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Anti-Interleukin Biologics for the treatment of the Atopic March Diseases

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Abstract

The atopic march refers to the natural history of allergic disorders as they develop from infancy to childhood. Classically, the atopic march begins with atopic dermatitis (AD), followed by food allergy, advancing to asthma, allergic rhinitis (AR), and finally to the fifth member eosinophilic esophagitis. The pathogenesis of the atopic march is complex, and involves genetic, immunological, and environmental factors. T helper type 2 (Th2) lymphocytes, and epithelial cells play a key role in the pathogenesis of the diseases in the atopic march. Th2 cells secrete cytokines, such as interleukin-5 (IL-5), IL-4, and IL-13, whereas, epithelial cell injury release alarmin cytokines, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). Th2 cells and alarmin cytokines play an important role in the development of eczematous skin lesions, airway inflammation and remodeling, and oesophageal mucosal inflammation. Treatment of eosinophilic asthma and associated comorbid disorders is challenging, and requires a precision targeted approach with biologics. Dupilumab is a fully humanized IgG4 monoclonal antibody to the IL-4Rα, which mediates signaling to both IL-4 and IL-13, and blocks their immunopathological effects. Dupilumab is the only biologic that has been approved for the treatment of eosinophilic asthma, AD, and eosinophilic esophagitis. In patients with eosinophilic asthma treatment with dupilumab has been shown to improve asthma control, reduce exacerbations, and improve lung function. In patients with atopic dermatitis dupilumab has been demonstrated to improve the Eczema Area Severity Index (EASI) score, Investigator's Global Assessment (IGA) response, SCORing Atopic Dermatitis (SCORAD) score, and the Peak Pruritus Numerical Rating (PNR) scale. Lebrikizumab and Tralokinumab (anti-IL-13) failed to show the expected results for the treatment of asthma, astoundingly, in several clinical trials they have been shown to significantly improvement EASI score, IGA response, SCORAD score, PNR scale, sleep architecture, and Dermatology Life Quality Index (DLQI). They have been granted First Tract Designation, and European Commission regulatory approval, respectively. Tezepelumab (anti-TSLP) is approved for the treatment of eosinophilic asthma, and has been shown to significantly reduce exacerbations, and improve asthma control, lung function, and HLQoL. However, tezepelumab did not meet the endpoints in phase II for the treatment of AD.

Keywords: Atopic March; Atopic Dermatitis; Eosinophilic Asthma; Interleukin; Dupilumab; Tralokinumab

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Introduction

Despite progress in advances in novel therapies, the incidence of allergic diseases constituting the atopic march continues to rise, especially in children, and affects about 20% of the population worldwide [1]. Allergic diseases, such as asthma, allergic rhinitis, and atopic dermatitis can be very severe, and inflict misery and suffering to the patients, and family members. Treatment of allergic disease is costly, particularly therapy with the new biologics; and consumes a colossal proportion of national healthcare budgets in most countries [2,3]. The atopic march refers to the orderly sequence of allergic disorders as they develop from infancy, and childhood [4-9]. Classically, the atopic march begins with atopic dermatitis (AD), followed by IgE-mediated food allergy (FA), progressing to asthma, allergic rhinitis (AR) [4,5,6], and finally to the fifth member eosinophilic esophagitis (EoE) [9]. The atopic march is characterized by a typical sequence of progression of clinical signs of atopic disease, with some signs becoming more prominent while others subside [8]. Usually atopic dermatitis is the "entry point" for subsequent allergic disorders, and may disappear in adolescence in some patients [1,4-9]. A list of the family member diseases in the atopic march is depicted in Table 1.

Approximately, 70% of infants and children with severe AD develop asthma compared to 20-30% of patients with mild AD, and about 8% of the general population [10]. Severe, early-onset eczema, and persistent symptoms further increase the risk of developing asthma and allergic rhinitis [11].

Table 1: Family member diseases of the atopic march according to inception

Family members
1. Atopic dermatitis (AD)
2. Food allergy (FA)
3. Allergic rhinitis (AR)
4. Eosinophilic asthma
5. Eosinophilic esophagitis (EoS)
Cousin family members
1. Chronic rhinosinusitis with nasal polyps (CRSwNP)
2. Aspirin exacerbated respiratory disease (AERD)
3. Obesity
4. Obstructive sleep apnoea (OSA)

The fifth member of the concordat eosinophilic esophagitis, is also strongly associated with atopic dermatitis and other allergic disorders, such as asthma and allergic rhinitis [12]. Genome-wide studies (GWAS) have shown that EoE share the same genetic loci with other allergic diseases in the atopic march, including polymorphism in TSLP, and STAT6 [13]. In addition, population-based studies have revealed that EoE is strongly associated with other allergic diseases, such as AD, eosinophilic asthma, and AR [9]. Mohammad et al. [14], have reported that EoE is frequently associated with atopic dermatitis, asthma, and allergic rhinitis. The prevalence rates of AD, asthma, and AR were 61.9%, 39%, and 46.1% respectively; and approximately 21.6% of the patient with EoE developed all the three atopic diseases. Conversely, the atopic march even in it's more liberal definition does not occur in about 50% of the children who develop asthma and AR [15-21]. Furthermore, the majority of children who develop asthma do not have early AD, and AD is not a prerequisite for the

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development of asthma and allergic rhinitis, or eosinophilic esophagitis [23,24].

Pathogenesis of the Atopic March

The pathogenesis of the atopic march is multifactorial, and involves genetic, immunological, and environmental factors [4,6]. T helper type 2 (Th2) lymphocytes, and epithelial cells play a very important role in the pathogenesis of diseases in the atopic march crusade. Th2 cells secrete cytokines, such as interleukin-5 (IL-5), IL-4, and IL-13, whereas, epithelial cell injury release "alarmin" cytokines, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). These cytokines and other molecules, such as filaggarin, chemokines, periostin, and adhesion molecules play a concerted role in pathogenesis and progression of the atopic march [6].

Filaggrin

Filaggrin (acronym of filament-aggregating protein) is a barrier protein which plays a key role in the integrity of the stratum corneum of the epidermis. Defect in the epidermal barrier protein filaggrin (FLG) is associated with both atopic dermatitis and allergic sensitization [6]. Loss-of-function mutation in the FLG genes can lead to impairment of the skin barriers due to reduced level of natural moisturizing factor (NMF) [25,26], and induce allergic responses and diseases [27-29). NMF consists of hydroscopic amino acids and is a derivative of filaggrin, and is produced by enzymatic activity of caspase-14 and other proteases [30,31]. Impairment of the barrier function of the skin, results in increased penetration of chemical irritants, allergens, antigens, and pathogens into the skin [32,33].

Loss-of-function mutation in FLG has been shown to increase the risk of early-onset and severe atopic dermatitis [28,34]. Carrier of FLG mutations have a higher risk of progression of the atopic march [4,35,36], and confer a significantly higher genetic risk of developing several other allergic diseases, such as eosinophilic asthma, allergic rhinitis, and eosinophilic esophagitis [4-9]. Filaggrin mutations are strongly associated with atopic dermatitis in an Irish population, and AD plus asthma in a Scottish population [29]. Additionally, several population-based studies and meta-analyses have reported a strong association between FLG mutations and atopic dermatitis [36-42], with an overall odd ratio for AD ranging from 3.12 to 4.78 [41,42]. The association of FLG mutation with asthma is complex and not fully understood. However, in population studies, FLG loss-of-function mutation have conferred an overall asthma risk of about 1.48 to 1.79 [43,44].

The respiratory epithelia does not express filaggrin [45], therefore, systemic allergen sensitization may be responsible for pathogenesis of asthma [46]. Epithelial dysfunction due to FLG mutations increases allergen and microbe penetration through the stratum corneum. This may lead to stimulation and liberation of TSLP from keratinocytes in the inflamed epidermis, which may circulate to distal sites, such as the airways, and gastrointestinal tract [47]. Patient with atopic dermatitis who have FLG mutations tend to have a much higher risk of asthma than those who do not have FLG mutations [4,43,44]. Furthermore, asthmatic patients with FLG mutations have severe and more difficult disease to treat, and have frequent exacerbations [15,47]. Loss-of-function in FLG mutations confer a significant genetic risk of allergic rhinitis [43,48,49], and there is strong association between variant FLG with food allergy [50], especially peanut allergy [51,52]. This is more preponderate in monozygotic twins compared with dizygotic twins (64% vs 7%) [51]. Brown et al. [52] have reported a residual odds ratio of 3.8 when corrected for atopic dermatitis. The fifth member of the concordat eosinophilic esophagitis (EoE) is also strongly associated with atopic dermatitis and other allergic disorders, such as asthma and allergic rhinitis [53].

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Other Genetic Polymorphisms

A part from loss-of-function mutations of filaggrin, there are other mutations which predispose to eczema and the atopic march. Polymorphisms in the gene encoding TSLP and its receptor TSLP-R influence a significant risk for AD, food allergy, AR, and asthma [54-56]. A single nucleotide polymorphism (SNP) r1837253 in the upstream region of TSLP has been shown to be highly associated with asthma [57,58]. Similarly, polymorphisms in the genes encoding IL-33 and its receptor (IL1RL1 also known as ST2) are associated with increased risk of AD and asthma [59,60]. Combined polymorphisms significantly increases the risk of allergic diseases, and the progression of the atopic march [55,61,62].

Progression of the Atopic March

Carriers of FLG loss-of-function mutations have a higher risk of developing atopic dermatitis and progression of the atopic march [63]. They have also a significant higher risk of developing asthma [64], allergic rhinitis [64], and peanut allergy [65] compared to non-carriers. Filaggrin is not expressed in the bronchial, nasal, and gastrointestinal (GIT) mucosa, therefore, mutations in FLG is very unlikely to be directly associated with asthma, AR, and eosinophilic esophagitis [66-68]. The mechanism by which FLG mutations promote allergic responses in the respiratory tract, and GIT mucosa is through systemic sensitization from allergens that penetrate through the dysfunctional skin barrier due to FLG mutations [69]. Filaggrin dysfunction has serious consequences on the epidermal barrier that affect the organization of the keratin filaments of the cytoskeleton, and the structure of the cornified envelop (CE) [69]. It is also accompanied by a fall in the number of keratohyalin granules which contain profilaggrin, a marked fall in NMF concentration that moisturize the stratum corneum [70], and alkalization of the skin [71]. All these factors favour penetration of chemical irritants, allergens, antigens, and microbes into the skin. The increase in the activity of some proteases due to elevation in pH favours release of proinflammatory mediators by keratinocytes, such as IL-25, IL-33, and TSLP. These cytokines stimulate Th2 cells, ILC2, mast cells, and eosinophils leading to secretion of several cytokines, chemokines, adhesion molecules, and growth factors [72], which cause acute atopic dermatitis. Simultaneously, these cytokine may circulate to distal sites, such as airways, and the gastrointestinal system, and provoke allergic responses.

Systemic sensitization begins when the altered stratum corneum allows penetration of allergens which are then taken up and processed by the Langerhans cells of the epidermis. The Langerhans cells migrate to the lymph nodes where they interact with T cells, and induce Th2-mediated immune responses [73-75]. Repeated entry of allergens cause more sensitization, and polarization of the adaptive immunity towards Th2 [74]. Activated Th2 cells production cytokines, such as IL-5, IL-4, and IL-13, which orchestrates eosinophilia inflammation, and the diseases of the atopic march. Epithelial dysfunction also leads to activation of keratinocytes and the production of “alarmin” cytokines such as IL-25, IL-33, and TSLP [75,76]. Both Th2 and epithelial-derived cytokines are capable of circulating and reaching other mucosal surfaces, such as the respiratory tract, and the GIT mucosa. Moreover, several studies have shown elevation of some of these cytokines in serum, bronchoalveolar (BAL) fluid, and in bronchial specimen of patients with atopic diseases, such as eosinophilic asthma [77-85]. The role of Th2 lymphocytes, and innate lymphoid group 2 cells (ILC2) cytokines, such as IL5, IL-4, and IL-13, and epithelial-derived cytokines, including IL-25, IL-33, and TSLP in the pathogenesis of eosinophilic asthma has been adequately propounded elsewhere [86-93]. This review discusses the roles of the most likely cytokines in the pathogenesis of the atopic march diseases, such the doublet IL-4/IL-13; 33, and TSLP, and biologics targeting these cytokines

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in the treatments of the disorders of the atopic march.

Biologics for the treatment of diseases of the Atopic March

Comorbid atopic diseases comprising the atopic march may be very difficult to treat with the standards of care (SoC), and contribute to inexorable pharmaco-economical healthcare costs [2,3]. Since the introduction of omalizumab in 2003, biologics have proved to be very effective and safe in the treatment of patients with eosinophilic asthma [94-97], and concomitantly the disorders associated with asthma, such as AR, AD, EoE,, and chronic rhinosinusitits with nasal polyps. The number of biologics approved for the treatment of eosinophilic asthma continues to increase, and include omalizumab (anti-IgE) [98,99] mepolizumab [100,101] and reslizumab (anti-IL-5) [102], benralizumab (anti-IL-5Rα) [103,104], dupilumab (anti-IL-4Rα) [105,106], and tezepelumab (anti-TSLP) [107,108]. All the above biologics have been shown to be very effective in controlling asthma symptoms, reducing exacerbations, hospitalization, and emergence room visits [94-108]. Additionally, they improve lung function and HLQoL, and allow patients to taper or stop corticosteroid therapy [100,103,104,106,108]. Table 2 shows the biologics approved, and in development for the treatment of eosinophilic asthma. Th2 cytokines, such as IL-4, IL-13, IL-33, and TSLP play a leading role in the pathogenesis of allergic diseases, including eosinophilic asthma, AR, AS, and EoE. Some biologics targeting these interleukins, such as dupilumab have been designated "silver bullet" because they are effective in treating all the diseases encompassing the atopic march. Conversely, some biologics, such as tezepelumab are more effective in the treatment of asthma, but failed to show the expected effects in the treatment of eczema. Similarly, lebrikizumab, and tralokinumab were not satisfactory for the treatment of asthma in phase II clinical trials, but they are very effective in clearing the skin lesions in patients with eczema. This explains the complexity of interleukin immune pathways in the pathogenesis of different atopic diseases, thus, each disease has its own unique pathophysiological mechanisms, and response to interleukins antagonists (ILA).

Table 2: Monoclonal antibodies, and interleukin receptor antagonists, and their target.

Agent	Target	Phenotype	Stage of Development
Omalizumab*	IgE	Th2	Marketed 2003
Mepolizumab*	IL-5	Th2	Marketed 2015
Reslizumab	IL-5	Th2	Marketed 2016
Benralizumab*	IL-5R	Th2	Marketed 2017
Dupilumab*	IL-4Rα	Th2	Marketed 2018
Tezepelumab	TSLP	Th2	Marketed 2018
Pitrakinra	IL-4Rα	Th2	IIa
Lebrikizumab	IL-13Rα1	Th2	III
Tralokinumab	IL-13Rα1, 2	Th2	III
Brodalumab	IL-17RA	Th17	17 II
Secukinumab	IL-17A	Th17	17 II
Fezakinumab	IL-22	Th22	22 II
Etokimab	IL-33	Th2	2 IIa
Imatinib	c-kit receptor	Th2/Th17	II
Masitinib	c-kit receptor	Th2/Th17	II

Biologics still in phase 2 clinical trials have either been dropped out of the clinical trials for the treatment of asthma, or they are being investigated for the treatment of other allergic disorders.
*Approved for the treat of childhood eosinophilic asthma.

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Anti-Tslp: Tezepelumab in Severe Asthma

Tezepelumab is a first-in-class fully human IgG2ʎ monoclonal antibody (mAb) that binds to TSLP, and prevents it to interact with its heterodimeric receptor TSLPR, thus inhibiting multiple downstream immunopathologic pathways, and production of cytokines, and chemokines [109]. Currently, tezepelumab is the only anti-alarmin biologic which has been approved by the FDA for add-on treatment of severe, uncontrolled asthma irrespective of biomarker status.

Phase 1b [110], Phase 2b PATHWAY [111], and Phase 3 [112] clinical trials have demonstrated the efficacy and safety of tezepilumab in the treatment of patients with asthma. The first Phase Ib clinical trial evaluated the efficacy of tezepelumab in an allergen challenge model of asthma in patients with mild, allergic asthma [110]. Tezepelumab 200 mg administered intravenously every 4 weeks for 3 months resulted in a decrease in blood eosinophil count at 2 weeks of treatment, and a reduction in the level of fractional exhaled nitric oxide (FeNO). Bronchoprovocation tests with allergen at days 42 and 84, showed that tezepelumab treatment significantly inhibited the early and late asthmatic responses [110].

Phase 2b PATHWAY, multicentre, randomized, double-blind, placebo-controlled, parallel-group trial assessed the efficacy of tezepelumab as add-on therapy in patients with moderate-to-severe asthma, and frequent exacerbations [111]. This dose-ranging study showed that tezepelumab significantly reduced exacerbation rates by 62% (70 mg every 4 weeks), 71% (210 mg every 4 weeks), and 66% (280 mg every 4 weeks); respectively compared with placebo. There was also improvement in lung function, and reduction in biomarkers of eosinophilic asthma (blood eosinophil count, and FeNO) in all the three treated groups. The improvements were observed in all the phenotypes of asthma, and independent of baseline blood eosinophil counts, IgE levels, and FeNO concentration [111]. This indicates that tezepelumab is effective in most phenotypes of asthma, regardless of the baseline biomarkers of inflammation [111]. The Phase 3 follow-up analysis of data of pro-inflammatory biomarkers and proteomics for patients who received tezepelumab 210 mg every 4 weeks revealed that tezepelumab reduced blood eosinophil count, decreased serum IL-5, and IL-13 levels by 30% at 1 year, FeNO by 25%, and total serum IgE by 20% [112,113]. This indicates that add-on treatment with tezepelumab is effective in reducing biomarkers of airway eosinophilia, and in reducing asthma exacerbations [112,113].

The NAVIGATOR trial [NCT03347279] investigating the safety and efficacy of tezepelumab in the treatments of adults and adolescents with severe, uncontrolled asthma [114,115]. Tezepelumab added to standard of care treatment demonstrated a statistically significant clinically meaningful reduction in annualised asthma exacerbation rates (AAER) over 52 weeks in the overall patients studies, compared with placebo plus SoC [115,116]. Because of the impressive clinical trial results, tezepelumab was granted breakthrough therapy designation by the US Food and Drug Administration (FDA) in 2018 for the treatment of patients with severe asthma without an eosinophilic phenotype, who are receiving ICS/LABA and additional asthma controllers with or without oral corticosteroids (OCS) [117]. The SOURCE Phase III (NCT03406078) randomized, double-blind, placebo-controlled, parallel group trial investigated the efficacy and safety of tezepelumab in 150 severe asthma patients who required OCS up to GINA step 4 or 5 guidelines. The 48 weeks clinical trial did not meet the primary endpoint of a statistically significant reduction in the maintenance dose of OCS, without patients losing asthma control [118,119]. This was possibly due to the experimental design, as the manufacturer suggested. However, the study showed significant reduction in the AAER, and improvement in lung function, and HLQoL, similar to those observed in the previous trials, such as the registration Phase III NAVIGATOR

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trial. The above clinical trials signify the importance of the sentinel cytokine (TSLP) in the pathophysiology of asthma, and the efficacy of tezepelumab in a broad population of patients with severe asthma. Emson et al. [120] in the post hoc analysis of Phase 2b PATHWAY study, have also shown that tezepelumab reduces asthma exacerbations, and Th2 inflammatory cytokines in patients with chronic rhinosinusitis with nasal polyps (CRSwNP), and chronic rhinosinusitis without nasal polyposis (CRSsNP). This study demonstrate the efficacy of tezepelumab in different asthma phenotypes, and in allergic diseases associated with asthma, such as chronic rhinosinusitis with nasal polyps [120].

Anti-Tslp: Tezepelumab in moderate-to-severe Atopic Dermatitis

Thymic stromal lymphopoietin plays a central role in the pathogenesis of atopic dermatitis. Tezepelumb 280 mg administered every 2 weeks plus topical corticosteroids (TCS) has been shown to produce a greater numerical percentage in the number of patients achieving an Eczema Area Severity Index 50% (EASI50) versus placebo plus TCS (64.7% vs 48.2%; p = 0.091) [120]. Thus, tezepelumab plus TCS did not demonstrate statistically significant improvement in skin lesions in patients with moderate-to-severe AD. Tezepelumab phase 2 clinical trial has been terminated, on the ground that tezepelumab is a monotherapy, and did not reach the targeted efficacy level.

Anti-Il-13: Etokimab in severe Eosinophilic Asthma

Etokimab (AnaptsBios) is a first-in-class IgG1 monoclonal antibody which blocks the activity of IL-33, thereby, inhibiting its biological effects. Phase 2a proof-of-concept clinical trial in 25 patient with severe eosinophilic asthma, showed that a single intravenous dose of etokimab (330 mg) resulted in a rapid and sustained improvement in lung function, and reduction in the asthma control questionnaire-5 (ACQ-5) scores throughout the study up to Day 64. Etokimab was well tolerated with no adverse events [121]. Phase IIb etokimab clinical trial did not meet end point in the treatment of moderate-to-severe AD. The gloomy news from Phase IIb atopic dermatitis study has resulted in postponement of phase II b clinical trials in eosinophilic asthma.

Anti-Il-33: Etokimab in moderate-to-severe Atopic Dermatitis

A first-in-class phase 2a study investigated the efficacy of a single intravenous dose of etokimab in 12 patients with moderate-to-severe dermatitis. The study demonstrated that etokimab rapidly and sustainably reduced the Eczema Area Severity Index 50 (EASI50) in 83% of the patients, and EASI75 in 33% of the patients at day 29 after administration [122,123]. Treatment with etokimab also resulted in a reduction in blood eosinophil count, and neutrophil infiltration of the skin compared with placebo [122,123]. However, the ATLAS clinical trial in about 300 patients with moderate-to-severe atopic dermatitis failed to show the expected effects [124]. The study demonstrated that there was no statistically significant difference between etokimab treatment and placebo in improvement in the EASI score by week 16 of the study. This has been a blow, and unfortunate for the company, because it has also postponed its phase IIb trials in eosinophilic asthma because of the disappointing ATLAS study results [124].

Anti-Il-13: Lebrikizumab in severe Eosinophilic Asthma

Lebrikizumab is an IgG4k humanized monoclonal antibody that binds to IL-13 with high affinity, and specifically prevent the formation of the IL-13Rα1/IL-4Rα heterodimer complex, and subsequent signaling, thereby inhibiting the immunological effects of IL-13 [125]. Lebrikizumab does not prevent IL-13 binding to IL-13Rα2 decoy receptor [126], which is believed to be involved in endogenous regulation of IL-13. The LUTE and VERSE

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replicate, randomized, double-blinded, placebo-controlled studies investigated the dose-ranging response of lebrikizumab (37.5, 125, and 250 mg subcutaneously (SC) every four weeks) for 24 weeks [125]. Treatment with lebrikizumab demonstrated a reduction in exacerbation rates which was more pronounced in patient with high periostin levels (based on cut-point ≥50 ng/ml) in all the doses studied compared with placebo. There was a 60% reduction in exacerbations in the periostin-high patients versus 5% in the periostin-low patients [127]. Lung function improvement was also noticed in the periostin-high patients (9.1%) compared with 2.6% in the periostin-low patients. Lebrikizumab was safe and well tolerated [127]. This study established the role of IL-13, and periostin in the pathogenesis of severe eosinophilic asthma, and the utility of periostin as a biomarker of eosinophilic asthma [127]. Periostin is an extracellular matrix protein belonging to the fasciclin family [128]. During allergic inflammation it is inducible by IL-4 and IL-13 [129], and is responsible for IL-13 effects in promoting subepithelial fibrosis, fixed airflow limitation, progressive decline in lung function, and severe asthma [130,131]. Periostin is also implicated in the pathogenesis of AD, AR, CRSwNP, and EoE. Phase 3 clinical trials LAVOLTA I, number NCT01867125, and LAVOLTA II, number NCT01868061, studied the efficacy of lebrikizumab in 1081 and 1067 patients, respectively, with uncontrolled asthma despite ICS. In both studies, lebrikizumab did not consistently show significant reduction in exacerbations in the high-periostin patients [132]. Therefore, lebrikizumab failed to show it expected effects in periostin-high patients, and did not meet the endpoint. The STRESSO clinical trial assessed the efficacy of lebrikizumab in 310 adults with mild-to-moderate asthma on SABA alone without ICS [133]. Lebikizumab was not associated with statistically significant improvement in lung function (FEV1). The mean change in absolute change in FEV1 from baseline at 12 weeks was higher in the lebrikizumab treated patients compared with placebo (150 ml versus 67 ml; p = .06) [133]. Thus, lebrikizumab failed to meet its endpoint in the treatment of severe eosinophilic asthma.

Anti-Il-13: Lebrikizumab in moderate-to-severe Atopic Dermatitis

Interleukin-13 plays a central role in the pathogenesis of atopic dermatitis, and in the pathophysiology of the symptoms and signs of AD, such as intense pruritus, dry skin, skin thickening, eczematous lesions, and infections. Phase 2a clinical trial investigated the efficacy and safety of lebrikizumab in 280 patients with moderate-to-severe atopic dermatitis [134]. Lebrikuzumab was very effective in the treatment of AD, and was well tolerated, and had a favourable safety profile. Lebrikizumab showed a dose-dependent, statistically significant improvement in the mean change in the Eczema Area and Severity Index score from baseline to week 16 versus placebo: 125 mg subcutaneously (SC) every 4 weeks (-62.3%, P = .02); 250 mg SC every 4 weeks (-69.2%, P = .002); and 250 mg SC every 2 weeks, P < .001). Significantly, more patients treated with lebikizumab 250 mg dose achieved the Investigator's Global Assessment (IGA) score 0/1 response, EASI50, EASI75, and AESI90 compared with placebo. Similarly, patients treated with lebrikizumab demonstrated dose-dependent, statistically significant improvement in the pruritic numerical rating (PNR) scale at week 16 versus the placebo group. Treatment with lebrikizumab also improved the sleep architecture, and the HLQoL [134]. Recently, the U.S. FDA has granted Fast Tract designation to lebrikizumab for moderate-to-severe atopic dermatitis in patient aged 12 and older and ≥ 40 Kg [135].

Anti-Il-13: Tralokinumab in severe Eosinophilic Asthma

Tralokinumab is a fully human IgG4 monoclonal antibody that effectively and specifically neutralizes IL-13, thus, preventing IL-13 interacting with its receptor subunits IL-13Rα1 and IL-13Rα2, and signaling [136,137].

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Phase II clinical trials (NCT00873860 and NCT01402986) investigated the safety, and efficacy of tralokinumab in improving lung function in patients with moderate-to-severe asthma inadequately controlled with medium- or high-dose ICS/LABA [138,139]. In both studies, tralokinumab improved lung function (FEV1) in patients with inadequately controlled asthma. Post hoc analyses of the two trial revealed that tralokinumab benefit was seen preferentially in participants with evidence of IL-13 activation [138,139], such as increased sputum IL-13 concentration (>10 $pg.ml^{-1}$) at baseline [138]. In Phase 2a study (NCT0073860) in a subgroup of patients with moderate-to-severe asthma who had increased sputum concentration of IL-13 at baseline, there were trends for tralokinumab treatment to have clinically meaningful improvements in markers of asthma control (Asthma Control Questionnaire-6 (ACQ-6), and FEV1 compared with placebo [138]. Brightling et al. [139] in Phase IIb study (NCT01402986) used blood concentrations of periostin, and dipeptidyl pepetidase-4 (DDP-4), which are matricellular proteins inducible by IL-13, to serve as a biomarker of IL-13 activation [139]. In post hoc analyses of this study, subgroups of participants with severe, uncontrolled asthma with FEV1 reversibility ≥12%, and were not receiving regular OCS at study entry demonstrated the potential of the efficacy of tralokinumab in biomarker-high patients. In patients with elevated concentrations of DDP-4 or periostin at baseline, tralokinumab (300 mg SC every 2 weeks (Q2W) demonstrated reduction in exacerbations, and improvement in lung function, and health-related quality of life (HLQoL) [139]. Tralokilumab was well tolerated and there were no safety signals of concern observed in both clinical trials [138,139].

An integrated pharmacokinetics (PK)-pharmacodynamic model cross-examined data from the two Phase II studies to select the most appropriate trakolinumab dosage to be used in Phase III trials. A near-maximal increase in FEV1 was predicted at a dosage of 300 mg SC Q2W, this dosage of tralokinumab was selected for subsequent Phase III clinical trials [140]. Based on population PK-pharmacodynamic modeling, weight-based dosing or dose adjustments of tralokinumab are not required for use in adolescents [141] or people of Japanese ethnicity [142]. With or without PK-pharmacodynamics, neither of the fully enrolled Phase II studies NCT00873860 and NC01402986) met their primary endpoints [138,139]. The most convincing clinical trial was Phase IIb study (NCT01402986). Brightling et al. [139] evaluated the safety and tolerability of tralokinumab 300 mg SC administered Q4W for 52 weeks in 452 patients with severe asthma, and 2-6 exacerbations in the previous years. At 52 weeks, they found no significant improvement in ACQ-6, AQLQ(S), and FEV1 in tralokinumab treated patients compared with placebo. Nevertheless, in a subgroup of patients with high levels of serum periostin, and DDP-4, they reported a significant reduction in exacerbations rates, but not in the patients with low serum periostin levels [139]. Their results suggested that a certain subgroup of patients with eosinophilic asthma respond to tralokinumab treatment, particularly in patients with high IL-13 specific biomarkers, such as DDP-4, and periostin.

In the TROPOS clinical trial, Busse et al. [143] examined the effects of tralokinumab in 140 patients with severe asthma who required maintenance oral corticosteroids. Patients were randomized to treatment with tralokinumab 300 mg or placebo administered subcutaneously every 2 weeks. At week 40, the percentage reduction in the final daily average oral glucocorticoid dose was not significantly different between tralokinumab and placebo (37.62% versus 29.85%; P = 0.27). There was also no significant difference in any of the secondary end-points that were examined [143]. Therefore, tralokinumab did not demonstrate oral corticosteroid-sparing effects in patients with severe asthma [143]. Combining the results from all the studies, tralokinumab has limited efficacy in a large population of asthmatic patients, and it has not

DOI: https://doi.org/10.36811/ojprm.2021.110012 OJPRM: October-2021: Page No: 01-27

been shown to be allow patients to taper or discontinue corticosteroid treatment.

ANTI-IL-13: Tralokinumab in moderate-to-severe Atopic Dermatitis

Phase IIb clinical trial (NCT02347176) investigated the efficacy, safety and tolerability of tralokinumab (Adtralza®) in adults with moderate-to-severe atopic dermatitis. Phase IIb randomized, double-blind, placebo-controlled, dose-ranging study enrolled 204 screened participants out of 299 across 55 sites in several countries [144]. Eligible participants were aged 18 to 75 years, with physician-confirmed diagnosis of AD (according to Hanifin and Rajka) [145]. Primary exploratory biomarkers of IL-13 activity, such as (DDP-4 and periostin); and CCL17/thymus- and activation-regulated chemokine (TARC), and IgE concentration were obtained from the participants. Phase II b trial showed that at week 12, the adjusted mean difference from baseline in EASI score was significantly different in the tralokinumab treated patients than the value in the placebo group: -4.36 (95% confidence interval (CI), -8.22 to -0.51; P = .03) for the 150 mg tralokinumab group, and -4.94 (95% CI, -8.76 to -1.13; P = .01) for the 300 mg tralokinumab group [144]. Improvement in the adjusted mean change from baseline in EASI was evident at week 4 and maintained beyond week 12 for the participants treated with 300 mg tralokinumab. A greater adjusted percentage of tralokinumab-treated participants achieved a reduction of 50% in EASI score (EASI50) versus placebo at week 12, and the differences were more substantial in the 300 mg tralokinumab group (73% vs 51.9%; P = .03). Similarly, the percentage of participants with a reduction in 75% or more in EASI score (EASI75) was significantly higher in the 300 mg tralokinumab group versus placebo (42.5% vs 15.5%) [144].

Participants treated with 150 mg and 300 mg tralokinumab achieve significant improvement in SCORing Atopic Dermatitis (SCORAD) score versus placebo -9.42 (95% CI, -15.56 to -3.29; P = 003), and -984 (95% CI, 15.91 to -3.77; P = .002, respectively). Improvement in SCORAD score were observed from week 2 onwards for the two doses of tralokinumab, and maintained beyond week 12. Of course, the greatest effects were observed in participants who received tralokinumab 300 mg dosage [144]. Additionally, the percentage of participants with a reduction of 50% or more of SCORAD score at 12 week was significantly greater in the 150 mg (44.2%, P = .008), and in the 300 mg tralokinumab group (44.1%, P = .009) versus placebo [144]. There was no significant difference in the percentage of participants with an Investigator's Global Assessment (IGA) response at week 12 in the pooled 150 mg and 300 mg tralokinumab participants group compared with placebo (23% vs 11.8; P = .10). However, there were observed numerical improvement in IGA response rates in the higher dose of tralokinumab. The greatest absolute percentage difference from the placebo was observed in participants treated with 300 mg of tralokinumab (26.7% vs 11.8%; 95% CI, 0.0 to 29.7; P = .06).

Furthermore, participants showed significant improvements from baseline at week 12 in pruritic numeric rating scale scores when receiving 300 mg tralokinumab versus placebo (-1.14, 95% CI, -1.88 to -0.41; P = .002). The improvements were observed from week 1 onward to beyond week 12 for all tralokinumab doses. Superbly, improvement in Dermatology Life Quality Index score were reported at week 12 in participants receiving 300 mg tralokinumab (-3-51, 95% CI, -6.00 to -1.02; P = .006). However, these improvements were short-lived, and were not maintained beyond 12-week treatment period [144].

Treatment with tralokinumab was safe and well tolerated by the participants, with an overall frequency and severity of adverse events comparable with placebo [146-148]. Two phase two 52-week, randomized, double-blind, placebo-controlled phase III trials ECZTRA 1 (NCT03131648) and ECZTRA 2

DOI: https://doi.org/10.36811/ojprm.2021.110012 OJPRM: October-2021: Page No: 01-27

(NCT03160885) investigated the safety and efficacy of tralikonumab 300 mg SC every four weeks in adult patients with moderate-to-severe AD [146]. At week 16, there were more patients who received tralikonumab versus placebo who achieved an IGA score of 0 or 1: 15.8% vs 7.1% in ECZTRA 1 (95% CI 4.1-13.1; P = 0.002), and 22% vs 10.9% in ECZTRA 2 (95% CI 5.8-16.4; P < 0.001) [146]. Similarly, there were more patients treated with tralokinumab versus placebo who achieved EASI75: 25% vs 12.7% in ECZTRA 1 (95% CI 6-5-17-7; P < 0.001), and 33.2% vs 11.4% (95% CI 15.8-27.3; P < 0.001) in ECZTRA 2. Additionally there were early improvements in pruritus, sleep quality, Dermatology Life Quality Index, SCORing Atopic Dermatitis score, and Patient-Oriented Eczema Measure from the first post-baseline measurements. Impressively, the majority of responders at week 16 maintained sustained response at week 52 on treatment with tralokinumab, and without rescue topical corticosteroids. Adverse effects in both studies were almost similar to those observed in the placebo groups [146], and other tralokinumab studies [145-147].

Phase III ECZTRA 3 double-blind, randomized, placebo-controlled, multinational 32-week clinical trial examined the safety efficacy of Adtralza with concomitant topical corticosteroids in 380 adult patients with moderate-to-severe atopic dermatitis [148]. At week 16 about 39% of patients on tralokinumab achieved an IGA score 0 (clear), and approximately 56% achieved a 75% improvement in the EASI. Additionally, 45% of the patients treated with tralokinumab plus TCS had reductions of itch, and achieved a four-point response of their worst daily itch [148], which is considered by the FDA to be clinically meaningful response in itch. More patients in the tralokinumab arm tapered TCS compared with those in the placebo group, and impressively, "super responders" had immediate clearing of the eczema and relief of itching [148].

Based and supported by data from the ECZTRA 1, 2, and ECZTRA 3 pivotal trials in which tralokinumab demonstrated significant improvement in AD symptoms and signs, the European Commission granted regulatory approval for Adtralza [146]. Adtralza will be available in a 150 mg/ml prefilled syringes for subcutaneous injection with an initial loading dose of 600 mg followed by 300 mg every other week [146].

IL-4/13: Dupilumab in severe Eosinophilic Asthma

Dupilumab (Dupixent®) is the only approved interleukin antagonist for the treatment of severe, uncontrolled eosinophilic asthma, and comorbid diseases in the atopic march. Dupilumab is a fully humanized IgG4 monoclonal antibody to the IL-4Rα, which mediate signaling to both IL-4 and IL-13 [149,150]. In a phase 2a clinical trial of 104 patients with moderate-to-severe asthma, treatment with dupilumab administered SC was associated with reduction in inflammatory biomarkers, including FeNO, serum IgE, and eotaxin-3 (CCL36) compared with placebo [151]. Treatment with Dupixent at 12 weeks was associated with a significant reduction in severe exacerbations by 87%, improvement in lung function (FEV1) by 29%-33%, and reduction in morning and evening symptom scores, nocturnal awakening, and use of rescue long-acting Inhaled beta-agonists (LABA). The improvement in FEV1 was maintained through week 12, despite the patients not taking LABA and inhaled corticortisteroids [151]. In Phase 2b trial in patients with uncontrolled persistent asthma, dupilumab administration SC demonstrated a reduction in the daily use of oral corticosteroids by 70% compared to 42% with placebo [158]. More than half of the patients treated with the drug completely eliminated the use of OCS [152]. A phase 3 dose-ranging trial examined SC dupilumab 200 mg (400 mg loading dose), or dupilumab 300 mg (600 mg loading dose) for 52 weeks compared with two separate placebo groups in patients with moderate-to-severe asthma [153]. Overall,

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patients on dupilumab had a lower rate of asthma exacerbations for the two different doses studied compared with placebo groups. The rate of annualized severe exacerbations was 0.64 versus 0.87 for the 200 mg dupilumab group versus matching control (47% lower, p <0.001). The rate was 0.52 versus 0.97 for the 300 mg dupilumab group versus matched control (46% lower, p <0.001). There was a significant improvement in the FEV1 of 0.14 L versus placebo for the lower dose (p <0.001), and 0.13 L versus placebo for the higher dose (p <0.001). Another well-conducted, randomized controlled clinical trial, assessed the role of dupilumab 300 mg (600 mg loading dose) in steroid-dependent asthma [154]. Patients in this trial were over the age of 12, and were on prednisone doses ranging from 5 mg to 35 mg, or equivalent, and on fluticasone propionate >500 mg daily, in combination with two other controller medications [154]. The patients (105 out of 210 patients enrolled) were more successful at reducing their OCS dose than patients in the placebo group. The reduction in glucocorticoid dose was 70.1% in the dupilumab group and 41.9% in the placebo group (p<0.001). Treatment with dupilumab was also associated with fewer severe exacerbations, greater FEV1 improvement, and improved asthma control (ACQ-5) compared with placebo [154].

Stratification and re-analysis of the patients in the moderate-to-severe asthma study into three groups, using biomarkers of eosinophilic asthma, such as blood eosinophil count, and FeNO revealed that the response to dupilumab depended on specific biomarkers of IL-4/IL-13 activity. The greatest reduction in exacerbations (66-67%) was seen in the group with blood eosinophil count greater than 300 cells/µL. The second group with eosinophil count of 150-300 cells/µL had a significant reduction of 36-40%, but the group with an eosinophil count <150 cells/µL did not have significantly less exacerbations than the control. In a separate study analysis of steroid-dependent asthma group, the subjects were divided into specific groups depending on their FeNO measurements [155]. Subjects with elevated baseline FeNO >50 ppb had a significant reduction in exacerbations compared with controls. However, subjects with FeNO <25 ppb did not have a significantly significant reduction in asthma exacerbations rates. The above results demonstrate that patient selection based on biomarkers, is essential for predicting response to treatment with dupilumab. Dupilumab was approved by the FDA on October 19, 2018, and later by the Committee for Medicinal Products for Human Use of the European Medicines Agent (EMA). It is approved as an add-on maintenance therapy in patients with moderate-to-severe eosinophilic asthma in adults, and children of 12 years and older. It is also approved by the FDA, for add-on treatment for patients with oral corticosteroid-dependent asthma regardless of phenotype. Dupixent is available as a single-dose pre-filled syringe and is administered subcutaneously under the guidance of a healthcare provider, or self-administered. It comes in two doses (200 mg and 300 mg) given on alternative weeks at different injection sites after an initial loading dose of 400 mg and 600 mg, respectively [156].

Dupilumab in other IL-4/13-Driven Atopic Diseases

The twin cytokines IL-4 and IL-13 play a central role in the pathogenesis and progression of the diseases of the atopic march, such as allergic rhinitis [157], atopic dermatitis [158-163], and eosinophilic esophagitis [164-168]. Dupilumab is atop of the biologics hierarchy. It is the only ILA which effective, and has been approved by the FDA for the treatment of IL-4/IL-13-driven diseases in the atopic march, such as eosinophilic asthma [98-108], AD [169-173], and EoE [174-176]. Providentially, comorbidities, such as atopic dermatitis, allergic rhinitis, and eosinophilic esophagitis respond to therapy with dupilumab intended to treat eosinophilic asthma. Therefore, coexisting diseases with eosinophilic asthma should be considered when selecting patients most likely to benefit from targeted precision treatment with biologics, including dupixent or any other

DOI: https://doi.org/10.36811/ojprm.2021.110012 OJPRM: October-2021: Page No: 01-27

ILA [177]. Noteworthy, the co-existing diseases require specific therapies in order to achieve asthma control.

IL-4/IL-13: Dupilumab in moderate-to-severe Atopic Dermatitis

Dupilumab is a fully humanized IgG4 monoclonal antibody to the IL-4Rα, which mediate signaling to both IL-4 and IL-13 [178]. This results in downregulation of receptor signaling downstream of the JAK/STAT pathway, which regulates the expression of many genes involved in the pathogenesis of atopic eczema [179]. Several randomized, double-blind, placebo-controlled multinational clinical trials have lucidly demonstrated that dupilumab significantly improves symptoms of eczema, such as the Eczema Area and Severity Index score, SCOring Atopic Dermatitis score, IGA score, Peak Pruritus Numerical Rating scale, and the Dermatology Life Quality Index in patients with moderate-to-severe AD [169-173]. Dupilumab was first approved for the treatment of atopic dermatitis before authorization for the treatment of eosinophilic asthma. Dupixent received its first approval from the FDA for the treatment of adult patients with moderate-to-severe AD whose disease is inadequately controlled with topical therapies, or when therapies are not advisable in March 2017. In September 2017, it was approved in the European Union by the European Medicines Agency (EMA) as a systemic first-line treatment for adult patients suffering from AD [180]. Dupixent can be used with or without concomitant TCS [181].

IL-4/IL-13: Dupilumab in acute Eosinophilic Esophagitis

Eosinophilic esophagitis is a chronic progressive Th2 immune-driven disorder, characterized by esophageal dysfunction and symptoms, and eosinophilic esophageal inflammation [182,183]. Th2 ctokines, such as IL-5 [184,185], IL-4, IL-13 [185-188], TSLP [189], and periostin [190] play critical roles in the pathogenesis of eosinophilic esophagitis. Multicentre, randomized, placebo-controlled, double-blind, parallel-group phase II studies have shown that dupilumab is efficacy and safe, and well tolerated by patients with acute eosinophilic esophagitis. Dupilumab has been shown to significantly improves, the Staumann Dysphagia Instrument (SDI) mean score, patient-reported outcome score, histologic features of EoE; endoscopic reference score, and eosophageal distensibility [174-176]. Recently, Dupixent has been approved by the FDA for the treatment of eosinophilic esophagitis. Table 3 lists the biologics approved, and in development for the treatment of atopic dermatitis, and eosinophilic asthma.

Table 3: Interleukin-antagonists and their targets and stage of development in the treatment of atopic dermatitis.

Biologic	Target	Stage of Development
Dupilumab	IL-4Rα (IL-4/IL-13	Approved 2017
Lebrikizumab	IL-13Rα1	Fast Track Designation
Tralokinumab	IL-13Rα1, IL-13Rα2	EC regulatory approval
Nemolizumab	IL-31Rα	Phase II
Tezepelumab	TSLP	Phase II, discontinued
Etokimab (ANB020)	IL-33	Phase II, discontinued
Fezakinumab	IL-22	Phase IIa
Ustekinumab	IL-5	Phase II, discontinued
Brodalumab	IL-17RA	Phase II
Secukinumab	IL-17	Phase II
Mepolizumab	IL-5	Phase IV

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Conclusion

The atopic march refers to the orderly progression of allergic diseases as they develop from infancy, and childhood, usually commencing with AD, followed by AR and asthma, and finally EoE. The pathophysiology of the heterogeneous diseases in the atopic march is complex. Some Th2 cytokines may play a key role in the pathogenesis of the allergic diseases, whereas, other may merely play supportive roles. Biotherapeutics of the diseases of atopic march is not "one fits all", because some biologics are able to treat more than three of the diseases, e.g. dupilumab (anti-IL4Rα). On the other hand, some biologics may be able to treat only one disease, and other ILAs may not be successful in treating any of the diseases in the atopic march, such as etokimab (anti-IL-33). In treating eosinophilic asthma with comorbid diseases, it is therefore prudent to choose the right ILA, because of the cost of the biologics, and the rare grade 3/4 adverse events.

Abbreviations

AA: Atopic Dermatitis
AR: Allergic Rhinitis
CI: Confindence Interval
CRSsNP: Chronic Rhinosinusitis without Nasal Polyps
CRSwNP: Chronic Rhinosinusitis with Nasal Polyps
DDP-4: Dipeptidyl Peptidase-4
DLQI: Dermatology Life Quality Index
EASI: Eczema Area Severity Index
ECZRA 1 and ECZTRA 2: ECZema TRAlokinumab Nos. 1 and 2
EoE: Eosinophilic Esophagitis
FDA: US Food and Drug Administration
FeNO: Fractional exhaled nitric oxide
FEV1: Forced expired volume in 1 second
IgE: Immunoglobulin E
IGA: Investigator's Global Assessment
IL: Interleukin
Mab: Monoclonal Antibody
PNR: Pruritic Numeric Rating
SCORAD: SCORing Atopic Dermatitis
TARC: Thymus and Activation-Regulated Chemokine
TCS: Topical Corticosteroids

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