

Reviews

JAK/STAT inhibitors and other small molecule cytokine antagonists for the treatment of allergic disease



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Key Messages

- Asthma, atopic dermatitis, and allergic rhinitis are characterized by increased janus kinase, phosphodiesterase, and prostaglandin/CRTH2 mediated inflammation.
- Novel molecular entities provide opportunity to target specific inflammatory pathways.
- Emerging phenotypes and endotypes in allergic diseases suggest there is opportunity for more personalized approaches to future therapeutic intervention.
- Practicing clinicians should become comfortable with understanding these immune pathways as newer endotypes that involve various combinations of these molecules are described in order to inform specific therapeutic choices for these patients.

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ABSTRACT

Objective: To provide an overview of janus kinase (JAK), chemoattractant receptor homologous molecule expressed on T_H2 cells (CRTH2), and phosphodiesterase 4 (PDE4) inhibitors in allergic disorders.

Data Sources: PubMed literature review.

Study Selections: Articles included in this review discuss the emerging mechanism of action of small molecule inhibitors and their use in the treatment of atopic dermatitis (AD), asthma, and allergic rhinitis (AR).

Results: Allergic diseases represent a spectrum of diseases, including AD, asthma, and AR. For decades, these diseases have been primarily characterized by increased T_H2 signaling and downstream inflammation. In recent years, additional research has identified disease phenotypes and subsets of patients with non-Th2 mediated inflammation. The increasing heterogeneity of disease has prompted investigators to move away from wide-ranging treatment approaches with immunosuppressive agents, such as corticosteroids, to consider more targeted immunomodulatory approaches focused on specific pathways. In the past decade, inhibitors that target JAK signaling, PDE4, and CRTH2 have been explored for their potential activity in models of allergic disease and therapeutic benefit in clinical trials. Interestingly, although JAK inhibitors provide an opportunity to interfere with cytokine signaling and could be beneficial in a broad range of allergic diseases, current clinical trials are focused on the treatment of AD. Conversely, both PDE4 and CRTH2 inhibitors have been evaluated in a spectrum of allergic diseases. This review summarizes the varying degrees of success that these small molecules have demonstrated across allergic diseases.

Conclusion: Emerging therapies currently in development may provide more consistent benefit to patients with allergic diseases by specifically targeting inflammatory pathways important for disease pathogenesis.

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Introduction

Allergic diseases represent a spectrum of disorders, including food allergies, certain forms of asthma, rhinitis, conjunctivitis, angioedema, urticaria, eczema, eosinophilic esophagitis, and drug and insect allergies.¹ During the past 20 to 30 years, the prevalence of allergic diseases has increased exponentially throughout the world and now affects approximately 1 in 5 people.¹ This significant

increase has driven the total health care burden for allergic disease into the tens of billions of US dollars¹ because of increased hospital admissions, physician visits, and treatments. In addition, the socioeconomic burden continues to increase as a consequence of increased absenteeism and presenteeism in inadequately treated patients.²

Allergic diseases can develop at any age because of a complex interaction of genetics and environmental factors, and often these allergic diseases are associated with one another, further illustrating the overlapping underlying mechanisms of disease and pathogenesis. Through the years, studies have found that allergic diseases are primarily characterized by increased T_H2 pathway activation, leading to increased serum IgE levels, blood eosinophil counts, and allergen reactivity.³ We review the pathogenesis of atopic dermatitis (AD), asthma, and allergic rhinitis and the opportunity for janus kinase (JAK), chemoattractant receptor homologous molecule expressed on T_H2 cells (CRTH2), and phosphodiesterase 4 (PDE4) inhibitors to specifically target pathways important for disease pathogenesis.

Emerging Therapeutic Targets

Corticosteroids and other anti-inflammatory medications are frequently used as first-line therapies in patients with allergic disease. These agents improve disease in patients with mild disease; however, there is a limited duration of effect, and those with more severe disease may not receive adequate treatment. In addition, current therapies nonspecifically address clinical improvement and symptomatic relief without targeting the specific pathways that initiate and potentiate allergic disease pathogenesis.^{4,5} During the past 2 decades, there have been significant advancements in medicinal chemistry, resulting in the development of novel therapeutics that specifically target inflammatory pathways.

In recent years, several kinase families have shown promise in the treatment of allergic diseases, such as members from the Bruton tyrosine kinase, phosphoinositide 3-kinase delta and gamma, and other tyrosine kinase families. Specifically, ibrutinib, an irreversible Bruton tyrosine kinase inhibitor, was recently found to reduce reactivity to aeroallergens in the skin test and basophil activation test.⁶ In addition, members of the phosphoinositide 3-kinase family have been implicated in respiratory disease, and

LY294002 has exhibited anti-inflammatory roles in murine models of airway hyperreactivity.^{7,8} Most recently, imatinib, which inhibits the tyrosine kinase activity of KIT, significantly decreased airway hyperresponsiveness, numbers of mast cells in the airway, and serum tryptase in severe refractory asthma.⁹ The positive results from these preclinical and clinical studies suggest opportunistic evaluation of these inhibitors in additional studies of allergic disease. Given their primary use in oncologic diseases, it will be important to monitor safety profiles of these inhibitors in future studies. In this review article, the authors have primarily focused on the JAK, CRTH2, and PDE4 families because of their status and advancement in industry-sponsored clinical trials across multiple allergic diseases.

JAK Inhibitors

The mammalian JAK kinase family (JAK1, JAK2, JAK3, and tyrosine kinase 2) is mainly expressed in hematopoietic cells.¹⁰ After activation, they phosphorylate signal transducer and activator of transcription (STAT) factors, resulting dimerization, translocation to the nucleus, and regulated gene expression. The JAK-STAT pathway is pivotal for the downstream signaling of inflammatory cytokines, including interleukins (ILs), interferons (IFNs), and multiple growth factors.¹¹ Genetic modulation that results in aberrant JAK-STAT signaling has clearly demonstrated the indispensable requirement of this pathway for immune and hematopoietic function.^{12–14}

Moreover, preliminary reports have identified the JAK-STAT pathway with susceptibility loci in asthma,¹⁵ AD,¹⁶ and allergic rhinitis (AR).¹⁷ Specifically, allergic diseases are primarily characterized by increased levels of IL-4, IL-5, IL-13, IL-31, and thymic stromal lymphopoietin (TSLP). Engagement of these cytokines with their respective receptors induces the JAK/STAT pathway. Specifically, IL-4 and IL-13 engage with IL-4 receptor α and either γ chain or IL-13 receptor α_1 to induce JAK1 and JAK3, leading to the activation of STAT6 (Fig 1). IL-5 engages with the IL-5 receptor and β chain to induce JAK1 and JAK2, leading to activation of STAT1, STAT2, and STAT5.¹⁸ TSLP binds to a heterodimeric receptor composed of TSLP receptor and IL-7 receptor α to induce JAK1 and JAK2 expression, leading to STAT5 activation.¹⁹ Several JAK inhibitors with differing selectivity profiles are currently in development for allergic

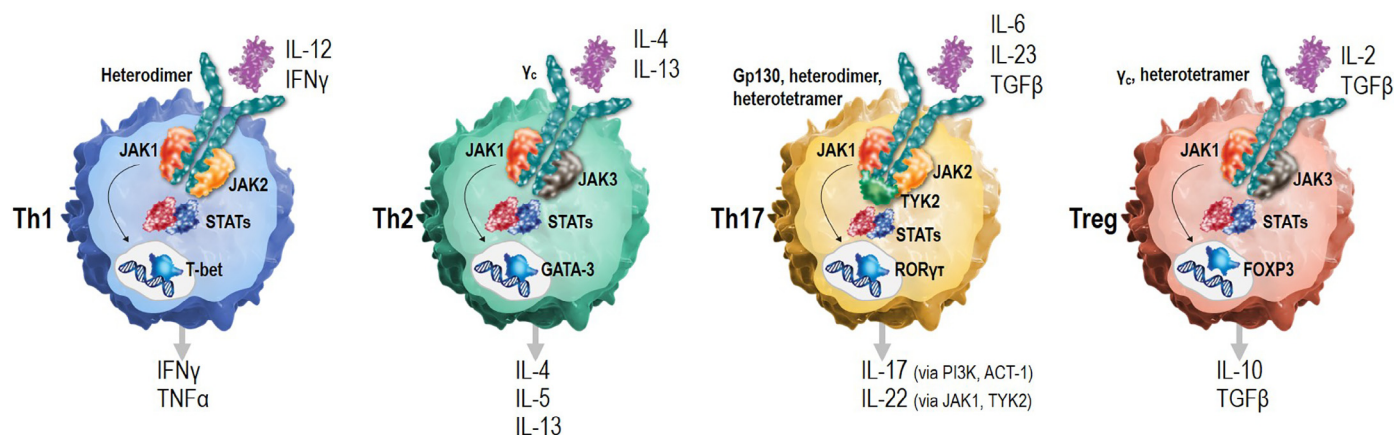


Figure 1. Janus kinase (JAK)-mediated cytokine signaling. In allergic diseases, cytokines and other inflammatory mediators released by inflamed cells engage with their respective receptors, triggering the activation of JAK1, JAK2, JAK3, tyrosine kinase 2 (TYK2), or some combination. Activated JAKs subsequently phosphorylate additional targets, including signal transducer and activator of transcription (STATs), to drive disease pathogenesis and potentiate immunologic diversity in patients with allergic disease. Despite increased disease heterogeneity and phenotypic differences in subpopulations, JAK-STAT signaling plays a central role in the disease pathogenesis of T_H2 and non- T_H2 -mediated inflammation in allergic disease. γ_c , common cytokine receptor γ chain; GATA-3, GATA-binding protein-3; gp130, glycoprotein 130; FOXP3, forkhead box P3; IFN- γ , interferon γ ; IL, interleukin; PI3K, phosphoinositide 3-kinase; ROR γ_t , retinoic acid–related orphan nuclear hormone receptor; T-bet, T-box-containing protein; TGF- β , transforming growth factor β ; TNF- α , tumor necrosis factor α .

Table 1
Interventional Studies Using Small Molecules in Atopic Dermatitis, Asthma, and Allergic Rhinitis

Immunologic target	Agent	Manufacturer	Indication	Registered clinical trial no.	Reference(s)
JAK1/JAK3	Tofacitinib	Pfizer	Atopic dermatitis	NCT02001181	20
JAK1/JAK2	Baricitinib (LY3009104/INCB028050)	Eli Lilly/Incyte	Atopic dermatitis	NCT02576938	
JAK1	Upadacitinib (ABT-494)	AbbVie	Atopic dermatitis	NCT02925117	21
	PF04965842	Pfizer	Atopic dermatitis	NCT02780167	
CRTH2	AMG853	Amgen	Asthma	NCT01018550	21
				NCT01137565	
	OC000459	Atopix Therapeutics/Oxagen	Atopic dermatitis	NCT02002208	22,23
			Asthma	NCT00890877	24
				NCT01057927	
				NCT01056692	
				NCT02341521	
				NCT02560610	
				NCT02660489	
			Allergic rhinitis	NCT00290381	
				NCT00697281	
				NCT01448902	
	BI671800	Boehringer Ingelheim	Asthma	NCT01090024	25,26
				NCT01092143	
				NCT01103349	27
			Allergic rhinitis	NCT01007721	
	QAW039/Fevipiprant	Novartis	Atopic dermatitis	NCT01785602	28–30
			Asthma	NCT01253603	
				NCT01437735	
				NCT01545726	
				NCT01836471	
				NCT02555683	
				NCT02563067	
				NCT03226392	
	AZD1981	AstraZeneca	Allergic rhinitis	NCT01804400	31
			Asthma	NCT00758589	
				NCT01196689	
				NCT01197794	
				NCT01265641	
	Setipiprant (ACT129968)	Actelion	Asthma	NCT01225315	
			Allergic rhinitis	NCT01241214	32
				NCT01484119	
PDE4	Apremilast	Celgene	Atopic dermatitis	NCT02087943	33,34
				NCT01393158	
				NCT00931242	
	GSK256066	GlaxoSmithKline	Asthma	NCT00163475	
	Roflumilast	AstraZeneca	Asthma	NCT00076076	35
				NCT01765192	
				NCT00163527	
				NCT01365533	
				NCT00246922	
				NCT00073177	
				NCT00242307	41
			Allergic rhinitis		

Abbreviations: CRTH2, chemoattractant receptor homologous molecule expressed on T_H2 cells; JAK, janus kinase; NCT, national clinical trial; PDE, phosphodiesterase.

diseases (Table 1).^{20–41} These clinical trials will advance our understanding of the relative contribution of T_H lymphocyte subsets and proinflammatory cytokines in driving disease pathogenesis (Fig 1 and Table 2).

CRTH2 Inhibitors

CRTH2, also known as prostaglandin D₂ (PGD₂) receptor 2, is 7-transmembrane G protein-coupled receptor expressed on T_H2 cells, eosinophils, and basophils. After allergen exposure, prostaglandin D₂ is released by IgE-activated mast cells, T_H2 cells, and other inflammatory cells to actively recruit eosinophils and basophils to the site of inflammation.⁴² In addition, engagement of CRTH2 leads to the production of T_H2 cytokines (IL-4, IL-5, IL-9, and IL-13), which further stimulates mast cells, type 2 innate lymphoid cells, basophils, and eosinophils.⁴² Several CRTH2 antagonists are currently in development for the treatment of asthma, AD, and AR (Table 1) with the aim of reducing T_H2-mediated

inflammation by blocking activation of mast cells, basophils, and eosinophils (Fig 2).

PDE4 Inhibitors

PDEs are a family of enzymes responsible for the hydrolysis and subsequent inactivation of cyclic nucleotides and have been organized into at least 11 families based on sequence homogeneity, inhibitor sensitivity, and biochemical properties.⁴³ PDE4, a critical regulator of intracellular cyclic adenosine monophosphate (cAMP) levels and compartmentalization,⁴⁴ is mainly expressed within inflammatory cells,⁴⁵ such as neutrophils, T lymphocytes, macrophages, and eosinophils (Fig 3).⁴⁶ Activation of PDE4 is triggered by epithelial damage, microbial invasion, and allergen sensitization, and this pathway modulates gene transcription of numerous cytokines and inflammatory mediators responsible for the pathogenesis of allergic disease. PDE4 inhibition results in the accumulation of the intracellular second messenger cAMP, downstream activation of

Table 2
Cytokine Signaling and the Corresponding JAK Pathway Activation

Cytokine	Signaling family	Receptor complex	JAK1	JAK2	JAK3	TYK2
IL-2	Common γ chain	IL-2Ra, IL-2R β , γ c	X	X	X	
IL-3	Common β chain	IL-3Ra, β c	X	X		X
IL-4	Common γ chain	IL-4Ra, γ c, IL-13Ra1	X	X	X	X
IL-5	Common β chain	IL-5Ra, β c	X	X		
IL-6	IL-6 family	IL-6Ra, gp130	X	X		X
IL-7	Common γ chain	IL-7Ra, γ c	X		X	
IL-9	Common γ chain	IL-9R, γ c	X		X	X
IL-10	IL-10 family	IL-10Ra, IL-10R β	X	X		X
IL-12	IL-12 family	IL-12R β 1, IL-12R β 2		X		X
IL-13	Common γ chain	IL-4Ra, IL-13Ra1	X	X	X	X
IL-15	Common γ chain	IL-15R, γ c	X	X	X	X
IL-19	IL-10 family	IL-20Ra, IL-20R β	X	X		
IL-20	IL-10 family	IL-20Ra, IL-20R β , IL-22Ra1		X		
IL-21	Common γ chain	IL-21R, γ c	X		X	
IL-22	IL-10 family	IL-10R β , IL-22Ra1	X			X
IL-23	IL-12 family	IL-12R β 1, IL-23R		X		X
IL-24	IL-10 family	IL-20Ra, IL-20R β , IL-22Ra1	X			
IL-26	IL-10 family	IL-10R β , IL-20Ra	X			X
IL-27	IL-12 family	IL-27R, gp130	X	X		X
IL-28	IL-10 family	IL-10R β , IL-28Ra		X		
IL-29	IL-10 family	IL-10R β , IL-28Ra	X			X
IL-31	IL-6 family	IL-31Ra, OSMR β	X	X		
TSLP		TSLPR, IL-7Ra	X	X		
IFN- γ	Type I/II interferons	IFN γ R1, IFN γ R2	X	X		X
IFN- α	Type I/II interferons	IFN α / β R1, IFN α / β R2	X	X		X
IFN- β	Type I/II interferons	IFN α / β R1, IFN α / β R2	X	X		X

Abbreviations: γ c, common cytokine receptor γ chain; gp130, glycoprotein 130; IFN, interferon; IL, interleukin; TSLP, thymic stromal lymphopoietin; OSMR β , oncostatin M receptor β chain; R, receptor (eg, IL-2Ra).

protein kinase A (PKA), and subsequent phosphorylation of the transcription factor cAMP-response element binding protein. Inhibition of PDE4 suppresses the expression of tumor necrosis factor α , among other cytokines and chemokines, by T cells and monocytes.^{47,48} PDE4

inhibitors are well-characterized pharmaceutical agents with a broad range of anti-inflammatory activity and promise in allergic disease.

Allergic Diseases, Pathogenesis, and Interventions

AD

AD is a highly pruritic, chronic inflammatory skin disease that affects up to 25% of children and 10% of adults.^{49,50} For many children, the early onset of AD within the first 6 months of life marks the beginning of a progression from AD to food allergy, AR, and eventually asthma, a scenario frequently described as the atopic march.^{3,51} This is further evidenced by reports of asthma and AR in up to 60% of children with AD^{52,53} and as comorbid conditions in adults.⁵⁴

T_H2 cytokines (IL-4, IL-5, IL-13, IL-31, and TSLP) play a central role in the pathogenesis of AD. IL-4 and IL-13 have previously been reported to modulate skin barrier integrity by inhibiting the expression of key proteins, such as filaggrin, loricrin, and involucrin, and the destabilization of tight junctions,^{55,56} leading to the enhanced penetration of allergens and pathogens. In addition, downstream signaling of IL-4 and IL-13 prevents the induction of innate immune response genes, such as β -defensins and cathelicidin,^{56,57} thereby increasing the susceptibility of these patients to skin infections with *Staphylococcus aureus* and herpes simplex virus.^{58,59} IL-5 plays a critical role in eosinophil differentiation, activation, and proliferation,^{60,61} which mediate allergen-specific reactions in the skin. IL-31 is a recently described cytokine produced primarily by T_H2 cells,⁶² keratinocytes, and mast cells in response to antimicrobial peptides.⁶³ Interestingly, overexpression of IL-31 in a murine model induced skin lesions and pruritus⁶² similar to the key characteristics of AD. TSLP is largely produced by epithelial cells in response to microbial invasion or tissue injury⁶⁴ and signals through dendritic cells to promote T_H2-cell maturation and allergic responses. In addition to an immunomodulatory role, TSLP directly induces an itching response by direct interaction with its receptors on sensory neurons.⁶⁵ In recent years, the role of the T_H17 pathway has been investigated in AD; however, the underlying mechanistic effect on disease pathogenesis is not well understood.

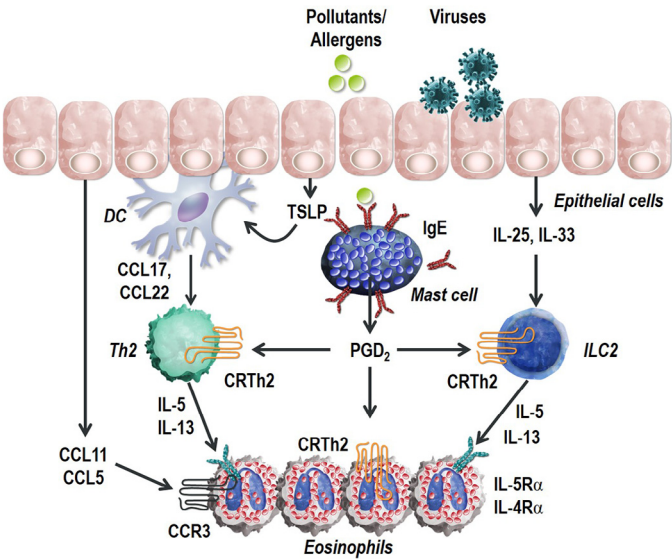


Figure 2. Chemoattractant receptor homologous molecule expressed on T_H2 cells (CRTH2)–mediated inflammation in allergic disease. Exposure to pollutants, allergens, and viruses initiates the release of the epithelial cytokines interleukin (IL) 25, IL-33, and thymic stromal lymphopoietin (TSLP). In addition, antigen uptake by dendritic cell (DC) primes T_H2 T cells to secrete release of IL-5 and IL-13. When combined, these inflammatory processes recruit mast cells and eosinophils to the site of inflammation. Crosslinking of IgE on mast cells results in the release of prostaglandin D₂ (PGD₂), which binds to CRTH2 expressed on T cells, eosinophils, mast cells, and basophils to accelerate allergic inflammation by promoting chemotaxis and upregulating cytokine production. CCR, C-C chemokine receptor; CCL, C-C chemokine ligand; IL-5R α , interleukin 5 receptor α ; IL-4R α , interleukin 4 receptor α ; ILC2, type 2 innate lymphoid cell.

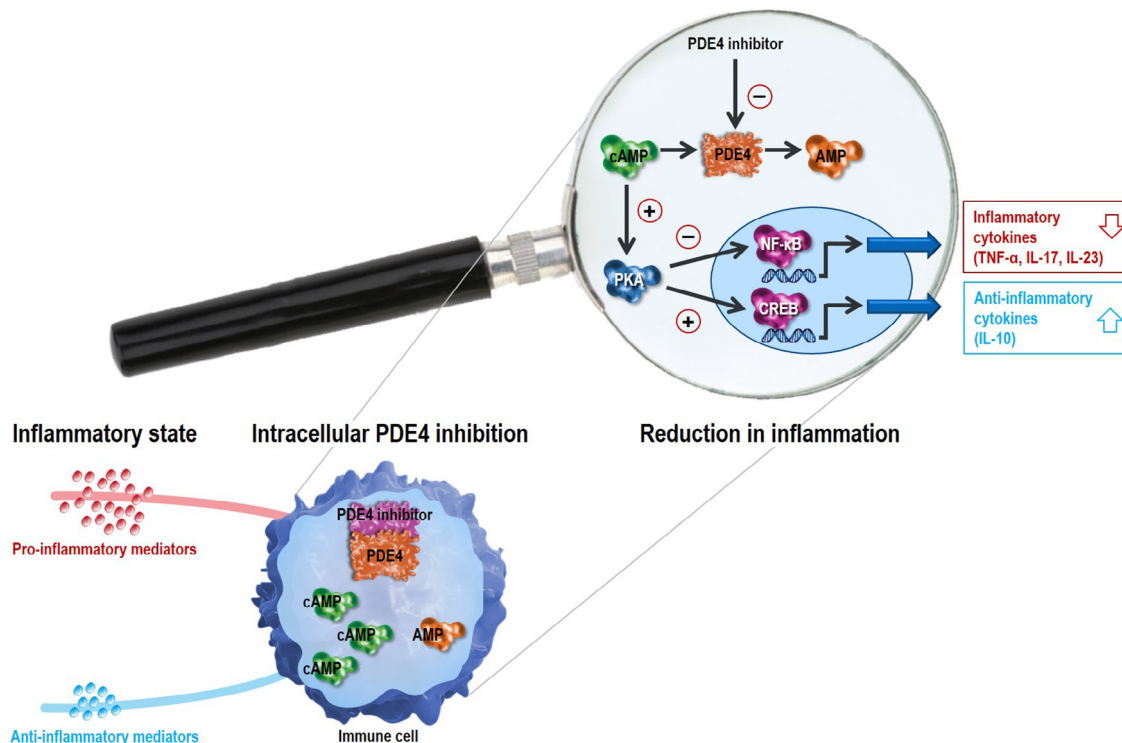


Figure 3. Phosphodiesterase 4 (PDE4)–mediated inflammation. PDE4 is a naturally occurring enzyme that degrades cyclic adenosine monophosphate (cAMP) to AMP within cells, resulting in immune cell activation, and promotes the release of proinflammatory mediators, such as tumor necrosis factor α (TNF- α), interleukin (IL) 17, and interferon γ (IFN- γ), while reducing the production of anti-inflammatory mediators, such as IL-10. Inhibition of PDE4 results in the accumulation of cAMP, which engages protein kinase A (PKA) to balance immune signaling through subsequent downstream signaling.

Interestingly, IL-22, which belongs to the IL-10 family of cytokines (eg, IL-19, IL-20, IL-24, and IL-26), is elevated in AD lesions and induces epidermal thickening by inducing JAK1 and tyrosine kinase 2 signaling and activating STAT1 and STAT3 activation.^{66,67}

JAK inhibitors provide the opportunity to prevent the downstream signaling of multiple cytokines and are currently being evaluated in patients with moderate to severe AD (Table 1). Tofacitinib, which targets JAK1 and JAK3, is currently approved for the treatment of rheumatoid arthritis and is under evaluation for the treatment of additional inflammatory diseases. Topical administration of tofacitinib to patients with mild to moderate AD was evaluated in a recently completed phase 2 clinical trial; results have not been published to date (clinicaltrials.gov identifier: NCT02001181) (Table 1). Oral tofacitinib administration was recently evaluated in 6 patients with moderate to severe AD and showed promising results. Investigators observed a 66% reduction in skin severity with no serious adverse events.²⁰ Additional clinical trials on the oral administration of upadacitinib (JAK1; clinicaltrials.gov identifier: NCT02925117), baricitinib (JAK1/JAK2; clinicaltrials.gov identifier: NCT02576938), and PF04965842 (JAK1; clinicaltrials.gov identifier: NCT02780167) have recently generated encouraging data, demonstrating a significant benefit in moderate to severe AD (Table 1). Specifically, upadacitinib, baricitinib, and PF04965842 observed a greater than 50% reductions in Eczema Area and Severity Index scores during 12 weeks,⁶⁸ further supporting the benefit of JAK inhibition for the treatment of AD.

Approximately 80% of patients with AD exhibit increased allergen-specific IgE, which on subsequent exposure to these allergens, triggers mast cell activation and the release of PGD₂. PGD₂ drives further through CRTH2 by mediating the recruitment and activation of T_H2 cells, type 2 innate lymphoid cells, eosinophils, and basophils.⁴² In murine models, D prostanoid receptor 2 agonists increased eosinophil recruitment and skin inflammation

through CRTH2,⁶⁹ and pharmacologic blockade of CRTH2 significantly reduced eosinophil recruitment, activation, and overall allergen-induced inflammation.^{70,71} Lesional skin of patients with AD is characterized by increased CRTH2 expression,⁷² and increased numbers of circulating CRTH2⁺ T cells correlate with the severity of AD.⁷³ There are several CRTH2 antagonists currently in development for moderate to severe AD, including QAW039 (fevipiprant, Novartis, Basel, Switzerland) and OC000459 (Oxagen, Atopix Therapeutics, Oxon, England); however, results have yet to be published (Table 1).

PDE activity has previously been reported to be elevated in the skin and blood of patients with AD.^{74,75} Recent advances in medicinal chemistry have resulted in the generation of high-quality molecules with improved safety profiles.⁷¹ Inhibition of PDE4 with topical application of 2% crisaborole ointment is efficacious in the treatment of mild to moderate AD,⁷⁶ leading to the approval of Eucrisa in 2016. Additional PDE₄ inhibitors are currently in development for the treatment of moderate to severe AD, including apremilast (Otezla, Celgene Corporation, Summit, NJ), an oral PDE₄ antagonist currently approved for psoriasis and psoriatic arthritis. Apremilast has been evaluated in several trials of patients with moderate to severe AD. In an open-label pilot study (clinicaltrials.gov identifier: NCT01393158) with 16 patients with AD, treatment with apremilast significantly improved clinical scores and inflammatory markers.³³ In addition, Celgene evaluated apremilast in a randomized, double-blind, placebo-controlled trial (clinicaltrials.gov identifier: NCT02087943) in which patients with moderate to severe AD were treated twice daily with placebo, apremilast (30 mg), or apremilast (40 mg) for 12 weeks. Overall, apremilast was well tolerated and reduced Eczema Area and Severity Index scores by 26% (30 mg) and 32% (40 mg). On the basis of these initial studies, additional trials are warranted to further evaluate PDE₄ antagonism in AD.

Asthma

Asthma is a chronic pulmonary disease characterized by airway obstruction, airway hyperresponsiveness, inflammation, and epithelial remodeling. More than 250 million people worldwide have asthma,⁷⁷ which is responsible for approximately 250,000 deaths each year. During the past 3 decades, there has been a rapid increase in the prevalence of asthma, which is believed to be in part due to increased awareness and proper diagnosis of the disease, altered lifestyle and activity patterns (eg, smoking and obesity),⁷⁸ and significant changes in environmental exposures.⁷⁹

In recent years, substantial research efforts have focused on understanding the underlying mechanisms that trigger asthma onset and disease pathogenesis. Comprehensive research into asthma has revealed multiple phenotypes and endotypes with distinct physiologic and mechanistic characteristics.⁸⁰ The heterogeneous nature of the disease prevents a one size fits all approach to therapeutic intervention.⁸¹ Currently, asthma phenotypes are primarily broken into mild to moderate allergic, moderate to severe allergic, eosinophilic asthma and sinusitis, very severe systemic (neutrophilic), and obese late onset.⁸¹ More than 70% of asthma cases are associated with allergen exposure,⁸¹ characterized by significant infiltration of lymphocytes, eosinophils, neutrophils, and mast cells in the airways.⁸² In addition, release of cytokines and inflammatory mediators further drive disease pathogenesis by triggering smooth muscle contraction, antibody generation and switching, and epithelial damage.²¹

Allergic asthma is primarily characterized by increased T_H2 cytokine (eg, IL-4, IL-5, IL-13, and TSLP) signaling through their respective receptors to activate the JAK/STAT pathway. Activation by T_H2 cytokines drives IgE isotype switching, mucus production, the recruitment and activation of eosinophils, and neuronal signal activation, leading to smooth muscle constriction.⁸³ The involvement of T_H2 cells in the pathophysiology of asthma has been corroborated by studies in both humans and mice. In recent years, many companies have focused on the development of antibody-based therapies (eg, mepolizumab, dupilumab) for the targeted treatment of T_H2 cytokine driven asthma.⁸¹ Approximately 25% of asthma is classified as nonallergic and is characterized by increased T_H1 and T_H17 responses, with IFN- γ overproduction and neutrophilic inflammation, respectively.^{83–85} More specifically, increased IL-12 signaling through STAT4 drives IFN- γ production, whereas IL-6, IL-21, and IL-23 all stimulate STAT3-dependent T_H17 differentiation.⁸⁶ Biologic therapies that target the non- T_H2 phenotypes have not been as positive, prompting evaluation of additional therapeutics. In a murine model, tofacitinib (Pfizer, New York, NY) demonstrated significant reduction of lung eosinophils, IL-13, and eotaxin after aerosol challenge in ovalbumin-sensitized mice.⁸⁷ Recently, short-term treatment with tofacitinib in combination with allergen immunotherapy was further shown to significantly reduce the infiltration of lung eosinophils, ovalbumin-specific IgE, and inflammatory cytokine production.⁸⁸ Using bronchial alveolar lavage cells from 21 healthy individuals and 25 patients with moderate to severe asthma, the study also found that tofacitinib inhibited T-cell receptor-mediated induction of IFN- γ , IL-13, and IL-17. In addition, tofacitinib significantly inhibited phospho-STAT5 activation on T cells.⁸⁹ Combined, these results support the further exploration of JAK inhibitors in various asthmatic conditions.

As mentioned previously, asthma is characterized by increased numbers of type 2 innate lymphoid cells, eosinophils, basophils, and T_H2 cells, which are primary expressors of CRTH2. For this reason, multiple CRTH2 antagonists are currently under investigation in clinical trials for asthma (Table 1). OC000459 is one of the more advanced CRTH2 antagonists and has been evaluated in multiple clinical trials with healthy individuals and multiple phenotypes of asthma. Treatment of patients with steroid-naïve

moderate asthma with OC000459, 200 mg twice daily for 4 weeks, led to a significant reduction in airway inflammation (as measured by sputum eosinophilia) and asthma symptoms, while steadily improving lung function.²² Subsequent studies with OC000459 have found that 200 mg twice daily for 16 days inhibits early and late asthmatic responses in an allergen challenge,²³ and treatment with 25 mg once daily, 200 mg once daily, or 100 mg twice daily significantly improved the forced expiratory volume in 1 second (FEV₁) in adults with uncontrolled eosinophilic asthma.⁹⁰ Additional studies have completed or are ongoing to further evaluate OC000459; however, results have not yet been published. Setipiprant (ACT-129968; Actelion, Allschwil, Switzerland) is another CRTH2 antagonist that significantly reduced the allergen-induced late asthmatic response and airway hyperreactivity in a study of 15 allergic males with asthma treated twice daily with setipiprant, 1,000 mg for 5 days,⁹¹ further supporting the role of CRTH2 antagonism in allergic asthma. AZD1981 (AstraZeneca, Cambridge, England) has been evaluated in several clinical trials with different phenotypes of asthma; however, limited information is currently available. In 2 separate phase 2 trials, AZD1981 was investigated in stable persistent asthma and uncontrolled asthma. Twice-daily treatment with AZD1981 was well tolerated by both asthmatic populations and demonstrated a significant improvement in the overall quality of life and increased peak expiratory flow in the 1,000-mg cohort.³¹ Similarly, QAW039 (fevipiprant; Novartis) has been evaluated in clinical trials and demonstrated a positive therapeutic benefit in asthmatic patients. Specifically, QAW039 500 mg administered once daily for 28 days improved the lung function and overall asthma control in a subset of individuals with asthma with FEV₁ less than 70% at baseline.²⁸ In addition, treatment with 225 mg twice daily for 12 weeks significantly reduced the percentage of sputum eosinophils.²⁹ Recently, the combination of QAW039 once daily or twice daily with budesonide positively affected FEV₁ in allergic patients with asthma.³⁰ These studies suggest that QAW039 has broad activity in a variety of asthmatic phenotypes and warrants further development. Additional CRTH2 compounds are currently in development for the treatment of asthma (Table 1), providing additional opportunities for further evaluation.

Initially, PDE inhibition in asthma was achieved through the use of theophylline; however, the long-term utility in clinical practice was limited because of the emergence of adverse events. The emergence of selective PDE4 inhibitors provided a more targeted approach to antagonism with a potentially safer profile.^{92,93} In 2011, roflumilast was approved by the US Food and Drug Administration for the treatment of patients with chronic obstructive pulmonary disease with severe airflow limitation, with a history of exacerbations, and in those whose disease is not adequately controlled by long-acting bronchodilators. On the basis of its broad anti-inflammatory activity and relative safe profile, roflumilast was further evaluated in clinical trials with various asthmatic populations (Table 1). Previously, roflumilast was found to reduce the release of inflammatory mediators from neutrophils, eosinophils, and T cells,⁹⁴ suggesting broad applicability in allergic asthma, eosinophilic asthma, and neutrophilic asthma. In allergen challenge studies, once-daily treatment with roflumilast significantly attenuated the last asthmatic response to known allergens,^{36,37} as well as allergen-induced airway hyperreactivity.³⁸ In addition, roflumilast significantly improved FEV₁ in patients with mild to moderate asthma treated once daily in a placebo-controlled, double-blind phase 2 trial.³⁹ Finally, roflumilast was as effective as low-dose inhaled beclomethasone in improving lung function and asthma symptoms⁴⁰; however, a greater number of adverse events were observed in patients treated with roflumilast, suggesting a stronger safety profile may be needed to advance PDE4 antagonists in asthma. Given the preclinical activity of roflumilast in several inflammatory cells known to drive

different asthma endotypes, additional investigations should evaluate whether the observed therapeutic benefit from roflumilast was greater in subsets of patients with asthma. Additional PDE4 antagonists and formulations (ie, those that are inhaled) are currently being explored in in vitro experiments, murine models, and early clinical trials in the hope of identifying compounds with improved safety profiles to complement their efficacy.

AR

AR (hay fever) is a common clinical condition that affects approximately 1 in 3 adults and 40% of children in industrialized countries.^{95,96} In addition to an impaired quality of life, there is a significant socioeconomic burden from AR, with approximately \$1.6 billion spent on prescription medications in the United States alone in 1996⁹⁷ and for more than 4 million lost work and school days because of AR.⁹⁸ The overall effect of AR on quality of life can differ, depending on the chronicity of the disease. Seasonal AR is often triggered by prevailing tree, grass, or weed allergens, whereas chronic perennial AR involves more indoor allergens (ie, those from house dust mites or animals).

In general, AR is an inflammatory disease of the upper airways that is characterized by rhinorrhea, sneezing, and nasal congestion. Similar to AD, T_H2 cytokines and cells play a central role in the pathogenesis of disease. Briefly, allergic sensitization drives the expansion of T_H2 cells that produce IL-4, IL-5, and IL-13. Engagement of T_H2 cells with B cells in the presence of these T_H2 cytokines drives total and allergen specific IgE production, which subsequently bind to FcεR on the surface of basophils, eosinophils, and mast cells. Ensuing exposure to allergen cross-links FcεR-bound IgE, triggering the degranulation of the cells and the release of cytokines as well as additional inflammatory mediators.⁹⁹ On the basis of the current understanding of disease pathogenesis, individuals with AR are often treated using one or more of the following approaches: (1) instructed to avoid triggering allergens; (2) oral or intranasal antiallergy medication (ie, decongestants, leukotriene inhibitors); (3) oral or intranasal steroids; or (4) immunotherapy to desensitize patients to a specific allergen.^{100,101} Given the heterogeneity of AR and increasing understanding of the inflammatory mechanisms, novel treatment strategies are under investigation for affected patients; and small molecule antagonists targeting specific inflammatory pathways and overlapping signaling axes may provide a therapeutic benefit.

Similar to AD, AR is characterized by increased T_H2 cytokines that signal through their respective receptors to induce JAK/STAT signaling.^{99,102} Shen et al¹⁷ found an association between polymorphisms in JAK1 and increased susceptibility to AR. In addition, CYT387, which functions as a pan-JAK inhibitor, inhibits TSLP-primed dendritic cells from subsequently driving naive T cells into IL-4⁺ T_H2 cells.⁹ Currently, there are no clinical trials that evaluated JAK inhibition in AR; however, increased T_H2 cytokine signaling and an increasing body of evidence of therapeutic benefit in other allergic diseases suggest that targeted JAK inhibition could provide a therapeutic benefit to patients with AR.

AR is characterized by increased numbers of CRTH2⁺ eosinophils, basophils, T_H2 cells, and neutrophils. In addition, PGD₂ engagement of CRTH2 triggers release of inflammatory mediators,⁹⁹ which further potentiates disease pathogenesis. Several clinical trials have been conducted evaluating the potential therapeutic of CRTH2 in patients with AR. OC000459 was tested in an allergen challenge chamber and reduced nasal and ocular symptoms in allergic individuals exposed to grass pollen.¹⁰³ In addition, setipirant was effective at reducing symptoms in patients with seasonal AR (clinicaltrials.gov identifier: NCT01241214) and is currently under further investigation in a phase 3 trial (NCT01484119). CRTH2 antagonism (QAV680) was initially explored in ragweed-sensitized patients with AR using an environmental chamber

(clinicaltrials.gov identifier: NCT00784732) and further explored using the combination of QAV680 with cetirizine (clinicaltrials.gov identifier: NCT01103050); however, results have yet to be published. In 2014, additional studies found that QAW039 exhibited superior potency compared with QAV680.¹⁰⁴ QAW039 has subsequently advanced into multiple clinical trials for AR (Table 1); results are not currently available. Additional CRTH2 compounds are in development for other allergic diseases and could be investigated in AR.

PDE4 inhibitors represent an interesting approach to the treatment of AR. It is hypothesized that selective PDE4 inhibitors block the hydrolysis of cAMP in lymphocytes, eosinophils, neutrophils, and monocytes, thereby attenuating their release of mediators and cytokines. On the basis of its activity in respiratory diseases, roflumilast was evaluated in a randomized, double-blind, placebo-controlled study of 25 patients with seasonal AR subjected to repeated allergen exposure. Oral once-daily therapy with roflumilast proved to be efficacious in increasing rhinal airflow and correspondingly decreasing itching and rhinorrhea during 9 days.⁴¹ Given the positive outcome and relative safety profiles of PDE4 antagonists, additional studies evaluating larger populations of patients with AR are warranted.

Conclusion

Current management of allergic diseases uses combinations of treatments to symptomatically alleviate disease by suppressing the inflammatory response, restoring epithelial surfaces, and reducing disease exacerbation and flare. Resolution is temporary and long-term use of these treatments, specifically oral and/or systemic corticosteroids, can be associated with significant adverse effects. The emergence of phenotypes and endotypes within allergic diseases has prompted more targeted approaches to therapeutic intervention. In recent years, there has been a significant increase in the number of clinical trials evaluating novel small-molecule and antibody-based therapies specifically targeting pathways and mechanisms in allergic disease. Many of these therapies hold promise for the future treatment of allergic diseases and are in various stages of clinical trials. Specifically, the JAK, PDE4, and CRTH2 inhibitors discussed in this review (Table 1) have demonstrated varying therapeutic benefit and may provide more effective and safer options for patients in the near future.

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