CAR T cells targeting CD19 for the treatment of ANCA vasculitis

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Abstract

Autoimmune ANCA-associated vasculitis (AAV) and glomerulonephritis is characterized by the presence of autoantibodies (so-called ANCA = anti-neutrophil cytoplasmic autoantibodies), which, by binding to the body's own antigens, lead to damaged blood vessels (vasculitis) and subsequently to organ damage, particularly of the kidneys. The primary endogenous antigens are the enzymes proteinase 3 (PR3) and myeloperoxidase (MPO) expressed by neutrophil granulocytes and monocytes. In addition to the autoantibodies, both T-cellular response to those autoantigens and monocyte/macrophage-mediated processes play a decisive role. Since conventional therapy is based on the widespread suppression of the immune system, susceptibility to infections or the development of cancer are possible side effects. Furthermore, not all patients respond to conventional therapy or despite responding first suffer multiple relapses. Therefore, there is a need for alternative treatment strategies and one promising option is the use of CD19-targeting CAR-T cells.

DISEASE

In AAV failure of the immune systems leads to the development of antibodies recognizing endogenous antigens namely the enzymes proteinase 3 (PR3) and myeloperoxidase (MPO)[1–3] As these antigens are expressed by both neutrophil granulocytes and monocytes and are mainly located in the cytoplasm the autoantibodies are called anti-neutrophil cytoplasmic autoantibodies (ANCA). AAV is classified in Granulomatosis with Polyangiitis (GPA), Microscopic Polyangiitis (MPA) and eosinophilic Granulomatosis with Polyangiitis (eGPA). For the first two, clinical, epidemiologic, genetic, and experimental evidence suggests that ANCA serotype (MPO-ANCA versus PR3-ANCA) may determine distinct but overlapping clinical and pathologic features of ANCA vasculitis: PR3-ANCA is associated with a higher prevalence of ophthalmologic and Ear, Nose, and Throat symptoms, an increased risk of relapse and a better response to rituximab-based induction therapy. In contrast, MPO-ANCA is associated with an increased frequency of renal involvement, the development of chronic kidney disease and pulmonary fibrosis.[4–10] In addition, candidate gene approaches and large genome-wide association studies have revealed heterogeneous genetic

backgrounds in which different regions of human leukocyte antigens with different polymorphisms were affected, as well as SERPINA1 and PRTN3 genes.[11,12] In vitro, too, there are fundamental differences in the activation of myeloid cells by PR3-ANCA or MPO-ANCA, as well as differences in the cytokine pattern induced by stimulation with the respective ANCA subtype.[13,14]

At the cellular level, the antigens are translocated to the membrane of the granulocytes and monocytes through a subliminal pre-activation, known as priming, and thus become accessible to the ANCA circulating in the blood. ANCA can bind to the exposed antigens and activate the affected cells via various signaling cascades. This neutrophil and monocyte activation leads to degranulation of toxic granula-proteins, generation of reactive oxygen species and formation of neutrophil extracellular traps (NETs).[15–18] In addition to these cells of the innate immune system, antigen-specific B and T cells also play an essential role in the formation of ANCA. $CD4^+$ T cells and MPO itself (released by activated neutrophils) were detected within lesions in glomeruli, so it is assumed that MPO-specific $CD4^+$ T cells can support autoreactive B cells directly on site in the production of autoantibodies. Those further increase neutrophil activation resulting in enhanced tissue damage.[19,20] In addition to their role as ANCA producers, B cells act as antigen-presenting cells, secrete pro-inflammatory and immunoregulatory cytokines, and are involved in the formation of lymphatic structures in affected organs.[21,22] How important these further tasks of B cells are shows the efficacy of rituximab-application in responsive patients despite persisting (although reduced) ANCA-levels.[23] Furthermore, activation of the complement system turned out to play a crucial role as well.[24] The final stage of the cascade is the destruction of the vascular system, which primarily affects the lungs and kidneys. This can lead to irreversible loss of organ function with life-threatening organ failure and the need for organ replacement therapy such as ventilation or dialysis.

The treatment of AAV is currently based on aggressive and rather non-specific immunosuppression. Treatment regimens consist of two phases, remission induction and remission maintenance. The aim of remission induction is to end disease activity as quickly as possible in the acute phase in order to restore organ function and prevent further loss of function and thus, for example, subsequent dialysis dependency. For this purpose, high doses of glucocorticoids are used in combination with either cytotoxic substances (cyclophosphamide) or B cell depleting antibodies (rituximab). Repeated doses of either cyclophosphamide or rituximab are administered over several weeks. In particularly life-threatening cases, there is also the option of plasma exchange, however there is an ongoing debate regarding its role.[27,28] Once the disease activity has come in remission, remission maintenance therapy is usually carried out for at least 2-3 years. Depending on the individual risk and initial therapy, patients receive either a different oral chemotherapeutic agent (azathioprine) or 6-monthly infusions of rituximab.[29] These regimens bring disease activity to a halt within 90 days in approximately 70 - 90 % of patients. Despite maintenance therapy, 8 - 60 % of patients develop a relapse of the disease within the first 2 years.[30] Mortality in the first year after diagnosis is approximately 12 % and is about 2.6 times higher compared to healthy controls.[31] It should be noted that 48 % of deaths in the first year in particular are due to infections, i.e. side effects of immunosuppressive therapy, and only 19 % are due to the AAV itself.[26] Rituximab, although highly effective in depleting circulating B cells, is partly inefficient in induction therapy of AAV because it does not fully eliminate the pathogenic immune mechanisms driving acute inflammation. Long-lived plasma cells, which are resistant to CD20-targeted depletion, continue to produce ANCAs and

sustain autoantibody-mediated neutrophil activation. In addition, tissue-resident B cells are only inefficiently depleted, further limiting its efficacy.

Novel CD20 antibodies such as obinutuzumab represent a promising extension of B-cell–targeted therapy in ANCA-associated vasculitis (AAV). Unlike rituximab, obinutuzumab is a type II glycoengineered CD20 antibody with enhanced antibody-dependent cellular cytotoxicity (ADCC) and reduced complement activation, leading to deeper and more sustained B-cell depletion. Early clinical reports suggest that obinutuzumab may achieve more complete depletion of pathogenic B cells, including in patients who are refractory to rituximab, and may provide longer remission intervals. Importantly, its distinct mechanism could offer advantages in reducing relapse risk and in patients who develop anti-rituximab antibodies.[32] ObiVas as a randomized, phase II, double-blind, study comparing obinutuzumab versus rituximab will test this hypothesis.[33]

The complement system—once considered marginal in ANCA-associated vasculitis (AAV)—is now recognized as a key driver of the disease's pathogenesis. Specifically, the alternative complement pathway is activated by ANCA-stimulated neutrophils, which release factors that lead to the generation of C5a, a potent chemoattractant and primer of neutrophils.[35] This C5a-driven feedback loop amplifies inflammation, promoting neutrophil recruitment and vascular injury.[24] Therapeutically, the C5a receptor antagonist avacopan targets this axis to mitigate neutrophil priming and inflammation, representing a novel and effective treatment modality in AAV.[36,37]

Finally, T cell engagers are an emerging class of immunotherapies that redirect cytotoxic T cells toward specific immune targets through bispecific antibody formats, typically linking CD3 on T cells to a disease-driving antigen. In autoimmune diseases, this approach is being adapted to eliminate autoreactive B cells or plasma cells by targeting markers such as CD19, CD20, or BCMA, thereby reducing pathogenic autoantibody production.[34] Unlike conventional B-cell–depleting agents, T cell engagers may provide faster and more selective immune clearance, with the potential to reset dysregulated immune networks. However, their use in autoimmunity is still experimental.

Therefore, there is still a great need for more specific therapeutic approaches with fewer side effects. For these reasons, research into additional novel therapeutic strategies is essential. One promising approach for difficult to treat AAV-patients has emerged recently – CD19-targeting CAR-T cells.

CD19 CAR-T CELLS

Chimeric Antigen Receptor (CAR)-T cell

The CAR is an engineered hybrid antigen receptor that combines the ability of B cell derived antibodies to bind unprocessed antigens and the feature of activated T cells to kill bound cells. The CAR redirects T cells toward cells or tissues expressing the antigen of interest and empowers the T cells to recognize surface antigens in an MHC-independent manner. The so-called first-generation CARs consist of an intracellular CD3ζ-derived signalling domain connected via a transmembrane and hinge domain to an extracellular antibody single chain fragment (scFv) recognizing the antigen of interest. Further development led to second generation CARs with an additional intracellular co-stimulatory domain

which improves activation and proliferation of the T cell while reduces susceptibility to immunosuppression. This latter effect is caused by increased NF-κB activation from the more strongly activated T cells. NF-κB-signaling counteracts inhibitory cytokine responses and regulatory T cell-induced proliferation-suppression. Widely used co-stimulatory domains derive from CD28, CD134 (OX40) or CD137 (4-1BB).[38–42] Meanwhile, third, fourth and fifth generation CARs exist with a wide variety of construct composition, e.g. different co-stimulatory domains, included chemokines or intracellular cytokine receptor domains as well as bispecific antigen binding domains or tandem CAR design.[43–45]

Therapeutical applications of CAR-T cells

In order to administer autologous CAR-T cells to patients, sufficient T cells must first be collected from them using leukapheresis. This requires that immunosuppressive drugs be reduced or discontinued completely approximately two weeks beforehand, so that the T cell population can recover sufficiently. The then collected cells are activated in vitro, genetically modified to express the CAR construct, expanded and then administered to the patient. To ensure that the CAR-T cells have a niche in which to implant, the patient must first undergo lymphodepletion. In most cases, a combination of cyclophosphamide and fludarabine is used for this purpose.

Application in autoimmune diseases: Systemic lupus erythematosus

In autoimmune diseases (AIDs) patients fail in proper differentiating of own and foreign. Therefore, B cells start to produce antibodies against autoantigens. Long-term elimination of the autoantibody-producing B cells or plasma cells would interrupt the pathologic cycle. Hence, usage of CD19 CAR-T cells seemed a promising approach. In preclinical studies using the NZB × NZW and MRL-lpr mouse models of the autoimmune lupus disease, CD19-targeting murine CAR-T cell-based therapies eliminated CD19-expressing B cells and attenuated the disease.[56] Furthermore, these CD19 CAR-T cells remained functional for months and removed transferred autologous $CD19^+$ B cells without harming other B cell populations.

For the first time in 2021, CD19 targeting human CAR-T cells have been successfully used to treat a patient with refractory systemic lupus erythematosus (SLE).[57] The results were verified in 5 additional patients in 2022.[58] Meanwhile, follow-up data of 8 SLE patients are published, showing still ongoing remission after 6 to 29 months post CD19 CAR-T cell-application.[59] In the same manuscript positive effects of CD19-targeting CAR-T cells in idiopathic inflammatory myositis and systemic sclerosis were described lasting at least for 4 to 18 months. This underscores the applicability of CD19 CAR-T cells in a wide AID spectrum. Recently, a phase 1 clinical trial in 11 SLE patients with lupus nephritis analyzed the safety and efficacy of a BCMA-CD19 compound CAR (cCAR), that leads to the expression of both single CARs in a T cell. By that, B cells and plasma cells were addressed simultaneously, which expands the effect to multiple antibody-producing cell populations. All patients had reduced symptom severity including decreased SLE Disease Activity Index 2000 (SLEDAI-2K) score, less proteinuria and increased estimated glomerular filtration rates. The therapy was well tolerated, only mild side effects (grade 1 cytokine release syndrome, mild fever) occurred.[60] The application has since been extended to pediatric patients. For example, in two twelve-year-old females CD19 CAR-T cells lead to highly decreased disease activity.[61] Those

mentioned above and other published studies[62,63] show that CD19 CAR-T cells could be a promising treatment option for patients who do not respond sufficiently to other treatment strategies.

Application in autoimmune diseases: wide range

CD19-targeting CAR-T cells were meanwhile used in a broad range of AIDs. Case reports of its successful application in multiple sclerosis,[64] myasthenia gravis,[65] Sjogren's disease,[66] idiopathic inflammatory myopathies,[67,68] systemic sclerosis,[69,70] rheumatoid arthritis,[71,72] and antiphospholipid antibody syndrome[73,74] were published. This list is for sure incomplete and is used to demonstrate the effectiveness of CD19 CAR-T cells in the autoimmune area. The application of the method has since been expanded to ANCA-associated vasculitis which is the main focus of this manuscript.

Application in autoimmune diseases: ANCA-associated vasculitis (AAV)

Experimental preclinical data

In a preclinical study of anti-MPO IgG-induced necrotizing crescentic glomerulonephritis (NCGN) CD19-targeting CAR-T cells were tested for their ability to reduce disease progression. In this disease model, MPO-knockout mice are immunized with MPO and subsequently produce antibodies against MPO. They are then irradiated, followed by injection of bone marrow cells from wild-type donor animals. The applied wild-type neutrophils and monocytes contain MPO and thus the antigen to which the anti-MPO antibodies of the recipient mice bind, thereby triggering the disease process. A CAR construct with a single chain fragment variable of an anti-CD19 antibody (clone 1D3), an IgG1 spacer, a CD4 transmembrane domain, an intracellular CD28 costimulatory domain and a CD3ζ activation domain was developed. Together with the wild-type bone marrow 2×10^6CAR T cells were applied and mice were analyzed 2, 5, and 8 weeks after cell transfer. CD19-targeting CAR-T cells and SP6 control CAR-T cells were detectable throughout the entire experimental period in lymphoid organs and the kidney. Mice that received CD19 CAR-T cells had near-complete B cell depletion, a significantly reduced number of plasmablasts and were protected from development of NCGN.[75] These results were fundamental for the translation to the human application.

Application in human AAV

Since now there are three publications dealing with CD19 CAR-T cells in AAV patients. Minopoulou et al. presented treatment results of a 52-year-old male patient with severe therapy-refractory PR3-ANCA-positive granulomatosis with polyangiitis (GPA). Despite taking various medications including cyclophosphamide, rituximab, azathioprine, mycophenolate mofetil, and methotrexate relapses could not be prevented and affected lungs, kidneys, joints, skin, sinonasal tract and eyes. Additionally, chronic damage occurred as optic atrophy, pulmonary fibrosis, elevated diastolic blood pressure, cutaneous ulcerations, and peripheral neuropathy. The patient presented again with fever, weight loss, myalgia, arthralgia, exertional dyspnoea, productive cough, new granulomatous formation, and elevated PR3-ANCA level. Rituximab infusion lead to improved exertional dyspnea and weight stabilization but myalgia, arthralgia and elevated ANCA levels remained unaffected.

Therefore, administration of CD19-targeting CAR-T cells was decided. Therapy resulted reduction of radiological findings (granuloma), fast decrease of PR3-ANCA level (undetectable at day 28 after CAR-T cell administration), no occurrence of arthralgia or myalgia, no new AAV-related symptoms up to the most recent follow-up (day 132), absence of $CD19^+$ B cells or CD19low PCs in the bone marrow biopsy 48 days after anti-CD19 CAR-T cell infusion. Circulating $CD19^+$ and $CD20^+$ B cells stayed undetectable until the last day of follow-up. IgG levels were detected within normal limits, vaccination titers (anti-Rubella, -Tetanus, -Varicella) remained stable. The patient experienced cytokine release syndrome (CRS) grade 1 and neutropenia grade 3, which were appropriately managed with tocilizumab and filgrastim, respectively. No immune effector cell-associated neurotoxicity syndrome, infections, or other therapy-related toxicities occurred.[76]

Treatment effects of a second patient were described by Uhlmann et al. who applied CD19-targeting CAR-T cells to a 40-year-old male patient with GPA with persistent severe pulmonary inflammatory lesions despite rituximab, cyclophosphamide, cyclosporin A, avacopan and prednisolone administrations. Four months after CAR-T cell infusion almost complete resolution of inflammatory activity in the lung was reached. Prednisolone dosage could be reduced from 10 mg per day before CAR-T cells to 2 mg per day after CAR-T cells without significant increases in CRP or PR3-ANCA levels. The patient did not develop CRS or immune effector cell-associated neurotoxicity syndrome (ICANS). A temporary leukopenia occurred for 14 days without subsequent hematologic toxicity. Follow-up at publishing was ~~18~~300 days, until then no B cell recovery occurred.[77]

Schultze-Florey et al. report about a 64-year-old Caucasian male with refractory MPO-positive AAV with kidney involvement. The patient got prednisolone, rituximab, cyclophosphamide, mycophenolic acid and avacopan. Nevertheless, MPO titer stayed elevated, crescentic glomerulonephritis was still active and BVAS was at 10. Application of CD19-targeting CAR-T cells was well-tolerated. The MPO-titer decreased, kidney function was stabilized, proteinuria dropped by 87%, no signs of hematuria were detectable, and BVAS decreased to 0 during the 6-week follow-up. Leukocytes recovered 18 days, absolute lymphocyte counts 25 days after CAR-T cell-treatment, B cell aplasia remained until end of follow-up.[78]

All three publications show a positive effect of CD19 CAR-T cell treatment. For a better overview, main facts are summarized in table 1.

Table 1. Summary of publications regarding CD19 CAR-T cell-usage in AAV.

	Minopoulou et al.[76]	Uhlmann et al.[77]	Schultze-Florey et al.[78]
Disease	Anti-PR3 ANCA GPA	Anti-PR3 ANCA GPA	Anti-MPO ANCA AAV
Patient	Male, 52 years	Male, 40 years	Male, 64 years
Affected organs	Lung, kidneys, joints, skin, sinonasal tract, eyes	Lung, none further mentioned	Kidneys, none further mentioned
Therapies before CAR-T cell therapy	CYC, RTX, azathioprine, MMF, methotrexate	CYC, RTX, CsA, avacopan, prednisolone	CYC, RTX, mycophenolic acid, avacopan, prednisolone
Disease activity before CAR-T cell therapy	Myalgia, arthralgia, BVAS 2*, elevated PR3-ANCA levels at 90 AU/ml, 0.00001/µl CD19+ B cells in peripheral blood	Lung: unresolved nodules, cavitary lesion in left lower lobe, heightened glucose metabolism, total lung capacity 76.0% Ref, forced vital capacity 60.2% Blood: normalized ANCA-level, near-complete B cell depletion General: BVAS 8/33	Elevated MPO titer, ongoing crescentic GN, BVAS 10
Lymphodepletion before CAR-T cell application	300mg/m² CYC + 30mg/m² fludarabine daily on days -5, -4, -3	300mg/m² CYC + 30mg/m² fludarabine daily on days -5, -4, -3	CYC + fludarabine (no further details)
CD19 CAR-T product	KYV-101, $1*10^8$ CAR-T cells	KYV-101, $1*10^8$ CAR-T cells/kg of body weight	Autologous, anti-CD19 CAR-T cells generated on site (Cellular Therapy Center GMP-Unit, CliniMACS Prodigy system (Miltenyi Biotec))
Immunosuppression during CAR-T cell therapy	RTX ceased 24 days, avacopan 7 days before leukapheresis	Prednisolone 10 mg daily	Avacopan
Side effects	CRS grade 1, neutropenia grade 3	Transient leukopenia	None mentioned
Follow-up time	132 days	300 days	6 weeks
Outcome	Granulomas remained stable, BVAS 0, VDI score of 5, no new AAV-related symptoms, persisting B-cell aplasia CAR T cells detectable at low amount (peak at day 14)	Lung: almost no inflammatory activity, improvement in total lung capacity (85.6% Ref) & forced vital capacity (72.6%) Blood: persisting B-cell aplasia General: improvements in physical fitness and quality of life, BVAS 0/33	Decreased MPO-titer, stable kidney function, reduced proteinuria (87%), reversal of hematuria, BVAS 0, persisting B-cell aplasia CAR T cells detectable at low amount (peak at day 10)

		CAR T cells still detectable (peak at day 9)	
Follow-up therapy	Cessation of immunosuppressive treatment	Prednisolone tapered to 2 mg/d	Avacopan

* BVAS version 2; CYC, cyclophosphamide; CsA, cyclosporin A; GN, glomerulonephritis; MMF, mycophenolate mofetil; RTX, rituximab

Usage of CD19 CAR-T cells in AAV is mentioned in an array of reviews concerning this therapeutic option in AIDs in general.[40,79–84] Data are so far only available in the above described publications but several studies have been registered on ClinicalTrials.gov that deal with the use of CD19 CAR-T cells in AAV (Table 2), so further data can be expected. It is noticeable that allogeneic cells are used in most studies. Some of their advantages and challenges are addressed below.

Table 2. CD19 CAR-T applying studies in AAV registered on ClinicalTrials.gov by 25th of August 2025.

NCT number	Study status	Conditions	CAR T-cells	Cellular resource	Age (years)	Phase (Interventional studies)	Start	Country
NCT06941129	Recruiting	AAV, SLE, SSc, IM	UCAR T-cell (universal anti-CD19/BCMA CAR-T cells)	Allogeneic	≥ 18	1	11.02.2025	China
NCT06508346	Recruiting	AAV	anti-CD19-CAR-T cells	Autologous	5-25	Observational study	01.08.2024	China
NCT06828042	Recruiting	AAV, SLE, SSc, IM, SjS, APS	QH103 (universal anti-CD19-CAR-γδT cells)	Allogeneic	18-80	1, 2	01.07.2025	China
NCT07033299	Not yet recruiting	AAV	CT1192 (universal CD19/20 CAR-T cells)	Allogeneic	18-60	1	01.07.2025	China
NCT06821659	Not yet recruiting	AAV, SLE, SSc, IM, SjS	UWD-CD19 (universial anti-CD19-CAR-T cells)	Allogeneic	18-80	1, 2	01.03.2025	China
NCT06986018	Not yet recruiting	AAV, IIM	RD06-04 (universial anti-CD19-CAR-T cells)	Allogeneic	18-70	Early 1	14.06.2025	China
NCT06775912	Recruiting	AAV, SLE, SSc, IIM, NMOSD, MS, MG	RD06-05 (anti-CD19/BCMA-CAR-T cells)	Not mentioned	18-70	Early 1	15.01.2025	China
NCT06462144	Recruiting	AAV, SLE, IIM	IMPT-514 (anti-CD19/CD20 CAR-T Cells)	Autologous	18-75	Early 1	13.06.2024	China
NCT06308978	Recruiting	AAV, SLE, SSc, IIM	FT819 (anti-CD19 CAR-T cells)	Allogeneic	12-70	1	28.03.2024	USA

APS, Antiphospholipid Syndrome; IIM, Idiopathic Inflammatory Myopathies; IM, inflammatory myopathy; MG, Myasthenia gravis; MS, multiple sclerosis; NMOSD, Neuromyelitis optica spectrum disorder; SLE, systemic lupus erythematosus, SjS, Sjogren's Syndrome, SSc, systemic sclerosis

Side effects

The side effects are best described in B cell malignancies, as the CD19 CAR-T cell therapy has been approved and used for the longest time there. One common complication is the susceptibility to infections caused by immunosuppression. A systematic study by Hill et al. found that 23% of patients (133 patients were analyzed, 47 with acute lymphoblastic leukemia, 24 with chronic lymphocytic leukemia, and 62 with non-Hodgkin lymphoma) suffered an infection within 4 weeks after CAR-T cell application, first infection was detected a median of 6 days (range: 1–27 days) after CAR-T cell infusion; 80% of the first infections occurred within the first 10 days. For five patients it was life-threatening or fatal. The severity of cytokine release syndrome (CRS) was associated with the occurrence of an infection in those patients. The median time to onset of CRS was 2 days before infection, and only 3 patients had infection preceding CRS. The median time to onset of CRS and first infection was 1.9 and 6 days, respectively.[85]

CRS and immune effector cell-associated neurotoxicity syndrome (ICANS), as well as movement disorders, immune effector cell-associated haematotoxicity (ICAHT) and immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) are meanwhile known as common side effects that should be considered.[86] CRS itself amplifies infection risk indirectly, mainly via immune dysregulation, mucosal barrier injury, and immunosuppressive therapy used for CRS control.

Furthermore, acute kidney injury (AKI) was reported to appear in 34% of patients with hematologic diseases (acute lymphoblastic leukemia, diffuse large B cell lymphoma, myeloma) after CD19 CAR-T cell therapy. Severity of CRS and elevated lactate dehydrogenase levels were associated with AKI occurrence.[87] A retrospective study by Gutgarts et al. reported a similar incidence (30% of any grade AKI) and subdivided into grade 1 AKI (incidence of 21.7%) and grade 2-3 AKI (incidence of 8.7%). No renal replacement was necessary.[88] Rousseau and Zafrani reviewed publications of diverse hematologic malignancies and reported AKI incidences between 2.3% and 46% which are associated with high-grade CRS, a prior autologous or allogeneic stem cell transplantation and admission to the intensive care unit.[89]

In AIDs (SLE, idiopathic inflammatory myopathies, systemic sclerosis, Sjogren's disease, rheumatoid arthritis, antiphospholipid antibody syndrome) data of the first patients let suggest that CRS and ICANS appear quite often but mainly mild.[90,91] CRS severity was reported to correlate with tumor burden[47], therefore, it can be assumed that the appearance of lower-grade CRS is due to a lower number of B cells compared to B cell malignancies that are lysed by CAR-T cells. Severe infections, hypogammaglobulinaemia and cytopenia occurred in some patients. No case of cancer was reported so far.[90,91] It remains to be seen whether additional side effects will be detected with the treatment of more patients and whether further adverse events will occur after a longer observation period.

Table 3. Side effects of CD19 CAR-T cell-therapy in autoimmune diseases. Exemplary list for various AIDs mentioned in this publication. For a better comparison, side effects in AAV-patients already stated in table 1 are listed again here.

Disease, number of patients	**CRS grade (number of patients)**	**treatment**	**ICANS grade (number of patients)**	**treatment**	**Infections (number of patients)**	**Additional side effects**	**treatment**
Kattamuri, L. et al[90]							
SLE, 51	1 (43)	Tocilizumab (3 of 43)	None	None	Non-fatal (10)	NR	NR
Ssc, 16	Mild (9)	None	None	None	None	NR	NR
RA, 2	Mild (2)	NR	None	None	None	NR	NR
IIM, 7	1 (5), 2 (1)	Tocilizumab (3 of 5, one not reported)	1 (2)	Anakinra (1)	(1)	NR	NR
APS, 2	1 (2)	NR	NR (1)	Methylprednisolone (1)	NR	NR	NR
SS, 1	2 (1)	Tocilizumab	NR (1)	Pulsed steroids	NR	Severe cytopentia (1)	Bone marrow stimulans
Scherlinger, M. et al.[91]							
AID (18): SLE (8), SSc (6), IIM (4)	1 (13), > 1 (1)	Tocilizumab (6) Azathioprine + MMF (1)	1 (1)	Glucocorticoid	Several (most upper respiratory tract), mostly mild, 3 to ≥ 12 months after treatment	Hypogammaglobulinaemia (5, 2 of them previously existing because of RTX)	IgG substitution (2)
Lidar, M. et al.[72]							
RA (1)	3 (1)	Tocilizumab	4 (1)	Anakinra + high dose corticosteroids (1)	NR	NR	NR
Zhang, Y. et al.[92]							
MG (1)	None	None	None	None	Mild infections (conjunctivitis and upper respiratory tract) within one month after treatment	symptomatic treatment	None
Minopoulou, I. et al.[76]							
AAV (1)	1 (1)	Tocilizumab	None	None	None	Neutropenia	Filgrastim
Uhlmann, L. et al.[77]							
AAV (1)	None	None	None	None	None	Leukocytopenia	NR
Schultze-Florey, C. R. et al.[78]							
AAV (1)	NR	NR	NR	NR	NR	NR	NR

MMF, mycophenolate mofetil; NR, not reported

LIMITATIONS, POSSIBLE RESOLUTIONS, FUTURE DIRECTIONS

Despite already promising results from first CD19-targeting CAR-T cell-therapies in AIDs and especially in AAV further research is invested in improving therapeutic strategies.

One issue is the absence of expression of CD19 on (auto)antibody-producing plasma cells which makes them unattackable by CD19-targeting CAR-T cells. First attempts were done using B-cell maturation antigen (BCMA) on the surface of long-lived plasma cells as a target. BCMA-CD19 compound CAR-T cells were applied in SLE patients to affect short- and long-lived antibody-

producing cells at once to overcome that problem.[60,63,93] Others applied CD138-targeting CAR-T cells to affect plasma cells in multiple myeloma.[94] Its usage in AIDs could be an additional route. A combination of CD19 CAR-T cells and anti-CD38 antibodies is also conceivable as both were already reported to be effective alone[59,95,96] and could work synergistically in patients with insufficient therapy response.

Antigen escape should be considered as well. This phenomenon occurs when CAR-T cells are unable to bind to their target cells because the antigen is either absent or not recognized for various reasons, e.g. its epitopes are masked by other proteins, it has a mutated or alternatively spliced variant of the antigen, or antigen processing is disrupted, to name just a few of the reasons that have been identified and discussed to date. These cells survive and can proliferate and antigen escape is already described as a cause of relapse of B-cell malignancies after treatment with CD19 CAR-T cells.[97] It might be countered by using two different CARs simultaneously or further compound CAR variants besides the already applied CD19 and BCMA compound. Another possibility was described by Choi et al. who designed a bicistronic construct that coded for a CAR and a secretable bispecific T-cell engager (BiTE) at once.[98] Their work aims to combat heterogeneous glioblastoma in which antigen escape occurs as well. The BiTE is a tandem single chain variable fragment (scFv) that binds with one scFv CD3 at T cells and with the other scFv an antigen at the target cell. By that it recruits T cells and increases cytotoxicity as not only the target cells of the CAR are attacked (binds to the mutated glioblastoma-specific tumor antigen) but as well the unmutated antigen-version that is expressed by a portion of the heterogenous tumor cells and by normal tissue.

T cell engagers (TCE), including BiTEs, that bind B and T cells simultaneously via CD19 or CD20 and CD3, respectively, are already approved for B cell malignancies. Successful application in AIDs seems highly probable, as, like CAR-T cells, they bring their target cells into contact with T cells, thereby inducing cytotoxic effects of the T cells.[99] Their advantages compared to CAR-T cells are faster applicability as they can be used immediately but autologous CAR-T cell-production needs up to six weeks from leukapheresis to infusion, lower production costs as they can be produced in larger quantities and easier administration as they can be injected like other routine monoclonal antibodies. No preconditioning of the patient is necessary but, at least in cancer patients, pre-medication to avoid CRS.[99] To overcome the time delay caused by CAR-T cell production, intensive research is being conducted into the use of allogeneic CAR-T cell (table 2). This approach eliminates the need for leukapheresis and enables the method to be used even in patients who, due to previous immunosuppressive treatments, have too few T cells for autologous CAR-T cell generation. Also, the faster start of treatment would reduce bridging medication and disease progression. Various options are being researched to circumvent graft-versus-host disease (GvHD) and host-versus-graft response (HvGR) that are possible side effects of allogenic cell application. For example genetic deletion of the T cell receptor α chain to prevent donor T cells from attacking host cells or using yδ T cells which function independent of HLA proteins or natural killer T cells instead of the more frequently occurring and GvHD-inducing $\alpha\beta$ T cells have been applied.[100,101]

Finally, when it comes to the advantages of CAR therapy, the ability of CAR-T cells to migrate to lymphoid and target organs must be mentioned first and foremost. This enables profound depletion of B cells including organ-resident ones and is probably a reason for the effectiveness of the therapy in patients who have not responded or have responded inadequately to conventional therapy.[58,64,102] Second, a large proportion of publications dealing with CAR-T therapy in AIDs report long-term

remission (as long-term data are already available), which makes it possible to discontinue or significantly reduce additional medication.[58,59,67,68,70–72,74,102,103] These remarkable results demonstrate the great potential of CAR-T cell-therapy to prevent disease relapses and to significantly improve patients' quality of life.

High costs are considered as a disadvantage of the therapy which limits its applicability. They are quoted at between US$350,000[100] and US$500,000[82] or £300,000.[99] Including the additional costs for lymphodepletion, leukapheresis and treatment of side effects, it can rise to approximately US$800,000.[104] Antibody-based therapies are significantly cheaper. TCE treatment, for example, is reported with $56,000.[99] However, considering that this treatment option is intended for patients who are multiply refractory and have already undergone various courses of treatment and would continue to do so, or for whom there would otherwise be no other option, the costs are put into perspective by the fact that it is usually only administered once. Further cost reduction is expected through the use of allogeneic T cells, which were already mentioned above.

Acknowledgements

The topic of this Review was also presented during the 62nd Congress of the European Renal Association in Vienna on June 4-7, 2025.

Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

Conflict of interest statement

None declared.

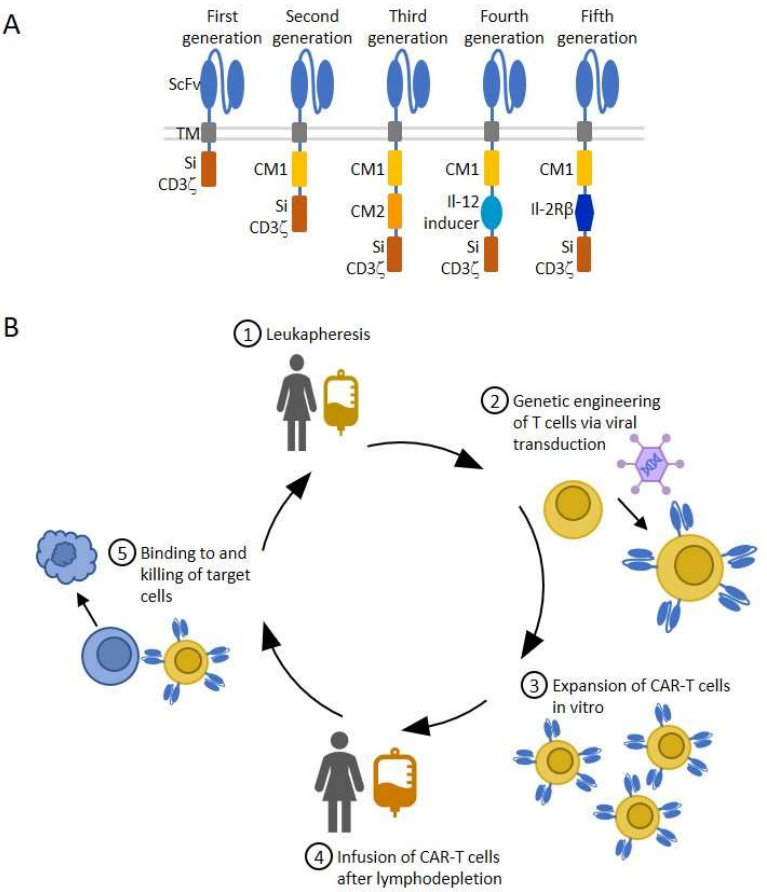

Figure 1. CAR-T cell composition, therapy and current development efforts. **(A)** First generation CAR constructs were composed of an extracellular antibody-derived domain (single chain variable fragment, scFv), a transmembrane domain (TM) and an intracellular signaling domain originating from the CD3 zeta chain (Si CD3ζ). In second generation CARs a co-stimulatory domain derived often from CD28 or 4-1BB was added, in third generation CARs a second one derived from OX40 or CD27 or others. Fourth generation contained additionally a cytokine-inducing protein and finally, fifth generation constructs included a signaling-influencing domain e.g. Il-2Rβ or PD-L1.[43,44,50,105] **(B)** Scheme representing the manufacturing steps involved in CAR-T cell therapy. **(C)** Examples for broaden the applicability, increasing the safety and raise specificity of CAR constructs are listed.[106–114]

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