Review

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Treatment of pemphigus beyond rituximab: chimeric autoantibody receptor T cell (CAAR-T cell) therapy

Pemfigus tedavisinde rituksimabın ötesi: Kimerik otoantikor reseptör T hücre (CAAR-T hücre) tedavisi

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Abstract

Pemphigus vulgaris is a rare, life-threatening, autoimmune bullous disease. After decades of systemic corticosteroids and corticosteroid-sparing immunosuppressants being used to control the disease, the efficacy of rituximab has been shown in randomized controlled studies. Hence rituximab constitutes the first-line treatment for mild and moderate-to-severe pemphigus vulgaris according to the most recent European S2K guideline. Despite promising results with rituximab, there is still no disease-specific treatment available. In that regard, chimeric autoantibody receptor therapy (CAAR-T cell therapy) is under the spotlight utilizing a cutting-edge technology.

Key words: *pemphigus, chimeric autoantibody receptor therapy, cellular immunotherapy, CAAR-T cell therapy*

Öz

Pemfigus vulgaris, nadir görülen, hayatı tehdit eden bir otoimmün büllöz hastalıktır. Hastalığı kontrol etmek için uzun yıllar sistemik kortikosteroid ve adjuvan immünsüpresiflerin kullanılmasının ardından, randomize kontrollü çalışmalarla rituksimabın hastalıktaki etkinliği gösterildi. Böylece rituksimab en güncel Avrupa S2K kılavuzunda hafif ve orta-şiddetli pemfigus vulgarisin ilk sıra tedavi seçeneği olarak yerini aldı. Rituksimab ile her ne kadar umut verici yanıtlar elde edilse de, henüz hastalığa spesifik bir tedavi bulunmamaktadır. Bu bağlamda, en son teknoloji kullanılarak yapılan kimerik otoantikor reseptör tedavisi (CAAR-T hücre tedavisi) tüm ilgiyi üzerine toplamıştır.

Anahtar kelimeler: *pemfigus, kimerik otoantikor reseptör tedavisi, hücresel immünoterapi, CAAR-T hücre tedavisi*

Introduction

Pemphigus constitutes a group of rare autoimmune bullous diseases affecting mucous membranes and/or skin. The disease is accepted to be fatal in almost every case until the effect of systemic corticosteroids was shown.

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Although the number of randomized controlled trials comparing different regimes was limited, the corticosteroid-sparing agents (azathioprine, mycophenolate mofetil, intravenous immunoglobulin, etc) in conjunction with systemic corticosteroids constituted the most preferred first-line treatment of pemphigus by many experts.[1] Subsequently, rituximab was shown to be effective in various studies[2] and rituximab was shown to be more effective compared to systemic corticosteroids in terms of achieving complete remission off therapy (89% vs 34%, respectively) in a randomized clinical trial (Ritux 3).[3] Considering this novel advance, the Autoimmune Blistering Diseases Task Force of the European Academy of Dermatology and Venereology suggests two infusions of 1 g rituximab two weeks apart as the first-line therapy for the management of the mild and moderate to severe pemphigus vulgaris/foliaceus.[1] Rituximab is proposed to be given alone or in conjunction with systemic corticosteroids which are to be supposed in 3 to 4 months in mild disease, and in 6 months in moderate to severe pemphigus vulgaris/foliaceus.[1] For the maintenance, in patients with complete remission on/off therapy at month 6 who have a severe disease at the beginning and show a high level of anti-desmoglein antibody titer at month 3, an additional 500 mg or 1 g rituximab is advised to be given. In patients who fail to achieve complete remission on/off therapy at month 6, the initial regime, namely, two infusions of 1 g two weeks apart, are recommended. Following, at months 12 and 18, in patients with complete remission, particularly the ones with still high autoantibody levels, one infusion of 500 mg rituximab is advised to be given at each time point. Current evidence does not suffice to comment on management beyond 18 months.[1]

Rituximab in the treatment of pemphigus

B cells have a major role in adaptive immune response and autoimmunity since they give rise to autoantibody-producing plasma cells and generate $CD4^+$T cell response via antigen presentation. While the aforementioned functions are attributed to effector B cells, there are B cells with regulatory functions (B_{reg}) which secrete IL-10 and IL-35 and cause peripheral tolerance.[4] Autoreactive B cells transform into plasma cells which produce autoantibodies binding specific endogenous target antigens. Autoantibodies lead to immune complex formations and via their Fc part complement activation, which contributes to the disease pathogenesis in some autoimmune diseases such as SLE. Contrary to that, in pemphigus vulgaris, there is a predominance of IgG4 autoantibodies. IgG4 antibodies are widely known not to activate complement cascade and bind weakly to the Fc receptor.[5-8]

CD20 is a transmembrane glycoprotein expressed on the surface of B cells at various differentiation stages from pre-B cells to pre-plasma cells.[9] Of note, hematopoietic stem cells, early pre-B cells, short-lived plasmablasts and long-lived plasma cells lack this surface antigen (Fig. 1). B cells first develop in the bone marrow and then migrate to secondary lymphoid tissues (lymph nodes and spleen) where they maturate and after giving rise to antibody-producing plasma cells, they relocate to bone marrow. Plasma cells do not ex-

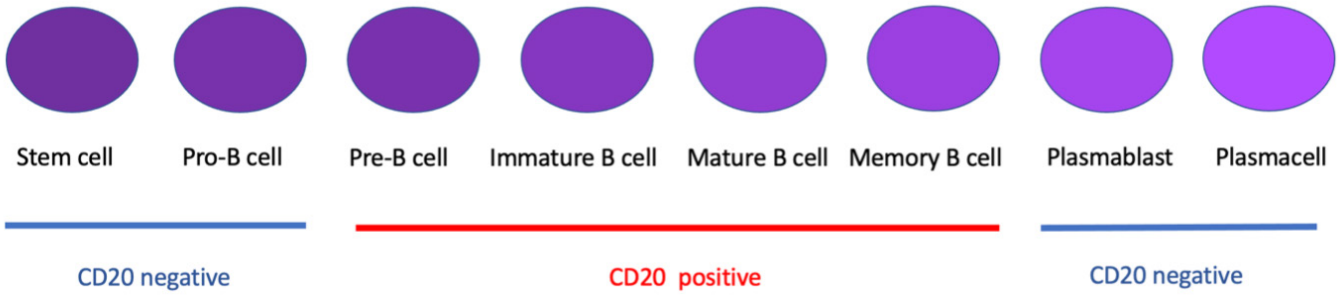

Fig. 1. B-cell lineage according to CD20 positivity

press common pan-B surface markers such as CD19 and CD20. The absence of CD20 renders them unrecognizable by rituximab.[5,7,8]

Rituximab exerts its effects mainly through the decrease of anti-desmoglein (anti-Dsg) autoantibodies. Studies show that patients in clinical remission had a decrease or a total absence of anti-Dsg-autoantibodies, while in disease relapse the autoantibody levels were detected higher or at least unaffected.[10,11] It is suggested that the incomplete depletion of B-cells locating in the bone and secondary lymph organs leads to the reappearance of the original disease-causing autoreactive B cell clones.[11]

There are a few arguments about the reasons behind the relapses after rituximab therapy. The first and the most supported reason to date is the residue B cell population in the bone marrow and secondary lymphoid organs.[12] Hammers et al. established the persistence of anti-Dsg3-B cell clones contributed to the rituximab relapse and newly derived clones are far to keep escaping from tolerance and unlikely to be causative of relapses.[13] Second one is the newly emerging autoreactive B cell clones after putative complete B cell depletion. Third, long-lived and short-lived plasma cells continue to produce autoantibodies. Since they are CD20 negative, they are spared from the effect of rituximab and able to survive after the infusions. Although they produce mainly IgG1-type autoantibodies and the IgG4 subgroup is the main cause of the disease, it can explain the elevated serum autoantibody titers among patients in clinical remission.[14]

Pemphigus vulgaris is a relatively well-understood autoimmune disease. With the introduction of rituximab, significant clinical improvement is achieved, and at the same time side effects of systemic corticosteroids and corticosteroid-sparing immunosuppressive agents are avoided. Nevertheless, taking into consideration the following broad immunosuppression, unresponsiveness to rituximab and that the drug is not appropriate for every patient, novel therapy options are sought. Among those, chimeric autoantibody-T (CAAR-T) cell therapy stands out with its cutting-edge technology and higher specificity.

CIR (chimeric immune receptor) therapy

Antigen-presenting cells (APC) interact with T cells via the formers major compatibility complexes which are determined by HLA class 2 genes. Once the antigen presentation to T cells is done, Dsg-specific $CD4^+$ T cells become able to polarize into either Th1, Th2 cells or Treg cells. Th2 cells produce IL-10 and IL-4 which results in IgG4 switching in B cells. Treg cells have a conflicting role by inhibiting the interaction between Th2 cells and B cells but also enhancing the Ig4 switch. Lastly, Th1 transformation leads to autoreactive Th2 cell inhibition via IFN-γ.

Regarding autoimmune diseases, it is mandatory to point out the interaction between B cells and T cells. B cells present antigen fragments to T cells and subsequently receive activator signals from T cells through cytokines and binding surface receptors and ligands. It is difficult to determine the initiating cell in this positive feedback loop.[9]

Chimeric immune receptors can be categorized into chimeric antigen receptors (CARs), B-cell antibody receptors (BARs) or chimeric autoantibody receptors (CAARs). As extracellular domains, CAR bears a monoclonal antibody called a single-chain variable fragment (scFv), while CAAR bears a specific antigen and if this antigen is a ligand of an autoreactive B cell's BCR, it is called BAR. Not only $CD8^+$ T effector cells but also $CD4^+$ T regulatory cells (Tregs) can be engineered to express CIR (chimeric immune receptor). Recently, natural killer cells (NK) were drawn to attention in this regard. Autoantibody- producing B cells can be targeted by CAAR-T cells, B-cell antibody receptor (BAR)-T $CD8^+$ cells and BAR-Tregs.[15] While CAR-Tregs suppress the auto-reactive T effector cell and indirectly rescue the normal cells from the detrimental properties of the autoreactive T effector cells

(Fig. 2), BAR-T cells exert its effects via killing the autoantibody-producing B cells.[15]

Based on the important roles of regulatory T cells in autoimmunity, developing CAR-Treg cells to down-regulate immunity against Dsg may bring new therapeutic insights. CAR-modified Tregs (CAR-Tregs) appear to be superior to TCR-Tregs which are engineered with

In 2016, MacDonald et al. developed HLA-A2-specific CAR-Treg which was shown to be superior to Tregs expressing an irrelevant CAR at preventing xenogeneic GvHD caused by HLA-A2$^+$ T cells.[18] Consistent with this study, Boardman et al. showed that in a human skin xenograft transplant model, adoptive transfer of CAR Tregs against donor MHC class I reduced the au-

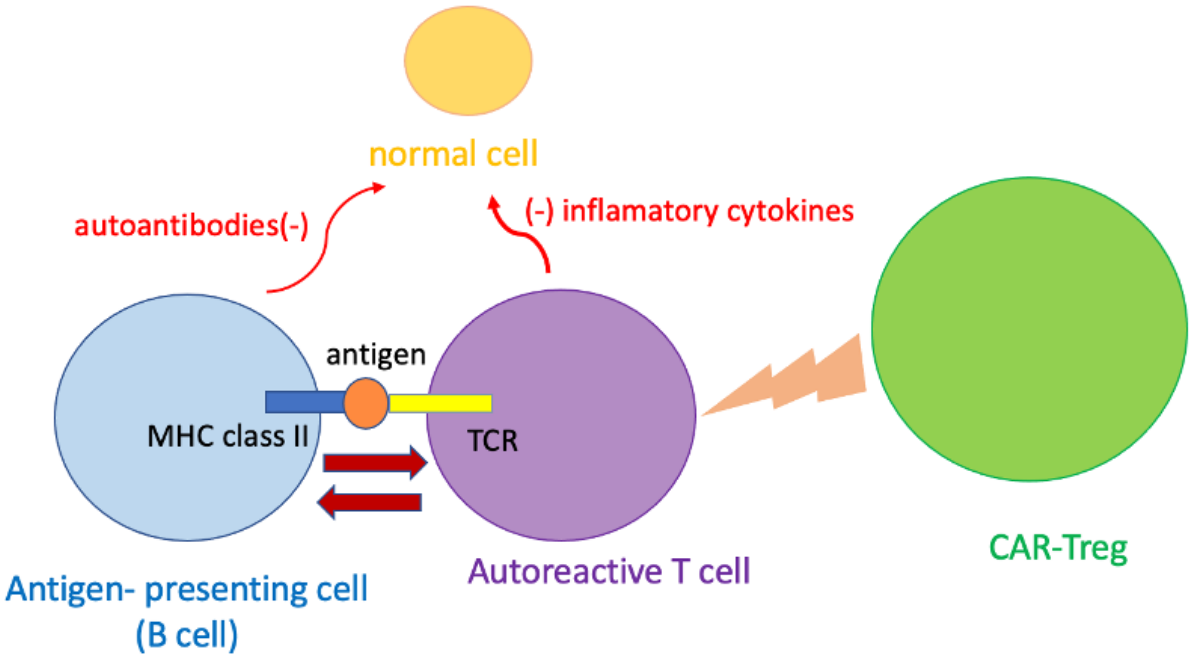

Fig. 2. Antigen-presenting cell (APC) presents the antigen (in orange) via MHC class II receptors to T cells. In the case of pemphigus vulgaris T cell may transform into Th2 cells which induces IgG4 production from autoreactive B cells. Suppression of autoreactive T cells may directly save the normal cells from the inflammatory cytokines produced by T cells and indirectly lead a decrease in autoantibody production.

TCRs owing to the former's non-MHC restricted formation and a lesser dependency on IL-2. Whether the cytokine storm observed with CAR-T cells also applies to CAR-Tregs is a matter of discussion, as well as possible Treg exhaustion.[16] In a murine experimental autoimmune encephalomyelitis model of multiple sclerosis, first CD4$^+$ T cells were engineered to express CAR targeting myelin oligodendrocyte glycoprotein (MOG) in trans with the murine FoxP3 gene that drives Treg differentiation. Finally, central nervous system targeting Tregs localized to the CNS diminished the disease symptoms as well as led to significantly decreased levels of IL-12 and IFN-gamma.[17]

toimmune-mediated skin injury more effectively than polyclonal Tregs without any toxicity. Interestingly, CAR-Tregs developed against HLA-A2 migrated to the tissues bearing the target alloantigen.[19]

TCR-engineered T effector cells (Teff) are designed to kill the target cell whereas TCR-engineered regulatory T (Treg) cells can either anergize, kill or protect target cells.[15] The main limitations of generating an antigen-specific immune response can be summarized as MHC-polymorphism, peptide antigens, unexpected combinations of TCRs and cross-recognition of irrelevant antigens by TCRs.[15]

While CAR-T CD8+ cells professionally kill tumor cells, application of CIR-T cell therapy for autoimmune disease is either direct protection of normal cells by CAR-Tregs, which suppress autoreactive T cells and/or indirect protection by BAR-T cells, which kills autoreactive B cell clones recognizing the specific BCR.

Producing autoantibodies against FVIII is a major problem for up to a third of hemophilia A patients who receive supplements. Accordingly, Zhang et al. developed BAR-Tregs which directly suppress the activity of autoantibody-producing B cell clones and indirectly suppress B cell functions following inhibition of autoreactive T effector cells which plays a key role in autoreactive B cell activation. Researchers observed a significant B cell tolerization while T cell response mainly remained unaffected, therefore it is speculated that the main autoantibody decreasing mechanism occurred due to the direct suppression of autoreactive B cell clones targeted by BAR-Tregs.[16]

CAR-T cell therapy

The efficacy of CAR-T-cell therapy has been shown first in otherwise untreatable hematologic malignancies.[20] In 2017, CAR-T-cell technology-based therapies targeting CD19, i.e. tisagenlecleucel and axicabtagene ciloleucel, has been approved by FDA for refractory/relapsed acute lymphoblastic leukemia and large B cell lymphoma, respectively. After displaying a durable and advanced therapeutic efficacy in patients with hematologic malignancies, in the treatment era of solid tumours including glioblastoma and melanoma and autoimmune diseases, a variety of clinical studies are conducted.[21,22]

Chimeric antigen receptors are artificial surface proteins that comprise three main domains 1) an extracellular domain consisting of a monoclonal antibody-derived single-chain variable fragment that recognizes a specific epitope 2) a transmembrane domain 3) an intracellular signaling domain. CARs are classified into three generations according to their intracellular domains. The intracellular domain can be categorized into three generations according to the existence of 1) a single T-cell-activation domain 2) an additional CD28 co-stimulatory region and 3) an additional 4-1BB co-stimulatory region to former parts, respectively (Fig. 3).[23] The first-generation CARs have a single intracellular signaling domain consisting of CD3ζ chain which is only capable of minimal killing due to the low-level activation of T cells. Second-generation CARs contain either 4-1BB or CD28 costimulatory

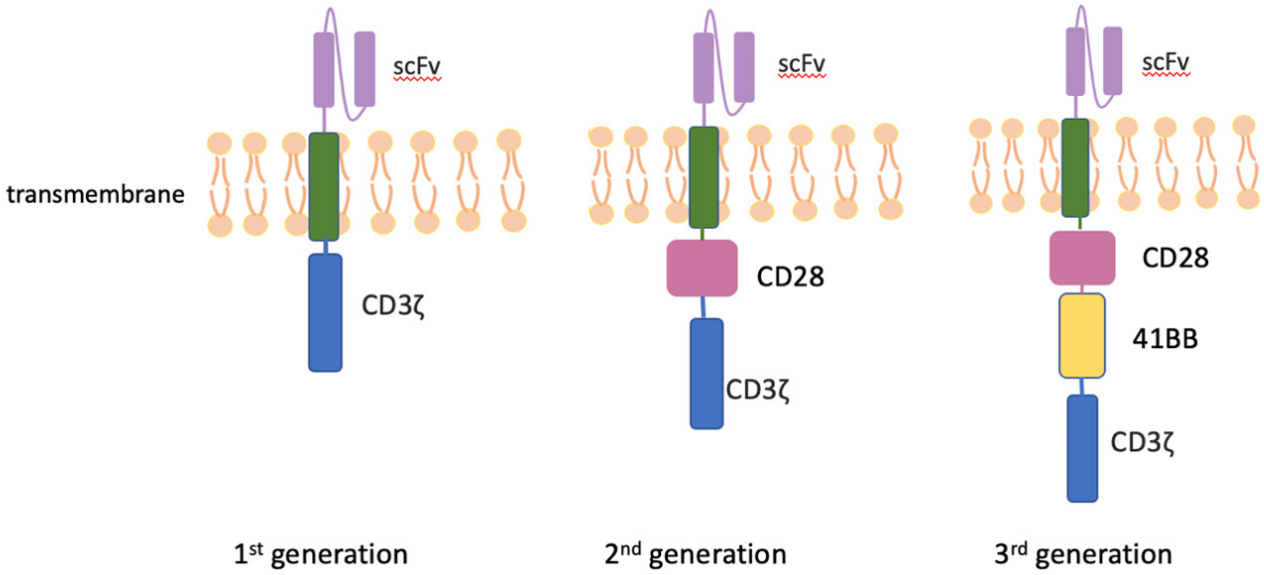

Fig. 3. Chimeric antigen receptors (CARs) are designed to have an extracellular single-chain variable fragment, a transmembrane domain and an intracellular activation domain. Intracellular activation domain varies in distinct generations of CARs.

moieties in addition to CD3ζ and the third generation is equipped with CD3ζ, 4-1BB and CD28 domains. The latter two generations express an advanced killing function.[23] Following antigen recognition, intracellular domains of CARs promote survival and proliferation signals to CAR-T cells.

The toxicities accompanying the therapy are of paramount importance. CAR-T cells prompt a high amount of inflammatory cytokines thus leading to cytokine release syndrome which can cause a fatal clinic characterized by capillary leak, severe hypotension/tachycardia and disseminated intravascular coagulation.[24] Moreover, in a case report, CAR-T cell associated Merkel cell carcinoma, unusual mononuclear cell dermal infiltrates, erythematous exanthema mimicking eruption of lymphocyte recovery and cutaneous infections have been described.[25]

The chimeric antigen receptor approach has also difficulties. First, the modulation of target antigens expressed by tumor cells rises as a challenge, forcing tumor cells to express essential antigens on their surface upon cytokine exposure, or developing next-generation CARs like universal cytokine-mediated killing (TRUCKs) and aromatic CAR-T cells are some of the suggested solutions for this problem.[15] On the other hand, immunogenicity developed against humanized-scFv was observed in patients with colorectal cancer.[26] To overcome this limitation designing the CIRs with ankyrin repair proteins (DAPRins) and adnectin was proposed.[27,28] The exogenous bispecific receptor tandem CAR (TanCAR) was developed to increase the specificity of killer activity[29] and the split, universal and programmable (SUPRA) CAR system was introduced to switch targets without reengineering T cells.[30] Furthermore, resistance mechanisms were identified in patients with multiple myeloma who had undergone anti-CD19 and anti-BCMA CAR-T cell therapies.[31]

In summary, to generate CAR-T cells, first CAR proteins need to be cloned into viral plasmids. After the cell lines such as HEK293 are transfected with these viral vectors, T cells of patients isolated by leukapheresis are incubated with these viral vectors to yield large amounts of plasmid-bearing CAR-RNA. Viral vectors enter the cells and their CAR-encoding RNA is reverse-transcribed and emerge into the patient's T-cell genome. Next, the CAR protein embedded in the patient's genome can be transcribed, translated, and located on the cell surface. Ultimately, these ex-vivo expanded CAR-T cells are reinfused to the patient.[23-25,32,33]

In 2016, Ellebrecht et al. innovated a CAAR (chimeric autoantibody receptor), whose extracellular domain consists of Dsg-3 fragments recognized by the BCR of Dsg-3-specific autoreactive B cells in vitro (Fig. 4).[33] The in vivo efficacy of Dsg3-CAAR-T-cells was exhibited PV hybrid models ie. AK23, AK19, AK18 hybridoma cells. Moreover, it is shown that anti-Dsg3 autoantibodies derived from patients' sera did not remove the CAAR-T cell activity. In murine models, CAAR-T-cells decreased pathogenic IgG antibody levels and the disease severity. In addition to these findings, Dsg3 BCR$^-$ cells were protected, as well as no Fc-mediated clearance of Dsg3-CAAR-T cells.[33]

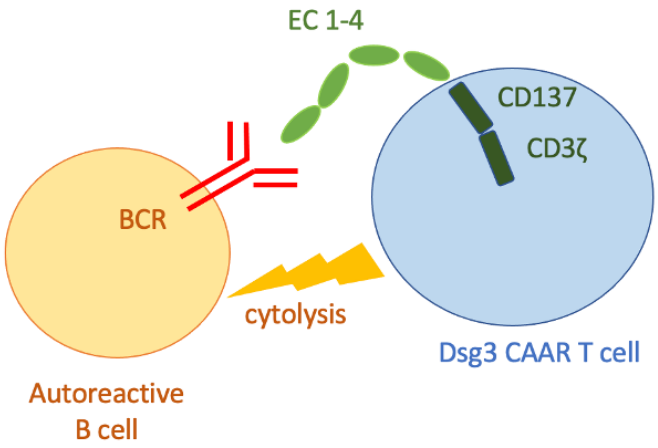

Fig. 4. Dsg3 CAAR-T cell which bears the extracellular domains 1-4 (EC 1-4) of desmoglein-3 recognizes the B-cell receptor (in the form of an immunoglobulin against desmoglein-3 epitopes) of an autoreactive B cell. The recognition results in cytolysis of the autoreactive B cell.

Of particular interest, B-cells having antibodies against distinct Dsg-3 epitopes were shown to be targeted by CAAR-T cells indicating that the efficacy of treatment has a range of oligoclonality. Whether the CAAR-T cells recognize and destruct the keratinocytes expressing desmogleins and desmocollins was a matter of debate. In contrast to the CAR-T cell therapies in hematologic malignancies, the researchers did not observe any significant off-target toxicity against keratinocytes. In addition to that, since Dsg-3 reactive B cells comprise a relatively small population of total B cell count, the tumor lysis and cytokine release syndrome, which have been observed in CAR-T cell-mediated therapies in hematologic malignancies, are unlikely to occur. Various combinations of CAARs could be combined to cover a range of distinct epitopes. Notably, in vivo CAAR-Ts were found to persist in the presence of soluble autoantibodies, suggesting that CAAR-Ts were not affected by Fc-mediated clearance due to the circulating autoantibodies.[33]

Another superiority of CAAR-T cell therapy over rituximab is the capability of targeting anti-Dsg3 memory B cells which give rise to Dsg-3-specific short-lived plasma cells. It is thought that the same anti-Dsg-3 B-cell clones derived from the $CD20^+$ memory B cells are the reason behind the relapse of the disease.[33] $CD20^+$ memory B cells become short-lived plasma cells which continue to secrete autoantibodies but lack $CD20^+$. Short-lived plasma cells account for one of the putative reasons behind rituximab resistance. As mentioned before, plasma cells lack pan-B surface markers such as CD19 and CD20 which render them unrecognizable by rituximab.[5,7,8] Interestingly, engraftment of CAAR-T cells was shown in the spleen 3 weeks after the transfer without existing target cells in that location.[33] Moreover, a part of CAAR-T cells gives rise to memory cells which were supposed to have control on the future clones of Dsg-3-reactive B cells and thus even a cure potential for the disease.[33]

As of December 2022, a phase 1, open-label, safety and dosing study of autologous Dsg3-CAART in patients with active, anti-Dsg3 positive, mucosal-dominant pemphigus is recruiting (NCT04422912).

In contrast to rituximab, which targets CD20 expressed on pre-and mature B-lymphocytes regardless of their clonality and results in pan immunosuppression, CAAR-Ts, which are loaded with autoantigen Dsg3 and specifically target B-cells, provides antigen-specific immunomodulation.

It has been shown that T cells targeting various epitopes are incorporated in pemphigus pathogenesis. $CD4^+$ T cells promote B-cells to secrete anti-desmoglein autoantibodies. Rituximab has also immunosuppressive effects on antigen-specific T cells without affecting overall T-cell count and function.[10]

Although CAAR-T cell therapy offers more specific abolishment of B-cell in comparison to rituximab, short-lived plasma cells are off the target in both therapies. Short-lived plasma cells can only be indirectly eliminated via CAAR-T-cells, whereby the memory B cells, which will ultimately give rise to short-lived plasma cells, are killed by CAAR-T cells. Hence, relapses can be expected. Further studies are required urgently to identify the short-lived and long-lived plasma cells. Since short-lived plasma cells can be easily found in the circulation and are mainly responsible for the autoantibody persistence in IgG4-mediated pemphigus vulgaris, they are under the spot for further characterization.

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Drafting the manuscript or revising the content: HEA

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