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

Henry C. Ezechukwu 1,2,*, Oyelola A. Adegboye 3,4,†, Wahab O. Okunowo 2,5 and Theophilus I. Emeto 3,4,*,†

1 School of Human Sciences, The University of Western Australia, Perth, WA 6009, Australia
2 Department of Medical Biochemistry, Eko University of Medicine and Health Sciences, Ijanikin, LOS 102004, Nigeria
3 World Health Organization Collaborating Center for Vector-Borne and Neglected Tropical Diseases, College of Public Health, Medical and Veterinary Sciences, James Cook University, Townsville, QLD 4811, Australia
4 Australian Institute of Tropical Health and Medicine, James Cook University, Townsville, QLD 4811, Australia
5 Department of Biochemistry, College of Medicine, University of Lagos, Ii-Araba, LOS 101014, Nigeria
* Correspondence: henry.ezechukwu@research.uwa.edu.au (H.C.E.); theophilus.emeto@jcu.edu.au (T.I.E.)
† Shared senior authors: Oyelola A. Adegboye and Theophilus I. Emeto.

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
(FccRI) 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 (MO)), 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 FccRI 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.](image-url)
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 multifunctional 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>
<thead>
<tr>
<th>Receptors</th>
<th>Effects</th>
<th>Clinical Manifestation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>Stimulates nociceptive nerve fiber; bronchoconstriction; increase mucus secretion</td>
<td>Itching; urticaria; allergic rhinoconjunctivitis; allergic asthma</td>
<td>[33,35]</td>
</tr>
<tr>
<td>H2</td>
<td>Gastric acid secretion; arrhythmia; increase intracellular cAMP</td>
<td>Peptic ulcer anaphylaxis; negative feedback on mast cell activation</td>
<td>[33,38]</td>
</tr>
<tr>
<td>H3</td>
<td>Inflammation on the neurons</td>
<td>Neuro-inflammatory diseases such as epilepsy; CNS disorder</td>
<td>[33,39]</td>
</tr>
<tr>
<td>H4</td>
<td>Induce eosinophil shape change; activates eosinophils</td>
<td>Lung asthma</td>
<td>[37]</td>
</tr>
</tbody>
</table>

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
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 FcεRI 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-FccRI-mediated pathway to neutralizing serum IgE to inhibit the FcεRI-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 I 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.

<table>
<thead>
<tr>
<th>Candidates</th>
<th>Type, Origin, and Target</th>
<th>Major Findings</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDI4212</td>
<td>Human IgG1λ mAb, an anti-IgE</td>
<td>Reduces both serum IgE and FccRI expression on dendritic cells and basophil in patients with atopy; Prevent IgE to FccRII interaction in asthma.</td>
<td>[82,83]</td>
</tr>
<tr>
<td>Quilizumab</td>
<td>Humanized IgG1 mAb, an anti-IgE+ B cell</td>
<td>Reduces serum IgE in patients with asthma, allergic rhinitis, and chronic spontaneous urticaria; No significant impact on lung function; Not better than omalizumab.</td>
<td>[84–86]</td>
</tr>
<tr>
<td>Bsc-IgE/CD3</td>
<td>Anti-IgE+ B cells</td>
<td>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.</td>
<td>[79,87]</td>
</tr>
<tr>
<td>XmAb7195</td>
<td>Humanized mAb; FcγRIIB-enhanced Fc</td>
<td>Inhibits plasma cell differentiation; Reduces total human IgE 40-fold relative to omalizumab.</td>
<td>[88]</td>
</tr>
</tbody>
</table>

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].

![Image of immune system](image_url)

**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-5Rx 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-4R 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-4Rx 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 regimes 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 VRC01 used in their study successfully integrated into host cells and directs the synthesis of broadly neutralizing anti-HIV antibody, VRC01, 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.


**Funding:** The authors received no funding.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** We are grateful to George K Ezechukwu for assisting in illustrating Figure 1 used in this review.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

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]


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]


81. Wedi, B.; Traidl, S. Anti-IL-4 for the Treatment of Chronic Urticaria. *ImmunooTargets Ther.* 2021, 10, 27–45. [CrossRef] [PubMed]


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


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


**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.