Fact Sheet

National Scleroderma Foundation

Cell-therapy Q & A

The information below is provided by the Research Committee of the National Scleroderma Foundation's Medical & Scientific Advisory Board. While it reflects the latest published research, treatments using CAR-based therapies for autoimmune diseases are changing quickly. Because of this, patients who are thinking about CAR-based therapy should consult with a rheumatologist at a specialized scleroderma center. This will help them understand the potential benefits and risks of this new treatment based on their specific condition, disease course, and medical history.

Q. WHAT IS CAR-T OR CAR-NK CELL THERAPY AND HOW DO THEY WORK?

A. CAR-T and CAR-NK therapies are forms of cell-based treatments that use modified immune cells—either T-cells or Natural Killer (NK) cells—as trained "living drugs." In these treatments, immune cells are collected and then modified in a laboratory (ex vivo) to carry a special receptor called a Chimeric Antigen Receptor (CAR). This receptor helps the cells recognize and attack specific targets, such as CD19, a protein found on B-cells. B-cells are a type of immune cell that contribute to autoimmune diseases like systemic sclerosis (scleroderma).

The goal of CD19-CAR based therapy is to remove the harmful B-cells thought to drive the disease process. These modified immune cells are thought to reach deeper into tissues and eliminate "bad" cells more effectively than standard treatments, such as rituximab or mycophenolate.

Although several CAR-T therapies have been approved for certain blood cancers, CAR-T and CAR-NK therapies are not yet approved by regulatory agencies for treating autoimmune diseases. Early reports from small studies have shown promising results, but larger clinical trials are still needed to confirm how well these treatments work and to better understand their potential side effects.

Because these treatments have only been used in a limited number of patients with autoimmune diseases, it is important that studies are done at medical centers with expertise in both cell-based therapies and scleroderma care. This means the research should be a collaboration between rheumatologists who specialize in scleroderma and hematologists who are experts in cell-based treatments.

Q. ARE THERE DIFFERENT TYPES OF CAR-BASED CELL THERAPIES? IF SO, WHAT ARE THEY?

A. Cell therapies differ based on the type of immune cells used for treatment. The most common types use specially modified **T cells** or **Natural Killer (NK) cells.**

There are two main kinds of cell therapy: autologous and allogeneic.

- **Autologous therapy** uses your own immune cells. Your cells are collected through a blood draw, modified to express CAR in a laboratory, and then returned to your body. This process takes more time (typically 3-5 weeks) and is more expensive, but since the cells come from you, there's no risk of your body rejecting them.

- **Allogeneic therapy** uses cells from a healthy donor. These cells are prepared and modified in advance, so they can be ready for treatment more quickly. However, because they come from another person, there is a small risk your body may recognize them as "foreign" and react against them. This risk is generally lower with **allogeneic NK cell therapies** compared to **allogeneic T-cell** therapies.

Q. IS IT COVERED BY INSURANCE?

A. CAR-based treatments are not FDA approved for treatment of scleroderma and are not covered by insurance. These treatment modalities are costly and are typically only available as part of clinical trials. In clinical trials, the study sponsor (typically a pharmaceutical company) covers the cost for the CAR-based cell therapies.

Q. HOW DID CAR-T COME TO BE?

A. Cell-therapies were first developed for blood-based cancers. In lymphoma and in types of leukemia, a protein called CD19 is expressed on the surface of B cells. The B cells are the types of cells that become cancerous in B cell lymphomas and they express CD19. The strategy of using CAR-T cells targeting CD19 protein has been used successfully in treating B cells lymphomas in the past several years. There has also been increasing appreciation of the role B cells as drivers of autoimmune disease including rheumatoid arthritis, systemic lupus, myositis, certain forms of vasculitis, as well as systemic sclerosis (scleroderma). A number of lines of evidence looking at cell populations in the lungs and skin of patients with scleroderma, proteins expressed in the blood, as well as clinical trials with drugs targeting B cells, have suggested that targeting B cells may be a promising strategy in the treatment of scleroderma. For example, rituximab, a drug that targets a protein called CD20 (like CD19, also expressed on B cells) has been shown to be helpful for manifestations of scleroderma including skin and lung. CAR-T or CAR-NK therapies, therefore, became intriguing as a strategy to similarly target those B cells which express that CD19 protein, which has been targeted in lymphoma. Small case series already published the literature suggested this strategy to be potentially effective even in people with severe scleroderma. It is now being tested more methodically in larger clinical trials in scleroderma, as well as in other autoimmune diseases.

Q. WHO IS A CANDDIATE FOR TREATMENT (i.e. DISEASE DURATION, TYPOE OF SCLERODERMA, ETC.) AND WHERE IS IT OFFERED?

A. Clinical trials studying CAR-T and CAR-NK therapies for scleroderma are currently accepting patients with diffuse scleroderma and/or lung fibrosis—that is, individuals who have more widespread skin thickening and/or significant lung scarring (interstitial lung disease). In general, these studies are open to patients who have had scleroderma for seven years or less, starting from the time they developed symptoms other than Raynaud's phenomenon that confirm the diagnosis of scleroderma. ***Eligible patients are those whose disease is progressing—for example, worsening skin thickening, lung disease, or, in some cases, heart involvement—despite current treatments. Participants must have previously received one or more standard therapies (such as mycophenolate) without showing a significant improvement.*** In other words, these trials are designed for people with treatment-resistant (refractory) scleroderma. At this time, the trials are limited to adult participants and are not open to children.

Because CAR-T and CAR-NK therapies can carry serious risks, participants must also meet certain health criteria. Specifically, they must have adequate heart, lung, and kidney function to safely undergo treatment. At the present time, given the enormous expense of CAR therapies, its access is mostly through clinical trials, which are sponsored by pharmaceutical companies. The landscape is evolving but trials are ongoing or about to start in major medical centers and institutions throughout the United States, Europe, and Asia. *Considering the novelty of this treatment approach, it is*

important that the clinical trials are conducted in centers with substantial expertise in scleroderma care and cell-based therapies.

Q. HOW QUICKLY WILL A PERSON SEE IMPROVEMENT?

A. CAR-based therapies typically remove the targeted B cells within 1 to 3 weeks. However, the time it takes for patients with systemic sclerosis to notice clinical improvement is not yet well defined.

Based on the limited studies available:

- Skin fibrosis (thickening or hardening of the skin) often shows improvement within about 3 months.
- Lung fibrosis results are less clear. In most cases, patients experience stabilization of lung function rather than major improvement.

These findings highlight the need for larger, multicenter clinical trials at specialized scleroderma centers to better understand how CAR-based therapies affect both skin and lung disease. Such studies should ensure that skin assessments are performed by trained, experienced scleroderma specialists and that lung volume measurements are obtained using standardized methods.

Q. WHAT IS THE REGIMEN FOR PARTICIPATING IN A CAR-BASED CELL THERAPY TRIAL?

A. The treatment plan depends on whether you receive autologous (using your own cells) or allogeneic (using donor cells) therapy.

Autologous treatment: In autologous therapy, a sample of your blood is collected and sent to a specialized laboratory. There, your T-cells are modified to create CD19 CAR cells, which are designed to recognize and attack specific targets in your body. Before these modified cells are returned to you, you will receive strong immunosuppressive medications, such as cyclophosphamide and Fludarabine. This step, called conditioning, helps clear some of your existing immune cells to make room for the new CD19 CAR cells to grow and function properly. Once your body is ready, the modified CD19 CAR cells are infused back into your bloodstream, similar to a blood transfusion.

Allogeneic treatment: In allogeneic therapy, the CD19 CAR cells come from a healthy donor, so the manufacturing process is faster. However, you will still need a conditioning treatment with immunosuppressive medications to prepare your body to accept the donor cells. After this step, the donor CD19 CAR cells are infused into your bloodstream, just like in the autologous approach.

Monitoring and Follow-Up for autologous or allogenic treatment: After the conditioning and CAR-CD19 cell infusion, you will be closely monitored — either in the hospital or as an outpatient — for about 30 days. During this time, you are at a higher risk of infections and side effects from treatment. Your care will be managed by hematologists experienced in cell-based therapies.

After the initial recovery period, you will continue regular follow-up visits with your rheumatologist and hematologist to track your treatment response and watch for any long-term side effects. The frequency and duration of these visits depend on your specific treatment plan or study protocol.

Q. HOW MANY SCLERODERMA PATIENTS HAVE HAD CAR-T CELL THERAPY?

A. Based on published manuscripts or conference abstracts, 33 patients with systemic sclerosis have thus far been treated with CAR-T cell therapies as part of single-center clinical experience in Europe or multicenter clinical trials.

Q. DOES CAR-T WORK IN SOMEONE WHO IS IMMUNOGLOBULIN A-DEFICIENT?

A. At the moment, we do not have data about these patients for CAR-T treatment in cancers or autoimmunity. Some of the ongoing trials in autoimmunity are specifically excluding patients with primary immunodeficiencies and these patients might have been/be excluded in other trials that have some broad criteria. CAR-T treatment could theoretically work in somebody who is IgA deficient and for now IgA deficiency is not a contraindication to the treatment in cancer patients. However, there are additional potential risks for these patients to consider. CAR-based therapies lead to a reduction in immunoglobulins including IgA which are protective against infections. As CAR-cell treated patients have a higher risk of infection, IgA deficient patients might need to be more closely monitored for infections after the treatment. More importantly, if immunoglobulin replacement is needed before or after the CAR-T treatment to prevent infections, the risks of such immunoglobulin infusions are known to be higher in patients with IgA deficiency and special precautions need to be taken by providers if such infusions are needed. Of note, at the moment at least one trial, testing whether immunoglobulin replacement before CAR-T treatment can prevent infection, is excluding patients with IgA deficiency.

Q. THE FDA RECENTLY ISSUED A BOX WARNING ON CAR-T, DOES THIS RAISE CONCERNS ABOUT THE TREATMENT'S SAFETY?

A. The FDA has issued a boxed warning for CAR-T treatment of individuals with blood cancers to alert patients and healthcare providers about the potential for serious side effects. These may *include an increased risk of infection* due to immune suppression caused by CAR-T cells or the conditioning regimen; *systemic inflammation* known as cytokine release syndrome (CRS), which can cause high fever, flu-like symptoms, and low blood pressure; as well as *neurological side effects* called Immune Cell-Related Neurotoxicity (ICANS), which occur from temporary brain inflammation and may cause neurological symptoms, such as confusion or difficulty speaking. In very rare cases—about one in 1,000 to 2,000 patients treated for cancer—CAR-T therapy has been linked to the *development of new blood cancers*. While these side effects can be serious, most can be managed effectively when recognized early and treated promptly, which is why CAR therapies should be performed only at medical centers experienced in using these treatments.

When considering CAR-T therapy for scleroderma, it is important for patients and providers to carefully weigh these potential risks against the possible benefits. No current scleroderma treatment is completely free of side effects, and future research may show that the risks listed in the current boxed warning are lower for autoimmune diseases than for cancer. This could occur if treatment approaches for autoimmune diseases are potentially adjusted to use less intense immune suppression or lower numbers of CAR-T cells. As the field advances, new safety recommendations are expected from organizations such as the American College of Rheumatology and the FDA to guide the safe use of cell therapies in people living with autoimmune diseases based on the results of the currently ongoing clinical trials.

Q. CAN YOU BE A CANDIDATE FOR CAR-BASED CELL THERAPIES IF YOU HAVE HAD AN IMMUNOABLATION FOLLOWED BY STEM CELL TRANSPLANT IN THE PAST?

A. CAR-based therapies are considered experimental for scleroderma and are currently available in the United States only as part of a clinical trial. Each clinical trial has its own set of unique criteria that would permit a patient to qualify. In general, though, CAR-based trials are currently excluding patients who have had a stem cell transplant in the past. If CAR-based therapy looks safe and effective in clinical trials and gains an FDA approval for treating scleroderma, doctors will have more latitude to determine who would be an appropriate candidate. It is certainly possible that people with

scleroderma who have had a stem cell transplant might be eligible for CAR-based therapy at some point in the future.

Q. CAN YOU EXPLAIN WHY SOMEONE MAY BE A BETTER CANDIDATE FOR IMMUNOABLATION FOLLOWED BY STEM CELL TRANSPLANTATION OVER CAR-T AND VICE VERSA?

A. Immunoablation followed by stem cell transplantation has been demonstrated to be an effective treatment for scleroderma in randomized control clinical trials and is offered at some specialized scleroderma centers as part of the standard of care. Stem cell transplantation carries significant risks, though, including the risk of serious infections, cancer, and potentially death. Because of these risks, stem cell transplantation is usually restricted to people with the most severe cases of scleroderma who have experienced progression despite other standard-of-care treatments. At many centers, stem cell transplantation is offered only if someone has interstitial lung disease.

In contrast, CAR-based therapies have not yet been demonstrated to be safe and effective for scleroderma in clinical trials. CAR-based therapies are considered experimental rather than part of the standard of care.

Some people may be good candidates for CAR-based therapy but not stem cell transplantation and vice versa. For example, there are CAR-based trials that permit someone to enter if they have severe skin disease WITHOUT interstitial lung disease, whereas stem cell transplantation is typically restricted to those who have interstitial lung disease. This means that some people whose severe skin disease has failed to respond to standard of care therapy may be good candidates for a CAR-based trial but not for stem cell transplantation. Conversely, though, some people who do not meet the strict entry criteria for a CAR-based trial might consider stem cell transplantation. For example, most CAR-based trials are limiting enrollment to people who have had scleroderma for less than 7 years, whereas the treating team has more discretion over who would be appropriate for stem cell transplantation. Therefore, people with severe, progressive disease who have had scleroderma for longer than 7 years may be better candidates for stem cell transplantation than CAR-based therapy.

Both stem cell transplantation and a CAR-based trial can be excellent options to consider in the setting of progressive, severe scleroderma. However, both of these treatments involve considerable risk and should be only limited to patients who have not responded to conventional treatment such as mycophenolate. *If you are considering either stem cell transplantation or CAR-based therapy, it is best to be seen at a specialized scleroderma center that can help to walk you through your options.*

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