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Allergen Immunotherapy for the Prevention and Treatment of Asthma

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ABSTRACT

Allergic asthma is the predominant phenotype among asthmatics. Although conventional pharmacotherapy is a central component in the management of asthma, it does not enable control of asthma symptoms in all patients. In recent decades, some uncontrolled asthmatic patients, especially those with allergic asthma, have benefited from biological therapies. However, biologics do not address all the unmet needs left by conventional pharmacotherapy. Furthermore, it is noteworthy that neither conventional pharmacotherapy nor biological therapies have disease-modifying properties. In this context, allergen immunotherapy (AIT) represents an indispensable component of the therapeutic arsenal against allergic asthma, due to its disease-modifying immunological effects. In this review article, funded by an AIT manufacturer, we find clinical trials support AIT as the only treatment option able both to improve allergic asthma symptoms and to prevent the onset and worsening of the condition. For patients with severe asthma or other safety concerns, the combination of AIT and biologics offers very promising new treatment modalities for the management of allergic asthma.

Trial Registration: clinicaltrials.gov identifier: NCT06027073

Abbreviations: AIT, allergen immunotherapy; BHR, bronchial hyperresponsiveness; Breg, regulatory B; C1q, complement component 1q; CD, cluster of differentiation molecule; CTLA-4, cytotoxic T-lymphocyte associated protein 4; DC, dendritic cells; DC2, type 2 dendritic cells; DCreg, regulatory dendritic cells; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; GINA, Global Initiative for Asthma; HDM, house dust mites; HR, hazard ratio; ICS, inhaled corticosteroids; iDC, immature dendritic cells; IFN-γ, interferon gamma; Ig, immunoglobulin; IL, interleukin; IL-13R, receptor for IL-13; IL-4R, receptor for IL-4; IL-4Rα, α-chain of the receptor for IL-4 and IL-13; IL-5R, receptor for IL-5; IL-5Rα, α-chain of the receptor for IL-5; ILC2, type 2 innate lymphoid cells; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; mAb, monoclonal antibody; NK, natural killer; nTreg, natural regulatory T; OCS, oral corticosteroids; OIT, oral immunotherapy; OR, odds ratio; RCT, randomised controlled trial; RDBPC:, randomised, double-blind, placebo-controlled; RIPK4, receptor-interacting serine/threonine-protein kinase 4; RPC, randomised, placebo-controlled; RR, risk ratio; SABA, short-acting β_2 agonist; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SQ, standardised quality; TFH, follicular helper T; TGF-β, transforming growth factor beta; Th1, type 1 helper T; Th17, type 17 helper T; Th2, type 2 helper T; Th2A, proallergic type 2 helper T; Tr1, type 1 regulatory T; Treg, regulatory T; TSLP, thymic stromal lymphopoietin; TU, therapeutic unit.

Mohamed H. Shamji and Laurent Mascarell contributed equally to this review.

Summary

- Allergen immunotherapy is a disease-modifying approach to be considered in the management of allergic asthma
- Numerous studies suggest that allergen immunotherapy may prevent asthma onset and worsening and improves asthma symptoms
- The combination of allergen immunotherapy and biologics may further improve the management of allergic asthma

1 | Introduction

Asthma is a chronic inflammatory respiratory disease of the lower airways that affects more than 350 million people worldwide, accounts for 0.4 million deaths per year, and is increasing in prevalence [1–5]. Especially when it is not controlled, it can result in a marked deterioration in quality of life [6], not to mention its economic burden, which increases with disease severity [1, 7–10].

Asthma is characterised by the combination, to varying degrees, of bronchial hyperresponsiveness (BHR), inflammation of the airways and their obstruction by mucus plugs and remodelling of their walls, which translates into respiratory distress, chest tightness, wheezing, coughing, sputum formation and exercise intolerance [4, 11, 12]. Both the complexity and heterogeneity of the disease [6, 13, 14] have led to the definition of the so-called 'asthma endotypes', with the aim to develop personalised therapies [14].

To begin with, one may distinguish between two major asthma subtypes, namely, Th2-high or type 2-high asthma, more simply called 'type 2 asthma', and Th2-low, type 2-low or 'non-type 2 asthma' [5]. Type 2 asthma is characterised by the role of Th2 cytokines, notably interleukin (IL)-4, IL-5 and IL-13, and involves dendritic cells, Th2 lymphocytes, type 2 innate lymphoid cells (ILC2), epithelial cells, fibrocytes, smooth muscle cells, M2 macrophages, natural killer (NK)-T cells producing type 2 cytokines, mast cells and eosinophils [6]. It is especially associated with high risk of exacerbations and accelerated lung function decline [5]. As for non-type 2 asthma, it involves IL-8, IL-17 and IL-23, as well as Th17 lymphocytes, neutrophils and mast cells [6, 15]. Type 2 asthma was reported to account for 50% of patients with mild-to-moderate asthma [16] and for 70% of those suffering from severe asthma [17].

Beyond the distinction between non-type 2 and type 2 asthma, the latter encompasses allergic and/or eosinophilic asthma [6]. It is worth noting that among the different types of asthma identified, allergic—that is, allergen-triggered—asthma is the most common [18–21] and the most easily recognised one [12].

In the following sections, we shall first overview the management of asthma using conventional pharmacotherapy and identify the needs it fails to meet when it comes to more severe forms of the disease. We will then address the management of the latter with biological therapies, and what needs are still unmet by them. Finally, following the strategy described in Data S1, we shall review the benefits of allergen immunotherapy (AIT), either as a standalone or as an add-on to conventional pharmacotherapy and/or biological therapy, in the management of allergic asthma, from both the preventive and therapeutic points of view.

2 | From Asthma Management by Conventional Pharmacotherapy to Severe Asthma and Its Unmet Needs

2.1 | General Principles of Asthma Management

Asthma management aims to achieve good symptom control, prevent asthma exacerbations and minimise future risk of persistent airflow limitation, asthma-related death and treatment-related side effects [12]. For both symptom control and future risk reduction, it implies a continual cycle of assessment, treatment and review of the patient's response. The treatment options to be considered depend on asthma severity. At the population level, these options mainly rely on evidence about symptoms and exacerbations, as obtained from randomised controlled trials, pragmatic studies and strong observational data, but also rely of course on the treatment availability and cost. Options can be adjusted at the individual patient level, taking into account the patient's characteristic or phenotype, the patient's views as well as practical issues [12, 22]. The management of asthma by conventional pharmacotherapy is described in detail in Data S2.

2.2 | Severe Asthma and Corresponding Unmet Needs

Severe asthma is defined as asthma requiring a high level of conventional pharmacological treatment, namely, high doses of inhaled corticosteroids (ICS). The definition of severe asthma most widely used in recent years is the one given by a task force supported by the European Respiratory Society and the American Thoracic Society [4]. Provided the diagnosis of asthma is confirmed and comorbidities have been addressed, this definition reads: 'asthma which requires treatment with high-dose ICS plus a second controller (and/or systemic corticosteroids) to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy' [23]. Actually, it was recently reported that asthma severity paralleled the intensity of drug treatment [24].

From about 3% to 13% of asthmatic patients suffer from a severe form of the disease, accounting for more than 50% of the asthma-related economic burden, not to mention substantial social overheads [4, 23, 25, 26]. Generally, patients suffering from severe asthma have their symptoms controlled by ICS plus short-acting β_2 agonists (SABAs) or long-acting β_2 agonists (LABAs), but ~4%–20% of them do not respond to these guideline-based treatments, accounting for ~80% of the total asthma-related economic burden [14, 26]. Several approaches have been developed to address the unmet needs of these uncontrolled severe asthma patients. Especially if they suffer from type 2 asthma, they may be prescribed biologics, provided that they are eligible and that such treatments are locally available [27].

3 | Biological Therapies: A Fast-Growing Approach to Asthma Treatment

3.1 | Biological Therapies in the Management of Asthma

Several monoclonal antibodies (mAbs) have been registered to treat moderate-to-severe asthma, as described in Data S3. It is worth stressing that, among the characteristics of asthma, they essentially target inflammation [6], and that, on the other hand, they are mainly intended to treat the type 2 form of the disease [4, 15, 27, 28], especially allergic asthma. As a matter of fact, they are specific for various factors involved in the allergen sensitisation and allergic reaction cascades, from TSLP and Th2 cytokines (typically IL-4, IL-5 and IL-13) or receptors thereof, upstream of this cascade, to IgE, more downstream [28] (Figure 1, Data S3 and Table S1). These biologics have revolutionised the management of severe asthma [26]. They indeed allow to reduce asthma exacerbations, improve asthma control, reduce the use of corticosteroids, typically oral corticosteroids (OCS, up to complete withdrawal) and/or improve lung function and/or asthma-related quality of life of patients [4, 6] (Table S2). As an illustration, eligibility criteria in the USA are described for some of them in Table S3, as well as the proportion of severe asthmatic patients that are eligible for each. Akenroye et al. reported the proportion of patients eligible for a given mAb that are also eligible for another one, such an overlap making it possible to switch between biologics. For example, 100% of patients eligible for reslizumab (anti-IL-5) and/or benralizumab (anti-IL-5Rα), and ~70%–80% of patients eligible for omalizumab (anti-IgE), are also eligible for mepolizumab (anti-IL-5) and dupilumab (anti-IL-4Rα) [26]. In practice, however, prescription criteria of biologics, as well as ease of access to them, differ significantly depending on the country [29].

3.2 | Still Unmet Needs in Allergic Asthma

Type 2 asthma, including allergic asthma, is overall associated with a good response to type 2-targeted biologics [5]. However, not all patients with asthma, whether allergic or not, respond to conventional pharmacotherapy and biological therapies, representing still unmet health needs [30, 31]. In addition, biological therapy does not generally make it possible to completely dispense with conventional pharmacotherapy, because of a possible decline in lung function associated with increase in fractional exhaled nitric oxide (FeNO) and decrease in forced expiratory volume in the first second (FEV_1) [32], although, on the other hand, pharmacotherapy is itself associated with adverse events. Notably, systemic corticosteroids can trigger serious side effects such as osteoporosis, diabetes and cardiovascular disease, even in case of infrequent short bursts, hence the phrase 'people remodelling' coined to denote steroid-induced health issues [27]. These side effects are especially likely, since neither conventional pharmacotherapy nor biological therapy are truly disease-modifying approaches [33], that is, able to induce so-called 'asthma remission off treatment' [34], so that they must be taken over long periods, potentially for life. For example, the benefits of ICS are lost as soon as they are stopped [33]. Likewise, in most patients with severe asthma, the benefits of biologics are only maintained during treatment, and discontinuation of the latter can lead to the so-called 'flare-up' of asthma, with a resurgence of asthma exacerbations and/or loss of asthma control [34]. Hence the importance of truly curative approaches.

4 | AIT and Allergic Asthma

So far, AIT is the only treatment known to address the underlying cause of IgE-mediated allergies, thereby offering long-term clinical benefits after its discontinuation [35–37]. This disease-modifying treatment consists of the administration of increasing doses of allergen extract, followed by the delivery of a maintenance dose, mainly through the subcutaneous or sublingual route (SCIT and SLIT, respectively) [36]. This results in the dampening of allergen-specific type 2 immunity and in the production of so-called 'blocking' IgG and IgA antibodies, which prevent IgE from binding to allergens [36, 38–40] (Figure 2). As regards asthma, AIT has the potential to prevent patients with allergic rhinitis to develop allergic asthma, or those with an established allergic asthma to see it aggravated. It also has the potential to treat such an established allergic asthma. With respect to the latter aim, AIT may be associated with biologics, especially when it comes to treating severe allergic asthma (Figure 3).

4.1 | AIT in the Prevention of the Onset and Worsening of Allergic Asthma

4.1.1 | The Rationale Behind AIT-Based Prevention of Allergic Asthma Onset and Worsening

It has been suggested that allergic rhinitis and allergic asthma represent a continuum of disease [41], simply called 'respiratory allergy' [42]. A study by Linneberg et al. supports the hypothesis that they are manifestations of the same disease entity [43], hence the so-called 'united airway disease hypothesis' [44] or 'unified airway model' [45]. The fact is that they are closely associated conditions, as expected from their being both the result of a Th2 bias [44, 46].

It has been reported that individuals with allergic rhinitis, especially children, often develop asthma over time [44, 47]. As a matter of fact, rhinitis is a significant risk factor for subsequent asthma development [48], especially when it is associated with BHR [49, 50]. More precisely, patients suffering from allergic rhinitis display a 2- to 7-fold increased risk of developing asthma [51–53]. That allergic rhinitis generally evolves into allergic asthma, rather than the other way around, is supported by the high prevalence of nonasthmatic patients with allergic rhinitis (> 50%), compared with the low proportion of patients displaying allergic asthma without rhinitis (< 20%) [45, 54–56]. Extension of inflammation to the lower airways is observed especially in patients with perennial allergic rhinitis [55]. The evolution of the allergic condition from rhinitis only to both rhinitis and asthma might be due, at least in part, to a strengthening of the underlying Th2 skewing [57, 58]. Insofar as AIT has an impact on such a bias [36, 59], this treatment is expected to halt [42, 44, 60], or at least slow [61],

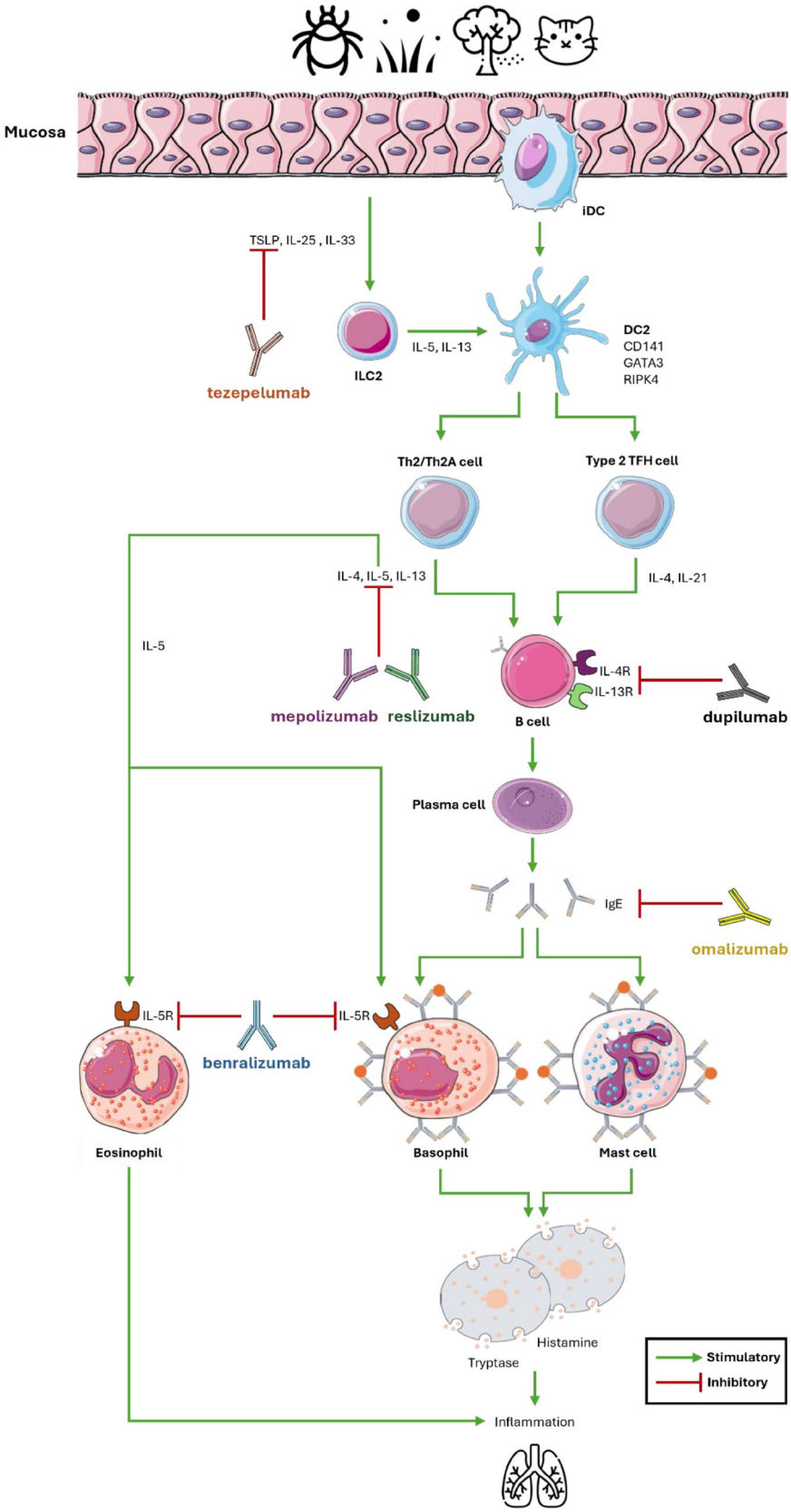

FIGURE 1 | The mAbs registered to treat moderate-to-severe asthma and their targets within the cascades leading to allergen sensitisation and allergic inflammation.

the progression from allergic rhinitis to allergic asthma. It is also expected to have an impact on the worsening of allergic asthma itself, given that uncontrolled allergic rhinitis may be associated with worsening of coexisting asthma [46], and that Th2 inflammation appears to be involved in the severity of asthma, as mentioned above. On the contrary, it has

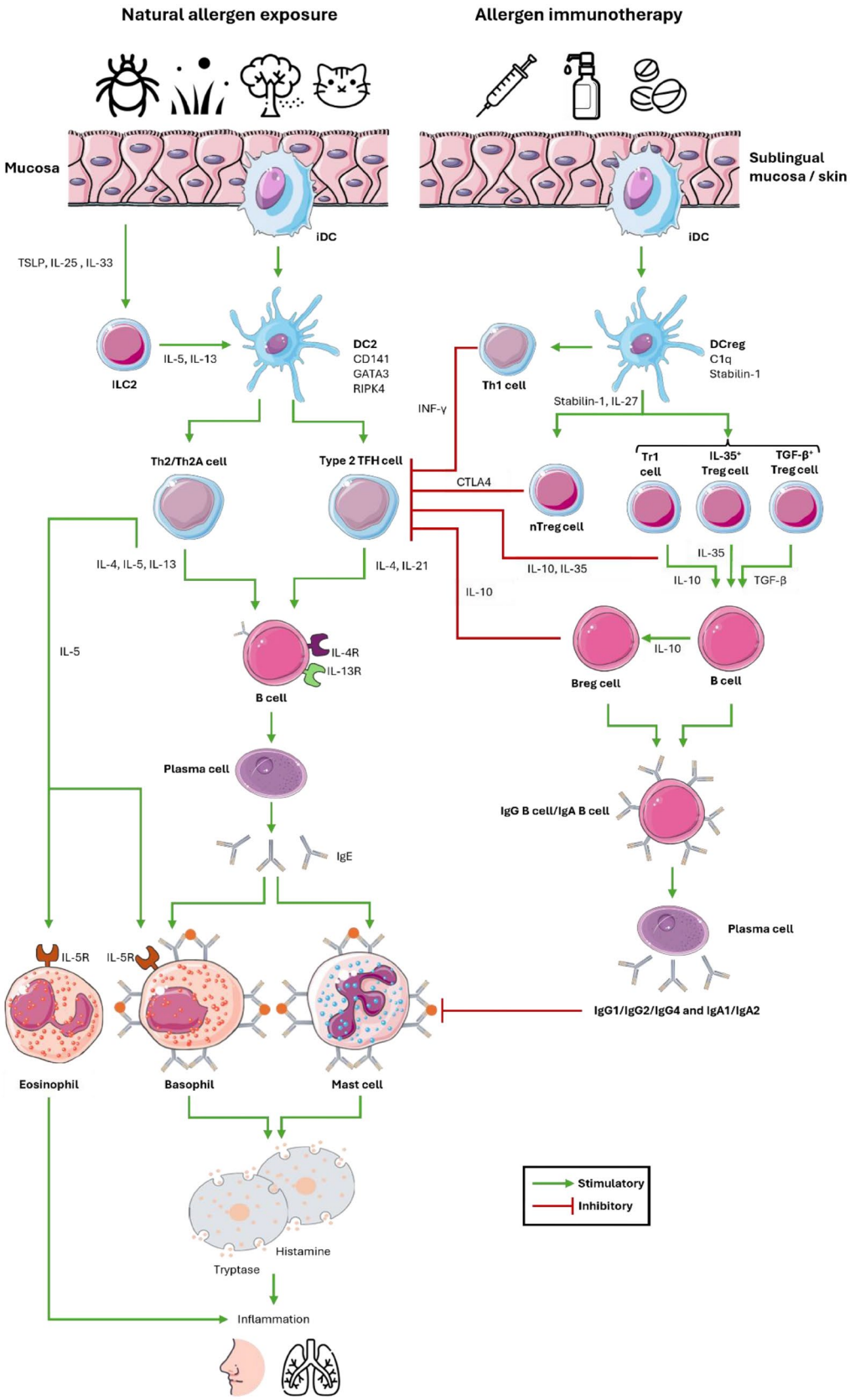

FIGURE 2 | The mechanisms of allergen sensitisation and allergic inflammation (left) and those of allergen immunotherapy (right).

been suggested that allergen-driven bronchial inflammation can promote nasal inflammation [62]. In this connection, it has been recently reported that asthma is associated with increased severity and duration of rhinitis [63]. In a virtuous circle, AIT-driven prevention or reduction of allergic asthma may therefore benefit allergic rhinitis.

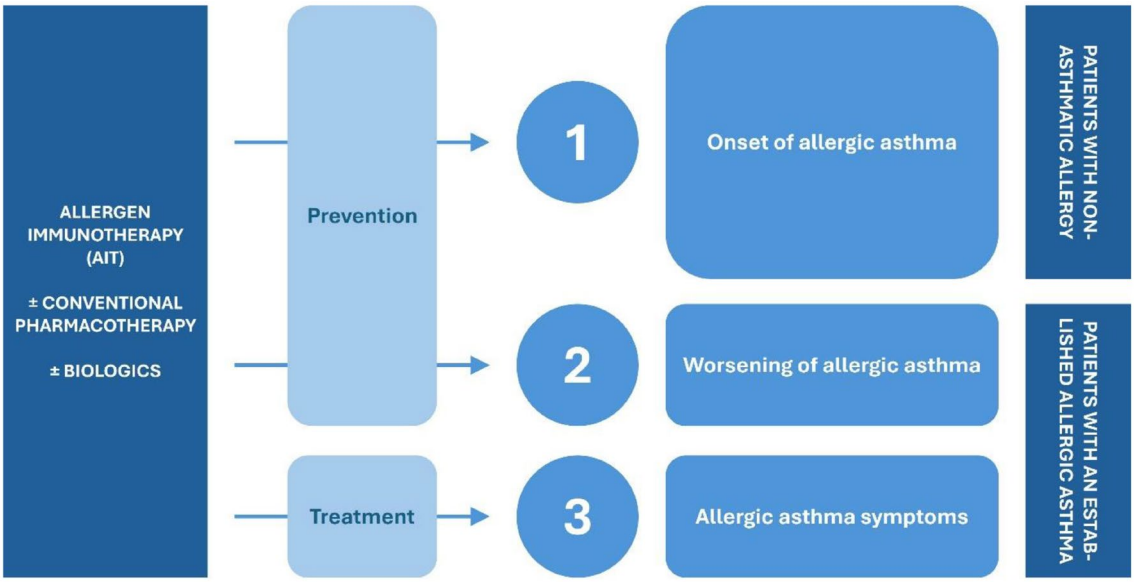

FIGURE 3 | Three levels at which AIT may be beneficial in relation to allergic asthma, either as a standalone treatment or as an add-on to conventional pharmacotherapy and/or biological therapy.

4.1.2 | AIT-Based Prevention of the Onset of Allergic Asthma

4.1.2.1 | Prospective Clinical Trials. An open randomised controlled trial (RCT) of SCIT was conducted as early as 1954 on 200 subjects over 10 years of age suffering from grass pollen-induced allergic rhinitis, with or without asthma. Among the 143 patients with no asthma before treatment, 3 developed asthma during the period of coseasonal SCIT treatment with grass pollen allergens, all of them being administered the placebo [64]. To focus on trials conducted within the last four decades, we identified 14 articles addressing the prospective clinical evaluation of AIT's preventive potential on asthma development. They involved a total of more than 1700 children, adolescents and adults suffering from allergic rhinitis, especially when it is associated with BHR (Table 1). They describe 10 studies ranging from open uncontrolled or controlled trials (2 studies) and open RCTs (4 studies) to randomised, double-blind, placebo-controlled (RDBPC) trials (4 studies), and covering AIT with extracts of either house dust mites (HDM) or grass, tree or weed pollens, whether administered subcutaneously (6 studies), sublingually (3 studies) or orally (1 study). Overall, these studies indicate that not only does AIT appear to prevent the development of asthma in patients with allergic rhinitis [65–67, 70–73, 75], but this preventive effect seems to be maintained for years after AIT termination [18, 68, 69, 74, 76]. Prevention of the onset of asthma [67, 72, 73] and its maintenance [68, 74] reached statistical significance in 4 clinical trials, all of them being open controlled studies, and 3 of which involved randomisation [67, 68, 72, 73]. They were conducted using either subcutaneous injection [67, 68, 74] or sublingual administration [72, 73] of HDM extracts [74], pollen extracts [67, 68, 72] or both (Table 1) [73].

Random-effects meta-analysis of six of the trials described above [65–67, 70, 72, 73] demonstrated a significantly reduced short-term risk of developing asthma in patients with established allergic rhinitis [78]. This significant preventive effect of AIT was especially observed in patients aged under 18 and those receiving pollen AIT [78].

The largest and optimally designed clinical study addressing the prevention of asthma development by AIT was a RDBPC trial conducted in 812 children aged 5 to 12 with grass pollen-induced rhinoconjunctivitis, treated by SLIT for 3 years and then followed for 2 years [77]. Admittedly, this trial did not meet its primary endpoint, namely, a difference in time to onset of asthma between the AIT and placebo groups (Table 1). However, it did show that AIT significantly reduced the risk of developing asthma symptoms or using pharmacotherapy for asthma in patients having developed the condition (OR 0.66; $p < 0.05$), whether during the 2-year follow-up period or the whole 5-year study period [77]. This study was part of a recent pooled comparison of SLIT and non-SLIT treatment, along with three other studies, two of which are mentioned above [72, 73], the third one being a non-randomised open case–control observational study on 171 children and adolescents [79]. According to this pooled analysis, the incidence of developing asthma was significantly lower in patients receiving SLIT, compared with the non-SLIT group (RR 0.43; $p < 0.05$) [80].

4.1.2.2 | Real-World Retrospective Database Analyses. Real-world retrospective studies relying on databases can be seen as complementary to prospective clinical trials. On the one hand, and compared with the latter, the former run the risk of bias, insofar as patients selected for AIT may differ from other allergic patients [44]. On the other hand, when compared with clinical trials, retrospective studies deserve credit for generally allowing for observation of larger, more inclusive populations of patients on longer periods [81–84]. We identified nine such studies addressing the preventive effect of AIT on asthma development [85–95], the treatment consisting of either subcutaneous or sublingual administration of natural extracts or allergoids (Table 2). These studies, relying on German and French databases, included a total of more than 840,000 children, adolescents and adults suffering from allergies to seasonal or perennial allergens. According to

TABLE 1 | Clinical trials addressing the prevention of asthma development by AIT.

Reference(s)	Type of trial	Type of patients	Number of patients	Allergen source(s)	Type of AIT	Outcomes
Moller et al. 1986 [65]	RDBPC trial	Swedish children aged 9 to 17 with birch pollen-induced rhinoconjunctivitis	30	Birch pollen	Oral immunotherapy (OIT, enteric-coated capsules)	After 10 months, 0 of 14 patients of the treated group developed asthma, compared with 5 of 16 patients in the placebo group
Jacobsen et al. 1997 [18]	Open uncontrolled trial	36 subjects aged 15 to 72 with tree pollen-induced rhinoconjunctivitis with or without asthma	36	Birch with or without alder and hazel pollen	SCIT	6 years after termination of 3-year AIT, for patients with no asthma at baseline, none had developed asthma
Grembiale et al. 2000 [66]	RDBPC trial	Subjects aged 10 to 38 with perennial rhinitis due to monosensitisation to HDM and BHR to metacholine	44	HDM	SCIT	After 2 years, 0 patient of the treated group developed asthma, compared with 2 in the placebo group ($p = 0.49$)
Moller et al. 2002 [67], Niggemann et al. 2006 [68], Jacobsen et al. 2007 [69]	Open RCT	European children aged 6 to 14 with grass and/or birch pollen-induced rhinoconjunctivitis with or without mild asthma	205	Grass and/or birch pollen	SCIT	After 3 years of AIT, for children without asthma at baseline, the odds ratio (OR) for no asthma was 2.5 in favour of AIT ($p < 0.05$); the preventive effect of AIT on asthma was maintained 2 years (OR 2.7; $p < 0.05$) and 7 years (OR of 2.5) after AIT termination
Crimi et al. 2004 [70], Polosa et al. 2014 [71]	RDBPC trial	Nonasthmatic subjects aged 20 to 54 with seasonal rhinitis and monosensitised to pellitory pollen	30	*Parietaria judaica* pollen	SCIT	After 3 years of AIT, 2 of 14 patients of the treated group developed asthma, compared with 7 of 15 in the placebo group ($p = 0.06$)

(Continues)

TABLE 1 | (Continued)

Reference(s)	Type of trial	Type of patients	Number of patients	Allergen source(s)	Type of AIT	Outcomes
Novembre et al. 2004 [72]	Open RCT	Italian children aged 5 to 14 with grass pollen-induced rhinoconjunctivitis	113	Grass pollen	SLIT	After 3 years of coseasonal AIT, the proportion of patients having developed asthma was significantly lower in the treated subjects compared with the control subjects ($p < 0.05$)
Marogna et al. 2008 [73]	Open RCT	Italian children aged 5 to 17 with allergic rhinitis with or without intermittent asthma	216	HDM, and grass, birch and *Parietaria* pollen	SLIT	After 3 years of AIT, 2% of treated subjects had persistent mild asthma compared with 29% of control subjects ($p < 0.001$)
Peng et al. 2013 [74]	Open controlled trial	Chinese children (≥ 5), adolescents and adults with HDM-induced rhinitis with or without asthma	146	HDM	SCIT	5 years after initiation of a 3-year course of AIT, for patients without asthma at baseline, the OR for no asthma was 3.6 in favour of AIT ($p < 0.05$)
Song et al. 2014 [75], Song et al. 2015 [76]	Open RCT	Chinese subjects with HDM-induced rhinitis	102	HDM	SCIT	After 3 years of AIT, 0 treated patient developed asthma, compared with 17% in the placebo group; the preventive effect of AIT on asthma was maintained 2 years after AIT termination, with still 0 treated patient with asthma, compared with 22% in the placebo group
Valovirta et al. 2018 [77]	RDBPC trial	European children aged 5 to 12 with grass pollen-induced rhinoconjunctivitis	812	Grass pollen	SLIT (tablets)	During the 5-year study (3-year treatment +2-year follow-up), there was no difference in time to onset of asthma between treated and control subjects ($p = 0.67$)

all nine studies but one, the risk of developing asthma was significantly lower in subjects receiving AIT, compared with control patients (Table 2). Two of them, focusing on grass pollen allergy, indicated that the preventive effect of AIT was significantly maintained after AIT termination [87, 88]. During the overall analysis period of two other studies, addressing allergy to tree or grass/cereal pollen, only SLIT with natural extract induced a significantly reduced risk of developing asthma, compared with SCIT involving either natural extracts or allergoids [89, 91]. The so-called 'EfficAPSI study' alone involved almost 450,000 patients aged 5 years and over and focused on liquid SLIT [92, 93]. It indicated that, depending on the definition of asthma onset, the risk of developing asthma was significantly reduced by ~20 up to ~40% in patients receiving liquid SLIT compared to non-SLIT patients, and that this significant reduction was observed whatever the age range, namely, 5–25 years, 25–40 years, 40–50 years and over 50 years, but also whatever the allergen source, except cat, namely, grass, birch and ragweed pollens, as well as HDM, and mould (*Alternaria*) (Table 2). An observational study as well as the preventive effect of AIT on the onset of allergic asthma are summarised in Data S4.

4.1.3 | AIT-Based Prevention of Asthma Worsening

We mentioned above nine real-world retrospective studies addressing the preventive effect of AIT on asthma onset. Six of them, either as such or in the form or related analyses, also addressed AIT's prevention of asthma worsening [87–90, 92, 93, 96], while an additional study exclusively addressed it [97]. The 7 studies involved a total of more than 765,000 children, adolescents and adults suffering from allergies to seasonal or perennial allergens, part of them being treated by AIT using the subcutaneous or sublingual routes (Table 3). According to all seven studies, AIT significantly prevents the progression of asthma, especially from mild to more severe asthma [97], as compared with no AIT. According to three studies [87, 88, 96], AIT prevents asthma worsening not only during the treatment but also after its discontinuation. Strikingly, one of them even indicates that SLIT-induced slowing of asthma progression is greater after than during AIT (40% and ≤10% decrease, respectively, in prescriptions for symptomatic asthma medications) [88]. This suggests a partly delayed benefit of AIT on asthma worsening, which might be explained by an AIT-induced long-term reversal of the mechanisms underlying allergic asthma, in particular the Th2 skewing and the resulting tendency to produce specific IgE. The prevention of asthma worsening after treatment cessation was confirmed by three studies [89, 90, 97]. In some cases at least, the younger the patient, the more beneficial the AIT's preventive effect on asthma progression [90, 97].

4.2 | The Treatment of an Established Mild-To-Moderate Allergic Asthma by AIT

4.2.1 | Prospective Clinical Trials

Early indications of AIT's benefits in the treatment of asthma can be found in the above-mentioned open RCT trial performed as early as 1954. According to this trial, almost 95% of those patients who suffered from allergic asthma and who received AIT reported no or improved symptoms, compared with only ~30% of allergic asthma patients administered a placebo [64]. Since then, a large number of clinical trials studying AIT in the treatment of allergic asthma have been reported. Abramson, Puy and Weiner reviewed no less than 90 such studies conducted between 1954 and 2005, and involving exclusively SCIT, performed with HDM, pollen, animal dander, mould or latex extracts, either alone or in combinations [98–103]. More than 60 of them were RDBPC trials, whereas another 220 performed during this period were never reviewed by these authors, primarily due to the absence of control or randomisation, or to irrelevant patient selection or clinical outcomes. The authors consistently concluded that SCIT not only reduced asthma symptoms and medication use, but also improved BHR. Of note, they also concluded that SCIT-treated patients were significantly less likely to report symptomatic deterioration or increased use of medication [103], thus supporting AIT's preventive effect on asthma worsening. However, they warned that SCIT is not without risk of significant adverse effects, including anaphylaxis, hence their reminder that adequate resuscitation measures must be available [103]. With respect to SLIT, Calamita et al. reviewed 25 RCTs up to 2005 involving a total of more than 1700 patients, 19 of these trials being RDBPC studies [104]. The authors came to the conclusion that AIT administered through the sublingual route is a safe alternative to SCIT for the treatment of allergic asthma.

For this review, we further analysed the clinical studies on AIT treatment of allergic asthma that have been published since 2005, excluding those already analysed by Calamita et al. and focusing on RDBPC trials involving a total of more than 50 patients. We identified 6 such trials, all involving the administration of HDM extracts, 3 by the subcutaneous route [105–107] and the other 3 by the sublingual route [108–110], in a total of more than 2500 patients (Table 4). All but one [110] confirmed the benefit of AIT in the treatment of asthma, provided the dose of extract administered was sufficiently high (Table 4), which, incidentally, highlights the importance of a good understanding of the dose labeling of allergen products [111]. This benefit was objectified by significantly improved bronchial provocation tests, improved symptoms and/or reduced medication intake. As regards the study by Tanaka et al. among the approximately 40% of randomised patients who had used SABA during the baseline period, those receiving AIT experienced a significantly longer time from randomisation to first asthma exacerbation, compared with patients receiving placebo (primary endpoint; $p < 0.05$) [110]. Among the same ~40% of patients, those receiving the highest dose of AIT, but not those receiving the lowest dose, experienced a significantly longer time to first asthma exacerbation from the start of the ICS reduction/withdrawal period of the trial, compared with placebo-administered patients ($p < 0.05$). The fact that, in this trial, the primary endpoint did not reach statistical significance for the whole population of randomised patients might be explained, at least partially, as follows: the ~60% of patients not using SABA during the baseline period had their asthma sufficiently controlled by ICS alone, so that asthma exacerbations did not occur, even when ICS were reduced or withdrawn, thanks to a carryover effect of the latter [110, 112]. A recent study of the patients from the trial by Virchow et al. [109] interestingly indicated that the effect of

TABLE 2 | Real-world retrospective database studies addressing the prevention of asthma development by AIT.

Reference(s)	Area	Type of patients	Number of patients	Allergen sources	Type(s) of AIT	Outcomes
Schmitt et al. 2015 [85]	Germany (state of Saxony)	Subjects with chronic allergic rhinitis and without asthma (mean age, 37 years)	118,754 (2431 having received AIT and 116,323 controls)	Seasonal, perennial or combinations thereof	SCIT, SLIT or combinations thereof	During a ~6-year period after the beginning of the study, the risk of developing asthma was significantly lower in patients receiving AIT (RR of 0.60; $p < 0.01$)
Devillier et al. 2017 [86], Zielen et al. 2018 [87]	Germany (nationwide)	Subjects aged ≥ 5 prescribed grass pollen SLIT tablets in at least two successive treatment cycles, or intranasal corticosteroids during the grass pollen season or in the month before the grass pollen season in three consecutive years	74,126 (2851 having received AIT and 71,275 matched controls)	Grass pollen	SLIT with tablets	During the 7-year analysis period, the risk of developing asthma was significantly lower in patients receiving AIT (OR 0.70; $p < 0.01$); during the follow-up period, patients with no asthma at the end of their AIT treatment had a significantly lower risk of developing asthma than control patients ($p < 0.01$)
Devillier et al. 2019 [88]	France	Subjects aged ≥ 5 having received at least two prescriptions of grass pollen SLIT tablets per course of treatment, or with at least two prescriptions of nasal corticosteroids over at least 2 successive years	28,574 (1099 having received AIT and 27,475 controls)	Grass pollen	SLIT with tablets	The risk of developing asthma was significantly lower in patients receiving AIT, compared with controls, whether during the treatment period, the 1 to 2-year follow-up period, or the ~5-year full analysis period (OR between 0.36 and 0.63; $p < 0.0001$ to 0.01)
Wahn et al. 2019 [89]	Germany (nationwide)	Subjects aged ≥ 5 prescribed birch family pollen AIT in at least two successive seasonal cycles, or pharmacotherapy for rhinitis during the birch family pollen season or in the month before that season in 3 consecutive years	54,006 (9001 having received AIT and 45,005 matched controls)	Birch with or without alder and hazel pollen	SLIT and SCIT with natural extracts and SCIT with allergoids	During AIT, the risk of developing asthma was significantly lower in patients receiving this treatment compared with controls (OR 0.83; $p = 0.001$); at the product level, only SLIT natural extract and one SCIT allergoid preparation induced such a significant reduced risk (OR 0.82 and 0.66, resp.; $p < 0.05$); during the overall ~8-year analysis period, only SLIT with natural extract induced a significant reduced risk of developing asthma (OR 0.69; $p < 0.001$)

(Continues)

TABLE 2 | (Continued)

Reference(s)	Area	Type of patients	Number of patients	Allergen sources	Type(s) of AIT	Outcomes
Jutel et al. 2020 [90]	Germany (nationwide)	Subjects aged 5 to 50 prescribed AIT in at least two successive seasonal cycles, or symptomatic medication for allergic rhinitis in at least three successive seasons	67,090 (2350 having received AIT and 64,740 controls)	HDM	SCIT with allergoids	During the ~9-year full analysis period, the risk of developing asthma was significantly lower in patients receiving AIT, compared with controls (OR 0.81; $p < 0.01$)
Zieglmayer et al. 2023 [91]	Germany (nationwide)	Subjects aged 5 to 50 without asthma prescribed AIT for at least 2 years or symptomatic treatment only	39,807 (10,033 having received AIT and 29,774 matched controls)	Grass/cereal pollen	SLIT and SCIT with natural extracts and SCIT with allergoids	Overall, and at least 2 years after AIT cessation, the risk of developing asthma was not significantly lower in patients receiving this treatment (~13%) compared with controls (~15%; OR 1.00; $p = 0.99$); only SLIT with natural extract induced a significant reduced risk of developing asthma (OR 0.83; $p < 0.05$)
Devillier et al. 2023 [92], Demoly et al. 2024 [93]	France	For the exposed cohort of patients: at least 1 dispensation of SLIT liquid from January 1st, 2010 to December 31st, 2013 in the Stallergenes Greer database (date of first dispensation is the index date); at least 2 years of follow-up after the last SLIT dispensation in the Stallergenes Greer database during the study period. For all patients: to be affiliated to the general scheme at least 2 years prior to the index date; at least 5 years old at the index date	445,574 (112,492 having received AIT and 333,082 controls)	Seasonal or perennial	SLIT (drops)	During the ~8-year analysis period, the risk of developing asthma was significantly reduced by 23% to 38% in patients receiving AIT, depending on the definition of asthma onset (HR 0.77 down to 0.62); the significant reduction was observed irrespective of the age group and the allergen source (except cat)

(Continues)

TABLE 2 | (Continued)

Reference(s)	Area	Type of patients	Number of patients	Allergen sources	Type(s) of AIT	Outcomes
Jutel et al. 2024 [94]	Germany (nationwide)	Subjects aged 5 to 70 having received AIT for at least 2 successive calendar years, or having received at least 2 prescriptions for intranasal corticosteroid and/or oral/systemic antihistamines in 2 successive seasons, all patients being followed for at least 2 years after the end of the AIT period	3568 (892 having received AIT and 2676 matched controls)	HDM	SCIT	According to the up to 6 years follow-up period, the risk of developing asthma was significantly reduced by 27% in patients receiving AIT compared to controls (OR 0.73; $p < 0.05$), the preventive effect of AIT on asthma occurring ~15 months after its start; the time to onset of asthma was significantly prolonged in the AIT group compared to controls ($p = 0.001$)
Vogelberg et al. 2024 [95]	Germany (nationwide)	Subjects aged 5 to 65 having received at least 1 prescription of a symptomatic medication for allergic rhinitis during the pre-index period, at least 4 prescriptions of AIT in at least 3 consecutive pollen seasons with at least 2 years of follow-up after treatment, or at least 3 prescriptions of a symptomatic medication for allergic rhinitis in 3 successive allergy seasons with at least 2 years of follow-up	11,918 (5959 having received AIT and 5959 matched controls)	Grass or tree pollen	SCIT with allergoids	According to the 6.3 years follow-up period (median duration), the risk of asthma medication onset in patients with no asthma at baseline was significantly reduced in those receiving AIT compared to controls (OR 0.77; $p = 0.001$), the time to asthma medication onset being significantly prolonged in the AIT group compared to controls ($p < 0.01$)

TABLE 3 | Real-world retrospective database studies addressing the prevention of asthma worsening by AIT.

Reference	Area	Type of patients	Number of patients	Allergen sources	Type(s) of AIT	Outcomes
Zielen et al. 2018 [87]	Germany (nationwide)	Subjects aged ≥ 5 prescribed grass pollen SLIT tablets in at least two successive treatment cycles, or intranasal corticosteroids during the grass pollen season or in the month before the grass pollen season in 3 consecutive years	74,126 (2851 having received AIT and 71,275 matched controls)	Grass pollen	SLIT with tablets	The progression of asthma was significantly slower in AIT-treated patients compared with control patients, whether during the treatment ($p < 0.01$), the over 2-year follow-up ($p < 0.01$) or the full analysis period ($p < 0.05$)
Devillier et al. 2019 [88]	France	Subjects aged ≥ 5 having received at least two prescriptions of grass pollen SLIT tablets per course of treatment, or with at least two prescriptions of nasal corticosteroids over at least 2 successive years	28,574 (1099 having received AIT and 27,475 controls)	Grass pollen	SLIT with tablets	Based on the number of prescriptions for symptomatic asthma medication, asthma progression was significantly slower in patients having received AIT, compared with control patients, whether during the treatment, the follow-up or the full analysis period ($p < 0.0001$)
Wahn et al. 2019 [89]	Germany (nationwide)	Subjects aged ≥ 5 prescribed birch family pollen AIT in at least two successive seasonal cycles, or pharmacotherapy for rhinitis during the birch family pollen season or in the month before this season in 3 consecutive years	54,006 (9001 having received AIT and 45,005 matched controls)	Birch with or without alder and hazel pollen	SLIT and SCIT with natural extracts and SCIT with allergoids	During the 2- to 6-year follow-up period, significantly less asthma medication was used in the AIT vs. non-AIT group, irrespective of the route of administration and the type of extract (26 up to 41 reduction; $p < 0.001$), the greatest reduction being observed with the sublingual administration of natural extract
Schmitt et al. 2020 [97]	Germany (state of Saxony)	Subjects aged ≥ 12 (average 49) having incident asthma and prescribed AIT or not	39,167 (4111 having received AIT and 35,056 controls)	Not reported	Not reported	During the up to 8-year follow-up period, significantly decreased risk of asthma progression from GINA step 1 to step 3 (HR 0.87) and step 3 to step 4 (HR 0.66) was observed in patients having received AIT, compared with control patients; the preventive effect of AIT on asthma progression from GINA step 1 to step 3 was strongest in adolescents (HR 0.72), followed by young adults (HR 0.89), no risk reduction being observed in patients aged ≥ 50 (HR 1.09); the preventive effect of AIT on asthma progression from GINA step 3 to step 4 was observed and similar in the 3 age groups

(Continues)

TABLE 3 | (Continued)

Reference	Area	Type of patients	Number of patients	Allergen sources	Type(s) of AIT	Outcomes
Jutel et al. 2020 [90]	Germany (nationwide)	Subjects aged 5 to 50 prescribed HDM AIT in at least two successive seasonal cycles, or symptomatic medication for allergic rhinitis in at least three successive seasons	67,090 (2350 having received AIT and 64,740 controls)	HDM	SCIT with allergoids	During the up to 6-year follow-up period, patients having received AIT required significantly and 11% fewer asthma prescriptions than control patients ($p < 0.05$); this reduction was of 39% in the paediatric population ($p < 0.001$)
Gerstlauer et al. 2023 [96]	Germany (nationwide)	Subjects aged 5 to 50 with allergic rhinitis with or without concomitant asthma, prescribed AIT for at least 2 years or symptomatic treatment only	56,740 (14,185 having received AIT and 42,555 matched controls)	Grass/ cereal pollen	SLIT and SCIT with natural extracts and SCIT with allergoids	Among patients with both allergic rhinitis and asthma, the number of asthma prescriptions was significantly and 31% lower in the AIT group, compared with the non-AIT group, both during AIT and up to 6 years after AIT cessation ($p < 0.0001$); this significant difference in favour of AIT was observed whatever the age group (28% to 35% difference; $p < 0.0001$)
Devillier et al. 2023 [92], Demoly et al. 2024 [93]	France	For the exposed cohort of patients: at least 1 dispensation of SLIT liquid from January 1st, 2010 to December 31st, 2013 in the Stallergenes Greer database (date of first dispensation is the index date); at least 2 years of follow-up after the last SLIT dispensation in the Stallergenes Greer database during the study period. For all patients: to be affiliated to the general scheme at least 2 years prior to the index date; at least 5 years old at the index date	445,574 (112,492 having received AIT and 333,082 controls)	Seasonal or perennial	SLIT (drops)	During the ~8-year analysis period, the risk of asthma treatment step-up was significantly reduced by ~30% in patients receiving AIT (HR ~0.7); the significant reduction was observed irrespective of the age group and whether the allergen source was HDM or grass pollen

HDM SLIT tablets was significantly higher in subjects with a higher number of elevated type 2 biomarkers ($p < 0.01$) [113].

Importantly, in none of the 6 above-mentioned trials did AIT last longer than ~1.5 year. Had this been the case, the results obtained may have been even better. Indeed, it is well known that AIT should be extended for at least 3 years to increase its benefits, especially its long-term clinical benefits [35–37].

4.2.2 | Prospective Epidemiological and Real-World Retrospective Analyses

Real-world retrospective database analyses support the long-term benefit of AIT as a treatment of allergic asthma. We identified 4 papers reporting such analyses, involving a total of more than 160,000 patients, followed for up to 9 years, part of them being treated by SLIT or SCIT mainly with extracts of tree pollens, grass pollens and HDM [89, 94, 95, 114]. All four studies reported a greater reduction of asthma pharmacotherapy prescriptions during the follow-up period in patients having received AIT, compared with control patients (Table 5). According to the two largest studies, each of which involved more than 50,000 participants, AIT-receiving patients were also more likely to step down their asthma treatment [114] and to become asthma medication-free [89], and less likely to experience a severe asthma exacerbation [114]. Overall, these analyses highlight the sustained, long-term benefit of AIT on allergic asthma, especially its ability to improve asthma control.

The ICS-sparing effect of AIT was confirmed by a small retrospective study performed in Korea [115], according to which the proportion of patients who reduced or even discontinued their use of ICS was significantly greater in patients receiving AIT than in the non-AIT group, whether 6 months or 1 to 3 years after the start of AIT (Table 5). In addition, Woehlk et al. published a register-based nationwide prospective epidemiological study [116] indicating that during the 3-year follow-up period after a minimum of 3 years of AIT, the number of patients with asthma exacerbations was significantly decreased compared with baseline, whether the patients suffered from perennial or seasonal allergic asthma (Table 5). However, and as acknowledged by the authors, the absence of a control population of patients not receiving AIT is clearly a limitation of this study [116].

4.3 | The Combination of AIT and Biological Therapies in Allergic Asthma

As such, AIT is contraindicated in patients with severe, uncontrolled or even partially or poorly controlled asthma, due to the associated increased risk of systemic allergic reactions [117–122]. Nonetheless, AIT remains the only causative treatment of allergic asthma. Its combination with a biological therapy appears to be a highly relevant approach for bringing its benefits to patients who are a priori not eligible for it. As mentioned above, the biologics available for the treatment of asthma were mainly designed to address the type 2 form of the disease, their mechanisms of action being highly complementary to those of AIT (compare Figures 1 and 2). Since available biologics have been shown to reduce the severity and/or improve the control of allergic asthma (section 3 above), they are expected to enable patients suffering from a serious form of the condition to benefit from the unique effects of AIT [37, 123]. Incidentally, combining AIT with biologics may also benefit subjects with less severe allergic asthma.

The combination of a biologics with AIT has already been evaluated as a treatment of various allergic conditions other than allergic asthma (see Data S1 for details). As regards the treatment of allergic asthma, many studies of different types have investigated the combination of AIT with a biologics, mainly omalizumab. Of the 13 studies we identified, 7 reported on just one or a few cases, while the other 6 involved from about 30 patients to almost 250 patients (Table 6). In most cases, treatment with biologics was given before initiating SCIT or SLIT with perennial (especially HDM) and/or seasonal (grass and tree pollens) allergen sources in children, adolescents and/or adults. According to several reported studies, pretreatment with biologics has been successful in initiating and continuing AIT in patients with uncontrolled moderate-to-severe allergic asthma [21, 127, 130, 132, 134], including patients who did not tolerate AIT prior to treatment with biologics [127, 130], but also a young boy with poorly controlled asthma suffering from ICS-induced growth deceleration and adrenal suppression [131]. In a patient with severe allergic asthma plus eosinophilia and high total and specific IgE, omalizumab pretreatment did not allow to initiate AIT, but mepolizumab did [135], highlighting the need to personalise the combined treatment of AIT and biologics (Table 6).

Globally, the combination treatment was safe [30, 136, 137], especially in patients with severe allergic asthma [21], and appeared to be safer than AIT plus placebo [126] or AIT only [133], although not significantly in all studies [124, 125]. A good safety profile was maintained when AIT was pursued while the biologics was discontinued, even during the AIT build-up phase [126], whether patients suffered from mild [125], at least moderate [126], or established severe allergic asthma [128, 129, 134].

The combined treatment enabled significantly more patients to reach the target maintenance dose [126], and to reach this dose, according to one study, as quickly as in 4 days [128, 129]. Compared with AIT plus placebo, the combined treatment induced a significantly higher improvement of asthma control and asthma-related quality of life [124]. In this connection, when compared with before biologics treatment, the latter followed by its combination with AIT allowed to achieve a significant improvement in asthma control, asthma-related quality of life, but also airway functions and structures [21, 30]. The asthma control obtained with the combined therapy persisted after cessation of the biologics [128, 129, 132, 134], even when the latter did not allow to maintain the absence of asthma exacerbations prior to AIT initiation [134]. Compared with before treatment with biologics only [21], and even with this treatment [128, 129], a reduction of the levels of maintenance pharmacotherapy could also be observed. In this vein, compared with patients treated neither with AIT nor biologics, the daily dose of ICS was significantly more reduced in patients treated by AIT combined with biologics than in those receiving the biologics only, no significant reduction being observed in patients receiving AIT without the biologics [137]. In addition, the combined treatment induced

TABLE 4 | RDBPC clinical trials addressing the treatment of allergic asthma by AIT.

Reference	Type of patients	Number of patients	Allergen sources	Type of AIT	Outcomes
Ameal et al. 2005 [105]	Subjects aged 14 to 48 (average 23) with HDM-induced rhinoconjunctivitis and mild-to-moderate asthma	55	HDM	SCIT with *D. pteronyssinus* depigmented polymerised extract	After 1 year of treatment, patients receiving AIT had significantly improved bronchial provocation test and symptom and medication scores ($p < 0.001$) contrary to patients receiving placebo ($p > 0.46$), with 78% and 68% decrease of symptoms and medication, respectively, in AIT-treated patients, compared with placebo; the difference between the active and the placebo groups in terms of improved provocation test was itself significant ($p < 0.05$ down to 0.001, depending on the way improvement was objectified)
Garcia-Robaina et al. 2006 [106]	Subjects with HDM-induced rhinoconjunctivitis and mild-to-moderate asthma (mean age, 37 years)	64	HDM	SCIT with 50% *D. pteronyssinus*/50% *D. farinae* depigmented polymerised extract	After 1 year of treatment, patients receiving AIT had significantly improved the bronchial provocation test score ($p < 0.001$) contrary to patients receiving placebo ($p = 0.65$); the median improvement in the bronchial symptom score and consumption of ICS in the active group, compared with the placebo group, was of 48% and 50%, respectively, when calculated throughout the whole study ($p < 0.001$ in both cases); the number of weeks free of ICS was significantly higher in the active group ($p < 0.001$)
Mosbech et al. 2014 [108]	Subjects aged ≥ 14 with mild-to-severe HDM-induced allergic rhinitis plus mild-to-moderate HDM-induced allergic asthma requiring 100–800 μg/day of ICS	604	HDM	SLIT with 1,3 or 6 SQ-HDM tablets	After 1 year of treatment, and compared with patients receiving the placebo, a significantly higher reduction from baseline in the dose of ICS required to maintain asthma control was observed only in patients administered the 6 SQ-HDM SLIT tablet (reduction of 81 μg; $p < 0.01$)

(Continues)

TABLE 4 | (Continued)

Reference	Type of patients	Number of patients	Allergen sources	Type of AIT	Outcomes
Virchow et al. 2016 [109]	European subjects aged 17 to 83 (average 33) with HDM-induced allergic rhinitis plus HDM-induced allergic asthma not well controlled by ICS or combination products	834	HDM	SLIT with 6 or 12 SQ-HDM tablets	According to the 6 months of ICS reduction/withdrawal phase at the end of the 13 to 18 months treatment period, both 6 and 12 SQ-HDM tablets induced a significantly reduced risk of moderate or severe asthma exacerbation compared with placebo (HR 0.72 and 0.69, resp.; $p < 0.05$ in both cases); a significantly reduced risk of an exacerbation with deterioration in asthma symptoms was observed only with the 12 SQ-HDM tablet (HR 0.64; $p < 0.05$)
Jutel et al. 2018 [107]	Polish or Spanish patients aged 18 to 40 with controlled HDM-induced allergic asthma	146	HDM	SCIT with 2000, 6000, 10,000 and 18,000 TU *D. pteronyssinus* allergoid	After ~7 months of treatment, in patients not having asthma control without ICS before treatment AIT, a significant decrease in the minimal ICS dose required for asthma control, compared with patients receiving placebo, was observed only with the 18,000 TU dose of extract ($p < 0.05$); 85% of patients reduced their ICS dose to 0 μg in the 18,000 TU group, compared with 40% in the placebo group ($p < 0.05$)
Tanaka et al. 2020 [110]	Japanese subjects aged 18 to 64 with allergic asthma	826	HDM	SLIT with 6 or 12 SQ-HDM tablets	According to the 6 months of ICS reduction/withdrawal phase at the end of the 13 to 19 months treatment period, there was no significantly reduced risk of asthma exacerbation compared with placebo, whether for the 6 or the 12 SQ-HDM tablets

TABLE 5 | Prospective epidemiological and real-world retrospective studies addressing the treatment of asthma by AIT.

Reference	Area	Type of patients	Number of patients	Allergen sources	Type(s) of AIT	Outcomes
Wahn et al. 2019 [89]	Germany	Subjects aged ≥ 5 prescribed birch family pollen AIT in at least two successive seasonal cycles, or pharmacotherapy for rhinitis during the birch family pollen season or in the month before this season in 3 consecutive years	54,006 (9001 having received AIT and 45,005 matched controls)	Birch with or without alder and hazel pollen	SLIT and SCIT with natural extracts and SCIT with allergoids	During the 2- to 6-year follow-up period, among subjects using asthma therapy at baseline, significantly more patients having received AIT were asthma medication-free (49%), compared with control patients (35%), irrespective of the administration route and the type of extract (OR 0.78 down to 0.49; $p < 0.05$ down to 0.001); also, a greater reduction from baseline for asthma medication prescriptions was observed in AIT-receiving patients (68% to 78% reduction), compared with controls (39% reduction), the greatest reduction being observed with the sublingual administration of natural extract
Rhyou et al. 2020 [115]	Korea	Subjects aged ≥ 18 with allergic asthma having received AIT for more than 1 year or not treated by AIT	117 (48 having received AIT and 69 controls)	HDM, tree or weed pollens, cat or dog dander, either alone or in combination	SCIT	The proportion of patients who reduced or stopped their ICS use was significantly greater in the AIT than in the non-AIT group, whether 6 months after the start of AIT (52% in the AIT group versus 24% in the non-AIT group, $p < 0.05$), or 1 year (71% vs. 35%, $p < 0.01$), 2 years (89% vs. 36%, $p < 0.001$), or 3 years after the start of AIT (96% and 51%, $p < 0.001$); during the first year, the proportion of patients with acute asthma exacerbation was significantly lower in the AIT than in the non-AIT group (8% vs. 28%, $p < 0.05$)

(Continues)

TABLE 5 | (Continued)

Reference	Area	Type of patients	Number of patients	Allergen sources	Type(s) of AIT	Outcomes
Fritzsching et al. 2022 [114]	Germany	Subjects with confirmed diagnosis of allergic rhinitis with or without asthma having received AIT or not (mean age, 30 years)	92,048 (46,024 having received AIT matched 1:1 with 46,024 controls)	Mainly tree pollens, grass pollens and HDM	SLIT with drops or tablets and SCIT	In subjects with pre-existing asthma, and as observed after 3 and 5 years of follow-up, a significantly greater reduction in asthma prescriptions was evidenced in patients having received AIT, compared with control patients, the between-group difference being mainly due to SABA and ICS/LABA prescriptions ($p < 0.01$ down to 0.0001); a significantly greater likelihood of stepping down asthma treatment is observed with AIT-receiving patients ($p < 0.0001$); from 2 to 8 years of follow-up, the risk of experiencing a severe asthma exacerbation was lower in the AIT group ($p < 0.05$ down to 0.0001)
Woehlk et al. 2022 [116]	Denmark	Subjects aged 18 to 44 with perennial or seasonal allergic asthma, and all treated by AIT	2688 (1249 with perennial allergic asthma and 1439 with seasonal allergic asthma)	HDM, birch pollen and/or grass pollen	SCIT or SLIT	During the 3 years following a minimum of 3 years of AIT, a significant decrease from baseline in the number of patients with asthma exacerbations was observed irrespective of the follow-up year considered and whether patients suffered from perennial or seasonal allergic asthma ($p < 0.001$ in all cases); although the average decrease was higher in the latter (74%) than in the former (57%), this difference was not statistically significant, except after the first follow-up year

(Continues)

TABLE 5 | (Continued)

Reference	Area	Type of patients	Number of patients	Allergen sources	Type(s) of AIT	Outcomes
Jutel et al. 2024 [94]	Germany	Subjects aged 5 to 70 having received AIT for at least 2 successive calendar years, or having received at least 2 prescriptions for intranasal corticosteroid and/or oral/systemic antihistamines in 2 successive seasons, all patients being followed for at least 2 years after the end of the AIT period	3568 (892 having received AIT and 2676 matched controls)	HDM	SCIT	During the up to 6 years follow-up period, in subjects with pre-existing asthma, the number of asthma prescriptions was significantly reduced by ~40% in patients having received AIT compared to controls ($p < 0.001$), whether AIT-receiving patients were children and adolescents ($p < 0.01$) or adults ($p < 0.05$)
Vogelberg et al. 2024 [95]	Germany (nationwide)	Subjects aged 5 to 65 having received at least 1 prescription of a symptomatic medication for allergic rhinitis during the pre-index period, at least 4 prescriptions of AIT in at least 3 consecutive pollen seasons with at least 2 years of follow-up after treatment, or at least 3 prescriptions of a symptomatic medication for allergic rhinitis in 3 successive allergy seasons with at least 2 years of follow-up	11,918 (5959 having received AIT and 5959 matched controls)	Grass or tree pollen	SCIT with allergoids	According to the 6.3 years follow-up period (median duration), the proportion of subjects with pre-existing asthma receiving anti-asthmatic medication was significantly reduced by ~14% to 16% for those having received AIT compared to controls, whether patients were adult or not (OR ~ 0.5 and $p < 0.001$ in all cases); in the subjects with pre-existing asthma, the reduction in asthma prescriptions during the follow-up period versus baseline was significantly greater by 29% in the AIT group, compared to controls ($p < 0.001$)

TABLE 6 | Studies on the combination of AIT and biologics in the treatment of allergic asthma.

Reference(s)	Type of study	Type of patients	Number of patients	Allergen source(s)	Type(s) of treatment	Outcomes
Kopp et al. 2009 [124], Kopp et al. 2013 [125]	Multicentre RDBPC trial	Subjects aged 11 to 46 with grass pollen-induced allergic rhinoconjunctivitis associated with mild allergic asthma	140 (70 receiving AIT + biologics and 70 controls receiving AIT + placebo)	Grass pollen	Average of 16 weeks of SCIT using modified extract with a rush build-up phase, combined with omalizumab or placebo, administration of the latter starting 2 weeks before combined treatment; SCIT was administered for 2 more years without omalizumab	No systemic reaction was observed during the whole trial; although more adverse events were observed in the control group, the difference was not statistically significant; compared with the control group, the combined treatment induced a significantly higher improvement of asthma control and asthma-related quality of life ($p < 0.05$ in both cases); these significant differences were not maintained in the following 2 years; in contrast, and compared with the control group, FEV_1 was significantly improved in year 3 in patients having received the combined treatment ($p < 0.05$)
Massanari et al. 2010 [126]	Multicentre RDBPC trial	Subjects aged between 18 and 55 with at least moderate persistent allergic asthma induced by HDM, cat and/or dog dander, and not adequately controlled with ICS	248 (126 receiving AIT + biologics and 122 controls receiving AIT + placebo)	HDM, cat and/or dog dander	16 weeks of administration of omalizumab or placebo followed by a 11-week SCIT, starting by 4 weeks of cluster regimen, including 3 weeks of overlap with omalizumab or placebo administration	Significantly fewer patients receiving the combined treatment experienced AIT-induced systemic reactions (14%), compared with control patients (26%; $p < 0.05$); significantly more patients receiving the combined treatment were able to reach the target maintenance AIT dose (87%), compared with control patients (72%; $p < 0.01$)
Larenas-Linnemann et al. 2014 [127]	Case report	34-year old woman with HDM-, tree pollen- and cat dander-induced difficult to control moderate persistent asthma	1	HDM, tree pollen and cat dander	1 month of SLIT build-up phase, SLIT cessation, 6 months of omalizumab treatment, and then 6 months of SLIT combined with omalizumab treatment (to be continued)	Whereas a first AIT initiation had to be interrupted, especially because of uncontrolled asthma, AIT could be restarted without difficulty in combination with the biologics

(Continues)

TABLE 6 | (Continued)

Reference(s)	Type of study	Type of patients	Number of patients	Allergen source(s)	Type(s) of treatment	Outcomes
Lambert et al. 2014 [128], Lambert et al. 2015 [129]	Uncontrolled observational study	Subjects aged 11 to 21 suffering from severe persistent HDM-induced allergic asthma controlled by omalizumab as an add-on therapy	6	HDM	Treatment with omalizumab for a 8-month median duration, then SCIT with a 4-day build-up phase during omalizumab treatment and, after a 8-month median duration of combined treatment, SCIT maintenance without omalizumab for a 25.5-month median duration	One patient had to stop SCIT, due not to severe asthma exacerbation, but to a loss of asthma control, regained by continuing the treatment with biologics; in the five other patients, no severe side effects of SCIT was observed, even after the treatment with biologics was discontinued, and asthma remained totally controlled, with levels of maintenance pharmacotherapy even being further reduced
Stelmach et al. 2015 [130]	Real-life, open, uncontrolled, observational study	Subjects aged between 7 and 30 with severe uncontrolled allergic asthma	12, of whom 5 had to discontinue, while the others did not receive, AIT alone before the study	Especially HDM and moulds	Combination of AIT (presumably SCIT) and omalizumab treatment after 3 to 9 months of omalizumab pretreatment	In concerned patients, AIT was introduced and successfully continued according to the AIT scheme
Forbush et al. 2016 [131]	Case report	8-year-old boy suffering from poorly controlled allergic asthma and ICS-induced growth deceleration and adrenal suppression	1	Not specified	Treatment with omalizumab followed by AIT (presumably SCIT) initiation with omalizumab as a continued adjunct	The subject's asthma symptoms, which were eventually controlled with the biologics even after ICS discontinuation for months, remained under excellent control during the combination treatment
Mbuila et al. 2016 [132]	Case report	16-year-old girl with HDM-, grass pollen- and cat dander-induced rhinitis and severe allergic asthma	1	HDM	12 months of treatment with omalizumab, followed by 2 years of SLIT combined with omalizumab treatment, the latter being then discontinued, while SLIT was pursued for a further 2 years	Treatment with biologics resulted in a marked improvement in asthma control, which was maintained after AIT initiation, and even after cessation of the biologics

(Continues)

TABLE 6 | (Continued)

Reference(s)	Type of study	Type of patients	Number of patients	Allergen source(s)	Type(s) of treatment	Outcomes
Har et al. 2019 [133]	Retrospective study	Subjects aged 6 to 18 with moderate-to-severe persistent allergic asthma	8 (30 treated with AIT, 30 with a biologics, and 29 with AIT plus the biologics)	Not specified	7 years of treatment with SCIT, omalizumab, or SCIT plus omalizumab	The rate of severe reactions was significantly lower in subjects receiving SCIT and the biologics (0.3% of injections in 10% of patients), compared with SCIT only (1.2% of injections in 33% of patients; $p < 0.05$), no significantly more frequent severe reactions being observed with the combined treatment, compared with the biologics only ($p = 0.73$)
Carrier et al. 2019 [134]	Case report	9-year-old girl with HDM-, grass pollen- and cat dander-induced rhinitis and severe allergic asthma	1	Mould (*Alternaria*)	41 months of treatment with omalizumab, followed by 10 months of SLIT combined with omalizumab treatment, the latter being then discontinued, while SLIT was pursued	~2 years after initiation of the treatment with biologics, the subject experienced asthma exacerbations again; 6 months after treatment with biologics was discontinued, AIT being pursued, the subject's asthma was fully controlled, no exacerbation occurring within the 12 months following discontinuation of the biologics
Gulsen et al. 2021 [135]	Case report	67-year-old man with severe allergic asthma and polyposis nasi, as well as eosinophilia and high total and tree pollen allergen-specific IgE levels	1	Birch, alder and hazel pollen	12 months of omalizumab treatment followed by ~6 months with no biologics, and then 15 months of mepolizumab treatment plus SCIT starting ~6 months after initiating mepolizumab	Omalizumab did not allow to obtain asthma control, whereas mepolizumab did, allowing for the initiation of AIT; after one season of AIT, the patient no longer required oral corticosteroids, while experiencing no asthma exacerbations or decrease in the respiratory function during the whole duration of mepolizumab treatment

(Continues)

TABLE 6 | (Continued)

Reference(s)	Type of study	Type of patients	Number of patients	Allergen source(s)	Type(s) of treatment	Outcomes
Valdesoiro-Navarrete et al. 2022 [21]	Retrospective, real-life study	Subjects aged 4 to 16 (mean age, 9 years) with severe allergic asthma	29	HDM, mould (*Alternaria*) or pollen	1 to 3 years (mean, 1 year) of omalizumab treatment, and then 1 to 5 years (mean, 2.5 years) of SCIT combined with omalizumab treatment	Less than 5% of the administered SCIT doses, in 2 of the 29 patients, induced systemic reaction during SCIT up-dosing, none of which required hospitalisation, and no major adverse reactions were observed during SCIT maintenance, although all patients have reached the target AIT doses; compared with before treatment with biologics, there was a significant improvement in asthma and FEV_1, along with a significant reduction in the levels of maintenance pharmacotherapy and in the number of hospital admissions because of asthma, at least after 1 year of combined treatment ($p < 0.001$ in all cases); whereas all 29 patients required systemic corticosteroids before treatment with the biologics, none of them used any corticosteroids after 1 year of combined treatment
Hoshino et al. 2022 [30]	Open uncontrolled real-world study	Subjects aged between 20 and 65 years with HDM-induced allergic asthma not well controlled with ICS plus LABA or LTRA plus dupilumab	47	HDM	SLIT with tablets combined with dupilumab after an average of 1 year of dupilumab-only treatment	6 patients withdrew from the study, 4 of them due to adverse events; however, no serious adverse events, including anaphylaxis, occurred in the 47 subjects, and no epinephrine was given; compared with baseline, significant improvement in asthma control, asthma-related quality of life and FEV_1 percent predicted was observed after 48 weeks of combined treatment, as well as significant decrease in the level of FeNO, airway wall area and thickness ($p < 0.05$, in all cases)

(Continues)

TABLE 6 | (Continued)

Reference(s)	Type of study	Type of patients	Number of patients	Allergen source(s)	Type(s) of treatment	Outcomes
Bozek et al. 2023 [136, 137]	RPC multicentre trial	Subjects aged over 16 (mean, 24) with HDM-induced mild-to-moderate controlled or partially controlled allergic asthma	82 (18 receiving the biologics plus AIT with a placebo, 21 receiving the biologics plus AIT with allergen extract, 22 receiving a placebo plus AIT with allergen extract, and 21 receiving a placebo plus AIT with a placebo)	HDM	24-month omalizumab treatment plus SCIT with a placebo, or SCIT with allergen extract combined with either omalizumab treatment or placebo administration, or SCIT with placebo combined with placebo administration	Compared with placebo, a significant reduction in the daily doses of ICS was observed in patients treated with the biologics ($p < 0.05$ after both 1 and 2 years of treatment), and those treated with the biologics plus AIT ($p < 0.05$ after 1 year and $p < 0.01$ after 2 years), with a significantly higher reduction in the latter patients ($p = 0.01$), while no significant reduction was observed in patients treated by AIT without the biologics; the reduction in the total asthma symptom score was more significant in patients treated with the biologics plus AIT ($p < 0.05$ after 1 year and $p < 0.01$ after 2 years) than in those treated with the biologics only (not significant and $p < 0.05$, resp.); during the whole study, only two mild systemic reactions were observed, namely, in patients treated by AIT without the biologics

a more significant reduction in the total asthma symptom score, compared with biological treatment alone (Table 6) [137].

Overall, the above studies strongly suggest that, thanks to its combination with biologics, AIT may better benefit patients and/or benefit a greater number of them than it does today. What is more, adding AIT to biologics in the approach to asthma treatment makes it possible to consider discontinuing the biological treatment earlier, thereby alleviating the rather high costs of the latter [138]. Admittedly, some standardisation is required regarding especially the duration of the biologics pretreatment and that of the combination treatment before biologics discontinuation [134]. Ongoing and future clinical trials should shed some light on this issue, as well as confirm, ideally in the form of prospective RCTs with large cohorts, the ability of biologics to extend the AIT's indications, help identify target populations, especially more severe patients and define the cost-effectiveness of combining biologics and AIT [139]. An example of such studies is an RCT about to be launched, aimed at evaluating the combination of 300 IR HDM tablets plus omalizumab in 150 adults with HDM-induced mild-to-moderate allergic asthma. Of course, the long-term benefits and safety of the combination of AIT with biologics need to be further explored [140].

5 | Conclusion

AIT is the only disease-modifying approach to the treatment of allergy. A very large number of studies, including RDBPC clinical trials, illustrate its benefits in managing and controlling asthma. In patients suffering from allergic rhinitis, it can prevent the progression of the disease to allergic asthma. In cases where allergic asthma is established, AIT can either improve the condition or at least prevent its deterioration. The possibility of bringing the benefits of its effects to a greater number of patients is emerging, thanks to its combination with biological therapy.

Since 2017, the Global Initiative for Asthma (GINA) proposes to consider SLIT in HDM-sensitised adult patients with allergic rhinitis and suboptimally controlled asthma despite low to high-dose ICS, provided that FEV_1 is above 70% predicted. Given the many positive prospective and retrospective studies published on AIT in recent years, it was reasonable to expect GINA to expand AIT's involvement in the management of asthma, in a context where AIT is most likely underused [141, 142], despite being the only causal treatment of allergic asthma. In fact, according to the recently updated GINA's report, AIT may be now considered as an add-on treatment for patients with severe asthma, but only after asthma symptoms and exacerbations have been controlled. More specifically, SCIT can now be considered in the management of allergic asthma, provided that the potential benefits be weighed against the risk of adverse effects and the duration and cost of AIT, and provided that, in case of severe asthma, SCIT be not initiated until good asthma control has been established. In addition, GINA's report now states that SLIT can also be considered before and during the ragweed pollen season in ragweed pollen-sensitised asthmatic children, provided FEV_1 is above 80% predicted [12].

Beyond the prospective clinical trials and long-term retrospective real world studies that have already been conducted, there is a need for long-term prospective phase 3 RCTs to further support the role of AIT, especially SLIT, in the management of asthma.

Author Contributions

Thierry Batard designed and wrote the manuscript; Camille Taillé, Laurent Guilleminault, Andrzej Bozek, Véronique Bordas-Le Floch, Oliver Pfaar, Walter G. Canonica and Cezmi Akdis revised the manuscript; Mohamed H. Shamji and Laurent Mascarell contributed to the design, writing and review of the manuscript.

Conflicts of Interest

Thierry Batard, Véronique Bordas-Le Floch and Laurent Mascarell are employees of Stallergenes Greer; Camille Taillé reports lecture for, or advisory board fees and grants from, AstraZeneca, Sanofi, GSK, Chiesi, Stallergenes Greer and Novartis; Laurent Guilleminault has been an investigator in clinical trials for ALK, AstraZeneca, Bayer, GlaxoSmithKline, MSD and Novartis, reports grants or fees for consulting from ALK, AstraZeneca, Bayer, Chiesi, GlaxoSmithKline, MSD, Novartis, Sanofi-Regeneron and Stallergenes Greer; Andrzej Bozek reports grants and research support from Stallergenes greer, AstraZeneca, HAL Allergy, GSK, Novartis, ALK-Abello and lectures for, or advisory board fees from, Merck, Stallergenes Greer, HAL Allergy, Dieter, Allergopharma, Astra Zeneca, Polpharma; Oliver Pfaar reports grants and/or personal fees and/or travel support from ALK-Abelló, Allergopharma, Stallergenes Greer, HAL Allergy Holding B.V./HAL Allergie GmbH, Bencard Allergie GmbH/Allergy Therapeutics, Laboratorios LETI/LETI Pharma, GlaxoSmithKline, ROXALL Medizin, Novartis, Sanofi-Aventis and Sanofi-Genzyme, Med Update Europe GmbH, streamedup! GmbH, Pohl-Boskamp, Inmunotek S.L., John Wiley and Sons/AS, Paul-Martini-Stiftung (PMS), Regeneron Pharmaceuticals Inc., RG Aerztefortbildung, Institut für Disease Management, Springer GmbH, AstraZeneca, IQVIA Commercial, Ingress Health, Wort&Bild Verlag, Verlag ME, Procter&Gamble, ALTAMIRA, Meinhardt Congress GmbH, Deutsche Forschungsgemeinschaft, Thieme, Deutsche AllergieLiga e.V., AeDA, Alfried-Krupp Krankenhaus, Red Maple Trials Inc., Königlich Dänisches Generalkonsulat, Medizinische Hochschule Hannover, ECM Expro&Conference Management, Technical University Dresden, Lilly, Japanese Society of Allergy, Forum für Medizinische Fortbildung, Dustri-Verlag, Pneumolive, ASIT Biotech, LOFARMA, Almirall, Paul-Ehrlich-Institut, outside the submitted work; and he is Vice President of the EAACI and member of EAACI Excom, member of external board of directors DGAKI; coordinator, main or co-author of different position papers and guidelines in rhinology, allergology and allergen immunotherapy; he is associate editor of Allergy and Clinical Translational Allergy; GWC reports having received in the last 3 years research grants as well as lecture or advisory board fees from Alk-Abello, Allergy Therapeutics, Anallergo, Hal Allergy, and Stallergenes Greer; Cezmi Akdis reports grants or contracts from Swiss National Science Foundation, EU CURE EU SynAir-G, Novartis Research Institutes, Stanford University and consulting fees from Sanofi-Regeneron, Stanford University Sean Parker Asthma Allergy Center, Novartis, GlaxoSmithKline, Bristol-Myers Squibb and SciBase; Mohamed H. Shamji has received research grants from Allergy Therapeutics, Angany Inc., Immune Tolerance Network, Laboratorios LETI, Medical Research Council, Revolo Biotherapeutics, Stallergenes Greer, consulting fees from Bristol-Myers Squibb and lecture fees from Allergy Therapeutics and Laboratorios LETI.

Data Availability Statement

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.