ABSTRACT
Autoimmune disorders occur when immune cells go wrong and attack the body's own tissues. Currently, autoimmune disorders are largely treated by broad immunosuppressive agents and blocking antibodies, which can manage the diseases but often are not curative. Thus, there is an urgent need for advanced therapies for patients suffering from severe and refractory autoimmune diseases, and researchers have considered cell therapy as potentially curative approach for several decades. In the wake of its success in cancer therapy, adoptive transfer of engineered T cells modified with chimeric antigen receptors (CAR) for target recognition could now become a therapeutic option for some autoimmune diseases. Here, we review the ongoing developments with CAR T cells in the field of autoimmune disorders. We will cover first clinical results of applying anti-CD19 and anti-B cell maturation antigen CAR T cells for B cell elimination in systemic lupus erythematosus, refractory antisynthetase syndrome and myasthenia gravis, respectively. Furthermore, in preclinical models, researchers have also developed chimeric autoantibody receptor T cells that can eliminate individual B cell clones producing specific autoantibodies, and regulatory CAR T cells that do not eliminate autoreactive immune cells but dampen their wrong activation. Finally, we will address safety and manufacturing aspects for CAR T cells and discuss mRNA technologies and automation concepts for ensuring the future availability of safe and efficient CAR T cell products.

CELL THERAPIES IN AUTOIMMUNE DISEASES: CURRENT NEEDS AND CONCEPTS
Autoimmune disorders encompass a wide range of diseases characterised by intricate pathologies. These conditions arise when the body's own immune cells, specifically autoreactive B and T cells, initiate aberrant attacks on the body's own tissues through various effector mechanisms. Although very heterogeneous in their characterisation and symptoms, autoimmune diseases typically arise from a combination of genetic predisposition and environmental cofactors. Due to an often rather limited understanding and/or the complex nature of underlying molecular mechanisms, current standard approaches to treat diseases such as systemic lupus erythematosus (SLE), multiple sclerosis, type I diabetes mellitus (T1DM), psoriatic arthritis, and rheumatoid arthritis typically focus on managing diseases instead of offering cure. Therefore, the main concept to treat autoimmune disease remains to prevent autoreactive immune cells from attacking host tissues by broad (and mostly non-targeted) immunosuppressive agents especially glucocorticoids and non-steroidal anti-inflammatory drugs. Additionally, detrimental immune cells can be more specifically blocked by therapeutic antibodies targeting B cells (by eg, anti-CD20 (Rituximab) or anti-BAFF (Belimumab) antibodies), T cells (by eg, anti-CD52 antibodies (alemtuzumab) and proinflammatory cytokines (eg, anti-TNF antibodies (infliximab)) or by small molecules that mainly act on B and T cell signalling and thus function by blocking intracellular pathways (eg, cyclosporine A or mycophenolate mofetil). Another, more drastic option is to
‘reset’ the patient’s immune system or to transplant a ‘new’ third-party immune system by an autologous or allogeneic haematopoietic cell transplantation (HCT), respectively. However, this can come at the expenses of an increased treatment-related mortality, such as severe cytopenic infections and graft-versus-host-diseases in case of allogeneic HCT and in autologous HCT the resetting may only be transient.² To date, for many autoimmune diseases, there is no definitive cure available and new treatment options are needed.

Cell therapy for targeting autoreactive immune cells is increasingly being considered as potentially curative approach in a range of autoimmune diseases. Overall, there are two concepts for cell therapy of autoimmune diseases: (a) eliminating and (b) dampening autoreactive immune cells (figure 1). The first one is ‘aggressive’ and relates to advances in B cell depleting therapies³ and to the successful treatment of haematological malignancies by adoptive transfer of chimeric antigen receptor (CAR)-modified T cells.⁴ The latter is based on the usage of tolerance-inducing cell types such as regulatory T cells (Tregs) including CAR Tregs, tolerogenic dendritic cells (DCs) and mesenchymal stromal cells (MSC), which restore self-tolerance through different mechanistic routes.⁵

In cancer medicine, harnessing the capacity of the patient’s own immune system to recognise and eliminate malignant cells has become a true breakthrough. Here, T cells are genetically modified ex vivo to express biosynthetic immune receptors that mediate binding to and lysis of cancer cells.⁶ The CD19 antigen expressed by B cell-derived malignancies (lymphoma and leukaemia) was the first clinically applicable target for cancer immunotherapy using autologous CAR T cells.

Figure 1  
Adoptive immune cell therapy using autologous chimeric antigen receptor (CAR) T cells for autoimmune diseases. (A) Elimination of autoreactive B cells can be achieved by using CAR T effector cells directed against B cell markers such as CD19 resulting in a broad depletion of B cells. (B) To tailor B cell depletion, researchers have developed precision targeting of specific pathogenic B cell subpopulations that express autoantibodies to known autoantigens on their cell surface, a technology called chimeric autoantibody receptor (CAAR) T cells. (C) An alternative strategy to elimination of autoreactive cells is to dampen their activity by CAR-modified T regulatory cells (Tregs).
Treatmet with T cells genetically equipped with CARs against CD19 (anti-CD19 CAR T) has led to impressive remission rates in patients with relapsed/refractory B cell malignancies and today six CAR T cell products are authorised and clinically implemented for cancer immunotherapy (targeting either CD19 or B cell maturation antigen (BCMA)).

**ELIMINATING AUTOACTIVE B CELLS BY CAR AND CHIMERIC AUTOANTIBODY RECEPTOR T CELLS**

Inspired by the success in cancer medicine, CAR T cells are now increasingly studied for diseases beyond cancer. In fact, the most advanced progress with applying CAR T cells against non-malignant diseases currently occurs in the field of autoimmune diseases. SLE is a severe and potentially life-threatening disease with central involvement of autoantibodies-producing B cells, which lead to a progressive tissue destruction due to the deposition of immune complexes. Therefore, depletion of CD19+ B cells through the use of anti-CD19 CAR T cells has emerged as a potential treatment approach for SLE. In preclinical SLE models, anti-CD19 CAR T cells depleted B cells, suppressed autoantibody production and strongly prevented or reduced SLE disease features. Moreover, clinical translation of this strategy is well on track as a few patients with SLE have been already treated with anti-CD19 CAR T cells in an experimental clinical setting based on a German exception scheme for critically ill patients. In these first five refractory patients with SLE, the infused CAR T cells peaked at around day 10 before they rapidly declined in the peripheral blood, similar to what has been observed in patients with cancer. Strikingly, at 3 months after CAR T cell infusion, complete remission rate (according to DORIS criteria) was 100% and even months later relapses have not been reported. This is in particular interesting as CD19+B cells are fully depleted immediately from the peripheral blood after the CAR T cell infusion but did return after approximately 110 days post-treatment. However, the reappearance of B cells was mainly of IgM subtype and memory B cells appeared very low in number indicating a ‘reset’ of the B cell compartment and potentially the long-term depletion of the autoreactive B cells clones. Further, no relevant toxicity especially in terms of cytokine release syndrome and/or neurotoxicity were observed in the treated SLE patients.

In the next step, these impressive yet individual results must be validated on the basis of a larger number of SLE patients with appropriate study design and biometric planning as well as powered primary and secondary endpoints. In addition, it will be vital to learn if the short persistence of CAR T cells in the peripheral blood will be sufficient in the long term. Therefore, several clinical trials for testing B cell elimination in patients with SLE through CAR T cell therapy have been registered around the world and started the recruiting process (using both autologous anti-CD19 and anti-BCMA CAR T cells). This important translational step showcases the potential of CAR T cell-mediated (deep) B cell elimination in B cell-driven autoimmunity, and conceivably, there will be more autoimmune diseases investigated. Indeed, in two recent independent clinical case reports, researchers demonstrated the potential efficacy of anti-CD19 CAR T cell therapy in patients with refractory antisyntetase syndrome, a form of myopathy caused by autoantibodies against tRNA synthetases. In one report, the administration of CD19-targeting CAR T cell therapy, combined with mycophenolate mofetil, proved to be safe and resulted in both clinical and serological remission in the patient. This patient’s condition had previously been unresponsive to existing treatments, including rituximab and azathioprine. In the second report, a 41-year-old man markedly improved in physical function according to all International Myositis Assessment and Clinical Studies Group core set measures after a short worsening due to cytokine release syndrome. Also, here, a clinical trial is in the recruitment phase. Furthermore, a patient with systemic sclerosis mediated by autoantibodies was successfully treated by application of anti-CD19 CAR T cells, again only minimal toxicity was observed.

Although CAR T cell therapy for B cell-driven refractory autoimmune diseases is still in its infancy, these early clinical results show promises for patients. Therefore, it is likely that CAR T cell products developed for cancer therapy will also be evaluated in autoimmune diseases. A summary of registered clinical trials using different CAR T cell types for the treatment of SLE and other autoimmune diseases is shown in table 1. In the future, it will be interesting how anti-CD19 and anti-BCMA CAR T cell therapy outcomes compare to each other as anti-BCMA CAR T cells can also target mature plasma cells, which can secrete autoantibodies and be refractory to immuno-suppressive agents.

Despite the significant successes observed in the use of anti-CD19/anti-BCMA CAR T cells for cancer and SLE, it is important to note that these strategies result in the depletion of all B cells. As a consequence, B cells are absent for several weeks (to months), rendering patients immunocompromised during this period. To overcome such broad B cell depletion, researchers are also developing precision targeting of specific pathogenic B cell subpopulations that express autoantibodies to known autoantigens on their cell surface. Here, the therapeutic T cells get genetically modified with a chimeric receptor containing the target antigen of the autoantibodies as extracellular domain instead of a single-chain variable fragment specific against an antigen. Such ‘reverse-engineered’ T cells are also known as chimeric autoantibody receptor (CAAR) T cells. For example, CAAR T cells have been generated for tackling pemphigus vulgaris (PV), a rare skin-blistering disease that is caused by autoantibodies against desmoglein 1 and 3 (DSG1/3). These two DSG proteins mediate cell-to-cell contacts (desmosomes) in the skin and disruption of DSG-based cell-cell adhesion by anti-DSG autoantibodies lead to the...
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SUPPRESSING AUTOACTIVE CELLS BY CAR TREGS

In contrast to the CAR T cell strategy, which is based on elimination of the pathogenic cell population, a targeted tolerance-promoting immunotherapy might represent a milder therapeutic approach. Harnessing the immunomodulatory potential of cells such as MSC, DC and Tregs aims at a systemic immune regulation that may also include suppressing autoreactive cells rather than their depletion. The procedure consists of isolating, expanding and reinfusing the patient’s polyclonal tolerogenic immune cells in high numbers, so that they dampen the immune system including the autoreactive cells responsible for the diseases. For Tregs, their potential in tolerogenic immunotherapy has been investigated in many preclinical and clinical studies for several decades. Taken together, all these studies have shown that the autologus Treg approach alone is not effective enough and clinical approvals are missing. Therefore, researchers are trying to improve the precision of Tregs by tailoring their accuracy, that is, making them artificially antigen-specific using the CAR technology. For CAR modification, Tregs are separated from T effector cells by selecting the CD25+/FoxP3+ fraction and, just as with conventional CAR T cells, genetically modified for recognising a specific antigen before they go back into the patient. In a pioneering proof-of-principle study, researchers have engineered CAR Tregs specifically targeting carcinoembryonic antigen (CEA) for potential application in ulcerative colitis (UC), a chronic inflammatory disorder of the colon. These anti-CEA CAR Tregs home to the colon in CEA-transgenic mice and specifically suppress colitis symptoms in different experimental UC models. In fact, this effect is not specific to the pathogenic immune cell population itself but rather specific to the affected (colon) tissue, where a bystander suppression of infiltrating pathogenic immune cells occurs. The strategy of customising CAR Tregs for autoimmune conditions is employed in the same manner in preclinical T1DM and encephalomyelitis (EM) models. Here, CAR Tregs directed against insulin and myelin oligodendrocyte glycoprotein were transferred. However, using CAR Tregs to target antigens that can be tumour-associated, such as CEA, bears the risk that the CAR Tregs will also induce immune tolerance in CEA-specific T effector cells thus promoting tumour immune escape. In this regard, it has recently been shown that CAR Tregs, which were generated as a by-product during anti-CD19 CAR T cell manufacturing, are associated with worse clinical outcomes in patients with cancer.

To the best of our knowledge, approaches with CAR Tregs for treatment of autoimmune diseases have not been tested in clinical studies yet. However, there are two clinical trials registered with CAR Tregs that are similarly inducing immunological tolerance, but in a different setting, which is solid organ transplantation. Here, the idea is that Tregs are directed by a CAR receptor to human leucocyte antigen (HLA) antigens present on...
the donated organ and thereby can induce immunotolerance and suppress organ rejection.27 Both clinical trials in kidney and liver transplantation are using CAR Tregs that recognise HLA-A2.

TRANSIENT CAR T CELLS FOR SAFE THERAPY IN AUTOIMMUNE DISEASES?

Transient mRNA-based CAR T cell therapy has emerged as a promising approach for the treatment of autoimmune diseases. 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. Since the safety bar for autoimmune trials will be set very high, likely higher than for cancer, 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 (figure 2). The mRNA is typically delivered using lipid nanoparticles (LNPs) or electroporation techniques.

A novel mRNA-based CAR T approach for the treatment of fibrosis in cardiac disease was recently presented by Rurik and coworkers.30 They propose the use of CAR-mRNA delivered through LNPs to generate transient anti-fibrotic CAR T cells in vivo. The efficacy of this approach was evaluated in a mouse model of heart failure by directly injecting CD5-targeted LNPs. The study showed efficient in vivo delivery of mRNA to T cells, resulting in the generation of transient and effective CAR T cells. Treatment with CD5-targeted mRNA-LNPs reduced fibrosis and restored cardiac function, suggesting the potential of in vivo CAR T cell generation as a therapeutic platform for various diseases.30 The technological advancement of in vivo delivery could result in significant savings in terms of personnel, equipment and potentially financial burden, without the need for GMP laboratories for CAR T cell manufacture.

The first clinical application of mRNA-based CAR T cells was directed against BCMA to treat myasthenia gravis.31 The MG-001 Study Team conducted a prospective, multicentre, open-label, phase 1b/2a study and treated 14 patients by electroporated mRNA-based anti-BCMA CAR T cells without lymphodepleting chemotherapy. The
follow-up was 3–9 months and the treatment appeared to be safe, was well tolerated and caused a clinically meaningful decrease on myasthenia gravis severity, highlighting the clinical relevance of mRNA-CAR T cells as potential new treatment approach for myasthenia gravis and other autoimmune diseases.

The advantages of transient mRNA-based CAR T cell therapy for autoimmune diseases include the ability to fine-tune the duration and intensity of CAR expression, reduced risk of off-target effects and the potential for repeated administration if necessary (figure 2). Although the permanent downregulation of certain cell types such as B cells in case of anti-CD19/anti-BCMA-CAR T cells results in per se well tolerable hypogammaglobulinaemia, which can be reconstituted by intravenous or subcutaneous IgG application, patients with permanent B cell depletion showed increased risks of infections and, for example, had an inferior outcome when diagnosed with COVID-19. Downregulation of CD4+ T cells, a central driver in several autoimmune diseases, by CD4-directed CAR immune cells as used in preclinical studies is even more severe, since it leads (similar to HIV infection) to impairment of cellular immunity and opportunistic infections, making the transient CAR T approach even more attractive.

Despite the promising results of mRNA-based CAR T cell therapy, there are still challenges to overcome. Optimising the delivery methods, enhancing the stability and longevity of mRNA in T cells, and ensuring effective targeting of autoantigens are areas of active research. Additionally, issues such as potential immune responses against the CAR T cells, the need for precise dosing and timing of treatment as well as the set-up of GMP-conform manufacturing of the respective LNPs require further investigation.

**OUTLOOK: ENSURING THE AVAILABILITY OF CAR T CELL PRODUCTS**

CAR T cell therapy is on its way to become an approved clinical option for severe refractory autoimmune disease within the next few years. Similarly, there are more non-malignant diseases for which CAR T cell therapy is considered a potential therapeutic option, with convincing preclinical data in fibrosis, in particular. Notably, in patients with cancer, CAR T cell therapy has shown advantageous outcomes as compared with standard therapy already in second-line treatments. Even though only a few autoimmune diseases will likely be treated by CAR T cell therapy, it is important to keep in mind that many more patients are affected by autoimmunity than by cancer. Therefore, with the range of approved clinical therapies growing continuously, the overall number of eligible patients for CAR T cell therapy is increasing, too. These great developments in the area of translational medicine put pressure on the CAR T cell community, which additionally is fueled by the extremely high costs of autologous CAR T cells bringing a dramatic burden to healthcare systems and to society as a whole. Taken together, new biological concepts and manufacturing technologies are needed to further drive the wave of success CAR T cell therapy is currently on. In our opinion, important options with high potential to ensure the availability CAR cell products are automation of production, optimised production processes and allogeneic off-the-shelf products.

Currently, automated manufacture of CAR T cells is more and more becoming a real-world scenario with many smart bioreactor technologies entering the market. These automation devices perform many steps of the CAR T cell manufacturing in a closed system and, in principle, enable a decentralised production of CAR T cells. In fact, several academic centres are already performing decentralised manufacturing of CAR T cells for early clinical trials. However, the actual potential to cut costs by automated manufacture still needs to be determined. Even though there have been intensive debates on how to properly calculate the cost of decentralised CAR T cell manufacturing, it seems obvious, that costs will be lower the more products can be produced in one facility. Indeed, McCoy et al. modelled different levels of automation used during CAR T cell production and their analysis showed a reduction in the cost of manufacturing by up to 30% depending on the automation level. Yet, more careful all-encompassing analyses and discussions are required to address and confirm the potential of automation for not only providing a higher throughput but also reduced costs. A second possibility to improve CAR T cell production, is the optimisation of the good manufacturing practice (GMP) processes and the investigation of parameters such as media composition, raw materials including the patient cells and manufacturing time. Major research efforts, for example, have made it possible to shorten the complex manufacturing process for CAR T cells from about 14 days to 2–3 days.

Finally, a very promising innovation is allogeneic CAR immunotherapy. Here, instead of using autologous patient material, cells from healthy donors serve as source material for CAR T cell production and clinical trials with allogeneic CAR T and CAR NK cells have been performed already within the cancer field — and the first trial for autoimmune diseases using universal CAR T started recently (table 1). Using allogenic CAR cells will bring the advantage that the possibility of generating autoreactive CAR T cells is excluded, as T cells are centrally involved in many autoimmune diseases.

In summary, CAR T cell therapy is a potential therapeutic option for severe autoimmune diseases such as SLE and several clinical case reports using anti-CD19 CAR T cells are already published. In the near future, planned and started clinical trials will show if the therapy will become an approved treatment. If so, this will further accelerate the interest in developing CAR T cells for other autoimmune disorders on the one hand, and the need to advance manufacturing concepts for producing clinical-grade CAR T cells at high scale on the other hand.
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