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Wraith, David C; Krishna, Mamidipudi T

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UNSOLICITED REVIEW

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Peptide allergen-specific immunotherapy for allergic airway diseases—*State of the art*

David C. Wraith[1] | **Mamidipudi T. Krishna**[1,2]

[1]Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK

[2]Department of Allergy and Immunology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Correspondence
Mamidipudi T. Krishna, Department of Allergy and Immunology, Birmingham Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust, Bordesley Green East, Birmingham B9 5SS, UK.
Email: mtkrishna@yahoo.com

Abstract

Allergen-specific immunotherapy (AIT) is the only means of altering the natural immunological course of allergic diseases and achieving long-term remission. Pharmacological measures are able to suppress the immune response and/or ameliorate the symptoms but there is a risk of relapse soon after these measures are withdrawn. Current AIT approaches depend on the administration of intact allergens, often comprising crude extracts of the allergen. We propose that the challenges arising from current approaches, including the risk of serious side-effects, burdensome duration of treatment, poor compliance and high cost, are overcome by application of peptides based on $CD4^+$ T cell epitopes rather than whole allergens. Here we describe evolving approaches, summarize clinical trials involving peptide AIT in allergic rhinitis and asthma, discuss the putative mechanisms involved in their action, address gaps in evidence and propose future directions for research and clinical development.

KEYWORDS
allergen-specific immunotherapy, asthma, epitopes, peptides, rhinitis, T cells

1 | INTRODUCTION AND A HISTORICAL TRIBUTE

The concept of allergen-specific immunotherapy (AIT) was described over a hundred years ago for treatment of grass pollen–induced hayfever. Bostock in 1819 delineated hayfever as a seasonal illness characterized by airway catarrh, and Dunbar in 1903 associated it with "pollen toxin".[1] Dunbar described the muco-cutaneous symptoms in hayfever and that injection of "pollen toxin" in animals induced production of neutralizing antibodies. In a landmark publication in The Lancet in 1911, Noon elegantly described that prophylactic pre-seasonal inoculation of "pollen toxin" induced "active immunity" against hayfever.[1] The concept of allergen challenge, then described as "sensitiveness," and how this was altered following repeated inoculation of "pollen toxin" was ingeniously employed to obtain an objective read out of therapeutic benefit. A standardized pollen extract was manufactured by Dunbar's method that involved extraction in distilled water, by repeated thawing and freezing.[1] The potency of different pollens was compared with a conjunctival challenge procedure, and it was established that *Phleum pratense* was most potent among different grass species in England. Noon developed a protocol of incremental subcutaneous inoculation of "pollen toxin" at regular intervals and discovered enhancement of "resistance" as evidenced by a "conjunctival challenge".[1] Noon administered a relatively small starting dose as 1/3rd of the minimal dose that elicited a conjunctival response to challenge.

This work was carried forward by Freeman[2] who inoculated 20 patients with pollen extract and described therapeutic efficacy in 16 patients. Frankland and Augustin conducted the first "controlled" clinical trial for hayfever and seasonal asthma and showed efficacy of "crude" and "purified pollen extracts".[3]

The fundamental principle underpinning AIT has not changed since it was first described in 1911, but great strides have been made with respect to standardization, purification and optimization of treatment protocols in order to maintain safety and maximize therapeutic benefit. The aim of AIT is to reduce allergic mucosal inflammation by induction of immune tolerance, thereby alleviating symptoms and improving health-related quality of life. Administration of crude allergen extracts for AIT is associated with a risk of provoking an immediate (type-1) hypersensitivity reaction due to recognition of antigen/s or allergen by specific IgE on the surface of mast cells and basophils. Hence, efforts have focussed on development of novel approaches involving administration of modified allergens (recombinant allergens or peptides) to reduce/circumvent IgE binding, that is reduce allergenicity but maintain immunogenicity.

An ideal AIT product should meet the following criteria: cost-effective, minimal allergenicity and maximal immunogenicity and tolerogenicity, needing few doses or a short treatment course with ease of administration (preferably self-administration unsupervised), providing long-term therapeutic efficacy and importantly carrying minimal side-effects in terms of provoking local and systemic allergic reactions.

2 | CURRENT APPROACHES IN CLINICAL PRACTICE

2.1 | Treatment modalities

The two main modalities currently employed world-wide for AIT in allergic rhinoconjunctivitis (ARC) include subcutaneous injection immunotherapy (SCIT) and sublingual immunotherapy (SLIT). As per current British and European guidelines, these treatments are offered to patients with moderate-severe ARC that is either unresponsive or partially responsive to standard pharmacotherapy.[4,5] An important recent development has been the recommendation by the European Academy of Allergy and Clinical Immunology (EAACI) and Global Initiative for Asthma (GINA 2020; https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf) regarding use of AIT in house dust mite–driven allergic asthma.[6] HDM SLIT tablets have been recommended for adults as an "add-on" or adjunct therapy in those with controlled or partially controlled disease[6] with an aim to reduce acute attacks. HDM SLIT drops have been similarly recommended for children with well-controlled disease in order to reduce medication use and better control of asthma symptoms. Similarly, HDM SCIT has been recommended for adults with well-controlled disease for better symptomatic control and reduction of medication usage.[6] It has been acknowledged by the authors of EAACI guidelines that the quality of evidence, however, is fairly limited at present with respect to use of AIT to treat chronic asthma. Well-designed studies are needed to delineate the role for AIT in the context of mild-moderate asthma endotypes[7] (type-2 "high" and non-type-2 or type-2 "low") based on predominant underlying inflammatory pathways, although it is likely to be more effective in type-2 "high."

2.2 | Safety aspects

Safety remains an important concern, as uncontrolled asthma is an important risk factor for fatal and near fatal systemic allergic reactions to AIT. Hence, patient selection is paramount, and AIT is restricted to specialist use only in a secondary care setting. As regards UK practice, use of AIT in ARC is a relative contraindication in patients with concomitant mild-moderate well-controlled asthma as per The British Society for Allergy and Clinical Immunology (BSACI) guidelines and an absolute contraindication in those with uncontrolled, severe or brittle asthma.[5] Furthermore, AIT is not recommended for the treatment of chronic asthma *per se* in the UK practice.

Several clinical trials with different AIT products have highlighted safety and efficacy (short-term and long-term) of SCIT and SLIT, particularly for grass pollen, birch pollen, ragweed and house dust mite.[8–12] They involve administration of a standardized intact whole allergen extract, although modified allergens (allergoids and polymerized extracts) have also been shown to be safe and effective. SCIT formulations include aqueous and depot (aluminium hydroxide or tyrosine to enhance immunogenicity) preparations. SLIT is available as dissolving tablets or drops. Systematic review and meta-analysis of SCIT and SLIT for ARC have shown that they have a modest/moderate therapeutic benefit.[11,12]

Whilst mild oropharyngeal reactions are relatively frequent and commonly associated with SLIT, systemic reactions and anaphylaxis are very rare.[4,5] SCIT is associated with the risk of systemic reactions and anaphylaxis, and rarely fatal anaphylaxis could occur.[4,5,13–15] The SCIT national surveillance project from North America reported 7 fatalities between 2004 and 2017 out of 54.7 million injection visits. SCIT-associated systemic reactions occurred in 0.1% of injection visits, involving varying severity with greater risks associated with accelerated (rush and ultra-rush) protocols.[15] Hence, preference is to employ a conventional up dosing protocol involving 12 weekly visits, particularly in the UK, where most whole allergen extracts for SCIT are currently unlicensed.[5]

2.3 | Practical aspects

There are recognized logistic issues with SCIT and SLIT.[4,5] SCIT should be administered under specialist supervision and in secondary care with access to critical care should anaphylaxis occur. Hence, there are overhead expenses attached to administration of SCIT. It involves considerable time commitment for patients with multiple visits and with a waiting time for an hour following each injection. SLIT, on the other hand, is initiated in hospital, and patients are trained for self-administration. Standard recommended duration of both treatments is 3 years. Those failing to show therapeutic response can be identified early and treatment may be withdrawn.

Compliance to treatment has been highlighted as a concern in a real-life setting. A study from The Netherlands in 6486 patients (2789 SCIT and 3690 SLIT)[16] reported an overall 18% compliance with respect to completion of the 3-year course of standard treatment (median 1.7 and 0.6 years, respectively, for SCIT and SLIT). One of the predictors for discontinuation was the prescriber, with patients more likely to persist with treatment with a general practitioner than with a specialist.

2.4 | Other AIT modalities

Other approaches that have shown some promise include AIT with adjuvants (TLR-4 agonist, monophosphoryl lipid A; TLR-9 agonist, bacterial DNA oligonucleotides containing a CpG motif), combination of AIT with omalizumab, recombinant Bet v 1, recombinant B cell epitope-based vaccine, comprising a recombinant hybrid grass allergen mix conjugated with a hepatitis B domain surface.[17–23] Other routes of administration have also been attempted including intradermal, epicutaneous and intralymphatic[24–26] routes. There have been several studies during the last 2 decades investigating efficacy and safety of short and long contiguous overlapping peptides (COPs) targeting dominant T cell epitopes of major allergens as an alternative to employing intact or whole allergens for AIT. Long COPs represent fragments of overlapping peptides covering the entire sequence of respective allergen, thereby preserving the relevant peptides for T cell recognition, but carrying an advantage of lacking conformation of the whole molecule to prevent IgE binding on the surface of mast cells of basophils. Similarly, short peptides, generally comprising single T cell epitopes, are usually 8–20 amino acids. Selection of the correct sequence and optimizing the length of peptide is critical to safety, success and cost of peptide AIT.

The main aim of this review is to critically appraise AIT involving peptide-based treatment for ARC. We will review clinical trials that have investigated the therapeutic efficacy and safety of peptide AIT for ARC, challenges associated with this modality, and describe putative mechanisms and future directions.

3 | RATIONALE BEHIND PEPTIDE IMMUNOTHERAPY

Peptide AIT in allergic airway disease rests on two fundamental principles,[27,28] (a) a pivotal role for T cells in orchestrating chronic allergic mucosal inflammation in ARC and asthma and (b) circumventing IgE-mediated recognition and cross-linking with allergen on the surface of mast cells and basophils, the mechanism underpinning systemic type-1 hypersensitivity reactions to whole allergen AIT.

Predefined and well-mapped short peptides (SPs) or long COPs of major allergens representing dominant T cell epitopes, with the ability to bind to a vast array of HLA class II alleles, can be administered at regular intervals, either intradermally or subcutaneously to induce allergen-specific T cell tolerance.[27,28] This concept has been also been tested with some success in the context of autoimmune diseases where there are recognized target antigens such as in autoimmune liver diseases, rheumatoid arthritis, type-I diabetes, multiple sclerosis and Graves' disease.[28–34] Targeting pathogenic T cells in organ-specific autoimmune diseases with T cell epitopes induces antigen-specific regulatory T cells and this strategy is under evaluation in clinical trials.

From a logistical and cost viewpoint, short peptides can be manufactured in a standardized fashion with low production costs and are relatively stable in a lyophilized form at room temperature.[35] Also, cost of production of peptide-based therapeutics is low since mass production of high purity product is achievable. Therefore, as soon as development costs are recovered, we predict that treatments for common allergic disorders will be inexpensive.

4 | ANALYSIS OF CLINICAL TRIALS AND STUDIES INVOLVING PEPTIDE AIT FOR ALLERGIC AIRWAY DISEASES

4.1 | Framework for peptide AIT

Phase 1–3 clinical trials have been conducted to investigate the efficacy and safety of peptide AIT for allergic airway diseases. These have mainly focussed on major allergens including birch pollen,[36,37] grass pollen[38–44] or cat.[45–56] The main approach taken in these studies has been to administer SPs or COPs over 4–6 weeks, either starting at a relatively low dose with structured escalation to reach a target cumulative dose or by delivering a fixed pre-determined dose administered weekly or fortnightly. Most studies have investigated a dose-response relationship employing at least 2 doses with injections administered either intradermally or subcutaneously. Efficacy was measured using a standardized clinical scoring system of combined nasal/bronchial and ocular symptom and medication scores, night-time nasal symptom scores, health-related quality of life scores, lung function (in some cases also airway hyperresponsiveness), early- and late-phase skin test response, measurement of biomarkers such as allergen-specific IgE (sIgE), allergen-specific IgG_4 and facilitated IgE binding assays.

4.2 | Therapeutic response to peptide AIT

Peptide AIT has been shown to improve clinical responses to allergen challenge either following a natural exposure or during/after a controlled exposure in an Environmental Exposure Chamber (EEC) alongside alteration in immunological parameters with a significant increase in $sIgG_4$ and reduction in $sIgE/IgG_4$ ratio. Recent studies have also shown a sustained clinical benefit at years 1–3 following a relatively short course of therapy, alongside persistent immunological signals as described above, *albeit* with a downward trend from immediate post-treatment metrics.[37,40]

Ellis et al[39] reported a phenomenon of a bell-shaped pharmacological response rather than a linear dose-response association with grass pollen peptides, highlighting the importance of dose titration in early clinical trials to inform robust design of phase III trials and beyond. Whilst a cumulative dose of 48 nmol of grass peptides (4 or 8 injections) induced a significant therapeutic benefit, a similar (or expected dose-response benefit) response was not detected with a higher dose of 96 nmol. This is in contrast to SCIT clinical trials involving an alum preparation of *Phleum pratense* which showed a linear dose-response relationship, that is a maintenance dose of 100,000 SQ. U was superior to 10,000 SQ. U of whole allergen extract in terms of therapeutic efficacy and associated with more frequent local and systemic treatment-emergent allergic reactions.[8]

4.3 | Safety aspects

Whilst recent studies with grass[39,41,42] and cat[55] peptides have been shown to be relatively safe with respect to grade 3 or 4 systemic reactions, as per the World Allergy Organization (WAO) grading system, others, particularly those involving grass pollen,[38] cat[47,52] and birch pollen[36] have reported relatively more severe early and delayed (>3 h) systemic allergic reactions. Specifically, lower airway symptoms with a decline in FEV_1 (>30%) have been reported, and this has been attributed to a MHC restricted allergen-specific T cell activation.[57] It has been suggested that the late asthmatic response to peptides improves with repeated dosing,[52] but this needs confirmation. Local injection site reactions have been less frequent and relatively less severe.

4.4 | Putting evidence into context

In summary, peptide AIT is a promising option as an immunomodulatory and disease modifying treatment for ARC and asthma, but further work is clearly required in well-characterized patients to demonstrate its long-term efficacy and safety. Current recommendations with whole allergen extracts of SLIT and SCIT are that 3 years of treatment is recommended to achieve long-term efficacy.[4,5] Whilst there is preliminary and promising evidence that a short course of peptide AIT for 4–6 weeks confers sustained[37,40,48] clinical benefit at years 1–3, without additional treatment, further studies are clearly warranted to determine long-term efficacy with optimization of dosing regimens, route of administration (intradermal vs subcutaneous), duration of therapy and safety specifically in asthma. Further research is also needed in children in order to determine the role for peptide AIT not only in established allergic airway disease, but also with respect to prevention of asthma and newer sensitizations as reported with whole allergen AIT.[58] Further research to investigate the efficacy and safety of peptide AIT in house dust mite–related ARC and asthma is also needed. Importantly, it would be crucial to have a proportionate representation of Black, Asian and Minority Ethnic population in peptide AIT clinical trials to be able to maintain credibility and generalizability of findings at a global level.

Table 1 summarizes key studies in peptide AIT undertaken during the last 3 decades and includes details regarding study design, efficacy and safety. Notably, AIT with Fel d 1–derived peptides showed a stable treatment effect when the clinical response was measured employing an EEC. The significance of this effect however was challenged in a phase 3 study (ClinicalTrials.gov Identifier: NCT01620762; unpublished) in which primary outcome was measured by a combined score [CS =Total Rhinoconjunctivitis Symptom Score (TRSS) + Rescue Medication Score (RMS)] involving natural cat allergen exposure over a 3-week period as opposed to challenge in an EEC, and no significant differences were detected between the treatment and placebo groups. The reason for this study not reaching its desired primary end-point is not clear. It is plausible that differences in study methodology, specifically method of cat allergen challenge (natural exposure vs EEC) and psychosomatic factors might potentially impact in cat allergy clinical trials. This needs due consideration in future peptide AIT clinical trials which should include a combined clinical cum biomarker approach, as successfully shown in recent studies involving grass pollen peptide AIT.

5 | PUTATIVE MECHANISMS UNDERPINNING PEPTIDE AIT IN ALLERGIC AIRWAY DISEASE AND LESSONS LEARNT FROM PEPTIDE IMMUNOTHERAPY IN AUTOIMMUNE DISEASES

5.1 | Lessons regarding induction of immune tolerance from whole allergen AIT studies

The fundamental question relating to effective AIT is the type of immune modulation required to produce effective tolerance towards the allergen. On the one hand, there is evidence that administration of conventional whole allergen-based immunotherapy leads to generation of allergen-specific blocking antibodies, that is IgG_2 and especially IgG_4 isotypes that compete for binding antigen and block cross-linking of IgE on mast cells. For example, Zhao and colleagues have shown that the IgE-blocking factor induced by AIT correlates with IgG_4 antibodies and a decrease of symptoms in HDM-allergic children.[59] Furthermore, Shamji and colleagues have shown that grass pollen SCIT leads to serum IgG_4 inhibitory antibodies that prevent IgE facilitated allergen binding by B cells and hence presentation to T cells.[60] On the other hand, there is evidence that AIT leads to the deletion, induction of immunological paralysis (anergy) or immune modulation (alteration of cytokine secretion with respect to dampening of Th2 and skewing towards a Th1 or Tr1 phenotype) of allergen-specific T cells.[61]

The key question is which form and mode of delivery of the antigenic component of an allergen is safe and effective in

TABLE 1 Clinical trials* involving peptide immunotherapy for allergic rhinoconjunctivitis

Study	Allergen	Protocol	Key observations	Comments
Birch pollen peptides				
Spertini et al[36] (2016)	Birch pollen (Bet v 1)	• Double-blind randomized placebo-controlled (DBRPC) parallel group phase IIb; Bet v 1 long contiguous overlapping peptides (COP; 25 or 50 and 100 mcg in aluminium hydroxide, subcutaneous injections) • 23 centres in 7 European countries • Placebo *n* = 79; 50 mcg *n* = 79 and 100 mcg *n* = 82; white adults with seasonal allergic rhinoconjunctivitis • Pre-seasonal administration of 5 injections • Half dose on day 1 • 50 mcg or 100 mcg on days 8, 15, 29 and 57 • *Inclusion criteria*: 18–55 years with moderate to severe rhinoconjunctivitis to birch pollen; positive skin prick test to birch pollen; positive specific IgE Bet v 1 • *Exclusion criteria*: FEV1 < 80% of predicted; treatment for chronic asthma; perennial allergies; positive skin prick test to Bet v1 COPs; pregnancy or lactation; immunosuppressive treatment or allergen-specific immunotherapy during last 5 years	• 50 and 100 mcg arms effective, with improvement in rhinitis combined symptoms and medication scores (RSMS) and mini rhinoconjunctivitis quality of life questionnaire (RQLQ) • 20-fold increase in allergen-specific IgG4 in active groups with no significant differences between active groups • Significance increase in Bet v 1-specific IgE in placebo but not in active group • Short-term benefit shown with an immunological response	• Local injection site reactions related to alum were common • 6.5% of patients reported decrement in FEV1 of ≥30% >3 h after injection, none graded as serious requiring hospitalization • Mild late respiratory reactions occurred in 55%, 35% and 13% of patients in 100 mcg, 50 mcg and placebo arms • Other mild non-respiratory side-effects reported • 3 serious adverse reactions in 50 and 100 mcg groups, were reported (urticaria, oropharyngeal angioedema, conjunctivitis), treated with antihistamines, oral corticosteroids, inhaler and intramuscular epinephrine • Long-term studies needed, and better characterization of those who are at risk of delayed reactions needed
Kettner et al[37] (2018); follow on study of the above (Spertini et al, 2016)	Birch pollen (Bet v 1)	• No further treatment offered prior to season-2; 240 participants (82%) returned for follow-up • *Inclusion and exclusion criteria*: see above under parent study	• Persistent significant improvement in RSMS in 50 mcg group • Persistent but a trend seen in 100 mcg group with RSMS • Persistent improvement in mini RQLQ and night-time nasal symptom scores in 50 mcg and 100 mcg groups • Bet v 1-specific IgG4 levels dropped but remained persistently elevated in 50 mcg and 100 mcg groups compared to placebo and pre-treatment levels	• Persistent clinical benefit for two seasons after a single pre-seasonal course with demonstrable immunological signals
Grass pollen peptides				

(Continues)

TABLE 1 (Continued)

Study	Allergen	Protocol	Key observations	Comments
Ellis et al[39] (2017)	Rye grass pollen (Cyn d 1, Lol p 5, Dag g 5, Hol l 5, Phl p 5)	• Multi-centre DBRPC study; pre-seasonal intradermal administration • Adults with a minimum 2-year history of seasonal allergic rhinoconjunctivitis • *4 groups*: 1. 8 × 6 nmol, 2-week intervals (*n* = 71) 2. 4 × 12 nmol, 4-week intervals (*n* = 70) 3. 8 × 12 nmol, 2-week intervals, (*n* = 71) 4. . Placebo, (*n* = 70) • Baseline and post-treatment challenge in an environmental exposure chamber (EEC) • *Inclusion criteria*: 18–65 years; minimum 2-year history of grass pollen–induced allergic rhinoconjunctivitis; positive skin prick test to rye grass pollen; environmental chamber challenge: minimum TRSS and TSS of 10/24 and 6/12, respectively • *Exclusion criteria*: grass pollen–induced asthma; anaphylaxis to grass pollen; FEV1<80% of predicted; allergen-specific immunotherapy in last 12 months or grass pollen immunotherapy during last 10 years; current or planned pregnancy; acute/chronic sinusitis; patients in whom epinephrine is contraindicated	• Significantly greater reduction total rhinoconjunctivitis symptom scores in 8 × 6 nmol group vs placebo	• 2 serious adverse events but not related to active treatment • No case of grade ≥3 hypersensitivity reaction as per World Allergy Organization (WAO) grading system, no case of anaphylaxis or treatment-induced asthma • Mild self-remitting local injection site reactions more frequent in active arm • No immune marker analysis carried out
Ellis et al[40] (2020); Follow on to parent study (above Ellis et al, 2017)	Rye grass pollen (Cyn d 1, Lol p 5, Dag g 5, Hol l 5, Phl p 5)	• *N* = 122 and *N* = 85 participants followed up in seasons of years 2 and 3, respectively • No further treatment offered • *Primary end-point*: change in mean total rhinoconjunctivitis symptom score (TRSS) from baseline to follow-up post-treatment challenge • Inclusion criteria: patients randomized in the previous study; completed all treatments and post-treatment challenge; mean baseline TRSS of ≥8/24 in previous study• Exclusion criteria: participants who were unblinded regarding treatment allocation in parent study; grass pollen–induced asthma since previous study; uncontrolled asthma or asthma requiring step-2 Global Initiative for Asthma (GINA) treatment or greater; FEV1<80% of predicted; allergen-specific immunotherapy since parent study completion; acute/chronic sinusitis; current or planned pregnancy; in whom epinephrine is contraindicated	There was a non-statistical but a trend to significance with greater improvement in TRSS compared to baseline in 8 × 6 nmol group vs placebo group in years 2 and 3 off treatment	• Indicates persistent benefit at year 3 after a short course of treatment • No immune marker analysis carried out

(Continues)

TABLE 1 (Continued)

Study	Allergen	Protocol	Key observations	Comments
Mosges et al[42] (2018)	Grass pollen (*Lolium perenne*)	• Open-label dose escalation study in adult patients (n = 65) with moderate-severe grass pollen–induced seasonal allergic rhinoconjunctivitis • Purified *lolium perenne* extracts denatured and enzymatically hydrolysed to generate 1000–10,000 Da *lolium perenne* peptides (LPP) • 12 incremental subcutaneous injections over 6 weeks, starting at 10 mcg, cumulative 490 mcg • Baseline and post-treatment (week 8) conjunctival provocation test (CPT) and blood tests for sIgE, IgG4 blocking abs • Inclusion criteria: moderate-severe grass pollen–induced seasonal allergic rhinoconjunctivitis for 2 years; positive skin prick test and specific IgE to grass pollen • *Exclusion criteria*: grass pollen immunotherapy during last 5 years; ongoing immunotherapy with other allergens; chronic asthma or emphysema with FEV1 <80% of predicted; uncontrolled asthma; severe autoimmune disease; pregnancy; antihistamines or corticosteroids in 3 weeks preceding the trial; those on beta blockers or ACE inhibitors, anti-IgE treatment, anti-leukotrienes or mast cell stabilizers	• Significant improvement in CPT, with 70% becoming non-reactive at week 8 • 12-fold increase in sIgG4 abs at week 8, 55% reduction in sIgE/sIgG4 ratio at week 8 • Significant decrease in IgE facilitated allergen binding at week 8	• No serious adverse events (SAEs) or anaphylaxis • N = 2 grade-1 and n = 4 grade-2 reactions • Relatively small injection site reactions (mean weal and flare <0.6 cm and 2.5 cm, respectively)
Mosges et al[41] (2018)	Grass pollen (*Lolium perenne*)	• Multi-centre DBRPC phase IIb parallel group study involving LPP devoid of adjuvant as an active arm • Subcutaneous escalating doses administered over 4 weeks • *Groups (LPP dose)* 1. Cumulative dose 70 mcg, n = 50 2. Cumulative dose 170 mcg, n = 49 3. Cumulative dose 370 mcg, n = 53 4. Placebo, n = 46 • 21% of patients had well-controlled asthma • *Assessments*: Baseline and post-treatment (week 8) CPT and blood tests for sIgE, sIgG4 blocking abs and facilitated IgE binding assays • *Inclusion criteria:* 18–70 years; at least 2-year history of grass pollen–induced seasonal allergic rhinoconjunctivitis needing therapy; positive skin prick test to grass pollen and positive specific IgE to recombinant Phleum pratense (phl p 1/5); positive conjunctival provocation test • *Exclusion criteria*: same as in above study and the following: fever; ongoing malignancy; PEF <70% of predicted; co-sensitizations to rag weed and mugwort with weal diameter and/or sIgE exceeding grass pollen; positive serology to hepatitis B or C, HIV-1/2 and use of immunosuppressive treatment (oral, nasal and topical steroids) directly prior to the study	• Significant improvement in CPT post-treatment compared to placebo arm • Significant improvement in facilitated allergen binding in a dose related fashion • Significant increase in sIgG4 abs post-treatment compared to placebo arm	• No cases of anaphylaxis or grade-3 or grade 4 allergic reactions • Mean weal diameter at injection sites up to 0.8 cm in active arm

(Continues)

TABLE 1 (Continued)

Study	Allergen	Protocol	Key observations	Comments
Mosges et al[44] (2018)	Grass pollen (*Lolium perenne*)	• DBRCPC parallel group phase III study; 57 centres in Europe • 1:2 randomization, placebo =182; active arm (LPP 170mcg) =372; 8 subcutaneous injections over 3 weeks • *Inclusion criteria*: Adults with moderate-severe grass pollen seasonal allergic rhinoconjunctivitis as per ARIA criteria during the last 2 years; positive skin prick test and serum specific IgE and conjunctival provocation test to grass pollen; seasonal asthma patients were included • *Exclusion criteria*: previous grass pollen immunotherapy; perennial allergic rhinitis; underlying systemic diseases; previous history of anaphylaxis; allergy to excipients in the vaccine; contraindication to epinephrine; FEV1 <80% of predicted and PEFR <70% of predicted	• Combined symptom and medication scores improved both over peak and during entire season by 15.5% and 17.9%, respectively in LPP group in comparison to placebo • Reduced reactivity to conjunctival provocation test in LPP group • Improvement in QOL in LPP group	• *Early systemic reactions*: (<30 min after injections): 1.1% vs 2.3%, LPP vs placebo; all except 3 were WAO grade 1 or 2; 1 grade-2, grade-3 and grade-4 (epinephrine given) WAO seen in patients with asthma in LPP group • Systemic reactions: (after 30 min): 11.1% vs 2.3%, LPP vs placebo; all grade-1 or −2 WAO criteria
Sharif et al[43](2019) Sub-study of above study by Mosges et al (2018)	Grass pollen (*Lolium perenne*)	• Protocol and selection criteria as above • Placebo =11; LPP group =21	• Combined symptom and medication score improved by 35% and 54% in LPP group in comparison to placebo during the peak period and entire pollen season, respectively • Significant decrease in CD63 and CD203c^{bright}CRTH2 positive basophils in LPP group but not in placebo group • Suppression of seasonal increase in grass pollen–specific IgE in LPP but not in placebo group • Significant reduction of IL-4^{+} Th2 cells and IL-4^{+} and IL-21^{+} follicular Th cells and dual IL-4^{+}IL-21^{+} follicular Th cells in LPP but not in placebo group • Induction of Foxp3^{+}, follicular T and IL-10^{+} regulatory B cells in all patients in LPP groupwith neutralizing IgG$_4$ blocking abs	Pre-seasonal LPP immunotherapy: • Suppressed seasonal basophil activation • Induced production of Foxp3 regulatory T cells • Induced regulatory B cells and IgG$_4$ blocking abs

(Continues)

TABLE 1 (Continued)

Study	Allergen	Protocol	Key observations	Comments
Shamji et al,[38] (2018)	Grass pollen (*Lolium perenne*)	• DBRCPC parallel group study • 1:1:1 (*n* = 27; grass pollen–induced seasonal allergic rhinoconjunctivitis) receiving 5 escalating subcutaneous injections of placebo, LPP or LPP/recombinant DnaK (bacterial homologue of heat shock protein 70 family, an adjuvant) • *Inclusion criteria*: 18–50 years; grass pollen–induced moderate-severe allergic rhinoconjunctivitis as per Allergic Rhinitis and Its Impact on Asthma (ARIA) classification for at least 2 previous years; positive skin prick test and specific IgE to grass pollen • *Exclusion criteria*: None specifically stated	• *Immunological signals*: 1. Induction of sIgG4 abs persisting for 24 weeks post-treatment 2. Significant reduction in IgE binding in LPP arm but not in LPP/DnaK or placebo	• LPP and LPP/DnaK was safe and well tolerated • 16 adverse reactions in LPP group and 12 in LPP/DnaK group; all mild-moderate and self-remitting • No alterations in haematological and biochemical parameters • First patient (at 50mcg) developed anaphylaxis after first LPP injection, and dose regimen was altered for rest of the study with starting dose at 5mcg
CAT peptides				
Patel et al[55] (2013)	Cat (Fel d 1)	• RDBPCS, adults with cat allergy ±mild well-controlled asthma • *N* = 202; intradermal injections • *3 Groups (treatment for 3 months)* 1. Placebo 2. 8 × 3 nmol 2 weeks apart 3. 4 × 6 nmol 4 weeks apart • Baseline challenge in EEC for 3 h/day for 4 days • 18–22 weeks, post-treatment challenge in EEC for 3 h/d for 4 consecutive days; 50 -54 weeks, post-treatment challenge in EEC for 3 h/d for 4 consecutive days • *End-point*—change in total rhinoconjunctivitis symptom score • *Inclusion criteria*: 18–65 years; history of cat-induced rhinoconjunctivitis and/or step-1 GINA asthma treatment for at least 1 year • *Exclusion criteria*: Persistent asthma or those using inhaled corticosteroids or leukotriene modifiers for asthma	• Clinical benefit of 4 × 6 nmol 4 weeks apart superior to placebo and 8 × 3 nmol arm• Benefit persistent at 1 year after start of treatment	• No serious treatment-emergent adverse reactions• No decrement in FEV1 >30% in any arm of the study • Good safety profile • Clinical benefit seen 1 year after start of treatment

(Continues)

TABLE 1 (Continued)

Study	Allergen	Protocol	Key observations	Comments
Couroux et al,[48] (2015) Follow on of above study (Patel et al 2013)	Cat (Fel d 1)	• 2 years follow on of a previous DBRPC parallel group study • Adult patients • Challenges in an EEC pre- and post-treatment • *Groups* 1. 8 doses of 3 nmol (*n* = 17) 2. 4 doses of 6 nmol (*n* = 12) of synthetic peptides of immunoregulatory epitopes 3. placebo *n* = 22 • intradermal administration over 3 months (SPIRES) • *Inclusion criteria*: Participants who completed all visits in parent study were invited • *Exclusion criteria*: None specifically stated	• Mean reduction in total rhinoconjunctivitis symptom score of 3.85 units in 4 × 6 nmol group	• No serious adverse events during 2-year follow-up • A clinically meaningful reduction rhinoconjunctivitis score seen after 2 years in 4x6 nmol group • Evidence of long-term benefit at 2 years • Larger multi-centre studies needed for further confirmation
Worm et al,[45] (2011)	Cat (Fel d 1)	• RDBPCS, adults with cat allergy ±controlled asthma • Single dose intradermal or subcutaneous dose (0.03–12 nmol) safety study • Late-phase skin test response assessed 3 weeks after treatment • *N* = 40 placebo or ToleroMune CAT by intradermal route • *N* = 48 placebo or ToleroMune CAT by subcutaneous route • *Inclusion criteria*: 18–65 years; cat-induced allergic rhinoconjunctivitis with or without controlled asthma (GINA 2006 classification 1); positive skin prick test and/or positive serum specific IgE to cats for at least 1 year • *Exclusion criteria*: None specifically stated	• Maximum suppression of late-phase skin test response was seen with 3 nmol	• No serious adverse events • 2 subjects in the active group developed late asthmatic reaction with a 25–29% decline in FEV1, requiring treatment • Relatively mild reactions -naso-pharyngitis, cough and headache, more in subcutaneous group • Local injection site reactions seen in both groups
Smith et al,[50] (2004)	Cat (Fel d 1)	• RDBPCS in adult patient with cat allergic rhinitis and asthma • *N* = 8 in active and *n* = 8 in placebo arms • 12 overlapping Fel d 1 peptides • Escalating intradermal dose of 5, 10, 25, 50, 100 and 100mcg • Blood samples taken at baseline and post-therapy • Inclusion criteria: 18–55 years with history of cat- allergic rhinitis and asthma; positive skin prick test to cat dander; withheld oral and inhaled corticosteroids for 2 months prior to the study • *Exclusion criteria*: None specifically stated	• significant reduction in both proliferation and IL-13 production by allergen-stimulated CD4+ T cells in the active arm • CD4+CD25+ T cells suppressed proliferation and IL-13 production by CD4+CD25- T cells in culture before and after treatment but peptide immunotherapy did not affect these responses significantly • Clinical responses and adverse events were not described in this report	• Fel d 1 peptide immunotherapy affects T cell response, but this may be independent of involvement of $CD4^{+}CD25^{+}$ T cells

(Continues)

TABLE 1 (Continued)

Study	Allergen	Protocol	Key observations	Comments
Oldfield et al[47] (2002)	Cat (Fel d 1)	• RDBPCS in patients with cat allergic asthma • Fel d 1 peptides 5 mcg, 10 mcg, 25 mcg and 50 mcg (cumulative—90 mcg) at 3- to 4-day intervals • 12 overlapping peptides spanning most of Fel d 1 • *n* = 16 active or placebo (*n* = 8) • Assessments at baseline, 40 weeks and 3–9 months • *Inclusion criteria*: 25–50 years; non-smokers; history of cat allergy in the past 12 months; FEV1 reversibility with short acting beta-2 agonist of >20%; PC20 (bronchial hyper-reactivity) with methacholine with <4 g/L methacholine; positive skin prick test to Fel d 1 with late-phase response to intradermal Fel d 1; no current illness and no clinically significant abnormalities in routine haematology, biochemistry and urine analysis • *Exclusion criteria*: None specifically stated	• Significant decline in early-phase skin test response to allergen and Fel d 1 in the active arm at follow-up visit 2 • Significant reduction in late-phase skin test response to allergen at follow-up visits 1&2 in active group • Significant reduction in late-phase skin test response to Fel d 1 at follow-up visits 1&2 in active group • *PBMC responses to in vitro cat allergen*: reduced proliferation and production of production of IL-4, IL-13 and IFNν, but not between groups. Increase in IL-10 production in active arm • Subjective improvement in clinical tolerance to cat allergen as per visual analogue scale in active arm compared to placebo • No significant changes in PD_{20} allergen and PC_{20} methacholine at the 2 visits between the 2 arms	• 4 out of 16 patients in active group developed late asthmatic reactions to Fel d 1 peptides, but could be desensitized with higher doses • This study provided proof of concept but was inconclusive
Norman et al[49] (1996)	Cat (Fel d 1)	• RDBPCS in patient cat allergic asthma • *N* = 95; placebo, 7.5 mcg or 75 mcg or 750 mcg of ALLERVAX CAT • Weekly subcutaneous injections for 4 weeks • Assessments at baseline and 6 weeks post-treatment with exposure a room with a live cat • *Inclusion criteria*: adults with rhinitis or asthma symptoms to cat exposure during the last 12 months; positive skin prick test to cat dander; positive cat room challenge—increase in 2 symptoms by 2 points or 1 symptom by 2 points and drop in FEV1 by 15% from baseline • *Exclusion criteria*: contraindication to immunotherapy (betablocker, major medical illness), tricyclic antidepressants, doxepin, astemizole, monoamine oxidase inhibitors during 6 weeks prior; women of childbearing age not using adequate contraception; FEV1 <70% predicted; previous immunotherapy to cat or HDM; unstable or severe asthma; previous peptide therapy; cat ownership or regular environmental exposure	• Significant improvements in nasal and lower airway symptom score in 75 mcg and 750 mcg group • Dose-response effect seen	• No serious adverse events • Relatively mild allergic reactions occurred ≥1 h post-first dose in 16/24 subjects in 750 mcg group • Study demonstrated short-term therapeutic efficacy and safety of Fel d 1 peptide immunotherapy in cat allergy

(Continues)

TABLE 1 (Continued)

Study	Allergen	Protocol	Key observations	Comments
Alexander et al[53] (2005)	Cat (Fel d 1)	• Adults with cat allergic asthma with early- and late-phase response *n* = 16 (8 in each arm, active and placebo); randomly assigned • 12 cat allergic subjects with early asthmatic response studied separately and openly • Fel d 1, 12 overlapping peptides • Intradermal sequential dose escalations of 1, 5, 10, 25, 50, 100 and 100 mcg (total 291 mcg) at 14-day intervals • Cat allergen-induced nasal and bronchial responses and QoI measures determined at baseline, 4–8 weeks and 3–4 months post-therapy • Inclusion criteria: 18–55 years; non-smokers; history of rhinitis and asthma symptoms following cat exposure in the preceding year; positive skin prick test to cat dander; positive late-phase intradermal response to cat dander; FEV1 >90% of predicted; no previous history of immunotherapy; no current illness; no clinically significant abnormalities in routine haematology, biochemistry and urine analysis; none received oral, inhaled or nasal corticosteroids for 6 months, 2 months and 7 days prior, respectively • *Exclusion criteria*: None specifically stated	*Double-blind study*: • Significant decrease in late-phase asthma response at 3–4 weeks in active arm • Significant improvement in quality of life and eye, nasal and lower airway symptom scores in active arm *Open-label study*: • Significant improvement in nasal symptoms following cat allergen challenge	• No serious adverse events. Five in active arm of double-blind study and 2 in open-label study, developed late asthmatic response, but did not require nebulized treatment, epinephrine or corticosteroids. Two patients required treatment with salbutamol accuhaler • Another proof of concept study demonstrating attenuation of early and late asthmatic response following treatment with Fel d 1 peptide immunotherapy
Alexander et al[54] (2005)	Cat (Fel d 1)	• Open-label study • *N* = 8 cat allergic asthmatics • Increasing doses of 11 Fel d 1 peptides (0.1, 1.0, 5, 10 and 25 mcg) administered intradermally at 14-day intervals • PC_{20} to histamine and skin biopsies were taken at baseline and post-treatment following intradermal allergen challenge and subjected to immunohistochemistry and *in situ* hybridization • *Inclusion criteria*: adults with history of cat allergic asthma; non-smokers; no other significant illness; PC20 histamine <4 mg/ml; FEV1 reversibility >20% with short acting beta-2 agonist; discontinued antihistamines, leukotriene antagonist and inhaled corticosteroids for 2 days prior, positive skin prick test and serum specific IgE to cat dander • *Exclusion criteria*: None specifically stated	• Significant improvement in airway hyperresponsiveness and late-phase skin test responses • Significant increase in $CD4^+$/$IFN\nu^+$ and $CD4^+/CD25^+$ cells post-treatment following intradermal challenge with cat allergen	• Proof of concept but inconclusive • 1 subject developed sneezing and cramping abdominal pain after the 3rd injection; epinephrine IM was administered although no change in vital parameters • Small sample size • Short course of Fel d 1 peptide immunotherapy reduces nonspecific bronchial hyperresponsiveness, reduces late-phase skin response to allergen challenge and is associated with an induction of Th1 immune response as evidenced by influx of Th1 cytokine positive cells

(Continues)

TABLE 1 (Continued)

Study	Allergen	Protocol	Key observations	Comments
Pene et al[51] (1998)	Cat (Fel d 1)	• RDBPCS (part of a large multi-centre European study with ALLERVAX CAT) • Adults with mild cat allergic asthma • Placebo (*n* = 6) or low (*n* = 8; 15–45mcg), medium (*n* = 6; 150–450 mcg) or high (*n* = 11; 1500–4500 mcg) dose of Fel d 1 • Subcutaneous weekly injections for 6 weeks • Assessments at baseline and 6 weeks post-therapy • *Inclusion criteria*: Adults with history of cat allergy with respiratory symptoms on exposure; positive skin prick test and serum specific IgE to cat dander; positive methacholine and cat allergen challenge tests • *Exclusion criteria*: FEV1 <70% of predicted; >3 asthma attacks per week; cat ownership or routine exposure; any form of immunotherapy in preceding 5 years; treatment with systemic or inhaled corticosteroids, sodium cromoglycate, nedocromil sodium ketotifen or theophylline in previous 3 months	• No significant difference in PD_{20}FEV1 between groups • Significant improvement baseline vs post-treatment in medium and high dose groups • IL-4 production significantly reduced in high dose group	• Proof of concept but inconclusive • Small sample size • Showed some immunological effect in high dose group
Maguire et al[52] (1999)	Cat (Fel d 1)	• Multi-centre RDBPCS (part of a large multi-centre North American study with ALLERVAX CAT) • *N* = 133 adult patients chronically exposed to cat or failed cat immunotherapy previously • *N* = 27 (placebo), *N* = 53 (75 mcg) and *N* = 53 (750 mcg). 8 injections weeks 1–19; 2 injections weeks 1, 2, 18 and 19 • *Dropouts*: 11%, 23% and 15% in placebo, 75mcg and 750mcg arms • 40–49% of participants in each group had history of asthma • Pre- and post-treatment evaluation • Inclusion criteria children and adults with history of cat allergy (age range 13–64 years); positive skin prick test to Fel d 1 • Exclusion criteria: unstable asthma; FEV1 <70% of predicted; underlying renal, hepatic, pulmonary, cardiovascular or psychiatric disease; women of childbearing age unless using effective and continuous birth control; history of alcohol or drug abuse; experimental drug within last 30 days; participated in ALLERVAX CAT trial previously	• Improved clinical tolerance to cat in active group but not placebo • Improvement in FEV1 in those with a reduce value at baseline	• Significantly greater adverse reactions in active group • Most adverse events reported were respiratory in origin and occurred in late phase following injection, improved with treatment • Early reactions—with 30 min, mostly respiratory; 2 in placebo, 5 each in active arm • *Late-phase reactions*: >30 min and <24 h, more frequent in active arm 36% vs placebo 19%. Mostly respiratory and after first injection • *Adrenaline requirement*: 3 patients required treatment with adrenaline, 1 from 75 mcg and 2 from 750 mcg groups. *First—20 min after injection 7 (750 mcg). Second—3.5 h after first injection (750 mcg). Third—2 h after first injection (75 mcg)*

(Continues)

TABLE 1 (Continued)

Study	Allergen	Protocol	Key observations	Comments
Simons, et al[56] (1996)	Cat (Fel d 1)	• RDBPCS • 2 long Fel d 1 peptides (IPC-1 and −2) • *N* = 42 adults with cat-induced rhinitis and/or asthma; 21 in active arm (750mcg of each peptide) and 21 in placebo arm • 4 weekly subcutaneous injections • Skin prick tests at baseline and 2, 6 and 24 weeks after last injection • Intradermal tests with cat at baseline and 2 weeks after last injection • PBMC cultures stimulated with Fel d 1 at baseline and 6 & 24 weeks after the last injection and measurement of IL-4, −10 and IFNν • *Inclusion criteria*: adults with history of rhinitis and/or asthma symptoms following cat exposure; positive skin prick test to Fel d 1 • *Exclusion criteria*: cat owners; pregnancy or women of childbearing potential; underlying medical disorders; those who receive allergen immunotherapy in preceding 12 months; ever received peptide injections; subjects requiring beta blockers, oral corticosteroids, ketotifen, astemizole, doxepin, tricyclic antidepressants or monoamine oxidase inhibitors,	• No significant changes in skin prick and intradermal tests following treatment • No significant changes *in vitro* T cell responses following treatment	• Adverse reactions within 24 h more frequent in active arm—rhinitis, worsening of asthma, reduction lung function and pruritus • No clear explanation offered by authors for the contrasting observations in this study compared to other studies with Fel d 1 peptides

**Search strategy*: The above studies were selected based on the following search strategy for this narrative review: *Databases used*: Pubmed.gov (advanced search) and Cochrane Library; dates—01 Jan'90 to 31 Dec'20; filters—clinical trial; secondary search was based on references cited within selected output. *Search terms used*: (a) rhinitis AND immunotherapy AND peptide (b) asthma AND immunotherapy AND peptide. *Outputs*: (a) PubMed =129; Cochrane Library =28; (b) PubMed =86; Cochrane Library =0.

eliciting either the induction of blocking antibodies or modulation of allergen-specific $CD4^+$ T cells. In other words, should AIT involve active immunization against the allergen or the induction of tolerance mechanisms designed to reduce the immune response to the antigen. One of the main barriers in our current understanding of AIT is that there are no reliable immunological correlates or biomarkers that determine therapeutic efficacy or indeed those that can accurately predict response to treatment at a patient level. The majority of patients remain sensitized to the respective allergen despite deriving clinical benefit post-AIT and this phenomenon is also well recognized in the context of hymenoptera venom immunotherapy (VIT).

5.2 | Peptides vs whole allergen

The advantage of using peptides rather than intact antigens is that peptides generally do not fold into the conformation found in the native antigen. As a result, it is most unlikely that a peptide would cross-link surface-bound IgE antibodies even if the peptide retained a low affinity B cell epitope. Furthermore, this is even less likely with short linear peptides that generally form a random coil state.

The aims for a safe, effective and durable impact of AIT are to:

1. Induce immunological tolerance by administering a preparation that limits the risk of cross-linking IgE and hence causing anaphylaxis
2. Develop a treatment strategy that induces effective and long-lasting tolerance within months rather than years
3. Reduce the levels of Th2 cells specific for the allergen
4. Increase levels of both $Foxp3^+$ Tregs and IL-10-secreting Tr1 cells responding to the allergen
5. Increase the ratio of IgG4:IgE-secreting B cells so as to increase levels of blocking antibodies

The only way to prevent IgE binding to a desensitizing agent is to disrupt the conformation of the allergen and its associated B cell epitopes. This can be achieved using allergen fragments generated by enzymatic digestion of the allergen or synthesis of either COPs[36,37,62] or the design of short synthetic peptides (SPs) representing dominant T cell epitopes of the allergen.[63] Here we will discuss the pros and cons of the latter two approaches.

5.3 | COPs vs SPs

COPs contain all of the $CD4^+$ T cell epitopes within the specific allergen and, therefore, have the desired immunomodulatory effect irrespective of individual variation in HLA type of the patient. This is more difficult with SPs; however, the promiscuous peptide binding properties of HLA-DR molecules mean that pan-DR-binding peptides can be designed that engage allergen-specific T cells in most individuals. The fundamental principle between COPs and SPs is, however, completely different. COPs are designed to be immunogenic, to induce immune modulation with induction of IL-10-producing T cells and an increase in the ratio of IgG_4:IgE. Importantly, it is known that IL-10-producing T cells such as Tr1 cells promote B cells to produce IgG_4.[64] IgG_4 has two important properties: first, it binds both complement and FcR poorly and hence does not promote inflammation; secondly, IgG_4 is functionally monovalent since its heavy and light chains can undergo half-Ig exchange.[65] Currently, COPs are administered with alum as adjuvant and as a result, there is a theoretical risk of both late-phase reaction and anti-drug antibody development with repeated administration. Nevertheless, COP treatment of birch pollen allergy has led to clinical benefit for two seasons after a single pre-seasonal course with demonstrable immunological signals.[37]

There is increasing evidence that SPs based on the $CD4^+$ T cell epitopes of allergens can induce tolerance and mediate suppression of the allergic response. The pioneers of this approach in allergy were Kay and Larche working with peptides from Fel d 1. They combined seven T cell epitopes from the allergen that was safe to administer and reduced the immune response to the antigen in allergic individuals. A short treatment with Fel d 1 SPs led to reduction in rhinoconjunctivitis symptoms that persisted for 2 years from the start of the treatment.[48] Campbell and colleagues confirmed that this approach generates $IL\text{-}10^+$ regulatory T cells capable of "linked" suppression of the response to distinct T cell epitopes within the same allergen.[66] Similar observations have been made in SP-AIT studies of bee venom,[67] grass allergen[39,40] and peanut allergy.[68] The induction of IL-10-secreting T cells in these SP-AIT studies is important since these Tr1 cells are known to promote IgG_4 production. Therefore, the induction of blocking antibodies, the aim of active immunization with whole allergens or COPs, can also be achieved by tolerance induction with SPs.

5.4 | Experience from peptide antigen immunotherapy in autoimmune diseases

The clinical trials summarized above are reminiscent of similar studies of SP administration in autoimmune diseases. SPs have been designed for a range of autoimmune diseases and have led to recent clinical trials in relapsing MS[32] and Graves' disease.[69] A phase 1b clinical trial of intradermal immunotherapy with SPs from a myelin antigen in saline solution showed a significant decrease in new/persisting T1 gadolinium-enhanced lesions from baseline to week 16, returning to baseline values at week 48.[32] Similarly, in Graves' disease, 7/10 mild to moderate hyperthyroid patients showed improvement in free thyroid hormone levels during the course of treatment. Importantly, no unexpected safety signals arose from administration of these SPs. It is interesting to note that a short course of treatment with SPs in ARC has been shown to induce long-term suppression of symptoms,[37,40] whereas the use of SPs produces only short-term benefit in autoimmune disease.[32,69] We propose that this is due to the continued exposure of allergic patients to strong antigens and the generation of memory B cells producing blocking antibodies. Effective use of SPs for autoimmune diseases will require repeated

administration to maintain suppression of the relatively weak response to their self-antigens.

5.5 | Mechanisms associated with peptide antigen immunotherapy

The Wraith laboratory has used experimental models to reveal the detailed mechanism of antigen-specific immunotherapy with SPs (Figure 1). Not all T cell epitopes induce tolerance and it transpires that peptides must bind directly to MHC II on antigen-presenting cells (APCs) to induce tolerance.[70] Recent work has shown that these antigen processing independent T cell epitopes (apitopes) bind preferentially to steady-state dendritic cells (DC) in lymphoid organs following subcutaneous injection (unpublished). Steady-state DC express low levels of costimulatory molecules and hence presentation of T cell epitopes by them is tolerogenic.[71] T cells responding to SPs presented by steady-state DC become anergic[72] and up-regulate expression of inhibitory receptors (CTLA-4, TIM3, TIGIT and LAG3) and the transcription factors, MAF and NFIL3, that dictate IL-10 production.[73] The resulting Tr1-like cells suppress costimulatory molecule expression on neighbouring APC in an IL-10 dependent manner[74] and hence mediate both linked and bystander suppression.[75] Immune regulation following immunotherapy with SPs is reinforced by the generation of myeloid-derived suppressor cells (MDSC)[76] and IL-10-secreting Breg cells.[29,77] Recent work has shown that the generation of immunoregulatory Tr1 cells is governed by epigenetic priming of genes characteristic of a tolerogenic gene signature.[78] It seems likely that the mechanisms leading to the generation of Foxp3 and Tr1 cells are similar for allergens and self-antigens: we have much to learn from the parallel development of antigen-specific immunotherapeutic approaches in the fields of allergy and autoimmune diseases.

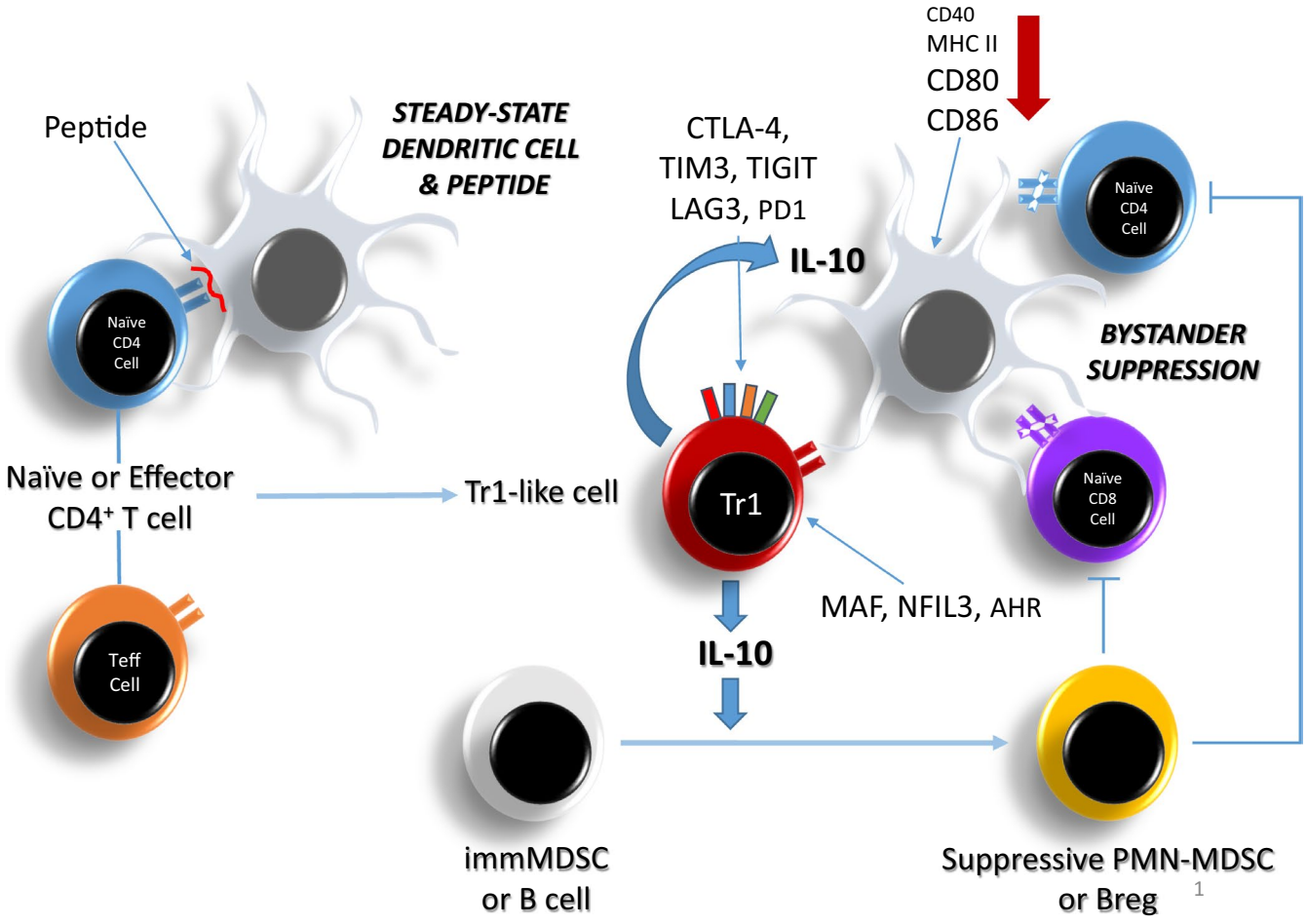

FIGURE 1 Induction of IL-10-secreting Tr1 cells by SPs. Soluble peptides administered without adjuvants are presented to naïve or effector T cells by antigen-presenting cell (APC), including steady-state dendritic cell (DC). When encountering MHC and antigen on these steady-state APC, where levels of costimulatory molecules are limited, T cells differentiate into IL-10-secreting Tr1 cells. The resulting Tr1 cells suppress costimulatory molecule expression, mediate linked and bystander suppression of the response of other T cells and promote differentiation of myeloid-derived suppressor cells (MDSC) and IL-10-secreting Breg cells. Furthermore, Tr1 cells induce class switching to IgG_4 in B cells

6 | FUTURE DEVELOPMENT OF PEPTIDE IMMUNOTHERAPY FOR TREATMENT OF ALLERGY AND ASTHMA

The time required to achieve effective tolerance by AIT for allergic airway diseases is currently months to years. Based on initial results of peptide therapy, however, it appears that tolerance to allergens is achievable with a short course of peptide AIT. Even so, there are likely to be combination therapies that could enhance AIT without disrupting tolerance induction. Whilst the use of steroids can inhibit T cell activation, previous studies have shown that combined dexamethasone and vitamin D3 promotes Tr1 cell differentiation.[79] In addition, antibodies targeting effector arms of the allergic response, including anti-IgE or anti-IL-5, could be given whilst concurrently inducing tolerance by peptide therapy. Furthermore, it may now be possible to reduce levels of plasma cells using anti-CD38 antibodies, as tested recently in systemic lupus erythematosus.[80]

As mentioned above, COPs and SPs depend on fundamentally different mechanisms of active immunization versus tolerization, respectively. It is possible that the effect of COPs could be improved by combination with virosomes. Anergis, the company producing COPs, has announced improved efficacy of their treatment when combined with virosomes from Mymetics, in an unpublished pre-clinical study. A number of groups are investigating different ways to deliver SPs for treatment of autoimmune diseases.[81] These include presentation by tolerogenic DCs, generated *in vitro* and then transferred back to the patient; delivery on red blood cells or nanoparticles designed to target the tolerogenic environment of the liver; combination with immunosuppressive drugs in nanoparticles or delivery on MHC coated nanoparticles. Although each of these approaches is tried and tested in pre-clinical models of autoimmune disease, none have yet been designed to treat allergic diseases. Any one of these approaches could improve on currently available approaches.

At present, we know little about the mechanism of action (MoA) of novel AIT approaches being test in clinical trials. We need to define the optimal conditions for induction of tolerance, immune correlates of effective desensitization, kinetics of tolerance, longevity of disease suppression and molecular basis of effective immunotherapy. We now have the tools allowing us to focus on antigen-specific cells isolated from patients[82] using peptide-MHC multimers and high-throughput transcriptional profiling to define MoA. These tools enable us to address the critical questions listed above. Furthermore, we must use precision medicine approaches to define why each patient does or does not respond to treatment and hence allow better patient stratification.

In conclusion, we are now beginning to understand the MoA of conventional and novel approaches to AIT. We propose that peptide AIT will greatly enhance the safety and ultimately compliance levels in those treated and hence improve management of this rapidly increasing group of diseases. A number of distinct approaches are in the pipeline and when proven to be both safe and effective these will greatly improve the armamentarium of the allergist.

CONFLICT OF INTEREST

MTK received grants from FSA, GCRF and NIHR for research outside submitted work. MTK received funds from ALK Abello to attend an international conference. MTKs department has received an educational grant from Thermo Fisher, ALK Abello, MEDA and other pharmaceutical companies for annual PracticAllergy course. The authors received a grant from MRC CiC for immunological validation of Der p 1 peptides for treatment of house dust mite allergy. DW serves as Chief Scientific Officer for Apitope Intl NV on a consultative basis; has sat on scientific advisory boards for Actelion Pharma, and Zealand Pharma; received travel funding from Apitope Intl NV; is a senior editor for Immunotherapy; holds patents for peptides, tolerization-inducing composition, FVIII peptides and their use in tolerizing haemophiliacs, composition, disease markers, tolerogenic peptides from myelin basic protein, peptide selection method; has consulted for Peptide Therapeutics Ltd., Teva, GSK Bio, Hoffman La Roche, Novartis, DTI, and the Food Standards Agency; received research support within the past 3 years from Apitope International NV, UCB Celltech, MRC, the Immune Tolerance Network, the Helmsley Trust, Diabetes UK and Wellcome Trust; holds stock and stock options with Apitope Int. NV; and was an expert witness for Geron.

ORCID

Mamidipudi T. Krishna https://orcid.org/0000-0003-2109-5777

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