Novel and emerging therapies for asthma

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At present, there are a wide variety of novel and emerging therapeutic approaches for the treatment of asthma. Here, we will summarize these state-of-the-art approaches, including specific and nonspecific mediator inhibition – a quest that has been on going for more than 25 years – together with cytokine modulation in asthma (primarily attempting to modulate the Th2–Th1 balance in asthma), targeting cell recruitment, angiogenesis, signal transduction and gene transduction pathways. Finally, we will discuss the recently approved anti-IgE therapy for the treatment of allergic asthma and immune modulation using CpG oligodeoxynucleotides.

Selective inhibitors of inflammatory mediators

Platelet activating factor and leukotriene antagonists

During the 1970s and 1980s, many of the pro-inflammatory mediators known only by their biological activities (i.e. platelet-activating factor, slow reacting substance of anaphylaxis) were characterized chemically. This led to the development and testing of highly selective inhibitors of the platelet-activating factor and the cysteinyl leukotrienes (particularly leukotriene D_4), with markedly different results. Although platelet-activating factor antagonists have been shown to have no clinical benefit in asthma [1,2], drugs that act on the cysteinyl leukotriene pathway, particularly leukotriene D_4 antagonists, have proven to be useful and, in the case of montelukast, profitable medication for chronic asthma [3–5].

Thromboxane and prostaglandin D_2 inhibitors

Targeting the 5-lipoxygenase pathway for asthma treatment has yielded leukotriene synthesis inhibitors (e.g. zileuton) and leukotriene receptor antagonists (e.g. zafirlukast and montelukast) [3], however, whether modulation of the cyclooxygenase pathway will prove beneficial in asthma remains to be seen. The role of the prostanoids in asthma, specifically prostaglandins and thromboxanes, has become more evident over time. Thromboxane A_2 (TXA_2) was first reported in 1977 and soon after was found to be elevated in human asthmatic subjects [6]. Multiple studies have investigated the role of TXA_2 in asthma and have found it to be a potent bronchoconstrictor [7,8]. Seratrodast, a TXA_2 antagonist, was first described in 1989 and is the first such drug to be approved for use in asthma (in Japan). Originally known as AA-2414, seratrodast is a quinone derivative. Guinea-pig studies demonstrated an inhibition of bronchoconstriction induced by leukotriene D_4 and platelet-activating factor when the drug was given orally [9]. Early human studies demonstrated that seratrodast decreased $PtdCho_{20}$ methacholine [the dose of methacholine that leads to a 20% drop in the forced expiratory volume $(FEV)_1$] significantly after four days of oral administration. However, there was no change in baseline FEV_1 and only 15 subjects were studied [10]. Theories on mechanism include a reduction of the number of activated

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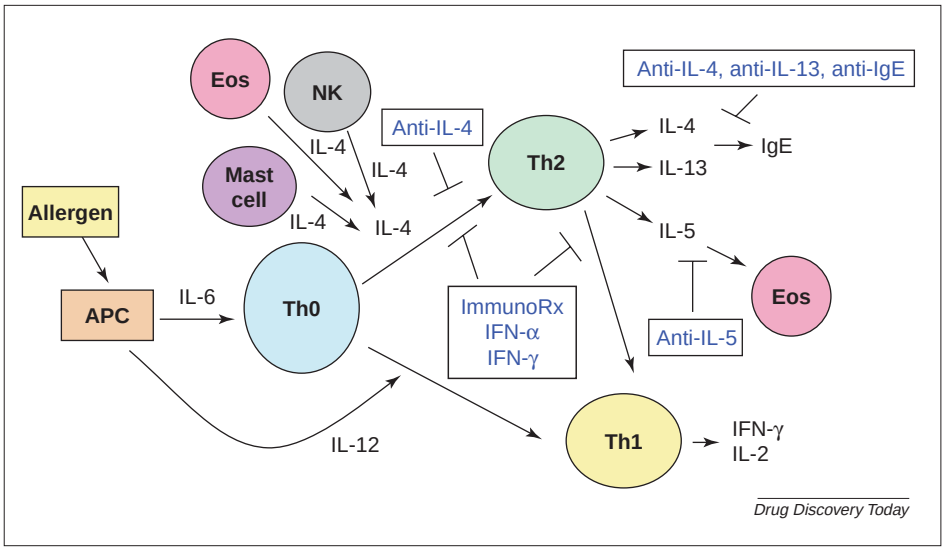

FIGURE 1

The development of T helper (Th) cells to Th1 or Th2 immune response. A Th0 (naïve helper cell) is stimulated, from an antigen presenting cell (APC) and interleukins IL-6 and IL-12, to become a Th1 cell. Stimulation from eosinophils (Eos), natural killer cells (NK) and mast cells, including IL-4, lead to Th2 development. Effector function from these two types of Th cells impact asthma in different ways [27].

eosinophils infiltrating the airways and releasing proinflammatory cytokines [11,12]. Human studies have shown a modest improvement in FEV_1, daytime symptoms and daytime β-agonist use after six weeks of treatment in mild to moderate asthmatics, and an excellent safety profile [13]. It is unclear if there is any further development of this drug occurring for the US market.

Other prostanoids, including prostaglandin D_2 (PGD_2), have also been found to have bronchoconstrictive effects. The bronchoconstrictive effects of PGD_2 were first described in a dog model and were subsequently also demonstrated in humans [14,15]. Furthermore, PGD receptor knockout mice do not develop changes associated with asthma: they demonstrate blunted Th2 cytokine response and decreased infiltration of eosinophils to airway after sensitization with ovalbumin (OVA) in comparison to wild-type mice sensitized to OVA [16]. This led to the thought that a PGD_2 antagonist could be effective in treating asthma. PGD_2 receptor antagonists have been developed, although there are currently no published human trials for these agents [17–19]. Although multiple other molecules have also been identified that function as PGD_2 receptor antagonists and are under further development, it is unclear whether they will eventually be approved for use in asthma.

Because multiple mediators, such as TXA_2 and PGD_2, have been shown to have similar biologic activities in asthma, the development of inhibitors with a broader inhibitory profile is an attractive concept. Although BAY u3405 (ramatroban) was initially developed as a TXA_2 antagonist, it was subsequently identified to also have activity as a PGD_2 receptor antagonist, specifically at the newly discovered PGD_2 receptor, CRTh2 [20]. Human studies have demonstrated safety and efficacy when used orally for allergic rhinitis and asthma [20,21]. Aizawa and colleagues [22] also demonstrated diminished bronchial hyperresponsiveness in patients with asthma after administration of ramatroban orally in a double-blinded placebo controlled study. This drug is approved in Japan, and is currently in clinical trials in Europe. Discovery of the CRTh2 receptor provides a promising area of research for effective asthma therapy.

Phosphodiesterase inhibitors

Theophylline, the prototypical phosphodiesterase inhibitor, was once a mainstay of asthma therapy. A more selective approach uses type 4 phosphodiesterase inhibitors, which not only exhibit bronchodilatory effects but also have been shown to have broad anti-inflammatory effects [23,24]. Inhibition of the conversion of cyclic AMP (cAMP) to AMP decreases many downstream processes involved in inflammation. These include decreased cytokine levels, chemokine levels and proliferation of inflammatory cells. Clinical trials for the use of type 4 phospodiesterase (PDE4) inhibitors have shown benefit in therapy for asthma and chronic obstructive pulmonary diseases (COPD). Although a PDE4 inhibitor was recently not approved by the FDA for the treatment of COPD, two such drugs, roflumilast and cilomilast are likely to be available for use in the near future. The asthma trials have shown that roflumilast attenuates both the early and late asthmatic response. In addition, there is evidence that both roflumilast and cilomilast protect against exercise challenge and can improve pulmonary function [24]. If the salutary effects of these drugs can be dissociated from their adverse gastrointestinal and other effects, they have the potential for a role in the treatment of both asthma and COPD.

Cytokine modulation in asthma

Asthma has been characterized as a Th2 predominant disease, therefore, efforts to alter the Th2–Th1 balance in asthma have been aggressively pursued, either by inhibiting Th2 cytokines or promoting the Th1 response (Figure 1). As discussed in subsequent sections, both of these approaches have had limited success to date [25,26].

Antagonism of Th2 cytokines: IL-4, IL-13 and IL-5

Interleukin (IL)-4 and its closely related cytokine IL-13 have an important role in Th2-mediated inflammatory events through a variety of biological activities, including B-cell isotype switching for the synthesis of IgE and altering adhesion molecule expression to enhance eosinophilic inflammation [27]. Although initial clinical trials for asthma in which IL-4 was inhibited using a soluble IL-4 receptor appeared promising [28,29], subsequent trials

could not confirm these results. Therefore, further development of this compound has been abandoned. Studies aimed at targeting the effects of IL-13 [30] have shown promise in murine studies [31]; however, further study is needed for human data. Targeting IL-5 with antibodies has decreased eosinophils in peripheral circulation and in sputum [32,33]. However, this inhibition has not been successful in either inhibiting antigen-induced late airway responses [32] or in initial clinical trials. Perhaps this failure is related to the inability to eradicate eosinophils completely from target tissues, including airways [34,35].

Enhancing Th1 responses: IL-12 and interferons

IL-12 is an important Th1 cytokine with many functions that oppose IL-4–IL-13 [27]. Many of these activities are transduced via interferon-γ. Administration of IL-12 to asthmatics resulted in a reduction in circulating and sputum eosinophils, without having an effect on the late asthmatic response induced by antigen inhalation [36].

Interferons are Th1-type cytokines that have a role in inhibiting IgE production and Th2-cell proliferation and function [37]. Trials have examined both interferon-α and -γ as a treatment for asthma. Interferon-α has significant antiviral activity, whereas interferon-γ has a greater role in allergic disease [38]. Interferon-α has been show in small studies to have benefit in the treatment of asthma [39]. Boguniewicz and colleagues have investigated both subcutaneous and inhaled recombinant interferon-γ in steroid resistant asthmatics. Neither study demonstrated clinical efficacy [40,41]; therefore, efforts to alter the Th2–Th1 cytokine balance biologically in asthma, either by inhibiting Th2 cytokines or by administering Th1 cytokines, have not been promising to date.

Tumor necrosis factor-α

Tumor necrosis factor α (TNF-α) is a cytokine related to both the Th1 and innate immunity axes that has been widely implicated in the pathophysiology of asthma. Increased expression of TNF-α has been observed in the airways of asthmatics [42]. TNF-α also promotes fibroblast growth and tissue remodeling [43], and inhaled TNF-α leads to increased airway hyperresponsiveness (AHR) [44]. Administration of TNF-α also leads to an increase in airway neutrophils, which is a feature of some asthmatics with severe persistent asthma [45]. These observations identified TNF-α as a target for asthma treatment. Although no peer-reviewed published data are available, small studies have been published in abstract form. Saadeh and colleagues retrospectively examined four patients who were receiving infliximab (anti-TNF-α monoclonal antibody) for rheumatoid arthritis, who also had asthma. Three of their patients saw an improvement in their FEV_1 (two patients saw a 15% or greater improvement and one saw 5%) and all had a subjective improvement in their symptoms and a decrease in their daily controller and rescue medication usage [46]. Babu and colleagues examined the use of etanercept (soluble TNF-α receptor) in chronic severe asthmatics. This open-label study enrolled ten patients that were already on oral and high-dose inhaled steroids to receive etanercept 25 mg injected subcutaneously twice a week for 12 weeks. Subjects had a statistically significant improvement in their FEV_1:FVC ratio and asthma symptom score, and an increase in methacholine dose response [47]. Currently, multiple trials involving agents with anti-TNF-α activity in more severe asthma are in progress.

Th2 cytokine inhibitors with multiple activities

Suplatast tosilate (IPD-1151T) is a drug with the unique property of inhibiting the production of multiple cytokines – specifically IL-4 and IL-5 [48]. This was assessed *in vitro* with dust-mite-sensitized peripheral blood mononuclear cells activated to produce IL-4 and IL-5; suplatast pre-treatment led to diminished IL-4 and IL-5 production. The mechanism-of-action has not been well described. In mice sensitized to *Dermatophagoides pteronyssinus,* Koda demonstrated a decrease in allergen specific IgE to after treatment with suplatast [49]. In a double-blind placebo controlled study, Tamaoki and colleagues [50] demonstrated in asthmatics that suplatast led to a decrease in total serum IgE levels and eosinophilic cationic protein, compared with placebo. Total blood eosinophil counts also dropped in asthmatics after treatment with suplatast [51].

Several studies have examined the efficacy of suplatast tosilate in treating asthma. One group examined 85 moderate to severe persistent asthmatics that were on high doses of inhaled steroids. They were randomized to suplatast or placebo and treated for four weeks, and then entered a steroid reduction phase of four weeks. The treatment group experienced an increase in FEV_1, morning peak expiratory flow, and a decrease in serum IgE when compared to placebo. In addition, during the steroid-reduction phase the active treatment group had fewer asthma symptoms and less rescue β agonist use [50]. Another open study of 38 subjects on inhaled steroids described an improvement in peak flow, asthma symptom scores and decreased eosinophil counts in patients when suplatast was added [51]. No evidence of toxicity or side effects was noted in studies reviewed. Suplatast tosilate represents a novel and promising treatment for asthma that probably works by inhibiting IL-4 and IL-5 production, which argues for inhibiting multiple aspects of Th2-mediated inflammation as a therapeutic strategy for treating asthma.

Targeting cell recruitment for asthma treatment

Chemokines

Chemokines and their receptors are intimately involved in inflammatory cell recruitment in the pathogenesis of asthma [52], therefore, therapies targeting these pathways have been under investigation for asthma treatment. One problem thus far has been isolating specific target ligands because considerable cross-reactivity exists amongst

chemokine receptors and their ligands [52]. Animal models targeting two chemokine receptors, CXCR4 and CCR3, with specificity for Th2 lymphocytes and eosinophils, have shown promise [52–55].

CXCR4 has been shown to be involved in eosinophil recruitment. AMD3100, a CXCR4 antagonist for SDF-1 (stromal derived factor, a ligand for CXCR4), has been shown to be specific for CXCR4, and reduced AHR and peribronchial eosinophilia during allergen challenge in a murine model [54,55]. In addition, significant reductions in IL-4 and IL-5 levels with significant increases in IL-12 and interferon-γ levels were noted in the bronchoalveolar lavage (BAL) fluid of the allergic mice [55]. To date, studies in human asthmatics have not been reported. However, AMD3100 also selectively blocks HIV-1 entry into CD4+ cells. These human trials have shown a good safety profile for AMD3100 [56].

Specific molecules antagonizing CCR3 have been shown to decrease eosinophil and mast cell recruitment, and AHR after allergen challenges of the airway in sensitized mice [53]. Although encouraging, further studies are needed to delineate the usefulness of this therapeutic approach in human disease.

Adhesion molecules

Adhesion molecules, including selectins, integrins and their corresponding ligands, are also logical targets for the treatment of underlying inflammation in asthma. Targeted research in this area has been conducted and data reported for multiple animal models and a handful of human studies [56]. Unfortunately, similar to the experience with chemokine inhibition, the involved pathways are redundant, thus reducing the likelihood that blocking one adhesion molecule–ligand interaction will be an effective treatment [56].

Animal data includes studies of several targets in models such as mice, sheep and rabbits. One study showed decreased eosinophils in BAL fluid collected after aerosol antigen challenge when interrupting vascular cell adhesion molecule-1 (VCAM-1) based interactions. These mice were treated with a variety of small molecule α4β1 antagonists administered intratracheally. One antagonist was also able to inhibit the BAL eosinophilia after subcutaneous administration [57]. Another study evaluated dual blockade of the P-selectin interaction with P-selectin glycoprotein ligand-1 (PSGL-1) and VCAM-1 interaction with CD49d. Treatment with soluble PSGL-1 reduced BAL eosinophils by 80% and BAL lymphocytes by 50%. Treatment with PS/2, an anti-CD49d monoclonal antibody, showed similar reductions in BAL inflammatory cells. In addition, AHR measured by methacholine challenge was eliminated and mucous cell metaplasia on histologic section was decreased. Interestingly, when both agents were given simultaneously, BAL eosinophils were decreased by 96%. No additive effect was seen in lymphocytes, AHR or mucous cell metaplasia [58]. A third study in mice showed that an anti-VLA-4 monoclonal antibody was able to decrease eosinophil, lymphocyte, IL-5 and leukotriene concentrations in BAL fluid. In addition, airway resistance, dynamic compliance and goblet-cell hyperplasia were reduced. Timing of the treatment was unimportant for BAL measurements and airway resistance but crucial for the noted changes in compliance and goblet-cell hyperplasia [59]. These are but a few of the many examples of promising data in animal models.

Early clinical trials in humans for several targets are underway. Published data, however, are sparse. They include a monoclonal antibody, efalizumab, directed against LFA-1 or CD11a. Subjects were treated with weekly subcutaneous doses and induced sputum was collected after allergen inhalation challenge. Treatment subjects reported headaches and flu-like symptoms, unlike the patients receiving placebo. Results showed decreased numbers of mast cells, basophils and activated eosinophils in sputum but no significant changes in FEV_1 [60]. Another study evaluating TBC1269, a pan-selectin antagonist, showed no changes in early or late airway responses (as reflected by FEV_1) when given a single intravenous dose before an allergen challenge [61]. Obviously, more data are required to determine if this strategy will be useful for asthma treatment.

Angiogenesis

Angiogenesis, or neovascularization, is an integral part of inflammation and offers another potential treatment target for asthma. An increase in vascularity has been a well described aspect of asthmatic airways [62]. More specifically, increases in vascular endothelial growth factor (VEGF) have been observed in asthma and correlated with disease severity [63]. Targeting VEGF for asthma therapy has shown potential in animal studies. Transgenic mice overexpressing VEGF were shown to develop physiologic markers of asthma, including neovascularization, and markers of inflammation consistent with a shift toward a Th2 phenotype [63]. Studies using anti-VEGF have been performed in humans primarily for treating cancer, including renal cell carcinoma [64]. One VEGF receptor blocker, SU5416, has been shown to induce emphysema in animal studies [65,66]. Although this approach offers promise, further research is needed before this line of therapy becomes a realistic option for asthma.

Targeting signal transduction pathways

Imatinib mesylate

Imatinib mesylate (Gleevec™; Novartis) represents the first signal transduction molecule and/or protein kinase inhibitor brought to market, and is indicated for the treatment of chronic myeloid leukemia (CML) [67]. Imatinib targets the BCR-ABL translocation found in the Philadelphia chromosome observed in CML. The tyrosine kinase linked to the BCR-ABL binding site is prevented from phosphorylating, hence turning off downstream pathways that drive the leukemia [68]. Developed to block BCR-ABL tyrosine

kinase activity, imatinib has been shown to also have effects on other protein tyrosine kinases. Inhibition of c-kit receptor kinase activity has led to a new treatment for gastrointestinal stromal tumors and platelet-derived growth factor receptor (PDGFR) associated malignancies [69–73]. There is emerging evidence in animal models that imatinib mesylate might also influence asthma and allergic disease.

Berlin and Lukacs have been the first to examine the use of imatinib in allergic disease by administering it to cockroach-sensitized asthmatic mice. They found that mice given imatinib had attenuated AHR, decreased peribronchial eosinophil accumulation, and reduced Th2 cytokines compared to sensitized untreated controls. This is also consistent with data demonstrating the efficacy of imatinib in the idiopathic hypereosinophilic syndrome [74,75]. These studies, although limited, demonstrate that imatinib should continue to be developed for the treatment of allergic and eosinophilic diseases.

STAT1 and STAT6

Signal transducer and activator of transcription molecules, or STATs, have been identified as important regulators in the transduction pathways of the interferon molecules [76]. The sequence of events involves interferon-α or -γ activating their receptors leading to Jak activation and phosphorylation. STATs recognize the phosphorylation, dimerize, translocate to the nucleus and then bind DNA to induce transcription [77]. STAT1 in particular is responsive to interferon-γ, leading to the transcription of multiple genes, including principally ICAM-1 and IRF-1, both of which have been implicated in asthma. In addition, there is clear evidence that the Th2 cytokines, IL-4 and IL-13, activate STAT1 signaling pathways across multiple cell lines [78]. Possible clinical application in asthma has been demonstrated in murine models. Quarcoo *et al.* [79] used decoy oligonucleotides to block STAT1 signaling in sensitized mice. Upon allergen challenge these mice had a significantly decreased total leukocyte and eosinophil count in BAL fluid, decreased IL-5 in BAL fluid, and diminished AHR compared to non-sensitized and sensitized but untreated mice.

STAT6 is another pathway in the family of STAT that has also been implicated in the development of allergic disease and asthma. Its primary activators are IL-4 and IL-13. Many have hypothesized that STAT6 might have a role in asthma, based upon its actions and location on chromosome 12 [80–82]. However, there are no data at this time demonstrating efficacy of blocking the STAT6 pathway for the treatment of asthma.

Imatinib mesylate and the STAT molecules are but two examples of signal transduction targets in asthma therapy. Others, such as the mitogen-activated protein kinases (MAPKs), are being studied with encouraging results. Further research pursuing signal transduction will probably yield other promising tools for the management of asthma.

Targeting gene transcription

The final stage of cell communication from cell membrane receptors through signal transduction is gene transcription. With multiple genetic factors influencing asthma phenotype, these are attractive targets. Gene transcription factors involved in asthma that could prove to be significant therapeutic targets after promising murine studies include activator protein-1 (AP-1) and nuclear factor κB (NF-κB) [83–85]. AP-1 is a promoter for several Th2 cytokine genes, including IL-4, IL-5 and IL-13. Decoy oligodeoxyribonucleotides (ODNs) given intratracheally to OVA-sensitized mice prevented multiple physiologic markers of asthma after challenge that included eosinophilic inflammation, AHR, antigen specific antibodies and cytokine synthesis [83]. Similarly, NF-κB is involved in the regulation of many pro-inflammatory genes, including TNF-α and RANTES [86]. In an OVA mouse model, decoy ODNs attenuated asthmatic response after challenge. Reductions were noted in eosinophilic inflammation, AHR and local production of mucous, IL-5, IL-13 and eotaxin. However, there was no noted reduction in either IL-4 or antigen specific antibody. [84]. In a slightly different approach, ABIN-1, an inhibitory protein NF-κB, was delivered via adenovirus to allergen sensitized mice. Among other findings, reductions in eosinophilic infiltration, IL-4 and antigen specific IgE were found [85]. Future research along these lines is likely to yield other promising targets.

Anti-IgE: omalizumab

Omalizumab (Xolair™; Genentech Novartis) is a recombinant humanized monoclonal IgG anti-IgE antibody designed to bind to IgE, thereby preventing it from binding to target cells, such as mast cells and basophils. It therefore reduces unbound (free) IgE levels in serum and has been shown to be effective when free IgE concentration is <10 IU ml^{-1} during treatment. It is approved for use in adults and adolescents (age 12 years and above) with moderate to severe persistent atopic asthma [as shown by a positive skin test or radioallergosorbent (RAST) test to a perennial allergen] whose symptoms are inadequately controlled with inhaled steroids, have total serum IgE levels of 30–700 IU ml^{-1}, and who weigh 30–150 kg (the drug is dosed based on a nomogram, which takes into consideration both the serum IgE level and weight of the patient).

In its two pivotal trials, omalizumab was shown to reduce asthma exacerbations both when the inhaled dose of corticosteroids was held constant and when the dose was aggressively reduced [87,88]. It also decreased rescue β-agonist use and nocturnal symptoms and improved quality of life, while permitting a reduction in inhaled corticosteroid dose. This finding was also observed in patients taking high dose inhaled corticosteroids (1000–2000 μg d^{-1} fluticasone propionate ± oral corticosteroids), where the primary outcome was the ability to reduce fluticasone dose to ≥500 μg d^{-1} [89]. Finally, a recent trial (INNOVATE) in very severe asthmatics (Step three and four according

TABLE 1

Therapeutic classes and agents for asthma

Class	Agent	Relative efficacy[a]	
		Animal model	Human
Selective inhibitors of inflammatory mediators	PAF		–
	Leukotriene antagonists		++
Prostanoid receptors	TXA_2	++	+
	PGD_2	+	NA
Type 4 phosphodiesterase inhibitors	Roflumilast		++
	Cilomilast		+
Cytokine – augmenting	Interferon-α		++
	Interferon-γ		–
Cytokine – inhibiting	Anti-IL-4		±
	Anti-IL-5		–
	Anti-IL-13	++	NA
	Anti-TNF		++
Chemokine receptors	Anti-CXCR4	+	NA
	Anti-CCR3	+	NA
Adhesion molecules	Anti-VCAM-1	+	NA
	Anti-VLA-4	+	NA
	Anti-LFA-1		+
	Selectins	+	±
Angiogenesis	Anti-VEGF	+	NA
Signal transduction	Imatinib mesylate	++	NA
	STAT1	++	NA
	STAT6	NA	NA
Gene transcription	AP-1	++	NA
	NF-κB	++	NA
Anti IgE	Omalizumab		++
Oligodeoxynucleotide	Monotherapy	+	NA
	Combination therapy		+

[a]Relative efficacy omitted for animal data when substantial human data available. Key: ++, excellent efficacy; +, good efficacy; ±, average efficacy; –, poor efficacy.
Abbreviations: PAF, platelet activating factor; NA, not available.

to GINA guidelines, where mean FEV_1 was 62% predicted), also showed a reduction in asthma exacerbations (when adjusted for baseline number of exacerbations) [90]. Omalizumab appears to be more effective in patients who are taking higher doses of inhaled corticosteroids (≥800 μg d^{-1} beclomethasone dipropionate), who have received emergency asthma treatment in the past year and who have an FEV_1 ≥65% predicted [91]. In a biopsy study of milder asthmatics, omalizumab has been shown to reduced the number of IgE-positive cells, FcεRI (high affinity receptor for IgE)-positive cells and eosinophils in bronchial biopsies, as well as eosinophils present in sputum [92].

Omalizumab received approval from the FDA in June 2003, making it one of the newest drugs and the first biologic agent approved for asthma in the USA (www.fda.gov/bbs/topics/ANSWERS/2003/ANS01236.html) [87,88,93]. It has been studied in children as young as six years for use in asthma, and has demonstrated safety and efficacy [94]. It has also been shown to be effective for rhinitis in patients with severe asthma [95], an indication for which its use has not been approved.

CpG oligodeoxynucleotides

Bacterial DNA with CpG dinucleotides have been shown to stimulate the immune system. In addition, synthetic ODNs with unmethylated CpG motifs added have been shown to produce similar effect. By interacting with toll-like receptor 9 (TLR9), these molecules not only stimulate a Th1 lymphocyte response but also inhibit the Th2 lymphocyte response [96,97]. These generalized effects have shown promise in both animal studies and Phase I and II human trials for treating atopic airway disease. These effects have been seen both when used alone and as an adjuvant to allergen immunotherapy.

In the murine model, CpG DNA has been shown to prevent airway inflammation when sensitized animals are challenged if the animals receive CpG at the time of sensitization. When compared with controls, mice receiving

CpG ODNs have been shown to have reduced airway eosinophilia, serum IgE and AHR [98,99]. In addition, Th2 response markers were reduced with an increase in Th1 markers. These results persist to a lesser extent even in the absence of Th1 responses when blocking Th1 response by knockout or anti-cytokine antibodies [99]. This data has been shown with the OVA and ragweed models [96]. It has also been shown that systemic administration of CpG ODNs with allergen can reduce markers of established asthma in contrast to mice receiving either allergen or CpG ODNs alone [96]. OVA sensitized mice showed reduced OVA-specific IgE and were protected against further eosinophilic inflammation and AHR with re-challenge. These effects were also associated with a shift from Th2 towards Th1 response [100]. Other studies have shown that ragweed sensitive mice have similar responses [96].

Airway remodeling is an irreversible consequence of allergic inflammation in the airways. Murine studies evaluating the effects of CpG ODNs administered with allergen have shown less features of remodeling when compared to untreated controls. In an OVA model, ODN treated mice had less thickness in the subepithelial layer, less goblet-cell hyperplasia, and less total lung collagen [101].

The human data, although less abundant, is similarly encouraging. Phase I and II clinical trials studying CpG ODNs conjugated with Amb a 1 for allergic rhinitis have been shown to be safe and effective [102–104]. One study also showed improvements in chest symptoms but further study for effectiveness in human asthma is necessary [103].

Conclusions

Here, we have summarized a wide variety of different and emerging approaches for the treatment of asthma (Table 1). A strategy involving specific and selective inhibition of various inflammatory mediators and a general discussion of cytokine modulation in asthma (primarily trying to alter the Th2–Th1 inflammatory balance in asthma), was followed by a discussion of targeting cell recruitment, angiogenesis, signal transduction and gene transcription pathways. The one effective immunomodulatory approach to the treatment of asthma, treatment with anti-IgE, was described, concluding with a possible role for immune modulation with CpG oligodeoxynucleotides for asthma and allergic diseases.

Notable points about the history of this search for successful approaches to the treatment of asthma were the following. First, only two agents targeting specific pathways have proven successful for asthma therapy: a specific inhibitor of cysteinyl leukotrienes and an inhibitor of IgE, which has long been associated epidemiologically with asthma and related phenotypes. Second, inhibitors of TNF-α and a signal transduction pathway have proven useful for other diseases, namely rheumatoid arthritis and chronic myeloid leukemia. Finally, inhibition of a wide variety of immune targets which should alter the immunopathogenesis of asthma (particularly Th2 cytokines such as IL-4, IL-5, and the Th2–Th1 balance) has not, to date, proven useful for asthma treatment. Whether this is because of insufficient potency of the agents employed thus far, or whether this strategy is doomed to failure, is not clear at present.

Our interpretation of 25 years observing this area is that our quest for superior specificity in asthma therapy (e.g. targeting only a specific mediator, cytokine) might have undervalued the redundancy of the inflammatory pathways important in asthma pathogenesis and could have doomed many of these approaches to failure. Less selective approaches to therapy, such as that represented by the dual IL-4, IL-5 inhibitor suplatast, might have a better chance for success. In any event, the quest continues and hopefully our patients will benefit from these important efforts.

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