Review Article

Immune Reset: CAR T Cell Therapy as a Novel Approach in Autoimmune Disease Treatment

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ABSTRACT

Autoimmune diseases arise from immune system dysregulation and lead to chronic inflammation and tissue damage. Aberrant B cell behavior, which includes autoantibody production and epitope spreading, plays a crucial role in disease exacerbation. Traditionally, therapies like corticosteroids, methotrexate, and monoclonal antibodies show efficacy in managing symptoms. However, they often fail to achieve durable remission, leading to patients requiring lifelong treatment. Recent advancements such as Chimeric Antigen Receptor (CAR) T cell therapy, bispecific T cell engagers (BiTES), and Bruton's tyrosine inhibitors (BTK) offer a novel approach for precisely targeting pathogenic immune cells, but most importantly, achieving immune reset. CAR T therapy demonstrates great potential in reducing patient reliance on immunosuppressive drugs while achieving sustained remission. This review discusses the history of autoimmune disease treatment and how the field evolves away from broad-spectrum immune suppressors towards targeted cell therapies which demonstrate curative outcomes for patients.

Keywords: Autoimmunity; immunotherapy; CAR T Therapy; immune reset; B cells

INTRODUCTION

The immune system is a complex and highly regulated network that maintains the body's defense against external threats while preserving tolerance to self-antigens. When this balance is disrupted, autoimmune diseases develop, characterized by the immune system targeting self-antigens and causing chronic inflammation, tissue damage, and organ dysfunction (1, 2). These disorders include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), myositis, and myasthenia gravis, among others. Despite the genetic and environmental causes, the downstream outcome results in aberrant B cell behavior. The persistence of self-reactive B cell clones, as described in Burnet's "forbidden clone" hypothesis, emphasizes how autoreactive B cells that escape immune tolerance checkpoints multiply and exacerbate autoimmune disease through peripheral self-antigen recognition (3). B cells also have the ability to undergo epitope spreading, or increase the diversity of antigens that they target, which worsens the immune response. In addition to producing autoantibodies, B cells interact with T cells to sustain inflammation by presenting antigens to CD4+ T cells as well as activating CD8+ T cells

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via dendritic cells that activate cytotoxic T cells, as observed in lupus-prone MRL-Faslpr mice (4).

Given the role of B cells in autoimmunity, targeting them becomes a therapeutic strategy. B cell depletion therapies, such as using monoclonal antibodies like rituximab, show efficacy in multiple autoimmune disorders. However, a major problem in treating autoimmune diseases is the difficulty in achieving durable remission. Many current therapies focus on suppressing inflammation and addressing symptoms rather than the root causes of immune dysregulation. This typically means that patients require lifelong therapy, which increases the risks of infections while interfering with the patient's life.

The development of autoimmune diseases rapidly becomes a global health concern because of its increasing prevalence. They are driven by many factors, including genetic predispositions, environmental triggers, and the failure of immune mechanisms to rid the body of autoreactive immune cells. Evidence suggests that this increase is also driven by factors like dietary changes, pollution, infections, stress, climate change, and exposure to xenobiotics (5). This review analyzes the evolution of B cell depletion therapy, starting with conventional approaches such as rituximab and steroids, which primarily aim at symptom management through the suppression of inflammation. It then explores other, more novel methods such as CAR T therapy. CAR T cell treatment differs from standard therapies because it introduces the idea of immunological reset, a process that selectively removes autoreactive immune cells, allowing the immune system to grow again with a naive and healthy phenotype. This immunological reset marks a big step forward from traditional treatments since it targets the fundamental causes of immune dysregulation instead of merely controlling symptoms. By analyzing CAR T therapy's outcomes in autoimmune diseases and comparing them to its application in cancer, this paper explores the transformative potential of these therapies and their ability to reshape the future of autoimmune disease management.

HISTORY OF AUTOIMMUNE DISEASE AND TREATMENT

This review examines the history of treatment for autoimmune disease, discussing both broadly immunosuppressive treatments and novel targeted modalities of the future. First, this section explores how older and less targeted medicines are used to deplete B cells, starting with steroids. Each of these treatments is evaluated in terms of their mechanisms, effectiveness, and limitations, providing a comparison among them.

Corticosteroids and Combination Therapies

When Prednisone was introduced in 1954, it built on the success of Cortisone, which was the first corticosteroid used to treat autoimmune diseases like RA in 1948. At that time, autoimmune diseases were poorly understood, but corticosteroids demonstrated success in suppressing inflammation and immune overactivation (6). In a study on MRL/MpSlac-lpr mice, daily doses of prednisone were administered over 13 weeks. It was found that levels of cytokines IL-21 and IL-10 were reduced and transcription factors Blimp-1 and Bcl-6 were suppressed, thus resulting in improved lupus symptoms. However, prednisone did not affect anti-dsDNA antibody levels because it does not target persistent plasma cells which are the primary source for these autoantibodies (7).

Prednisone's inability to impact anti-dsDNA autoantibody levels was not uncommon as its mechanism does not target the primary source of autoantibodies. To address refractory cases of SLE, combination therapies emerged as a promising approach. The 2022 study by Leandro *et al.* utilized rituximab, cyclophosphamide, and corticosteroids to achieve B lymphocyte depletion, thus targeting precursors of autoantibody producing plasma cells. At six months, five out of six patients showed reduced disease activity. Laboratory markers like serum C3 levels increased in all patients and anti-dsDNA antibody levels varying amongst patients, but with all levels decreasing to some extent. The treatment was generally safe with only mild side effects like nausea/vomiting. Overall, these findings highlighted the potential of combination therapies to improve outcomes in severe SLE and offer new therapeutic avenues for other autoimmune diseases characterized by persistent autoantibody production (8).

The introduction of rituximab and cyclophosphamide marked a shift in autoimmune disease treatment by targeting B cells, which were recognized as key drivers of autoimmunity. While these therapies improved outcomes in lupus nephritis (LN), their limitations became apparent as autoreactive B cells often re-emerged during reconstitution due to elevated BAFF levels. This paved the way for belimumab, a BAFF-targeting monoclonal antibody designed to impair naive B cell maturation and enhance the negative selection

of autoreactive B cells. Overall, belimumab altered B cell reconstitution by enhancing autoreactive B cell censoring, however there was only a 11% difference between the belimumab group and the non-belimumab group in renal response which suggests that belimumab did not significantly improve outcomes when combined with cyclophosphamide and rituximab (9).

Methotrexate and Biologic Therapies

Advancements like those previously mentioned have most definitely shaped the treatment of lupus nephritis and other mechanisms of autoimmunity, however other autoimmune diseases like rheumatoid arthritis (RA) have heavily relied on methotrexate (MTX). It has long been regarded as the standard for treating RA because of its efficacy in preventing long-term joint damage while reducing disease activity.The introduction of biologic therapies, such as etanercept, a tumor necrosis factor (TNF) receptor fusion protein designed to inhibit the inflammatory processes central to RA, has provided new options for disease management. In a study comparing etanercept and methotrexate, 632 early RA patients were given over 12 months. Etanercept demonstrated lower erosion scores at both 6 and 12 months and 12% more patients showing no increase in erosion scores compared to those treated with MTX. While MTX effectively reduces disease activity over time, patients treated with etanercept experience faster symptom relief. Thus, while MTX may be effective, newer biologic therapies like etanercept might offer faster disease control which would be beneficial for patients with aggressive disease (10).

As mentioned previously regarding the potential of combination therapies, the distinct effects of MTX and etanercept on the B cell compartment further emphasize their complementary roles in autoimmune disease treatment. In juvenile idiopathic arthritis (JIA) patients, researchers compared serum immunoglobulin and BAFF levels amongst the two treatments and found that MTX directly impacted early B cell development, significantly reducing transitional B cells and serum immunoglobulin levels compared to untreated patients and those treated with etanercept. On the other hand, etanercept lowered BAFF levels and increased follicular helper T (Tfh) cells which are important for antibody production. Overall, this suggests that combination therapy with MTX and etanercept could be more effective than monotherapy as these drugs are able to target differing immune pathways.However, their limitations, such as MTX's inability to target persistent plasma cells, and etanercept's indirect effects on B cell pathways highlight the need for more precise and targeted therapies that can fully address the complexities of autoimmune disease mechanisms (11).

While MTX has proven effective in modulating autoimmune pathways and reducing disease activity, its impact on broader immune functions raises concerns, particularly regarding vaccine responses. For instance, Nived investigated the effects of MTX on the immune response to vaccination in rheumatoid arthritis (RA) patients. The study compared 11 RA patients starting MTX treatment, 12 RA patients not on any drugs (0DMARD group) and 13 controls had their B and T cells and antibody levels measured before MTX treatment, 6-12 weeks after MTX treatment, and 6-7 days after vaccination of the MTX group. Findings showed that the patients treated with MTX had a weaker immune response as there was no increase in plasmablasts in the MTX treated patients in comparison to the control and 0DMARD group. Furthermore, MTX treated patients did not see any increase in switched memory B cells like in the control or 0DMARD group. Additionally, only 56% of MTX treated patients showed positive antibody responses compared to 90% of the control group and 87.5% of the 0DMARD group. These results suggest that MTX could weaken the immune system's ability to respond to vaccines which can leave patients on MTX more vulnerable to infections, even after vaccination (12).

Monoclonal Antibodies

The limitations of traditional immunosuppressive therapies, such as methotrexate and cyclophosphamide, underscored the need for more precise treatments in autoimmune diseases. This led to the development of monoclonal antibodies (mAbs), such as rituximab and daratumumab, which marked a significant shift in therapeutic strategies. Rituximab, targeting CD20, demonstrated improved symptom management when combined with methotrexate or cyclophosphamide, though complete disease resolution remained rare. Daratumumab, targeting CD38, further highlighted the potential of mAbs by reducing B cell activity and plasma cell differentiation. For example, a randomized double-blind study investigated the combination of rituximab with methotrexate or cyclophosphamide in 161 RA patients, evaluating responses at weeks 24 and 48. The study found that rituximab combined with methotrexate or cyclophosphamide improved symptoms for many patients, with 43% and 41% showing

significant improvement by week 24 compared to 13% with methotrexate alone. However, complete resolution of disease activity was rare with only 15% achieving notable improvement at week 48 (13).

While rituximab targets CD20 and spares plasma cells, daratumumab offers a different approach by directly targeting CD38, which is highly expressed on plasma cells. To study the effects of daratumumab on B cell function, researchers performed *in vitro* experiments using peripheral blood mononuclear cells (PBMCs) from health donors. These cells were stimulated under T cell-dependent and T cell-independent conditions, with or without darumumab. Results showed Daratumumab reduced B cell proliferation and plasma cell differentiation. As a result, daratumumab shows a process in treating autoimmune disease as reducing B cell activity and plasma cell differentiation can control an overactive immune system. However, plasma cells are necessary for producing antibodies that fight infections and provide immunity after vaccination, so by reducing plasma cell differentiation, daratumumab has the potential to weaken the body's ability to respond to infections or vaccinations (14). Plasma cells are more potent instigators of autoimmunity because they are responsible for secreting antibodies that attack the body's tissues, while being resistant to many treatments. Targeting plasma cells may be a more effective strategy because it allows for the direct depletion of antibody-producing cells (15). Daratumumab specifically targets CD38 which is expressed on plasma cells while mAbs like rituximab targets CD20 which allows plasma cells to persist even after treatment. However, as seen by the results of this trial, targeting plasma cells can be challenging because of its key role in producing antibodies that fight infections and provide immunity after vaccinations. Reducing plasma cell activity can weaken the body's overall immune function.

One study, involving 39 SLE patients, evaluated the efficacy of rituximab combined with steroids in achieving B cell depletion and reducing disease activity. Peripheral blood B cell subsets were measured and clinical responses. At the end of the trial, 51% of patients achieved a major clinical response, 31% patients received a partial response, and 18% showed no response. Overall, complete B cell depletion correlated with better clinical responses, while incomplete B cell depletion was associated with no clinical responses. This exemplifies a central weakness of mAbs in their inability to fully eliminate autoreactive B cells and long-lived plasma cells, which continue to produce pathogenic autoantibodies (16).

While rituximab does not target plasma cells, daratumumab directly targets them. This makes daratumumab potentially more effective in autoimmune diseases driven by autoantibody production, such as SLE. However, the depletion of plasma cells raises concerns about weakening the immune system's inability to fight infections or respond to vaccinations, which is less of a concern with rituximab. This is because rituximab targets CD20, which is expressed on mature B cells. Plasma cells are responsible for producing protective antibodies that remain intact after rituximab treatment. These earlier methods of treatment demonstrate possibility in symptom improvement through partial B cell depletion, however, they signify the need for more advanced approaches like CAR T cell therapy which can achieve complete B cell depletion for prolonged remission.

EMERGING STRATEGIES FOR AUTOIMMUNE DISEASE

B cell targeted therapies have evolved significantly over the recent decade. The introduction of monoclonal autoantibodies like rituximab as previously mentioned, marked a period of rapid development for treatment of autoimmune disease. However, therapies like those often led to incomplete B cell depletion. Building on the limitations of traditional B cell targeted therapies, recent advancements such as CAR T cell therapy, BiTEs, and BTK inhibitors offer a possible alternative by achieving complete and durable B cell depletion. These therapies focus on long term remission while limiting side effects. This section will explore the potential of these advancements and explore how they address the challenges of more traditional approaches.

In Vivo and *Ex Vivo* CAR T Cell Therapy

During a proof of concept study, In a lupus mouse model, the mice receiving CD19 CAR T treatment showed complete depletion of B cells over a year with reduction in autoantibodies, extended survival and decreased proteinuria. Additionally, the CAR T cells stayed in the mice, thus increasing central memory CD8+ T cells which are important in continuously eliminating harmful B cells and maintaining remission (17). In a reported case, a 41 year old man with refractory antisynthetase syndrome, a rare autoimmune disease characterized by the presence of autoantibodies against enzymes involved in protein synthesis, had received *ex*

vivo engineered CD19 CAR T cells despite previously failing traditional treatments like glucocorticoids and rituximab. Following therapy, circulating B cells were completely depleted for 100 days, and the patient showed improved muscle strength and endurance. While the patient suffered from mild cytokine release syndrome (CRS), the treatment showed success in achieving remission for refractory antisynthetase syndrome (18). Additionally, another study demonstrated the efficacy of anti-CD19 CAR T cells in treating SLE. Four women received the therapy following lymphodepletion chemotherapy and experienced rapid B cell depletion and a significant decline in plasma cells. All four patients achieved clinical remission and biomarkers like autoantibodies returned to normal levels. Remarkably, one patient achieved drug free remission, while others maintained minimal side effects with low-dose corticosteroids. Overall, the results show potential in anti CD19 CAR T therapy for durable B cell depletion and the possibility of long term remission without reliance on immunosuppressive drugs (19). An interesting study uncovered a subset of B cells: CXCR5-CD19low B cells which were similar to plasmablasts, although not fully mature yet. The researchers found that CXCR5-CD19low cells were more common in SLE patients than in healthy people. When studied *ex vivo*, the cells secreted IgA antibodies, which are often correlated to autoimmune activity. The presence of these cells are also linked to increased amounts of plasmablasts, which suggested that they might be a specific type of B cell that could be driving the immune response in SLE. By targeting CXCR5-CD19low B cells, treatments could possibly prevent cells from even maturing into plasmablasts, which are key in producing the autoantibodies that attack healthy tissues, thus offering a new possibility in therapies aimed at controlling SLE (20). Another method of *in vivo* CAR T therapy investigated involved the use of Fox19CAR-Tregs which are T cells engineered to express a CD19 targeted CAR and overproduce FoxP3. Unlike typical CAR T cell treatments that aim to deplete all CD19+ B cells, Fox19CAR-Tregs only suppress pathogenic B cells while preserving the healthy B cells. In lupus mouse models, Fox19CAR-Tregs successfully stabilized B cell counts and reduced autoantibody levels (anti-dsDNA). By restoring immune balance without wiping out the entire B cell population and avoiding the causation of B cell aplasia, CRS and hemophagocytic lymphohistiocytosis (HLH), Fox19CAR-Tregs shows potential in a safer approach of treating SLE (21). These studies collectively highlight the versatility of CAR T therapy in autoimmune diseases, with varying approaches tailored to different disease mechanisms and patient needs. While traditional CD19 CAR T cells focus on complete B cell depletion to reset the immune system, subsets like CXCR5-CD19low cells and Fox19CAR-Tregs offer more targeted and safer alternatives, reducing side effects like B cell aplasia and CRS.

Bispecific T Cell Engagers

Alongside the emergence of CAR T cell therapy are Bispecific T Cell Engagers (BiTEs), which are proteins that simultaneously bind two different antigens, thus redirecting T cells to target and kill harmful cells. By binding to both the T cell and the target cell, BiTEs enhance precision of pathogenic cell elimination while minimizing damage to healthy tissues Unlike CAR T cell therapy, BiTEs allow for quick administration and their short half-life allows treatment to be discontinued if unfavorable effects occur (22). A lthough n ot y et FDA-approved for autoimmune diseases, BiTEs are currently approved for certain cancers, such as acute lymphoblastic leukemia (23). To further explore the implications of the efficacy of BiTEs, a phase II study evaluated blinatumomab in patients with large B cell lymphoma. Although BiTEs have primarily been studied in oncology, their mechanism of action, redirecting T cells to target specific cells, provides a proof-of-concept that could be applicable to autoimmune diseases, where autoreactive cells need to be selectively targeted. The treatment was administered using stepwise dose escalation or flat dosing. Overall, 67% of patients whose cancer came back after previous treatments responded to the treatment, while only 19% of refractory patients received a meaningful response. Moreover, patients who received step by step dosage showed less severe side effects compared to those that received a full dose right away. Thus, while blinatumomab shows potential in addressing aggressive disease like lymphoma, dosing strategies and resistance mechanisms need to be further investigated in maximizing its efficacy (24).

Bruton's Tyrosine Kinase Inhibitors

Another therapy in treating autoimmune disease is the use of Bruton's Tyrosine Kinase (BTK) inhibitors which are currently undergoing clinical trials. BTK inhibitors specifically target B cell signaling pathways, selectively disrupting autoreactive B cells without broadly suppressing the immune system as a whole, offering a safer alternative to older less targeted treatments (25). In a placebo controlled Phase II trial

investigating the use of evobrutinib, 267 MS patients were given daily doses of the evobrutinib. Relapse rates were lower in the treatment group compared to the placebo and those receiving the evobrutinib had fewer MRI detected lesions. However, the researchers concluded that longer and larger trials were required to further determine the exact effects of evobrutinib (26). Similarly, fenebrutinib has been evaluated in a phase II RA study. In this study, fenebrutinib helped improve symptoms and showed significant effects on biomarkers linked to myeloid and B cells which are crucial in driving inflammation and autoimmunity. Fenebrutinib significantly reduced the levels of both, which shows its potential in suppressing autoantibody production while addressing symptoms. However, similar to the previous trial mentioned with evobrutinib, longer studies are needed to determine if these effects are sustainable and safe (27).

Immunotherapies such as CAR T therapy, BiTEs, and BTK inhibitors hold transformative potential in autoimmune disease treatment by offering targeted approaches to achieve remission while minimizing systemic side effects. These therapies, originally developed for cancer, leverage mechanisms like immune cell activation and selective cytotoxicity, which have proven effective in eradicating malignant cells. However, autoimmune diseases present a fundamentally different challenge, where the goal is not destruction but restoring balance to an immune system mistakenly attacking the body. This distinction underscores the complexity of adapting immunotherapies for autoimmune conditions, requiring precision to avoid exacerbating immune dysregulation or triggering unintended consequences.

DIFFERENTIAL MECHANISMS OF CAR T CELL THERAPY IN AUTOIMMUNE DISEASE AND CANCER

Clinical trials investigating CAR T cell therapy in autoimmune disease and cancer show significant differences in therapeutic mechanisms. These differences are based on the nature of the diseases and the interactions between CAR T cells and their targets**.** Autoimmune diseases benefit from therapeutic approaches that reset the immune system to a healthy state, however cancers require sustained depletion of malignant cells to prevent recurrence as summarized in Figure 1. Thus, these differences highlight CAR T cell therapy's potential in addressing these disease populations.

Autoimmune Disease: Immune Reset

The trials conducted on autoimmune disease, particularly SLE, myositis, and systemic sclerosis demonstrate that CAR T cell therapy has great ability in achieving immune reset. In a study by Muller *et al*, CD19 CAR T cells were administered to 15 patients with these autoimmune diseases. The results were extremely promising, with all patients achieving sustained drug free remission for up to 29 months.

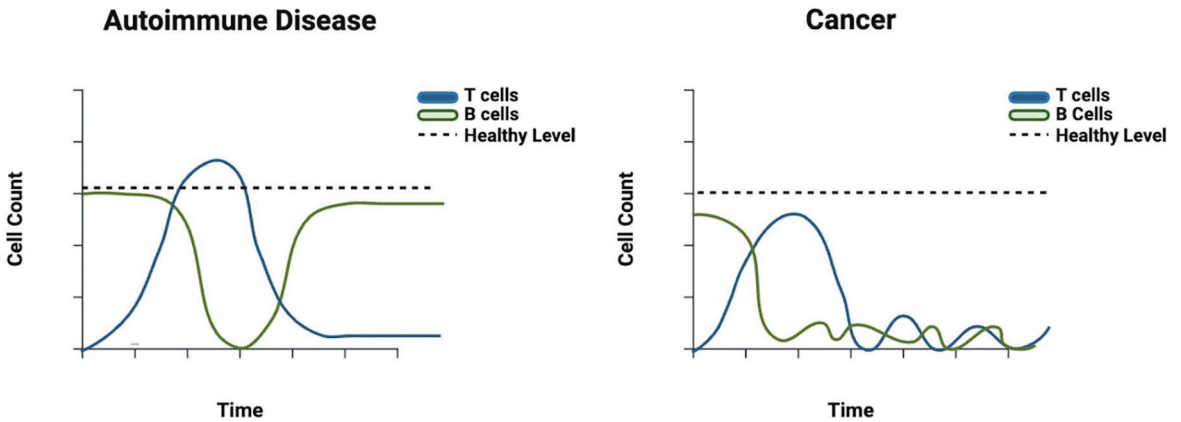

Figure 1. Immune Cell Dynamics in Autoimmune Disease vs Cancer. The graphs illustrate the concept of immune reset and its distinct effects on immune cell populations in autoimmune diseases and cancer. In autoimmune diseases, CAR T cell therapy leads to a temporary depletion of T and B cells, followed by the reestablishment of B cells and a return to immune balance. In cancer, CAR T cells persistently target and deplete B cells, leading to cyclical suppression as T cells rise and continue to deplete B cells over time.

In fact, in SLE patients, markers characteristic of the disease like anti-dsDNAs disappeared. Similarly, in idiopathic inflammatory myositis, creatine kinase levels normalized, and systemic sclerosis patients showed reduced disease activity. Thus, these outcomes emphasize the therapy's ability to fully deplete pathogenic B cells and allow for immune reset with a naive B cell phenotype (28).

An additional study investigated the preservation of T memory stem cells which have the ability to migrate to lymphoid organs and demonstrate longer survival and robust expansion when activated. When using cytokines IL-7 and IL-15 during CAR T expansion, the presence of these cells significantly increased. This discovery had many inspiring implications as expanding these T memory stem cells could allow the regeneration of healthy naive immune cells when eliminating autoreactive ones which would decrease the need for immunosuppressive treatments which present many side effects (29).

Cancer: Sustained Depletion

In contrast, clinical trials for hematological malignancies like in acute lymphoblastic leukemia (ALL) show that CAR T cell therapy depends on chronic depletion of such cells. This is because cancer is driven by continuous growth of abnormal cells, so sustained CAR T cell activity is important to prevent relapses. In a study where patients with refractory ALL were treated with CD19 CAR T cells and the results showed that remission was closely linked to the persistence of CAR T cells even after treatment. Unlike autoimmune diseases, cancer treatment requires CAR T cells to remain active in the patient's system to continuously suppress any malignant cells that might develop in comparison to just a signal round of depletion which would reset the immune system (30). Moreover, studies have shown that durability of CAR T cell responses in leukemia is based on specific CAR T cell subpopulations like CD4+ CAR T cells and gamma delta CAR T cells which suggest that their continuous presence contributes to long-term remission (31).

Understanding the mechanisms of CAR T cell therapy in different disease populations is important in optimizing therapeutic outcomes. CAR T cell therapy's mechanisms significantly differ between autoimmune diseases and cancer. In autoimmune diseases, the therapy focuses on achieving immune reset by eliminating autoreactive B cells. Doing so allows the immune system to regenerate naive B cells. In contrast, CAR T cell therapy in cancer emphasizes chronic suppression to prevent relapse. The therapy targets malignant cells and requires CAR T cells to persist in the patient's system over time. This persistence is crucial to ensuring that residual cancer cells or newly emerging cancer cells are kept in check.

CONCLUSION

CAR T cell therapy is increasingly explored in its applications to autoimmune diseases. Its ability to achieve immune reset offers many possibilities in the treatment. In the future, there is likely to be more research going into precision targeting of autoreactive immune cells which could enable the therapy to minimize side effects and other complications. In vivo CAR T engineering also has the ability to bypass the need for manipulation *ex vivo*, which could reduce manufacturing costs and make this therapy more accessible to patients. Furthermore, CAR T therapy may be integrated with other therapies like BiTEs or BTK inhibitors to create more efficient therapies that could tailor treatments to patients and reduce chances of harmful side effects.

In contrast to autoimmune diseases, where the goal is immune reset, cancer therapy requires sustained depletion of malignant cells to prevent recurrence. CAR T cells must remain active within the patient's system to continuously target and eliminate abnormal cells. This prolonged activity is critical for ensuring durable remission and reducing relapse rates. Unlike autoimmune diseases, where the goal is to reset the immune system, cancer treatment relies on persistent suppression of disease-driving cells. As illustrated in **Figure 1**, CAR T cells in cancer therapy lead to cyclical suppression of malignant cells, with T cells continuing to eliminate these cells over time to prevent regrowth. On the other hand, in autoimmune disease, CAR T cells eliminate autoreactive B cells while preserving the ability of the immune system to rebuild itself, ultimately restoring immune balance. **Figure 1** visually represents this process, where immune reset leads to the depletion of pathogenic cells, followed by the regeneration of naive immune cells and the stabilization of immune function.

While the promise of CAR T cell therapy in autoimmune diseases is undeniable, its application is not without risks, and its true capacity is still unknown. A major limitation of current evidence is the small sample sizes in clinical trials. Many studies involve only a small

number of patients, making it difficult to generalize findings. Furthermore, the short follow up durations in these trials result in ambiguity regarding the durability of remission and the potential for other complications in the future, such as relapse. Larger, long-term studies are essential in confirming the sustainability of CAR T therapy's benefits and effectiveness.

Another significant challenge of immune system reset is the potential for compromised immune responses to infections or vaccinations. For autoimmune disease patients, this risk is particularly concerning, as their immune systems are often already impaired. Strategies to mitigate this risk include preventive measures like using antiviral medications such as acyclovir or valacyclovir to stop viral infections like varicella-zoster virus (VZV). Other steps include antibiotics during low white blood cell counts to prevent bacterial infections, antifungal treatments for patients at risk, and regular immune-boosting therapies like intravenous immunoglobulin (IVIG) for those with weakened immunity. Careful monitoring of immune recovery and good timing of vaccinations can help reduce infection chances (32). Future research is likely to focus on precision targeting of autoreactive immune cells rather than broadly depleting all CD19+ cells. For example, experiments could focus on targeting CXCR5-CD19low B cells which are implicated in autoantibody production in diseases like SLE. Similar to plasmablasts, they contribute to the disease pathology but aren't fully mature. By targeting these subsets, researchers can possibly minimize the risk of B cell aplasia while allowing regeneration of a completely new B cell population.

In conclusion, autoimmune diseases are a growing health concern driven by genetic predispositions and environmental triggers. While traditional therapies have provided symptom relief, they often fail to achieve durable remission, leaving patients reliant on lifelong treatments with significant risks. CAR T cell therapy represents a transformative approach to addressing autoimmune diseases, offering the potential for long-term remission and reduced dependence on immunosuppressive drugs. However, as this therapy is still in its early stages, many challenges remain, including risks of infection, side effects, and accessibility. Further research focuses on refining these therapies and exploring other novel targets and modalities for tailored treatments. As advancements continue, improved quality of life for autoimmune disease patients becomes increasingly attainable.

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CONFLICT OF INTEREST

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