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Review

Monoclonal antibodies and other biologic agents in the treatment of asthma

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Abbreviations: T_H, T helper cell; TLR, toll-like receptor; TNF, tumor necrosis factor; NOD, nucleotide-binding oligomerization domain; RIG, retinoic inducible gene; $F_C\varepsilon R1$, crystalizable fragment of IgE receptor type 1; MHC, major histocompatibility complex; CD, cluster of differentiation; IL, interleukin; IFN, interferon; TGF, transforming growth factor; CpG, cytosine phosphate guanosine; ISS, immunostimulatory sequences; Amb-a 1, ambrosia artemesia first allergen; TSLP, thymic stromal lymphopoietin; OX-40, a secondary co-stimulatory molecule and member of the tumor necrosis receptor super family; Daclizumab, monoclonal antidody against the alpha sub-unit of the IL-2 receptor, or CD25 or Tac; FDA, food and drug administration; Keliximab (IDEC CE9.1), monoclonal antibody against CD4; Altrakincept, soluble extracellular component of the α chain of IL-4 receptor; Pascolizumab, monoclonal antibody against IL-4; Mepolizumab, monoclonal antibody against IL-5; Rezlizumab, monoclonal antibody against IL-5; HES, hypereosinophilc syndrome; EE, eosinophilic esophagitis; Medi 528, monoclonal antibody against IL-9; CAT-354, monoclonal antibody against IL-13; Pitakinra, mutant protein that binds the shared alpha chain of IL-4 and IL-13; Omalizumab, monoclonal antibody against IgE; Lumilixumab (IDEC 152), monoclonal antibody against the low affinity receptor got IgE (CD23); Infliximab, monoclonal antibody against TNFα; Etanercept, fusion protein containing TNFα receptor and Fc portion of human IgG1; Efalizumab, monoclonal antibody against LFA-1 alpha chain (CD11a); LFA, lymphocyte function antigen; DBPCRCT, double-blind, placebo-controlled, randomized clinical trial

Key words: cytokine blockers, dendritic cell, monoclonal antibodies, immunomodulators, T_H2 cells, T_H1 cells, airway inflammation, IgE, omalizumab

Asthma represents a syndrome of airway inflammatory diseases with complex pathology. The immunologic pathogenesis is being increasingly revealed and provides opportunity for targeted biological intervention. Current experience with immunomodulators as targeted therapy in asthma is described in this literature review. Targeted therapies have included strategies to activate dendritic cells through the TLR-9 receptors, to interrupt the action of T_H2 cytokines with cytokine blockers and monoclonal antibodies, to promote development of T_H1 responses, to block IgE mediated pathways and to block TNFα. Omalizumab is the only biological therapy that has an approved indication in asthma at this time. An improved understanding of the heterogeneity of asthma should allow for specific targeting of different disease phenotypes specific therapies including immunomodulators.

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The Pathobiology of Allergic Asthma

Asthma affects 5% of the population, making it one of the most common chronic diseases worldwide.[1] Asthma represents a complex syndrome broadly defined by inflammation of the airways associated with airway hyperresponsiveness and mucous hypersecretion with clinical features including shortness of breath, mucus production and wheezing, together with objectively measurable reversible airway narrowing. Our increased understanding of the pathophysiology of asthma in recent years is leading to new therapeutic approaches including monoclonal antibodies and other biologic agents that could have profound repercussions for the treatment of this condition.

The pathological changes seen in the asthmatic airway are multiple and complex. The epithelium lining the asthmatic airway exhibits sloughing/denudation, ciliary dysfunction, goblet cell hyperplasia and mucous gland hypertrophy. The mucus produced by the asthmatic epithelium exhibits increased elasticity, increased viscosity, increased content of mucin, cellular debris and surfactant dysfunction. There is fibrosis in the sub-epithelial compartment, and the submucosal tissues also demonstrate a significant inflammatory cellular infiltrate characterized by lymphocytes, eosinophils, neutrophils, increased numbers of mast cells and new blood vessel formation (angiogenesis). Abnormalities of the airway smooth muscle layer include increased mass, consisting of both

hypertrophy and hyperplasia and increased contractility together with mast cell infiltration and angiogenesis. In a majority of patients these pathological changes are seen during active disease, but largely reverse during periods of disease control. In some patients failure to resolve or repair these changes is observed with many of the above changes becoming fixed, a process referred to as airway remodeling.[1-3]

The immune responses underpinning the pathologic changes seen in the asthmatic airway are also complex and involve both the innate and the adaptive immune systems. Among the processes involved are epithelial cell disruption and activation with cytokine production, dendritic cell activation and antigen presentation, activation and expansion of T_H2 cells with cytokine secretion, activation of resident inflammatory cells, including mast cells, and recruitment from the blood stream of other inflammatory cells including lymphocytes, eosinophils and neutrophils which also release mediators and cytokines.[1-3]

The airway inflammatory response in asthma is conceptualized as beginning in the airway lumen (Fig. 1). Here allergens, viruses or other pathogens interact with airway epithelial cells and dendritic cells. Some aeroallergens have enzymatic properties capable of directly cleaving tight junctions between epithelial cells or activating the epithelial cells through protease activated receptors. The activated epithelium and other tissue cells release factors including cytokines and chemokines that can prime or otherwise influence the response of the dendritic cell[4] and other cells of the innate (basophils, eosinophils and mast cells) and of the adaptive immune systems (B and T lymphocytes).[5] Both airway epithelial cells and dendritic cells carry surface pattern recognition receptors for pathogens including Toll-Like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and retinoic inducible gene (RIG) receptors which recognize surface characteristics of pathogens and, upon ligation, initiate responses of the innate immune system. In addition to pattern recognition receptors, antigen uptake by the dendritic cell may occur through either nonspecific mechanisms including macropinocytosis, or through a highly antigen-specific mechanism using immunoglobulin Fc receptors. For example, in sensitized individuals, expression of the high affinity receptor for IgE (FcεR1) on airway dendritic cells probably strongly facilitates the processing of specific allergen, captured by bound IgE.[6-8] The dendritic cell internalizes and processes antigen into fragments which are then cognately presented in the context of MHC molecules to naïve (T_H0) CD4 lymphocytes. Factors associated with the antigen, the presence of TLR ligands and factors from the activated epithelium can influence the dendritic cell activation status.[5] The patterns of co-stimulatory molecule expression, the ligand-receptor interactions between the dendritic cell and the lymphocyte at the immunological synapse, and cytokines released by the activated dendritic cell combine to direct the subsequent differentiation of the antigen-specific T_H0 cell. The signals that the T_H0 cell receives lead it to differentiate along one of several possible lineages including T_H1, T_H2, T_H17 and T regulatory cells. The presence of IL-4 appears to favor differentiation of T_H0 cells into T_H2 type cells, and has an inhibitory effect on the development of a T_H1 response. IL-12 and IFNγ have a negative developmental effect on T_H2 phenotype cells, while preferentially driving the differentiation of T_H0 cells towards a T_H1 phenotype. Factors favoring the development of T_H17 cells indicate a primary role for IL-6 with subsidiary roles for TGFβ and IL-23. Factors favoring the development of regulatory T-cells continue to be elucidated, but also appear to include TGFβ.

Immunomodulation in Allergic Asthma

The antigen presenting cell, or dendritic cell, plays a key role in initiating and propagating the allergic inflammation and much of the abnormal pathology can be linked to cytokine products of activated proliferating T_H2 cells, basophils and mast cells. This knowledge has exposed many potential targets for immune modulation as described below. Strategies have included approaches aimed at skewing the dendritic cell towards promotion of T_H1 responses by TLR activation, direct targeting of CD4 positive T_H2 cells, anti-T_H2 or pro-T_H1 cytokine-based biologic therapies or targeting of specific effector cells such as mast cells or eosinophils. There is increasing evidence for the role of cytokines derived from resident tissue cells in amplifying T_H2 type allergic inflammation. Therapeutic agents aimed at interrupting such antigen-independent pathways will undoubtedly be soon explored. Anti-cytokine therapies might theoretically include (1) receptor-specific non-activating/blocking antibodies which prevent cytokine binding, (2) soluble receptors which would competitively inhibit binding of cytokine to cell surface cytokine receptors or (3) other compounds, such as mutant ligands, designed to block the cytokine receptor. The discussion of immunomodulatory strategies below follows the process of allergic inflammation from its beginning at the dendritic cell, through the innate immune system, the adaptive immune system and ultimately effector cells.

Dendritic Cell Based Therapies

TLR-9 agonists. The dendritic cell has been described as a sophisticated information transfer system linking the environment with the adaptive immune system.[9] Hence, the dendritic cell interacts with antigens through a number of important mechanisms including pattern recognition receptors such as TLRs (Fig. 2A). A large number of animal studies have demonstrated activation of TLR-9 through the use of CpG rich unmethylated DNA segements commonly found in bacteria. These are also known as immunostimulatory DNA sequences (ISS) and can result in skewing of immune responses towards T_H1.[10-13]

Human studies have now been undertaken with TLR-9 agonist ISS covalently linked to allergen, delivered as a series of subcutaneous injections, with a goal of ameliorating allergic inflammatory disease. Creticos et al. reported a randomized, double-blind, placebo-controlled Phase II trial of ragweed Amb-a 1, a major ragweed allergen, bound to a TLR-9 agonist (six weekly injections versus placebo) in the treatment of ragweed-associated seasonal allergic rhinitis.[14] They observed a diminution in peak seasonal symptoms of allergic rhinoconjunctivitis in the year in which treatment was administered and during the following year's ragweed season, as well as reduction in the need for allergy medications. An accompanying report looking at nasal biopsies of these patients

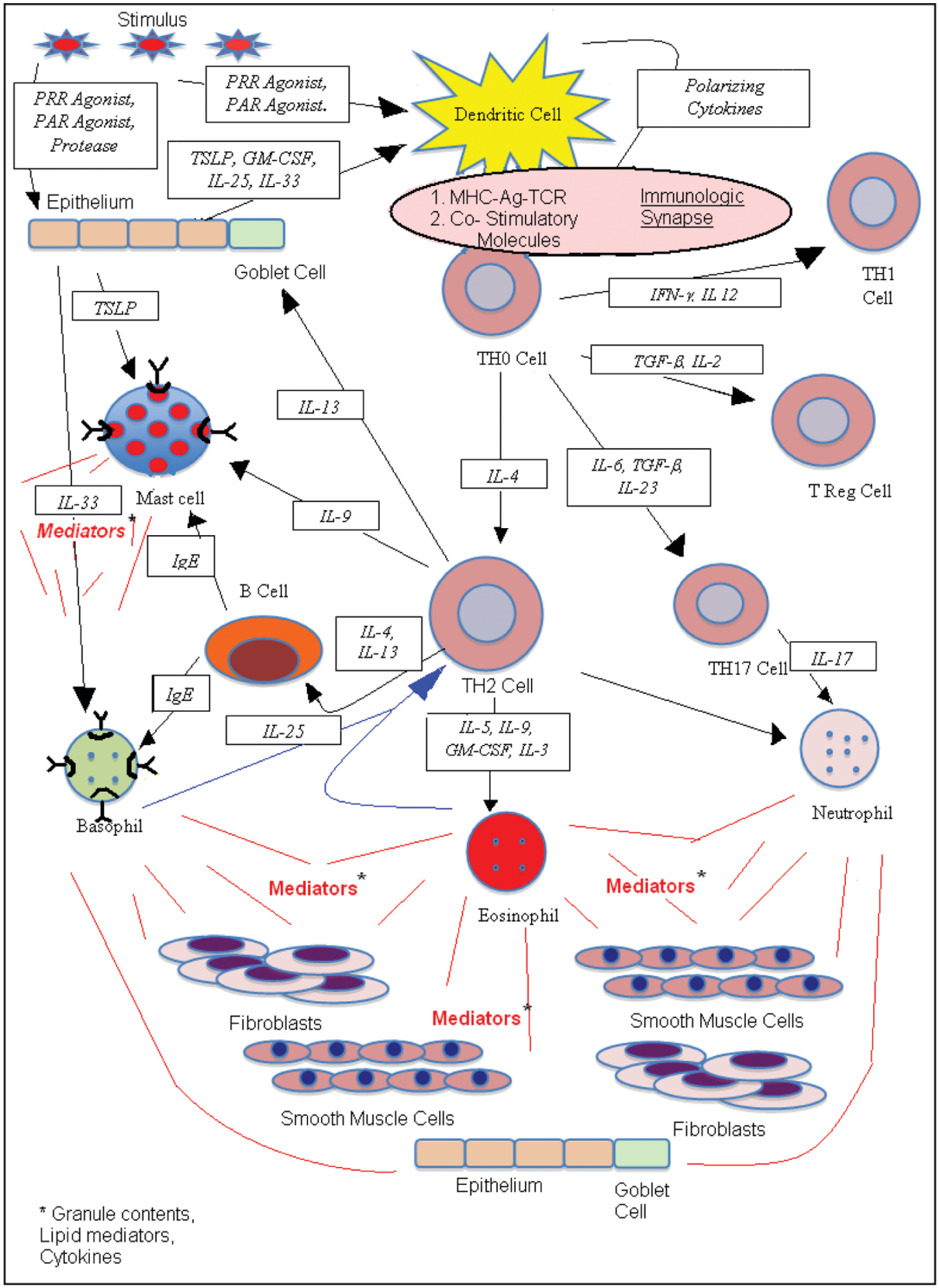
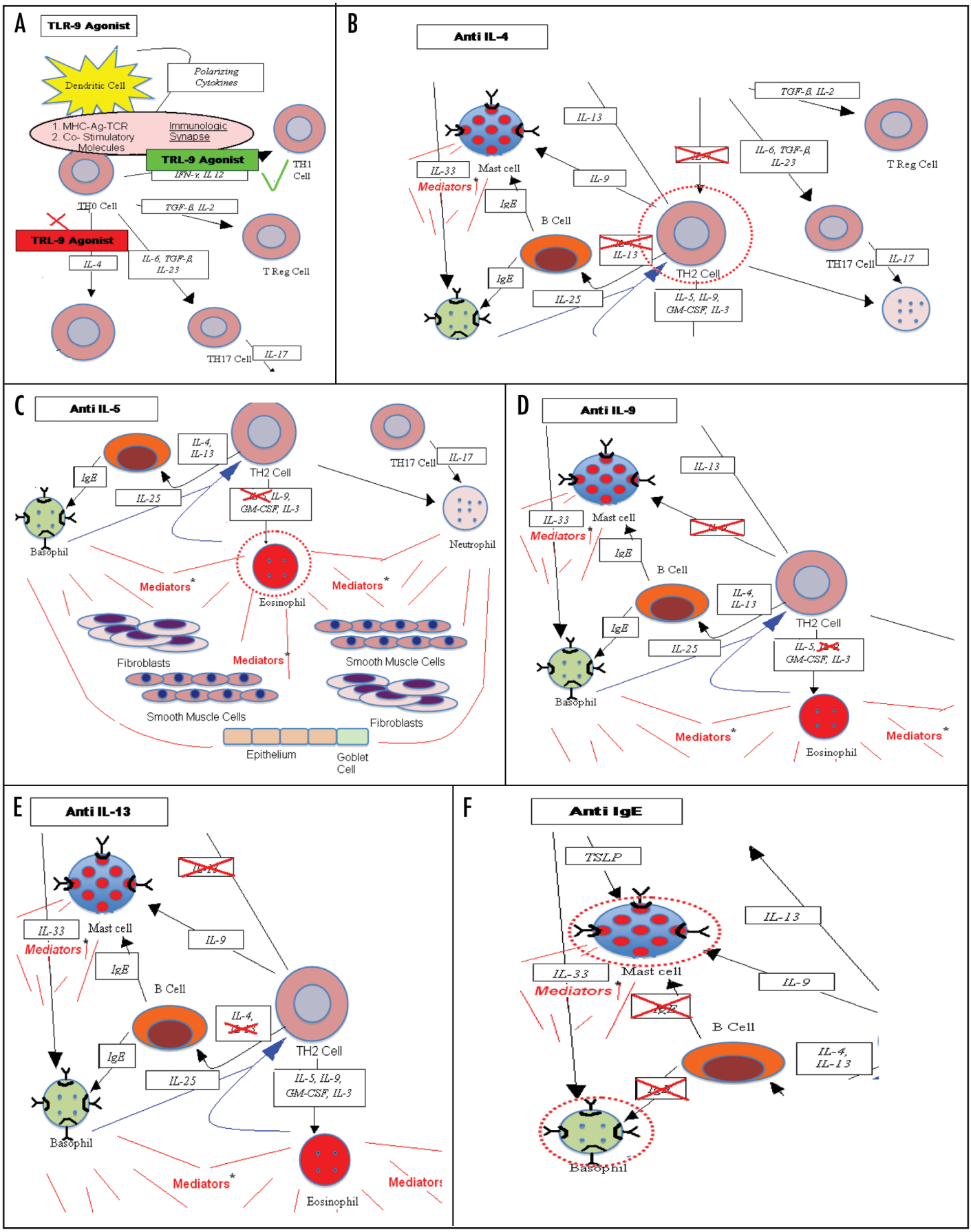


Figure 1. Schematic depiction of the components of the airway allergic inflammatory response. PRR (pattern recognition receptor); PAR (protease activated receptor); TSLP (thymic Stromal Lymophopoietin); GM-CSF (granulocyte-macrophage colony stimulating factor). Arrows indicate the direction in which the identified signal is acting. Red lines indicate the discharge of cellular mediators (including granular contents, lipid mediators and cytokines).


A
TLR-9 Agonist
Dendritic Cell
Polarizing Cytokines
1. MHC-Ag-TCR
2. Co- Stimulatory Molecules
Immunologic Synapse
TRL-9 Agonist
IFN-γ, IL 12
TH1 Cell
TH0 Cell
TGF-β, IL-2
TRL-9 Agonist
IL-4
IL-6, TGF-β, IL-23
T Reg Cell
TH17 Cell
IL-17
B
Anti IL-4
IL-33
Mast cell
Mediators
IL-13
IL-9
IgE
B Cell
TGF-β, IL-2
T Reg Cell
IL-6, TGF-β, IL-23
TH17 Cell
IL-17
IgE
IL-25
TH2 Cell
IL-5, IL-9, GM-CSF, IL-3
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Neutrophil
Basophil
Mediators
Eosinophil
Mediators
Fibroblasts
Mediators
Smooth Muscle Cells
Smooth Muscle Cells
Fibroblasts
Epithelium
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D
Anti IL-9
IL-13
IL-33
Mast cell
Mediators
IgE
B Cell
IL-4, IL-13
IgE
TH2 Cell
IL-25
IL-5, GM-CSF, IL-3
Basophil
Mediators
Eosinophil
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E
Anti IL-13
IL-33
Mast cell
Mediators
IL-9
IgE
B Cell
IL-4,
IgE
TH2 Cell
IL-25
IL-5, IL-9, GM-CSF, IL-3
Basophil
Mediators
Eosinophil
Mediators
F
Anti IgE
TSLP
IL-13
IL-33
Mast cell
Mediators
IL-9
B Cell
IL-4, IL-13
Basophil

Figure 2 (See previous page). (A) TLR 9 agonists act on dendritic cells in conjunction with antigen and result in a preferential activation of antigen specific T_H12 cells (green line) and inhibition of development of antigen specific T_H2 cells (red X). (B) Anti IL-4 agents block the development of T_H2 cells, whether the source of the IL-4 is from activated basophils or eosinophils or from the stimulated T_H0 cells. This in turn has the potential to diminish production of all T_H2 products-indicated by broken red circle surrounding the T_H2 cell. (C) Anti IL-5 agents block the development and release from the bone marrow of eosinophils. This has the potential to result in less tissue eosinophilia in allergic inflammation and less exposure to mediators from activated eosinophils-indicated by broken red circle surrounding the eosinophil. (D) IL-9 is a product of activated T_H2 cells which can directly activate mast cells. Anti IL-9 could inhibit this. (E) IL-13 is a product of activated Th2 cells with activities in determining isotype switch to IgE of allergen specific B cells, direct activation mast cells and effects on airway goblet cell activity and mucus production. Anti IL-13 has the potential to inhibit these various activities. (F) Anti-IgE results in loss of high-affinity IgE receptors of mast cell and basophils with result diminished capacity for activation after allergen exposure. Anti-IgE reduces high affinity IgE receptors on dendritic cells which may in turn decrease allergen processing and presentation.

demonstrated increased amounts of IFNγ suggesting T_H1-skewed immune responses, but there was no decrease in the amount of IL-4 or eosinophils in the nasal biopsies.[15] A separate study reported a diminished ex-vivo ragweed-specific T_H2 responses and a transient T_H1 biasing effect of this therapy in patients with ragweed allergic rhinitis.[16] The initial proof of concept clinical trial was followed by a larger multicenter randomized controlled clinical trial. Improvement was observed in the treatment groups, again over two years, but a higher treatment dose group apparently showed no incremental benefit over those receiving a lower dose equivalent to what had been studied in the first trial. Enthusiasm has waned somewhat for this single-allergen immunotherapy approach, but it is believed that additional studies are being designed and other studies are ongoing to investigate therapy of allergic asthma by TLR-9 agonists alone or conjugated to allergen.[13]

The promotion of T_H2 type allergic inflammation by cytokines released from resident tissue cells of the innate immune system, such as epithelial cells, is an area of active investigation. Thymic stromal lymphopoietin (TSLP), derived largely from activated epithelial cells, influences the expression of co-stimulatory molecules on dendritic cells, particularly OX-40 ligand. This represents a T_H2 polarising signal which preferentially drives naïve T_H0 CD4 T-cells towards an allergic inflammatory T_H2 phenotype.[17-18] TSLP can also cause immature cord blood-derived mast cells to secrete increased amounts of the T_H2 cytokines IL-5 and IL-13 and certain chemokines, as well as demonstrate an enhanced rate of mast cell maturation.[19] More recently, a novel IL-1 family member cytokine, IL-33, has also been demonstrated to increase T_H2 allergic inflammation. IL-33 has a very high level of expression in high endothelial venules of lymphoid tissue, is thought to play a role in the chemotaxis of T_H2 cells, and was shown to be capable of increasing cytokine production from T_H2 polarized lymphocytes.[20] IL-33 has been shown to cause a direct activation of basophils resulting in increased secretion of IL-4, IL-13, IL-8, as well as enhanced $F_C\varepsilon R1$ dependent mediator release and cytokine production. It is also capable of activating human eosinophils.[21] Targeting TSLP, IL-33 and other allergen-independent cytokine pathways which promote T_H2 type allergic inflammatory disease might offer an important potential to interrupt chronic allergic inflammation, and these approaches are currently under investigation in animal models of asthma.

T-Cell Blocking Therapies

Daclizumab (anti-IL-2 receptor α subunit/anti-Tac, anti-CD25) monoclonal antibody acts to decrease T-cell proliferation and cytokine (T_H1 and T_H2) production, and is FDA approved for use in the prophylaxis of renal allograft rejection. It decreases the binding of IL-2 to its receptor and has greater effects on activated than resting T-cells. Regulatory T-cells, which also use IL-2 for proliferation and survival, do not appear to be functionally inhibited in patients treated with daclizumab.[22-24] A double blind placebo controlled trial in patients with moderate to severe persistent asthma of daclizumab, administered IV every two weeks, has shown improvement in asthma control (both impairment and risk) including improvements in pulmonary function and deceased peripheral blood eosinophils.[25] This proof of concept study will need to be followed by larger trials in asthma to more fully define the role of this agent therapeutically.

Keliximab is a primatized anti-CD4 monoclonal antibody that has been studied in patients with steroid dependent asthma as a single infusion, with a four week follow up. There was a dose-dependent decrease in peripheral CD4 counts and a decrease in mitogen-induced T-cell proliferation. The highest dose used resulted in an increase in morning and evening peak expiratory flow rates, but there were no significant changes in asthma symptoms.[26,27] Additional studies have not been reported in asthma.

Earlier T-cell based strategies in asthma have included evaluation of calcinuerin inhibitors cyclosporine and tacrolimus. In patients with chronic severe asthma, treatment with cyclosporine resulted in modest improvement.[28]

T_H2 Cytokine Blocking Therapies

The cytokines produced by T_H2 type lymphocytes, basophils and mast cells (IL-4, IL-5, IL-9 and IL-13) have been linked to many of the pathologic findings in asthma detailed above. Such knowledge has led to the development of several anti-cytokine agents with potential utility in interrupting the T_H2 dependent allergic inflammation characteristic of asthma. Human studies so far have included attempts to target most of the major T_H2 cytokines including IL-4, IL-5, IL-9, IL-13, and joint targeting of IL-4 and IL-13.

Targeting IL-4. IL-4 has been demonstrated to have an important role in the development of allergic inflammation at several levels and is an attractive target for therapy. In the presence of dendritic cell-presented allergen, IL-4 (possibly basophil-derived) strongly influences the differentiation of T_H0 cells into T_H2 cells. Furthermore, along with IL-13, IL-4 is a primary signal influencing the B lymphocyte to undergo isotype switch from IgM to IgE. IL-4 has also been demonstrated to upregulate the high affinity and low affinity IgE receptor expression on mast cells and

basophils (Fig. 2B). Finally, IL-4 can also contribute to inflammatory cell recruitment via vascular cell adhesion molecule-1/very late antigen-4 dependent mechanisms, and can also directly contribute to goblet cell hyperplasia. In mouse models of asthma, many studies have shown that IL-4 removal or blockade profoundly abrogates the allergic inflammatory response and other features of asthma.[29]

The solubilized IL-4 receptor fragment altrakincept, consisting of an extracellular portion of human IL-4R-α chain that competitively inhibits the binding of IL-4 to its receptor, appeared promising in early human studies of mild to moderate asthma. Delivered by nebulizer, it appeared safe and well-tolerated and had a serum half-life of about five days. After a single dose it resulted in a reduction in exhaled nitric oxide and stabilization of asthma symptoms, despite inhaled corticosteroid withdrawal.[30] In a subsequent 12-week proof of concept study that included 62 atopic patients with mild-to-moderate persistent asthma, weekly administration by nebulizer safely permitted withdrawal of inhaled steroid while maintaining asthma control. Thus, in contrast to the control group, patients treated with soluble IL-4 receptor showed no decline in FEV1 or increase in symptoms after inhaled corticosteroid therapy withdrawal. However, the study discontinuation rate due to asthma exacerbations was similar between the soluble IL-4 receptor and placebo groups.[31] While no further reports of clinical studies have been published, it is understood that a larger, Phase III trial failed to confirm this benefit or efficacy suggested by the earlier, smaller trials.[32]

IL-4 and IL-13 overlap in several functions and share a common α-chain in their receptors. Recent research has suggested that the soluble IL-4R under certain conditions may even enhance IL-13 responses. This observation may be relevant to the soluble IL-4 receptor's ultimate lack of efficacy in clinical trials.[33]

An alternative approach to targeting IL-4 has been the use of an anti-IL-4 humanized monoclonal antibody, pascolizumab. This antibody effectively blocked IL-4 responses in vitro, and showed a favorable in-vivo pharmacokinetic profile in cynomolgus monkeys. A Phase II clinical trial in humans with asthma yielded unimpressive results, and further development was discontinued.[34]

Targeting IL-5. IL-5 plays an important role in the differentiation of CD34 positive hematopoietic precursor cells into eosinophils, their subsequent maturation and passage out of the bone marrow into peripheral blood. IL-5 also induces activation of mature eosinophils and promotes their survival (Fig. 2C).[35] As eosinophils express the pro-fibrotic growth factor TGFβ, IL-5 has also been linked to airway remodeling.[36] A series of animal studies highlighted the important role of IL-5 in asthma,[37,38] and demonstrated that removal of IL-5 resulted in improved parameters of asthmatic disease activity.[39,40]

In humans, a 12-week double-blind, placebo-controlled, randomized controlled trial (DBPCRCT) of the anti-IL-5 monoclonal antibody mepolizumab in patients with mild to moderate asthma was reported. While the study showed a rapid, dose-dependent and sustained reduction in eosinophil counts in blood and sputum, no differences in bronchial hyperresponsiveness, late phase allergic responses or other asthma outcomes were identifiable between the two treatment groups.[41]

A separate study in patients with severe persistent asthma of another anti-IL-5 monoclonal antibody, rezlizumab, yielded similar findings. That is, eosinophil numbers were decreased in peripheral blood, but changes in asthma outcomes were not observed over ten weeks of treatment.[42] A subsequent study using mepolizumab confirmed the suppression of eosinophilia in blood, in bone marrow and in airway lavage fluid, with a limited reduction in the number of the eosinophils seen in airway biopsies.[43] The reduction in airway eosinophil levels was associated with decreased expression of eosinophil TGFβ mRNA, decreased levels of TGFβ in bronchoalveolar lavage fluid (BAL), as well as decreased levels of tenascin, lumican and procollagen 3 in the bronchial subepithelial basement membrane.[44] These findings in patients suggest that anti-IL-5 therapies might have potential in regulating tissue remodeling in asthma.

A possible explanation for the observations of less impressive reductions of eosinophils in the airways than in the blood or BAL might be that airway eosinophils do not express the IL-5 receptor making them less amenable to modulation by this therapy than circulating eosinophils.[45,46] Specific strategies to reduce tissue eosinophils in the airways might prove more beneficial in asthma treatment; these might include targeting either the shared beta chain between IL-3 and IL-5 or eotaxin. Anti-IL-5 monoclonal antibodies may be useful in other diseases characterized by high levels of eosinophils in blood and tissues, including hyper-eosinophilic syndrome (HES), eosinophilic esophagitis (EE) and other eosinophilic enteritides, and chronic rhinosinusitis with nasal polyps. Preliminary data in patients with HES and EE treated with anti-IL5 have revealed promising results including improvement in clinical parameters and levels of tissue in eosinophilia.[47-50] A recent randomized, double-blind, placebo-controlled trial in patients with HES demonstrated an anti-IL-5 therapy resulted in clinical stabilization, decreased peripheral blood eosinophil levels and decreased oral steroid requirements.[51] Two recent small, proof of concept studies report use of mepolizumab in a subset of asthmatic patient who demonstrate persistent blood and sputum eosinophilia despite treatment with systemic corticosteroids.[52,53] It is felt that this select subgroup might account for only approximately 5% of all adult-onset asthmatics.[54] Both of these studies report a decrease in asthma exacerbations when compared to a control group of asthmatics, but there was no change in lung function tests, asthma symptoms or quality of life assessments.[52,53] This finding indicates that one particular phenotype of asthmatics might stand to benefit from use of an anti-IL-5 monoclonal antibody.

Targeting IL-9. IL-9 has been demonstrated to have a direct effect on the development and activation of human mast cells, to contribute to goblet cell hyperplasia in the airways and to other aspects of airway remodeling (Fig. 2D).[36] In mouse models of asthma, blocking IL-9 reduces allergen-induced airway inflammation and airway hyperresponsiveness. Early human studies of an anti-IL-9 monoclonal antibody (MEDI-528) have been conducted. These include two Phase I dosing studies that have been completed in healthy subjects without major adverse events. Phase II studies are currently in progress in patients with symptomatic moderate to severe asthma, but trial results are not yet available.[4]

Targeting IL-13. IL-13 shares many functional properties with IL-4, stemming from the fact that they share a common receptor sub-unit, the α-receptor of the IL-4 receptor (IL-4Rα). Even though the precise molecular mechanism by which IL-13 achieves downstream effects separate from IL-4 has not yet been elucidated, it has been clearly demonstrated to have distinct functions.[55] IL-13, in addition to its role in promoting IgE isotype switching by B cells, also has important effects on epithelial cell maturation, goblet cell hyperplasia and mucous production, generation of extracellular matrix proteins and enhanced contractility of airway smooth muscle cells. IL-13 is also involved in the recruitment of eosinophils, monocytes, macrophages and T-cells (Fig. 2E).[56,57] These properties make it a key potential target in the treatment of allergic inflammatory diseases including asthma.[58] In animal models including mice and primates, reduction of lung inflammation, decreased airway responsiveness and diminished mucus production have been associated with use of anti-IL-13 monoclonal antibodies or a soluble form of IL-13 receptor.[57,59,60]

Human anti-IL-13 specific monoclonal antibodies are under development and some are in Phase I and II trials. A Phase I clinical trial with CAT-354 showed that increasing single doses of intravenously administered anti-IL-13 monoclonal antibody in 34 patients with mild asthma were well-tolerated at all doses with no identified safety concerns.[4] No outcome data related to asthma improvement are yet available.

Joint targeting of IL-4 and IL-13. Both IL-4 and IL-13 use the IL-4Rα as a component of their receptor, and this chain is integral to transmission of signals by both cytokines. Blocking this shared component of the receptor has the potential to inhibit signaling by both IL-4 and IL-13, two potent T_H2 cytokines with several overlapping properties.

An IL-4 mutant protein, pitakinra, that inhibits the effects of both IL-4 and IL-13 through its ability to bind to the IL-4R α-chain, has been developed both as a subcutaneous injection and as an inhaled therapy. A Phase III study of the inhaled formulation in allergen-induced asthma in humans, involving twice daily inhalation for 27 days, demonstrated decreases in the late phase allergic responses, decreases in exhaled nitric oxide and improved pulmonary function in asthmatics. In contrast to results from animal studies, bronchial hyperresponsiveness did not change.[61] Further studies are under way.

Promoting T_H1 Cytokines

As mentioned, IL-12 and IFNγ have a negative developmental effect on T_H2 phenotype cells, while preferentially driving the differentiation of T_H0 cells towards a T_H1 phenotype. An alternative biological approach to the treatment of allergic asthma therefore might include use of recombinant T_H1 cytokines, such as IL-12, with a goal of downregulating T_H2 type responses.

In animal models of allergic asthma, administration of IL-12 during sensitization suppresses allergen-induced T_H2 cellular responses in favor of T_H1 responses, inhibits airway hyperresponsiveness and results in diminished airway eosinophilia after allergen challenge. In humans, a clinical trial involving injection of recombinant human IL-12 in patients with mild asthma resulted in a decrease in the number of circulating blood eosinophils after allergen challenge, but not in sputum eosinophilia, the late phase asthmatic responses or in airway hyperresponsiveness. This therapy was accompanied by flu-like symptoms, abnormal liver function tests and cardiac arrhythmia.[62]

T_H17 Cells as a Target

T_H17 cells have been identified as a distinct T-helper cell lineage that follows a distinct differentiation pattern requiring IL-6 and TGFβ.[63] This novel T-helper subset is characterized by the production of IL-17 cytokines that produce tissue inflammation by inducing the release of pro-inflammatory and neutrophil immobilizing cytokines. T_H17 cells have been demonstrated experimentally to have an important role in the development of autoimmune diseases, but may also contribute to the pathogenesis of classically recognized T_H2 mediated allergic diseases.[64] Experimental evidence suggests that IL-17 decreases tissue eosinophil recruitment and bronchial hyperreactivity, but may on the other hand increase neutrophil infiltration and increase mucus proteins.[65] Additionally, more recent evidence suggests that IL-17 is associated with a steroid-resistant phenotype in asthma.[66] These observations may eventually lead to targeting this pathway in the treatment of severe neutrophilic asthma.

Targeting IL-25. Interleukin 25 (IL-25, IL-17E) is also a member of the IL-17 family, but is distinct from all the other IL-17 family members in that it has been shown to provoke T_H2 cell mediated inflammatory responses in animal studies. Animal studies have also shown that a neutralizing antibody against IL-25 significantly abrogates airway hyperresponsiveness, reduces IL-5 and IL-13 production, reduces tissue eosinophil infiltration, goblet cell hyperplasia and serum IgE.[67] In humans, it has been shown that eosinophils and basophils likely represent the primary source of IL-25, and that its major affect may be upon T_H2 memory cells.[68] While human studies have not yet been reported, this might be a potential therapeutic target.

Anti-IgE

Omalizumab, an IgE-specific humanized IgG_1 monoclonal antibody binds to the Fc-region of the IgE molecule, prevents IgE from interacting with high or low-affinity IgE receptors (FcεR1 and FcεR11) and results in rapid decreases in levels of circulating free IgE. Omalizumab does not directly bind to receptor-bound IgE, but downregulates FcεR1 on circulating basophils, on skin mast cells, and on circulating dendritic cells. It has the potential to inhibit allergen-induced mast cell activation regardless of the allergen specificity of the IgE molecules (Fig. 2F). The mechanisms of action of omalizumab might also include reduced presentation of allergen by dendritic cells to T-cells. Early studies in asthma showed that this antibody inhibited both early asthmatic responses and late asthmatic responses to inhaled allergen in patients with asthma.[69]

Demonstration of the anti-inflammatory properties of omalizumab was provided in a 16-week placebo-controlled bronchial biopsy and sputum study of 45 patients with corticosteroid naive mild persistent asthma. Omalizumab-treated subjects demonstrated

a reduction in sputum and tissue eosinophils, a reduction in the number of IgE positive and FcεR1 positive cells in the submucosa, a decrease in the number of cells staining positive for IL-4, and a decreased overall number of CD4 and CD8 lymphocytes. However, perhaps surprisingly, bronchial hyperresponsiveness to methacholine was not significantly changed.[70]

Omalizumab is administered by subcutaneous injection. Although the level of circulating free IgE decreases rapidly after the first dose of omalizumab, up to 16 weeks of treatment might be required before optimal clinical effects are seen. Large placebo-controlled clinical trials in adults, adolescents and children with poorly-controlled IgE-mediated asthma have shown that omalizumab improves symptom control, decreases the frequency of asthma exacerbations and allows patients to be managed with lower doses of inhaled corticosteroids.[71,72] Recent studies have demonstrated efficacy of omalizumab in patients with more severe asthma, and in pooled analyses of several large clinical trials, omalizumab significantly reduced asthma exacerbations (by 38%), emergency department visits (by 61%) and hospital admissions (by 52%) and unscheduled doctor visits (by 47%) when compared to control subjects.[73,74] Omalizumab has also been studied as a treatment for other allergic diseases including allergic rhinoconjunctivitis,[75,76] as adjunctive therapy with allergen immunotherapy,[77,78] and as a treatment for chronic urticaria and angioedema,[79-82] atopic dermatitis,[83,84] allergic bronchopulmonary aspergillosis,[85,86] Churg-Stauss syndrome[87,88] and latex allergy.[89] Further study is ongoing; none of these conditions are approved indications for use of this drug.

Lumiliximab (antiCD23). Lumiliximab is a primatized macaque/human monoclonal antibody directed against the low affinity IgE receptor CD23 (F_CεRII) which is expressed on several cell types including monocytes, alveolar macrophages, B cells and dendritic cells of allergic individuals. CD23 is felt to have a role in the regulation of IgE production and IgE-mediated inflammatory processes, and its activation can result in increased antigen presentation by B cells and increased production of proinflammatory cytokines. A Phase I single dose trial in patients with allergic asthma resulted in decreased IgE levels by 40%, and in vitro studies showed reduced allergen-specific PBMC proliferation and reduced production of proinflammatory cytokines (IL-1β and TNFα).[90] Additional studies are needed to determine the true clinical efficacy of this agent in asthma or other allergic diseases.

TNFα based Therapy

Recent studies have suggested TNFα may serve as a marker of severity in asthma and possibly as a target for biological therapy of asthma.[91] TNFα is important in the innate immune response. It is a cytokine principally produced by macrophages in response to activation of membrane bound pattern recognition molecules, such as toll-like receptors, but is also produced by several other pro-inflammatory cells including monocytes, dendritic cells, B lymphocytes, T lymphocytes, neutrophils, mast cells and eosinophils, as well as structural cells including fibroblasts, epithelial cells and smooth muscle cells. TNFα has been linked to several chronic inflammatory diseases including rheumatoid arthritis and Crohn disease in which anti-TNFα therapy has proved useful as a treatment.

The possibility that TNFα contributes to the inflammatory response seen in the asthmatic airway is supported by several observations. A biopsy study showed that TNFα mRNA is up to 30-fold higher in the airways of severe asthmatics compared to well-controlled asthmatics. This finding was paralleled by increased levels of TNFα protein in bronchoalveolar lavage fluid and mucosal biopsies.[92] Administration of recombinant TNFα to normal subjects led to development of airway hyperresponsiveness and airway neutrophilia.[93] Silvestri et al. examined the level of four cytokines TNFα, IL-8, IL-6 and IL-13 in the circulation of severe, mild/moderate asthmatics and normal controls.[94] They report that TNFα and IL-8 levels are higher in those with severe asthma and are inversely correlated with baseline forced expiratory volume. They also report correlations between serum TNFα levels, exhaled nitric oxide and circulating neutrophil counts. They suggest that circulating levels of TNFα and IL-8 may serve as biomarkers to identify those severe asthmatic patients in whom anti-TNFα therapy may be efficacious.[94]

Based on these observations and a clear unmet clinical need in corticosteroid refractory asthma, a small number of recent clinical trials have evaluated the efficacy of anti-TNFα therapy in asthma.[95] Biologic agents targeting the TNFα axis include infliximab (a chimeric mouse/humanized monoclonal antibody), etanercept (a soluble fusion protein combining TNFα receptors with an F_C fragment of human IgG_1) and adalimumab (a fully human monoclonal antibody).

In a 12-week open-label uncontrolled study of etanercept in patients with severe asthma, Howarth et al. reported a significant improvement in methacholine airway hyperresponsiveness, an improvement in FEV1 and in improvement in quality of life.[92] This was followed by a randomized controlled crossover trial of etanercept in ten patients with severe asthma in which it was confirmed that treatment resulted in an improvement in airway hyperresponsiveness, FEV1 and asthma-related quality of life. There was no effect of etanercept therapy on the number of sputum eosinophils or neutrophils. It was, however, shown that membrane associated TNFα on circulating mononuclear cells appeared to be a predictor of the therapeutic response to etanercept.[96] A subsequent 12 week long randomized, placebo-controlled, paralleled group study of etanercept in a patients with severe asthma demonstrated no beneficial effect.[97] In a randomized placebo-controlled trial, Erin et al. reported the efficacy of infliximab in patient's with moderate asthma.[98] No improvement in morning peak flow occurred, but there were decreases in diurnal variation of peak expiratory flow rate, and a 50% reduction in the number of mild asthma exacerbations. There were no significant improvements in lung function.[98] It has been stated that unpublished longer-term randomized, placebo-controlled, paralleled group studies of patient with moderate severe asthma have questioned the efficacy of anti-TNFα therapy in asthma as discussed by Brightling et al.[91]

Efalizumab is a humanized IgG1 monoclonal antibody against lymphocyte function antigen-1 (LFA-1) alpha chain (CD11a) that

can block trafficking of leukocytes from the circulation to sites of inflammation by interrupting LFA-1/intercellular adhesion molecule-1 interactions. In a DBPCRCT study of patients with mild allergic asthma, statistically significant differences in late phase allergic responses were not seen after allergen inhalational challenge.[99]

Conclusion

Recent increases in our understanding of the pathobiology of asthma, and of the innate and adaptive immune responses underlying those changes, including the role of various cellular elements and cytokines, has resulted in the identification of a large number of potential therapeutic targets for biologic agents in asthma. Many such therapies have been developed and subjected to clinical study, but, to date at least, the vast majority of these have not received FDA approval for treatment of asthma or other allergic diseases. Omalizumab is a notable exception. Asthma is clearly a complex disease or syndrome of diseases, and the possibility that separate populations of asthmatic patients are responsive to different biological therapies emphasizes the likely importance of tailoring novel therapies to individual patients. It is anticipated that, as the heterogeneity of asthma becomes more fully understood, new targeted biologic therapies will realize their potential as therapeutic agents. This is a very exciting time in the treatment of allergic diseases, and the future seems full of promise.

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