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Review

Targeting IgE and Th2-Cytokines in Allergy: Brief Updates on Monoclonal Antibodies and Antibody Gene Therapy

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Abstract: The search for an effective treatment of allergic conditions is an ongoing global health challenge due to the high prevalence of allergies. Epinephrine and glucocorticosteroids remain the oldest and most widely used treatment regimen for allergy, and these medications are for short relief. In extreme allergy manifestations, the current treatment options aim to use monoclonal antibody (mAb) to target pathological pathways of inflammation involving mast cells, eosinophils, and basophils. These cells have the propensity to induce an allergic-inflammatory response. Studies have shown that they are responsible for several allergic diseases, such as allergic asthma, atopic dermatitis, rhinitis, and conjunctivitis. Studies evaluating monoclonal antibodies against serum IgE (Omalizumab), Th-2 cytokines, such as IL-4, IL-13 (dupilumab), and IL-5 suggest an attenuation of allergic symptoms and improvement in patients' overall well-being. However, several factors such as cost of production (i.e., antibody purification), host immunogenicity, safety, and efficacy have hindered the availability of purified mAb in developing countries. Gene therapy is a promising tool for treating allergy, and emerging studies have suggested that antibody gene therapy may be the future for treating extreme cases of allergy manifestations. This paper describes the use of purified monoclonal antibodies for treating severe allergic responses and the associated limitations. It explores the prospects of antibody gene therapy for modulating allergy episodes.

Keywords: monoclonal antibodies; allergy; inflammation; gene therapy; IgE and Th-2 cytokine

1. Introduction

Allergic inflammation is a type 2 immune disorder [1]. It is characterized by an abnormal immune response against potentially harmless substances [2]. This response is often classified into three phases: the early phase reaction, which occurs within seconds to minutes, the late phase reaction, which occurs within several hours, and the chronic phase, characterized by persistent exposure to inflammatory mediators and stimuli [2]. Tissue mast cells, blood basophils, and eosinophils are important immune cells that play a crucial role in the allergic-inflammatory response [3,4]. Hallmarks of allergy and allergic inflammation include a rise in serum immunoglobulin E (IgE) (with an exception for contact dermatitis), eosinophilia, cytokine and chemokine secretion, and airway mucus production depending on the site of the inflammation [4,5].

The prevalence of allergic-inflammatory diseases in Western countries is quite alarming, with an estimated 30–40% of the world population living with one or more allergic

conditions [6,7]. These diseases, including rhinitis, asthma, urticaria (hives), eczema (atopic dermatitis), food allergy, insect-bite allergy, anaphylaxis, and drug-related allergies, can affect anyone regardless of age [8]. Several factors, including genetic factors, environmental factors, dietary habits, exposure to dust or pollens, and the prevalence of microbial infection, contribute to this endemic problem [9]. In developing communities, most allergic cases involve seasonal exposure to dust/or pollen particles. Murine studies have shown that prolonged exposure to particulates induces symptoms similar to allergic conjunctivitis [10] and allergic asthma [11]. The majority of these allergic reactions occur either via IgE-mediated [12] or non-IgE-mediated mechanism(s) with the participation of an array of immune cells, such as tissue mast cells, blood basophils, eosinophils, neutrophils, T cells subpopulation, and specific tissue epithelial cells [13].

Glucocorticosteroids are commonly prescribed for short-term relief of allergies [14,15] because their prolonged use had previously been associated with several adverse outcomes, such as increased predisposition to diabetes, osteoporosis, and cardiovascular pathologies [16,17]. There are conflicting evidence on corticosteroids efficacy in short-term relief of allergy [15,18]. One Cochrane review reported that corticosteroids are effective in acute sinusitis [15], while another suggested that they are ineffective in the management of anaphylaxis [18]. Due to the inconclusive and mixed reports on the effectiveness of glucocorticoids, there has been a need to explore specific treatment modalities for allergies. The application of immunotherapy and antibody gene therapy has revolutionized the approach in allergy therapy research.

The early phase of allergen-specific immunotherapy was hypo-sensitization, which began in the first half of the 20th century [19]. This method involves tricking the immune cells not to react to allergens responsible for hypersensitivity or allergic reaction via oral or intravenous administration of high doses of the inert allergen extract. This method is credited to Leonard Noon, who demonstrated that subcutaneous administration of pollen extract could suppress immediate conjunctival sensitivity to the pollen [20]. This therapy was promising in inducing a state of specific immune tolerance to selected allergens. However, caution and close monitoring of patients taking such therapy is required in cases of severe reactions.

Of concern in this review is the emerging research in the development of monoclonal antibodies (mAb) that targets IgE and Th-2 cytokines, and that of mRNA-mediated antibody therapy. The mechanism of action of mAb is diverse and may include aggregating serum IgE and downregulating the expression of the high-affinity IgE receptor (FcεRI) on mast cells and basophils (omalizumab) [21]. It may also involve the inhibition of IL-4 and IL-13 signaling via IL-4α (dupilumab) [22,23], and the inhibition of IL-5 signaling [24]. Most mAb used in allergy are designed to target the interaction of IgE and Th-2 cytokines to their receptors in a well-fashioned manner in order to curb episodes of allergic inflammation [25,26]. Laffer et al. [27] reported that mechanistically, mAb12, a high affinity monoclonal anti-human IgE antibody, depletes serum IgE and IgE$^+$ cells, including basophils, eosinophils and IgE$^+$ antigen-presenting cells from the peripheral blood of allergic patients. Similarly, in mice, Chen et al. [28] reported that another mAb, anti-CεmX which binds to membrane-bound IgE on IgE-switched B cells, depletes blood IgE$^+$ B cells via induction of complement-mediated cytotoxicity. This might be useful in depleting memory B cells producing IgE in the secondary response to allergens. Further, Lupinek et al. [29] reported that IgEnio$^®$, an IgE-immunoadsorber, depletes IgE in pollen-induced asthma patients. This biologic also has the potential of removing serum IgE even in the presence of omalizumab, thus suggesting that both might be used in treating extreme cases of allergy to prevent the potentially harmful effect of immune complexes such as IgE-bound omalizumab [29].

Omalizumab (trade name Xolair) was the first FDA-approved humanized mAb in 2003 for patients with severe and persistent asthma where inhaled corticosteroid fails [13,30]. This therapy prevents the cross-linking of serum IgE with its high-affinity IgE receptor

(FcεR1) on mast cells and blood basophils, thereby inhibiting cell degranulation of secretory granules [13,30].

In this review, we summarized the existing literature that focuses on targeting IgE and Th-2 cytokines (IL-4, IL-5, IL-13) in allergy. Further, we briefly discuss antibody gene therapy as the future therapy for managing and treating extreme manifestations of allergic inflammation.

2. Search Strategy

In this narrative review, a literature search was performed using keywords and phrases such as "monoclonal antibodies in allergy", "gene therapy in allergy", "allergy", "allergic-inflammation", "anti-histamine", "corticosteroids", "allergy prevalence" on PUBMED database. Articles discussing the therapeutic use of monoclonal antibodies and gene therapy in allergy in humans or animal models were selected and reviewed.

3. Monoclonal Antibody Therapy for Allergy

3.1. Mechanism of an Allergic Reaction

Allergic reaction is a fundamental pathological condition that encompasses type 1 hypersensitivity involving innate and adaptive immune cells [31]. There are three steps involved in an allergic-inflammatory response: the sensitization step, also known as the induction phase, the effector step, and the clinical outcome or manifestation step, as depicted in Figure 1.
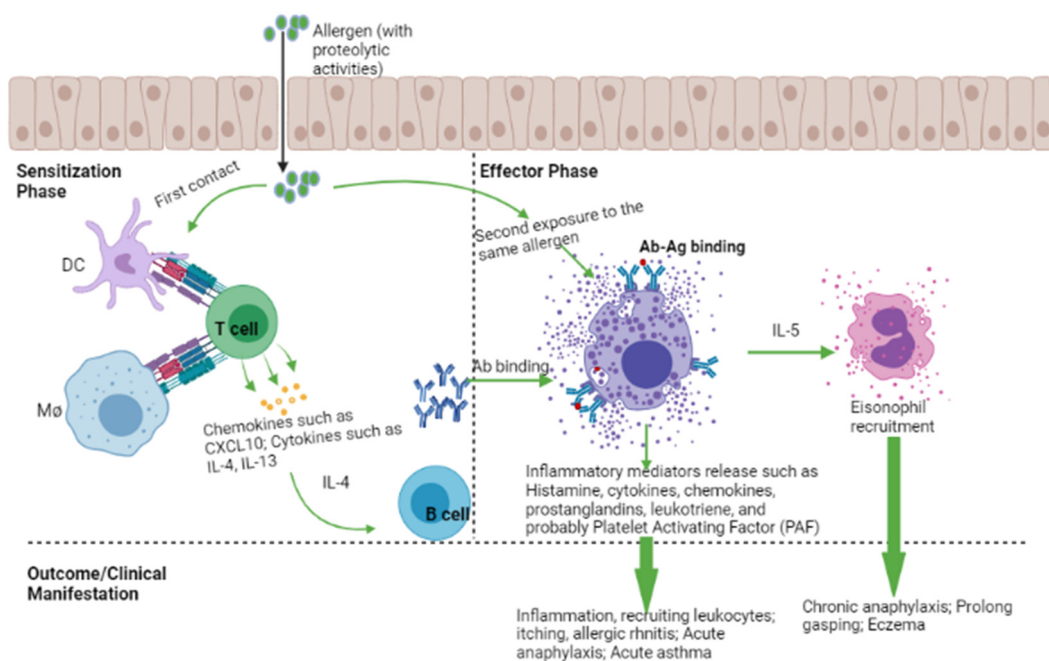

Figure 1. Mechanism of an allergic reaction. Allergy pathogenesis involves three phases: sensitization phase, effector phase, and clinical manifestation/outcome. The sensitization phase includes the proteolytic activity of allergen disrupting the tight epithelial junction to gain entry, and on the first contact with antigen-presenting cells (APC, such as dendritic cells (DC) and macrophages (MØ)), follows allergen processing and presentation to Th-2 cells, thus producing chemokines (such as CXCL 10) and cytokines such as IL-4. IL-4 acts on B-cells to induce B-cell Ig class switching to produce IgE, which binds to FcεRI on mast cells. The effector phase includes the second exposure to the same allergen, allergen-antibody cross-linking occurs, and mast cell degranulation results in the release of inflammatory mediators that facilitate effector cells (such as eosinophils) recruitment. The contributory responses of these effector cells and mediators present clinical outcomes such as itching and eczema dependent on the exposure surface. When multiple organs are involved, anaphylaxis sets in. This image was created in bio render.

Most allergens including *Aspergillus fumigatus* and house dust mite (Der p 1 and Der p 5) possess proteolytic activities that disrupt the epithelial barrier and promote antibody IgE/IgG1 production, eosinophilia, as well as the release of inflammatory mediators such as cytokines and histamine [32]. The interaction of histamine, and other inflammatory mediators with their respective receptors expressed on immune cells and epithelial cells are key to allergic clinical manifestation.

3.2. Histamine, Histamine Receptors, and Clinical Outcome

Histamine is one of the inflammatory mediators released during basophils or mast cell degranulation. Histamine is a key to the induction of allergic inflammation [33] through its interaction with its respective receptors expressed on several immune cells (mast cells, eosinophils, basophils, dendritic cells, and T cells), on endothelial and epithelial cells, and even on some tissues such as skin and lungs [33,34]. Aside from immune cells, histamine can be secreted by brain neurons [34], which makes histamine a multi-functional biomolecule that can regulate both the central and peripheral nervous systems. Histamine receptors (H1R, H2R, H3R, and H4R) are all members of the G-protein coupled receptor family [33,35]. The binding of histamine to its receptor, [36] leads to several clinical manifestations or outcomes [33,35,37–39], as depicted in Table 1.

Table 1. Histamine, its receptors, and associated clinical outcome.

Receptors	Effects	Clinical Manifestation	References
H1	Stimulates nociceptive nerve fiber; bronchoconstriction; increase mucus secretion	Itching; urticaria; allergic rhinoconjunctivitis; allergic asthma	[33,35]
H2	Gastric acid secretion; arrhythmia; increase intracellular cAMP	Peptic ulcer anaphylaxis; negative feedback on mast cell activation	[33,38]
H3	Inflammation on the neurons	Neuro-inflammatory diseases such as epilepsy; CNS disorder	[33,39]
H4	Induce eosinophil shape change; activates eosinophils	Lung asthma	[37]

Lippert et al. [40] demonstrated that H2R and H4R are highly expressed in human dermal mast cells, while Xu et al. [41] reported that H1R, H2R, and H3R are upregulated in brain astrocytes following histamine treatment. Although Xu et al. reported a neuroprotective role of histamine on astrocytes, several studies highlight the importance of mast cells in histamine–microglial crosstalk in inducing neuroinflammation [42,43]. The expression of histamine receptors is altered during an episode of allergy, and this may be one of the enabling hallmarks of allergic-inflammatory diseases, including allergic rhinitis, and eosinophilic esophagitis [44,45]. Merves et al. [45] demonstrated that H2R is highly expressed in the esophageal biopsies of a patient with active eosinophilic esophagitis, followed by H1R and H4R. These biopsies are comprised of esophageal resident mast cells, circulating basophils, and epithelial cells. Further, Merves et al. [45] also showed that treatment with histamine induces cytokine release in primary human esophageal epithelial cell lines in an H1R-dependent manner. This suggests that histamine–histamine receptor interaction might be associated with a different form of allergy, such as asthma, rhinitis, and conjunctivitis, as depicted in Table 1. The expression of histamine receptors on a wide range of cells and or tissue contributes to the clinical outcome (see Table 1).

Following the administration of omalizumab in allergic asthma patients, studies have reported a reduced basophil sensitization to an allergen [46], and decreased histamine release [47]. However, there is a certain drawback to the administration of anti-IgE monoclonal antibodies. In a clinical trial (NCT01003301), omalizumab was shown to increase the sensitivity of IgE-mediated basophil sensitization resulting in an increased release of

inflammatory mediators such as histamine [48]. In contrast, a different study reported that omalizumab reduced histamine expression via the inhibition of β-hexosaminidase activity, without enhancing allergen-specific IgE levels or IgE-omalizumab complex formation [49]. The reduction in histamine release induces a negative feedback effect on the expression of histamine receptors on immune cells, thus modulating immune response [41].

Another follow-up study involving 154 patients with asthma and/or allergic rhinitis indicated no evidence of omalizumab directly or indirectly inducing peripheral basophil histamine release [50]. Results from emerging studies on anti-IgE monoclonal antibodies must be interpreted carefully, bearing in mind that several inherent factors might modulate anti-IgE monoclonal antibodies efficacy. Collectively, anti-IgE monoclonal antibody alters the natural process in basophil and mast cell responsiveness, sensitization, stimulation, and release of histamine.

4. Possible Therapeutic Targets That Alleviate Allergic Diseases

The search for an effective therapeutic target against endotype-specific markers (such as free serum IgE, and cytokines) in allergic asthma has long been an active area of allergology research, and most developed biologics are still in clinical trials. Inhaled corticosteroids (ICS) are the first line-medication for both asthmatic children [51] and adults [52]. ICS helps to modulate blood eosinophil levels [52] and improve lung function. The drawback of this treatment is its inherent heterogeneity and patients' genetic variation [53], toxicity [54,55], such as adrenal complications, muscle weakness, osteoporosis [56], and impaired immunity against pneumonia and tuberculosis [57]. In April 2019, the Global Initiative for Asthma (GINA), no longer recommended the use of asthma-only short-term bronchodilators in its guidelines [58]. This is because the administration of only beta-2 agonist bronchodilators increases the risk for asthma and its comorbidities such as hypertension [59]. Instead, a combinatorial approach which involves the use of both ICS and bronchodilators should be explored. This will facilitate the aim of reducing asthma-associated mortality and morbidity as outlined in the GINA guidelines.

In a hospital-based study, Chen et al. [60] reported that asthma patients with underlying chronic obstructive pulmonary disease (COPD) benefited from the ICS and bronchodilator combinatorial therapy [60]. A meta-analysis study showed that ICS with long-acting β2 agonist bronchodilators reduced the risk of death or hospitalization [61]. Another study also showed that this combinatorial treatment improves lung function in post-infectious bronchiolitis obliterans (PIBO) patients [62]. However, care should be taken when diagnosing PIBO, because allergic asthma and PIBO have similar clinical presentations and may be misdiagnosed [63]. Despite advances in the GINA guidelines, there are still some fractions of patients that such combination therapy (bronchodilator and ICS) failed to adequately control their allergic symptoms [64–66]. Thus, host-targeted immunotherapy might offer protection against allergies. Targeting specific host immune crosstalk by either neutralizing serum IgE or blocking cytokines may address the drawback in patients who do not respond effectively to ICS and bronchodilator administration.

4.1. Targeting IgE in Allergic Inflammation

As earlier discussed, the first successful biologic to target free serum IgE was omalizumab. Omalizumab is now used to treat moderate-to-severe asthma patients where bronchodilators and ICS have failed [67–69]. Omalizumab is a recombinant humanized mAb that suppresses both the early and the late asthmatic responses by preventing the interaction of serum IgE with FcεR1 on mast cells, blood basophils, and eosinophils [70,71]. Omalizumab has also been reported to effectively reduce respiratory symptoms associated with allergic asthma in a randomized control trial [72]. Likewise, Esquivel et al. [73] reported that omalizumab reduces serum IgE levels and promotes viral load clearance in asthmatic children infected with rhinovirus. In a separate study, omalizumab was found to reduce platelets and leukocytes count, and C-reactive protein (CRP) levels in chronic urticaria patients [74]. Furthermore, omalizumab was shown to substantially reduce nasal

and bronchial mucosal inflammation in patients with rhinitis experiencing severe allergic asthma [75]. Omalizumab is also promising in older patients with asthma-associated COPD [76]. Patients receiving omalizumab show improved asthma control test (ACT) scores accompanied by a reduced number of exacerbation [76].

Another antibody, ligelizumab (trade name QGE031) is the next-generation humanised mAb specific for IgE [13,77]. Similar to omalizumab, ligelizumab acts by inhibiting the IgE-FcεRI-mediated pathway to neutralizing serum IgE to inhibit the FceRI-mediated pathway [78,79]. The results of the phase III trial of ligelizumab (NCT03580356) in treating patients with moderate-to-severe chronic spontaneous urticaria are yet to be published [80,81]. However, Maurer et al. [78] recently reported that ligelizumab therapy is more effective than omalizumab in alleviating spontaneous urticaria symptoms in patients who do not respond to antihistamine drugs [78]. Other biologics that have shown promising results in phase 1 clinical trials include MEDI4212 [79]. Emerging research has demonstrated that anti-IgE-specific monoclonal antibodies could alleviate symptoms associated with allergies and might improve patient life as depicted in Table 2.

Table 2. Studies on the use of anti-IgE monoclonal antibody for allergies.

Candidates	Type, Origin, and Target	Major Findings	References
MEDI4212	Human IgG1λ mAb, an anti-IgE	Reduces both serum IgE and FcεR1 expression on dendritic cells and basophil in patients with atopy; Prevent IgE to FcεRII interaction in asthma.	[82,83]
Quilizumab	Humanized IgG1 mAb, an anti-IgE[+] B cell	Reduces serum IgE in patients with asthma, allergic rhinitis, and chronic spontaneous urticaria; No significant impact on lung function; Not better than omalizumab.	[84–86]
Bsc-IgE/CD3	Anti-IgE^{+} B cells	Eliminates serum IgE, B-IgE^{+} cells via cytotoxicity; Prevent mast cell degranulation in rat basophilic cell lines (RBL-2H3); May be useful in treating IgE-mediated allergic disorders.	[79,87]
XmAb7195	Humanized mAb; FcγRIIb-enhanced Fc	Inhibits plasma cell differentiation; Reduces total human IgE 40-fold relative to omalizumab.	[88]

4.2. Targeting Th2-Associated Cytokines in Allergic Disease

IL-4 is a crucial cytokine involved in the differentiation of naïve CD4^{+} T cells into Th-2 effector cells, and it is an essential signature of type II inflammatory response [5,89]. Murine model studies have revealed that IL-4 but not IL-5 is central to both inducing Th-2 cell activation/response and airway eosinophilic recruitment/inflammation [90,91]. Blockade of IL-4 is a possible target for alleviating most allergic diseases such as asthma, rhinitis, and eczema. Studies have shown that both altrakincept and pascolizumab reduce the recruitment of eosinophils at the site of allergic inflammation by masking the patient's serum IL-4 (Figure 2), but with low clinical efficacy [13,54,77]. Both altrakincept and pascolizumab could not make it through phase III clinical trials and, as such, were suspended from being launched into the market [92]. Similar to IL-4, IL-13 is also a central mediator of allergic inflammation. IL-13 can induce most of the key characteristic features of experimental asthma and allergy, including allergen-induced airway hypersensitivity, goblet cell hyperplasia with mucus hyper-production, and eosinophilia [93–95]. Lebrikizumab is a humanized mAb that blocks IL-13 functionality (Figure 2) [54,84]. In both phase II and III clinical trials, lebrikizumab was shown to reduce late asthmatic response in patients with mild asthma

via the inhibition of IL-13 induction of IgE, CLL13, and CCL17 expression [54,84]. However, these findings were not statistically significant in cases where patients were administered lebrikizumab without ICS. This finding indicates that IL-13 might not be the sole dominant driver of airway function in asthmatics [54,84].
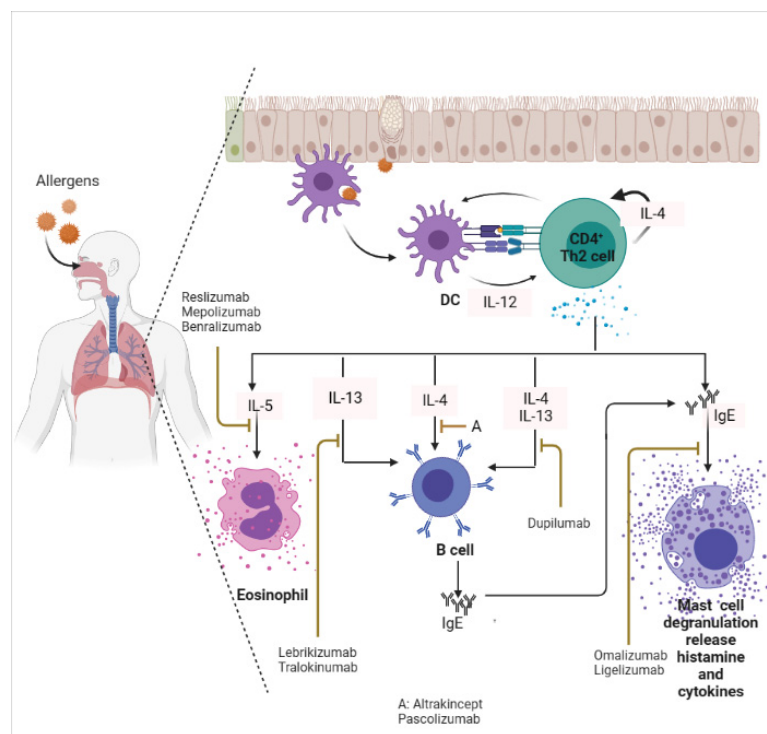

Figure 2. Targeting IgE, and Th-2 (IL-4, IL-5, IL-13) in an allergic inflammatory response. Monoclonal antibodies that target these biomarkers can alleviate symptoms associated with allergies. DC: Dendritic cells. This image was created in bio render.

Therefore, inhibiting IL-13 in patients not receiving ICS will not produce significant improvement in the patient's forced expiratory volume, which describes the amount of air forced out from the lung. Similar to lebrikizumab, tralokinumab, a human mAb that blocks IL-13, has also been shown to be safe and effective for atopic dermatitis treatment [96]. Interestingly, both lebrikizumab and tralokinumab are still used to treat and manage extreme manifestations of allergies.

Targeting IL-5 and IL-5Rα is another strategic approach toward reducing eosinophil recruitment and increasing the survival of patients with allergic reactions. Reslizumab and mepolizumab (brand name: Nucala; GSK) are currently available. They block IL-5 action by neutralizing (or masking off) serum IL-5 (Figure 2) [97,98]. Benralizumab is another biologic that binds to IL-5Ra (Figure 2) to induce antibody-dependent cell cytotoxicity (ADCC) on eosinophils and basophils [98]. To date, only benralizumab, reslizumab, and mepolizumab are approved for treating severe persistent asthma accompanied by hyper-eosinophilia [99].

Despite these advances, single-target immunotherapy fails to alleviate allergic symptoms in some patients. This has led to targeting dual cytokines that share a common signaling pathway. For example, IL-4/IL-13 share similar signaling pathways via IL-4Rα and therefore have a shared functionality along the path [54,92]. Thus, mAb that masks off serum IL-4 and IL-13 would modulate IL-4Rα signaling in allergy.

4.3. Monoclonal Antibodies Targeting Dual Inflammatory Mediators

Emerging reports on the development of mAb targeting multiple Th-2 cytokine responses during allergy episodes have achieved a milestone. For example, Kasaian et al. [100] developed a murine IL-4/IL-13 antagonist that efficiently neutralizes IL-4 and IL-13, as well as reduces serum IgE, lung eosinophilia, lung Mu5ac expression, and air-

way resistance in OVA-challenged mice. Dupilumab is the only approved mAb with the capability to inhibit the IL-4/IL-13 pathway in patients with atopic dermatitis [98], and allergic asthma [101], via IL-4Rα blockade [102]. Dupilumab neutralizes IL-4 and IL-13 cytokines (Figure 2). Dupilumab received this approval because it improves the quality of patient's life where other treatments had failed [98]. It has also been reported that dupilumab modulates eosinophils infiltration, B-cells activation, Th2cell-driven dendritic cell activation and blocks the expression of pro-inflammatory cytokines (*Il4*, *Il13*, *Il5*, *Il1α*) and chemokines in mouse asthma model [23]. Further, Jonstam et al. [103] reported that dupilumab reduces type 2 inflammatory biomarkers such as serum IgE, and eosinophil chemokine release in patients suffering from multiple allergic chronic rhino-sinusitis with nasal polyposis.

Taken together, anti-Th2 cytokines and anti-IgE mAb have specific blockade functions (Figure 2) and may be effective in managing severe allergies. The potential use and clinical trial status of these mAb and other emerging mAb for different allergic diseases had already been discussed elsewhere [104].

4.4. Setbacks and Limitations

Despite the successes in the current mAb therapy for mild-to-severe allergy, there is a range of side effects associated with mAb intake. These include serum sickness, headaches, mild gastrointestinal symptoms, itching, cardiac toxicity, and anaphylaxis which could be life-threatening [105]. For example, a side effect of omalizumab is the induction of immunogenicity and anaphylaxis [106,107]. In a clinical trial study (XTEND-CIU study), clinical symptoms worsened following the discontinuation of omalizumab in chronic idiopathic urticarial patients [108]. In a follow-up study, Nopp et al. [109] reported a rebound occurrence of mild and stable asthma three years after the withdrawal of six years of omalizumab (trade name: Xolair) treatment in patients sensitive to cat allergen. The decision of when mAb therapy should be withdrawn or discontinued is a major concern, and strict follow-up in an allergic patient is essential.

Other limitations include the inconsistencies in mAb, the cost of mAb production, including its purification, efficacy, and safety [110,111], as well as the skewed results from inconclusive clinical trials. For example, the cost of producing mAb is too high, and the annual cost per patient is exorbitant [111]. Zimmermann et al. [112] reported that dupilumab would be more cost-effective than other traditional therapeutic regimens such as emollients in managing moderate-to-severe atopic dermatitis, but this is dependent on how long the patients remained on dupilumab. The estimated annual net cost of dupilumab is about $31,000.00/300 mg dose every two weeks. This price is hugely exorbitant, and most patients cannot afford such treatment except in wealthy Western nations where the governments are solely responsible for biologics procurement. Furthermore, the conventional production of mAb is plagued by other challenges, such as protein misfolding, and inappropriate post-translational modification leading to altered immunogenicity of the biologic.

Taken together, cost-effectiveness, inherent factors, and host genetic variation play a crucial role in utilizing mAb in mild-to-severe allergy treatment. Additionally, the availability and accessibility to mAb in developing nations within the Sub-Saharan Africa continent are greatly affected by the cost of mAb procurement.

5. Antibody Gene Therapy: The Future for Antibody Therapy

The transfer of genes into host cells began in the late quarter of the 20th century using suitable vectors such as the Adeno-associated virus (AAV) vector, which were thought not to be associated with any illness in the human population [113,114]. Ever since then, it became possible to transfer mAb and/or any therapeutic proteins of interest using an AAV vector, and the use of this approach in several studies has been well-described [115,116]. The use of AVV coding antibody to reduce allergic events have been extensively studied in animal models [117–119]. For example, AAV vector coding for high-affinity anti-IgE

reduces IgE-mediated peanut histamine release and anaphylaxis score in NOD scid gamma mice [118].

However, this approach became a major concern when Nault et al. [120] reported clonal integration of AAV genomes in tumor-driver genes of hepatocellular carcinomas, suggesting that the use of AAV may induce mutagenesis. Other setbacks include the possibility of the host developing an immune response against AAV capsid in patients who had been predisposed to the wild-type AAV [113]. The involvement of Toll-like receptor (TLR)9 and MyD88-mediated pathways in CD8$^+$ T cells mediated responses to AAV-mediated gene transfer in mice had already been reported [121]. Emerging clinical trials also show similar findings of the host inducing an immune response to AAV [122,123].

These discoveries led to the birth of an alternative route of producing and delivering antibodies with fewer challenges. Studies on the delivery of mRNA-mediated antibody gene into host cells for passive immunity against pathogenic infection, vaccination against tumor growth, and allergy management are still evolving. In contrast to the manufacturing of purified monoclonal antibodies for severe allergy treatment, mRNA-directed antibody therapy can be cost-effective and safe and might only require a single local or systemic targeted shot to exert its therapeutic function [124,125].

Currently, there are only a few preclinical studies on mRNA-encoding antibodies [125]. The use of mRNA-mediated antibodies against viral infection has been extensively studied [124,126]. Thran et al. [124] reported that a single shot of mRNA-LNP encoding anti-rabies antibody provides complete protection against rabies infection even when pre-exposed and/or after several post-exposed challenges with rabies virus. The authors [124] further compared the efficacy of mRNA-LNP encoding rituximab to that of recombinant rituximab administration on tumor growth and found that the anti-tumor effect of mRNA-LNP encoding rituximab was higher than recombinant rituximab. This suggests a promising therapeutic option for the future. Further, Pardi et al. [126] also reported that a single injection of a modified mRNA encoding the light and heavy chain of an anti-HIV1 antibody, VRC01, in mice confers full protection against SF162 and JR-CSF HIV-1 isolates challenge. This suggests that the mRNA-LNP encoding VRCO1 used in their study successfully integrated into host cells and directs the synthesis of broadly neutralizing anti-HIV antibody, VRCO1, capable of conferring host-passive immunity against HIV-1 infection [126]. To date, there are limited/or no studies on the use of mRNA-encoding antibodies for protection against allergy. The current literature on mRNA encoding antibodies on other disease models has been described elsewhere [127,128]. The application of mRNA as a vaccine has also been successful in conferring protection against the dreadful SARS-CoV-2 virus.

Despite this, a few challenges may affect antibody gene therapy for allergy. These include: (1) the potential dangers associated with implanting genes into human hosts to express antibodies against host-inherent allergy biomarkers; (2) this implanted gene may induce endogenous pathogenic viruses' reactivation and mutagenesis; (3) problems related to large-scale good manufacturing practice production; (4) the half-life of the antibodies encoded by mRNA; and (5) the safety and efficacy of antibody gene therapy for allergies in humans have not translated to its use clinically.

Gene therapy in allergy is an emerging and exciting field, but with limited data. Hopefully, future studies on mRNA encoding either monospecific or bispecific antibodies against allergy biomarkers will continue to evolve and improve in the coming years.

6. Conclusions

Monoclonal antibodies targeting serum IgE and Th-2 cytokines can mitigate the outcome of extreme allergic asthma, atopic dermatitis, and rhinitis. The heterogeneity of allergy, the effectiveness and clinical safety of mAb, the cost of mAb production, and availability are major drawbacks in the therapeutic use of purified mAb. Gene therapy using an AAV vector was promising but was later discovered to have side effects, such as host immune response against AAV, which led to the discovery of mRNA-mediated

antibody gene therapy as the future for antibody therapy. The mRNA-mediated antibody is promising in the treatment of patients with extreme manifestations of allergy because it only requires a single shot and boosters later in life. Therefore, future research studies should focus on developing antibody gene therapy to treat a broad spectrum of atopic diseases/allergies.

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References

1. Kubo, M. Innate and Adaptive Type 2 Immunity in Lung Allergic Inflammation. *Immunol. Rev.* **2017**, *278*, 162–172. [CrossRef] [PubMed]
2. Galli, S.J.; Tsai, M.; Piliponsky, A.M. The Development of Allergic Inflammation. *Nature* **2008**, *454*, 445–454. [CrossRef] [PubMed]
3. Yoshimoto, T.; Tsutsui, H.; Tominaga, K.; Hoshino, K.; Okamura, H.; Akira, S.; Paul, W.E.; Nakanishi, K. IL-18, Although Antiallergic When Administered with IL-12, Stimulates IL-4 and Histamine Release by Basophils. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 13962–13966. [CrossRef] [PubMed]
4. Barnes, P.J. Pathophysiology of Allergic Inflammation. *Immunol. Rev.* **2011**, *242*, 31–50. [CrossRef] [PubMed]
5. Junttila, I.S. Tuning the Cytokine Responses: An Update on Interleukin (IL)-4 and IL-13 Receptor Complexes. *Front. Immunol.* **2018**, *9*, 888. [CrossRef]
6. Pawankar, R. Allergic Diseases and Asthma: A Global Public Health Concern and a Call to Action. *World Allergy Organ. J.* **2014**, *7*, 12. [CrossRef]
7. Pawankar, R.; Canonica, G.W.; Holgate, S.T.; Lockey, R.F. Allergic Diseases and Asthma: A Major Global Health Concern. *Curr. Opin. Allergy Clin. Immunol.* **2012**, *12*, 39–41. [CrossRef]
8. Cayrol, C.; Duval, A.; Schmitt, P.; Roga, S.; Camus, M.; Stella, A.; Burlet-Schiltz, O.; Gonzalez-de-Peredo, A.; Girard, J.-P. Environmental Allergens Induce Allergic Inflammation through Proteolytic Maturation of IL-33. *Nat. Immunol.* **2018**, *19*, 375–385. [CrossRef]
9. Mackay, I.R.; Rosen, F.S.; Kay, A. Allergy and Allergic Diseases. *N. Engl. J. Med.* **2001**, *344*, 30–37.
10. Tang, Y.-J.; Chang, H.-H.; Chiang, C.-Y.; Lai, C.-Y.; Hsu, M.-Y.; Wang, K.-R.; Han, H.-H.; Chen, L.-Y.; Lin, D.P.-C. A Murine Model of Acute Allergic Conjunctivitis Induced by Continuous Exposure to Particulate Matter 2.5. *Investig. Ophthalmol. Vis. Sci.* **2019**, *60*, 2118–2126. [CrossRef]
11. Woo, L.N.; Guo, W.Y.; Wang, X.; Young, A.; Salehi, S.; Hin, A.; Zhang, Y.; Scott, J.A.; Chow, C.W. A 4-Week Model of House Dust Mite (HDM) Induced Allergic Airways Inflammation with Airway Remodeling. *Sci. Rep.* **2018**, *8*, 6925. [CrossRef]
12. Gray, C.L.; Levin, M.E.; Zar, H.J.; Potter, P.C.; Khumalo, N.P.; Volkwyn, L.; Fenemore, B.; du Toit, G. Food Allergy in South African Children with Atopic Dermatitis. *Pediatr. Allergy Immunol.* **2014**, *25*, 572–579. [CrossRef]
13. Canonica, G.W.; Senna, G.; Mitchell, P.D.; O'Byrne, P.M.; Passalacqua, G.; Varricchi, G. Therapeutic Interventions in Severe Asthma. *World Allergy Organ. J.* **2016**, *9*, 40. [CrossRef]
14. Dvorin, E.L.; Ebell, M.H. Short-Term Systemic Corticosteroids: Appropriate Use in Primary Care. *Am. Fam. Physician* **2020**, *101*, 89–94.
15. Venekamp, R.P.; Thompson, M.J.; Hayward, G.; Heneghan, C.J.; Mar, C.B.D.; Perera, R.; Glasziou, P.P.; Rovers, M.M. Systemic Corticosteroids for Acute Sinusitis. *Cochrane Database Syst. Rev.* **2014**. [CrossRef]
16. Aasbjerg, K.; Torp-Pedersen, C.; Vaag, A.; Backer, V. Treating Allergic Rhinitis with Depot-Steroid Injections Increase Risk of Osteoporosis and Diabetes. *Respir. Med.* **2013**, *107*, 1852–1858. [CrossRef]
17. Hox, V.; Lourijsen, E.; Jordens, A.; Aasbjerg, K.; Agache, I.; Alobid, I.; Bachert, C.; Boussery, K.; Campo, P.; Fokkens, W.; et al. Benefits and Harm of Systemic Steroids for Short- and Long-Term Use in Rhinitis and Rhinosinusitis: An EAACI Position Paper. *Clin. Transl. Allergy* **2020**, *10*, 1. [CrossRef]
18. Choo, K.J.L.; Simons, E.; Sheikh, A. Glucocorticoids for the Treatment of Anaphylaxis: Cochrane Systematic Review. *Allergy* **2010**, *65*, 1205–1211. [CrossRef]

19. Ring, J.; Gutermuth, J. 100 Years of Hyposensitization: History of Allergen-Specific Immunotherapy (ASIT). *Allergy* **2011**, *66*, 713–724. [CrossRef]
20. Durham, S.R.; Nelson, H. Allergen Immunotherapy: A Centenary Celebration. *World Allergy Organ. J.* **2011**, *4*, 104–106. [CrossRef]
21. Saavedra, M.C.; Sur, S. Down Regulation of the High-Affinity IgE Receptor Associated with Successful Treatment of Chronic Idiopathic Urticaria with Omalizumab. *Clin. Mol. Allergy CMA* **2011**, *9*, 2. [CrossRef] [PubMed]
22. Bagnasco, D.; Ferrando, M.; Varricchi, G.; Passalacqua, G.; Canonica, G.W. A Critical Evaluation of Anti-IL-13 and Anti-IL-4 Strategies in Severe Asthma. *Int. Arch. Allergy Immunol.* **2016**, *170*, 122–131. [CrossRef] [PubMed]
23. Le Floch, A.; Allinne, J.; Nagashima, K.; Scott, G.; Birchard, D.; Asrat, S.; Bai, Y.; Lim, W.K.; Martin, J.; Huang, T.; et al. Dual Blockade of IL-4 and IL-13 with Dupilumab, an IL-4Rα Antibody, Is Required to Broadly Inhibit Type 2 Inflammation. *Allergy* **2020**, *75*, 1188–1204. [CrossRef] [PubMed]
24. Ghassemian, A.; Park, J.J.; Tsoulis, M.W.; Kim, H. Targeting the IL-5 Pathway in Eosinophilic Asthma: A Comparison of Mepolizumab to Benralizumab in the Reduction of Peripheral Eosinophil Counts. *Allergy Asthma Clin. Immunol.* **2021**, *17*, 3. [CrossRef]
25. Damask, C.C.; Ryan, M.W.; Casale, T.B.; Castro, M.; Franzese, C.B.; Lee, S.E.; Levy, J.M.; Lin, S.Y.; Lio, P.A.; Peters, A.T.; et al. Targeted Molecular Therapies in Allergy and Rhinology. *Otolaryngol.–Head Neck Surg. Off. J. Am. Acad. Otolaryngol.-Head Neck Surg.* **2021**, *164*, S1–S21. [CrossRef]
26. Landolina, N.; Levi-Schaffer, F. Monoclonal Antibodies: The New Magic Bullets for Allergy: IUPHAR Review 17. *Br. J. Pharmacol.* **2016**, *173*, 793–803. [CrossRef]
27. Laffer, S.; Lupinek, C.; Rauter, I.; Kneidinger, M.; Drescher, A.; Jordan, J.-H.; Krauth, M.-T.; Valent, P.; Kricek, F.; Spitzauer, S.; et al. A High-Affinity Monoclonal Anti-IgE Antibody for Depletion of IgE and IgE-Bearing Cells. *Allergy* **2008**, *63*, 695–702. [CrossRef]
28. Chen, H.Y.; Liu, F.-T.; Hou, C.M.H.; Huang, J.S.W.; Sharma, B.B.; Chang, T.W. Monoclonal Antibodies against the C(Epsilon)MX Domain of Human Membrane-Bound IgE and Their Potential Use for Targeting IgE-Expressing B Cells. *Int. Arch. Allergy Immunol.* **2002**, *128*, 315–324. [CrossRef]
29. Lupinek, C.; Derfler, K.; Lee, S.; Prikoszovich, T.; Movadat, O.; Wollmann, E.; Cornelius, C.; Weber, M.; Fröschl, R.; Selb, R.; et al. Extracorporeal IgE Immunoadsorption in Allergic Asthma: Safety and Efficacy. *EBioMedicine* **2017**, *17*, 119–133. [CrossRef]
30. Rajakulendran, M.; Tham, E.H.; Soh, J.Y.; Van Bever, H.P. Novel Strategies in Immunotherapy for Allergic Diseases. *Asia Pac. Allergy* **2018**, *8*, e14. [CrossRef]
31. He, S.; Zhang, H.; Zeng, X.; Chen, D.; Yang, P. Mast Cells and Basophils Are Essential for Allergies: Mechanisms of Allergic Inflammation and a Proposed Procedure for Diagnosis. *Acta Pharmacol. Sin.* **2013**, *34*, 1270–1283. [CrossRef]
32. Kamijo, S.; Takeda, H.; Tokura, T.; Suzuki, M.; Inui, K.; Hara, M.; Matsuda, H.; Matsuda, A.; Oboki, K.; Ohno, T. IL-33–Mediated Innate Response and Adaptive Immune Cells Contribute to Maximum Responses of Protease Allergen–Induced Allergic Airway Inflammation. *J. Immunol.* **2013**, *190*, 4489–4499. [CrossRef]
33. Thangam, E.B.; Jemima, E.A.; Singh, H.; Baig, M.S.; Khan, M.; Mathias, C.B.; Church, M.K.; Saluja, R. The Role of Histamine and Histamine Receptors in Mast Cell-Mediated Allergy and Inflammation: The Hunt for New Therapeutic Targets. *Front. Immunol.* **2018**, *9*, 1873. [CrossRef]
34. Albrecht, M.; Dittrich, A.M. Expression and Function of Histamine and Its Receptors in Atopic Dermatitis. *Mol. Cell. Pediatr.* **2015**, *2*, 16. [CrossRef]
35. Bakker, R.A.; Schoonus, S.B.; Smit, M.J.; Timmerman, H.; Leurs, R. Histamine H1-Receptor Activation of Nuclear Factor-KB: Roles for Gβγ-and Gαq/11-Subunits in Constitutive and Agonist-Mediated Signaling. *Mol. Pharmacol.* **2001**, *60*, 1133–1142. [CrossRef]
36. Wernersson, S.; Pejler, G. Mast Cell Secretory Granules: Armed for Battle. *Nat. Rev. Immunol.* **2014**, *14*, 478–494. [CrossRef]
37. Buckland, K.F.; Williams, T.J.; Conroy, D.M. Histamine Induces Cytoskeletal Changes in Human Eosinophils via the H4 Receptor. *Br. J. Pharmacol.* **2003**, *140*, 1117–1127. [CrossRef]
38. Seifert, R.; Strasser, A.; Schneider, E.H.; Neumann, D.; Dove, S.; Buschauer, A. Molecular and Cellular Analysis of Human Histamine Receptor Subtypes. *Trends Pharmacol. Sci.* **2013**, *34*, 33–58. [CrossRef]
39. Singh, M.; Jadhav, H.R. Histamine H3 Receptor Function and Ligands: Recent Developments. *Mini Rev. Med. Chem.* **2013**, *13*, 47–57. [CrossRef]
40. Lippert, U.; Artuc, M.; Grützkau, A.; Babina, M.; Guhl, S.; Haase, I.; Blaschke, V.; Zachmann, K.; Knosalla, M.; Middel, P.; et al. Human Skin Mast Cells Express H2 and H4, but Not H3 Receptors. *J. Investig. Dermatol.* **2004**, *123*, 116–123. [CrossRef]
41. Xu, J.; Zhang, X.; Qian, Q.; Wang, Y.; Dong, H.; Li, N.; Qian, Y.; Jin, W. Histamine Upregulates the Expression of Histamine Receptors and Increases the Neuroprotective Effect of Astrocytes. *J. Neuroinflammation* **2018**, *15*, 41. [CrossRef] [PubMed]
42. Theoharides, T.C.; Tsilioni, I.; Bawazeer, M. Mast Cells, Neuroinflammation and Pain in Fibromyalgia Syndrome. *Front. Cell. Neurosci.* **2019**, *13*. [CrossRef] [PubMed]
43. Dong, H.; Zhang, X.; Wang, Y.; Zhou, X.; Qian, Y.; Zhang, S. Suppression of Brain Mast Cells Degranulation Inhibits Microglial Activation and Central Nervous System Inflammation. *Mol. Neurobiol.* **2017**, *54*, 997–1007. [CrossRef] [PubMed]
44. Dinh, Q.T.; Cryer, A.; Dinh, S.; Peiser, C.; Wu, S.; Springer, J.; Hamelmann, E.; Klapp, B.F.; Heppt, W.; Fischer, A. Transcriptional Up-Regulation of Histamine Receptor-1 in Epithelial, Mucus and Inflammatory Cells in Perennial Allergic Rhinitis. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* **2005**, *35*, 1443–1448. [CrossRef]

45. Merves, J.; Chandramouleeswaran, P.M.; Benitez, A.J.; Muir, A.B.; Lee, A.J.; Lim, D.M.; Dods, K.; Mehta, I.; Ruchelli, E.D.; Nakagawa, H.; et al. Altered Esophageal Histamine Receptor Expression in Eosinophilic Esophagitis (EoE): Implications on Disease Pathogenesis. *PLoS ONE* **2015**, *10*, e0114831. [CrossRef]

46. Eckman, J.A.; Sterba, P.M.; Kelly, D.; Alexander, V.; Liu, M.C.; Bochner, B.S.; Macglashan, D.W.; Saini, S.S. Effects of Omalizumab on Basophil and Mast Cell Responses Using an Intranasal Cat Allergen Challenge. *J. Allergy Clin. Immunol.* **2010**, *125*, 889–895.e7. [CrossRef]

47. Noga, O.; Hanf, G.; Kunkel, G.; Kleine-Tebbe, J. Basophil Histamine Release Decreases during Omalizumab Therapy in Allergic Asthmatics. *Int. Arch. Allergy Immunol.* **2008**, *146*, 66–70. [CrossRef]

48. MacGlashan, D.; Saini, S.S. Omalizumab Increases the Intrinsic Sensitivity of Human Basophils to IgE-Mediated Stimulation. *J. Allergy Clin. Immunol.* **2013**, *132*, 906–911.e1-4. [CrossRef]

49. Eckl-Dorna, J.; Fröschl, R.; Lupinek, C.; Kiss, R.; Gattinger, P.; Marth, K.; Campana, R.; Mittermann, I.; Blatt, K.; Valent, P.; et al. Intranasal Administration of Allergen Increases Specific IgE Whereas Intranasal Omalizumab Does Not Increase Serum IgE Levels—A Pilot Study. *Allergy* **2018**, *73*, 1003–1012. [CrossRef]

50. Kowal, K.; Bielecki, P.; DuBuske, I.V.; DuBuske, L.M. In Vitro Impact of Anti-Immunoglobulin E Monoclonal Antibodies, Including Omalizumab on Whole Blood Basophil Histamine Release: Assessment of Direct Induction of Basophil Histamine Release and Evaluation of Modulation of Allergen-Induced Basophil Histamine Release. *Allergy Asthma Proc.* **2017**, *38*. [CrossRef]

51. Wu, Y.-F.; Su, M.-W.; Chiang, B.-L.; Yang, Y.-H.; Tsai, C.-H.; Lee, Y.L. A Simple Prediction Tool for Inhaled Corticosteroid Response in Asthmatic Children. *BMC Pulm. Med.* **2017**, *17*, 1–6. [CrossRef]

52. Rhyou, H.-I.; Nam, Y.-H. Predictive Factors of Response to Inhaled Corticosteroids in Newly Diagnosed Asthma: A Real-World Observational Study. *Ann. Allergy. Asthma. Immunol.* **2020**, *125*, 177–181. [CrossRef]

53. Keskin, O.; Farzan, N.; Birben, E.; Akel, H.; Karaaslan, C.; Maitland-van der Zee, A.H.; Wechsler, M.E.; Vijverberg, S.J.; Kalayci, O. Genetic Associations of the Response to Inhaled Corticosteroids in Asthma: A Systematic Review. *Clin. Transl. Allergy* **2019**, *9*, 2. [CrossRef]

54. Kau, A.L.; Korenblat, P.E. Anti-Interleukin 4 and 13 for Asthma Treatment in the Era of Endotypes. *Curr. Opin. Allergy Clin. Immunol.* **2014**, *14*, 570. [CrossRef]

55. Nabe, T. Interleukin (IL)-33: New Therapeutic Target for Atopic Diseases. *J. Pharmacol. Sci.* **2014**, *126*, 85–91. [CrossRef]

56. Volmer, T.; Effenberger, T.; Trautner, C.; Buhl, R. Consequences of Long-Term Oral Corticosteroid Therapy and Its Side-Effects in Severe Asthma in Adults: A Focused Review of the Impact Data in the Literature. *Eur. Respir. J.* **2018**, *52*, 1800703. [CrossRef]

57. Kaur, S.; Singh, V. Asthma and Medicines–Long-Term Side-Effects, Monitoring and Dose Titration. *Indian, J. Pediatr.* **2018**, *85*, 748–756. [CrossRef]

58. Reddel, H.K.; FitzGerald, J.M.; Bateman, E.D.; Bacharier, L.B.; Becker, A.; Brusselle, G.; Buhl, R.; Cruz, A.A.; Fleming, L.; Inoue, H. GINA 2019: A Fundamental Change in Asthma Management: Treatment of Asthma with Short-Acting Bronchodilators Alone Is No Longer Recommended for Adults and Adolescents. *Eur. Respir. J.* **2019**, *53*, 1901046. [CrossRef]

59. Eff, A.R.Y. Incidence of Hypertension in Asthma Patients Who Treated with Beta-2 Agonists Bronchodilators. *Int J Pharm Pharm Sci* **2017**, *9*, 181–184. [CrossRef]

60. Cheng, S.-L.; Wang, H.H.; Lin, C.-H. Effect of Allergic Phenotype on Treatment Response to Inhaled Bronchodilators with or without Inhaled Corticosteroids in Patients with COPD. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2017**, *12*, 2231. [CrossRef]

61. Amegadzie, J.E.; Gorgui, J.; Acheampong, L.; Gamble, J.-M.; Farrell, J.; Gao, Z. Comparative Safety and Effectiveness of Inhaled Bronchodilators and Corticosteroids for Treating Asthma–COPD Overlap: A Systematic Review and Meta-Analysis. *J. Asthma* **2021**, *58*, 344–359. [CrossRef] [PubMed]

62. Calabrese, C.; Corcione, N.; Rea, G.; Stefanelli, F.; Meoli, I.; Vatrella, A. Impact of Long-Term Treatment with Inhaled Corticosteroids and Bronchodilators on Lung Function in a Patient with Post-Infectious Bronchiolitis Obliterans. *J. Bras. Pneumol.* **2016**, *42*, 228–231. [CrossRef] [PubMed]

63. Onay, Z.R.; Gursoy, T.R.; Aslan, A.T.; Eyuboglu, T.S.; Kibar, B.S.; Pekcan, S.; Hangul, M.; Kose, M.; Budakoglu, I.İ.; Gokturk, B. Misdiagnosis of Asthma May Delay the Post Infectious Bronchiolitis Obliterans Diagnosis. *Eur. Respir. J.* **2019**, *54*, PA1015.

64. Buhl, R.; FitzGerald, J.M.; Busse, W.W. Tiotropium Add-on to Inhaled Corticosteroids versus Addition of Long-Acting B2-Agonists for Adults with Asthma. *Respir. Med.* **2018**, *143*, 82–90. [CrossRef]

65. Kupczyk, M.; Wenzel, S. US and European Severe Asthma Cohorts: What Can They Teach Us about Severe Asthma? *J. Intern. Med.* **2012**, *272*, 121–132. [CrossRef]

66. Pike, K.C.; Levy, M.L.; Moreiras, J.; Fleming, L. Managing Problematic Severe Asthma: Beyond the Guidelines. *Arch. Dis. Child.* **2018**, *103*, 392–397. [CrossRef]

67. Busse, W.; Corren, J.; Lanier, B.Q.; McAlary, M.; Fowler-Taylor, A.; Cioppa, G.D.; van As, A.; Gupta, N. Omalizumab, Anti-IgE Recombinant Humanized Monoclonal Antibody, for the Treatment of Severe Allergic Asthma. *J. Allergy Clin. Immunol.* **2001**, *108*, 184–190. [CrossRef]

68. Deleanu, D.; Nedelea, I. Biological Therapies for Atopic Dermatitis: An Update. *Exp. Ther. Med.* **2019**, *17*, 1061–1067. [CrossRef]

69. Holgate, S.; Bousquet, J.; Wenzel, S.; Fox, H.; Liu, J.; Castellsague, J. Efficacy of Omalizumab, an Anti-Immunoglobulin E Antibody, in Patients with Allergic Asthma at High Risk of Serious Asthma-Related Morbidity and Mortality. *Curr. Med. Res. Opin.* **2001**, *17*, 233–240. [CrossRef]

70. Fahy, J.V.; Fleming, H.E.; Wong, H.H.; Liu, J.T.; Su, J.Q.; Reimann, J.; Fick, R.B., Jr.; Boushey, H.A. The Effect of an Anti-IgE Monoclonal Antibody on the Early- and Late-Phase Responses to Allergen Inhalation in Asthmatic Subjects. *Am. J. Respir. Crit. Care Med.* **1997**, *155*. [CrossRef]

71. Trischler, J.; Lieb, A.; Arnold, M.; Schulze, J.; Rosewich, M.; Schubert, R.; Bottoli, I.; Zielen, S. Omalizumab Effectively Protects against Early and Late Allergic Responses in Asthma after 4 Weeks. *Allergy* **2017**, *72*, 1912–1915. [CrossRef]

72. Pelaia, G.; Canonica, G.W.; Matucci, A.; Paolini, R.; Triggiani, M.; Paggiaro, P. Targeted Therapy in Severe Asthma Today: Focus on Immunoglobulin, E. *Drug Des. Devel. Ther.* **2017**, *11*, 1979. [CrossRef]

73. Esquivel, A.; Busse, W.W.; Calatroni, A.; Togias, A.G.; Grindle, K.G.; Bochkov, Y.A.; Gruchalla, R.S.; Kattan, M.; Kercsmar, C.M.; Khurana Hershey, G. Effects of Omalizumab on Rhinovirus Infections, Illnesses, and Exacerbations of Asthma. *Am. J. Respir. Crit. Care Med.* **2017**, *196*, 985–992. [CrossRef]

74. Acer, E.; Kaya Erdogan, H.; Yüksel Çanakçı, N.; Saracoglu, Z.N. The Effect of Omalizumab on Hematological and Inflammatory Parameters in Patients with Chronic Spontaneous Urticaria. *Cutan. Ocul. Toxicol.* **2019**, *38*, 5–8. [CrossRef]

75. Masieri, S.; Cavaliere, C.; Begvarfaj, E.; Rosati, D.; Minni, A. Effects of Omalizumab Therapy on Allergic Rhinitis: A Pilot Study. *Eur. Rev. Med. Pharmacol. Sci.* **2016**, *20*, 5249–5255.

76. Ricciardi, L.; Papia, F.; Liotta, M.; Cicero, F.; Isola, S.; Tartarisco, G.; Furci, F.; Gangemi, S. Omalizumab in Middle-Aged or Older Patients with Severe Allergic Asthma-COPD Overlap. *Adv. Dermatol. Allergol. Dermatol. Alergol.* **2022**, *39*, 88–93. [CrossRef]

77. Heck, S.; Nguyen, J.; Le, D.-D.; Bals, R.; Dinh, Q.T. Pharmacological Therapy of Bronchial Asthma: The Role of Biologicals. *Int. Arch. Allergy Immunol.* **2015**, *168*, 241–252. [CrossRef]

78. Maurer, M.; Giménez-Arnau, A.M.; Sussman, G.; Metz, M.; Baker, D.R.; Bauer, A.; Bernstein, J.A.; Brehler, R.; Chu, C.-Y.; Chung, W.-H. Ligelizumab for Chronic Spontaneous Urticaria. *N. Engl. J. Med.* **2019**, *381*, 1321–1332. [CrossRef]

79. Hu, J.; Chen, J.; Ye, L.; Cai, Z.; Sun, J.; Ji, K. Anti-IgE Therapy for IgE-Mediated Allergic Diseases: From Neutralizing IgE Antibodies to Eliminating IgE+ B Cells. *Clin. Transl. Allergy* **2018**, *8*, 27. [CrossRef]

80. Wedi, B. Ligelizumab for the Treatment of Chronic Spontaneous Urticaria. *Expert Opin. Biol. Ther.* **2020**, *20*, 853–861. [CrossRef]

81. Wedi, B.; Traidl, S. Anti-IgE for the Treatment of Chronic Urticaria. *ImmunoTargets Ther.* **2021**, *10*, 27–45. [CrossRef] [PubMed]

82. Cohen, E.S.; Dobson, C.L.; Käck, H.; Wang, B.; Sims, D.A.; Lloyd, C.O.; England, E.; Rees, D.G.; Guo, H.; Karagiannis, S.N. A Novel IgE-Neutralizing Antibody for the Treatment of Severe Uncontrolled Asthma. *mAbs* **2014**, *6*, 756–764. [CrossRef] [PubMed]

83. Sheldon, E.; Schwickart, M.; Li, J.; Kim, K.; Crouch, S.; Parveen, S.; Kell, C.; Birrell, C. Pharmacokinetics, Pharmacodynamics, and Safety of MEDI4212, an Anti-IgE Monoclonal Antibody, in Subjects with Atopy: A Phase I Study. *Adv. Ther.* **2016**, *33*, 225–251. [CrossRef] [PubMed]

84. Scheerens, H.; Arron, J.R.; Zheng, Y.; Putnam, W.S.; Erickson, R.W.; Choy, D.F.; Harris, J.M.; Lee, J.; Jarjour, N.N.; Matthews, J.G. The Effects of Lebrikizumab in Patients with Mild Asthma Following Whole Lung Allergen Challenge. *Clin. Exp. Allergy* **2014**, *44*, 38–46. [CrossRef] [PubMed]

85. Harris, J.M.; Cabanski, C.R.; Scheerens, H.; Samineni, D.; Bradley, M.S.; Cochran, C.; Staubach, P.; Metz, M.; Sussman, G.; Maurer, M. A Randomized Trial of Quilizumab in Adults with Refractory Chronic Spontaneous Urticaria. *J. Allergy Clin. Immunol.* **2016**, *138*, 1730–1732. [CrossRef]

86. Harris, J.M.; Maciuca, R.; Bradley, M.S.; Cabanski, C.R.; Scheerens, H.; Lim, J.; Cai, F.; Kishnani, M.; Liao, X.C.; Samineni, D. A Randomized Trial of the Efficacy and Safety of Quilizumab in Adults with Inadequately Controlled Allergic Asthma. *Respir. Res.* **2016**, *17*, 29. [CrossRef]

87. Kirak, O.; Riethmüller, G. A Novel, Nonanaphylactogenic, Bispecific IgE-CD3 Antibody Eliminates IgE+ B Cells. *J. Allergy Clin. Immunol.* **2015**, *136*, 800–802. [CrossRef]

88. Chu, S.Y.; Horton, H.M.; Pong, E.; Leung, I.W.; Chen, H.; Nguyen, D.-H.; Bautista, C.; Muchhal, U.S.; Bernett, M.J.; Moore, G.L. Reduction of Total IgE by Targeted Coengagement of IgE B-Cell Receptor and FcγRIIb with Fc-Engineered Antibody. *J. Allergy Clin. Immunol.* **2012**, *129*, 1102–1115. [CrossRef]

89. Saggini, A.; Maccauro, G.; Tripodi, D.; De Lutiis, M.A.; Conti, F.; Felaco, P.; Fulcheri, M.; Galzio, R.; Caraffa, A.; Antinolfi, P. *Allergic Inflammation: Role of Cytokines with Special Emphasis on IL-4*; SAGE Publications Sage UK: London, UK, 2011.

90. Corry, D.B.; Folkesson, H.G.; Warnock, M.L.; Erle, D.J.; Matthay, M.A.; Wiener-Kronish, J.P.; Locksley, R.M. Interleukin 4, but Not Interleukin 5 or Eosinophils, Is Required in a Murine Model of Acute Airway Hyperreactivity. *J. Exp. Med.* **1996**, *183*, 109–117. [CrossRef]

91. Coyle, A.J.; Le Gros, G.; Bertrand, C.; Tsuyuki, S.; Heusser, C.H.; Kopf, M.; Anderson, G.P. Interleukin-4 Is Required for the Induction of Lung Th2 Mucosal Immunity. *Am. J. Respir. Cell Mol. Biol.* **1995**, *13*, 54–59. [CrossRef]

92. Akdis, C.A. Therapies for Allergic Inflammation: Refining Strategies to Induce Tolerance. *Nat. Med.* **2012**, *18*, 736–749. [CrossRef]

93. Vladich, F.D.; Brazille, S.M.; Stern, D.; Peck, M.L.; Ghittoni, R.; Vercelli, D. IL-13 R130Q, a Common Variant Associated with Allergy and Asthma, Enhances Effector Mechanisms Essential for Human Allergic Inflammation. *J. Clin. Investig.* **2005**, *115*, 747–754. [CrossRef]

94. Walter, D.M.; McIntire, J.J.; Berry, G.; McKenzie, A.N.; Donaldson, D.D.; DeKruyff, R.H.; Umetsu, D.T. Critical Role for IL-13 in the Development of Allergen-Induced Airway Hyperreactivity. *J. Immunol.* **2001**, *167*, 4668–4675. [CrossRef]

95. Wang, I.-M.; Lin, H.; Goldman, S.J.; Kobayashi, M. STAT-1 Is Activated by IL-4 and IL-13 in Multiple Cell Types. *Mol. Immunol.* **2004**, *41*, 873–884. [CrossRef]

96. Wollenberg, A.; Howell, M.D.; Guttman-Yassky, E.; Silverberg, J.I.; Kell, C.; Ranade, K.; Moate, R.; van der Merwe, R. Treatment of Atopic Dermatitis with Tralokinumab, an Anti–IL-13 MAb. *J. Allergy Clin. Immunol.* **2019**, *143*, 135–141. [CrossRef]

97. Bagnasco, D.; Caminati, M.; Ferrando, M.; Aloè, T.; Testino, E.; Canonica, G.W.; Passalacqua, G. Anti-IL-5 and IL-5Ra: Efficacy and Safety of New Therapeutic Strategies in Severe Uncontrolled Asthma. *BioMed Res. Int.* **2018**, *2018*, 5698212. [CrossRef]

98. Lawrence, M.G.; Steinke, J.W.; Borish, L. Cytokine-Targeting Biologics for Allergic Diseases. *Ann. Allergy. Asthma. Immunol.* **2018**, *120*, 376–381. [CrossRef]

99. Wegmann, M. Targeting Cytokines in Asthma Therapy: Could IL-37 Be a Solution? *Expert Rev. Respir. Med.* **2017**, *11*, 675–677. [CrossRef]

100. Kasaian, M.T.; Marquette, K.; Fish, S.; DeClercq, C.; Agostinelli, R.; Cook, T.A.; Brennan, A.; Lee, J.; Fitz, L.; Brooks, J. An IL-4/IL-13 Dual Antagonist Reduces Lung Inflammation, Airway Hyperresponsiveness, and IgE Production in Mice. *Am. J. Respir. Cell Mol. Biol.* **2013**, *49*, 37–46. [CrossRef]

101. Corren, J.; Castro, M.; Chanez, P.; Fabbri, L.; Joish, V.N.; Amin, N.; Graham, N.M.H.; Mastey, V.; Abbé, A.; Taniou, C.; et al. Dupilumab Improves Symptoms, Quality of Life, and Productivity in Uncontrolled Persistent Asthma. *Ann. Allergy. Asthma. Immunol.* **2019**, *122*, 41–49.e2. [CrossRef]

102. Olin, J.T.; Wechsler, M.E. Asthma: Pathogenesis and Novel Drugs for Treatment. *BMJ* **2014**, *349*, g5517. [CrossRef] [PubMed]

103. Jonstam, K.; Swanson, B.N.; Mannent, L.P.; Cardell, L.-O.; Tian, N.; Wang, Y.; Zhang, D.; Fan, C.; Holtappels, G.; Hamilton, J.D.; et al. Dupilumab Reduces Local Type 2 Pro-Inflammatory Biomarkers in Chronic Rhinosinusitis with Nasal Polyposis. *Allergy* **2019**, *74*, 743–752. [CrossRef] [PubMed]

104. Chen, Y.; Wang, W.; Yuan, H.; Li, Y.; Lv, Z.; Cui, Y.; Liu, J.; Ying, S. Current State of Monoclonal Antibody Therapy for Allergic Diseases. *Engineering* **2021**, *7*, 1552–1556. [CrossRef]

105. Baldo, B.A. Adverse Events to Monoclonal Antibodies Used for Cancer Therapy. *Oncoimmunology* **2013**, *2*, e26333. [CrossRef]

106. Cox, L.S. How Safe Are the Biologicals in Treating Asthma and Rhinitis? *Allergy Asthma Clin. Immunol. Off. J. Can. Soc. Allergy Clin. Immunol.* **2009**, *5*, 4. [CrossRef]

107. Hansel, T.T.; Kropshofer, H.; Singer, T.; Mitchell, J.A.; George, A.J.T. The Safety and Side Effects of Monoclonal Antibodies. *Nat. Rev. Drug Discov.* **2010**, *9*, 325–338. [CrossRef]

108. Kaplan, A.P.; Murphy, T.R.; Holden, M.; Iqbal, A.; Yoo, B.; Bernstein, J.A. Impact of Omalizumab Treatment Withdrawal After 24 and 48 Weeks in Patients with Chronic Idiopathic Urticaria: Results From the XTEND-CIU Study. *J. Allergy Clin. Immunol.* **2019**, *143*, AB209. [CrossRef]

109. Nopp, A.; Johansson, S.G.O.; Adédoyin, J.; Ankerst, J.; Palmqvist, M.; Oman, H. After 6 Years with Xolair; a 3-Year Withdrawal Follow-Up. *Allergy* **2010**, *65*, 56–60. [CrossRef]

110. Wu, A.C.; Fuhlbrigge, A.L.; Robayo, M.A.; Shaker, M. Cost-Effectiveness of Biologics for Allergic Diseases. *J. Allergy Clin. Immunol. Pract.* **2021**, *9*, 1107–1117. [CrossRef]

111. Samaranayake, H.; Wirth, T.; Schenkwein, D.; Räty, J.K.; Ylä-Herttuala, S. Challenges in Monoclonal Antibody-Based Therapies. *Ann. Med.* **2009**, *41*, 322–331. [CrossRef]

112. Zimmermann, M.; Rind, D.; Chapman, R.; Kumar, V.; Kahn, S.; Carlson, J. Economic Evaluation of Dupilumab for Moderate-to-Severe Atopic Dermatitis: A Cost-Utility Analysis. *J. Drugs Dermatol. JDD* **2018**, *17*, 750–756.

113. Mingozzi, F.; High, K.A. Immune Responses to AAV Vectors: Overcoming Barriers to Successful Gene Therapy. *Blood* **2013**, *122*, 23–36. [CrossRef]

114. Wang, D.; Tai, P.W.L.; Gao, G. Adeno-Associated Virus Vector as a Platform for Gene Therapy Delivery. *Nat. Rev. Drug Discov.* **2019**, *18*, 358–378. [CrossRef]

115. Naso, M.F.; Tomkowicz, B.; Perry, W.L.; Strohl, W.R. Adeno-Associated Virus (AAV) as a Vector for Gene Therapy. *Biodrugs* **2017**, *31*, 317–334. [CrossRef]

116. Xu, X.; Chen, W.; Zhu, W.; Chen, J.; Ma, B.; Ding, J.; Wang, Z.; Li, Y.; Wang, Y.; Zhang, X. Adeno-associated Virus (AAV)-Based Gene Therapy for Glioblastoma. *Cancer Cell Int.* **2021**, *21*, 76. [CrossRef]

117. Camilleri, A.E.; Nag, S.; Russo, A.R.; Stiles, K.M.; Crystal, R.G.; Pagovich, O.E. Gene Therapy for a Murine Model of Eosinophilic Esophagitis. *Allergy* **2021**, *76*, 2740–2752. [CrossRef]

118. Pagovich, O.E.; Wang, B.; Chiuchiolo, M.J.; Kaminsky, S.M.; Sondhi, D.; Jose, C.L.; Price, C.C.; Brooks, S.F.; Mezey, J.G.; Crystal, R.G. Anti-HIgE Gene Therapy of Peanut-Induced Anaphylaxis in a Humanized Murine Model of Peanut Allergy. *J. Allergy Clin. Immunol.* **2016**, *138*, 1652–1662.e7. [CrossRef]

119. Zavorotinskaya, T.; Tomkinson, A.; Murphy, J.E. Treatment of Experimental Asthma by Long-Term Gene Therapy Directed against IL-4 and IL-13. *Mol. Ther. J. Am. Soc. Gene Ther.* **2003**, *7*, 155–162. [CrossRef]

120. Nault, J.-C.; Datta, S.; Imbeaud, S.; Franconi, A.; Mallet, M.; Couchy, G.; Letouzé, E.; Pilati, C.; Verret, B.; Blanc, J.-F.; et al. Recurrent AAV2-Related Insertional Mutagenesis in Human Hepatocellular Carcinomas. *Nat. Genet.* **2015**, *47*, 1187–1193. [CrossRef]

121. Rogers, G.L.; Suzuki, M.; Zolotukhin, I.; Markusic, D.M.; Morel, L.M.; Lee, B.; Ertl, H.C.J.; Herzog, R.W. Unique Roles of TLR9- and MyD88-Dependent and -Independent Pathways in Adaptive Immune Responses to AAV-Mediated Gene Transfer. *J. Innate Immun.* **2015**, *7*, 302–314. [CrossRef]

122. Manno, C.S.; Pierce, G.F.; Arruda, V.R.; Glader, B.; Ragni, M.; Rasko, J.J.; Rasko, J.; Ozelo, M.C.; Hoots, K.; Blatt, P.; et al. Successful Transduction of Liver in Hemophilia by AAV-Factor IX and Limitations Imposed by the Host Immune Response. *Nat. Med.* **2006**, *12*, 342–347. [CrossRef] [PubMed]

123. Nidetz, N.F.; McGee, M.C.; Tse, L.V.; Li, C.; Cong, L.; Li, Y.; Huang, W. Adeno-Associated Viral Vector-Mediated Immune Responses: Understanding Barriers to Gene Delivery. *Pharmacol. Ther.* **2020**, *207*, 107453. [CrossRef] [PubMed]

124. Thran, M.; Mukherjee, J.; Pönisch, M.; Fiedler, K.; Thess, A.; Mui, B.L.; Hope, M.J.; Tam, Y.K.; Horscroft, N.; Heidenreich, R.; et al. MRNA Mediates Passive Vaccination against Infectious Agents, Toxins, and Tumors. *EMBO Mol. Med.* **2017**, *9*, 1434–1447. [CrossRef] [PubMed]

125. Van Hoecke, L.; Roose, K. How MRNA Therapeutics Are Entering the Monoclonal Antibody Field. *J. Transl. Med.* **2019**, *17*, 54. [CrossRef]

126. Pardi, N.; Secreto, A.J.; Shan, X.; Debonera, F.; Glover, J.; Yi, Y.; Muramatsu, H.; Ni, H.; Mui, B.L.; Tam, Y.K.; et al. Administration of Nucleoside-Modified MRNA Encoding Broadly Neutralizing Antibody Protects Humanized Mice from HIV-1 Challenge. *Nat. Commun.* **2017**, *8*, 14630. [CrossRef]

127. Deal, C.E.; Carfi, A.; Plante, O.J. Advancements in MRNA Encoded Antibodies for Passive Immunotherapy. *Vaccines* **2021**, *9*, 108. [CrossRef]

128. Schlake, T.; Thran, M.; Fiedler, K.; Heidenreich, R.; Petsch, B.; Fotin-Mleczek, M. MRNA: A Novel Avenue to Antibody Therapy? *Mol. Ther.* **2019**, *27*, 773–784. [CrossRef]