March 10, 20

Approved Allergic Conditions for biologics

These conditions are approved indications for biologic use in allergic diseases other than ASTHMA. Date of approval and biologics currently approved are noted. .



Ann Allergy Asthma Immunol 124 (2020) 318–325

Contents lists available at ScienceDirect

CME Review

Use of endotypes, phenotypes, and inflammatory markers to guide treatment decisions in chronic rhinosinusitis

Anna G. Staudacher, MS [*]; Anju T. Peters, MD [*,†]; Atsushi Kato, PhD [*]; Whitney W. Stevens, MD, PhD [*,†]

[*] Division of Allergy and Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois
[†] Department of Otolaryngology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Key Messages

- While few criteria are currently available to help physicians select the best treatment modality for patients with CRS, certain inflammatory endotypes, clinical phenotypes, and/or clinical biomarkers may be of assistance.
- The type 2 endotype is predominantly observed among patients with CRSwNP or CRSsNP living in the United States. However, there can be variation in inflammatory endotypes based upon geographical location.
- Smell loss has been significantly associated with a type 2 inflammatory endotype but additional studies are needed to identify if other clinical symptoms could be used to predict inflammatory endotypes.
- The number of tissue and/or peripheral eosinophils may indicate disease severity in patients with CRSwNP but they may not necessarily predict treatment responses.
- Additional studies are needed to identify clinical phenotypes or biomarkers that could predict type 1 or type 3 inflammation in CRSwNP or type 1, type 2, or type 3 inflammation in CRSsNP.

CRS2wNP

- Complex Disease
- Consider mechanisms: phenotypes
- ICAR-RS 2021*

Staudacher AG et al. Ann Allergy, Asthma and Immunol. (2020) 124:318-325.
*Orlandi RR et al. International Foum of Allergy and Rhinology. (2021) 11(3): 213-739

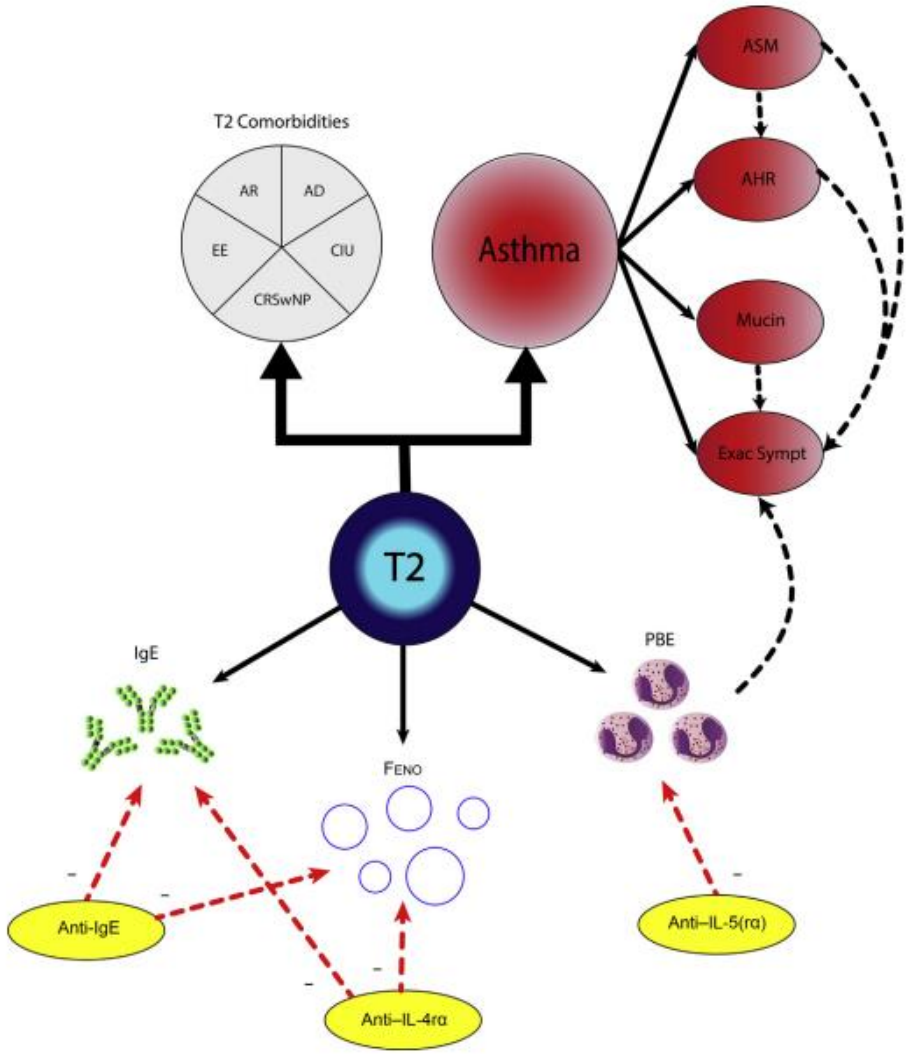


FIGURE 1. Activation of T2 inflammation elevates levels of IgE, FENO, and PBE. These biomarkers are targeted by various biological therapies as depicted. Relationship between T2 inflammation with asthma and relevant comorbidities shown. *AD*, Atopic dermatitis; *AHR*, airway hyperresponsiveness; *AR*, allergic rhinitis; *ASM*, airway smooth muscle; *CIU*, chronic idiopathic urticaria; *EE*, eosinophilic esophagitis; *Exac*, exacerbations; *Sympt*, symptoms.

Pragmatic Clinical Perspective

- Asthmatics often have comorbidities.
- When deciding on an initial biologic for asthma, keep the comorbidities in mind, and use a biologic that will provide the patient with the most overall relief (precision medicine).

Chan R, et al. Pragmatic Clinical Perspective on Biologics for Severe Refractory Type 2 Asthma. JACI in Practice. 2020;8(10): 3363-70

cells

MDPI

Review

The Role of Airway Epithelial Cell Alarmins in Asthma

Christiane E. Whetstone, Maral Ranjbar, Hafsa Omer, Ruth P. Cusack and Gail M. Gauvreau *

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* Correspondence: gauvreau@mcmaster.ca; Tel.: +1-905-525-9140 (ext. 22791)

Abstract: The airway epithelium is the first line of defense for the lungs, detecting inhaled environmental threats through pattern recognition receptors expressed transmembrane or intracellularly. Activation of pattern recognition receptors triggers the release of alarmin cytokines IL-25, IL-33, and TSLP. These alarmins are important mediators of inflammation, with receptors widely expressed in structural cells as well as innate and adaptive immune cells. Many of the key effector cells in the allergic cascade also produce alarmins, thereby contributing to the airways disease by driving downstream type 2 inflammatory processes. Randomized controlled clinical trials have demonstrated benefit when blockade of TSLP and IL-33 were added to standard of care medications, suggesting these are important new targets for treatment of asthma. With genome-wide association studies demonstrating associations between single-nucleotide polymorphisms of the TSLP and IL-33 gene and risk of asthma, it will be important to understand which subsets of asthma patients will benefit most from anti-alarmin therapy.

Keywords: airway epithelium; alarmin cytokines; TSLP; IL-33; IL-25; asthma

Citation: Whetstone, C.E.; Ranjbar, M.; Omer, H.; Cusack, R.P.; Gauvreau, G.M. The Role of Airway Epithelial Cell Alarmins in Asthma. *Cells* **2022**, *11*, 1105. https://doi.org/10.3390/cells11071105

Academic Editors: Barbara Ruaro,

1. Introduction

Epithelial cell-derived mediators including the alarmin cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) have emerged as key players in propagating asthma pathogenesis. Release of these alarmins from the airway epithelium of asthmatics leads to the downstream production of type 2 cytokines, most notably IL-4, IL-5, and IL-13 from multiple effector cells. With upregulation of type 2 cytokine expression, many allergic

Alarmins

Alarmin cytokines: IL-25, IL-33 and TSLP may be key players in the pathogenesis of inflammation.

Whetstone CE, et al. Cells (2022), 11,1105. https://doi.org/10.3390/cells11071105

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Table 3. TSLP and pathogenic effects in asthmatic airways.

	Cell Type	Functional Effect of TSLP on Cellular Function
Innate Immunity	Monocytes/ macrophages	↑ TARC/CCL17, PARC/CCL18, MDC/CCL22, MIP3β/CL19 [168] ↑ CD80 [165] ↑ M2 macrophages [169]
	Myeloid DC	↑ MHC class II, CD40, CD86, CD54, CD80, CD83 [170] ↑ OX40L [170,171] ↑ IL-8, eotaxin-2, TARC/CC17, MDC/CCL22, I-309/CCL1 [156,172,173] ↑ Expansion of CRTH2+ CD4+ Th2 memory cells [166,174] ↑ Differentiation of Tregs [174,175] Signals through Jagged-1, JAK1, JAK2, Akt, ERK, JNK, NF-kB (p50, RelB), STAT1, STAT3, STAT4, STAT5, STAT6 [172,176–182]
	Mast cells	↑ IL-5, IL-13, IL-6, IL-10, IL-8, GM-CSF [153,183] ↑ CXCL8, CCL1 [153,184] ↑ TGF- β [153]
	Basophils	↑ CD69, CD62L, CD11b, CD123, IL-33R, IL-18R surface expression [167] ↑ IL-4, IL-13 [45] ↑ CD203c, IL17RB expression [45]
	Eosinophils	↑ Survival, adhesion [185] ↑ CD18, ICAM-1, CXCL8, CXCL1, CCL2, IL-6 [185] ↓ L-selectin [185] Signals through ERK, p38, NF-kB [185]
	ILC2s	↑ IL-25R, IL-33R expression [186,187]
	Natural killer T cells	↑ IL-4, IL-13 [188]
	CD34+ progenitor cells	↑ Eosinophilopoiesis and basophilopoiesis [189,190] ↑ IL-5, IL-13, GM-CSF, CCL22, CCl17, CXCL8, CCL1 [189,190] ↑ IL-5Rα expression [189,190]
Adaptive Immunity	B cells	↑ Proliferation [191,192] ↑ Development [191,192] Signals through STAT1, STAT3, STAT5, JAK1, JAK2 [193]
	Th2 cells	↑ Proliferation [156] ↑ Differentiation [156] ↑ IL-5, IL-4, IL-13 [156,171]
	CD4+ T cells	↑ Proliferation [156] ↑ Differentiation [156,191] Signals through STAT1, STAT5, JAK1, JAK2 [177–179,194,195]
	CD8+ T cells	↑ Proliferation [196] Signals through STAT5, Bcl-2 [196]
	T regulatory cells	↓ Development [176] ↑ Differentiation [166,174–176] ↓ IL-10 [197]
Structural Cells	Epithelial/endothelial cells	↑ Airway obstruction mechanisms [198,199] Signals through TARC/CCL17, MDC/CCL22, IP-10/CXCL10 [198,199]
	Airway smooth muscle	↑ IL-6, CXCL8, CCL11 [200] ↑ Migration, actin polymerization, cell polarization [200] Signals through STAT3, MAPKs (ERK1/2, p38 and JNK) [200]

TSLP

- TSLP pathogenic effects in asthmatic airways.
- Alarmins are released in response to danger signals from the environment
- Have effects on Innate Immunity, Adaptive Immunity and on structural cells.
- May also play important roles in other allergic diseases.

Whetstone CE, et al. Cells (2022), 11,1105. https://doi.org/10.3390/cells11071105

cells

MDPI

Article

Comparative Efficacy and Safety of Tezepelumab and Other Biologics in Patients with Inadequately Controlled Asthma According to Thresholds of Type 2 Inflammatory Biomarkers: A Systematic Review and Network Meta-Analysis

Koichi Ando [1,2,*], Yosuke Fukuda [1], Akihiko Tanaka [1] and Hironori Sagara [1]

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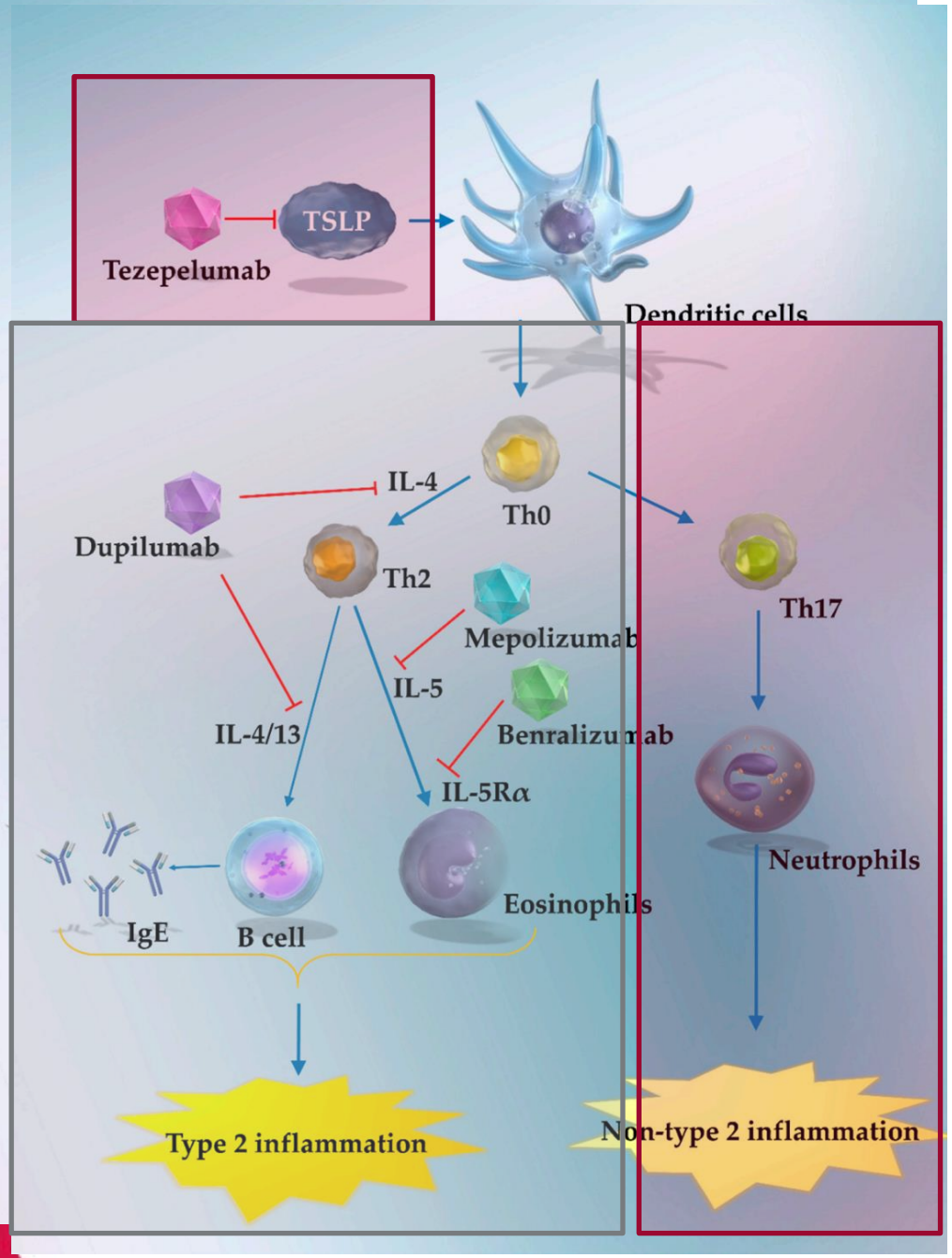
Abstract: The anti-thymic stromal lymphopoietin antibody (tezepelumab) has therapeutical potential for inadequately controlled asthma. However, evidence comparing tezepelumab with other biologics is scarce. To address this issue, we performed a network meta-analysis to compare and rank the efficacy of five treatments (tezepelumab, dupilumab, benralizumab, mepolizumab, and placebo) in overall participants and in subgroups stratified by the thresholds of type 2 inflammatory biomarkers, including peripheral blood eosinophil count (PBEC) and fractional exhaled nitric oxide (FeNO). The primary endpoints were annualized exacerbation rate (AER) and any adverse events (AAEs). In the ranking assessment using surface under the cumulative ranking curve (SUCRA) of AER, tezepelumab ranked the highest overall and across subgroups (based on PBEC and FeNO level thresholds). A significant difference was observed between tezepelumab and dupilumab in the patient subgroup with PBEC < 150, and between tezepelumab and benralizumab in overall participants and the patient subgroup with PBEC ≥ 300 and ≥150, respectively. There was no significant difference in the incidence of AAEs in the overall participants between each pair of five treatment arms. These results provide a basis for the development of treatment strategies for asthma and may guide basic, clinical, or translational research.

Citation: Ando, K.; Fukuda, Y.; Tanaka, A.; Sagara, H. Comparative Efficacy and Safety of Tezepelumab and Other Biologics in Patients with Inadequately Controlled Asthma According to Thresholds of Type 2 Inflammatory Biomarkers: A Systematic Review and Network Meta-Analysis. *Cells* **2022**, *11*, 819. https://doi.org/10.3390/

TSLP

- Can Anti-TSLP and other Biologics help patients with inadequately controlled asthma?
- In the sub group with peripheral blood eosinophils < 150 cells/mm, anti-TSLP (Tezepelumab) did significantly better.

Inflammatory Cascade



- Overview of the thymic stromal lymphopoietin (TSLP) – triggered immune response and pathogenesis of asthma. The cytokine TSLP is secreted by mucosal epithelial cells and its receptors are highly expressed on dendritic cells. TSLP induces a Th2-type immune response involving IL-4, IL-5, and IL-13 and is responsible for the pathogenesis of type 2 asthma. TSLPs are also involved in the pathogenesis of non-type 2 asthma by inducing the differentiation of Th17 cells by the activation of dendritic cells. Dupilumab targets IL-4 and IL-13, benralizumab targets IL-5Rα, and mepolizumab targets IL-5, and these drugs are mainly clinically effective in type 2 asthma. Tezepelumab Figure 7. Overview of the thymic stromal lymphopoietin (TSLP)-triggered immune response and pathogenesis of asthma. The cytokine TSLP is secreted by mucosal epithelial cells and its receptors are highly expressed on dendritic cells. TSLP induces a Th2-type immune response involving IL-4, IL-5, and IL-13 and is responsible for the pathogenesis of type 2 asthma. TSLPs are also involved in the pathogenesis of non-type 2 asthma by inducing the differentiation of Th17 cells by the activation of dendritic cells. Dupilumab targets IL-4 and IL-13, benralizumab targets IL-5Rα, and mepolizumab targets IL-5, and these drugs are mainly clinically effective in type 2 asthma. Tezepelumab targets TSLP and is expected to have clinical efficacy in both type 2 and non-type 2 asthma; IL, interleukin; IgE, Immunoglobulin E; IL-5Rα, interleukin-5 receptor alpha

Cells 2022, 11, 819. https://doi.org/10.3390/cells11050819

The effect of tezepelumab on airway hyperresponsiveness to mannitol in asthma (UPSTREAM)

Asger Sverrild[1], Susanne Hansen[1,2], Morten Hvidtfeldt[1], Carl-Magnus Clausson[3], Olga Cozzolino[3], Samuel Cerps[3], Lena Uller[3], Vibeke Backer[4], Jonas Erjefält[3] and Celeste Porsbjerg[1]

[1]Dept of Respiratory Medicine, University Hospital Bispebjerg, Copenhagen, Denmark. [2]Center for Clinical Research and Prevention, Frederiksberg Hospital, Copenhagen, Denmark. [3]Dept of Experimental Medicine, Lund University, Lund, Sweden. [4]Dept of ENT and Centre for Physical Activity Research (CFAS), Rigshospitalet, Copenhagen University, Copenhagen, Denmark.

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Shareable abstract (@ERSpublications)
Blocking TSLP in patients with uncontrolled asthma reduces the proportion of patients with airway hyperresponsiveness and decreases eosinophilic airway inflammation (two key defining features of asthma) https://bit.ly/3yyPxB0

Cite this article as: Sverrild A, Hansen S, Hvidtfeldt M, *et al*. The effect of tezepelumab on airway hyperresponsiveness to mannitol in asthma (UPSTREAM). *Eur Respir J* 2022; 59: 2101296 [DOI: 10.1183/13993003.01296-2021].

Abstract

Background Thymic stromal lymphopoietin (TSLP), an epithelial upstream cytokine, initiates production of type 2 cytokines with eosinophilia and possibly airway hyperresponsiveness (AHR) in asthma. This study aimed to determine whether tezepelumab (a human monoclonal antibody targeting TSLP) decreases AHR and airway inflammation in patients with symptomatic asthma on maintenance treatment with inhaled corticosteroids.

Methods In this double-blind, placebo-controlled randomised trial (UPSTREAM), adult patients with asthma and AHR to mannitol received either 700 mg tezepelumab or placebo intravenously at 4-week

Sverrild A, Hansen S, Hvidtfeldt M, et al. The effect of tezepelumab on airway hyperresponsiveness to mannitol in asthma (UPSTREAM). Eur Respir J 2022; 59: 2101296 [DOI: 10.1183/ 13993003.01296-2021].

Anti-TSLP may help non T2 Asthma

- 40 adult patients
- Conclusions: Inhibiting TSLP signaling with tezepelumab reduced the proportion of patients with AHR and decreased eosinophilic inflammation in BAL and airway tissue
- Newly released data from two phase III trials with tezepelumab in asthma show that tezepelumab reduces exacerbations in patients both with and without eosinophilic disease, although most pronounced in patients with eosinophilia [27]. The results presented here suggest the main effect of tezepelumab on AHR and mast cell infiltration is in patients with eosinophilic asthma. The mechanisms behind the clinical benefit of tezepelumab in noneosinophilic asthma remain unexplained, but an effect on AHR in noneosinophilic asthma, although smaller than in patients with eosinophilic asthma, cannot be ruled out based on this study due to lack of statistical power.

Editorial

Tezepelumab administration in moderate-to-severe uncontrolled asthma: Is it all about eosinophils?

Pier Giorgio Puzzovio, MSc,[a] Ron Eliashar, MD,[b] and Francesca Levi-Schaffer, PharmD, PhD[a] *Jerusalem, Israel*

Key words: *Allergic effector unit, airway hyperresponsiveness, allergic inflammation, asthma, eosinophils, mast cells, TSLP*

Moderate/severe uncontrolled asthma greatly contributes to the socioeconomic burden of asthma due to its recurring symptoms and exacerbations despite the administration of high doses of corticosteroids (CSs). Patients suffering from this illness are characterized by chronic airway inflammation, resulting in airway remodeling, lung obstruction, and functional impairment.[1,2] In the long-term, this condition impairs the quality of life and increases the chances of developing comorbidities and hospitalization.[2] Currently, severe uncontrolled asthma requires high doses of CSs and occasionally a biological agent, either anti-IgE or anti–IL-5/R or anti–IL-4R mAbs, based on endotype-related biomarkers. Nevertheless, these approaches do not cover the asthma characteristics completely. Therefore, effective treatment strategies in the management of uncontrolled severe asthma are needed.

Thymic stromal lymphoprotein (TSLP) is a promising candidate for uncontrolled asthma management. TSLP, released by the epithelium after contact with bacteria, viruses, and chemical and physical agents,[1] binds to the TSLP receptor (TSLPR), a heterodimer composed of TSLPR and IL-7R, which is expressed by mast cells (MCs), eosinophils (Eos), group 2 innate lymphoid cells (ILC2s), dendritic cells (DCs), airway smooth muscle cells, monocytes/macrophages, and lymphocytes.[3] Moreover, TSLP levels are increased in patients with asthma.[1] It was also demonstrated to influence the expression of T_H2-related mediators, such as IL-4 and IL-5.[3] Therefore, it is acknowledged as one of the drivers of T_H2 inflammation in asthma. The main approach for blocking TSLP in asthma is by use of the mAb tezepelumab, which has already been investigated in clinical studies such as UPSTREAM and NCT01405963 for severe uncontrolled asthma. Another existing anti-TSLP mAb is BSI-045B, which will be studied in a phase 1 clinical trial, NCT05114889, for atopic dermatitis.

In their recent work, Diver et al[1] investigated in a double-blind, randomized, placebo-controlled, phase 2 trial, the effect of tezepelumab (AMG-157, MEDI9929), a fully humanized IgG2λ anti-TSLP mAb, on moderate to severe uncontrolled asthma. Tezepelumab, 210 mg, was administered every 4 weeks, for 28 weeks, followed by a 12-week follow-up period. Participants in the study (18-75 years old) were diagnosed with asthma and were already receiving medium/high doses of CSs for 12 months or more, accompanied by at least 1 asthma controller. Moreover, the participants were stratified according to blood Eos count (<150 cells/μL, 150-300 cells/μL, ≥300 cells/μL). Lung biopsies were assessed for neutrophils, Eos, T cells, $CD4^+$ T cells, and $tryptase^+/chymase^+$ MCs. Airway inflammation biomarkers were analyzed in blood samples retrieved at different times. Other markers investigated included fractional exhaled nitric oxide and airway hyperresponsiveness (AHR), measured by mannitol challenge.

Tezepelumab significantly decreased airway submucosal Eos in comparison to placebo throughout the study period (89% vs 25%, respectively), together with reductions in fractional exhaled nitric oxide, IL-5, and IL-13. In addition, tezepelumab decreased AHR in comparison to placebo. However, the numbers of the other analyzed cell types, serum IgE levels, and reticular

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Puzzovio et al. Tezepelumab administration in moderate to severe uncontrolled asthma: Is is all about eosinophils? J Allergy Clin Immunol (2022) In press.

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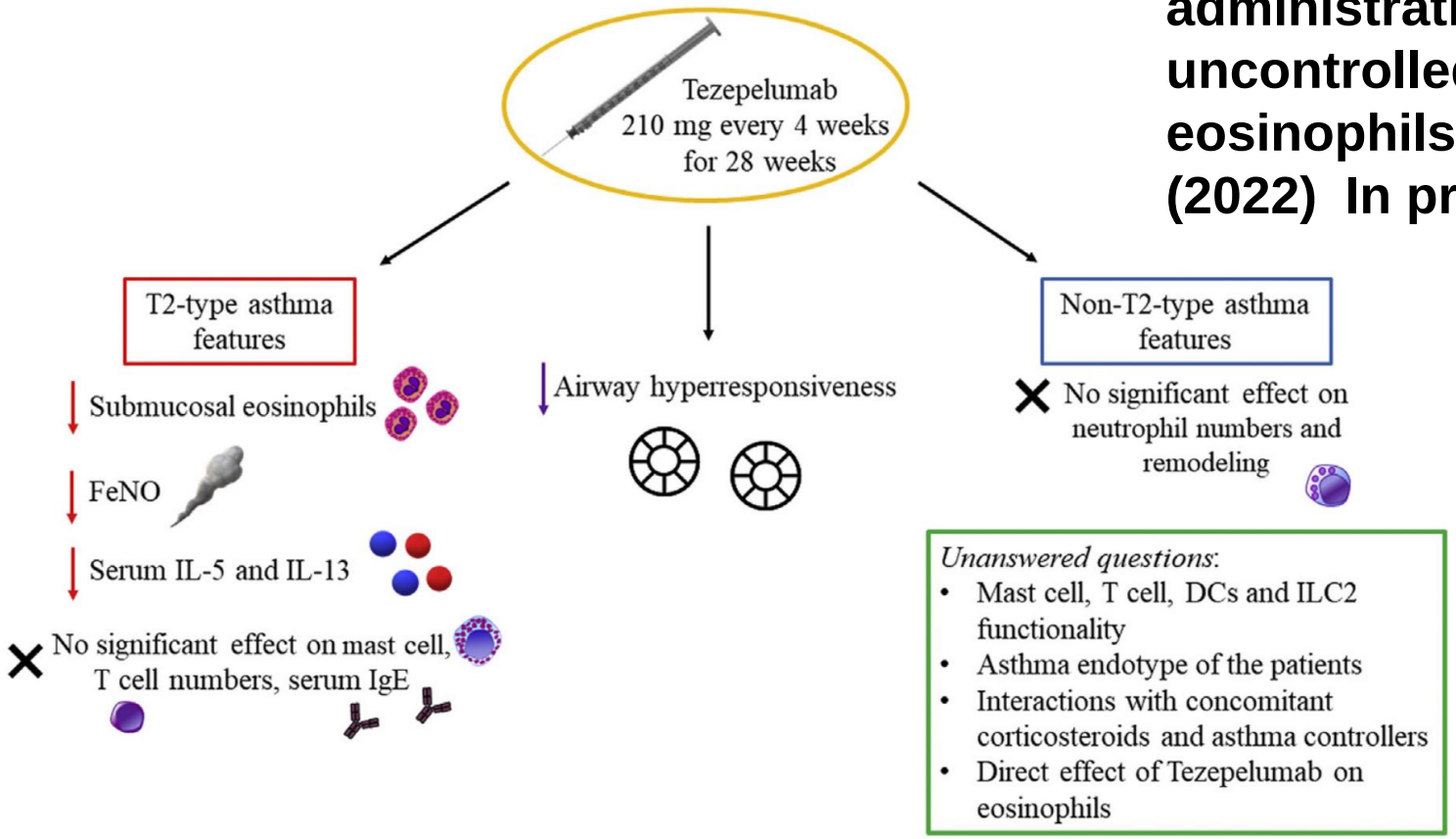

FIG 1. Tezepelumab reduces T2 biomarkers and AHR in moderate to severe uncontrolled asthma. Summary of the main findings of the CASCADE clinical trial. In this clinical study, administration of 210 mg tezepelumab resulted in reduction of submucosal eosinophils, fractional exhaled nitric oxide, and levels of IL-5 and IL-13. No effect was detected on the numbers of other cells (neutrophils, MCs, T cells) and on cell functionality. Interestingly, tezepelumab reduced AHR, but did not have any effect on airway remodeling.

Cell Reports Medicine

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Spotlight

Precision medicine in pediatric severe asthma: Targeted blockade of type 2 inflammation

Allyson S. Larkin[1] and Sally E. Wenzel[2,*]
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[2]Department of Environmental and Occupational Health, School of Public Health, University of Pittsburgh, Pittsburgh, PA USA
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A study by Bacharier et al. demonstrated that children with uncontrolled moderate-to-severe asthma with elevated type 2 biomarkers who received dupilumab had fewer exacerbations and better lung function.[1] These results highlight precision medicine approaches in pediatric asthma.

Our understanding of asthma has dramatically improved over the last 20 years. Perhaps most striking is the recognition that asthma is a heterogeneous disease driven by complex biologic processes that presents with combinations of cough, wheeze, airway obstruction, and inflam-

October 2021, Dupilumab is FDA approved for children from 6-11 years old with Moderate-Severe Asthma.

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Asthma Biomarkers

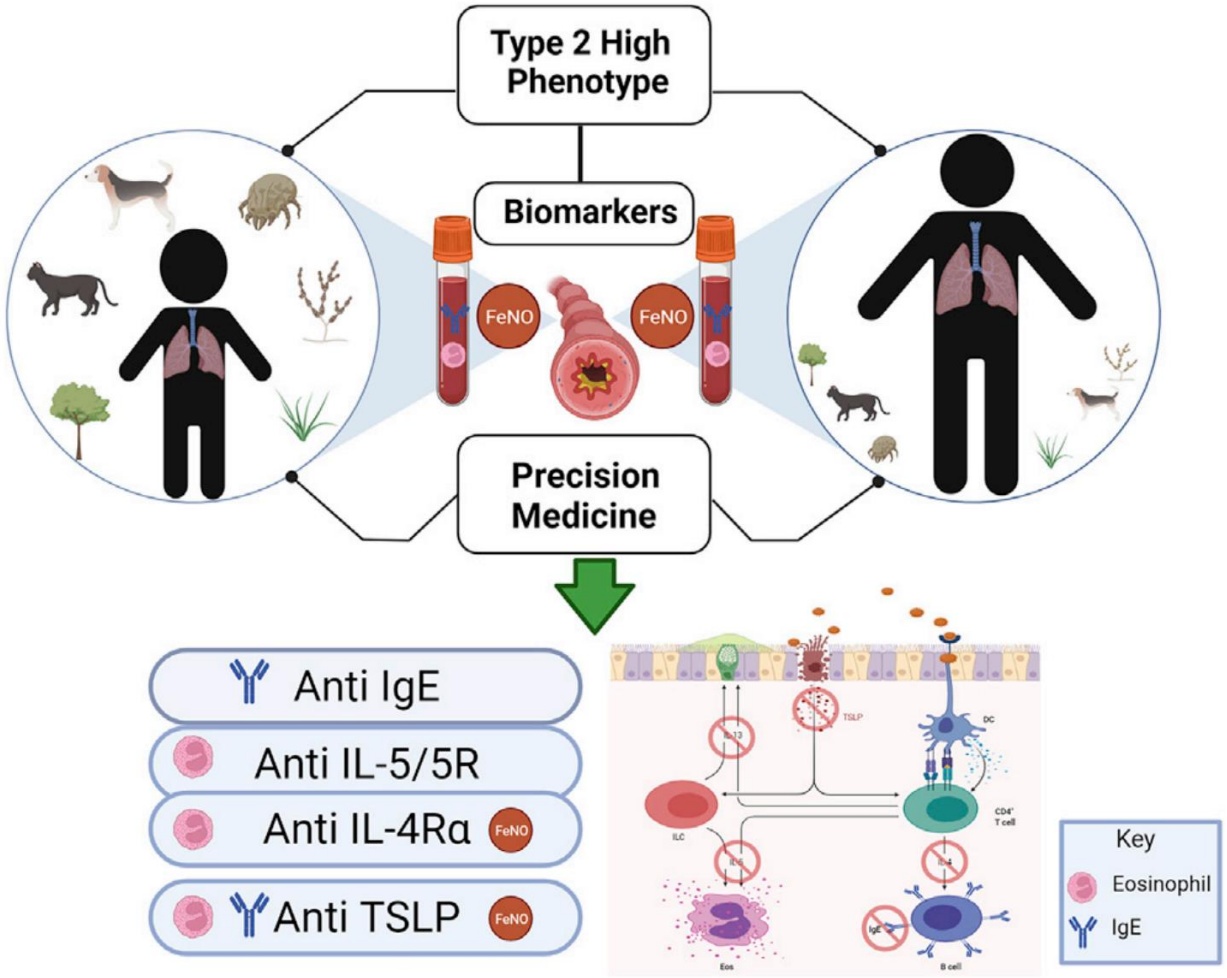


Figure 1. Biomarkers and biologic therapies for type 2 high asthma
Although both adults and children can have a type 2 high phenotype, allergic disease is more commonly associated with severe pediatric asthma. A blood sample measuring total and specific IgE as well eosinophils and measurement of FeNO can help predict response to various type 2 high targeted therapies. Created with BioRender.com.

- Data to support efficacy and safety of biologics is limited, illustrating the need for more studies.
- Need a better understanding of the duration of treatment, particularly in children
- Does inhibition of a biologic process cause immune deviation toward Th1/autoimmunity or cancer?

Cell Reports Medicine 3, 100570, March 15, 2022

REVIEW ARTICLE

Darren B. Taichman, M.D., Ph.D., *Editor*

January 13, 2022

Biologic Therapies for Severe Asthma

Guy G. Brusselle, M.D., Ph.D., and Gerard H. Koppelman, M.D., Ph.D.

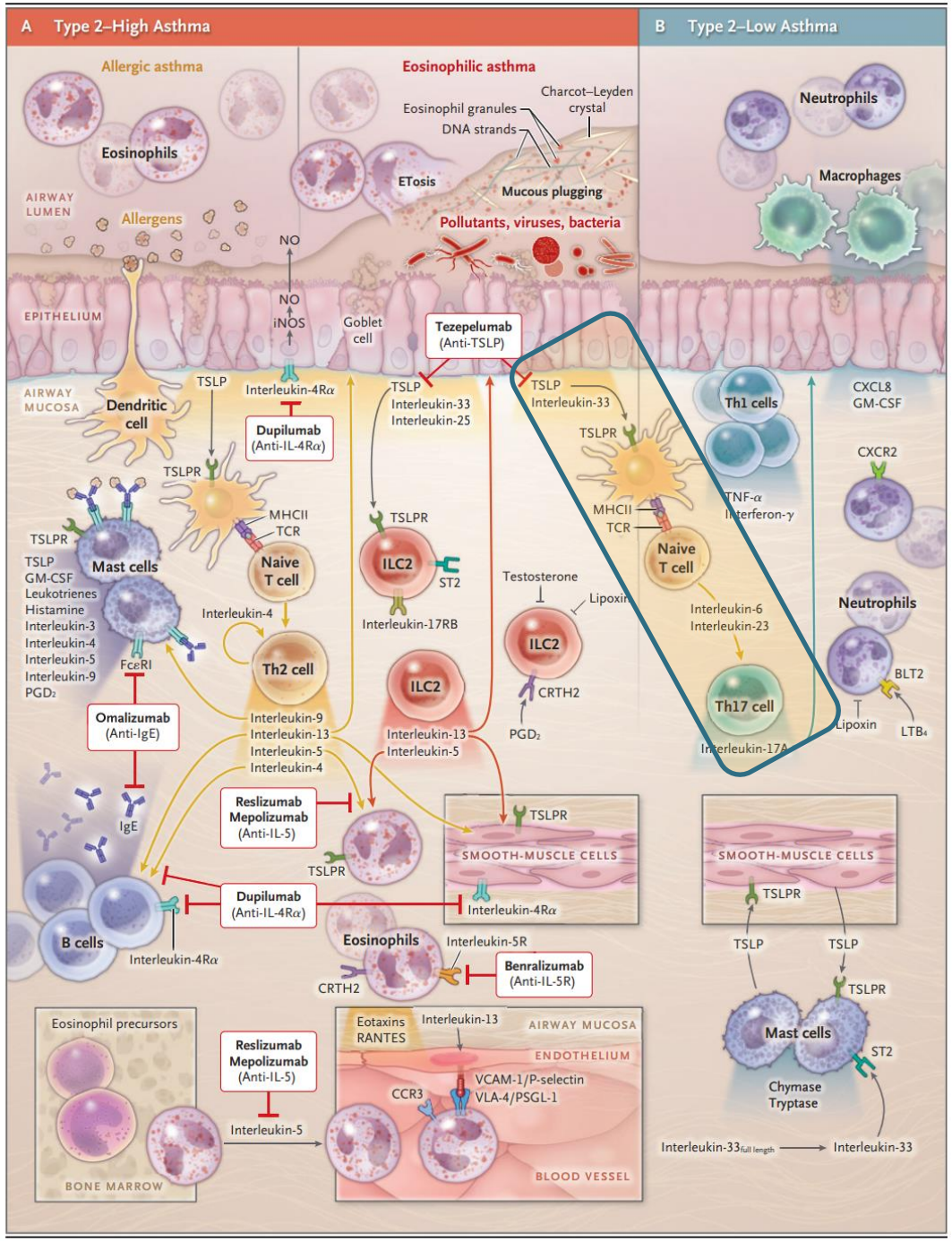
ASTHMA AFFECTS MORE THAN 300 MILLION PEOPLE WORLDWIDE. CHARacterized by variable symptoms of shortness of breath, cough, and chest tightness, asthma is associated with chronic airway inflammation, reversible expiratory airflow limitation, and airway hyperresponsiveness.[1] In difficult-to-treat asthma, poor control can be linked to poor adherence to inhaled glucocorticoids, incorrect inhaler technique, and coexisting conditions, including exposure to allergens and irritants.[2] Asthma that is difficult to treat is considered to be severe when control remains poor despite measures that adequately address each of these three variables (see Section I in the Supplementary Appendix, available with the full text of this article at NEJM.org).[3,4]

Up to 10% of adults and 2.5% of children with asthma have severe asthma, with a reduced quality of life and an increased risk of fixed airflow limitation, exacerbations, health care resource use, hospitalization, and death.[5] Patients with severe asthma have persistent symptoms or frequent exacerbations that require repetitive glucocorticoid bursts, maintenance oral glucocorticoid therapy, or both, despite adequate treatment with high-dose inhaled glucocorticoids, long-acting β-agonists

From the Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium (G.G.B.); and the Departments of Epidemiology and Respiratory Medicine, Erasmus University Medical Center, Rotterdam (G.G.B.), and the Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, and the Groningen Research Institute for Asthma and COPD, University Medical Center Groningen, University of Groningen, Groningen (G.H.K.) — all in the Netherlands. Dr. Brusselle can be contacted at guy.brusselle@ugent.be or at Ghent University Hospital, C. Heymanslaan 10, B-9000 Ghent, Belgium.

N Engl J Med 2022;386:157-71.
DOI: 10.1056/NEJMra2032506

ERSITY

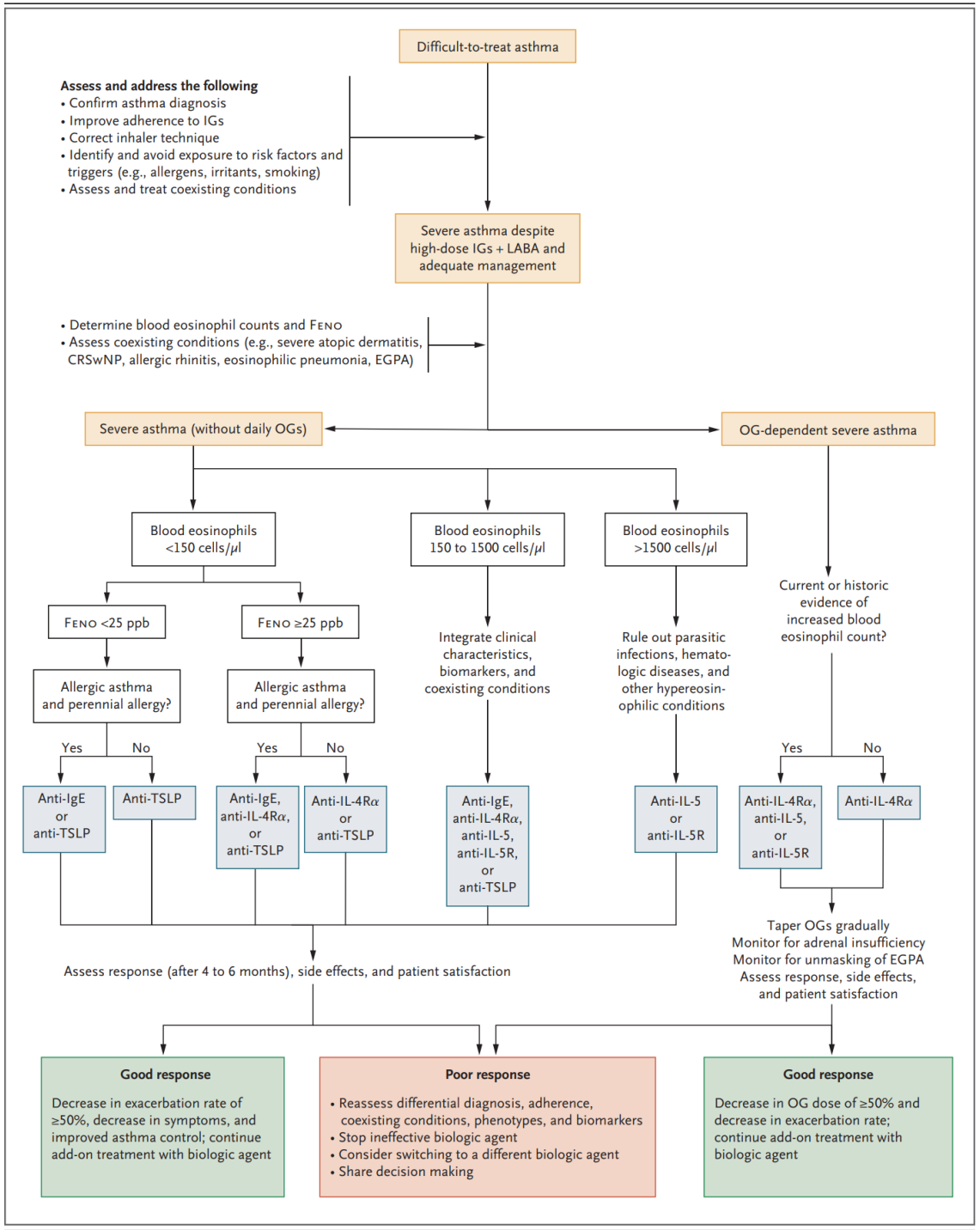


Anti-TSLP may help with T-2 Low asthma

This may be the first biologic agent we have that may help with Type-2 low asthma.

TSLP is released by the epithelium and can provide effects through the dendritic cell.

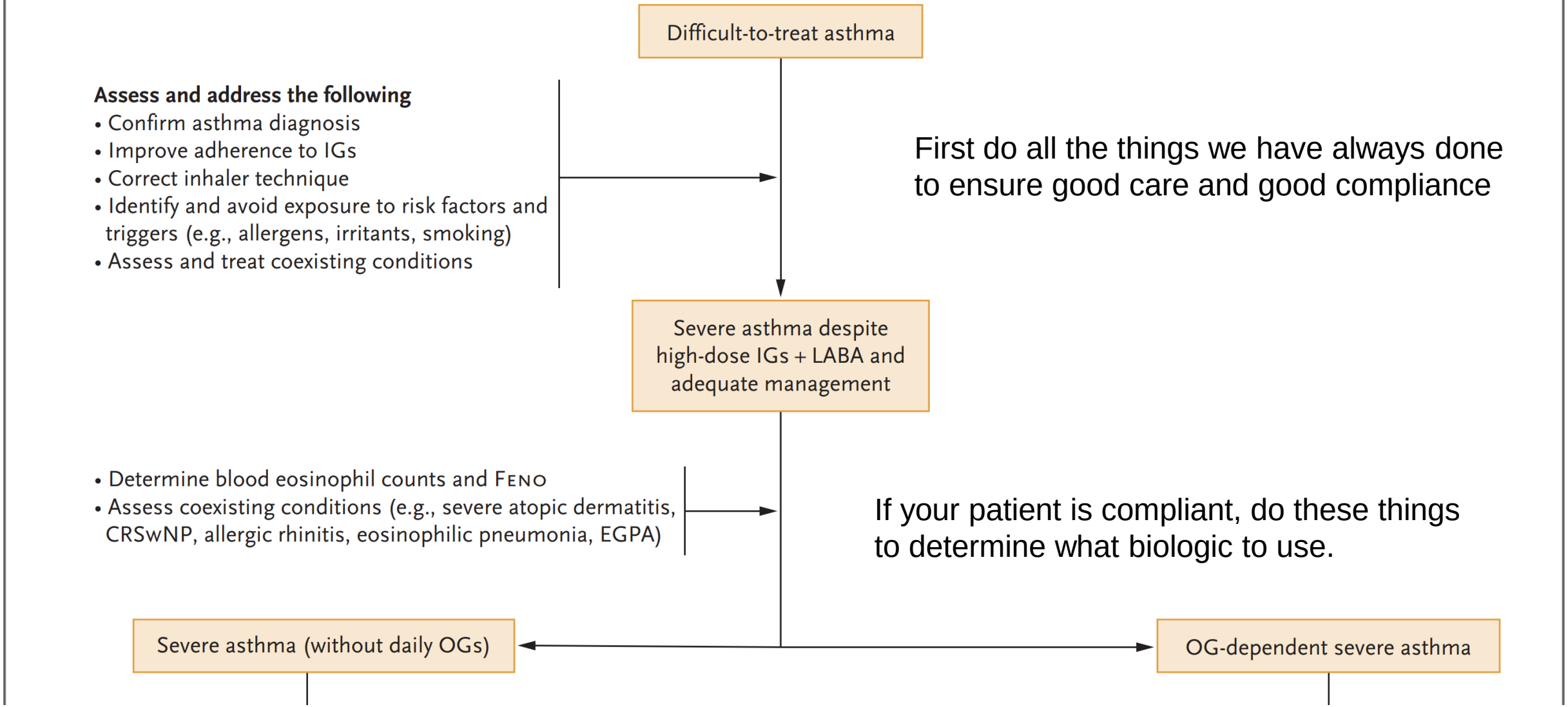
Brusselle and Koppelman. Biologic Therapies for Severe Asthma. New England Journal of Medicine (2022)386:157-71



The decision chart: Biologics for asthma

- Anti-IgE: omalizumab
- Anti-IL4 Alpha: Dupilumab
- Anti-IL5: mepolizumab, reslizumab
- Anti-IL5R: benralizumab
- Anti-TSLP: Tezepelumab

Brusselle and Koppelman. Biologic Therapies for Severe Asthma. New England Journal of Medicine (2022)386:157-71



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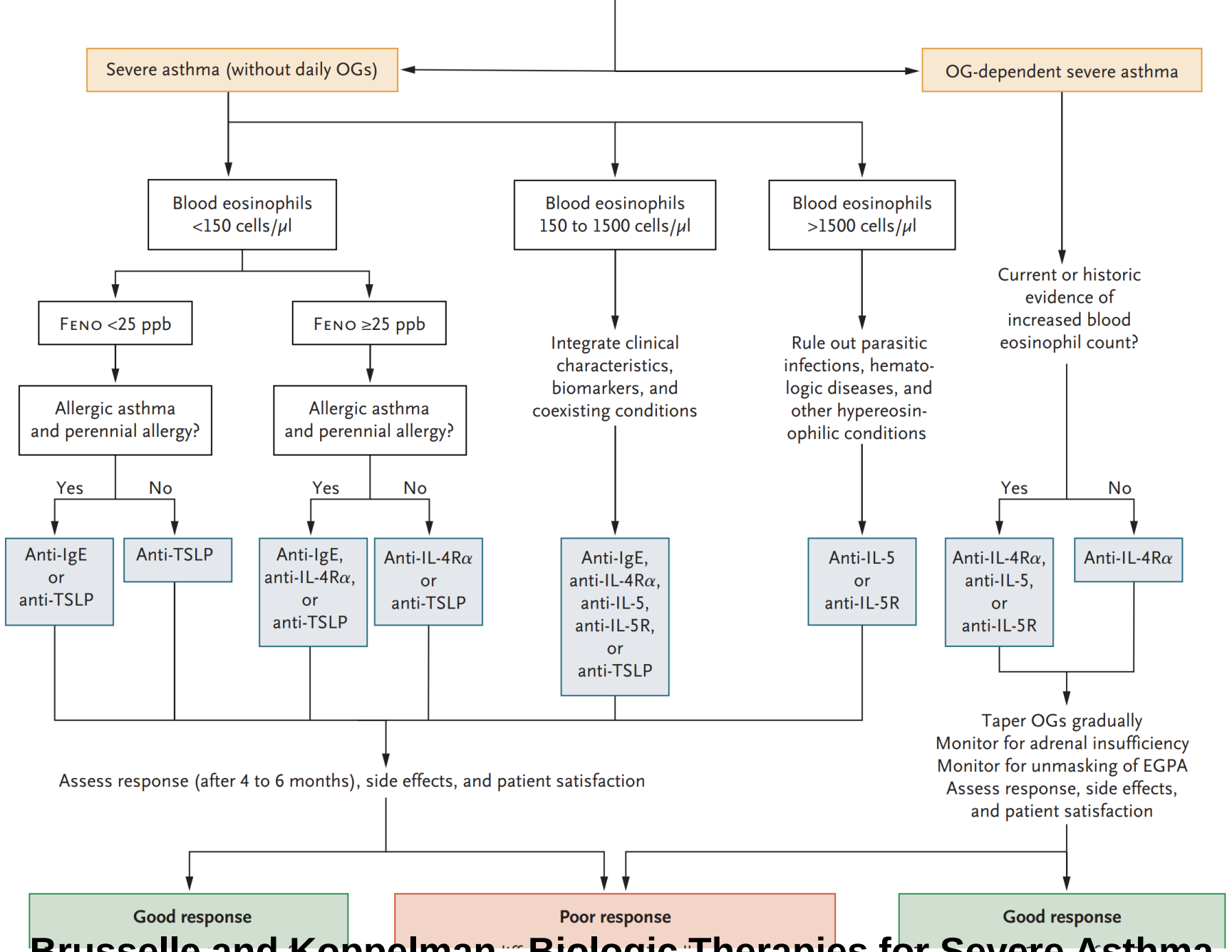


Oral steroid response suggests T-2 High asthma.

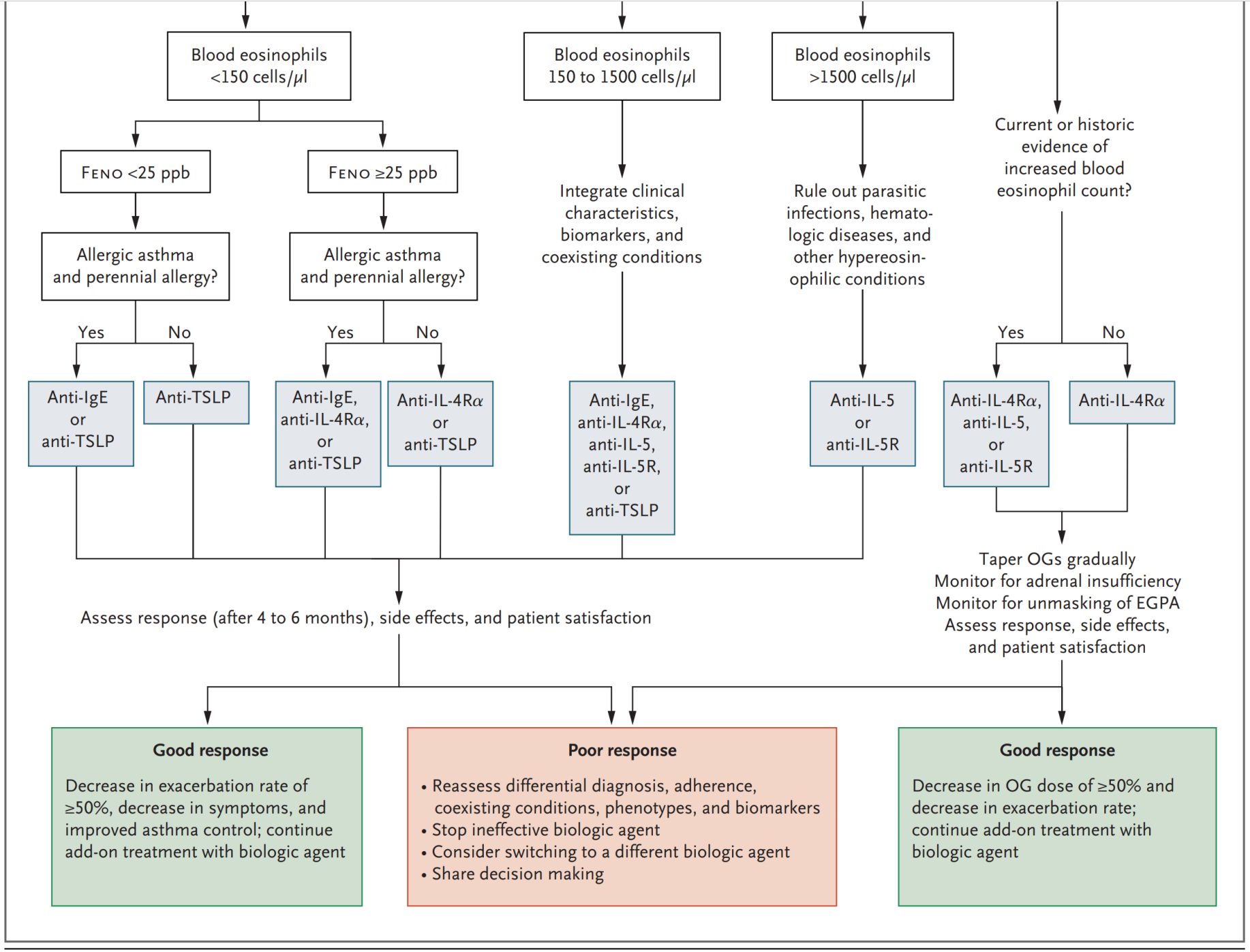
If not on oral steroids, blood eosinophils may be helpful.

Moderate to severe eosinophilia, use anti-IL5 or IL5R

Mild eosinophilia (500-1,500 cells/microliter) all should work

Normal eosinophils, FENO may help

Brusselle and Koppelman. Biologic Therapies for Severe Asthma. New England Journal of Medicine (2022)386:157-71



- Access response
- Share decision making

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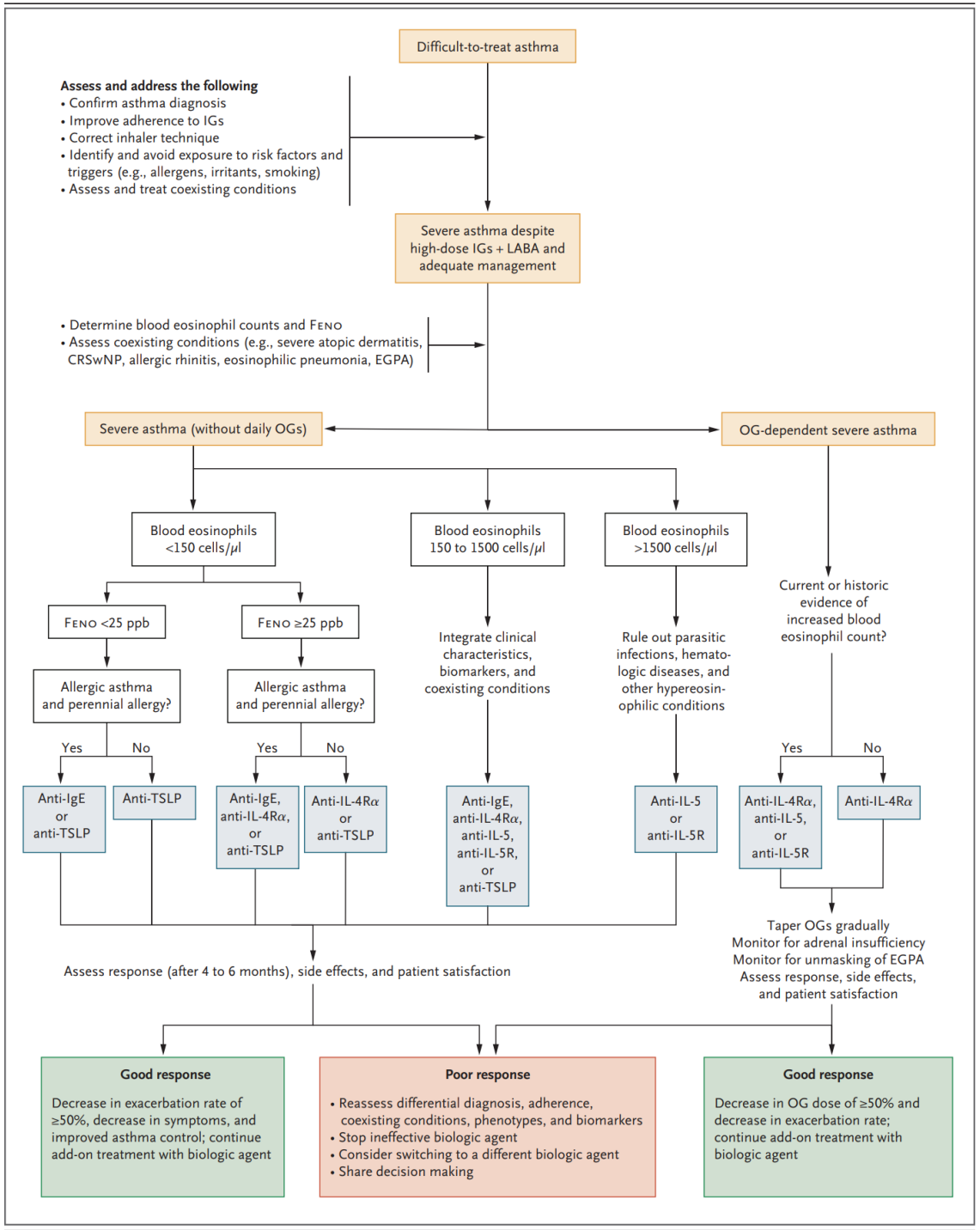

- Anti-IgE: omalizumab
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Brusselle and Koppelman. Biologic Therapies for Severe Asthma. New England Journal of Medicine (2022)386:157-71

cells

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Article

Comparative Efficacy and Safety of Tezepelumab and Other Biologics in Patients with Inadequately Controlled Asthma According to Thresholds of Type 2 Inflammatory Biomarkers: A Systematic Review and Network Meta-Analysis

Koichi Ando [1,2,*], Yosuke Fukuda [1], Akihiko Tanaka [1] and Hironori Sagara [1]

[1] Division of Respiratory Medicine and Allergology, Department of Medicine, School of Medicine, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan; y.f.0423@med.showa-u.ac.jp (Y.F.); tanakaa@med.showa-u.ac.jp (A.T.); sagarah@med.showa-u.ac.jp (H.S.)

[2] Division of Internal Medicine, Showa University Dental Hospital Medical Clinic, Senzoku Campus, Showa University, 2-1-1 Kita-senzoku, Ohta-ku, Tokyo 145-8515, Japan

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Abstract: The anti-thymic stromal lymphopoietin antibody (tezepelumab) has therapeutical potential for inadequately controlled asthma. However, evidence comparing tezepelumab with other biologics is scarce. To address this issue, we performed a network meta-analysis to compare and rank the efficacy of five treatments (tezepelumab, dupilumab, benralizumab, mepolizumab, and placebo) in overall participants and in subgroups stratified by the thresholds of type 2 inflammatory biomarkers, including peripheral blood eosinophil count (PBEC) and fractional exhaled nitric oxide (FeNO). The primary endpoints were annualized exacerbation rate (AER) and any adverse events (AAEs). In the ranking assessment using surface under the cumulative ranking curve (SUCRA) of AER, tezepelumab ranked the highest overall and across subgroups (based on PBEC and FeNO level thresholds). A significant difference was observed between tezepelumab and dupilumab in the patient subgroup with PBEC < 150, and between tezepelumab and benralizumab in overall participants and the patient subgroup with PBEC ≥ 300 and ≥150, respectively. There was no significant difference in the incidence of AAEs in the overall participants between each pair of five treatment arms. These results provide a basis for the development of treatment strategies for asthma and may guide basic, clinical, or translational research.

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TSLP

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Cells 2022, 11, 819. https://doi.org/10.3390/cells11050819

Clinical Management Review

How to Assess Effectiveness of Biologics for Asthma and What Steps to Take When There Is Not Benefit

Amber N. Pepper, MD[a], Nicola A. Hanania, MD[b], Marc Humbert, MD, PhD[c,d], and Thomas B. Casale, MD[e] *Tampa, Fla; Houston, Texas; and Le Kremlin-Bicêtre, France*

Five biologic medications are approved in the United States for the treatment of asthma that is not well controlled with other therapies. All target asthma with elevated type 2 inflammatory markers, such as elevated eosinophils, fractional exhaled nitric oxide, or total and specific IgE. Asthma severity, phenotype, age, biomarkers, treatment goals/outcomes, comorbid conditions, safety, and cost should all help guide the initial biologic choice. In addition, a shared decision-making process with the patient is needed to optimize adherence, with special attention to patient preference regarding outcomes, safety concerns, and medication administration options. **After a biologic agent is initiated, sufficient time is needed to monitor efficacy and response. For patients who do not respond favorably, patient-, disease-, and medication-related factors should be considered and remedied, if possible. Persistent suboptimal responders necessitate a reexamination of asthma phenotype, biomarkers, and the suspected immune response pathways.** For some patients, a change in biologic therapy or other therapeutic options may be warranted. In this review, we examine the clinical approach for choosing an initial biologic for the treatment of asthma, the assessment of response to biologics, and the process of troubleshooting and adjusting biologic treatment for those patients with suboptimal responses.

JACI in Practice. 2021;9:1081-8

Clinical Management Review

How to Assess Effectiveness of Biologics for Asthma and What Steps to Take When There Is Not Benefit

Amber N. Pepper, MD[a], Nicola A. Hanania, MD[b], Marc Humbert, MD, PhD[c,d], and Thomas B. Casale, MD[e] *Tampa, Fla; Houston, Texas; and Le Kremlin-Bicêtre, France*

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Caminati et al. World Allergy Organization Journal (2021) 14:100502
http://doi.org/10.1016/j.waojou.2020.100502

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Biologics and global burden of asthma: A worldwide portrait and a call for action

M. Caminati[a]*, M. Morais-Almeida[b], E. Bleecker[c], I. Ansotegui[d], G.W. Canonica[e], C. Bovo[f] and G. Senna[a,g]

ABSTRACT

Biologics for severe asthma can significantly impact on the burden of disease and also have the potential to reduce asthma mortality. By reviewing the literature and contacting the pharmaceutical companies, the present paper aims at providing a worldwide snapshot of biologic drugs availability, related with the trend of asthma mortality rate, as a marker of the burden of the disease.

Caminati et al. World Allergy Organization Journal (2021) 14:100502
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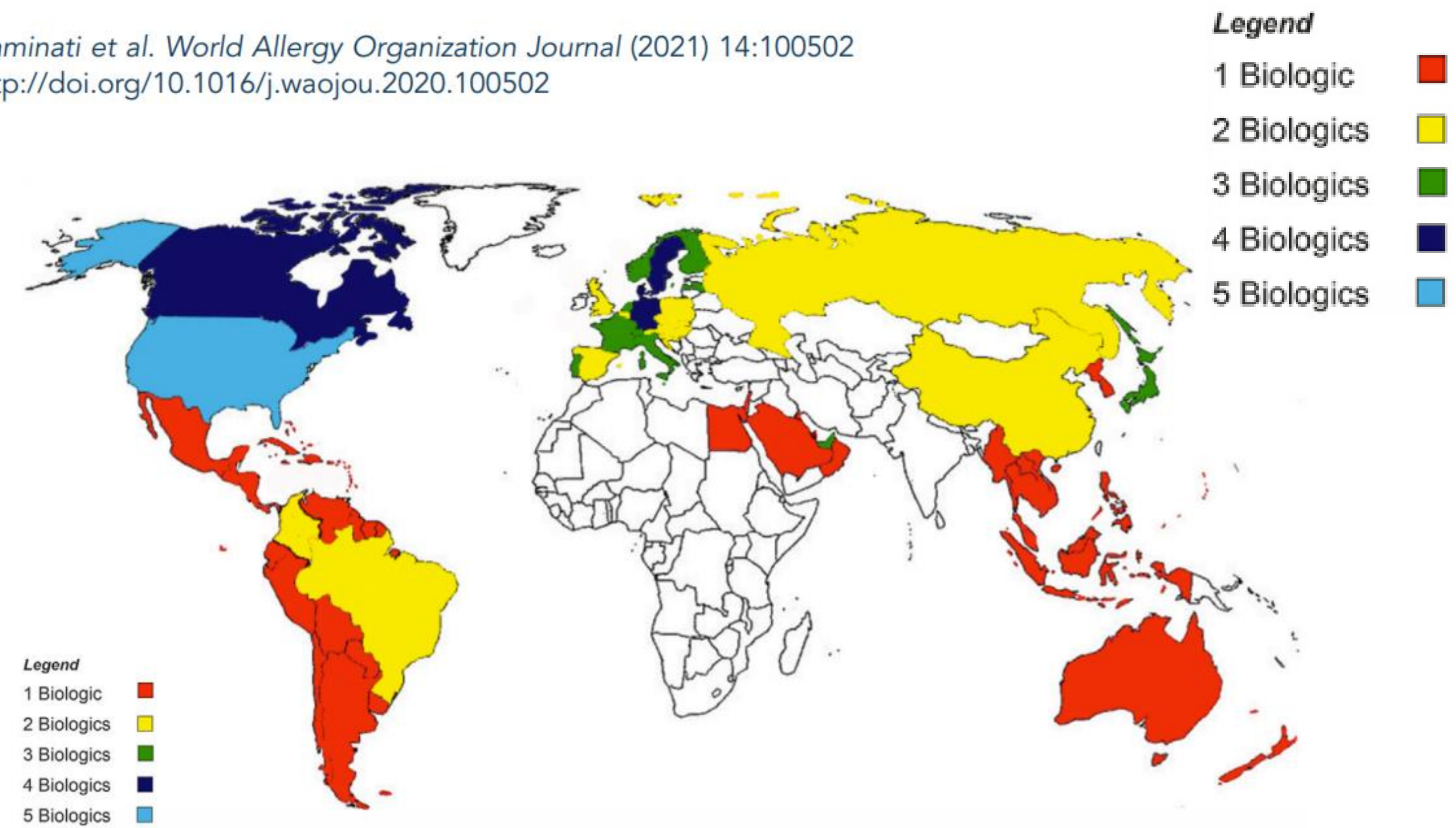

Fig. 1 Worldwide availability of biologics for severe asthma. The different colors identify the number of marketed biologics in each country.

Who cares what is available if I cannot use it?

ARTICLE IN PRESS

Special Article

Global Variability in Administrative Approval Prescription Criteria for Biologic Therapy in Severe Asthma

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What is already known about this topic? Five biologics are licensed for severe asthma treatment by the European Medicines Agency and US Food and Drug Administration. However, accessibility is restricted by clinical, administrative, and reimbursement criteria that differ among countries.

What does this article add to our knowledge? We developed the Biologic Accessibility Score, which compared country-specific biologic prescription criteria across 28 countries in the International Severe Asthma Registry, uncovering marked variations in biologic accessibility depending on the country of residence.

How does this study impact current management guidelines? The large international variation in country-specific prescription criteria for biologics, among other factors (not just the gross domestic product), may affect the implementation of personalized medicine. National regulators and payers should focus on minimizing this global variation.

Conclusions: This study showed a high degree of variability in the criteria used to prescribe severe asthma biologics globally. These differences resulted in profound differences in ease of access to biologics across countries. To ensure the availability of personalized treatment options for patients with severe asthma independently of the country of residence, standardization of prescribing and access criteria is recommended.

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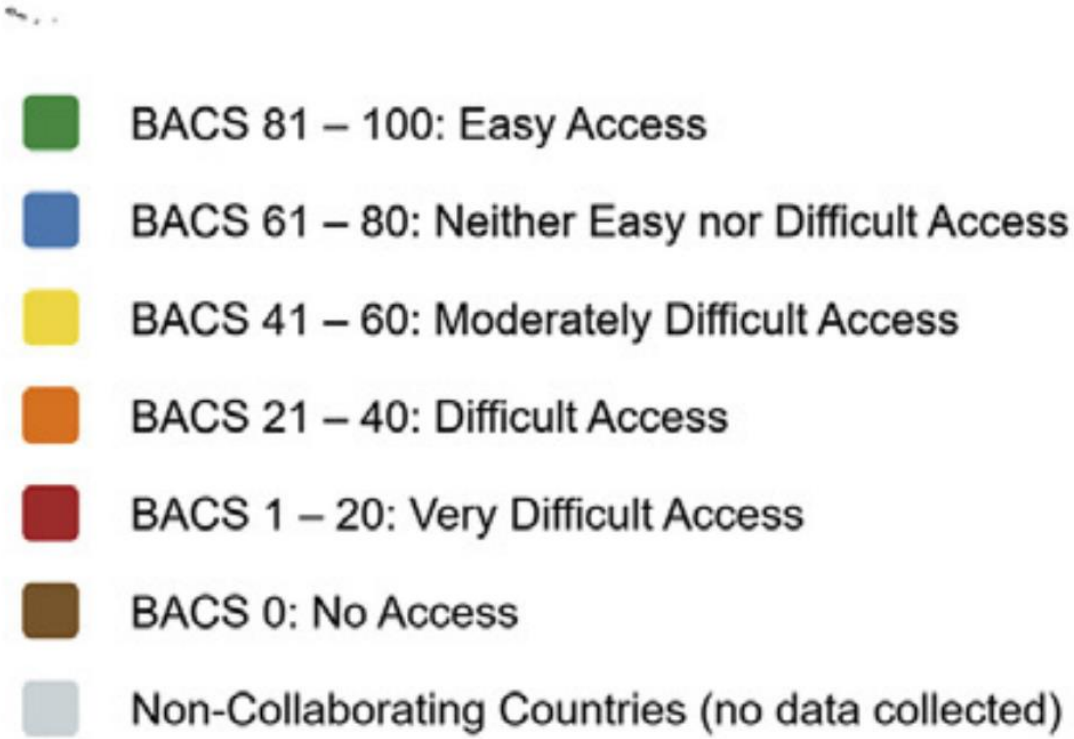
Availability of Biologics



- Each of the slides to follow use the same legend
- Tezepelumab is not listed as it was not approved when this article was written.

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Omalizumab

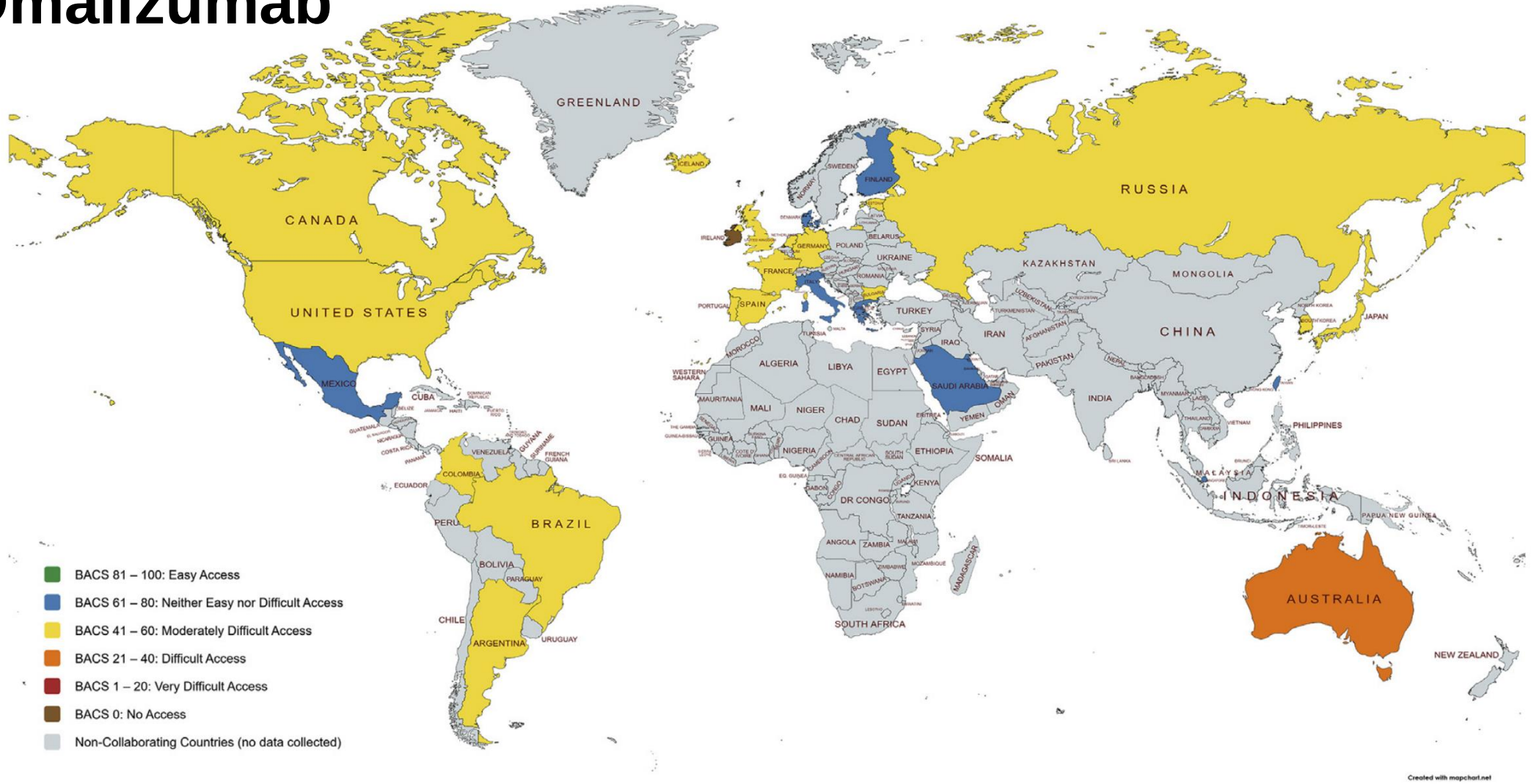

FIGURE 1. Omalizumab Biologic Accessibility Score (BACS) for International Severe Asthma Registry (ISAR) countries.

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Mepolizumab

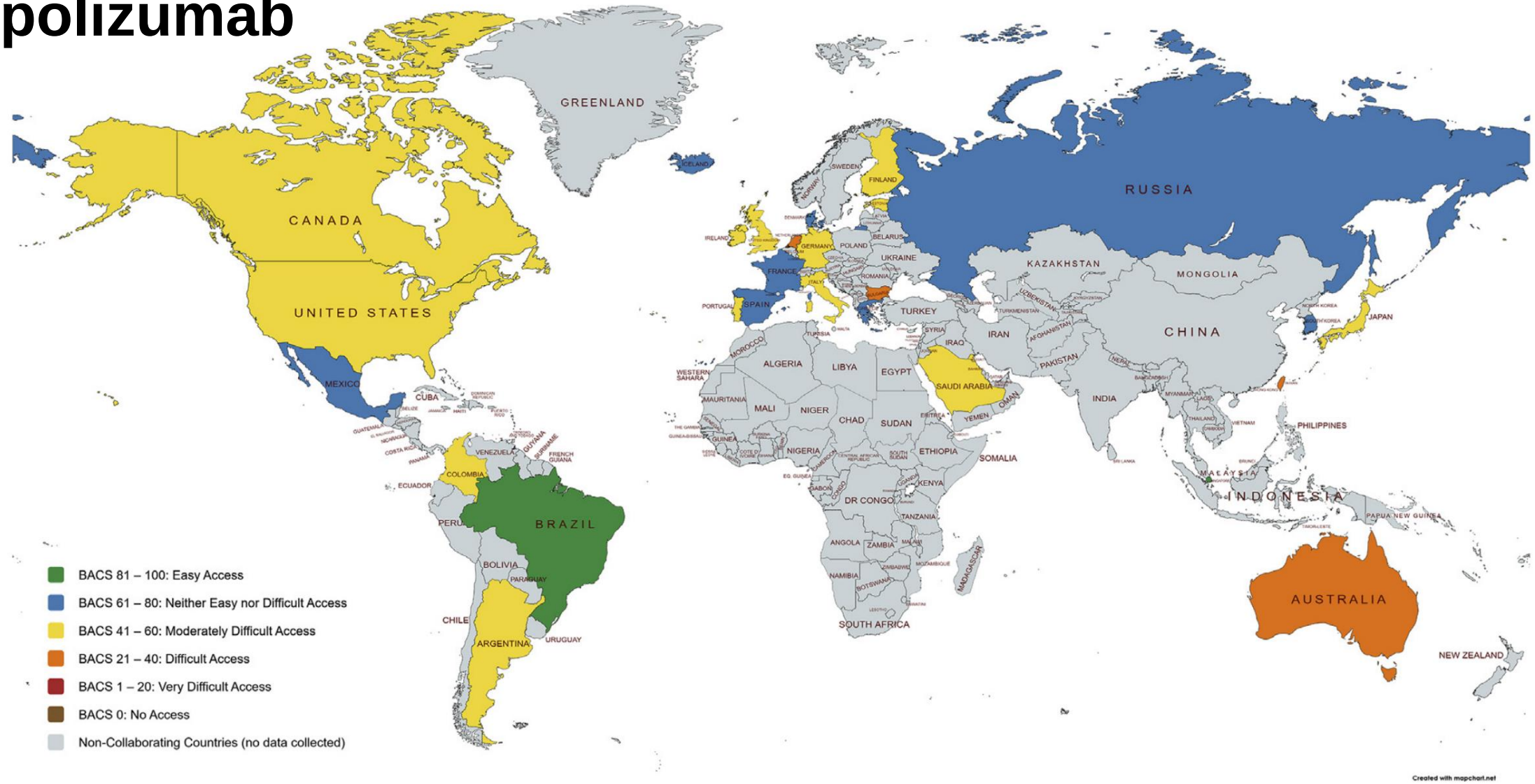

FIGURE 2. Mepolizumab Biologic Accessibility Score (BACS) for International Severe Asthma Registry (ISAR) countries.

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Reslizumab

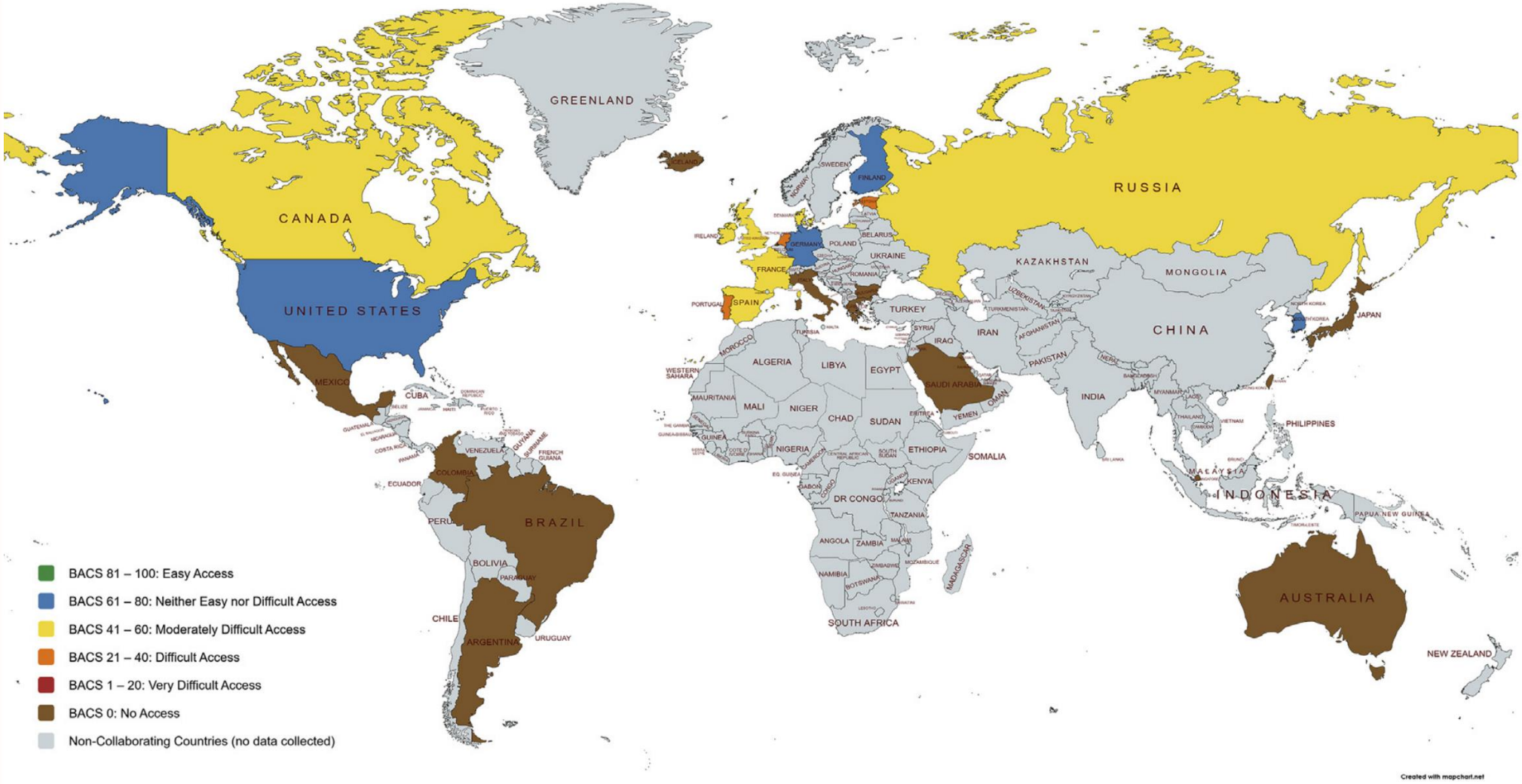

FIGURE 3. Reslizumab Biologic Accessibility Score (BACS) for International Severe Asthma Registry (ISAR) countries.

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Benralizumab

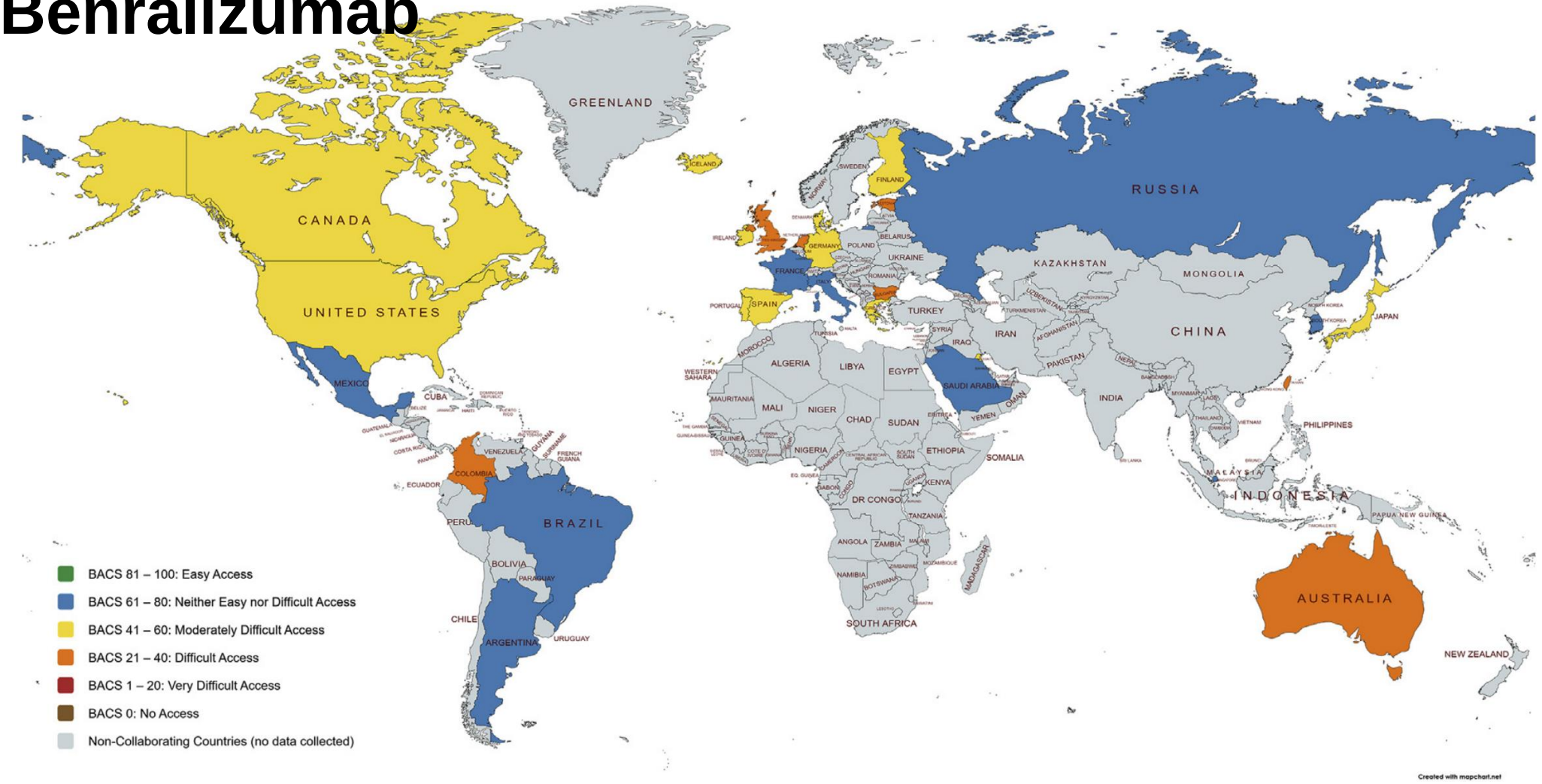

FIGURE 4. Benralizumab Biologic Accessibility Score (BACS) for International Severe Asthma Registry (ISAR) countries.

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Dupilumab

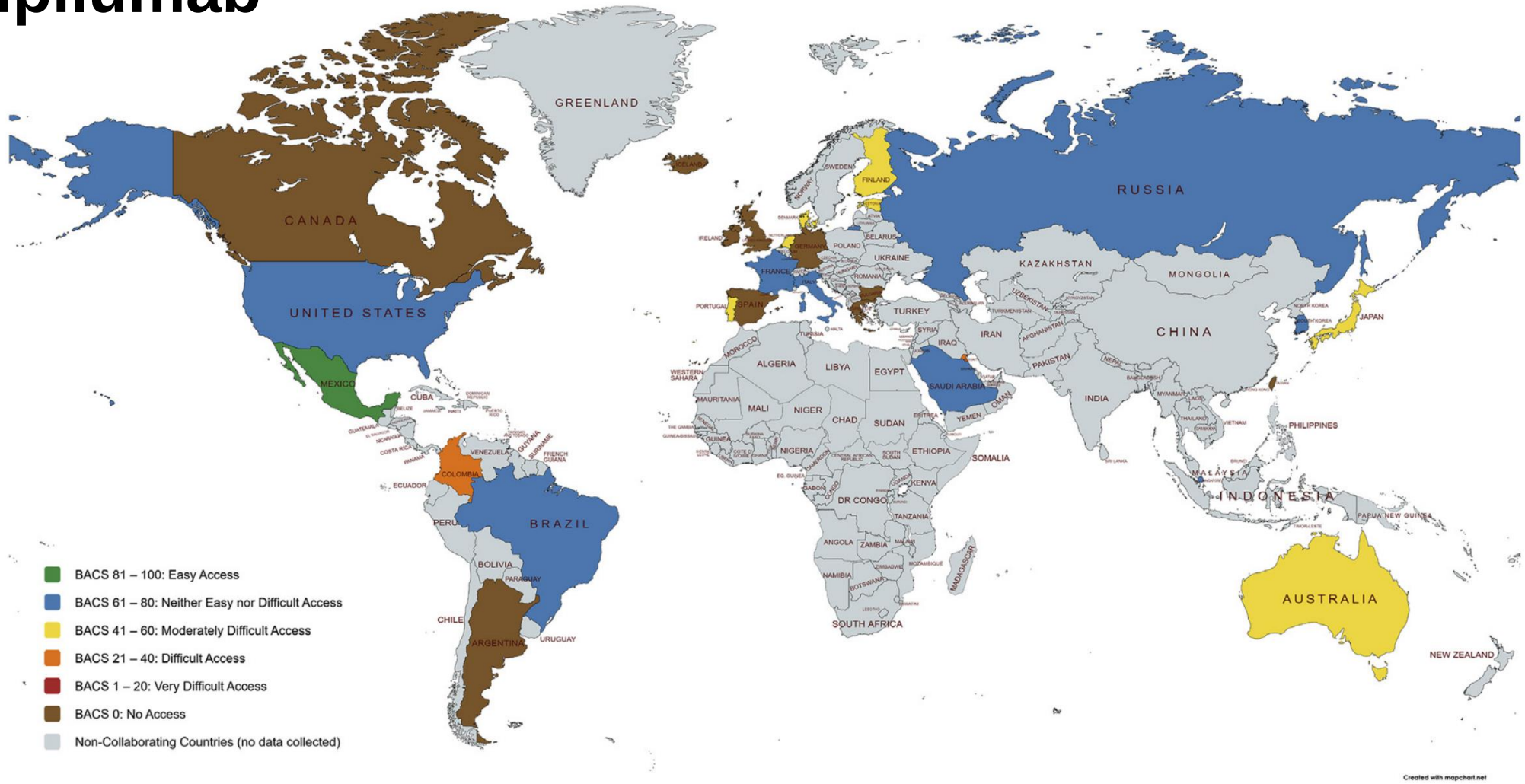

FIGURE 5. Dupilumab Biologic Accessibility Score (BACS) for International Severe Asthma Registry (ISAR) countries.

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Conclusions

- Biologics have ushered in a Brave new world of therapy that focuses on the particulars of the individual's underlying causes of asthma, AND emphasizes the importance of comorbidities.
- Biologics represent a step forward in personalized medicine
- Biologics are NOT a panacea. We need to use them carefully and in the right patients at the right time.

Conclusions: Biologics in 2022

- Anti-TSLP is approved for use by the FDA
  - Give clinicians the first biologic for T2 Low asthma
  - Anti-TSLP will still be effective for T2 High asthma, it may be used in both
- These medications can provide significant relief for patients who are suffering.
  - We are gaining more experience in using these medications for allergic diseases as exemplified by severe asthma and by the approval of these medications for diseases other than asthma.
- These medicines are expensive. We need to ensure that our patients are compliant on cheaper, readily accessible medications before we think of utilizing biologics.
- More biologic targets have been identified, and we should expect additional biologic medications to be approved.
- We still don’t know the long term effects of using these agents.

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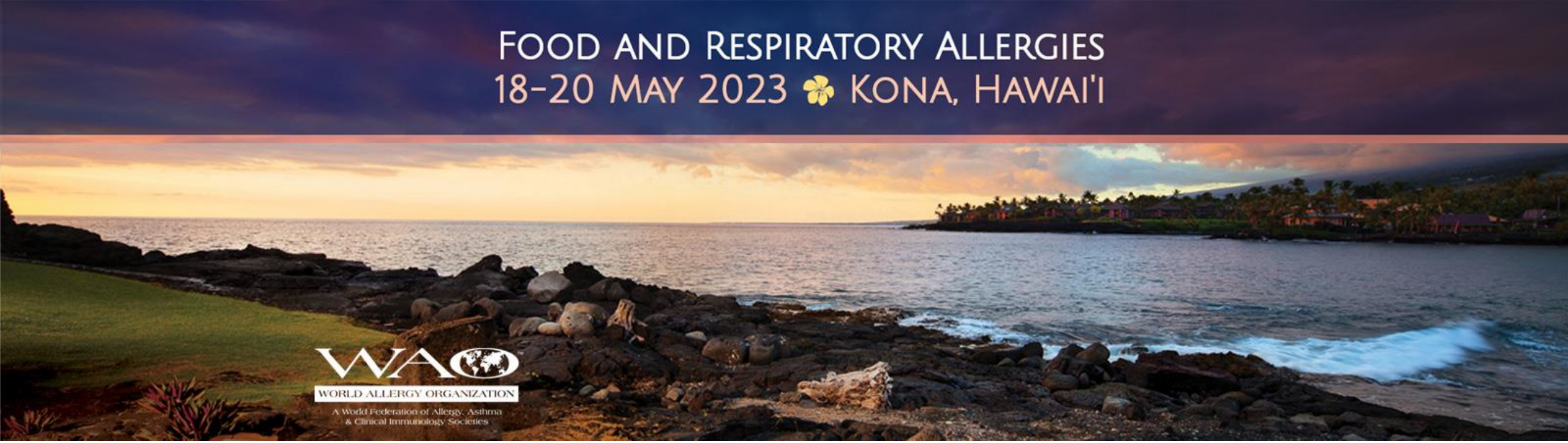

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Questions?