

CAR-T Cell Therapy in Rheumatic Diseases

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Abstract

CAR-T cell (Chimeric Antigen Receptor-T cell) therapy has revolutionized the treatment of various hematologic malignancies. CD19 targeted CAR-T cell therapy is coming in a big way in rheumatic diseases. Recent case reports and case series have shown encouraging results in diseases like systemic lupus erythematosus (SLE), systemic sclerosis and antisynthetase syndrome which have been refractory to multiple existing therapies. The dramatic response encompasses objective improvement across multiple clinical domains as well as seroconversion. Side effects of concern with CAR-T cell therapy are related to release of pro-inflammatory cytokines and include cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS). The reported side effects of this therapy for autoimmune diseases were of low grade and were managed without any fatality. Several modifications in CAR-T cell therapy have been proposed to maximize the safety and improving the efficacy. This therapy has got the potential to be a major breakthrough in management of rheumatic diseases, especially wherein existing therapies have been refractory.

Key words: CAR-T Cell Therapy, Rheumatic Disease, Cytokine-release Syndrome

Origin and evolution of CAR-T cells

What seems like a recent development, has indeed taken years of persistent efforts of some visionary scientists. CAR-T cell therapy, is yet another discovery in the world of oncology which is promising to revolutionize the therapeutics of rheumatic diseases as well. The evidence of anti-cancer efficacy of immune cells was demonstrated in mice as early as 1960s. Later in 1973, bone marrow transplant was first used for treatment of cancer wherein immune cells from donor will kill cancer cells in recipient. Michael Sadelain, in 1992, thought of engineering T-cells, using retroviral vectors to incorporate desired gene into the T-cell genome with the goal of making souped up fighters. Soon after, in 1993, Immunologist Zelig Eshhar, engineered T-cells with chimeric antigen receptors (CARs) wherein an antigen binding portion of antibody is fused with to a part of T-cell receptor. These first generation CARs although technically innovative, did not persist in the body and were clinically ineffective. Same group discovered that adding a co-stimulatory molecule (CD 28) helps in persistence of T-cells in the body and makes them effective, these are the second generation CARs. In 2003, CD 19 targeting CAR-T cells were designed for

treatment of acute lymphoblastic leukemia and the results of this therapy were published in 2013. Seeing the astonishing results, it was designated as a breakthrough therapy by FDA and first CAR-T cell therapy was approved for relapsed, refractory ALL in children and young adults in 2017. This was followed by approval of multiple other CAR-T cell therapies for various hematological malignancies.¹

In the currently approved second-generation CD19 CAR-T cells, CD28 or 4–1BB co-stimulatory domains are used. CD28-driven CARs are considered to elicit faster and more intense downstream signalling, promoting differentiation into effector memory CAR-T cells, than 4–1BB-driven CARs.² However, CD28-driven tonic signalling favours early exhaustion. In contrast, 4–1BB-driven CARs lead to slower and more persistent signalling, skewing T cells towards a central memory phenotype.³ In cases of early recurrence of autoimmune diseases, such modifications could be necessary, such as the use of third-generation CARs that combine 4–1BB and CD28 co-stimulation, to improve the robust signalling that is important for better longevity and effector functions of CAR-T cells.⁴

History of CAR-T cell therapy in autoimmune disease dates back to 2021 when Zhang et al.⁵ used a CD19-BCMA compound CAR (cCAR) to treat autoimmunity through dual targeting of B cells and long-lived plasma cells in a 41-year-old female with SLE and recently diagnosed diffuse large B-cell lymphoma (DLBCL) who was intolerant to chemotherapy. They demonstrated that 23 months post-cCAR, the patient's SLE remained stable and DLBCL in remission despite receiving no additional immunosuppressive or chemo/radiotherapy.

Efficacy and safety of CAR-T cells in autoimmune diseases

Despite the advent of promising biologic agents, lupus nephritis in particular still remains a difficult to treat domain in SLE. This reflects an unmet need in the effective treatment for lupus nephritis. In 2022, Mougiakakos et al.⁶ demonstrated efficacy of CD-19 CAR-T cell therapy in a 20-year-old woman with SLE (Lupus nephritis class IIIA, serositis, musculoskeletal manifestations) refractory to multiple immunomodulators including rituximab, cyclophosphamide and belimumab. There was dramatic reduction in SLE disease activity (SLEDAI), reduction in proteinuria and serological response in form of anti-dsDNA turning undetectable and normalization of complements without any major adverse events. Soon after, Mackensen et al. in Germany, published a case series of 5 patients with lupus nephritis refractory to multiple immunomodulatory agents treated with CD 19 CAR-T therapy. At 3 months follow up, all 5 patients achieved remission and anti-dsDNA seroconversion. Three patients experienced therapy related side effects in form of fever which is graded as mild cytokine release syndrome (grade 1). On long term follow up (5-17 months), mean B-cell repopulation time was 110 days. However, most of the repopulated B cells were naïve and did not contribute to disease relapse in any of the patient.⁷ Such encouraging results reflect that probably a single cycle of CAR-T cell therapy can help in, much needed, closure of the treatment gap.

CAR-T cell therapy has produced promising results in other rheumatic diseases as well. Muller et al. reported the efficacy of CAR-T cell therapy in a 41-year-old patient with antisynthetase syndrome (interstitial lung disease, myositis, Jo-1 positivity) refractory to IV immunoglobulins, rituximab and tacrolimus. At 6 month follow up, patient had substantial clinical response in form of improvement in muscle power (manual muscle testing score improved from 115/150 to 149/150), improvement of respiratory systems such that he no longer required oxygen support. This was accompanied by objective improvement in form of absolute normalization of CPK, resolution of inflammation in muscles on MRI, improvement in HRCT chest and seroconversion.⁸

In May 2023, Bergmann et al. reported first use of CD19-CAR T cells for treatment of severe, refractory diffuse systemic sclerosis in 60-year-old male patient. At baseline, the patient presented with diffuse myocardial fibrosis, lung fibrosis, pulmonary hypertension, Raynaud's phenomenon and carpal arthritis. His disease was refractory to mycophenolate mofetil

and rituximab. In the following 6 months after CAR-T cell therapy, there was seroconversion, resolution of arthritis, improvement in pulmonary hypertension, stabilization of pulmonary function and reduced molecular fibroblast activation in the myocardium (as determined by 68Ga-FAPI-04-positron emission tomography-CT). Skin fibrosis (modified rodnan skin score) and disease activity showed improvement and the patient subjectively reported less frequent and less severe attacks of Raynaud's phenomenon.⁹

The dramatic efficacy of this therapy comes at a cost of unique side effects which can sometimes be lethal. The two adverse effects of major concern are cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS). Mild cytokine release syndrome manifests as fever, headache, arthralgia, and myalgia, but can also lead to hypotension and even cytotoxic shock in severe cases. CRS is mediated by CAR T-cell activation upon target cell engagement and the release of proinflammatory mediators, such as IL-6. ICANS can manifest as fine motor impairment leading to dysgraphia and speech alterations. Headache, confusion, seizures, and behavioural changes have also been reported. Endothelial activation and disruption of the blood-brain barrier is postulated to be involved in the pathogenesis. Treatment of CRS and ICANS is based on antipyretics, steroids, and IL-6 receptor blockade with tocilizumab.¹⁰ Fortunately, all reported adverse events associated with the use of CAR-T cell therapy in autoimmune diseases are usually low grade without any fatality because the burden of autoreactive cells in autoimmune diseases is substantially lower than the tumour cells in malignancies.

Innovations to improve the safety of CAR-T cell therapy

Traditional CAR-T cell therapy uses lentiviral or gammaretroviral vectors to introduce permanent genetic modifications to the T cells carrying genotoxicity risk and regulatory challenges and a potentially lifelong presence of CAR-T cells. mRNA-based CAR-T cell therapy offers an alternative strategy by delivering CAR-encoding mRNA into T cells without permanently altering their genomes. This approach allows for the transient, temporal restricted expression of CARs, providing a controlled and reversible therapy. The mRNA is typically delivered using lipid nanoparticles (LNPs) or electroporation techniques.¹¹

CD 19 targeted CAR-T cell therapies indiscriminately deplete all B cells and their use may be limited by the risk of infection. Precision therapies that target only autoreactive B lymphocytes without altering the normal B cells may provide an advantage of eliminating autoimmunity without compromising the protective immunity. Mog et al. described Chimeric Autoantigen-T Cell Receptor (CATCR)-T Cell Therapies to selectively target autoreactive B Cells. They demonstrated that autoantigen specific T cells can be engineered to identify and target anti beta-2 glycoprotein 1 (anti B2GP1) B cells in APS which are autoreactive without affecting normal B cells.¹²

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