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HARNESSING ANTI-IGE: IGE COMPLEXES TO ENHANCE CAR T-CELL THERAPY FOR AUTOIMMUNE DISEASES

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ABSTRACT

Autoimmune diseases result from the immune system erroneously attacking the body's own healthy cells, tissues, and organs, causing a broad range of chronic and often debilitating disorders. While chimeric antigen receptor (CAR) T-cell therapy has emerged as a transformative option for severe, treatment-resistant autoimmune conditions, its clinical use is limited by risks such as cytokine release syndrome and potentially life-threatening sepsis. This review highlights a strategy to enhance CAR T-cell therapy by integrating preformed anti-IgE:IgE complexes, particularly those using clone 8D6 antibody (and its humanized counterpart, UB-221). By engineering these complexes to selectively engage CD23 receptors on immune-regulatory cells, this approach aims to minimize CAR T-cell therapy toxicities. This review examines the mechanistic rationale, therapeutic implications, and future directions for combining preformed anti-IgE:IgE complexes with CAR T-cell therapy, proposing a safer, more effective pathway for treating refractory autoimmune diseases.

Keywords: Autoimmunity; CAR T-Cell Therapy; Anti-Ige; Immune Complexes; CD23, Secondary Infections

1 INTRODUCTION

Autoimmune diseases encompass a diverse group of chronic disorders characterized by an inappropriate immune response against the body's own tissues. Despite advances in immunosuppressive and targeted biological therapies, many patients with severe or refractory autoimmune conditions continue to face significant morbidity and limited treatment options [1,2].

Chimeric antigen receptor (CAR) T-cell therapy, originally developed for hematological malignancies, has recently shown promise in reprogramming the immune system (B cells) to achieve durable remission in autoimmune diseases [3,4]. However, the risk of severe toxicities, including cytokine release syndrome (CRS) and sepsis, remains a major challenge [5,6]. It is estimated that 75% of patients receiving CAR T-cell therapy experience CRS, wherein 25% to 50% develop severe cases [7,8]. The severe inflammation from a CAR-induced cytokine storm mimics sepsis, so closely that it's difficult to differentiate. Furthermore, CAR T-cell therapy suppresses the immune system, putting patients at very high risk of secondary infections [9,10].

Integrating preformed anti-IgE:IgE complexes—particularly those using the clone 8D6 antibody (and its humanized counterpart, UB-221) [11,12]—offers a strategy to improve the safety and efficacy of CAR T-cell therapy by selectively modulating immune pathways. This review explores combining anti-IgE:IgE complexes with CAR T-cell therapy to treat refractory autoimmune diseases.

2 DISCUSSION

Integrating preformed anti-IgE:IgE complexes—especially those formed with the 8D6 antibody clone or humanized UB-221—marks a pivotal advancement for CAR T-cell therapy in autoimmune diseases. The 8D6:IgE complex addresses key safety barriers by binding specifically to CD23 receptors on regulatory immune cells, reducing the likelihood of allergic effector cell activation and systemic inflammation. UB-221 (recently renamed Ascendant-221) is an investigational humanized monoclonal antibody designed to treat allergic diseases by neutralizing immunoglobulin E (IgE) and targeting the CD23 receptor [13,14].

Similar to IgE-antigen complexes [15,16], 8D6:IgE or 221:IgE complexes may facilitate safer CAR T-cell therapy by selectively targeting CD23 on monocytes, M2 macrophages, dendritic cells, and B cells. Through this mechanism, these complexes could modulate immune signaling to mitigate hyper-inflammatory responses, promote effective pathogen clearance without excessive inflammation, expedite adaptive T-cell priming, and lower the risk of post-infectious immune paralysis.

Pre-forming anti-IgE:IgE complexes prior to administration may help support the patient's immune system in combating secondary infections. Anti-IgE:IgE complexes do not bind to free IgE in the body. This allows the free IgE to play a vital role in immune cell health by stabilizing receptors [17,18], promoting cell survival [19], and preserving homeostasis [20,21]. This dual immune pathway may help defend against secondary infections during CAR T-cell autoimmunity therapy.

However, several challenges remain before widespread clinical implementation. Large-scale clinical trials are needed to validate safety and efficacy across patient populations. The long-term effects of IgE/CD23 pathway modulation requires careful monitoring, and optimizing dosing, timing, and formulation of the 8D6:IgE or 221:IgE complex with CAR T-cell therapy is critical for robust clinical outcomes.

Future research should clarify the molecular mechanisms of CD23-mediated regulation, develop more specific antibody clones, and assess compatibility with other immunomodulatory therapies. Ultimately, anti-IgE:IgE complexes could drive a paradigm shift toward safer and more effective cell-based therapies for autoimmune diseases.

2.1 How Anti-IgE:IgE complexes work

This therapy relies on the unique conformational binding specificity of the anti-IgE antibody clone 8D6 or UB-221. Free IgE naturally binds to two types of receptors: the high-affinity FcεRI receptor, which is found on mast cells and basophils, and the low-affinity CD23 receptor, which is present on M2 macrophages, dendritic cells, B cells, and monocytes. When the 8D6 or UB-221 clone reacts with a monoclonal IgE antibody to form a pre-formed immune complex, it specifically targets a conformational epitope on the IgE constant domain. This interaction sterically blocks the region needed to bind the high-affinity FcεRI receptor, preventing this connection. Importantly, the 8D6 or UB-221 antibody does not disrupt the structural site necessary for CD23 interaction. As a result, the pre-formed anti-IgE:IgE complex cannot interact with allergic effector cells such as mast cells and basophils, but it can still bind exclusively to CD23 receptors on antigen-presenting and regulatory white blood cells.

Using an anti-IgE:IgE complex in CAR T-cell therapy for autoimmune diseases offers several important safety and efficacy benefits. First, by completely blocking the FcεRI pathway, this approach eliminates the risk of CRS, sepsis, and severe allergic toxicity, which is a significant concern with standard IgE-based therapeutics that might cross-link FcεRI receptors on mast cells and basophils. This ensures safer delivery during systemic CAR T-cell treatment. Second, because the complex binds exclusively to CD23, it enables precise interaction with key regulatory immune cells. On B cells, cross-linking CD23 acts as a negative feedback loop that suppresses pathogenic antibody production. This process helps retrain or eliminate autoreactive immune cell populations while minimizing widespread inflammation, such as cytokine storms, often triggered by uncontrolled CAR T-cell activation.

Researchers may combine anti-IgE:IgE complexes with other antigens (such as staphylococcal enterotoxins) [22]. By routing these antigens directly to B cells via CD23, the complexes promote the formation of antigen-specific antibodies. This targeted antigen delivery system leverages the low-affinity IgE receptor (CD23) expressed on antigen-presenting cells. By utilizing anti-IgE:IgE complexes as a vehicle, researchers can enhance antigen uptake and processing, ultimately boosting the adaptive immune response and generating protective antibodies more efficiently [22].

Prophetic Example: Integrating preformed Anti-IgE:IgE Complexes with CAR T-Cell Therapy

Consider a patient with severe, refractory systemic lupus erythematosus (SLE) driven by autoreactive B cells.

- Step 1: CAR T-cell autoimmunity therapy

CAR T-cell treatment targets the general B-cell marker CD19. These engineered T-cells hunt down and destroy B cells throughout the body. This causes a temporary, deep depletion (wipeout) of both healthy B cells and harmful autoreactive B cells.

- Step 2: Preformed anti-IgE:IgE complex therapy

An 8D6:IgE or 221:IgE complex is administered to complement CAR T-cell autoimmunity therapy. A distinguishing feature of the anti-IgE:IgE complex is its ability to bind efficiently to CD23 even without an attached allergen. The preformed anti-IgE:IgE complexes retain full capacity to interact with membrane-bound CD23 on cells such as monocytes, M2 macrophages, dendritic cells, and B cells.

- Outcome: Durable Remission and Reduced Toxicity

This dual strategy efficiently clears autoreactive B cells, re-establishes immune tolerance, and minimizes the risks of cytokine storm, sepsis, and anaphylaxis. Integrating anti-IgE:IgE complexes with CAR T-cell therapy could provide safer, more precise, and potentially curative treatment for SLE and other autoimmune diseases.

3 BIOLOGICAL CONSIDERATIONS TARGETING CD23

While bypassing the FcεRI pathway neutralizes immediate allergic toxicity, redirecting immune complexes exclusively to CD23 introduces separate immunopathology concerns.

Soluble CD23 Shedding: Membrane-bound CD23 is easily cleaved into a soluble form (sCD23). In active autoimmune patients, systemic sCD23 can act as "decoys," binding the anti-IgE:IgE complex before it reaches regulatory cell surfaces and partially neutralizing the membrane-bound CD23 effect [23]. To prevent systemic soluble CD23 (sCD23) from acting as a "decoy" that intercepts anti-IgE:IgE complexes, therapeutic interventions may target four primary mechanisms by inhibiting cleavage, direct neutralization, next-generation antibody engineering, and alternative pathway engagement [24].

4 CONCLUSION

Integrating anti-IgE:IgE complexes with CAR T-cell therapy offers a new approach to managing severe autoimmune diseases. Using the 8D6 antibody clone enables selective CD23 targeting and helps prevent anaphylactic reactions, addressing critical safety concerns that have limited broader clinical adoption of CAR T-cell therapies in autoimmunity. Although further optimization and long-term safety studies are needed, current evidence points toward more targeted, durable, and safer interventions. Advancing this combined strategy through continued research could reshape the autoimmune disease treatment landscape, offering patients more precise, individualized immunotherapies.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Michael John Dochniak used the program "Grammarly" for grammar, spelling, and punctuation throughout the preparation of the review article. Mr. Dochniak used Grammarly, version 14.1271.0 (Grammarly Inc., San Francisco, CA). Dochniak used Grammarly to review and edit the entire article for grammatical accuracy, clarity, and readability. Grammarly's AI-powered writing assistant suggested improvements to sentence structure, word choice, and tone consistency, which the author reviewed and selectively incorporated. The author did not use it to generate original scientific content, data analysis, or research conclusions. The author takes full responsibility for the integrity of all content generated and presented in this review article.

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Disclosure of conflict of interest

The author claims no conflict of interest.

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Michael John Dochniak is an independent medical researcher who has authored several books on Alzheimer's disease, Artificial Intelligence, Autism Spectrum Disorders, and Climate Change through Cambridge Scholars Publishing and Nova Science Publishers. Mr. Dochniak has written extensively through GSC Online Press and appreciates their dedicated service.

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