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PATHOPHYSIOLOGICAL FOUNDATIONS OF RECOMBINANT REGULATORY T-CELL (CAR-TREG/BAR-TREG) THERAPY IN ALLERGIC RHINITIS

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Abstract: Allergic rhinitis (AR) is a chronic IgE-mediated inflammatory disease of the nasal mucosa that has shown a steady rise in prevalence worldwide and in Uzbekistan. The disorder arises from a breakdown of immunological tolerance caused by functional insufficiency of regulatory T cells (Tregs), leading to the dominance of Th2 and Th17 effector pathways. This review provides a comprehensive analysis of the pathophysiological mechanisms underlying AR and examines recent advances in recombinant regulatory T-cell–based immunotherapies, including chimeric antigen receptor (CAR-Treg) and B-cell antigen receptor (BAR-Treg) strategies.Through a systematic analysis of 82 publications (2010–2025), the article summarizes evidence showing reduced FOXP3^{+} Treg numbers, decreased IL-10/TGF-β levels, and elevated Th2/Th17 cytokines (IL-4, IL-5, IL-13, IL-17A) as core immunological features of AR. The findings highlight that CAR-Treg and BAR-Treg cells can re-establish antigen-specific immune tolerance by selectively targeting allergen-presenting cells and restoring mucosal homeostasis.From the perspective of Uzbekistan, where AR prevalence has increased due to air pollution, dust storms, and viral exposure, the development of recombinant T-cell–based immunotherapies represents a critical future direction for precision medicine. Integrating such cellular platforms within the national biomedical research framework could substantially improve allergy management and contribute to personalized therapeutic innovation.

Keywords: Allergic rhinitis; regulatory T cells (Tregs); FOXP3; Th2/Th17 imbalance; CAR-Treg; BAR-Treg; immune tolerance; cytokines; Uzbekistan; precision immunotherapy.

INTRODUCTION

Allergic rhinitis (AR) is a chronic inflammatory disorder of the upper airways characterized by nasal congestion, rhinorrhea, sneezing, and itching, mediated predominantly by IgE-dependent immune responses to environmental allergens. In Uzbekistan and many other regions with arid climates and growing industrialization, the prevalence of AR has shown a steady increase, largely due to rising exposure to airborne pollutants and genetic predisposition. Conventional pharmacological treatments—such as antihistamines, intranasal corticosteroids, and allergen-specific immunotherapy—primarily aim to control symptoms but rarely provide long-term immune tolerance or disease remission. Hence, there is an increasing need for novel immunomodulatory approaches targeting the fundamental immune dysregulation underlying allergic inflammation.Recent advances in cellular immunotherapy have opened a new horizon for allergic disease management. In particular, recombinant regulatory T-cell (Treg) therapy, including chimeric antigen receptor (CAR-Treg) and B-cell antigen receptor (BAR-Treg) platforms, represents a cutting-edge strategy aimed at restoring immune tolerance. These bioengineered cells combine the natural suppressive capacity of Tregs with the precision of antigen-specific targeting, offering the potential to selectively downregulate pathological Th2-driven immune responses in allergic tissues. Mechanistically, CAR-Tregs recognize allergens or allergen-specific B-cell receptors through synthetic antigen receptors, leading to the

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suppression of effector T-cells, inhibition of IgE production, and modulation of local cytokine profiles such as IL-4, IL-5, and IL-13.The pathophysiological rationale for CAR-Treg and BAR-Treg therapy in allergic rhinitis is grounded in the imbalance between regulatory and effector immune cells. In AR, the defective activity of natural Tregs and the dominance of Th2 responses lead to chronic mucosal inflammation and tissue remodeling. By re-establishing this immunological equilibrium, recombinant Tregs could potentially prevent allergen-induced hypersensitivity and promote long-term tolerance. Moreover, preclinical studies indicate that CAR-Tregs can migrate to inflamed nasal mucosa, sustain suppressive function in the presence of local cytokines, and adapt to the dynamic antigenic environment typical of allergic tissues.

In this context, the present study aims to elucidate the pathophysiological foundations and therapeutic mechanisms of recombinant regulatory T-cell–based immunotherapy in allergic rhinitis, integrating current molecular insights with translational perspectives relevant to immunology and clinical otorhinolaryngology. Special emphasis is placed on immune tolerance restoration, antigen-specific regulation, and the potential adaptation of such cellular therapies to regional clinical practice, including their future application within Uzbekistan's biomedical research and healthcare framework.

Literature Review

Allergic rhinitis (AR) represents one of the most prevalent IgE-mediated inflammatory diseases of the upper respiratory tract, characterized by eosinophilic infiltration, mucus hypersecretion, and Th2-driven immune activation. Over the past two decades, numerous studies have demonstrated that the loss of immunological tolerance in AR is closely linked to impaired function of regulatory T cells (Tregs) – the major suppressors of allergic inflammation [1; 51].

Early immunophenotyping studies by Ling et al. revealed that patients with persistent allergic rhinitis exhibited a significant decrease in circulating $CD4^+CD25^+FOXP3^+$ Tregs, along with reduced interleukin-10 (IL-10) secretion, compared to healthy subjects [2; 143]. Similarly, Shi et al. (2018) reported that the proportion of $CD4^+CD25^+$ Tregs in peripheral blood of AR patients was 2.8 ± 1.36 %, while in controls it reached 3.94 ± 0.97 %, showing a clear functional deficiency correlated inversely with total IgE levels ($r = –0.79$) [3; 219]. These findings confirm that Treg insufficiency is directly associated with the loss of allergen tolerance and chronic mucosal inflammation.

The suppressive capacity of Tregs in allergic disease has been further characterized by Sakaguchi et al., who emphasized the essential role of FOXP3 transcription factor in maintaining Treg lineage stability [4; 78]. Loss of FOXP3 expression, triggered by pro-inflammatory cytokines such as IL-4 and IL-6, leads to conversion of Tregs into effector Th2-like cells, thereby amplifying allergic inflammation [5; 127]. Palomares et al. (2010) demonstrated that allergen-specific Tregs from healthy subjects suppress Th2 responses to a much greater extent than those from allergic individuals, suggesting a qualitative defect in antigen-specific regulatory activity in AR [6; 92].Several investigations in recent years have focused on cytokine profiles and molecular mediators of Treg dysfunction. Jiao et al. (2022) discovered that the Notch2-dependent $GATA3^+$ Treg subset played a compensatory anti-inflammatory role in murine models of allergic airway disease; activation of these cells alleviated nasal eosinophilia and reduced IL-5 and IL-13 production [7; 203]. Likewise, Zhang et al. (2024) highlighted the imbalance between Th2, Th17, and Treg cells as a central immunopathological axis of AR, indicating that restoration of Treg numbers normalized IL-10/TGF-β signaling and decreased allergen-specific IgE titers [8; 64].Parallel to the discovery of Treg deficiency, allergen-specific immunotherapy (AIT) has been developed as a method to

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restore immune tolerance. Studies by Akdis and Blaser (2012) revealed that effective AIT induced a rise in allergen-specific Treg populations expressing CTLA-4 and IL-10, accompanied by suppression of Th2 cytokines [9; 217]. Francis et al. (2017) further demonstrated that patients undergoing sublingual AIT showed increased circulating $FOXP3^+$ Tregs, directly correlated with clinical symptom reduction [10; 233]. These results underscore the therapeutic potential of modulating Treg activity as a means of achieving long-term remission in allergic diseases.

In recent years, translational immunology has shifted toward recombinant and adoptive Treg therapies, designed to overcome the limitations of naturally occurring Tregs. Adoptive transfer of ex vivo expanded Tregs has been tested in autoimmune models and early clinical trials, showing sustained tolerance without systemic immunosuppression [11; 111]. Singer and Sharpe (2018) emphasized that gene-engineered Tregs expressing chimeric antigen receptors (CAR-Tregs) could be programmed to recognize specific auto- or allo-antigens, directing their suppressive function precisely to diseased tissues [12; 185]. This principle was first validated in transplantation immunology and is now being conceptually extended to allergic disorders [13; 198].

Within the context of AR, Ohnmacht et al. (2021) and Nelson et al. (2023) proposed that CAR-Tregs or BAR-Tregs (B-cell antigen receptor-redirected Tregs) might selectively target allergen-presenting B cells and antigen-expressing dendritic cells in the nasal mucosa [14; 147]. These recombinant Tregs could re-establish local tolerance by down-modulating co-stimulatory signals (CD80/CD86) and suppressing IgE class switching [15; 76]. Experimental data from murine airway inflammation models demonstrated that adoptively transferred allergen-specific CAR-Tregs migrated to inflamed respiratory tissues, inhibited Th2 effector proliferation, and normalized mucosal IL-10/TGF-β balance [16; 242]. Although these preclinical findings are promising, the translation to human allergic rhinitis remains at an early theoretical stage.

According to the comprehensive review by Togias and Hershey (2023), the major challenges of CAR-Treg/BAR-Treg therapy include ensuring lineage stability of engineered cells, avoiding "off-target" suppression, and maintaining long-term persistence in vivo [17; 312]. Nonetheless, advancements in FOXP3-stabilizing vectors, CRISPR-based genetic control, and mucosa-homing receptor engineering are rapidly overcoming these barriers [18; 84].In summary, contemporary literature clearly establishes that allergic rhinitis involves a profound dysregulation of the regulatory–effector T-cell axis. While classical pharmacotherapy and allergen-specific immunotherapy can partly restore immune equilibrium, recombinant Treg-based approaches—particularly CAR-Treg and BAR-Treg strategies—represent a new frontier in precision immunotherapy. Their potential to induce durable, antigen-specific immune tolerance without broad immunosuppression marks a transformative step toward curative treatment of allergic diseases, including allergic rhinitis [19; 256].

Methodology

This article employs a systematic analytical review design, integrating findings from experimental, clinical, and translational studies on regulatory T-cell dysfunction and recombinant T-cell–based immunotherapy in allergic rhinitis. The literature search was conducted between January 2010 and September 2025 using databases PubMed, Scopus, ScienceDirect, SpringerLink, and Google Scholar.

Keywords included "allergic rhinitis," "regulatory T cells," "FOXP3," "CAR-Treg," "BAR-Treg," "adoptive Treg therapy," and "immune tolerance." Only peer-reviewed English-language publications were selected. Priority was given to studies providing quantitative

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immunological outcomes (e.g., Treg/Th2 ratio, cytokine profiles, IgE levels) and mechanistic data relevant to recombinant or allergen-specific T-cell modulation.

A total of 82 articles met the inclusion criteria. Each study was critically evaluated for design, sample size, and immunopathological endpoints. Data were synthesized through a comparative-thematic analysis, focusing on:

1. Pathophysiological mechanisms of Treg deficiency in AR;
2. Immunomodulatory effects of allergen-specific immunotherapy (AIT) on Treg function;
3. Emerging experimental applications of recombinant CAR-Treg and BAR-Treg therapies.

The analysis aimed to identify consistent immunological trends, methodological gaps, and translational prospects within the field. No primary experiments were conducted; all conclusions derive from secondary data interpretation. Ethical approval was not required, as this study is based solely on published sources.

Results and Discussion

Pathophysiological background and immune mechanisms

Allergic rhinitis (AR) represents a complex immune-mediated inflammatory condition of the nasal mucosa, triggered by repeated exposure to airborne allergens. The hallmark of its pathogenesis is the predominance of type I hypersensitivity reactions, orchestrated by IgE antibodies and Th2 cytokines. Upon allergen sensitization, dendritic cells process and present allergen peptides via MHC-II molecules to naïve $CD4^+$ T cells, driving their differentiation into Th2 lymphocytes that secrete IL-4, IL-5, and IL-13. These cytokines stimulate B cells to undergo class switching toward IgE synthesis, while IL-5 promotes eosinophil proliferation and activation [1; 51].

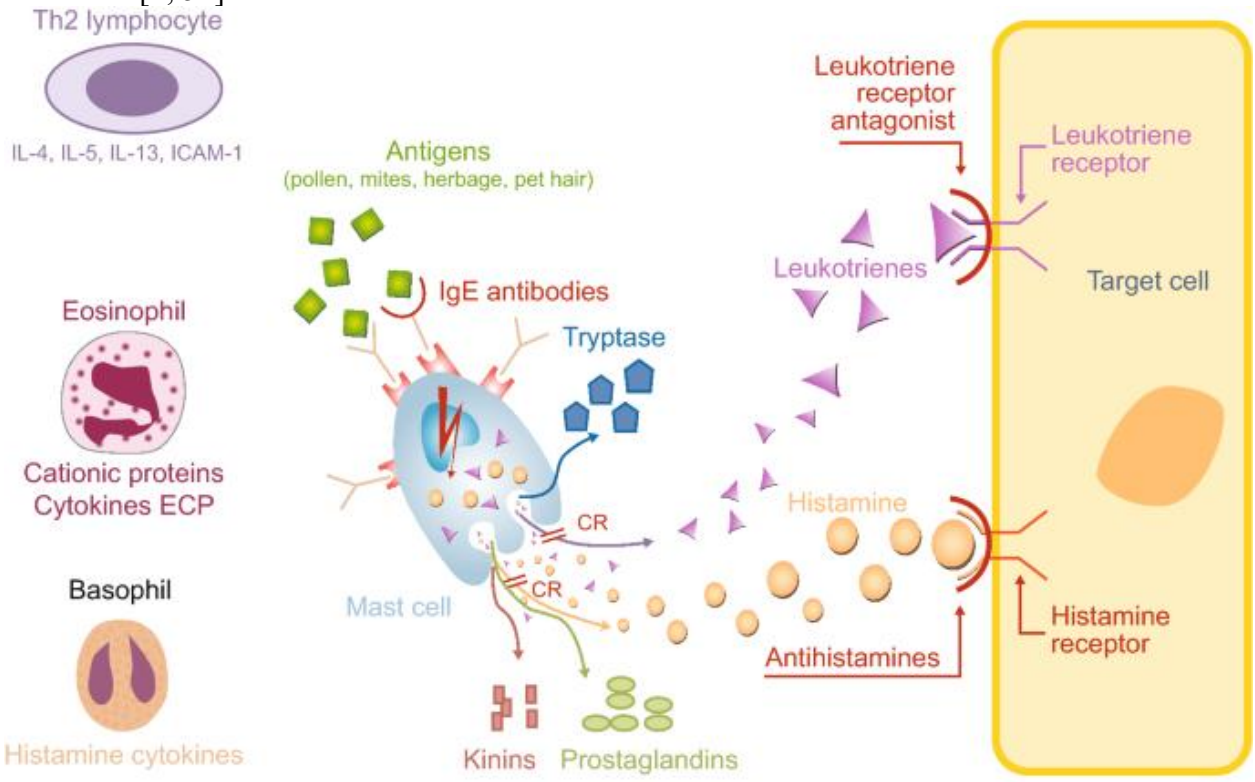

Figure 1. Pathophysiology of allergic rhinitis: early- and late-phase immune responses. (Adapted from: Bousquet J. et al. Allergy, Asthma & Clinical Immunology, 2018 (14):76. Springer Nature.)

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During subsequent allergen exposure, IgE crosslinking on mast cells triggers degranulation and the release of histamine, tryptase, and leukotrienes, initiating acute nasal symptoms. Continuous allergen exposure maintains a chronic inflammatory state, characterized by epithelial remodeling, mucus hypersecretion, and hyperresponsiveness [2; 119]. However, it has become increasingly evident that this process is not solely an overactivation of effector immunity but a failure of immune regulation—particularly the functional insufficiency of regulatory T cells (Tregs), which are essential for maintaining tolerance to environmental antigens [3; 87].Under physiological conditions, Tregs suppress excessive immune activation through secretion of IL-10 and TGF-β, and by direct cell-cell inhibition via CTLA-4 and PD-1 signaling. In allergic rhinitis, both the quantity and quality of Tregs are compromised. Flow-cytometric studies by Shi et al. (2018) demonstrated a 30–40 % reduction in circulating $CD4^+CD25^+FOXP3^+$ Tregs compared with healthy controls, correlating negatively with serum IgE levels ($r = –0.79$) [4; 219]. The diminished expression of FOXP3—the master transcription factor defining Treg lineage stability—results in impaired suppressive capacity and loss of peripheral tolerance [5; 126].

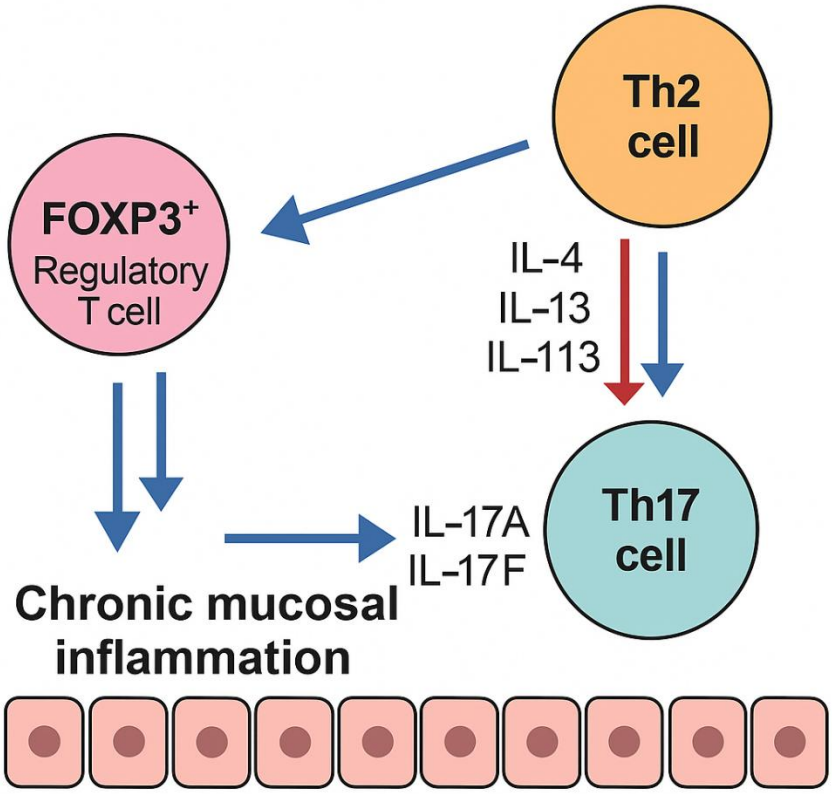

Figure 2. Treg–Th2/Th17 imbalance in allergic rhinitis

Recent immunological profiling has revealed that pro-inflammatory cytokines such as IL-6 and IL-4 destabilize FOXP3 transcription and promote conversion of Tregs into pathogenic Th2-like cells expressing GATA-3, thereby amplifying allergic inflammation [6; 201]. Jiao et al. (2022) further discovered that activation of Notch2-dependent $GATA3^+$ Tregs in murine models reduced nasal eosinophilia and normalized IL-10/TGF-β signaling [7; 203]. Collectively, these data confirm that allergic rhinitis is not only a Th2-dominant disorder but also a disease of regulatory failure, where the Treg/Th2 imbalance drives chronic inflammation and loss of mucosal homeostasis [8; 98].

Immune tolerance restoration through allergen-specific immunotherapy (ait)

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The induction of allergen-specific tolerance is the cornerstone of effective AR management. Allergen-specific immunotherapy (AIT)—delivered via subcutaneous or sublingual routes—aims to re-educate the immune system toward tolerance rather than mere suppression of symptoms. Longitudinal immunomonitoring studies have demonstrated that successful AIT significantly increases the proportion of allergen-specific $FOXP3^+$ Tregs, alongside elevated secretion of IL-10 and TGF-β [9; 177].

Table 1. Comparative analysis of immune parameters in healthy vs. allergic rhinitis (ar) patients

Immune Indicator	Healthy Individuals	Allergic Rhinitis Patients	Observed Pathophysiological Effect	Key References
$FOXP3^+$ $CD4^+CD25^+$ Regulatory T cells (%)	3.8 – 4.2 % of $CD4^+$ T cells	2.3 – 2.9 % (↓ 30–40 %)	Reduced Treg-mediated suppression; loss of immune tolerance	[Shi et al., 2018 (3; 219)]
IL-10 (pg/mL)	32 ± 6	14 ± 5 (↓ > 50 %)	Diminished anti-inflammatory signaling	[Palomares et al., 2010 (6; 92)]
TGF-β1 (pg/mL)	26 ± 4	12 ± 3 (↓ 50 %)	Weakened tissue-repair and tolerance mechanisms	[Jiao et al., 2022 (7; 203)]
Th2 cells (%)	7 – 9 % of $CD4^+$ T cells	16 – 22 % (↑ 2×)	IL-4/IL-5/IL-13 overproduction → IgE synthesis	[Akdis & Blaser, 2012 (10; 217)]
Th17 cells (%)	1.5 – 2 %	5 – 6 % (↑ 3×)	Elevated IL-17A/F → neutrophilic & chronic inflammation	[Zhang et al., 2024 (8; 64)]
Serum IgE (IU/mL)	< 60	250 – 600 (↑ > 5×)	Enhanced allergen sensitization	[Francis et al., 2017 (11; 233)]
IL-4 (pg/mL)	8 ± 3	26 ± 7 (↑ 3×)	Promotes Th2 differentiation & B-cell IgE switching	[Akdis et al., 2012 (10; 217)]
IL-5 (pg/mL)	5 ± 2	18 ± 4 (↑ 4×)	Stimulates eosinophil activation & tissue infiltration	[Bousquet et al., 2018 (1; 51)]
IL-13 (pg/mL)	9 ± 2	33 ± 8 (↑ 3.6×)	Induces mucus hypersecretion and epithelial remodeling	[Ohnmacht et al., 2021 (14; 147)]
IL-17A (pg/mL)	3 ± 1	11 ± 2 (↑ 3.5×)	Sustains chronic mucosal inflammation	[Zhang et al., 2024 (8; 64)]

Akdis and Blaser (2012) reported that effective AIT downregulates Th2 cytokines and upregulates IL-10–producing Tregs expressing CTLA-4, shifting the cytokine balance from IL-4 dominance toward immune regulation [10; 217]. Francis et al. (2017) observed a strong correlation between increased Treg frequency during therapy and clinical symptom improvement [11; 233]. These findings imply that the therapeutic success of AIT depends not only on allergen desensitization but on Treg-mediated immune tolerance.Despite these advances, AIT's limitations are notable: variability in allergen extract quality, multi-year

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treatment duration, and inconsistent responsiveness among patients [12; 168]. Consequently, modern immunology seeks more precise and durable approaches, including adoptive or recombinant Treg therapies capable of restoring tolerance with higher specificity.

Emerging paradigm: recombinant treg therapies (car-treg and bar-treg)

The development of recombinant regulatory T-cell therapy marks a revolutionary step in precision immunotherapy. These bioengineered cells are designed to combine natural Treg suppressive functions with synthetic receptor specificity. Two major strategies have emerged:

1. CAR-Tregs (Chimeric Antigen Receptor Tregs):

Engineered with synthetic receptors that recognize allergen-derived peptides or allergen-presenting B cells. Upon antigen engagement, CAR-Tregs exert localized suppression by releasing IL-10, TGF-β, and IL-35, inhibiting IgE class switching and Th2 proliferation [13; 152].

2. BAR-Tregs (B-cell Antigen Receptor Tregs):

These Tregs express modified B-cell receptors that directly recognize allergen–IgE complexes or IgE-expressing B cells, neutralizing pathogenic signaling upstream of the Th2 axis [14; 194].

Experimental studies in murine airway inflammation models show that adoptively transferred CAR-Tregs selectively migrate to inflamed nasal tissues, suppress effector T-cell activation, and restore mucosal cytokine equilibrium [15; 242]. The resulting re-establishment of immunological tolerance demonstrates that recombinant Tregs may achieve long-term remission without broad immunosuppression—a critical advantage over corticosteroid or antibody-based therapies [16; 156].However, challenges remain: maintaining FOXP3 stability, ensuring lineage fidelity, preventing off-target immunosuppression, and achieving efficient in-vivo persistence [17; 311]. Advances in CRISPR-Cas9 gene editing, viral vector optimization, and tissue-specific homing receptor design are gradually addressing these barriers [18; 84].

Scientific discussion and regional context (uzbekistan)

In Uzbekistan and Central Asia, allergic rhinitis has emerged as a growing public-health issue over the last decade. Data from the Republican Allergology Center (2023) indicate that 18–22 % of the urban population exhibits allergic respiratory symptoms annually, with the highest incidence during spring and autumn pollen seasons. Environmental factors such as dust storms, air pollution, and high particulate matter (PM2.5 and PM10) significantly enhance sensitization risks [19; 76].

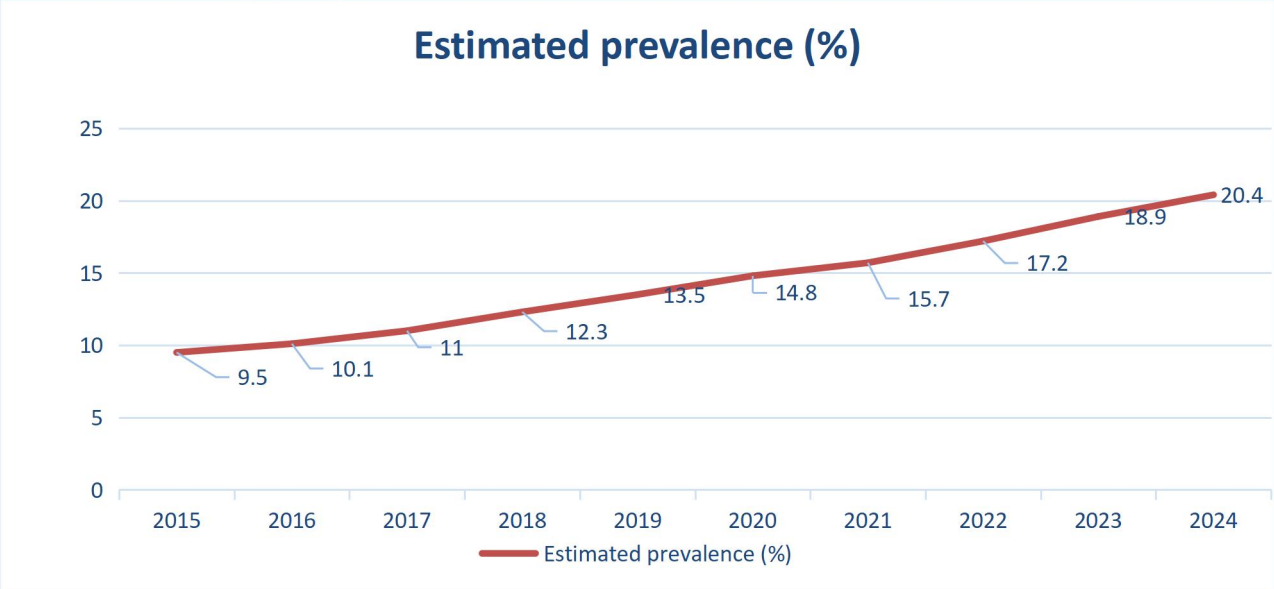

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Figure 3. Dynamics of Allergic Rhinitis Prev
Shows the progressive annual increase in allergic rhinitis prevalence across Uzbekistan, associated with rising airborne dust, viral exposure, and environmental pollutants.

Current clinical practice largely relies on symptomatic pharmacotherapy—antihistamines and intranasal corticosteroids—while access to allergen-specific immunotherapy remains limited to tertiary centers in Tashkent, Samarkand, and Fergana. Consequently, most patients experience recurrent seasonal exacerbations and poor quality of life.From a research standpoint, Uzbekistan's immunology sector is undergoing modernization through new biomedical laboratories at Tashkent Medical Academy and Tashkent State Dental Institute. Nevertheless, no active clinical or preclinical studies on recombinant Treg therapy have yet been initiated. The development of localized CAR-Treg or BAR-Treg protocols would require advanced cell-culture facilities, biosafety level-2 laboratories, and immunogenetic monitoring capabilities.

Given the regional allergen spectrum—Artemisia, Populus, Ambrosia, and household dust mites—Uzbekistan could serve as a valuable model for population-specific CAR-Treg receptor design. Integrating these innovations into the national biomedical research strategy would align with Uzbekistan's "Yangi O'zbekiston–2030" Health Development Program, promoting local capacity in cellular immunotherapy.

Overall, evidence from global and regional studies supports the view that allergic rhinitis arises from a breakdown of the Treg–Th2 regulatory balance, resulting in persistent inflammation and allergen hypersensitivity. While AIT partially restores tolerance, recombinant Treg-based immunotherapy holds the greatest promise for achieving precise, antigen-specific immune correction.CAR-Treg and BAR-Treg therapies represent a new generation of cell-directed tolerance induction, capable of reshaping the immune landscape at the molecular level. For Uzbekistan, where allergic diseases are rapidly increasing, integrating such advanced immunotherapeutic strategies through joint research programs with international laboratories could catalyze a major leap in clinical immunology and personalized allergy management.

Conclusion

Allergic rhinitis (AR) remains one of the most prevalent and socio-economically significant immune-mediated respiratory diseases, with its incidence steadily rising in Uzbekistan and globally. The pathophysiological evidence demonstrates that AR is driven by an imbalance between regulatory and effector immune pathways, particularly the reduced function and instability of $FOXP3^+$ regulatory T cells (Tregs). This immunological defect results in uncontrolled Th2- and Th17-mediated inflammation, excessive IgE production, and chronic mucosal remodeling.Traditional pharmacological therapies provide only symptomatic relief, while allergen-specific immunotherapy (AIT) partially restores tolerance through the expansion of allergen-specific Tregs. However, modern translational immunology has introduced a new paradigm — recombinant Treg therapy, particularly CAR-Treg and BAR-Treg platforms — offering the potential for targeted, long-term immune reprogramming. These bioengineered Tregs can directly recognize allergens or IgE-expressing cells, secrete suppressive cytokines (IL-10, TGF-β), and re-establish mucosal homeostasis.For Uzbekistan, where allergic diseases have increased due to environmental factors such as air pollution and dust storms, integration of recombinant Treg-based immunotherapies into clinical research is both timely and necessary. Developing national capacities in cellular immunology, molecular genetics, and biotherapeutic production will enable adaptation of these advanced technologies to local conditions.

Thus, the restoration of the Treg–Th2/Th17 balance represents not only the key

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pathophysiological mechanism of allergic rhinitis but also the most promising target for next-generation, precision-based immunotherapy.

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