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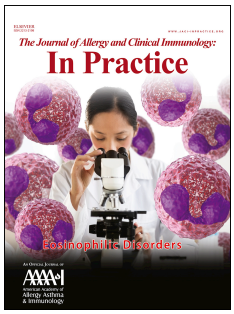

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PII: S2213-2198(22)00128-3

DOI: https://doi.org/10.1016/j.jaip.2022.01.043

Reference: JAIP 4086

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 13 December 2021

Revised Date: 17 January 2022

Accepted Date: 28 January 2022

Please cite this article as: Dellon ES, Simon D, Wechsler ME, Controversies in Allergy: The potential role of biologics as first line therapy in eosinophilic disorders, *The Journal of Allergy and Clinical Immunology: In Practice* (2022), doi: https://doi.org/10.1016/j.jaip.2022.01.043.

Invited article for JACI-IP

Controversies in Allergy: The potential role of biologics as first line therapy in eosinophilic disorders

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Financial support: Dr. Dellon is supported by NIH grants R21 DK122297 and R01 ES031940.

Disclosures: Dr. Dellon has received research funding from Adare/Ellodi, Allakos, Arena, AstraZeneca, GSK, Meritage, Miraca, Nutricia, Celgene/Receptos/BMS, Regeneron, Shire/Takeda; consulting fees from Abbott, Abbvie, Adare/ Ellodi, Aimmune, Allakos, Amgen, Arena, AstraZeneca, Avir, Biorasi, Calypso, Celgene/Receptos/BMS, Celldex, Eli Lilly, EsoCap, GSK, Gossamer Bio, Landos, Morphic, Nutricia, Parexel/Calyx, Phathom, Regeneron, Revolo, Robarts/Alimentiv, Salix, Sanofi, Shire/Takeda; and educational grants from Allakos, Banner, Holoclara.

Dr. Simon has been an investigator, advisory board member, or consultant for AbbVie, AstraZeneca, Eli Lilly, Galderma, GSK, LEO, Pfizer, Roche Pharma, Sanofi Genzyme.

Dr. Wechsler has received honoraria from AstraZeneca, Amgen, Glaxosmithkline, Sanofi, Genzyme, Regeneron, Boehringer Ingelheim, Novartis, Genentech, Pulmatrix, Teva, Equillium, Cytoreason , Restorbio, Cohero Health, Cerecor, Incyte, Sound biologics, Kinaset.

Word count: 3506

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Abstract

With advances in understanding the role of eosinophils in disease pathogenesis, particularly in the airways, gastrointestinal (GI) tract, and skin, targeting eosinophils or the cytokines that lead to their production, activation, and survival has become an increasingly pursued therapeutic approach. Newly developed biologic agents target eosinophils directly, other cells interacting with or activating eosinophils, or cytokines in the Type 2 inflammatory pathway with specific antibodies. Current treatment paradigms reserve therapy with biologics for patients refractory to or intolerant of corticosteroids or immunosuppressants. Given accumulating data for safety and efficacy of these biologics, however, there is the question of whether targeted treatments should be used earlier in the treatment algorithm. In this article, we discuss the pros and cons of using biologics as first-line therapy for eosinophilic diseases of the airways, GI tract, and skin. We highlight emerging biologic agents and future directions for research, as well as a rationale for the early use of some biologics to prevent tissue damage, disease progression, and organ dysfunction in selected conditions.

Keywords: asthma; eosinophilic granulomatosis with polyangiitis; eosinophilic esophagitis; eosinophilic gastrointestinal disease; atopic dermatitis; hypereosinophilic syndrome; therapuetics

Introduction

Eosinophilic disorders comprise a large and diverse spectrum of diseases. While blood eosinophilia is well defined (absolute eosinophil count (AEC) >0.5 G/l; hypereosinophilia >1.5 G/l), tissue eosinophilia in organs that physiologically harbor eosinophils such as the lungs, stomach, small and large intestine, uterus, thymus, spleen, and lymph nodes, is not.[1] In other tissues where resident eosinophils are not present during homeostasis, eosinophil infiltration or eosinophil granule protein deposition indicate a pathologic condition.[2] Eosinophilia can be either primary (intrinsic), owing to a gene fusion or mutation in a hematopoietic stem or immature cell population, or secondary (reactive).[3]

Immense progress has been made in understanding the role of eosinophils in disease pathology.[4] Therefore, targeting eosinophils or the cytokines that lead to their production, activation, and survival is a worthy therapeutic approach. However, in the context of treating reactive eosinophilic diseases, other factors should be considered given the complexity of their pathogenesis. These include the interaction of eosinophils with accompanying inflammatory cells and tissue resident cells, the cytokine milieu in the tissues, the recruitment and activation of eosinophils, epithelial barrier defects, and invading pathogens. Therefore, targeting eosinophils alone might not always be sufficient to achieve clinically relevant and sustained effects.

The anti-inflammatory therapy of eosinophilic disorders has been mainly based on corticosteroids as first-line treatment with immunosuppressants reserved as second-line. With the increasing knowledge of eosinophil disease pathogenesis, however, a number of biologics are available that target eosinophils directly (benralizumab), target other cells interacting with or activating eosinophils (omalizumab, rituximab), or target Type 2 cytokines such as IL-5 (mepolizumab, reslizumab) or IL-4/IL-13 (dupilumab) with specific antibodies. The current

treatment paradigm is to reserve therapy with biologics for patients refractory to or not tolerating corticosteroids or immunosuppressants. Given the potential toxicity of these first line medications related to their broad spectrum of action, it is reasonable to raise the question of whether targeted treatments such as biologics should be used earlier in the treatment algorithm. In this article we will discuss the pros and cons of using biologics as first-line therapy, with a focus on diseases with reactive eosinophilia of the airways, GI tract, and skin that are mediated by cytokines most frequently produced by T cells or, less common, by tumor cells. These include airway, gastrointestinal (luminal), and skin diseases.

Airway diseases

Much of our understanding about therapies that target eosinophils comes from asthma and related diseases. Asthma is well appreciated as an inflammatory disease characterized by airflow obstruction and airway hyperreactivity. Increased blood and/or sputum eosinophil levels are observed in over two thirds of asthma patients and it has been well recognized that eosinophil levels are associated with increased disease activity and risk of exacerbations.[5, 6] While inhaled corticosteroids (ICS) and long acting beta agonists (LABA) remain the mainstay of therapy, 10-15% of asthma patients remain poorly controlled despite use of these inhaled regimens and warrant additional step up medications. Following the 2003 approval of omalizumab for allergic asthma, three therapies that target IL-5 or its receptor have been approved since 2015 for patients with eosinophilic asthma. Mepolizumab, reslizumab, and benralizumab have all been shown to improve outcomes, reducing exacerbations, improving lung function and helping facilitate oral corticosteroid tapering in a safe manner.[7-9] Dupilumab, a monoclonal antibody that targets the IL-4 receptor alpha, has been shown to have similar efficacy, also reducing exacerbations and

substantially improving lung function, with sustained benefits out to at least 2 years.[10] While these therapies have revolutionized the way we manage patients with severe asthma, as many as 60% of patients treated with biologics continue to have symptoms,[11] bespeaking the complexity and heterogeneity of asthma pathophysiology. Nonetheless, could there be a role for asthma biologics as first-line therapy? The vast majority of asthma patients achieve adequate control with ICS +/- LABA, so for most this would not be necessary although the dosing frequency (every 2 to 8 weeks) may result in substantial improvement in adherence to asthma care. As for more severe patients, many individuals treated with biologics achieve symptom control and taper off inhaler therapy (with or without physician guidance). As many of these patients continue to thrive and remain free of exacerbations, first line biologic treatment could be an effective strategy. However, based on data from placebo groups of clinical trials where patients continue to thrive, it is probable that many patients would do just as well if they were adherent to standard inhaler regimens. That being said, the cost-benefit ratio of using biologics as first line therapy would not make economic sense based on current costs, with biologics being priced approximately 10 times that of standard controller regimens.

Eosinophilic granulomatosis with polyangiitis (EGPA) and chronic eosinophilic pneumonia (CEP) are two conditions related to asthma that have also been observed to respond well to biologics. EGPA is characterized by asthma, eosinophilia, sinusitis, pulmonary infiltrates, neuropathy, and vasculitis affecting other organ systems, while chronic eosinophilic pneumonia is characterized by asthma, sinusitis, and eosinophilic inflammation of the airways and pulmonary infiltrates. Anti IL5 therapy with mepolizumab was approved for EGPA based on a double-blind placebo-controlled study in which mepolizumab 300 mg given monthly facilitated corticosteroid tapering and reduced exacerbations in patients with relapsing and

refractory disease.[12] While it is the only therapy approved for this condition, it is generally used after corticosteroids (and/or other immunosuppressants) have been given, and for patients who remain refractory or who are unable to taper corticosteroid dosing. It is often utilized for the asthma/sinusitis components of this disease, with limited data on the vasculitis aspects; the pivotal trial did not allow for this therapy to be given as first line as patients needed to have a history of EGPA for at least 6 months prior to trial onset. As other anti IL5 therapies have shown success in small open label studies,[13] it is probable that these would also be effective; indeed, a head to head trial comparing mepolizumab with benralizumab is currently ongoing (ClinicalTrials.gov NCT04157348). Nonetheless, while there is reason to believe that anti-IL5 therapy may be effective as a first line option in EGPA given its effective reduction of eosinophilia, no first line biologic studies have been conducted to date. In EGPA in particular, mepolizumab only reduced relapses by 53%, and thus there are concerns that there may be mechanisms beyond just eosinophilia that could go unchecked and result in life threatening vasculitis, or that the reduction in eosinophilia required to achieve disease control may not be as quick with biologics as with systemic corticosteroids. Furthermore, given the cost of these therapies (~$100,000/year for mepolizumab at the 300 mg/dose), it may be challenging logistically to get these drugs approved in the acute setting when patients first present.

Dupilumab, mepolizumab and omalizumab have all been approved in the last few years for treatment of chronic rhinosinusitis with nasal polyps. These biologics have significantly reduced the size of nasal polyps and obstruction, as well as the number of patients who had surgery due to polyps or severe symptoms.[14-16] In addition, fewer patients who received biologics vs. placebo required systemic corticosteroids. While it is unlikely that biologics would replace inhaled nasal corticosteroids as first line therapy given their relative efficacy and cost, it

is probable that biologics would replace polyp surgery as a first line treatment. This is because nasal polyps frequently recur postoperatively and require revision surgery.

Gastrointestinal diseases

The eosinophilic gastrointestinal diseases (EGIDs) are chronic conditions characterized by GI symptoms and pathologic infiltration of eosinophils into the GI tract, in the absence of secondary causes of eosinophilia.[17] The most well studied of the EGIDs is eosinophilic esophagitis (EoE), a Type 2-mediated allergic/immunologic condition.[18, 19] While there are emerging data that eosinophilic gastritis (EoG) also has Type 2 features,[20] less is known about eosinophilic enteritis and eosinophilic colitis. The available first line treatments include topical corticosteroids (targeting the mucosa of the esophagus, stomach, or small bowel) and dietary elimination (based on the premise that EoE and EoG are largely driven by an aberrant response to food antigens in the setting of barrier dysfunction). However, the increasing knowledge of EGID pathogenesis has allowed rapid identification of novel therapeutic targets and development of biologics.[21] Most data to date have been in EoE, with trials of anti-IgE (omalizumab),[22] anti-IL-5 (mepolizumab; reslizumab),[23-25] anti IL-13 (QAX576; RPC4046, now termed cendakimab),[26-28] and anti-IL-4r (dupilumab)[29-31] published, and trials of anti-IL-5r (benralizumab) and anti-siglec-8 (lirentelimab) ongoing. In EoG and eosinophilic duodenitis (EoD), phase 2 data have been published on lirentelimab,[32] and benralizumab and dupilumab are under study. Notably, dupilumab, cendakimab, benralizumab, and lirentelimab have reached phase 3 for EoE, and lirentelimab and benralizumab have reached phase 3 for EoG/EoD, based on promising results from early phase investigations. The therapeutics and data available for interpretation continue to evolve rapidly, and preliminary results for a proof of concept study of

benralizumab in EoG (NCT03473977), and the phase 3 studies of lirentelimab for EoE and EoG/EoD (NCT04322708 and NCT04322604, respectively) did not meet all co-primary endpoints, with histologic responses noted, but without symptom improvement above that seen in the placebo groups.

There are a number of reasons to consider biologics as first line pharmacologic therapies in EoE. First, as opposed to topical steroids or proton pump inhibitors, biologics target the pathogenesis of EoE. Second, efficacy of many of these agents appears to be very good. For example, in the phase 2 study of cendakimab, 50% of patients had a histologic response (<15 eosinophils per high-power field [eos/hpf]) and a similar effect was seen in the steroid refractory subgroup,[27] and in a phase 3 study of dupilumab, 64% of patients had a histologic response (<15 eos/hpf).[30] In both of these studies, the initial responses appeared to be maintained for 6-12 months, there were accompanying improvements in symptoms and endoscopic severity, and the medications were well-tolerated.[27-31] These histologic response rates are on the same order of magnitude as what has been reported for topical steroids.[33] Third, biologics offer the promise of personalization of treatment choice based on individual patient features. For example, a patient with multiple atopic conditions such as asthma, atopic dermatitis, and chronic rhinosinusitis with nasal polyposis, as well as EoE, might be able to replace 4 separate steroid medications (inhaled, cutaneous, intranasal, and swallowed) with a single agent effective across multiple atopic conditions. Emerging data also show that EoE patients have different cytokine profiles,[34] and this perhaps implies that an "IL-5 high" or an "IL-13 high" patient might be best treated with biologics targeting these cytokines or associated receptors. Finally, biologics that patients administer weekly to monthly might improve medication adherence over a daily or twice daily topical steroid, or a restrictive elimination diet.[35]

These reasons in favor of a biologic for first line EoE therapy are countered by a lack of data for many critical areas. In comparison to the very strong data for current EoE first line treatments that have informed current guidelines,[36, 37] there are no data for use of biologics in newly diagnosed EoE patients, no comparative effectiveness data showing superiority over topical steroids, PPIs, or diet elimination, and few data (though these are starting to emerge) for long-term use. In particular, if an EoE patient is responsive to PPI therapy, it may be hard to justify use of a biologic. In addition, long-term safety and immunogenicity data are needed, there are no cost-effectiveness studies for this very expensive class of medications, and there is no proof of principle of the role for personalized treatment. In sum, it is likely that biologics will first be positioned for treatment of refractory EoE – those patients who either do not respond to or do not tolerate the first line treatments.[38] However, as more data become available, there is no reason (apart from high costs) why biologics could not move up the treatment algorithm, particularly as we learn how best to individualize treatment for the patient sub-groups who might benefit most from these novel agents.

The outlook may be different for EoG/EoD, however. In contrast to EoE, there are no randomized trials of topical steroids in these non-EoE EGIDs, there is only one prospective diet elimination study using elemental formula,[39] and nearly all data for treatment options currently used are from case series. Because of this, biologics under study with rigorously designed randomized trials,[32] if shown to be safe and effective, may be an option for first line treatment in these conditions, particularly because of the goal to minimize chronic systemic corticosteroid use in these difficult to treat diseases.

Skin diseases

Eosinophilic dermatoses comprise a broad spectrum of skin diseases presenting with various morphologies and having different underlying pathogenic mechanisms. They all are characterized by tissue eosinophilia with or without accompanying blood eosinophilia.

Atopic dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin disease presenting with recurrent eczematous lesions and intense pruritus. Epidermal barrier structure and function, type 2 inflammation, the microbiome, and their interactions play a role. AD is a common disease that affects both children and adults, and often starts in infancy. Current guidelines recommend a stepwise therapeutic approach depending on the severity.

Dupilumab is the first biologic approved for the therapy of AD, and there are a number of arguments that would justify its use as first-line therapy. Dupilumab blocks the shared IL-4/IL-13 receptor resulting in a decrease of inflammatory cells, including eosinophils, and cytokines as well as a restoration of epidermal barrier proteins.[40, 41] A number of clinical trials and real-life observations have shown that dupilumab effectively reduces clinical signs and symptoms of AD in children and adults[42-44] with sustained efficacy upon continuous treatment over 52 weeks[45] and an excellent safety profile.[46] Patients on dupilumab therapy also report an improved quality of life.[47] Beyond the skin, dupilumab is effective in treating conditions often associated with AD such as asthma, chronic rhinosinusitis with nasal polyps and eosinophilic esophagitis (as discussed above).[29, 48]

As AD is often the onset of the so-called atopic march, one might speculate that an effective therapy of skin inflammation starting as early as in infancy might delay or even stop this process.[49] However, information on dupilumab as first-line therapy for AD is not yet

available. Dupilumab has been studied in patients not responding to topical therapy with corticosteroids and calcineurin inhibitors, and those with previous cyclosporin therapy.[50] Mainly due to high costs, dupilumab is available in most countries only for patients with severe AD and/or who have not responded to immunosuppressants despite the fact that it is superior in terms of efficacy and safety to most other available treatments.[44, 51] Additionally, the recent observation that upadacitinib achieved a more rapid onset of itch relief and skin improvement compared with dupilumab might favor JAK inhibitors to be used first-line for the therapy of acute AD flares.[52]

Other biologics such as mepolizumab (two single doses of 750 mg, given 1 week apart) and omalizumab (0.016 mg/kg/IgE [IU/ml] per 4 weeks over 3 months) did not show any significant effects on AD severity and pruritus.[53, 54]

Bullous pemphigoid

Bullous pemphigoid (BP) is an autoimmune bullous disease presenting with generalized pruritus, urticarial plaques and typical tense blisters (bullae). BP is characterized by the presence of autoantibodies directed against the hemidesmosomal proteins BP180 and BP230 that can be detected in the skin and serum of BP patients.[55]

The observation that 77% of BP patients have IgE autoantibodies has justified the use of omalizumab.[56] Moreover, omalizumab has been shown to downregulate FcεRI and IgE in lesional skin in parallel with clinical improvement.[57] As omalizumab is usually well tolerated, it is suitable for the therapy of BP patients who are the elderly and who often have comorbidities.[58] Rituximab depletes B cells, resulting in a reduction in autoantibody titers as well as loss of the

antigen-presenting and immunomodulatory functions of B cells.[59] Currently, randomized trials investigating omalizumab or rituximab in BP are not available.

There is evidence that eosinophils are abundantly present in lesional skin and actively contribute to BP pathogenesis by inducing blister formation[60] and inducing pruritus.[61] However, mepolizumab therapy failed to show superiority over placebo in terms of clinical and serological outcomes.[62] Whether other eosinophil targeting antibodies, e.g. benralizumab, are effective in BP remains to be investigated.

Drug rash with eosinophilic and systemic symptoms

Drug rash with eosinophilia and systemic symptoms (DRESS) is a rare severe hypersensitivity reaction presenting with exanthema, facial edema, lymphadenopathy, fever, as well as liver, kidney and lung dysfunction. Increased blood IL-5 levels driving eosinophilia have been observed in early stages of DRESS.[63] There is evidence that eosinophils directly contribute to organ damage in DRESS.[64, 65] As biologics targeting eosinophils were shown to be successful in the treatment of DRESS in case reports,[66-68] clinical trials would be useful to further study efficacy in larger cohorts.

Urticaria

Urticaria that presents with wheals, angioedema, or both, is presumed to be a mast cell-driven disease.[69] If antihistamines are not sufficient in controlling skin lesions, omalizumab is applied in chronic spontaneous urticaria (CSU). Its onset of action is short in most patients, as omalizumab directly blocks IgE directed to autoantigens, but delayed in cases with CSU mediated by IgG or IgM autoantibodies that target activating mast cell receptors.[70]

Eosinophils that are scattered among cells infiltrating the skin may contribute to urticaria pathology by stimulating mast cell degranulation and increasing vascular permeability.[71-73] A single-center, single-blind, repeated-measures study revealed rapid and prolonged effects of benralizumab in CSU patients.[74] The results of a phase 2 trial investigating an antibody targeting siglec-8, which is a receptor expressed by eosinophils, mast cells and basophils, showed excellent effects in both omalizumab-naïve and resistant CSU patients and thereby also make it a candidate for first-line therapy.[75]

Prurigo nodularis

Prurigo nodularis (PN) manifests with firm, hyperkeratotic, excoriated nodules that are induced by persistent scratching due to chronic pruritus.[76] Eosinophils can be detected on histology, are thought to contribute to pruritus by producing toxic proteins, cytokines and mediators that can activate nerve cells.[77] Nemolizumab, which targets the IL-31 receptor, has bene shown to interrupt the vicious cycle of chronic pruritus giving raise to permanent scratching and inflammation in PN.[78]

Experiences with biologics in specific but rare eosinophilic dermatoses is minimal and limited to case reports including the use of mepolizumab in eosinophilic cellulitis and Kimura disease,[79, 80] benralizumab in eosinophilic pustular folliculitis,[81] and dupilumab in eosinophilic dermatosis of hematologic malignancy.[82, 83] Consideration of use of biologics as first-line therapy in these conditions would be premature.

Hypereosinophilic syndrome

In hypereosinophilic syndromes (HES), pathologically elevated levels of activated eosinophils contribute to organ damage in multiple systems throughout the body. Biologics targeting eosinophils in early disease stages would therefore be logical. In the reactive forms of HES, eosinopoietins such as IL-5, IL-13 and GM-CSF induce hypereosinophilia by stimulating eosinophil production, activation and survival.[1] Therefore, these cytokines and their receptors serve as therapeutic targets. Mepolizumab, which has been approved for patients with HES in several countries, has been shown to have corticosteroid-sparing effects[84] and significantly reduced the number of HES flares.[85] Benralizumab therapy in PDGFRA-negative HES led to a significant and rapid decrease of AEC in 17/19 patients, who all had subsequent clinical improvement.[86] Based on this, a phase 3 study is ongoing (NCT04191304). Both mepolizumab and benralizumab exerted excellent effects in HES patients with skin involvement.[86, 87] The efficacy of mepolizumab and benralizumab depends on the clinical subtype of HES, with no or poor response in myeloproliferative-variant HES or lymphocytic-variant HES.[86, 88, 89] To date, the effects of biologics targeting eosinophils in HES have been studied as add-on therapy, so it is currently not possible to draw conclusions above whether biologics targeting eosinophils qualify as first-line therapy for HES. However, the rationale is there and should be further studied.

Future directions and conclusions

In addition to the myriad treatments discussed above, there are some additional therapies with either some mechanistic or proof-of-principle data available. For example, the anti-IL-33 antibody itepekimab has been shown to be effective in patients with asthma compared with placebo,[90] and another anti IL-33 antibody etokimab has been shown to induce rapid and sustained improvements in AD severity scores, pruritus and DLQI.[91] In contrast, while clinical

improvements in asthma were observed with tezepelumab,[92] an anti-TSLP antibody, this therapy did not yield benefits in AD after 12-16 weeks of treatment.[93] Fezankinumab, and antibody that blocks IL-22, showed best efficacy in patients with severe AD.[94] Therefore, for different diseases, these biologics are unlikely to be candidates as first-line therapy. While theoretically promising, scientific reports on the efficacy of bertilimumab, an anti-eotaxin 1 antibody, in BP (Phase 2a Study (NCT02226146)) are still lacking. Additional future directions of research, above and beyond the development on additional novel agents, are for studies to specifically focus on the efficacy of biologics as first-line therapy, ideally in the form of comparative effectiveness studies, for eosinophilic diseases. These studies would form the basis of the cost-effectiveness studies that would be required to justify earlier and more wide-spread use of these expensive treatments.

In conclusion, the field of eosinophilic diseases, particularly as it applies to the lung, gastrointestinal tract, and skin, has been rapidly expanding with an increasing knowledge base about pathogenesis. This, in turn, has led to multiple novel therapeutic targets and rapid drug development, particularly with biologic agents. The preponderance of studies to date have focused on the use of biologics in patients who are either resistant or refractory to other treatments or intolerant to those treatments. Accordingly, for the biologics that are approved by regulatory authorities, the patient population is restricted to these more difficult to treat or severely affected patients. While cost-related issues may prohibit their use early on in disease course, based on scientific data there is a strong rationale for the use of biologics early in the disease course in order to prevent severe inflammation and tissue damage resulting in organ dysfunction as well as progression and remodeling. Perhaps more widespread use earlier in

disease course could result in lower costs of these therapies. As data are developed to support this premise, treatment algorithms should be updated.

References

1. Valent P, Klion AD, Horny HP, Roufosse F, Gotlib J, Weller PF, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. J Allergy Clin Immunol 2012; 130:607-12.e9.
2. Kato M, Kephart GM, Talley NJ, Wagner JM, Sarr MG, Bonno M, et al. Eosinophil infiltration and degranulation in normal human tissue. Anat Rec 1998; 252:413-25.
3. Simon D, Simon HU. Eosinophilic disorders. J Allergy Clin Immunol 2007; 119:1291-300; quiz 301-2.
4. Simon HU, Yousefi S, Germic N, Arnold IC, Haczku A, Karaulov AV, et al. The Cellular Functions of Eosinophils: Collegium Internationale Allergologicum (CIA) Update 2020. Int Arch Allergy Immunol 2020; 181:11-23.
5. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med 2015; 3:849-58.
6. Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN, et al. Characterization of Severe Asthma Worldwide: Data From the International Severe Asthma Registry. Chest 2020; 157:790-804.
7. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012; 380:651-9.
8. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015; 3:355-66.
9. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med 2017; 376:2448-58.
10. Wechsler ME, Ford LB, Maspero JF, Pavord ID, Papi A, Bourdin A, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. Lancet Respir Med 2021.
11. Reibman J, Tan L, Ambrose C, Chung Y, Desai P, Llanos JP, et al. Clinical and economic burden of severe asthma among US patients treated with biologic therapies. Ann Allergy Asthma Immunol 2021; 127:318-25.e2.
12. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. N Engl J Med 2017; 376:1921-32.
13. Guntur VP, Manka LA, Denson JL, Dunn RM, Dollin YT, Gill M, et al. Benralizumab as a Steroid-Sparing Treatment Option in Eosinophilic Granulomatosis with Polyangiitis. J Allergy Clin Immunol Pract 2021; 9:1186-93.e1.
14. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet 2019; 394:1638-50.

15. Bachert C, Sousa AR, Lund VJ, Scadding GK, Gevaert P, Nasser S, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial. J Allergy Clin Immunol 2017; 140:1024-31.e14.
16. Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. J Allergy Clin Immunol 2020; 146:595-605.
17. Gonsalves N. Eosinophilic Gastrointestinal Disorders. Clin Rev Allergy Immunol 2019; 57:272-85.
18. Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, Zevit N, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: Proceedings of the AGREE conference. Gastroenterology 2018; 155:1022-33.e10.
19. O'Shea KM, Aceves SS, Dellon ES, Gupta SK, Spergel JM, Furuta GT, et al. Pathophysiology of Eosinophilic Esophagitis. Gastroenterology 2018; 154:333-45.
20. Caldwell JM, Collins MH, Stucke EM, Putnam PE, Franciosi JP, Kushner JP, et al. Histologic eosinophilic gastritis is a systemic disorder associated with blood and extragastric eosinophilia, TH2 immunity, and a unique gastric transcriptome. J Allergy Clin Immunol 2014; 134:1114-24.
21. Greuter T, Hirano I, Dellon ES. Emerging therapies for eosinophilic esophagitis. J Allergy Clin Immunol 2020; 145:38-45.
22. Clayton F, Fang JC, Gleich GJ, Lucendo AJ, Olalla JM, Vinson LA, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. Gastroenterology 2014; 147:602-9.
23. Straumann A, Conus S, Grzonka P, Kita H, Kephart G, Bussmann C, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. Gut 2010; 59:21-30.
24. Assa'ad AH, Gupta SK, Collins MH, Thomson M, Heath AT, Smith DA, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterology 2011; 141:1593-604.
25. Spergel JM, Rothenberg ME, Collins MH, Furuta GT, Markowitz JE, Fuchs G, 3rd, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: Results of a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol 2012; 129::456-63, 63.e1-3.
26. Rothenberg ME, Wen T, Greenberg A, Alpan O, Enav B, Hirano I, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. J Allergy Clin Immunol 2015; 135:500-7.
27. Hirano I, Collins MH, Assouline-Dayan Y, Evans L, Gupta S, Schoepfer AM, et al. RPC4046, a Monoclonal Antibody Against IL13, Reduces Histologic and Endoscopic Activity in Patients With Eosinophilic Esophagitis. Gastroenterology 2019; 156:592-603.e10.
28. Dellon ES, Collins MH, Rothenberg ME, Assouline-Dayan Y, Evans L, Gupta S, et al. Long-Term Efficacy and Tolerability of RPC4046 in an Open-Label Extension Trial of Patients With Eosinophilic Esophagitis. Clin Gastroenterol Hepatol 2020.
29. Hirano I, Dellon ES, Hamilton JD, Collins MH, Peterson K, Chehade M, et al. Efficacy of Dupilumab in a Phase 2 Randomized Trial of Adults With Active Eosinophilic Esophagitis. Gastroenterology 2020; 158:111-22.e10.

30. Dellon ES, Rothenberg ME, Collins MH, Hirano I, Chehade M, Bredenoord AJ, et al. A Phase 3, Randomized, 3-Part Study to Investigate the Efficacy and Safety of Dupilumab in Adult and Adolescent Patients with Eosinophilic Esophagitis: results from Part A. Am J Gastroenterol 2020; 115 (Suppl 1):LB3.
31. Dellon ES, Rothenberg ME, Collins MH, Hirano I, Chehade M, Bredenoord AJ, et al. LIBERTY EoE TREET: Results from Parts A and C of the Phase 3, Randomized, 3-Part LIBERTY EoE TREET Study to Investigate the Efficacy and Safety of Dupilumab in Adult and Adolescent Patients with Eosinophilic Esophagitis up to 52-Weeks. Am J Gastroenterol In press, 2021 (ACG meeting, presentation #52).
32. Dellon ES, Peterson KA, Murray JA, Falk GW, Gonsalves N, Chehade M, et al. Anti-Siglec-8 Antibody for Eosinophilic Gastritis and Duodenitis. N Engl J Med 2020; 383:1624-34.
33. Cotton CC, Eluri S, Wolf WA, Dellon ES. Six-Food Elimination Diet and Topical Steroids are Effective for Eosinophilic Esophagitis: A Meta-Regression. Dig Dis Sci 2017; 62:2408-20.
34. Dunn JLM, Shoda T, Caldwell JM, Wen T, Aceves SS, Collins MH, et al. Esophageal type 2 cytokine expression heterogeneity in eosinophilic esophagitis in a multi-site cohort. J Allergy Clin Immunol 2020.
35. Wang R, Hirano I, Doerfler B, Zalewski A, Gonsalves N, Taft T. Assessing Adherence and Barriers to Long-Term Elimination Diet Therapy in Adults with Eosinophilic Esophagitis. Dig Dis Sci 2018; 63:1756-62.
36. Hirano I, Chan ES, Rank MA, Sharaf RN, Stollman NH, Stukus DR, et al. AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis. Gastroenterology 2020; 158:1776-86.
37. Rank MA, Sharaf RN, Furuta GT, Aceves SS, Greenhawt M, Spergel JM, et al. Technical Review on the Management of Eosinophilic Esophagitis: A Report From the AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters. Gastroenterology 2020; 158:1789-810 e15.
38. Dellon ES. Management of refractory eosinophilic oesophagitis. Nat Rev Gastroenterol Hepatol 2017; 14:479-90.
39. Gonsalves N, Doerfler B, Zalewski A, Yang GY, Gregory DL, Martin LJ, et al. Results from the ELEMENT study: Prospective study of elemental diet in eosinophilic gastroenteritis nutrition trial. Gastroenterology 2020:S-43 (AB 229).
40. Guttman-Yassky E, Bissonnette R, Ungar B, Suárez-Fariñas M, Ardeleanu M, Esaki H, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. J Allergy Clin Immunol 2019; 143:155-72.
41. Rohner MH, Thormann K, Cazzaniga S, Yousefi S, Simon HU, Schlapbach C, et al. Dupilumab reduces inflammation and restores the skin barrier in patients with atopic dermatitis. Allergy 2021; 76:1268-70.
42. Paller AS, Siegfried EC, Thaçi D, Wollenberg A, Cork MJ, Arkwright PD, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial. J Am Acad Dermatol 2020; 83:1282-93.

43. Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014; 371:130-9.
44. Siegels D, Heratizadeh A, Abraham S, Binnmyr J, Brockow K, Irvine AD, et al. Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis. Allergy 2021; 76:1053-76.
45. Cork MJ, Thaçi D, Eichenfield LF, Arkwright PD, Sun X, Chen Z, et al. Dupilumab provides favourable long-term safety and efficacy in children aged ≥ 6 to < 12 years with uncontrolled severe atopic dermatitis: results from an open-label phase IIa study and subsequent phase III open-label extension study. Br J Dermatol 2021; 184:857-70.
46. Silverberg JI, Thyssen JP, Fahrbach K, Mickle K, Cappelleri JC, Romero W, et al. Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis. J Eur Acad Dermatol Venereol 2021; 35:1797-810.
47. Cork MJ, Eckert L, Simpson EL, Armstrong A, Barbarot S, Puig L, et al. Dupilumab improves patient-reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and health-related quality of life in moderate-to-severe atopic dermatitis: analysis of pooled data from the randomized trials SOLO 1 and SOLO 2. J Dermatolog Treat 2020; 31:606-14.
48. Boguniewicz M, Beck LA, Sher L, Guttman-Yassky E, Thaçi D, Blauvelt A, et al. Dupilumab Improves Asthma and Sinonasal Outcomes in Adults with Moderate to Severe Atopic Dermatitis. J Allergy Clin Immunol Pract 2021; 9:1212-23.e6.
49. Hill DA, Grundmeier RW, Ramos M, Spergel JM. Eosinophilic Esophagitis Is a Late Manifestation of the Allergic March. J Allergy Clin Immunol Pract 2018; 6:1528-33.
50. de Bruin-Weller M, Thaçi D, Smith CH, Reich K, Cork MJ, Radin A, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). Br J Dermatol 2018; 178:1083-101.
51. Pino Lopez J, Kromer C, Herr R, Schmieder A, Bayerl C, Schaarschmidt ML. Drug survival rates and reasons for drug discontinuation in patients with atopic dermatitis: a retrospective study of adult outpatients. Eur J Dermatol 2021; 31:233-8.
52. Blauvelt A, Teixeira HD, Simpson EL, Costanzo A, De Bruin-Weller M, Barbarot S, et al. Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol 2021; 157:1047-55.
53. Oldhoff JM, Darsow U, Werfel T, Katzer K, Wulf A, Laifaoui J, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. Allergy 2005; 60:693-6.
54. Heil PM, Maurer D, Klein B, Hultsch T, Stingl G. Omalizumab therapy in atopic dermatitis: depletion of IgE does not improve the clinical course - a randomized, placebo-controlled and double blind pilot study. J Dtsch Dermatol Ges 2010; 8:990-8.
55. Feliciani C, Joly P, Jonkman MF, Zambruno G, Zillikens D, Ioannides D, et al. Management of bullous pemphigoid: the European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology. Br J Dermatol 2015; 172:867-77.

56. Messingham KA, Noe MH, Chapman MA, Giudice GJ, Fairley JA. A novel ELISA reveals high frequencies of BP180-specific IgE production in bullous pemphigoid. J Immunol Methods 2009; 346:18-25.
57. Seyed Jafari SM, Gadaldi K, Feldmeyer L, Yawalkar N, Borradori L, Schlapbach C. Effects of Omalizumab on FcepsilonRI and IgE Expression in Lesional Skin of Bullous Pemphigoid. Front Immunol 2019; 10:1919.
58. Lee S, Rastogi S, Hsu DY, Nardone B, Silverberg JI. Association of bullous pemphigoid and comorbid health conditions: a case-control study. Arch Dermatol Res 2021; 313:327-32.
59. Silverman GJ, Weisman S. Rituximab therapy and autoimmune disorders: prospects for anti-B cell therapy. Arthritis Rheum 2003; 48:1484-92.
60. de Graauw E, Sitaru C, Horn M, Borradori L, Yousefi S, Simon HU, et al. Evidence for a role of eosinophils in blister formation in bullous pemphigoid. Allergy 2017; 72:1105-13.
61. Rüdrich U, Gehring M, Papakonstantinou E, Illerhaus A, Engmann J, Kapp A, et al. Eosinophils are a Major Source of Interleukin-31 in Bullous Pemphigoid. Acta Derm Venereol 2018; 98:766-71.
62. Simon D, Yousefi S, Cazzaniga S, Bürgler C, Radonjic S, Houriet C, et al. Mepolizumab failed to affect bullous pemphigoid: A randomized, placebo-controlled, double-blind phase 2 pilot study. Allergy 2020; 75:669-72.
63. Choquet-Kastylevsky G, Intrator L, Chenal C, Bocquet H, Revuz J, Roujeau JC. Increased levels of interleukin 5 are associated with the generation of eosinophilia in drug-induced hypersensitivity syndrome. Br J Dermatol 1998; 139:1026-32.
64. Amante MF, Filippini AV, Cejas N, Lendoire J, Imventarza O, Parisi C. Dress syndrome and fulminant hepatic failure induced by lamotrigine. Ann Hepatol 2009; 8:75-7.
65. Gonçalo MM, Cardoso JC, Gouveia MP, Coutinho I, Gameiro AR, Brites MM, et al. Histopathology of the Exanthema in DRESS Is Not Specific but May Indicate Severity of Systemic Involvement. Am J Dermatopathol 2016; 38:423-33.
66. Ange N, Alley S, Fernando SL, Coyle L, Yun J. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome successfully treated with mepolizumab. J Allergy Clin Immunol Pract 2018; 6:1059-60.
67. Thein OS, Sutton B, Thickett DR, Parekh D. Mepolizumab rescue therapy for acute pneumonitis secondary to DRESS. BMJ Case Rep 2019; 12.
68. Schmid-Grendelmeier P, Steiger P, Naegeli MC, Kolm I, Lang CCV, Maverakis E, et al. Benralizumab for severe DRESS in two COVID-19 patients. J Allergy Clin Immunol Pract 2021; 9:481-3.e2.
69. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 2018; 73:1393-414.
70. Maurer M, Eyerich K, Eyerich S, Ferrer M, Gutermuth J, Hartmann K, et al. Urticaria: Collegium Internationale Allergologicum (CIA) Update 2020. Int Arch Allergy Immunol 2020; 181:321-33.
71. Cugno M, Marzano AV, Tedeschi A, Fanoni D, Venegoni L, Asero R. Expression of tissue factor by eosinophils in patients with chronic urticaria. Int Arch Allergy Immunol 2009; 148:170-4.

72. Tedeschi A, Asero R, Marzano AV, Lorini M, Fanoni D, Berti E, et al. Plasma levels and skin-eosinophil-expression of vascular endothelial growth factor in patients with chronic urticaria. Allergy 2009; 64:1616-22.
73. Altrichter S, Frischbutter S, Fok JS, Kolkhir P, Jiao Q, Skov PS, et al. The role of eosinophils in chronic spontaneous urticaria. J Allergy Clin Immunol 2020; 145:1510-6.
74. Bernstein JA, Singh U, Rao MB, Berendts K, Zhang X, Mutasim D. Benralizumab for Chronic Spontaneous Urticaria. N Engl J Med 2020; 383:1389-91.
75. Altrichter S, Staubach P, Pasha M, Rasmussen H, Singh B, Chang A, et al. Clinical activity of AK002, an anti-siglec-8 monoclonal antibody, in treatment-refractory chronic urticaria. J Allergy Clin Immunol 2020; 145 (Suppl):AB239.
76. Weigelt N, Metze D, Ständer S. Prurigo nodularis: systematic analysis of 58 histological criteria in 136 patients. J Cutan Pathol 2010; 37:578-86.
77. Zeidler C, Ständer S. The pathogenesis of Prurigo nodularis--'Super-Itch' in exploration. Eur J Pain 2016; 20:37-40.
78. Ständer S, Yosipovitch G, Legat FJ, Lacour JP, Paul C, Narbutt J, et al. Trial of Nemolizumab in Moderate-to-Severe Prurigo Nodularis. N Engl J Med 2020; 382:706-16.
79. Herout S, Bauer WM, Schuster C, Stingl G. Eosinophilic cellulitis (Wells syndrome) successfully treated with mepolizumab. JAAD Case Rep 2018; 4:548-50.
80. Kinoshita M, Ogawa Y, Onaka M, Shimada S, Kawamura T. Mepolizumab-responsive Kimura disease. J Allergy Clin Immunol Pract 2021; 9:2928-30.
81. Bürgler C, Guillet C, Kolm I, Theiler M, Schmid-Grendelmeier P, Kroiss S, et al. Treatment of eosinophilic pustular folliculitis with benralizumab in a 13-year-old girl. J Eur Acad Dermatol Venereol 2021; 35:e401-e3.
82. Goyal A, Lofgreen S, Mariash E, Bershow A, Gaddis KJ. Targeted inhibition of IL-4/13 with dupilumab is an effective treatment for eosinophilic dermatosis of hematologic malignancy. Dermatol Ther 2020; 33:e13725.
83. Jin A, Pousti BT, Savage KT, Mollanazar NK, Lee JB, Hsu S. Eosinophilic dermatosis of hematologic malignancy responding to dupilumab in a patient with chronic lymphocytic leukemia. JAAD Case Rep 2019; 5:815-7.
84. Rothenberg ME, Klion AD, Roufosse FE, Kahn JE, Weller PF, Simon HU, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. N Engl J Med 2008; 358:1215-28.
85. Roufosse F, Kahn JE, Rothenberg ME, Wardlaw AJ, Klion AD, Kirby SY, et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: A phase III, randomized, placebo-controlled trial. J Allergy Clin Immunol 2020; 146:1397-405.
86. Kuang FL, Legrand F, Makiya M, Ware J, Wetzler L, Brown T, et al. Benralizumab for PDGFRA-Negative Hypereosinophilic Syndrome. N Engl J Med 2019; 380:1336-46.
87. Plötz SG, Simon HU, Darsow U, Simon D, Vassina E, Yousefi S, et al. Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. N Engl J Med 2003; 349:2334-9.
88. Kuang FL, Fay MP, Ware J, Wetzler L, Holland-Thomas N, Brown T, et al. Long-Term Clinical Outcomes of High-Dose Mepolizumab Treatment for Hypereosinophilic Syndrome. J Allergy Clin Immunol Pract 2018; 6:1518-27.e5.

89. Roufosse F, de Lavareille A, Schandené L, Cogan E, Georgelas A, Wagner L, et al. Mepolizumab as a corticosteroid-sparing agent in lymphocytic variant hypereosinophilic syndrome. J Allergy Clin Immunol 2010; 126:828-35.e3.
90. Wechsler ME, Ruddy MK, Pavord ID, Israel E, Rabe KF, Ford LB, et al. Efficacy and Safety of Itepekimab in Patients with Moderate-to-Severe Asthma. N Engl J Med 2021; 385:1656-68.
91. Chen YL, Gutowska-Owsiak D, Hardman CS, Westmoreland M, MacKenzie T, Cifuentes L, et al. Proof-of-concept clinical trial of etokimab shows a key role for IL-33 in atopic dermatitis pathogenesis. Sci Transl Med 2019; 11.
92. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. N Engl J Med 2021; 384:1800-9.
93. Simpson EL, Parnes JR, She D, Crouch S, Rees W, Mo M, et al. Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: A randomized phase 2a clinical trial. J Am Acad Dermatol 2019; 80:1013-21.
94. Guttman-Yassky E, Brunner PM, Neumann AU, Khattri S, Pavel AB, Malik K, et al. Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: A randomized, double-blind, phase 2a trial. J Am Acad Dermatol 2018; 78:872-81.e6.

Table 1 Potential use of biologics as first line therapy in eosinophilic diseases. A summary of biologics that have been shown to be effective in a certain disease/disease group is given. For critical discussion and references, see text.

Biologic	**Target**	**Mode of action**	**Effects on eosinophil numbers**		**Disease**	**Potential use as first line therapy**	
			Peripheral blood	**Tissue**		**Hypothesis**	**Limitations/comments**
Mepolizumab	IL-5	Blocks eosinophil production, activation, survival	↓	↓	Eosinophilic asthma	Yes	Superiority to ICS +/- LABA not proven
					EGPA	Limited	Effect on asthma/sinusitis component, not vasculitis
					CRwNP	Yes	To replace polyp surgery
					HES	Limited	Add-on therapy to corticosteroids/immunosuppressives Depending on subtype
					DRESS	Yes	
Reslizumab	IL-5	Blocks eosinophil production, activation, survival	↓	↓	Eosinophilic asthma	Yes	Superiority to ICS +/- LABA not proven
Benralizumab	IL-5R	Inhibits binding of IL-5	↓	↓	Eosinophilic asthma	Yes	Superiority to ICS +/- LABA not proven
					EGPA	Limited	Effect on asthma/sinusitis component, not vasculitis
					Eosinophilic GI disease	Limited	Studies ongoing
					DRESS	Yes	Case reports
					CSU	Yes	Proof-of-concept study
					HES	Limited	Add on therapy to corticosteroids/immunosuppressives Depending on subtype
Lirentelimab	Siglec 8	Blocks activated eosinophil, mast cells	↓	↓	EoG, EoD	Yes	Phase 2 study
					CSU	Yes	Open-label, proof-of-concept study available
Cendakimab	IL-13	Blocks IL-13 binding to both IL-13Rs	NA	↓	Eosinophilic esophagitis	Yes	Phase 2 study
Dupilumab	IL-4/ IL-13R	Inhibits type 2 inflammation	↓ transient ↑	↓	Asthma	Yes	Superiority to ICS +/- LABA not proven
					CRwNP	Yes	To replace polyp surgery
					Eosinophilic esophagitis	Yes	Phase 3 study
					Atopic dermatitis	Yes	First line systemic therapy

					Multiple atopic diseases (AD + asthma + CPwNP + EoE)	Yes	One fits all
Omalizumab	IgE	Blocks IgE, reduces high affinity IgE receptor expression, thus activation of mast cells	↓	↓	Allergic asthma	Yes	Add on therapy to ICS +/- LABA not proven
					CRwNP	Yes	To replace polyp surgery
					Bullous pemphigoid	Yes	Good safety profile
Rituximab	CD20	Blocks B cells	NA	NA	Bullous pemphigoid	No	Safety profile
Nemolizumab	IL-31R	Blocks IL-31 binding, reduces itch	NA	NA	Prurigo nodularis	Yes	Rapid effect on pruritus

CSU, Chronic spontaneous urticarial; EGPA, Eosinophilic granulomatosis with polyangiitis; EoD, Eosinphilic duodenitis; EoG, Eosinophilic gastritis; CRwNP, Chronic rhinosinusitis with nasal polyps; HES, hypereosinophilic syndromes; IL, Interleukin; ICS, inhaled corticosteroids; LABA, long acting beta agonists; NA, not available; R, receptor