Allergen Immunotherapy

Subjects: Allergy

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Allergen immunotherapy (AIT) is the sole disease-modifying treatment for allergic rhinitis; it prevents rhinitis from progressing to asthma and lowers medication use. AIT against mites, insect venom, and certain kinds of pollen is effective. The mechanism of action of AIT is based on inducing immunological tolerance characterized by increased IL-10, TGF-β, and IgG4 levels and Treg cell counts. However, AIT requires prolonged schemes of administration and is sometimes associated with adverse reactions. Over the last decade, novel forms of AIT have been developed, focused on better allergen identification, structural modifications to preserve epitopes for B or T cells, post-traductional alteration through chemical processes, and the addition of adjuvants. These modified allergens induce clinical-immunological effects similar to those mentioned above, increasing the tolerance to other related allergens but with fewer side effects. Clinical studies have shown that molecular AIT is efficient in treating grass and birch allergies.

Keywords: hypoallergenic immunotherapy ; allergen immunotherapy ; recombinants ; adjuvants

1. Introduction

Allergen immunotherapy (AIT) originated in the early twentieth century [1]. In 1954, the first controlled clinical trial was developed, and AIT improved the symptoms in the group receiving the pollen extract compared with the control group [2]. AIT is recommended for the treatment of allergic rhinitis (AR) and asthma by many medical organizations, based on controlled clinical trials and meta-analyses [3][4][5]. Many of these beneficial effects are due to AIT being the unique therapy able to induce allergen long-term tolerance after discontinuation. The administration of AIT for three years produces persistent clinical-immunological changes for at least two years [6][7].

However, the conventional schemes used in AIT are prolonged. Subcutaneous immunotherapy (SCIT) comprises a build-up phase (in which the allergen concentration increases gradually) and a maintenance phase (in which the projected dose is applied), which must be administered for at least three years (Figure 1a). Additionally, the development of adverse reactions is associated with first dosages, leading to treatment abandonment [8][9]. Likewise, AIT has not shown clinical benefits with all allergens.

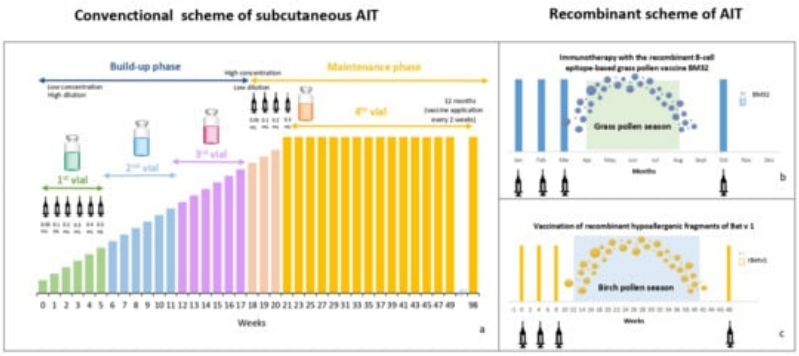

Figure 1. Schemes of allergen immunotherapy. (**a**) Classical subcutaneous immunotherapy scheme consisting of build-up and maintenance phase. (**b**) Recombinant scheme with grass (**c**) Recombinant scheme with birch allergen.

New methods and novel molecules have been developed to improve AIT for the last 30 years. Currently, allergoids, recombinant allergens based on specific epitopes or joined to immunological adjuvants—also known as hypoallergenic immunotherapy—even applied by new routes, constitute new variants of this therapeutic. The present review describes the best advances reported concerning each of the AIT areas.

2. Efficacy of Allergen Immunotherapy

The benefits of AIT are not the same for each allergen responsible for sensitization and the different allergic diseases. For example, SCIT or SLIT is strongly recommended for seasonal AR induced by pollen, while SLIT is recommended for HDM in mild asthma but not for all allergens [10][11][12][13], and there is limited evidence for allergic respiratory disease caused by fungal spores [14][15]. The meta-analyses are considered the highest level of evidence, the SCIT meta-analyses for seasonal AR showed an improvement in symptoms (SMD, −0.73; $p < 0.0001$; $I^2 = 63.21\%$) and medication scores (SMD, −0.57; $p < 0.0001$; $I^2 = 64.02\%$). Interestingly, this evidence is mainly derived from articles on AIT for grass pollen. However, SCIT against HDM also showed similar results (For the symptoms: SMD, −2.17; $p = 0.001$; $I^2 = 96\%$%/For the medication score: (SMD, −1.17; $p = 0.03$; $I^2 = 86\%$). Concerning SLIT, the most up-to-date version of the Cochrane review reports described a reduction in the outcomes mentioned above, primarily for grasses (For the symptoms: SMD, −0.49; $p < 0.00001$; $I^2 = 81\%$/For the medication score: SMD, −0.32; $p = 0.00035$; $I^2 = 50\%$), and other robust reports concluded the same for HDM (For the symptoms: SMD, −0.95; $p < 0.00001$; $I^2 = 92\%$/For the medication score: SMD, −1.88; $p < 0.00001$; $I^2 = 95\%$) [12][16]. Some reports have found similar levels of efficacy using both routes, even comparing different forms of SLIT (drops and tablets) [17][18]. In relation to SLIT and asthma, a recent meta-analysis could not draw clinically useful conclusions due to the non-validated scores and limited evidence for relevant outcomes such as asthma exacerbations [11]. For other allergens, there is scarce high-quality information. However, evidence supports a clinical improvement in SCIT and SLIT for epitheliums in clinical outcomes such as ocular, nasal, or asthma symptoms, peak expiratory flow rate, and medication scores [19].

Notably, some meta-analyses, particularly those using SLIT, are controversial because of the heterogeneity of the few included trials, different presentations, and doses of the extracts used, and/or of the use of non-validated scales of symptoms and medication scores, limiting the provision of clear clinical conclusions. Additionally, heterogeneity exists in the different clinical trials included in the meta-analyses. Throughout history, an attempt has been made to improve the effectiveness criteria and propose a consensus on the duration of SCIT and SLIT [20]. Furthermore, one of the most interesting properties of AIT is that it provides benefits for many years after the therapy schemes have been concluded. Patients have a reduction in medication and the percentage of eosinophils, as well as an increase in the threshold to the response to methacholine four years after finishing the AIT, according to prospective studies evaluating SLIT regimens administered for at least three years, and even these effects are more prolonged with schemes applied for a longer time [21][22]. In a similar context, the application of a complete AIT scheme for mites avoids the development of new sensitizations in 75% of patients at least three years after its conclusion [23][24].

Regardless of these scores, some previously discussed interleukins (IL-10, TGF-β), antibodies titers (IgG4) [24], IgE [25], specific IgE/total IgE [26], and cell lines (Treg cells, B regs and DC) have been used as biomarkers [27]. Although the modification of other types of lymphocytes and immune cells have also been described. For example, AIT for grasses increase the expression of the transcriptional factor of DCreg (C1QA, FcεRIIIA, FTL) and reduced that of DC2 (C1QA, FcεRIIIA, FTL,); in a similar way, it diminished the expression of CD63/CD203c in basophils, which correlates with the medical score and is considered as a biomarker of efficacy [26][28].

SCIT and SLIT are generally well tolerated. However, as another therapeutic approach, they are not exempt from the development of adverse reactions. The risk of a systemic reaction is more frequent with SCIT than SLIT. A systemic response to AIT injection is documented in approximately 2% of patients, and the mortality related to a SCIT injection is higher in non-controlled asthma patients in the build-up phase and maintenance [8][22]. Low-risk fatal reactions occur in 1 per 2.5 million injections, although this rate has decreased in recent years [29][30]. SLIT is considered the safest route, even in asthma patients [11].

Recently, attempts have been made to improve the adaptability and success of immunotherapy using monoclonal antibodies, particularly with the anti-IgE monoclonal antibody (Omalizumab). Omalizumab in immunotherapy is an off-label treatment. However, clinical trials have shown that the use of Omalizumab in rapid regimens of AIT, such as rush, reduces the adverse reactions attributed to immunotherapy [31]. Another trial showed benefits in the symptom control of seasonal rhinoconjunctivitis and asthma when used before or during immunotherapy schemes [32][33]. However, it will unlikely be approved as a general indication because of its high cost and limited and probably temporary clinical benefits.

3. Clinical-Immune Efficacy of Recombinant Allergens

3.1. Cat

Fel d 1 is the most common cat allergen. Fel d 1 hypoallergenicity can be synthesized by introducing duplications of T cell epitopes (DTE). In a murine cat allergy model, a type of recombinant DTE III induced high IgG2 levels. In mice, IgG can reduce skin reactivity and improve airway hyperreactivity by blocking the binding of patients' IgE to rFel d 1 [34]. AIT for Fel d 1 has been tested in vaccines based on T cell epitope peptides (SPIRES), which are short allergen peptides that make up the allergen's primary T cell epitopes, and MHC II has been used to construct immune-therapeutic mechanisms [35]. Allervax cats (cat peptide for AIT) showed clinical benefits; however, they had late adverse reactions in clinical phases [36]. Conversely, in phase-II and -III studies, a Cat PAD (also known as ToleroMune Cat) has also shown a reduction in rhinoconjunctivitis symptoms and safety in cat-allergic patients using four intradermal doses of 6 nmol [37][38], decreasing the CRTh2 expression but not altering the number of Fel d 1-TCD4+ cells [39].

In a phase-I research, rFel d 1 was also fused to the HIV-derived translocation peptide (TAT), mediating the cytoplasmic uptake of extracellular proteins and the truncated human invariant chain (MALT-Fel d 1), which was administered intralymphatically in a scheme of three dosages. MALT-Fel d 1 improved the symptoms during the nasal challenge and increased the IgG4 and IL-10 levels [40]; this humoral response was greater than that of another IgG subclass, which increased after the first month of treatment. Interestingly, rIgG4 for cat allergy has been evaluated in cat-allergic patients in a phase-Ib study, demonstrating its ability to increase the IgG/IgE ratio and decrease the clinical symptoms in nasal provocation, with similar results in a scheme of eight days. These data suggest that passive immunization can treat allergies using allergen-specific IgG antibodies [41].

3.2. Birch

rBet v 1 is one of the first molecules evaluated as allergen immunotherapy [42]. Niederberger V. realized in 2004 a phase-II study and administered two fragments of rBet v1 (F1, aa 1–73 without methionine; F2, aa 74–159) and two trimers (comprising three covalently linked copies of Bet v 1) applied in eight doses (maximum dose of 80 µg) before the birch season. These recombinants induced the synthesis of IgG1 and IgG4 after treatment; despite a slight decrease, the antibodies remained present during the pollination season and decreased the release of histamine in serum and IgE levels [43]. Interestingly, an increase in IgG1, IgG2, and IgG4 was identified in the nasal secretion and is associated with reduced nasal sensitivity in the nasal birch challenge [44]. Additionally, the trimer of Bet v 1 decreased the production of the Th2 profile but increased the IL-12 levels, and both recombinant proteins decreased the nasal symptoms and skin reactivity [45].

Allergen-specific T lymphocytes (LT CLA^+ and $CCR4^+$, necessary for the migration of T cells from the blood to the skin) were found to increase after an epicutaneous injection of both rBet v1 and two fragments of this protein, in addition to a slight increase in IgG levels and its subclasses but a null humoral IgE response [46].

Other recombinants have been studied. For example, Meyer W. evaluated the response to the rBet v 1-folding variant, which has intact T cell epitopes, in a phase-III study. After exposure to AR patients for eight hours in an environmental exposure chamber with birch, the researcher applied a 10-dose injection scheme (20, 80, 160, and 320 µg) applied weekly, noting that the 80-µg dose of this recombinant induced the greatest synthesis of IgG1, reduced the nasal symptoms, and induced minimal adverse effects [47]. rBet v1 was also tested sublingually in a phase-II study, administering one sublingual tablet per day for five months before the pollination season; this treatment decreased the symptoms and use of rescue medications during the pollination season, with mild effects [48].

3.3. Grasses

From 1999, Gehlhar K. applied two recombinants (5a and 5b) with a homogeneity of approximately 70% with Phl p 5 in pediatric patients. These molecules decreased the AR symptoms and increased the levels of IgG, IgG2, and IgG4 at the end of the study; even the quotient IgG1/IgG4 correlated with the clinical scenario [49].

Recently, a fusion protein based on allergen-derived peptide B cell epitopes of the four major allergens of timothy (Phl p 1, 2, 5, and 6) and PreS protein (an immunogenic carrier that fosters antibody responses [50] from the hepatitis B virus—HBV), adsorbed to aluminum hydroxide, known as BM32, has been proven in patients with AR to grasses [51]. A two-year scheme was used to test BM32 in a phase-IIb study. In the first year, the researchers applied four injections; the initial three dosages were applied three months prior to the European grass pollen season and a booster in the fall (after the season) (**Figure 1**b). In the second year, they reapplied the first three doses of the scheme mentioned before the next

pollination season. With this scheme, an increase in IgG, IgG1, and IgG4 was observed, but this effect declined after five months, particularly for IgG1. However, the booster was sufficient to restore the titers of IgG1 and increase the allergen-specific IgG4 levels. BM32 did not significantly modify the IgE levels compared with the baseline values. In terms of therapeutic advantages, phase-IIb studies showed benefic changes in AR life quality and asthma symptoms during the pollination, and these effects increased in the second year of treatment [52], with the main adverse reactions classified as mild [53].

Allergic mast cell and basophil degranulation may be prevented by the presence of blocking IgG1 and IgG4 antibodies against the IgE binding sites of the major grass pollen allergens. Likewise, as observed in phase II studies, blocking antibodies hinders the IgE-facilitated allergen presentation and the consecutive T cell activation [50]. In the same context, it inhibited the allergen-specific T cell reactivity in both treated patients and in vitro models [54]. Additionally, BM32 induces IL-10 synthesis and low levels of IL-5 and interleukins used as markers of immunological efficacy and tolerance [55].

4. Conclusions

Despite the development of novel allergen-specific immunotherapy, licensing any vaccine for the clinic has proven difficult. Currently, allergen-specific immunotherapy with natural allergen extracts is the only viable disease-modifying treatment for allergic patients based on long-term symptom relief, and it can also prevent AR from progressing to asthma. However, caution should be taken because allergen injection can be associated with adverse reactions and because of the allergenicity of natural extracts. The side effects are usually harmless and, in rare cases, can cause fatal reactions. Importantly, patients must not show symptoms because of AIT allergenicity, particularly in asthma [56]. Traditional allergen extract-based AIT may be revolutionized in the future by some molecular AIT technologies. The latest generation of carrier-bound B-cell epitope-based allergy vaccines has the potential to transform AIT because it may prevent side effects, allowing the administration of high doses to induce strong allergen-specific IgG responses and providing sensitized patients with lasting effects (Supplementary Table S1).

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