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Broad-Spectrum Grass Pollen Immunotherapy: Revisiting the Role of Species Diversity in Allergy Treatment

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Abstract

Purpose of Review This review examines whether allergen immunotherapy (AIT) for grass pollen allergy should expand beyond the recent trend towards a mono-species approach based on *Phleum pratense*. It explores whether multi-species formulations better reflect natural exposure and could improve clinical outcomes.

Recent Findings Research from aerobiology and immunology shows that grass pollen exposure involves diverse species with distinct flowering periods, influenced by climate and geography. Molecular analyses reveal species-specific allergen profiles, including unique peptides and variations in major allergens such as Group 1 and 5. Patient data confirm symptom variability across the season. In-vitro studies have observed limits to the cross-reactivity of T-cell epitopes, and comparative clinical studies suggest benefits for multi-species treatment options.

Summary Evidence indicates that mono-species extracts alone do not represent the full allergenic spectrum of grass pollen. Broad-spectrum AIT formulations incorporating multiple grass species provide a more comprehensive repertoire of allergens and epitopes, potentially enhancing immunogenicity and therapeutic benefit. This supports the hypothesis that diversity does not equate to dilution in broad-spectrum formulations. The approach aligns with patient symptom patterns and may improve efficacy and asthma prevention. Future research could further refine species selection and leverage molecular diversity to optimize treatment strategies.

Keywords Grass pollen allergy · Aerobiology · Allergic rhinitis · Allergen immunotherapy · Climate change

Introduction

Grass pollen allergy affects a significant proportion of the global population, particularly in temperate regions. Due to the morphological similarity of grass pollen grains, the identification of clinically relevant allergen sources is complicated, despite the diversity of grass species and their phenological variability. Historically, *Phleum pratense* (timothy grass) has served as the model species for allergen immunotherapy (AIT), originally based on early observational studies of sensitization patterns in the United Kingdom [1]. However, emerging evidence from aerobiology, immunology, and patient-reported outcomes challenges the adequacy of this mono-species approach. This review explores the advantages of incorporating a broader range of grass species in treatment formulations and explains the limitations of current mono-allergen AIT strategies.

Diversity of Grass Species and Pollen Exposure

Grass pollen currently represents the leading aeroallergen worldwide, and it is the main cause of pollinosis in most developing countries [2]. Grasses belong to the *Poaceae* family, a large botanical family, comprising nearly 12,000

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species [3] with a cosmopolitan distribution. Most grass species are wind-pollinated, and produce and emit large amounts of pollen into the atmosphere.

While grass pollen grains from many species are morphologically indistinguishable in optical microscopy, their flowering periods and regional prevalence vary significantly. Aerobiological studies in Northern Europe reveal that species such as *Poa pratensis*, *Dactylis glomerata*, *Arrhenatherum elatius*, *Festuca spp.*, and *Lolium perenne* contribute most to pollen exposure during the early and mid-seasons. In contrast, *Phleum pratense* typically flowers later and is inconsistently present across regions, particularly in Southern Europe [4–6]. Notably, climate change affects the grass diversity and geographic distribution favoring the invasion of (tropical) grass species such as *Cynodon dactylon* with better tolerance strategies [7].

Aerobiology Meets Clinical Relevance

Aerobiology studies the emission, passive dispersion and transport, and deposition of microorganisms and biological particles (e.g., airborne pollen) into the atmosphere. These studies offer important information on aeroallergen exposition in the air we breathe. Currently, several instruments are used for pollen and fungal spore monitoring, the traditional Hirst-type sampler [8], and the recent automatic monitoring instruments [9]. However, all grass species (aside from cultivated rye) share similar pollen morphology, which complicates their identification at genus and species level. In parallel to microscopy-based monitoring, eDNA metabarcoding of airborne samples (e.g., from filters or volumetric traps) is emerging as a complementary approach to resolve Poaceae composition beyond 'Poaceae' at genus/species level, enabling biogeographical comparisons and improved attribution of exposure to local flora. While methodological biases remain (marker choice, reference databases, quantitative interpretability), this approach will directly address the core limitation of morphological indistinguishability in grass pollen aerobiology [10].

For this reason, studies have focused both on pollen production by species and on field phenology for presenting which species contributes most to the airborne pollen curve. Studies on pollen production by plants have shown differences between annual and perennial species, and among species living in different habitats [11, 12]. Studies focused on grass field phenology in different countries, for example in Austria (Vienna) [13], in Italy (Perugia) [14], and in different cities in Spain: Córdoba [6, 12, 15] and Toledo [16], have shown which species bloom during the different seasons. In the Mediterranean Basin most of them bloom during spring. On the other hand, these studies also support that only some species represent the major source of airborne grass pollen, depending on the rural-urban context and on the biogeographical area. For instance, the species most frequently cited in the preceding references include: *Arrhenatherum album* (oat-grass), *Cynodon dactylon* (bermuda grass), *Dactylis glomerata* (orchard grass), *Lolium rigidum* (ryegrass) and *Trisetaria panicea* (wild oats). These species belong to different subfamilies (*Pooideae* and *Chloridoideae*), and contain allergens belonging to different allergen groups, some with possible cross-reactivity rates.

A recent study on field phenology during 15 years at different altitudes in Cordoba (Spain) showed a constant prolongation of the grass flowering season, with earlier blooming for species early-flowering in spring and a delay in some of those blooming during late-flowering spring [17]. This study also presents different responses of grass species on the recent climate change. For example, considering the species cited before, the study observed an earlier onset of flowering of *Arrhenatherum album* (flowering in early spring), but only at high altitude, and a significant delay in all study sites for *Dactylis glomerata* (flowering in late spring). However, the other late spring flowering species *Lolium rigidum* and *Trisetum paniceum* presented an advance on flowering start. In addition, the amount of pollen produced per inflorescence varies per species, with some grass species like Dactylus glomerata being more productive than others [12]. Thus number of plants in a certain area does not necessarily represent the same number of pollen of that species in ambient air. Once in the air, the pollen from the different species cannot be discriminated by the standard techniques used for pollen monitoring.

While the principle of pathogenesis-related allergen expression is well established in tree pollen, recent lab experiments indicate that also grasses respond to environmental changes: Flood- (rather than drought- or salt) stress caused the release of higher amounts of pollen grains from maize and rice [18].

The above mentioned studies in comparing field phenology and airborne grass pollen have shown that local species affect the pollen curve the most; however, a mismatch has sometimes been observed during sporadic episodes [19]. These episodes are related to the mismatch between pollen emission and allergen burden. Pollen emission from anthers depends more on humidity, but allergen emission from pollen not only depends on weather, but also on external events, i.e. pollutant exposition or high humidity before storm episodes. On the other hand, it is important to also consider pollen vs. allergen transport. Particulate aeroallergens (for example pollen fragments or free allergenic proteins) can be transported over longer distances than pollen, and they can remain in the air for a longer period [19, 20]. Taken together, pollen exposure serves as an indicator of allergen

concentration in the ambient air but does not represent an exact correlate. Important is also that the amount of allergen per pollen depends on the day and location when the pollen are released by the plants, due to different stages of ripening of the grass pollen [21]. Symptoms in patients correlate better to the amount of allergen in ambient air than to the airborne pollen concentration [22]. Taken together, pollen exposure serves as an indicator of allergen concentration in the ambient air but does not represent an exact correlate.

Allergic sensitization profiles result from a variety of factors (exposome). Geographical, climate and pollution are not the only conditions influencing allergen sensitization. Moreover, an important percentage of population is moving regularly across regions, increasing the chance to influence IgE sensitization and reactivity [23, 24]. Taking all these aspects into consideration, airborne grass pollen represents a mixture of allergens, interconnected between themselves and with other pollutants like ozone and particulate matter, responding to the weather and climate. This supports the hypothesis that a greater variety of epitopes enables better coverage of sensitization patterns in individual grass pollen allergic patients.

Immunological Cross-Reactivity and its Limits

The regulatory framework for allergen products relies primarily on IgE cross-reactivity, particularly among group 1 and 5 allergens. While this supports the use of timothy grass as a representative species, it overlooks the complexity of T-cell responses and IgG-mediated immunogenicity. Evidence suggests that T-cell epitopes are not universally cross-reactive, and that species-specific allergens contribute independently to the immune response [25]. Notably, timothy grass exhibits relatively weak immunogenicity in certain in vitro models, raising concerns about its adequacy as a sole allergen source in AIT [26]. Such differences in immunogenicity have already prompted earlier studies to recommend broader mixtures of grass species in AIT, in particular *Anthoxanthum odoratum*, *Dactylis glomerata*, *Lolium perenne*, *Poa pratensis* and *Phleum pratense*, for an optimized repertoire of T- and B-cell epitopes [27].

Diversity not Dilution; Characterizing Pollen Mixtures

High homology among sweet grasses of the *Poaceae* family has been demonstrated [26], however, new technologies are enabling greater understanding of the differences between the species of sweet grasses. This may provide new insights into broad spectrum AIT products. A liquid chromatography mass spectrometry (LC-MS) feature-mapping approach (where a feature is a peptide component of a protein, from a protein extract from each species, as defined by a mass and retention time) enables the assessment of peptide differences between species. Proteins were extracted from 13 species of sweet grasses and analysed using LC-MS. A feature extraction software was used; the features were identified for each species and then compared against each other to determine unique features for each species (Table 1).

The feature mapping approach highlights protein differences between members of the *Poaceae* family of grasses at the peptide level, indicating that the diversity of proteins between the different species is even larger than previously thought. Each individual species having their own unique elements to offer could serve as beneficial to broad spectrum preparations.

Whilst the feature mapping approach does not enable the distinction of specific allergens from species, a Western blot analysis was performed on extracts from a range of *Poaceae* grass species using a group 5 monoclonal antibody.

The Western blot (Fig. 1) shows that each species tested contains a group 5 allergen homologue. This is supported by previously published work where group 5 allergens were quantified in protein extractions of various grass species [26]. The relevant allergen bands (Fig. 1) highlight the varying molecular weights of the group 5 allergens identified, indicating that they have distinguishable properties. A study investigating the immunological relevance of the differences among Group 5 allergens, through analysis of specific T and B cell epitopes, showed that distinct grass species have both shared and specific epitopes [28].

Table 1 Unique features identified per species by LC-MS from 13 species of Poaceae family grasses

Species	English Name	Number of Unique Features per Species
Agrostis capillaris	Bent Grass	77
Bromus inermis	Brome	148
Dactylis glomerata	Cocksfoot	64
Secale cereale	Cultivated Rye	103
Cynosurus cristatus	Crested Dogstail	32
Arrhenatherum elatius	False Oat	98
Festuca pratensis	Fescue Meadow	18
Alopecurus pratensis	Foxtail Meadow	90
Poa pratensis	Kentucky Blue / Meadow Grass	33
Lolium perenne	Rye Grass	16
Anthoxanthum odoratum	Sweet Vernal	123
Phleum pratense	Timothy	30
Holcus lanatus	Yorkshire Fog	98

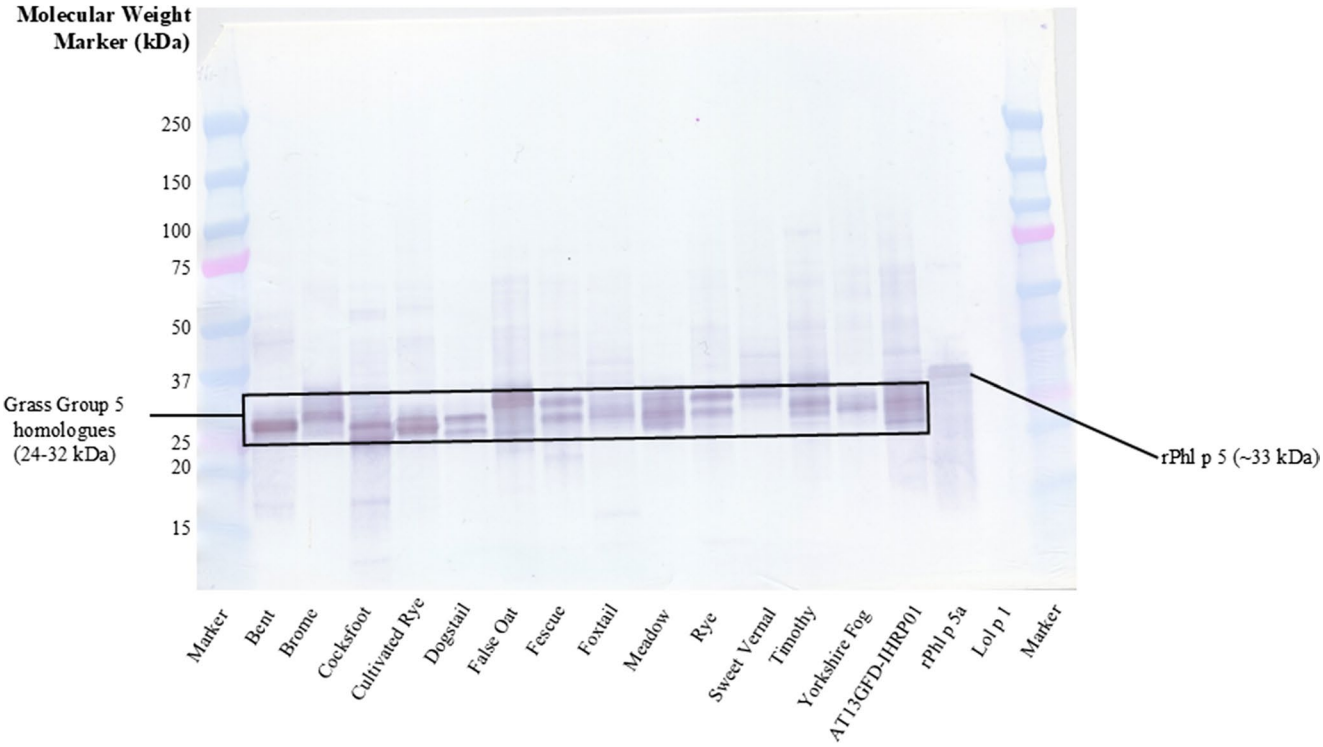

Fig. 1 Group 5 homologues identified in individual extracts and a mixed extract of 13 species of Poaceae family grasses, using a monoclonal antibody

Assessments of IgG or IgE reactivity [26] generated by independent assessment of various species of the *Poaceae* family showed varying levels of both. Importantly, a high IgE reactivity did not equate to a high IgG reactivity, suggesting that therapeutic benefits that are driven by IgG reactivity could be greater from a broad-spectrum product.

Whilst there is a large clinical focus on the role of major allergens in AIT, including Group 1 and 5, further advances in protein databases have allowed the identification of a wider variety of allergens from AIT products. LC-MS was performed from a ~ 30–34 kDa gel slice containing 13 species of *Poaceae* family grass: Bent Grass (*Agrostis capillaris*), Brome (*Bromus inermis*), Cocksfoot (*Dactylis glomerata*), Cultivated Rye (*Secale cereale*), Crested Dogstail (*Cynosurus cristatus*), False Oat (*Arrhenatherum elatius)*, Fescue Meadow (*Festuca pratensis*), Foxtail Meadow (*Alopecurus pratensis*), Meadow Grass (*Poa pratensis*), Rye Grass (*Lolium perenne*), Sweet Vernal (*Anthoxanthum odoratum*), Timothy (*Phleum pratense*), Yorkshire Fog (*Holcus lanatus*). Although enhancements in databases are continuously happening, the focus often remains on exemplar species. Representative data for lesser studied species is lacking and therefore the analysis of a wide variety of species against such a database is not possible.

In this exemplary molecular weight distribution, a variety of different allergens were found within a 13-grass mixture (Table 2). This demonstrates further that different species are contributing different allergens, both group 1 and 5 homologues, but also minor allergens, to broad spectrum preparations. This suggests that diversity of species does not equal dilution of allergens with broad spectrum AIT.

The unique contribution from each species within broad spectrum products reflects the nature of the grass pollen season experienced by patients. Studies have shown that patients develop symptoms at different stages throughout the pollen season [29]. This has been linked to the various flowering times of *Poaceae* grasses during the season [30]. Therefore, offering a broad-spectrum preparation covering various species of grass which flower at different times could be beneficial for a wider range of patients.

Patient-Centered Perspectives

Symptom tracking data from large cohorts of grass-allergic individuals reveal heterogeneous reactivity profiles [31], in which symptom load fluctuates over the full duration of the grass pollen season [29]. This fluctuation shows a high degree of inter-individual variability: A majority of patients (~ 70%) experience peak symptoms during the flowering of species such as from *Arrhenatherum*, *Festuca*, and *Lolium*, while only a minority (~ 10%) react during the late season when timothy grass is most active [29]. Controlled exposure studies investigating species-specific exposure to

Table 2 Allergens identified by LC-MS from a ~ 30–34 kDa gel slice from a mixture of 13 species of Poaceae family grasses

Protein Name	Accession Number	MW (kDa)	Coverage (%)	Number of Unique Peptides
Dac g 5	Q93XD9	26.2	31	2
Fes p 5	G3C8U9	29.6	17	2
Lol p 1	A0AAD8QK05 P14946 Q9SC98	28.3	38	8
Phl p 1	P43213 Q40967	28.2	51	7
Phl p 5	Q40960 O65319 (fragment)	31.1	52	3
Phl p 13 (partial)	Q9XG86 G9I6F6	41.7	13	10
Hol l 1	Q9ZP13 P43216 G9I6H2 G4XH73	28.3	49	8
Sec c 5	G9I6H0 F4MJM3	24.9	8	3
Poa p 1	Q9ZP03	28.2	33	2
Poa p 9	P22285 P22284	32.6	37	3
Poa p IX/Phl p VI	A0AAD8VQV8	33.7	19	5

Dactylis glomerata, *Festuca pratensis* and *Phleum pratense* in the GA2LEN exposure chamber model further confirm that different grass species elicit distinct clinical responses, underscoring the need for personalized or diversified AIT formulations [30]. This also appears to translate into a response to AIT for at least some patients: A recent study of two different SLIT tablets, one with only *Phleum pratense* and one with a five-grass mix, showed significantly stronger IgE-binding inhibition for the five-grass product, with a stronger effect observed in Southern European patients [32].

Lessons from Other Allergen Systems

The limitations of mono-allergen AIT are not unique to grasses. In tree pollen allergy, for example, formulations based solely on birch (*Betula spp.*) have shown reduced efficacy outside the birch season, likely due to sensitizations to other *Fagales* (Fagaceae and Betulaceae) species [33–35]. A prospective head-to-head study of three-tree SLIT and birch-only SLIT showed similar effectiveness on allergic rhinitis symptoms for both products. However, one important observation was better reduction in new-onset asthma in those patients treated with the three-tree product. As the prevention of new-onset allergic asthma is an important goal of AIT, these findings are of interest and underscore the relevance of broad-spectrum AIT products. The authors summarize: "3-tree SLIT-liquid covering a broader repertoire of epitopes mimicking natural exposure throughout the year may be valuable for patients sensitised to birch and/or alder and/or hazel pollen suffering from overlapping tree-pollen seasons." [36]. Recent studies have also observed limitations to T cell-mediated responses similar to those in grass pollen allergens, demonstrating a surprisingly low cellular cross-reactivity between type 1 allergens from different tree species pollen, and posing the question on whether Bet v 1-independent allergic responses may persist despite successful immunization to the major birch pollen allergen [37]. These findings support a broader immunotherapeutic approach in tree pollen allergy that accounts for the full spectrum of relevant allergens.

Conclusion

The natural grass pollen season is shaped by ecological diversity and complex immunological interactions, largely driven by environmental changes. Current evidence from aerobiology, immunology, and patient data converges on the conclusion that *Phleum pratense* alone does not adequately represent the allergenic landscape. Allergen assessment indicates that multiple relevant *Poaceae* species contribute unique isoforms of the major allergens leading to diversity, not dilution, of the major and minor allergen profile. A broad-spectrum approach to grass pollen AIT is more reflective of natural exposure and holds promise for improved patient outcomes.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

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