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REVIEW ARTICLE

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Biomarkers and immune cells in allergen-specific immunotherapy: toward objective evaluation

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Abstract
Background: Allergen-specific immunotherapy (AIT) is the only intervention capable of modifying the natural course of allergic diseases by inducing long-term immune tolerance. Its clinical efficacy depends on complex regulations of humoral and cellular immunity, yet objective assessment remains hindered by the absence of standardized biomarkers.
Summary: This review summarizes recent advances in the immunological mechanisms of AIT and highlights emerging biomarkers—including allergen-specific immunoglobulin G4, regulatory T and B cells, and innate lymphoid cells—that may provide objective measures of efficacy and support individualized treatment strategies.
Key messages: (1) AIT uniquely modifies the natural history of allergic diseases; (2) current evaluation relies on subjective measures, highlighting the urgent need for standardized and clinically applicable biomarkers; (3) molecular markers and immune cell subsets offer promising tools for bridging mechanistic insights with clinical endpoints, supporting real-time monitoring and precision-guided optimization of AIT.

Introduction

Allergen-specific immunotherapy (AIT) is the only disease-modifying intervention for allergic disorders and is widely applied in allergic rhinitis, asthma, allergic conjunctivitis, and selected food allergies.[1] Its therapeutic effect is mediated through the induction of immune tolerance, modulation of T and B cell subsets, inhibition of mast cell and basophil activation, and suppression of inflammatory mediator release.[2] Although current guidelines strongly recommend AIT, and its long-term efficacy is well established, its broader implementation in clinical practice is hampered by the lack of standardized, objective measures to evaluate treatment response.[3] Symptom scores and medication use remain the most common endpoints but are inherently subjective and poorly reproducible and may not fully correlate with underlying immunological changes observed in peripheral blood or target tissues.[4]

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Clinical variability in symptom perception, adherence, and allergen exposure further complicates efficacy evaluation, highlighting the need for biomarkers that not only capture immunological changes but also align with patient-reported outcomes and objective measures, such as provocation tests or reduction in medication use. Recent advances in immunology and multi-omics technologies have accelerated the search for reliable biomarkers that can reflect or predict AIT efficacy, encompassing humoral responses, regulatory and effector cell populations, and components of innate immunity.[5] These developments not only improve our understanding of AIT mechanisms but also provide the foundation for objective monitoring and individualized treatment strategies. Integrating immunological biomarkers with clinical endpoints may ultimately facilitate personalized treatment adjustments and more accurate evaluation of therapeutic benefit. This review summarizes recent progress in the immunological mechanisms of AIT and highlights emerging molecular and cellular biomarkers that may enhance objective efficacy assessment and guide personalized therapeutic approaches.

Humoral Immune-Related Biomarkers

Allergen-specific IgG4, IgG2, IgA, and IgD antibodies

Dynamic changes in allergen-specific antibody profiles during AIT are recognized as key indicators of immune modulation and therapeutic efficacy. AIT induces regulatory immune responses characterized by enhanced interleukin 10 (IL-10) and transforming growth factor-beta (TGF-β) secretion that suppress T helper 2 cell (Th2)-driven inflammation and promote B-cell isotype switching away from immunoglobulin E (IgE) toward non-IgE isotypes, particularly IgG4 and IgA.[6] Among these, IgG4 is widely regarded as the prototypical "blocking antibody." It mitigates type I hypersensitivity by competitively inhibiting allergen–IgE binding and preventing high-affinity IgE Fc epsilon receptor (FcεRI)-mediated activation of mast cells and basophils.[7] Moreover, the Fab-arm exchange property of IgG4 generates bispecific, functionally monovalent antibodies, thereby limiting immune complex formation and reducing tissue inflammation.[8] Its weak affinity for Fc gamma (Fcγ) receptors and inability to activate complement further underscore its anti-inflammatory role.[9] The clinical relevance of IgG4 has been validated in passive immunization models: administration of monoclonal IgG4 antibodies targeting Fel d 1 significantly alleviated nasal symptoms upon allergen challenge, supporting IgG4 as both biomarker and potential therapeutic mediator in AIT.[10]

In addition to IgG4, AIT also enhances IgG2 and IgA responses. For example, sublingual immunotherapy (SLIT) with grass pollen allergens elevates both IgG2 and IgG4 levels, suggesting a complementary contribution of IgG2 to allergen neutralization and immune tolerance.[11] Similarly, post-AIT increases in mucosal IgA1 and IgA2 secretion may strengthen epithelial barrier function and reduce allergen translocation,[12] which could clinically manifest as reduced nasal congestion, decreased bronchial hyperreactivity, or lower frequency of allergen-induced exacerbations. Emerging evidence also implicates immunoglobulin D (IgD) in immune regulation. Prolonged AIT in patients with house dust mite (HDM)-allergic asthma has been associated with elevated allergen-specific IgD.[13] Similarly, in children with cow's milk allergy, both oral immunotherapy and natural tolerance were accompanied by increased milk-specific IgD levels, paralleled by B cell regulatory features and enhanced IL-10/TGF-β secretion, indicating that IgD upregulation correlates with measurable clinical desensitization and tolerance induction.[14]

IgE–CD23 complex

The low-affinity IgE receptor CD23, predominantly expressed on B cells, binds IgE-allergen complexes and facilitates antigen uptake and presentation to T cells, thereby shaping adaptive immune responses. Allergen-specific IgE (sIgE) further promotes CD23 upregulation on B cells, amplifying allergen capture and presentation.[15] Clinical evidence supports the IgE–CD23 complex as a dynamic biomarker: in a Japanese cohort with *Cryptomeria japonica* pollen allergy, 3 years of subcutaneous immunotherapy (SCIT) resulted in a marked reduction in circulating IgE–allergen–CD23 complexes, paralleled by an increase in IgE-blocking antibodies, reflecting a shift toward immune tolerance.[16] These findings underscore the potential of the IgE–CD23 complex as a supplementary biomarker for monitoring AIT efficacy.

Immunoregulatory Cellular Biomarkers

Regulatory B cells (Bregs)

Regulatory B cells exert immunosuppressive effects mainly through two mechanisms: (1) secretion of anti-inflammatory cytokines, including IL-10, IL-35, and TGF-β, which suppress Th2-driven inflammation and promote the differentiation of regulatory T cells (Tregs); and (2) expression of inhibitory surface molecules—such as PD-L1, CD39, CD73, CD80/CD86, ICOS-L, CD40, and the aryl hydrocarbon receptor (AhR)—that modulate antigen presentation and co-stimulatory signaling.[17] Bregs can be activated by inflammatory cytokines (e.g., IL-6, IL-1β, i*nterferon* alpha [IFN-α]), pathogen-associated molecular patterns (PAMPs) via toll-like receptor 4–toll-like receptor 9 (TLR4/TLR9), and CD40 ligation,[18] placing them at the interface of innate and adaptive immunity.

Allergen-specific immunotherapy influences both frequency and function of Bregs. In venom-allergic patients, AIT increased IL-10$^+$ Br1 cells specific to phospholipase A2, accompanied by enhanced IgG4 production.[19] Similar findings are observed in grass pollen and HDM allergy, where AIT or natural allergen exposure elevated IL-10$^+$ Br1 cells, Der p 1-specific B cells, plasmablasts, and IL-10$^+$ IL-1RA$^+$Bregs.[20,21] In these cohorts, higher frequencies of IL-10-producing Bregs coincided with clinical improvement evidenced by reduced symptom–medication scores and diminished skin prick test responses, supporting their role as a cellular marker of successful immunotherapy. Functionally, Bregs regulate immunoglobulin class switching: IL-10 suppresses

IgE synthesis while promoting IgG4 production, which attenuates allergic inflammation by competitively inhibiting allergen–IgE binding, enhancing antigen clearance, and suppressing mast cell degranulation via Fc-gamma receptor II (FcγRII or CD32)-dependent pathways.[22] AIT-induced increases in mucosal IgA1/IgA2 also strengthen epithelial barrier integrity,[23] while allergen-specific IgD has been implicated in the inhibition of IgE-mediated basophil activation.[24] Clinically, nasal IgG4 levels after SCIT in grass pollen-allergic individuals correlated positively with symptom improvement, underscoring antibody profiling as a potential biomarker for monitoring treatment efficacy.[25]

Regulatory T cells

Regulatory T cells are central to AIT-induced immune tolerance by suppressing Th2 responses and restoring the Th1/Th2 balance.[26] They are broadly classified into thymus-derived natural Tregs (nTregs) and peripherally induced Tregs (iTregs), which include FOXP3$^+$ iTregs, IL-10-producing Tr1 cells, and TGF-β-secreting Th3 cells.[27] AIT increases both frequency and suppressive function of Tregs, often accompanied by a Th2-to-Th1 shift—hallmarks of peripheral tolerance induction.[28] Tregs mediate suppression via four principal mechanisms: (1) secretion of inhibitory cytokines, such as IL-10, TGF-β, and IL-35; (2) modulation of metabolic pathways, including IL-2 consumption and production of immunosuppressive mediators (adenosine, cyclic adenosine monophosphate [cAMP], and histamine); (3) expression of co-inhibitory receptors (PD-1, CTLA-4, LAG-3, ICOS); and (4) direct cytolysis of effector T cells via granzyme/perforin pathways.[29] In addition to dampening Th2 and ILC2 responses, Tregs promote humoral tolerance by facilitating IgG4 and other blocking antibody production.[30] Clinical evidence consistently links Treg expansion to successful tolerance induction. In beekeepers and allergic patients receiving AIT, increased Treg frequencies were associated with Th2 suppression and sustained clinical benefit.[31] In HDM-allergic patients, AIT enhanced functionally competent Tregs while reducing dysfunctional ILT3$^+$ Tregs,[32] a change that paralleled reductions in symptom scores. Epigenetic stabilization, such as FOXP3 promoter demethylation, further reinforces Treg lineage stability and suppressive function.[33] Increases in IL-10$^+$ Tregs during AIT correlate with symptom improvement, while IL-35$^+$ iTregs have been shown to inhibit Th2 inflammation, suppress T cell proliferation, and reduce ILC2 cytokine release.[34] Consistently, SCIT has been associated with elevated serum IL-35 and increased circulating IL-35$^+$ Tregs.[35]

T Helper Cell Subsets (Tfh/Tfr)

T follicular helper (Tfh) cells—particularly IL-4-producing subsets—play a pivotal role in allergen-sIgE synthesis and are closely associated with AIT outcomes.[36] Circulating Tfh (cTfh) cells, phenotypically CXCR5$^+$PD-1$^+$, co-secrete IL-4 and IL-21 to drive B cell differentiation into IgE-producing plasma cells. Elevated cTfh activity has been documented in pollen-allergic patients.[37] AIT modulates this compartment by reducing cTfh frequencies while expanding IL-10-producing cTfh and T follicular regulatory (Tfr) cells, thereby restoring the Tfh/Tfr balance and suppressing pathogenic IgE responses.[38] Concurrently, AIT reduces allergen-reactive memory Th2 subpopulations—including HDM-reactive ST2$^+$CD45RO$^+$ memory Th2 cells and IL-5$^+$IL-13$^+$CD27$^-$CD161$^+$ Th2 cells—which are strongly implicated in chronic allergic inflammation.[39] Their reduction highlights effective immunomodulation and underscores their value as predictive biomarkers of AIT efficacy.

Effector Cells and Inflammatory Markers

Eosinophils (EOS) and their mediators

Eosinophils are key effector cells in allergic inflammation, particularly within the nasal mucosa and bronchial epithelium, where they contribute to chronic tissue damage and symptom persistence. Circulating eosinophil counts and activation status are widely used as clinical indicators of allergic activity and therapeutic response. In allergic rhinitis, eosinophil infiltration in the nasal mucosa is increased markedly and correlates with disease severity.[40] Immunotherapy studies have demonstrated that AIT can effectively modulate eosinophilic inflammation. For example, in patients with seasonal allergic rhinitis treated with SCIT for more than 6 months, Otsuka et al. observed a significant reduction in eosinophil counts in nasal secretions, reflecting suppression of local eosinophilic activity.[41] This decrease was accompanied by improvement in total symptom severity scores, suggesting that eosinophil suppression directly contributes to clinical benefit. Among eosinophil-derived mediators, eosinophil cationic protein (ECP) has emerged as a useful biomarker. Elevated ECP levels correlate with skin prick test reactivity, higher serum allergen-sIgE levels, and more severe clinical symptoms, highlighting its potential for monitoring disease activity and treatment efficacy.[42] Nonetheless, its specificity is limited by the fact that ECP can also be released by neutrophils and other granulocytes.[43]

Mast cells and basophils

Mast cells and basophils are central to type I hypersensitivity, serving as primary effector cells that orchestrate allergic inflammation. Allergen exposure cross links IgE bound to FcεRI on their surface, triggering rapid degranulation and the release of histamine, prostaglandins, leukotrienes, and type 2 cytokines (IL-4, IL-5, and IL-13), thereby amplifying the allergic cascade.[44] AIT induces early functional desensitization of mast cells and basophils, leading to reduced reactivity to allergen stimulation, even before significant decreases in serum sIgE levels are detectable.[2] More substantial reductions in effector cell infiltration and mediator release typically appear in the mid-to-late phases of therapy, reflecting progressive immune normalization. Two major mechanisms have been proposed to explain this desensitization:

1. IgG4-mediated competitive inhibition: AIT enhances allergen-specific IgG4 production and upregulates

low-affinity Fcγ receptors (FcγRIIa and FcγRIIb) on mast cells and basophils. IgG4 competes with IgE for allergen binding and, through FcγRII engagement, delivers inhibitory signals that suppress degranulation and cytokine release.[45]
2. Histamine H2 receptor (H2R) modulation: AIT increases H2R expression on basophils, and activation of these receptors strongly inhibits FcεRI-mediated degranulation. Clinical studies support this pathway as a key mechanism for reducing basophil reactivity.[46]

Given these findings, basophil activation testing (BAT), based on allergen-induced upregulation of surface markers, such as CD63 and CD203c, is gaining traction as a functional biomarker for AIT monitoring. BAT offers the potential to distinguish transient desensitization from sustained unresponsiveness, thereby informing treatment efficacy assessment and guiding decisions on therapy duration.

The Regulatory Role of Innate Immune Cells

Innate lymphoid cells (ILCs)

Innate lymphoid cells are a heterogeneous family of lymphocytes that lack antigen-specific receptors but are essential for rapid immune activation at mucosal surfaces. They are broadly divided into two groups: cytotoxic ILCs (natural killer [NK] cells and lymphoid tissue inducer [LTi] cells) and helper-like ILCs (ILC1, ILC2, and ILC3), which functionally mirror Th1, Th2, and Th17 cells, respectively. Among them, ILC2s are most relevant to allergic diseases. By secreting IL-5 and IL-13, they drive eosinophil recruitment, IgE class switching, and mucosal hyperreactivity, contributing to allergic rhinitis and asthma pathogenesis.[47] Elevated circulating ILC2 levels persist in patients with seasonal allergic rhinitis even during asymptomatic periods, and allergen exposure further increases their accumulation in nasal mucosa alongside IL-5 and prostaglandin D_2 (PGD_2) production.[48] Importantly, AIT reduces ILC2 frequency, highlighting their susceptibility to immunomodulation.[49] ILC2s also exhibit functional plasticity. Under cues such as IL-33 and retinoic acid, they can transdifferentiate into IL-10-producing inducible ILCs, which are enriched in inflamed mucosa of allergic patients.[50] These IL-10$^+$ ILCs suppress ILC2 and T cell proliferation, inhibit type 2 cytokine release, and support epithelial barrier integrity.[51] In SLIT-treated patients, IL-10$^+$ ILC levels are significantly increased and correlate positively with clinical improvement.[52] This correlation underscores the functional relevance of IL-10$^+$ ILCs as a mucosal biomarker reflecting tolerance acquisition during AIT. They may also adopt an "exhausted" phenotype with reduced inflammatory potential, reinforcing their role in tolerance induction during AIT.[53]

Dendritic cells (DCs)

As professional antigen-presenting cells, DCs orchestrate both initiation of type 2 inflammation and induction of tolerance, placing them at the core of AIT. Clinical studies show that AIT increases plasmacytoid DCs (pDCs), which promote Treg differentiation and mucosal tolerance while reducing CD1c$^+$ conventional DCs (cDCs), typically associated with Th2 polarization.[54,55] In murine models, CD11b$^+$c DCs cooperate with macrophages to deliver sublingual antigens to lymph nodes, where they foster allergen-specific Tregs and tolerance.[56] Particular attention has been given to tolerogenic DCs (tDCs), which are characterized by IL-10 secretion, reduced co-stimulatory molecule expression (CD80 and CD86), and diminished T cell activation. Although their precise phenotypic markers remain debated, their tolerogenic function is well documented. For example, allergoid–mannan conjugates induce IL-10$^+$t DCs and reprogram monocytes/macrophages toward tolerance.[57] Similarly, mannan–OVA polylactic-co-glycolic acid (PLGA) nanoparticles generate IL-10-producing DCs that expand allergen-specific Tregs *in vitro*.[58] Other approaches, such as cannabinoid-mediated autophagy and metabolic reprogramming, also promote tDC differentiation.[59] Additionally, DC-derived IL-27 suppresses allergen-driven proliferation of peripheral blood mononuclear cells (PBMC), while endogenous IL-10 signaling within DCs is crucial for induction of tolerance in allergic airway inflammation.[60] Together, these findings suggest that clinical AIT efficacy is at least partly dependent on the induction of functionally stable tDC populations capable of sustaining immune tolerance.

Macrophages

Macrophages represent a highly heterogeneous population of phagocytic cells with crucial roles in both innate defense and modulation of adaptive immunity. Depending on the activation signals they encounter, macrophages are broadly classified into pro-inflammatory M1 macrophages, induced mainly by interferon-γ (IFN-γ), and alternatively activated M2 macrophages, stimulated by type 2 cytokines, such as IL-4 and IL-13.[61] Within the M2 compartment, functional specialization further divides them into subsets with distinct immunological roles. For example, M2a macrophages are generally associated with the promotion of Th2-driven allergic inflammation through the production of IL-4, IL-13, and chemokines, such as CCL17, thereby contributing to asthma and other allergic disorders.[62] In contrast, M2b macrophages are characterized by their robust production of IL-10 and TGF-β and are thought to support the activation of Tregs and the establishment of immune tolerance while attenuating allergic inflammation.[63] This functional duality underscores the context-dependent behavior of macrophages in allergy, where they may either exacerbate inflammation or promote tolerance depending on the surrounding cytokine milieu. Although accumulating evidence highlights the immunoregulatory complexity of M2 macrophages, their precise contributions to AIT remain poorly defined. Further studies are needed to delineate how macrophage subsets influence treatment responsiveness, contribute to tolerance induction, and whether their phenotypic signatures could serve as predictive biomarkers of AIT outcomes.

Circulating monocytes

Circulating monocytes, derived from the bone marrow, constitute a critical component of the innate immune

system with roles extending beyond pathogen clearance and inflammation to include antigen presentation and tolerance induction. Based on CD14 and CD16 expression, human monocytes are divided into three major subsets: classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$), and non-classical ($CD14^{+}$ $CD16^{++}$) monocytes.[64] These subsets display distinct functional properties and undergo dynamic changes during AIT. Nonclassical monocytes are generally pro-inflammatory, secreting TNF-α and other mediators that amplify allergic responses; notably, their frequency significantly decreases after several months of AIT, suggesting that treatment suppresses their inflammatory potential.[65] By contrast, intermediate monocytes are thought to exert anti-inflammatory functions and are observed to expand following one year of AIT, implying a role in promoting regulatory pathways, such as Treg induction.[66] Additional evidence indicates that AIT increases the overall proportion of $CD16^{+}$ monocytes, a marker shared by both intermediate and nonclassical subsets, supporting the notion that therapy induces a dynamic reshaping of the monocyte compartment.[67] These phenotypic and proportional changes in circulating monocytes—particularly increases in IL-10-producing subsets—have been proposed as peripheral biomarkers that mirror clinical efficacy. Although the mechanistic contributions of individual monocyte subsets to tolerance are to be fully elucidated, these phenotypic and proportional changes strongly suggest that circulating monocytes may serve as accessible biomarkers for monitoring therapeutic response in AIT.

Natural killer (NK) cells

Natural killer cells mediate antiviral defense, tumor surveillance, and immune regulation. They are classified into NK1 (Th1-like, cytotoxic) and NK2 (Th2-like, regulatory) subsets.[68] More recently, regulatory NK cells (NKreg) producing IL-10 and TGF-β have been described.[69] These cells suppress T cell proliferation, inhibit IL-13 and IFN-γ secretion, and reduce IgE production,[70] suggesting a potential tolerogenic role in AIT. However, evidence is limited: one clinical study found no significant change in peripheral NK cell frequencies during AIT.[71] This may reflect patient heterogeneity, variable sampling, or subset-specific differences. Given their immunomodulatory capacity and ease of detection in peripheral blood, further work is warranted to determine whether functional or transcriptional profiling of NK subsets could provide clinically relevant biomarkers of AIT-induced tolerance.

Conclusion and Future Perspective

Allergen-specific immunotherapy remains the only clinically validated intervention capable of inducing long-term immune tolerance and modifying the natural course of allergic diseases. Its efficacy results from a coordinated network of immunoregulatory mechanisms involving antigen presentation, modulation of T- and B-cell responses, effector cell desensitization, and antibody isotype switching. Clinically, these immunologic adaptations translate into sustained improvements in symptom–medication scores and durable remission after discontinuation of treatment, confirming that AIT reprograms allergic immunity, rather than merely suppressing symptoms. Recent advances in immunology and multi-omics technologies have led to the identification of a growing panel of potential biomarkers—such as allergen-specific IgG4, $IL\text{-}10^{+}$ regulatory T cells, IL-10-producing type 2 innate lymphoid cells, and regulatory B cells—that closely mirror therapeutic outcomes. The integration of these immune signatures with longitudinal symptom trajectories and provocation test data provides an opportunity to bridge mechanistic insights with clinical endpoints. These biomarkers hold promises for predicting treatment efficacy, tracking tolerance induction, and guiding individualized treatment optimization. Despite these encouraging developments, the clinical translation of biomarker research remains limited by methodological heterogeneity, small sample sizes, and variable analytical approaches. The future research should focus on standardizing biomarker assays, establishing clinically interpretable thresholds, and integrating systems-level analyses to improve reproducibility and predictive accuracy. Equally important, standardized and optimized assays will be essential for the reliable adoption of biomarkers into routine clinical practice, bridging mechanistic insights with patient management. Large, multicenter, prospective cohorts are essential to validate candidate biomarkers and to confirm their robustness across diverse populations. At the same time, emerging therapeutic innovations—including nanoparticle-based vaccines, peptide immunotherapy, and tolerogenic dendritic cell strategies—offer new opportunities to expand the immunomodulatory repertoire of AIT. Coupling these approaches with validated biomarkers may enable real-time monitoring of immune tolerance and support precision-guided adjustment of dosing and treatment duration. In conclusion, deepening our understanding of tolerance-inducing mechanisms and establishing standardized, clinically applicable biomarker frameworks will be central to the evolution of AIT. Such integrated efforts are expected to enhance efficacy, improve safety, and enable true precision in allergy management—ultimately transforming AIT from an empirical intervention into a mechanism-driven, personalized immunotherapeutic strategy.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

Author Contributions

Chengzhi Huang was responsible for manuscript drafting and revising. Zhiyuan Tang supervised the work.

Conflict of Interest

The authors reported no conflict of interest for this work.

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