RESEARCH PAPER

Cell-Based Therapies for Autoimmunity: CAR-T and CAR-Treg Approaches

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Abstract
Autoimmune disorders present a complex challenge, characterized by the abnormal attack of the immune system on the body's own cells. Current therapies primarily aim to manage symptoms through non-targeted immunosuppressants, failing to offer definitive cures. In recent years, cell treatment strategies, particularly those involving chimeric antigen receptor-modified T cells (CAR-T) and regulatory T cells (CAR-Tregs), have garnered attention as promising alternatives. This review explores the emerging landscape of cell therapies targeting autoimmune diseases, delineating two primary approaches: the elimination and suppression of autoreactive immune cells. Elimination strategies, including CAR-T cell therapies, show potential in depleting pathogenic B and T lymphocytes, while suppression strategies, such as CAR-Tregs and tolerogenic dendritic cells, aim to restore immune tolerance.

Key advancements in universal CAR-T cell technology are highlighted, which facilitate mass production and immediate availability for treating autoimmune rheumatic diseases. The implications of these strategies are discussed in the context of systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis, with emphasis on recent clinical findings demonstrating the efficacy of CAR-T therapies. However, concerns regarding safety, persistence, and production costs are acknowledged, indicating the need for refinement in these approaches.

In conclusion, innovative CAR-T and CAR-Treg therapies represent a significant step toward specialized treatment modalities for autoimmune disorders, necessitating further research to optimize their clinical application and improve patient outcomes while addressing safety and efficacy challenges.

Keywords: cell-based therapy,T cells,lymphocytes,immunity,autoimmunity,inflammation
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.Introduction

Autoimmune diseases include numerous disorders featured by complex pathophysiology. Such disorders develop when organism's immunity cells (ICs), particularly auto-reactive B lymphocytes and T lymphocytes, engage in abnormal attacks on the organism's cells and tissues via different effector mechanisms. Whereas auto-immune disorders very much vary in their properties and manifestations, they usually develop from a conjunction of genomic propensity and lifestyle factors [1,2]. Since there is frequently very little understanding of the intricate molecular processes lying and the heart of these disorders, presently available treatment strategies for SLE, multiple sclerosis (MS), T1D, psoriatic arthritis, RA and other autoimmune disorders usually concentrate on management of the disorder instead of curing it. Hereby, typically the goal is to avert attacks of auto-reactive ICs on cells and tissues by nontargeted immunity suppressants, such as GCSs and NSAIDs [3,4]. Moreover, adverse ICs may be suppressed by using antibodies (Abs) to target B lymphocytes (Rituximab, Belimumab), T lymphocytes (alemtuzumab) and pro-inflammatory cytokines

(infliximab) or by using small molecules that affect B lymphocyte and T lymphocyte signaling hereby serve to block cell pathways (cyclosporin A, mycophenolate mofetil) [5-7]. There are more radical options, such as rebooting the subject's immunity or transplantation of a foreign immunity by autologous haematopoietic stem-cell transplantation or allogeneic stem-cell transplantation. Although, these options may elevate therapy-associated mortality, e.g., serious cytopenia or GVHD after allogeneic stem-cell transplantation, and the immunity reboot can be only temporary after autologous stem-cell transplantation [8,9]. Currently, for numerous auto-immune disorders there is no known cure, and novel therapy strategies are necessary.

Cell treatment that targets auto-reactive ICs is presently gaining more and more interest being a promising therapeutic strategy in the field of auto-immune disorders. In general, there are 2 strategies of cell treatment of such disorders: elimination and suppression of auto-reactive ICs. Elimination of ICs is considered aggressive, it is associated with depletion of B lymphocytes and blood cancer treatment by adoptive cell transfer (ACT) of T lymphocytes modified with chimeric antigen receptors (CAR-T cells) [10,11]. Suppression involves using of T-reg cells which increase tolerance, e.g., chimeric antigen receptor T-reg cells, tolerogenic DCs, MSCs, cells that are capable of restoring tolerance via multiple mechanisms [12,13].

In oncology, using the ability of the subject's immunity to identify and eliminate cancerous cells was a crucial discovery. T lymphocytes are genetically altered to induce expression of bio-synthetic immunity receptors capable of mediating binding to malignant cells and their disintegration. CD-19 molecule is released by malignancies of B-lymphocyte origin. This molecule was the first to be used as a target for immune therapy for malignancy with usage of autologous chimeric antigen receptor-modified T lymphocytes [14-16]. Therapy with T lymphocytes modified with chimeric antigen receptors against CD-19 molecule resulted in significant levels of remission in subjects with relapsed or refractory B lymphocyte cancer. To date, there are 6 chimeric antigen receptor-modified T lymphocyte drugs targeting CD-19 and BCMA licensed for immune therapy of malignancies [17-19].

Table 1. Comparison of Cell Treatment Strategies for Autoimmune Disorders

Strategy	Mechanism	Target Cells	Examples
Elimination	Depletes autoreactive immune cells	Pathogenic B and T lymphocytes	CAR-T cell therapies targeting CD-19, CD-20, or other specific markers
Suppression	Restores immune tolerance	Effector T cells and autoreactive cells	CAR-Tregs, tolerogenic dendritic cells, mesenchymal stem cells (MSCs)

Universal chimeric antigen receptor-modified T cells

These chimeric antigen receptor-modified T lymphocytes are developed from healthy subjects and not from subjects with disorder. Using genetic alterations, e.g., ZFN, TALEN and CRISPR/Cas9, universal chimeric antigen receptor-modified T lymphocytes may be set to target abnormal auto-immune cells and thus treat autoimmune rheumatic diseases [20-22]. Moreover, typically universal chimeric antigen receptor-modified T lymphocytes genetically induces impairment of expression of T cell receptor or human leukocyte antigen class 1, hereby increasing their compatibility with different recipients. Furthermore, universal chimeric antigen receptor-modified T lymphocytes are available for mass production with no editing of T lymphocytes required. Thereby, universal chimeric antigen receptor-modified T lymphocytes need less amount of time, require less resources and provide instant availability. Considering this evidence, implication of such cells appears to be a very promising strategy of specific targeting autoimmune rheumatic diseases [23-25].

Accessible chimeric antigen receptor-modified T cells

Since viral vectors are utilized for genetic editing, LSCC facilities are necessary, moreover, multiple biosafety testing protocols increase time and cost required for production of chimeric antigen receptor-modified T cells. To solve this complication, there are other approaches being investigated, such as transposon tools and CRISPR/Cas9. These methods are suggested to speed up the development of the compounds in shorter time and with lower cost, contemporaneously decreasing contamination risk [26-28]. Whereas the efficacy of genetic transferring is still lower than that of viral vectors, this strategy demonstrated a potential. Numerous researchers reported a successful genetic transfer in chimeric antigen receptor-modified T cells. Hence, these developments show great promise for making treatment with chimeric antigen receptor-modified T cells more available for individuals suffering from ARDs and malignancies [29-31].

Autoimmune rheumatic diseases treatment with CAAR-T or CAR-Tregs

Presently, multiple therapeutical approaches for autoimmune rheumatic diseases based on chimeric antigen receptor-modified T cells being researched and engineered. Among them are chimeric auto-antibody (AAb) receptor T cell treatment and chimeric antigen receptor-modified regulatory T cell treatment. These two approaches have already been tailored to unique issues related to autoimmune rheumatic diseases [32,33].

Chimeric AAb receptor T lymphocytes are altered versions of chimeric antigen receptor-modified T cells that are able to identify and target AAb-releasing auto-reactive ICs through a particular antigen. Selective targeting of B lymphocytes that contribute to AAb genesis enables more targeted treatment of autoimmune rheumatic diseases than traditional chimeric antigen receptor-modified T cells which widely target CD-19+ B lymphocytes, affecting healthy ones as well [34-36]. Thus, this targeted method is believed to induce a more robust response by targeting the source of AAb genesis, reducing toxicity risk by excluding healthy ICs. Ellebrecht and colleagues conducted research and revealed chimeric auto-antibody receptor T lymphocytes' capacity of identifying and targeting AAbs against DSg3, which contribute to the development of pemphigus. These results demonstrate that chimeric AAb receptor T cell therapy is efficient and precise in autoimmune rheumatic diseases treatment [37-39]. These findings also emphasize the necessity of discovering auto-antigens specific for autoimmune rheumatic diseases. Hereby, apart from further investigation of chimeric AAb receptor T cell therapy, more study is necessary to concentrate on the recognition and description of autoantigens specific for autoimmune rheumatic diseases in order to facilitate the use of chimeric AAb receptor T cells for autoimmune rheumatic diseases treatment [40-42].

Chimeric antigen receptor-modified T lymphocyte methods have expanded to T-regs, cells that are vital for retaining immunity tolerance, inhibiting immune responses and repairing the immunity. Whereas regulatory T cells constitute the smaller part in circulation, FOXP-3 cDNA is inserted into CD3+ and CD4+ T lymphocytes together with chimeric antigen receptor-modified T lymphocyte compounds targeting particular molecule [43-45]. Chimeric antigen receptor-modified regulatory T cells are able to induce cellular death and to inhibit activity of effector T cells by releasing interleukin 10, interleukin 35, and transforming growth factor beta, and by inducing apoptotic processes mediated by Fas/Fas-L. This ability is a great advantage of chimeric antigen receptor-modified regulatory T cell therapy over traditional chimeric antigen receptor-modified T cell treatment. Moreover, as chimeric antigen receptor-modified regulatory T cells have FOXP-3 cDNA inserted, they do not rely on interleukin 2 and major histocompatibility complex stimulation [46-48]. The chimeric antigen receptor-modified regulatory T cells therapy demonstrates efficacy in pre-clinical models of auto-immune disorders such as T1DM, UC, MS. Provided their capacity of precise regulation of immunity response, these cells show a great potential for autoimmune rheumatic diseases treatment with minimal detrimental effects [49-51].

The use of chimeric antigen receptor-modified T cells in SLE

Systemic lupus erythematosus is a severe auto-immune disorder which involves impairment of immunity tolerance to nuclear antigens such as dsDNA and nuclear proteins. Such impairment results in appearance of AAbs against double-stranded DNA, that consequently promote inflammatory process in various organs [52-54].

Whereas a remarkable progress has been made in therapeutic approaches, such as monoclonal Abs which are capable of depletion of CD-20 B lymphocytes, there are still subjects who are not responding to presently available anti-lupus therapy, suffering from severe organ damage which sometimes has lethal consequences. Such cases can be explained by not sufficiently depleted B lymphocytes, difficulty of access to injured tissues, and not sufficient CD-20 release on effector B cells and plasmablasts, which are involved in anti-nuclear Abs genesis [55,56].

Chimeric antigen receptor-modified T lymphocyte treatment is gaining attention, particularly in treatment of malignancies, but also in auto-immune disorders such as lupus. Depleting CD19 B lymphocytes with precision has great potential for future therapeutic approaches. Kansal and colleagues conducted studies on the matter in a mouse model [57,58]. They utilized purified CD 8+ T lymphocytes because of the possible disorder-aggravating impact of auto-reactive CD 4+ T lymphocytes. The subjects were irradiated to enable T lymphocyte engraftment. This led to an elevation of the lifespan of two strains of subjects. The most CD-19-d NZB/W subjects lived up to eighteen months following the therapy. Of twelve MRL-Ipr mice treated with chimeric antigen receptor-modified T lymphocytes, 8 subjects lived for twelve months and reached fourteen months of age, outperforming the controls [59,60]. These results demonstrated that chimeric antigen receptor-modified T lymphocyte therapy considerably affected development of auto-immune disorder in the two mice strains. The researchers assessed levels of proteins in the urine of mice with SLE and discovered that five months after the therapy the levels of proteins were not drastically elevated compared to the healthy controls. They revealed a reduction in the CD-4/CD-8 ratio observed in the controls together with a reduction in renal, osseous and splenic CD-19 release [61-63]. They demonstrated that CD-19 targeted chimeric antigen receptor-modified T lymphocytes stayed alive and active after months following the administration, together with the efficient elimination of AAb genesis. The researchers proposed that CD-19 targeted chimeric antigen receptor-modified T lymphocytes could be more efficient than Ab-mediated cytotoxicity, since CAR-T cells straightforwardly eliminate the target, and Ab-mediated cytotoxicity needs the aggregation of bound Abs for lysis of cells or

phagocytosis. In auto-immune disorders, elevated concentrations of endogenous Abs and immunity complexes may negatively affect B lymphocyte depletion by macrophages. On the contrary, chimeric antigen receptor-modified T lymphocytes are able to eliminate B lymphocytes efficiently and do not require additional cells [64-66].

Mackensen and colleagues performed a study in 5 human subjects with SLE disease activity index 2000 level from eight to sixteen [67]. These subjects had received numerous treatments which had resulted in failure. The study showed a reduction in the SLE disease activity index 2000 score, involving active urinary sediments, proteins in urine, kidney inflammation, elevation in complement concentrations after three months. Other symptoms such as cardiac fibrosis, arthritis, pulmonary disruptions, fatigue, were also alleviated. Anti-dsDNA concentrations were decreased below threshold, interferon alpha was not detectable. Administration of immunomodulators was terminated resulting in drug-free remission in all five subjects. In long-term observation, the 5 subjects did not have a relapse of lupus, but showed B lymphocyte reconstitution. The authors sis not detect a decrease in responses to vaccines, which implies that chimeric antigen receptor-modified T lymphocyte treatment mostly impacted genesis of AAbs and not cells generating Ig. CRS is believed to be a toxicity that is found often after such treatment. In this case that effect was detected in modest degree. ICANS was not found, and there were no infections detected in the course of the therapy [67].

Salmon and colleagues noticed that in the research by Mackensen and colleagues, the 5 subjects had reduced or none anti-retinol binding protein Abs and postulated that in subjects with pathologic AAbs [68]. E.g., anti-retinol binding protein generated by long-lived effector B cells will possibly need another type of treatment than the treatment described in the study by Mackensen and colleagues. Salmon also proposed that whereas that research demonstrated a reboot of B lymphocytes with re-populating B lymphocytes releasing Immunoglobulin M/ Immunoglobulin D over Immunoglobulin G/ Immunoglobulin A in the short period of time, in prolonged period of time B lymphocytes will probably start producing AAbs again.

Kretschmann and colleagues studied the functioning of antiCD19 chimeric antigen receptor-modified T lymphocyte treatment in subjects with systemic lupus erythematosus after gradual reduction of the GCS dose and discontinuation of T lymphocyte inhibition, which proved to be viable and extensive, enough for successful clinical application [69].

Multiple sclerosis

Multiple sclerosis is a chronic immunity CNS disorder that destroys myelin sheath. Whereas its etiology is still not fully studied, its pathophysiology implicates genetic sensitivity and lifestyle cofactors. Multiple sclerosis is believed to be an auto-immune disorder with demyelinating properties, with auto-immune responses by CD-4+ T helper 1 and T helper 17 cells specific for myelin. Numerous genetic, immunologic and histologic trials in subjects with multiple sclerosis showed that auto-immunity might be of critical importance in multiple sclerosis development [70,71]. Chimeric antigen receptor T lymphocyte therapy for multiple sclerosis concentrated on transforming chimeric antigen receptor regulatory T cells. Fransson and colleagues applied lentiviral vectors to transform CD 4+ T lymphocytes to release chimeric antigen receptor-targeting MOG, that were later enhanced by murine FOXP-3 for differentiation to regulatory T cells and CD 28-CD 3ζ signaling sites [72]. The authors utilized chimeric antigen receptor regulatory T cells for trials in vitro and in vivo and revealed that CAR-alpha-MOG-FOXP-3-T-regs are able to permanently suppress proliferation of T lymphocytes with myelin oligodendrocyte glycoprotein+ cells and active macrophages present. In vivo trials involved nasal administration of cells into mice with EAE. The advantages of chimeric antigen receptor T lymphocyte therapy for multiple sclerosis are evident. Firstly, nasal administration enables the deposition of chimeric antigen receptor regulatory T cells in the right spot under small dosage, preventing the systemic impact affecting different organs. Secondly, chimeric antigen receptor regulatory T cells demonstrate potent targeting and good duration [73,74]. E.g., if experimental autoimmune encephalomyelitis is triggered by antigens, chimeric antigen receptor regulatory T cells are able to suppress the disorder progression. Although, chimeric antigen receptor regulatory T cells treatment has several safety problems. Firstly, chimeric antigen receptor regulatory T cells could penetrate nasal vessels and get into the bloodstream. Secondly, upon intranasal administration, the mucosa cells could be carried to the brain and CSF via first cranial nerve lamina, as was reported by Danielyan and colleagues [75].

After twenty-four hours of administration of green fluorescence protein and CAR-alpha-MOG-FOXP-3-coexpressing regulatory T cells, immuno-histochemical myelination biomarkers and astrocytosis were restored in murine model after treatment. This implies that chimeric antigen receptor regulatory T cells performed precise targeting [76,77]. In a murine model of experimental autoimmune encephalomyelitis score of 4, the treatment led to a decrease in the score in CD 4+ T lymphocyte and chimeric antigen receptor regulatory T cell cohorts. By the seventh day, only chimeric antigen receptor regulatory T cell cohort demonstrated prolonged alleviation of symptoms. By the twenty-fifth day, that cohort did not show any symptoms. These subjects were challenged with another dose of inoculative material to trigger experimental autoimmune encephalomyelitis, but they stayed healthy [78,79]. This shows the persisting impact of engineered regulatory T cells. Subjects in the chimeric antigen receptor regulatory T cells cohort also demonstrated reduced interleukin 12 and interferon gamma messenger RNA expression in the brain. This could be explained by a decrease in inflammatory process and suppression of maturing of dendritic cells, as was reported by Fransson and colleagues [72]. In 2020, De

Paula Pohl and colleagues studied myelin basic protein-chimeric antigen receptor regulatory T cell treatment and myelin oligodendrocyte glycoprotein-chimeric antigen receptor regulatory T cell treatment in a model of experimental autoimmune encephalomyelitis [74]. The researchers observed that the two combined were able to suppress inflammatory process and myelin-specific response of T lymphocytes, hereby suppressing development of experimental autoimmune encephalomyelitis.

Rheumatoid arthritis

Rheumatoid arthritis is an auto-immune disorder featured by elevated RF and ACPA, swelled joints and systemic inflammatory process. In early phases, AAbs and inflammatory process are mild, but the acquired immunity response and tissue injury aggravate with time [80].

Zhang and colleagues performed a trial where anti-FITC chimeric antigen receptor-modified T lymphocyte therapy was used for rheumatoid arthritis subjects in order to kill auto-reactive B lymphocytes [81]. The researchers identified type of AAbs in subjects using ELISA, making fluorescein isothiocyanate chimeric antigen receptor-modified T-cells and fluorescein isothiocyanate-labeled AAb-positive peptides. Auto-reactive B lymphocytes were killed by chimeric antigen receptor-modified T lymphocytes targeted at the peptides. Rheumatoid arthritis is featured by genesis of ACPAs, hereby citrullinated vimentin, citrulline fibrinogen and cTNC, citrulline type 2 collagen, and CCP1 may be chosen as auto-antigens for targeting auto-reactive B lymphocytes. Only chimeric antigen receptor-modified T cells and auto-immune B cells can identify fluorescein isothiocyanate. Thereby, anti-fluorescein isothiocyanate chimeric antigen receptor-modified T cells may be targeted at different auto-reactive B lymphocytes through identification of fluorescein isothiocyanate-labeled auto-antigen peptides. In vitro trials showed that fluorescein isothiocyanate chimeric antigen receptor-modified T cells are able to identify and eliminate hybridoma cells via genesis of Abs against related antigens, through binding process with related antigen fluorescein isothiocyanate-coupled peptides, and through identification and elimination of antiCOII Ab-generating B lymphocytes in a mouse model of arthritis caused by collagen [82,83]. In 2021, Zhang and colleagues also discovered that in vitro fluorescein isothiocyanate chimeric antigen receptor-modified T cells shows cytotoxic properties in human rheumatoid arthritis auto-immune B lymphocytes. As was noted by Orvain and colleagues in 2021, citrullinated protein antigens that release CAAR-T cells were applied to decrease the count of B lymphocytes resistant to this protein, preserving protective B lymphocytes [84]. AntiCV chimeric antigen receptor-modified regulatory T cells demonstrate promising results in rheumatoid arthritis therapy, although they are yet to be developed into something greater than a concept.

Anti-fluorescein isothiocyanate chimeric antigen receptor-modified T cells treatment does not demonstrate adverse side effects or effects of withdrawal. Trials show that with specific Abs present, anti-fluorescein isothiocyanate chimeric antigen receptor-modified T cells eliminate target cells releasing Abs, and not cells that release Fc gamma receptor [85-87]. When there is a large count of specific Abs, chimeric antigen receptor-modified T cells cytotoxicity is not as high as cytotoxicity of target cells which release Abs. That effect may be decreased by blockade of Fc gamma receptor with other Abs. Such a process prevents the fluorescein isothiocyanate chimeric antigen receptor-modified T cell effect on NK cells and macrophages releasing Fc gamma receptor. Preventing large-scale ICs injury allows to avoid severe attenuation of the immune system, decreasing the infection risk and risk of progression of various disorders including cancer which might be caused by the therapy, simultaneously making the treatment more specific and stable [88,89]. Moreover, hypothetically, anti-fluorescein isothiocyanate chimeric antigen receptor-modified T cells might not only target and kill B lymphocytes that express specific BCR, but they also might have an impact on the processes of dividing and differentiating of memory B cells in order to generate AAb-releasing effector B cells. This approach is mostly restricted by the fact that its safety and capacity of killing auto-reactive B lymphocytes were not proven in vivo yet, and its toxicity on auto-immune B lymphocytes is yet to be investigated. Also, auto-antigens and mediators coupling fluorescein isothiocyanate have to be made more stable. It can be achieved by elevating molar mass and improving the structure, for example, immunogenic Ab regions and anti-genic peptides may be added [90,91].

Table 2. Specific Applications of CAR-T Therapy in Autoimmune Diseases

Autoimmune Disease	**CAR-T Therapy Application**	**Key Findings**
Systemic Lupus Erythematosus(SLE)	Targeting CD-19 B lymphocytes to reduce autoantibody production	Significant reduction in disease activity and organ damage in preclinical models and early clinical trials.
Multiple Sclerosis	CAR-Treg therapy to suppress inflammatory responses	Demonstrated ability to maintain myelin protection and reduce symptom severity in

Autoimmune Disease	CAR-T Therapy Application	Key Findings
		experimental models.
Rheumatoid Arthritis	Anti-FITC CAR-T therapy targeting autoreactive B cells	Effective in eliminating auto-antibody producing B lymphocytes, with no adverse side effects observed in initial studies.

Perspectives

Whereas chimeric antigen receptor-modified T cells and chimeric antigen receptor-modified regulatory T cells have beneficial properties, e.g., ability to target and persist, and they do not have severe side effects, there are still safety issues related to them, as well as efficacy, persistence and mass production issues. We will focus on these 4 problems and investigate possible advancements [92-94].

In terms of safety, there is a number of problems with chimeric antigen receptor-modified T cell treatment. Breslin reported the possibility of CRS development, Bonifant and colleagues [95] found a possibility of neural toxicity, Makita and colleagues reported the chance of an off-target recognition attack [96]. Currently, several aspects were modified in order to decrease side effects of chimeric antigen receptor-modified T cell treatment and control their function in areas associated with tumors. The integrated methods may be utilized in future development of therapy for auto-immune disorders. The 1st used mechanism is to activate suicide genes [97]. In numerous trials performed by Bonini [98], Quintarelli [99], and others, HSV-TK and iCasp-9 are genes that were added to chimeric antigen receptor-modified T cells. Activation of cellular death is carried out by rimiducid infusion, that regulates the side effect severity by enhancing apoptotic processes in the chimeric antigen receptor-modified T lymphocytes. Another mechanism involves switching, e.g., the ON-switch mechanism used in tumors. The chimeric antigen receptor-modified T lymphocytes are broken down into different unrelated proteins [100]. One of them comprises EC region binding to antigens, and the other one comprises signaling agents and costimulatory molecules, e.g., CD-3ζ or 41 BB, as was reported by Wu and colleagues in 2015 [101]. These 2 proteins can only be dimerized by activating benign molecules of foreign origin. As a result, chimeric antigen receptor-modified T lymphocytes are able to fight tumors, but their aberrant activation is regulated. The 3rd method, suggested by Gallo and colleagues [102], is to produce bi-specific linkers via SMDC, that might possibly be used for auto-immune disorders. Such bi-specific linkers contain tumor homing and fluorescein isothiocyanate molecules, that are able to precisely link universal chimeric antigen receptor-modified T lymphocytes and malignant cells, hereby activating local T lymphocytes. Moreover, correcting the dosage of adapter molecules may accurately regulate chimeric antigen receptor-modified T lymphocytes side effects. Chimeric antigen receptor-modified T lymphocytes has some safety issues regarding its delivery [103,104]. Nasal administration for multiple sclerosis therapy has its risks, and more study is necessary to decrease this risk and work out the dosage, as was reported by Danielyan and colleagues [75].

Schultz and Mackall established that efficacy of chimeric antigen receptor-modified T lymphocytes is restricted by insufficient antigens [105]. In systemic lupus erythematosus MRL-lpr murine model, chimeric antigen receptor-modified T cell therapy resulted in Ig Mlo groups of B lymphocytes still present. Hence, chimeric antigen receptor-modified T cell therapy is unable to fully cure the disorder since the cells that generate Abs continue existing after the therapy, as was reported by Kansal and colleagues [61]. Moreover, Schultz and Mackall suggested that prolonged survival of chimeric antigen receptor-modified T cells in leukemia is pretty low since deletion of antigens led to an immunity escape [105]. Thereby, bi-specific targeting of chimeric antigen receptor-modified T cells to bypass the reduction of CD-19 antigen appears to be a promising area to study. Another problem, reported by Zhang and colleagues, is the instability of the chimeric antigen receptor-modified T cells upon administration in vivo, for example, that of fluorescein isothiocyanate in rheumatoid arthritis therapy [81]. Zhang and colleagues suggested to optimize the structure of the bi-functional target ligands, for example, to ameliorate coupled immuno-genic region comprising antigen peptides and fragments of Abs to elevate molar mass [82].

As to the persistence issue, chimeric antigen receptor-modified T cells are unable to provide the stability, activity and prolonged proliferative activity in inflammation in vivo. E.g., Zhang and colleagues demonstrated that chimeric antigen receptor-modified T cells may hold back the manifestation of type 1 diabetes in non-obese diabetic murine model, but are unable to prevent type 1 diabetes, and that could be an issue regarding the chimeric antigen receptor-modified T cells usage in vivo [81,82]. In order to find ways to expand metastatic function of chimeric antigen receptor-modified T cells, there has been genomic sequencing of chimeric antigen receptor regions in T lymphocytes was performed to elucidate the activity and persistence of chimeric antigen receptor-modified T cells in vivo, as was reported by Li and colleagues [106]. Moreover, alterations of chimeric antigen receptor-modified T cell structure are presently performed. Chmielewski [107], Kueberuwa

and colleagues [108] reported that chimeric antigen receptor-modified T cells of 4th generation have several integrated factors (interleukin 2, interleukin 5, interleukin 12, costimulatory ligands) in order to improve persistence, antitumor action and expansion. Moreover, treatment with chimeric antigen receptor-modified T cells which include interleukin 2 receptor beta chain, TERT co-transduction, or phosphoinositide 3-kinase inhibitor might ameliorate persistence of chimeric antigen receptor-modified T cells in vivo.

Regarding production issue, chimeric antigen receptor-modified T cells treatment implies an individual plan and needs sophisticated production in a specialized facility. Moreover, because of such risks as cytokine release syndrome, permanent clinical care is necessary after chimeric antigen receptor-modified T cells treatment. Hereby, the treatment cost is typically high. Hence, there is a need to improve the progress of chimeric antigen receptor-modified T cells treatment approach and market supervision to decrease the cost of chimeric antigen receptor-modified T cells treatment [109,110].

It is agreed that regulatory T cells specific for antigens, e.g., T-cell receptor regulatory T cells and chimeric antigen receptor-modified regulatory T cells, have better inhibiting parameters than polyclonal regulatory T cells, since they are specific for antigens and are prone to migration to the targeted organs containing the antigen. Furthermore, chimeric antigen receptor-modified regulatory T cells surpass the T-cell receptor regulatory T cells since they are not major histocompatibility complex-limited and they do not rely on interleukin 2 [111,112]. Although, chimeric antigen receptor-modified regulatory T cells have their own restrictions and shortcomings.

As to safety of chimeric antigen receptor-modified regulatory T cells, immune suppressing phenotype of regulatory T cells may be altered upon loss of FOXP-3 expression in inflammation, and such regulatory T cells can transduce to pathologic effector T cells specific for antigens which can exacerbate the disorder. A number of methods to retain regulatory T cells immunosuppressive phenotype were identified. For example, targeting regulatory T cells with all-trans retinoic acid to keep regulatory T cells stable and functional; applying regulatory T cells-favouring microbiome to the intestine; and stimulation of FOXP-3 ectopic expression to make regulatory T cells phenotype stable [113,114]. It was established that therapy with chimeric antigen receptor-modified T cells has side effects associated with neurotoxicity and hypercytokinemia. But it is yet to investigate if chimeric antigen receptor-modified regulatory T cells themselves promote these detrimental effects. Regulatory T cells tend to generate inflammation cytokines, but this defect may be corrected with application of CRISPR to delete interferon-gamma or interleukin-17 genes [115,116]. Chimeric antigen receptor-modified regulatory T cells treatment can also involve off-target attacks. E.g., in case of nasal administration of chimeric antigen receptor-modified regulatory T cells, mucosa cells are moving into the brain which leads to injury, as was reported by Danielyan and colleagues [75]. Mohseni and colleagues [43] suggest that it may lead to decreased immunity response against pathogens, progression of malignancies, pan-immunity suppression. Adding suicide genes to the cells prior to the administration could be a method to regulate this.

Considering efficacy, it is hard to establish if chimeric antigen receptor-modified regulatory T cells are efficient in all disorders. Characterization of Abs specific for self-antigens or alloantigens is required for constructing effective chimeric antigen receptor-modified regulatory T cells. Although, selecting the target antigens and engineering special Abs might require long time periods and could be challenging in some disorders. When the antigen is not selected accurately, chimeric antigen receptor-modified regulatory T cells could be not effective and not specific [117,118].

As to the persistence of chimeric antigen receptor-modified regulatory T cells, the drainage of chimeric antigen receptor-modified regulatory T cells might reduce their effectiveness in inhibition. Blat and colleagues revealed that carcinoembryonic antigen-chimeric antigen receptor-modified regulatory T cells quickly decrease in vivo, thus significantly restricting their clinical use in UC [119]. Bour-Jordan [120], Bluestone [121] and colleagues reported that CD-28 is of great importance in regulatory T cells developing, and hereby numerous trials in chimeric antigen receptor-modified regulatory T cells utilize 2nd generation chimeric antigen receptors with CD-28 costimulatory region for expansion of regulatory T cells. Although, multiple studies showed that replacing CD-28 with CD-137 is costimulatory and is able to alleviate drainage of T lymphocytes, ameliorating persistence of chimeric antigen receptor-modified regulatory T cells. Although, regulatory T cells homeostasis requires CD-28, which is also important for their proliferative, differentiative and surviving properties, for expression of FOXP-3 and for genesis of interleukin 2, as was reported by Jordan and Bluestone [120,121]. Hereby, integration of CD-28 and CD-37 costimulatory regions can facilitate the persistence of chimeric antigen receptor-modified regulatory T cells. Further research is necessary to choose the most suitable costimulatory signals for improvement of chimeric antigen receptor-modified regulatory T cells inhibition [122,123].

Production of chimeric antigen receptor-modified regulatory T cells is intricate and expensive, and that affects their clinical success. Presently, chimeric antigen receptor-modified regulatory T cells production has a number of issues regarding purifying of cells, yield, expanding, vector production, vector transduction, cryonic preservation, release tests [124]. Elinav and colleagues were presented with challenges considering vector transduction in the course of manufacturing trinitrophenyl (TNP) transfer PCR regulatory T cells [125]. Different approaches may be used to ameliorate production of chimeric antigen receptor-modified regulatory T cells. E.g., designing a multiparameter flow cytometry panel and adding marker profiles might make isolating and sorting

easier. Using self-dissolving or simple-to-remove beads may make activating easier. In chimeric antigen receptor development and administration, mass manufacturing utilizing Uni-CAR and other flexible module techniques enhances safety, reduces cost, optimizes CRISPR/Cas9 and transposon, elevates efficiency [126,127]. Sleeping Beauty transposon system could decrease the cost considerably, removing the necessity of clinical virus vector production, and reduce risk of inserted oncological process. Novel possibilities are emerging by virtue of utilizing CRISPR/Cas-9 with nonviral template DNA administration to kill genes as well as orthotopic placing of trans-genic constructions. For expansion of chimeric antigen receptor-modified regulatory T cells, semiautomatic or automatic closed-system biological reactors with built in gas transportation and automatic regulation of the processes might open doors to automatic standard expansion process ex vivo, and also might ameliorate safety and reduce the production cost [128,129]. Depil [130], MacDonald and colleagues [131] reported that introduction of ready-to-use allogeneic products, killing endogenous T-cell receptors and major histocompatibility complex molecules applying genetic editing, elevating the release of natural killer cell suppressive molecules, and use of regulatory T cells obtained from induced pluripotent stem cells could ameliorate the 3rd generation chimeric antigen receptor-modified regulatory T cells safety on an industrial scale.

Further research is necessary to enhance efficacy, safety, persistence and production of chimeric antigen receptor-modified T lymphocytes and chimeric antigen receptor-modified regulatory T cells. Notwithstanding the existing flaws, use of these cells represents a very promising therapeutic approach for auto-immune disorder treatment.

Conclusion

The advent of chimeric antigen receptor-modified T cells (CAR-T) and regulatory T cells (CAR-Tregs) marks a transformative shift in the treatment landscape for autoimmune disorders. These therapies offer targeted strategies to eliminate or suppress autoreactive immune cells, moving beyond traditional symptomatic management to potentially disease-modifying approaches. Key findings from recent studies highlight the promise of CAR-T therapies in conditions like systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis, showcasing their ability to achieve significant clinical outcomes and improved patient quality of life.

However, several critical challenges remain. Safety concerns, including the risk of cytokine release syndrome and off-target effects, underscore the necessity for rigorous monitoring and innovative safety measures. Furthermore, the persistence of therapeutic effects and the scalability of production methods require ongoing exploration and refinement to ensure broader accessibility and cost-effectiveness.

Future research should focus on optimizing CAR-T and CAR-Treg technologies to enhance their efficacy and safety profiles, utilizing advances in genetic engineering and production techniques. Identifying and characterizing autoantigens specific to various autoimmune conditions will also be essential to tailor treatments effectively.

In conclusion, while the journey toward effective cell therapies for autoimmune disorders is still in its early stages, the potential benefits they offer make them a compelling avenue for investigation. Continued interdisciplinary collaboration and innovative approaches are crucial for translating these promising findings into routine clinical practice, ultimately transforming the management of autoimmune diseases and improving outcomes for affected patients.

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