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Review Article

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Chimeric Antigen Receptor (car) Therapy: A Precision Medicine Approach to Rheumatoid Arthritis

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Abstract

The therapeutic landscape for autoimmune illnesses has been completely transformed by the novel immune cell therapy that known as (chimeric antigen receptor) T cell (CAR-T) therapy. Many patients do not respond to the current medications, despite significant advancements in the therapeutic management of autoimmune illnesses. Autoreactive B cells have a significant role in the development of autoimmune diseases including rheumatoid arthritis. Autoimmune illnesses are difficult to treat with rituximab and other B-cell-depleting monoclonal antibodies, because autoreactive B cells persist in inflammatory tissues and lymphatic systems. Adoptive transplantation of T cell that have genetically altered to target the tumor cells by using chimeric antigen receptors, is one possible treatment option for B-cell malignancies. Autologous CAR T cell therapy targeting the CD19 antigen has been incorporated into the management of autoimmune illnesses throughout the past two years. Circulating B cells were rapidly and steadily reduced by CD19 CAR T cells. This study looks at the new techniques for targeting autoreactive B cells with CAR T cells, which could result in focused treatment for autoimmune diseases. Notable response including improved the clinical symptoms, lowered autoantibody levels in serum, and prolonged reductions in progression of the disease. In vitro and preclinical studies using animal as well as human clinical samples support the important efficacy of CAR-T cells and offer additional information on special mechanisms of action against rheumatoid arthritis and anti-neutrophil cytoplasmic antibody-associated vasculitis.

Keywords: CAR-T, Autoimmune Rheumatic Diseases, Immunotherapy Introduction

Rheumatoid arthritis (RA) is a long-term, inflammatory disease that causes pain, swelling, stiffness, and maybe even loss of joint function. It is an attack on the joints by the immune system. As opposed to osteoarthritis, which is the consequence of wear and tear, RA arises from the body's own tissues being wrongly attacked by the immune system. This mostly affects the synovium, which is the lining of the membranes surrounding the joints. Joint abnormalities and injury may result from this over time [1]. RA is a systemic illness since it can also impact other organs and other systems, such as the blood vessels, the skin, eyes, and the heart. Although the precise origin of RA is unknown, immunological, environmental, and genetic variables all play a role. The goals of current therapeutic approaches are to control symptoms and delay the course of the disease, although they frequently have drawbacks and adverse effects [2]. Even with the most recent developments in the identification, categorization, and management of RA, there remain important obstacles that must be overcome. Various kinds of immunosuppression are the conventional treatment for management; But not every patient responds well to these therapies, and in order to maintain the patient's recovery, long-term pharmaceutical treatment is required [3]. A novel and quickly evolving therapeutic approach called chimeric antigen receptor (CAR) T cell therapy uses lentivirus or retrovirus genetic engineering to deliver a CAR fusion protein into a patient's own T cells7,8. The ability of these CAR T cells to specifically target and eliminate antigen-expressing cells triggers robust t cell activation and powerful responses against tumor [4].

Because CAR T cells having the ability to recognize and destroy abnormally activated cells of the immune system or rebuild tolerance in the organs that affected by immunological dysfunction, investigations have demonstrated that they may be a viable new therapy option for autoimmune diseases12–14. Since autoimmune disorders are characterized by aberrant immune responses that result in tissue damage and chronic inflammation, this has significant therapeutic potential14. It could be able to lessen inflammation and enhance patient outcomes Through using CAR t cells to specifically target the cells triggering the autoimmune response. Nevertheless, further research is required to assess the effectiveness of CAR t cells in autoimmune disorders and the safety of this treatment, as this is still an emerging field of study. Therefore, our goal in this review is to provide an overview and also assessment of the present

body of knowledge about the application of CAR T therapy to the management of RA, with an emphasis on investigating the possible advantages and drawbacks of this treatment approach [5,6].

1. Pathophysiology of Rheumatoid Arthritis

The pathophysiology of this condition involves a wide range of various cellular responses, such as local growth factors, inflammatory cell activation, cytokine production, and angiogenesis. The extracellular matrix (ECM) of cartilages and bones is broken down by the inflammatory and degradative chemicals produced by T-cells, B-cells, neutrophils, and macrophages, which are mostly found in synovial tissue [7]. Based on the existence or lack of the anti-citrullinated protein antibodies, there are two main subgroups of RA. ACPAs are found in the condition in about 67% of those with RA. Since ACPAs can predict the chance that a patient's early, undifferentiated arthritic conditions would advance to RA, they can be a helpful tool for diagnosis for those patients. The clinical appearance of the ACPA-positive fraction of RA is more severe in comparison to the ACPA-negative subset [8]. An aberrant antibody response to several citrullinated proteins, such as histone, fibrins, vimentin, fibronectins, Epstein-Barr Nuclear Antigen 1 and α-enolase, type II collagen, and fibrin, which are found all over the body, causes ACPA. There is evidence linking genetic and environmental variables to the generation of ACPA.

In RA, the environment serves as a trigger for the creation of ACPA, and genes and the environment are combined through epigenetic control. In RA, the gene-environment interaction affects autoantibodies' response to citrullinated antigens. ACPAs can be found much before joint discomfort appear. This event raises the possibility that the joints are not the site of autoimmune onset. In addition to antigen-presenting cells (APCs) like B cells and conventional dendritic cells (DCs), Toxic substances, such as smoke, particles of nanosized silica, or nanoparticles generated from carbon, can cause lung irritation by activating mucosal toll-liking receptors (TLRs), which in turn triggers Ca2+-mediated PADs [9].

Three infectious agents—Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans (Aa), and also Epstein-Barr virus (EBV)—are well-supported by data as autoimmune triggers in RA. Leukotoxin A can be secreted by pathogen Aa, and it can also create holes in neutrophil membranes that cause hyper-citrullinated neutrophils, which in turn releases citrullinated autoantigens into the gums [10]. Citrullinated autoantigens and ACPA formation are produced by P. gingivalis infection through two pathways that have been described, the first involves the formation of neutrophil extracellullar traps (NETs), which is triggered by P. gingivalis during the processes of NETosis, and the other involves the action of P. gingivalis's arginine ginpains (Rgps) and PAD, which has been shown to citrullinate proteins and cleave protein at arginine residues to make additional neoantigens. Citrullinated autoantigens are produced by NETosis, which is induced by ACPAs. B cells that produce ACPA are susceptible to EBV influence, and RA patients have decreased EBV control. Because the overabundance of specific uncommon bacterial lineages in RA patients might lead to dysbiosis, another mucosal organ connected to the pathogenesis of RA is the digestive tractIt is well established that the gut microbiota could be contributing to the pathophysiology of RA through a number of biological pathways [11,12] Joint involvement due to RA typically presents characteristically, with symmetrical tiny joints experiencing synovitis. Following immunological activation, inflammation of the synovial membrane is reflected externally as joint swelling.

The typical synovial compartment is invaded by leukocytes, and the synovial fluid is overflowed with substances that promote inflammation. The clinical interactions between fibroblast-like synoviocytes (FLSs) and the cells of innate immune system, including macrophage, mast cell, DCs, and so on, and also the adaptive cells, including T lymphocytes and B cells of the humoral immunity, characterize the inflammatory cascade that is produced by these factors combined. When ACPA-positive RA develops, an attempt to treat inflammation fails, leading to persistent synovitis. This condition is strongly related to the two immune systems and how they interact. ACPA can raise TNF-α production and NF-kB activity by binding to citrullinated Grp78, which is expressed on the surface of monocytes and macrophages. On the surface of macrophages and monocytes, α-enolase produces pro-inflammatory mediators [13,14].

The RA maturation stage starts where the bone marrow or secondary lymphoid tissues are located. The process by which the production of self-antigens sets off the emergence of immune responses against endogenous epitopes is known as "epitope spreading". Before the disease shows symptoms, the immune system's responses to autoantigen can exist outside the joints for many years. During this stage, epitope clinical dispersion and a continuously increasing the titer of ACPA might lasting for several years prior to joint symptoms manifesting. Predicting the interval time to disease start seems to heavily depend on initial ACCP levels [15]. The breakdown of immunological tolerance is reflected in the generation of ACPA. Numerous citrullination neoantigens would therefore stimulate T cells that are dependent on MHC class II, which would then assist B cells in producing more ACPA. In RA, the ACPA can causes discomfort, inflammation, and also bone loss [16].

One of the pathological characteristics of RA is the bone loss, that can be systemic, periarticular, or localized. Bone loss results from the suppression of osteoblasts and the activation of osteoclasts. The term "periarticular" bone loss most likely describes cellular alterations in the subchondral bone marrow, including the creation of inflammatory infiltrates and osteoclast differentiation. Whether inflammation or autoimmunity is the primary cause of bone loss is still up for debate. The following data supports the traditional inflammatory theory: TNF-α, IL-6, IL-1β, IL-17, and other inflammatory cytokines associated with RA may, in the right conditions, through the right signals, such as macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor kappa-B ligand (RANKL), pro-osteoclastogenic effects and limit bone formation [17]. These promoting the inflow and monocytes differentiation into osteoclast in an inflammatory environment [18], whereas anti-inflammatory drugs for RA prevent the onset of bone losses and vice versa.

2. Pathogenic Role of the Immune System in RA

Normally, the immune system protects the body from pathogens such as viruses and bacteria. However, rheumatoid arthritis (RA) is a condition in which the immune system mis attacks the tissues within the joints, leading to discomfort, swelling, stiffness, inflammation, and eventual joint destruction. The immune system attacking the body's own tissues in rheumatoid arthritis, particularly the synovium, which lines the membranes around your joints. Chronic inflammation brought on by this autoimmune onslaught can lead to a number of symptoms and problems. immune cells, including B and T-cell, and macrophages, are important in the RA pathophysiology. These cells may circulate in peripheral circulation or dwell in the synovium.

B-cells release physiologically important protein molecules, such as rheumatoid factors (RFs), pro-inflammatory cytokines, and anti-citrullinated protein antibodies (ACPA), to sustain RA. Costimulatory molecules are also produced by B-cells, and they aid in T-cell activation. The main functions of T-cells in RA are converting the macrophages and also fibroblasts into tissue-destructive cell by activating them. To help with joint inflammation, activated macrophages such as T- and B-cells release a variety of cytokines and chemokines [19]. Though important for human adaptive immunity, B-cells also have a role in the development of rheumatoid arthritis (RA).

In RA, autoreactive B-cells attack and eliminate host antigens, which may cause tissue damage. Normally, these B-cells are destroyed by mechanisms controlled by central and peripheral B-cell tolerance checkpoints either during their growth in the bone marrow or prior to their maturation. The central checkpoint is governed by B-cell growth factors that have an impact on B-cell receptor (BCR) and toll-like receptor (TLR) signaling. Peripheral tolerance is influenced by external factors such as serum B-cell activating factor (BAFF) and regulatory T-cells (Treg) [20].

An important factor in rheumatoid arthritis (RA) inflammation is CD4+ T-cells. Through their interactions with chemicals on antigen-presenting cells (APCs), these cells cause the maturation of APCs through a signaling cascade. CD8+ T-cell activation may also result in inflammation. Their pivotal role in the disease is further supported by the association seen in RA with particular MHC-II alleles and in major problems related to RA with CD4+ T-cells [21]. In addition to directly interacting with other cells, CD4+ T-helper cells also indirectly combat RA by releasing substances. These substances, chemokines and cytokines, have the ability to either promote or inhibit inflammation. The most active type of RA cells, Th1 cells, emit compounds that exacerbate inflammation. Th2 cells, on the other hand, release substances that lessen it. Treg cells and other subtypes of Th cells, such as Th17, are also involved. Th17 cells release IL-17, a cytokine associated with the severity of RA, which exacerbates inflammation. Another type of cell that has been detected in RA patients is called Th9 cells, and it may have a role in inflammation [22].

Cytokines, which are substances of the immune system, are important in RA. Certain cytokines, such as IL-13, 14 and 15, are the first to cause inflammation. Others that cause more damage later on, including TNF-α and IL-6, become more noticeable. In RA, the mismatch between pro- and defensive cytokines promotes persistent inflammation. T cells release cytokines that damage bone and cartilage in response to inflammatory cues from immune cells such as macrophages and B cells [23]. While many immune cells are capable of producing cytokines, activated CD4+ T cells are essential. These T cells, particularly the Th17 subtype, release IL-17 and other chemicals that exacerbate inflammation and break down bone. TNF-α and IL-6 are examples of cytokines that promote tissue damage and increased immune cell activity, which quickens this process even further. This sets up a vicious loop that makes RA worse [24].

Autoantibodies are important players in the pathophysiology of rheumatoid arthritis and the other autoimmune disorders. The antibodies produced by the body target their own antigens when immunological dysregulation takes place. Patients with RA have routinely been shown to have several antibodies, including ACPA, RF, and regulatory rheumatoid factor (regRF). An autoantibody called RF attacks immunoglobulin G's Fc region. In diagnostic labs, this autoantibody is frequently tested to help diagnose RA patients. While not all cases of RA have RF, it is noteworthy that those that do typically have worse prognoses and bone degradation [25,26]. The pathogenic activity of ACPA in RA is associated with the formation of neutrophil cellular traps (NETosis), a specific type of cellular death in which neutrophils extrude intracellular material (DNA, histones, IL-17A, TNF-α, granular and cytoplasmic proteins). Anti-citrullinated vimentin antibodies have been shown to potently promote NET synthesis. Through rapid NETosis, a supply of citrullinated autoantigens and PAD enzymes that, when released from intracellular compartments, can citrulline extracellular proteins, speeds up the development of ACPA in RA. Thus, the inflammatory and autoimmune processes of RA may be prolonged by ACPA-induced NET formation activation [27].

3. Current Challenges in RA Treatment

The previous few decades have seen significant advancements in the treatment of rheumatoid arthritis (RA), making therapeutic objectives like clinical, structural, and functional resolution achievable. However, a sizable percentage of people demonstrate drug resistance to many drugs. Patients with disease activity that is uncontrolled even after utilizing two or more disease-modifying biological anti-rheumatic medications or targeting synthetic DMARDs with the different mechanism of actions were referred to having difficult to treat (D2T) RA.

(D2T) RA is complicated and diverse state of disease. Its main problem that the disease activities are uncontrolled, a reduction in the life quality, and the financial increasing resulting from recurrent hospital admissions and the healthcare utilization. Given the novelty of D2T RA and the paucity of research on the subject, little is known about the mechanism driving DMARD inefficacy and the characteristics that contribute to a "difficult-to-treat" state in these patients. Additionally, it's probable that the causes of D2T RA vary depending on the patient's gender, race, nation, and nationality. The definition, prevalence, and contributing variables of D2T RA are all covered in this Mini Review, along with the current state of the idea and unresolved

issues surrounding it. The management and treatment approaches for D2T RA are then covered. Lastly, we investigate a therapeutic strategy to stop patients from getting D2T RA [28,29].

4. Basic of Chimeric Antigen Receptor Therapy

Immunotherapy that targets autoimmune disorders and cancer by utilizing genetically altered immune cells is called chimeric antigen receptor (CAR) T cell therapy. This therapy, which has just recently gained popularity, involves genetically modifying a patient's own T cells to deliver a CAR fusion protein by the use of a retrovirus or lentivirus [30]. The ability of these CAR T cells to specifically target and eliminate antigen-expressing cells triggers robust T cell activation and powerful antitumor response. This treatment shown remarkable responses in most of hematological malignancies such as lymphoma, leukemia, and also the multiple myeloma, as well as in certain solid tumor; in fact, some patients may have experienced a long-term remission or even a cure [31].

Research has indicated that although CAR T cells were initially developed for use in cancer, they may offer a promising new therapeutic choice for autoimmune disorders because of their capability to either targeting and eliminate pathologically active immune cell or restoring the tolerance in organs damaged by immune dysregulation [32]. Given that autoimmune illnesses are typified by aberrant immune responses that result in tissue damage and persistent inflammation, this has significant therapeutic promise. It could be able to lessen inflammation and enhance patient outcomes by employing CAR t cell targeting and destroy particular cell that causing autoimmune reaction. Since autoimmune illnesses are still an emerging topic of study, further research is required for evaluation the safeties and efficacies of CAR t cells in these conditions [33]. Therefore, our goal in this review is to provide an overview and also assessment of the present body of knowledge about the use of CAR t therapy to the treatment of RA, with an emphasis on investigating the possible advantages and disadvantages of this treatment.

The four primary parts of CARs are an extracellular target antigen-binding domain, a hinge region, a transmembrane domain, and one or more intracellular signaling domains. CARs are modular synthetic receptors. We'll talk about the current tenets of CAR designing here. The antigen- binding -domain of the CAR is the region conferring target antigen-specificity. Traditionally, the variable heavy (VH) and light (VL) chains of monoclonal antibodies are joined by a flexible linker to form single-chain variable fragments (scFv), which produce the antigen-binding domains. The antigen binding affinity of the CAR must be strong enough, but not so high as to produce toxicities or activation-induced death of the T cells containing the CAR, for recognizing antigen on the tumor cell, initiate CAR signaling, and stimulate T lymphocytes [34]. The hinge, also known as the (spacer region), is the extracellular structural space that extending the binding unit from the transmembrane domains and makes up the second component of CAR.

Hinges also can impact the overall function of CAR t cells by contributing to the length and providing flexibility to overcome steric hindrance, which in turn allows the antigen-binding domain to access the targeted epitope. Two Ig-like domains, CH2 and CH3, found in human IgG-derived spacers, are used for effective antigen recognition and are particularly helpful in determining the degree of CAR expression on the surface of T cells Nonetheless, a number of studies show that even after being integrated into CARs, IgG-based spacers are still for binding the Fc gamma receptor (FcηR) via their (CH2) domain.

This characteristic causes FcγR-bearing myeloid and lymphoid cells to become activated off-target; the transmembrane domain of CARs is perhaps the least understood of all its components. The transmembrane domain's major purpose is to connect the CAR to the T cell membrane, yet research also suggests that it may be crucial for CAR-T cell activity. specifically, studies show that the (CAR) transmembrane domain can act as active mediators of synapses formation and the signaling, dimerizing with the endogenous- signaling molecules, and influence the stability and level of CAR production. The transmembrane domain of the CAR, comprising a hydrophobic α helix that traverses the cell membrane, is probably the portion of the protein that is least understood. The transmembrane's main job is to attach the CAR in the T cell membranes, but there is evidence that it may also be crucial for (CAR t) cell function [35].

In CAR engineering, the most focus has probably gone toward understanding the effects of CAR co-stimulation in order to generate CAR constructions with the optimal end domain. In the latter part of the 1990s, first-generation CARs containing an FcRγ or CD3ζ signaling domain were developed. To activate CAR-T cells, the great majority of CARs rely on immunoreceptor tyrosine-based activation patterns derived from CD3ζ. But these patterns by themselves are insufficient for efficient T cell responses when it comes to signaling [36].

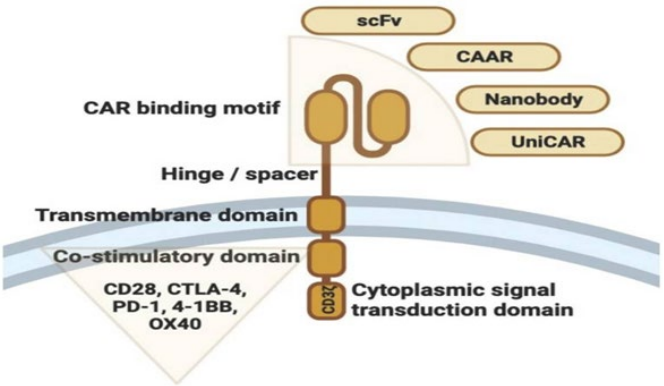

Figure 1: Schematic Representation of The Structure of The Chimeric Antigen Receptor.

5. Application of CAR-T Cell Therapy in Autoimmune Diseases

Many patients do not respond to the current medications, despite significant advancements in the therapeutic management of autoimmune illnesses. The pathophysiology of autoimmune illnesses, particularly multiple sclerosis and rheumatoid arthritis, is greatly impacted by B cells that are autoreactive. Autoimmune diseases are difficult to treat with rituximab and other B-cell-depleting monoclonal antibodies because autoreactive B cells persist in inflammatory tissues and lymphatic organs. The adoptive transferring of t cells that genetically altered to target tumor cell using the chimeric antigen receptor is one effective

treatment option for B-cell malignancies. Autologous CAR T cell therapy, which targets the CD19 antigen, has been used in the treatment of autoimmune diseases throughout the last two years. When refractory systemic lupus erythematosus and dermatomyositis were completely remitted clinically and serologically, CD19 CAR T cells caused a fast and long-lasting reduction in the number of circulating B cells [36]. CAR therapy against RA was achieved by modulating the immune system's response to target and eliminate cells responsible for autoimmune reactions. Given the synthetic receptor, CAR-T cells may identify and attach to target proteins linked to the autoimmune response on cells that express them. Once attached, the CAR-T cells trigger the immune system to go after the targeted autoimmune cells and destroy them. CAR-T therapy seeks to suppress the aberrant immune response and maybe bring about an autoimmune disease remission by specifically targeting the cells implicated in the autoimmune process.

6. Particular Antigen that CAR T-cell Therapy Targets in RA

The anti-citrullinated protein antibody, which attaches to citrullinated residues in various self-proteins such as vimentin, α-enolase, fibronectin, fibrinogen, type II collagen, and so on, is the subject of research. Early on, the autoantibodies and the systemic inflammations are decreased, but tissue damage and the adaptive responses progressively rise. Anti-fluorescein isothiocyanate (FITC) CAR-T cells have been used in the therapy of RA to eradicate autoreactive B cells [37].

Important procedures include the production of (FITC-labeled) autoantibodies positive peptide and CAR-T, the determination of autoantibody type in patients by the use of the enzyme-linked immunosorbent test (ELISA), and the use of peptides targeting CAR-T to eradicate autoreactive B cells. Since the autoantibodies production against the citrulline antigen defines (RA), citrulline vimentin, citrulline type II collagen, and cyclic citrulline peptide-1 selected as autoantigen to target autoreactive (B cells). CAR-t cells and the autoimmune (B cells) are the only cells that are able to identify FITC. Thus, by recognizing FITC-labeled autoantigen peptides, anti-FITC CAR-T can specifically target several types of autoreactive B cell. By producing of antibodies against the corresponding antigen, attaching to the corresponding (antigenic FITC-coupled peptide), and recognize and eradicating (anti-COII) antibody-producing B cell from the collagen-induced- arthritis animals, FITC CAR-T can identify and eliminate hybridoma cells in vitro models. In vitro, FITC CAR-t also makes human RA autoimmune B cells cytotoxic [38]. Citrullinated antigens that express chimeric autoantibodies receptor t cells also used to protect B cells while reducing the percentage of B cells that are resistant to the citrullinated proteins. Additionally, showing promise in the treatment of RA [38].

Anti-(FITC CAR-t) is not prone to the abrogation and has less side effects. Studies have shown that when specific antibodies are present, FCγR-expressing cells, including CD64-expressing macrophages, are less likely to be killed by (anti-FITC CAR-t cells) than targeting antibodies-secreting immune cells. Even when a specific antibody is present in large quantities, the cytotoxicity of CAR-T cells is stilling more less than that of target cells that release antibodies. You can lessen this minor off-target effect by using irrelevant antibodies to inhibit FCγR. This method avoiding the impact of (FITC CAR-t) on (FCγR)-expressing macrophage and also natural killer cells. Preventing undue harm to immune cells prevents an excessive thinning of human immunity. This preserves the specificity and longevity of the CAR-T treatment while reduce the high risk of acquiring new diseases or cancer as a result of the treatment. Not only does (anti-FITC CAR-t) eliminating the high-level of specific (B cell receptor) which express autoantigen- B cell, but it may indirectly affect the memory B cell development and differentiation to generate autoantibodies-secreting plasma cell. The specific disadvantage of this strategy is that, although it's the ability for elimination of the (autoreactive B cells) has only in vitro proven, it is yet uncertain whether it is safe to use in vivo or whether it will have negative effecting on the autoimmune B cell. Second, autoantigens and mediators of FITC coupling must be made more stable. Stability may be increased by raising the molecular weight and strengthening the structure, for example, by adding immunogenic regions to antibodies and antigenic peptides [39].

7. Mechanism of CAR Therapy in RA.

Chimeric antigen therapy is a promising special treatment approach for autoimmune illnesses since it can target and destroy pathologically activated immune cells, as well as restore tolerance in organs damaged by dysregulated immunity. CAR T cells have the benefit of efficiently eliminating B cells in autoimmune disorders without the need for an additional cell type. Furthermore, the benefits of CAR t cells that target CD19 established for overall B cells aplasia, preserving the humoral immunity that already exists, and also specifically eliminate the pathogenic immune B cells. The use of CAR t cell therapy in (SRDs) is restricted since it is unable to effectively target the many autoreactive cells that are present. In a global CAR T cell treatment, researchers are using major epitope peptides to detect and target autoreactive cells. even though more research is needed [40]. Immuno-depletion found to improve the efficacy of CAR t cell therapy for autoimmune diseases. For better results, immunodepleting could be used prior to CAR T cell treatments in individuals with autoimmune disorders, as the condition might respond favorably to it [41].

Numerous studies have been conducted to investigate the effectiveness of CAR T cell therapy in treating RA, following its successful deployment in 2017. However, like other SRDs, CAR t cell treatment for RA is limited in that it only targets a single cell type, which makes it unsuitable for treating the diverse population of autoreactive lymphocytes that RA patients have. In order to get over this restriction, Zhang et al. conducted a proof of concept investigation in 2020 using FITC-labeled RA-immunodominant peptides in combination with the universal anti-fluorescein isothiocyanate (FITC) CAR t cells. This demonstrate that the availability of the pertinent (FITC-labeled antigenic peptide), numerous strains of the hybridoma cell can be targeted and killed by the (anti-FITC CAR t cell) via lysis, providing a special solution for the varied nature of (RA) treatments with CAR t cells. By targeting distinct autoreactive B cell subsets, this strategy attempted to give RA patients a more targeted and long-lasting therapeutic alternative [41].

The toxicity resulting from CAR-T cell therapy can vary

depending on a number of parameters, including patient heterogeneity, dosage of CAR-T cells, manufacturing technique, starting material for autologous products, and baseline tumor load [42]. Many more CAR-T cells that target different antigens than (CD19) are either in the pre-clinical developments or are now undergoing clinical trial in an effort to treat a wide range of human problems. It is anticipated that CAR-t cell therapy field will keep growing and that additional CAR-t cell will be developed for treating illnesses that were previously thought to be incurable in humans [43]. It is possible that CAR-T cells will not proliferate or survive after infusion, which would lessen the therapeutic responses. One of the routes that can lead to function loss is CAR-t cell depletion [44]. Checkpoint inhibitors (anti-PD-1 or anti-PD-L1) are used in clinical research to prevent CAR-T cells from interacting with cancer cells through PD-1 and PD-L1. This helps to restore CAR-T cell activity. More techniques to lessen CAR-t cell fatigue are developing. CAR-t cells can be curative for individuals who responding to therapy, according to clinical trials using CD19 CAR-T cell therapies. However, there have been reported cases of resistance and relapses, and not all the patients respond well to the treatments in the same way [45].

8. Chimeric Autoantibody Receptor T Cells

Pemphigus vulgaris is a type of autoimmune disease that autoantibodies are frequently known to target. This potentially lethal illness characterized by skin blistering is often caused by autoantibodies against Desmoulins 3. (DSG3). An anti-CD20 monoclonal antibody called rituximab was used in clinical studies to try and nonspecifically decrease the B cells that produce these antibodies. Nearly all patients experienced a brief remission despite the treatment's significant safety concerns and extraordinarily high relapse rates [46]. In 2016, Payne and associates published a study described their effective re-engineering of the CAR to reduce DSG3-autoreactive (B cell) preferentially, hence lowering the dangers related to generic B cell aplasia [47]. This structure was dubbed the "chimeric autoantibody receptor" (CAAR). Recombinant DSG3, the target of the autoantibodies, is fused to the CD137–CD3ζ signaling domains in CAARs, as opposed to using a (single-chain variable fragment) (scFv) unique to an antigen, as seen in conventional CARs. DSG3-specific CAAR t cells preferentially eliminate only B cell expressing DSG3-specific B cell-receptor, without affecting other B cells. This medication enhanced the skin phenotype in a pemphigus vulgaris mice model without having any unintended side effects [48].

9. Anti-B cell CAR T cells

Other approaches are required because the autoantibody target is typically unknown in autoimmune illnesses. One such tactic is nonspecific B cell reduction, however rituximab failed to show any benefit in two different clinical trials intended to treat systemic lupus erythematosus [49]. This was most likely caused by failing to ablate autoantibody-producing clones and insufficient B cell depletion in both cases. However, anti-B cell CAR t cells, such as CD19-specific CARs, have been shown to totally and continuously reduce B cells, in contrast to monoclonal antibodies. B cells ablation by (CD19-specific CAR t cells) effectively suppressed the disease's symptoms, treated established disease, and extended longevity in animal models of systemic lupus erythematosus (SLE)[50]. There are currently clinical trials using CD19-specific CAR T cells, which is a promising SLE therapeutic option. These T cells have already received FDA approval to treat B cell malignancies. Promising outcomes from a patient with (SLE) on this drug were reported recently [51]. Myasthenia gravis is a neuromuscular disorder that is being treated with the anti-B cell maturation antigens CAR t cells, which are also undergoing clinical trials [52].

9.1 CAR Treg Cells

Up till now, we have talked about rerouting cytotoxic t cells to target and ablate particular cells utilizing CARs or modified CAR constructions. Targeting autoreactive immunological regions with Treg cells to locally inhibit the immune response is an alternative strategy with significant therapeutic potential. Three instances of preclinical research utilizing CAR Treg cells to treat autoimmune illnesses are colitis, multiple sclerosis [53], and type 1 diabetes (T1D) Furthermore, it has been suggested that human leucocyte antigen (HLA)-targeted CAR Treg cells could aid in preventing immunological rejection of an organ transplant [54].

10. Possible Drawbacks with the Present CAR-T Cell Therapy

Even so, scope of these groundbreaking trials is restricted, and before CAR-T cell therapy is widely used in clinical settings to treat ARDs, a number of issues pertaining to its efficacy, durability, safety, and manufacturing may need to be resolved.

11. Safety

The primary issues with CAR-T cell therapy as a treatment for cancer include cytokine release syndrome (CRS), immune effector cell associated neurotoxicity syndrome (ICANS), and on-target off-tumor toxicity [53]. These issues also pertain to the treatment of ARDs using CAR-T cell therapy. Particularly, after using CAR-T cells, the most frequent toxicities seen in hematological malignancies are CRS and ICANS [54, 55]. These toxicities have also been described in ARDs. After receiving CAR-T cell therapy, an overactive immune response can cause a range of neurological toxicities known as ICANS, while an excess of cytokines can cause a severe systemic inflammatory reaction known as CRS [56]. Making ensuring that using CAR-T cells to treat rheumatic disorders doesn't lead to excessive toxicity from off-target diseases and subsequent harm to good tissue is vital. Thus, it is critical to adapt CAR-T cell therapyies for rheumatic diseas while maintaining safety and therapeutic efficacy. This emphasizes the necessity for accurate targeting techniques and strong toxicity management methods.

12. Effectiveness and Durability

The endurance and THE efficacy of CAR-T cells therapy remain a concern in field of oncology, and this difficulty is probably going to extend to the treatment of rheumatic disorders as well. To put things in perspective, between 40% and 60% of people relapse with their illness even with the extraordinary complete remission rates that CD19 CAR-T cells achieve for the relapsed B-cells and the B-cells lymphoma [57]. The possible underlying reason is that CAR-t cells eventually deteriorate, which can result in a reduction in their anti-tumor impact, the persistence of cancer, and recurrence [58]. This weariness problem probably

causes ARD persistence and relapse and lessens the treatment impact against pathogenic autoimmune cells. Additionally, The tumor population might not be entirely eliminated by CAR-T cells or might be able to escape these antigens since they only target a small subset of antigens; this would allow the condition to worsen [59]. Rheumatic illnesses are diverse, therefore it's likely that CAR-t cell won't be able to effectively cure them. If this happens, the condition may remain and recur years later. Even though a recent report [60]. Observed that in 15 ARDs patients were received the CD19 CAR-t cell treatment and demonstrated the disease remission for several months, addressing this limitation through ongoing the innovative researches are necessary to unlock the full potentials of CAR-t cell therapies in the treatments of rheumatic diseases.

13. Manufacturing

The production of CAR-t cells is a labor-intensive, intricate, and costly process because of the difficulties involved in the genetically modifying t cell, the patient-specific nature of the treatment, the requirements for stringent qualities control measures, and the requirements for specific facilities to generate and process these cells [61]. This intricacy is highlighted by the current standard gene transfer technique used to create CAR-T cells, which involves the use of viral vectors [62].

14. Future Directions

Although CD19 is now the only practical target for CAR-t cell therapy, It holds great promise as an ARDs therapy. To provide ARD patients with a wider range of more efficient therapy choices, future research must concentrate on identifying the antigens linked to ARDs in addition to developing new (CAR-t cells) that can specifically target these antigen-bearing cells. Furthermore, the necessity for more advancements and thorough research is highlighted by the difficulties and dearth of preclinical and clinical investigations. Regarding future paths, it is critical to carry out additional research to maximize the manufacture, efficacy, and safety of CAR-t cells. This can achieve by refining the CAR build, the structural architecture of the CAR-t cell, and the manufacture of process for the CAR-t cell. Furthermore, improvements over the current structure and production process of CAR-t cells may improve manufacturing constraints, lower toxicity, and increase efficacy [63].

Conclusion

For ARDs that are refractory, CAR-t cell treatment shown to be quite effective. While there aren't any alarming symptoms at this time, it's important to strike a specific balance between the therapeutic efficacy and also the safety while modifying CAR-t cell therapy for RA. Furthermore, Technology development has a great deal of promise to improve how this treatment are given to patients, resulting in a more secure and effective management of their illness.

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