cells

MDPI

Review

Targeted Cellular Treatment of Systemic Lupus Erythematosus

Panagiotis Athanassiou [1,*], Lambros Athanassiou [2], Ifigenia Kostoglou-Athanassiou [3] and Yehuda Shoenfeld [4]

[1] Department of Rheumatology, St. Paul's Hospital, 55134 Thessaloniki, Greece
[2] Department of Rheumatology, Asclepeion Hospital, Voula, 16673 Athens, Greece; lambros.ath@gmail.com
[3] Department of Endocrinology, Asclepeion Hospital, Voula, 16673 Athens, Greece; ikostoglouathanassiou@yahoo.gr
[4] Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Reichman University, Herzliya 4610101, Israel; yehuda.shoenfeld@sheba.health.gov.il
* Correspondence: pathanassiou@yahoo.gr; Tel.: +30-694-475-7675

Abstract: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease affecting all organ systems. The disease preferentially affects females of childbearing age. It runs a variable course. It may run a mild course that may never lead to severe disease and manifestations from critical organ systems. However, it may also run an undulating course with periods of mild and severe disease. It may run as a mild disease, quickly deteriorating to severe disease and affecting multiple organ systems. Various immune pathways related both to the innate and adaptive immune response are involved in the pathogenesis of SLE. Various drugs have been developed targeting cellular and molecular targets in these pathways. Interferons are involved in the pathogenesis of SLE, and various drugs have been developed to target this pathway. T and B lymphocytes are involved in the pathophysiology of SLE. Various treatment modalities targeting cellular targets are available for the treatment of SLE. These include biologic agents targeting B lymphocytes. However, some patients have disease refractory to these treatment modalities. For these patients, cell-based therapies may be used. Hematopoietic stem cell transplantation involving autologous cells is an option in the treatment of refractory SLE. Mesenchymal stem cells are also applied in the treatment of SLE. Chimeric antigen receptor (CAR)-T cell therapy is a novel treatment also used in SLE management. This novel treatment method holds major promise for the management of autoimmune diseases and, in particular, SLE. Major hurdles to be overcome are the logistics involved, as well as the need for specialized facilities. This review focuses on novel treatment modalities in SLE targeting cellular and molecular targets in the immune system.

Keywords: systemic lupus erythematosus; B lymphocyte; stem cell transplantation; mesenchymal cell transplantation; CAR T cell therapy

Academic Editor: Györgyi Műzes

Received: 23 December 2024
Revised: 18 January 2025
Accepted: 30 January 2025
Published: 31 January 2025

Citation: Athanassiou, P.; Athanassiou, L.; Kostoglou-Athanassiou, I.; Shoenfeld, Y. Targeted Cellular Treatment of Systemic Lupus Erythematosus. *Cells* **2025**, *14*, 210. https://doi.org/10.3390/cells14030210

1. Introduction

Systemic lupus erythematosus (SLE) is the prototype of systemic autoimmune diseases. The disease affects all organ systems and runs a variable course. It may run as a mild disease with periods of exacerbation and remission. It may affect critical organ systems such as the kidneys and the central nervous system. The disease may also run a very mild course. In such cases, the diagnosis and careful follow-up of the disease with the respective management is critical.

The exact etiology and pathophysiology of the disease remains elusive. It appears, however, that environmental agents act and induce the disease. Such factors are viruses and ultraviolet light, which induce the activation of the immune system and the development

of an autoimmune response. Antibodies against intranuclear particles are formed, such as antinuclear antibodies, anti-ds DNA antibodies, anti-SSA (Ro) and anti-SSA (La) antibodies, and anti-Smith antibodies. Antibodies form complexes with the respective antigens and are deposited in the respective organ systems, thereby causing disease. In lupus, the clearance pathways of the organism are defective. Thus, apoptotic cells and antibody–antigen complexes are not properly cleared. In patients with severe lupus disorders of hematopoietic progenitor cells, the following have been described: increased proliferation, differentiation, and activation of cytokines and chemokines leading to differentiation toward myeloid cells [1]. Increased risk of myelodysplastic syndrome has been observed in patients with autoimmune diseases including SLE [2], indicating shared genetic susceptibility between myelodysplastic syndrome and SLE. The disease has been managed in the past through the administration of corticosteroids in various dose schedules. Various modes of treatment have been utilized over the years in cases of severe SLE. As biological drugs have emerged, a biologic agent, has been applied to the management of SLE, namely belimumab. However, recently modes of treatment and applications of modern technology have entered the field of SLE treatment (Figure 1). These treatment modalities will be discussed in this paper. In particular, hematopoietic stem cell transplantation (HSCT), mesenchymal stem cell transplantation, and CAR-T cell therapy will be discussed.

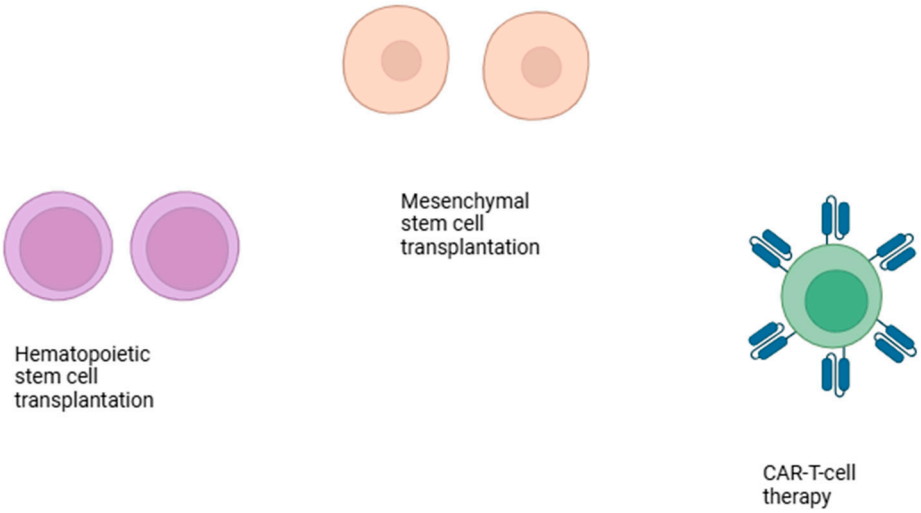

Figure 1. Cell-based treatment modalities for treatment of refractory systemic lupus erythematosus.

2. Stem Cell Transplantation

The application of modern disease-modifying modes of treatment has significantly improved outcomes in autoimmune diseases [3]. Despite these therapeutic improvements and innovations, a fraction of patients are refractory to both conventional and innovative modes of treatment [4,5]. Cure or long-term disease remission is not common [6,7]. HSCT has been applied in the management of autoimmune diseases since the last decade of the twentieth century [8–13]. Most of the cases in which it has been applied are cases of multiple sclerosis [9,14–17], systemic sclerosis [11,18,19], and Crohn's disease [20–23], and only a minority of the cases have been of SLE [24–28]. It is thought that the conditioning regimen before the procedure and the subsequent infusion of the stem cells may reset the immune system as it is considered to eradicate autoreactive immune cells and allow the generation of a novel immune system that is self-tolerant [29,30]. Hematopoietic stem cell transplants, as shown in a review published in 2017, are mainly autologous [31], while allogeneic stem cell transplants are performed almost exclusively in pediatric patients. Almost two thirds of autologous stem cell transplants are delivered to patients with multiple sclerosis and systemic sclerosis. This trend is on the rise.

HSCT is a form of cellular immunotherapy [27,32–34]. This treatment modality involves the transfusion of hematopoietic stem cells to the recipient in order to replace the patient's hematopoietic stem cells. Stem cell transplantation has been effectively and successfully applied in the treatment of malignant diseases [35,36]. However, it has also been applied in the treatment of autoimmune conditions. Based on the fact that SLE is a disease characterized by disorders of stem cells [37], stem cell transplantation has been applied in the treatment of SLE in cases of severe or treatment refractory disease. Stem cell transplantation is a procedure performed in multiple steps. These steps include the collection of stem cells and conditioning of the recipient with a proper regimen followed by infusion of the stem cell transplant [38]. The aim is the creation of a novel hematopoietic and a novel immune system.

HSCT has been applied in patients with hematologic diseases [35]. Early observations of remission of concurrent autoimmune disease in patients with hematologic diseases undergoing HSCT led to its application in patients with severe autoimmune diseases [39–41]. HSCT has been applied in patients with multiple sclerosis. It involves immunoablative treatment followed by autologous HSCT and has been found to have positive results [9]. Autologous HSCT has also been applied in patients with systemic sclerosis and has been found to improve lung function in patients with systemic sclerosis [42,43]. It has been suggested that autologous stem cell transplantation might be an option for progressive systemic sclerosis if major organ failure is imminent. Crohn's disease has also been treated with autologous stem cell transplantation, and it may be an option for treatment-resistant disease [44].

HSCT has been used in patients with SLE [24]. Patients with disease refractory to standard and biologic treatment are candidates for this form of treatment. In a review article published in 2017, the use of hematopoietic stem cell transplantation was reviewed [31]. Hematopoietic stem cell transplantation has been applied in 279 patients with SLE, including 54 patients who also fulfilled the criteria of antiphospholipid syndrome. In the majority of the studies, an improvement in disease control as assessed with the SLEDAI (SLE Disease Activity Index) or in time free from disease was noted. In one of the studies included in the abovementioned review, no net benefit was found from HSCT compared to immunosuppression. In five patients who also had antiphospholipid syndrome, antiphospholipid antibodies were negative after stem cell transplantation, while 73% of the patients with SLE and antiphospholipid syndrome were able to discontinue coagulation. Infections were observed in 30.8% of the patients who were subjected to HSCT, while three patients succumbed to the infection. An annual incidence of infections of 11.9% was observed in the SLE patients subjected to hematopoietic stem cell transplantation. Autologous HSCT has been complicated by the appearance of aplastic anemia [45]. Secondary autoimmune diseases may also complicate HSCT [46–48]. Infections are a major adverse effect of HSCT [49].

Allogeneic stem cell transplantation in SLE has been fraught with adverse effects, and it may be reserved only for patients with concurrent malignant disease [26]. Autologous stem cell transplantation has been explored in a large trial with a group of 339 patients. In this trial, a disease-free survival of 50–60% at 5 years was observed [50]. Relapse risk increased with longer follow-up. The conditioning regimen before transplantation has been shown to affect the rate of remission, as a conditioning regimen of cyclophosphamide, thymoglobulin, and rituximab is related with a better remission rate [50].

HSCT is an option in the treatment of SLE, in severe cases refractory to standard treatment regimens. However, the experience so far has shown that there are major difficulties to be overcome before it enters widespread clinical practice. HSCT is characterized by mortality related to the transplant procedure and in long-term follow-up with relapse of

the underlying disease. In a study [51], HSCT was related to relapse in one-third of the recipients and mortality in more than 10% related to transplantation. In a study in which hematopoietic stem cell transplantation was performed to treat lupus nephritis, a mortality of 5% was noted. The disease-free survival at 5 years was 53% and the rate of relapse was 27% [52]. As noted above, infections may occur, including cytomegalovirus infection, bacterial and/or fungal infections, allergic reactions, bone pain, and heart failure. The secondary emergence of autoimmune diseases is also a problem to be expected [48,53].

3. Mesenchymal Stem Cell Transplantation

Mesenchymal stem cells are adult stem cells that harbor the innate ability to self-renew and further differentiate into various types of cells. Mesenchymal stem cell treatment has been described as an option for the management of various diseases of autoimmune etiology. Such diseases, amongst others, are rheumatoid arthritis, type 1 diabetes mellitus, and multiple sclerosis [54]. The application of mesenchymal stem cell transplantations as a treatment for SLE has been investigated [55–57].

Sources for mesenchymal stem cells include bone marrow, umbilical cord, and adipose tissue. The procedure involves the isolation of mesenchymal stem cells, cell expansion, and infusion in the patient. Prior chemotherapy is not required. The availability of stem cells, the low rejection rate, and the absence of necessity for prior chemotherapy are advantages of this treatment modality for SLE patients refractory to standard treatment. Mesenchymal stem cells, when transplanted, regulate adaptive and immune response. The cells may downregulate inflammation and alleviate autoimmunity [58]. Findings from various studies suggest that mesenchymal stem cell transplantation is safe and has shown encouraging results as far as disease activity is concerned. However, it is not a curative option [59]. Allogeneic mesenchymal stem cell transplantation has been applied in 15 patients with active refractory SLE [56]. The patients were followed-up with for a period of up to 24 months. Severe adverse events were not noted. Disease remission was observed in this cohort, and SLE disease activity, anti-dsDNA antibodies, and proteinuria decreased. However, a relapse in proteinuria was observed in two of the patients in further follow-up. In a study involving follow-up for 6 years, it was found that allogeneic mesenchymal cell transplantation performed for refractory SLE was well tolerated by the patients and led to a decreased SLEDAI, decreased autoantibody levels, and decreased proteinuria [60]. The increased risk of infection and tumor formation was not noted. In a retrospective study, mesenchymal cell transplantation mortality was only 0.2% [61]. Mesenchymal stem cell transplantation is performed with allogeneic mesenchymal stem cells and is not yet standardized.

4. CAR-T Cell Therapy

Chimeric antigen receptor T (CAR-T) cell therapy is a form of technologically advanced treatment that has been applied successfully for the treatment of different types of B cell hematologic neoplasms. It was suggested that it might also be applied for the treatment of severe autoimmune disease. SLE is managed through the administration of various agents targeting B lymphocytes. However, cases of severe disease not responding to treatment or cases with severe adverse effects to this type of treatment exist. In these cases, it was thought that chimeric antigen receptor T cell therapy might be applied.

B cells are critical for the defense of the immune system against pathogens through various mechanisms, which include antibody production, the handling of antigen presentation, T cell activation and subsequent differentiation, and the production of cytokines [62]. B lymphocytes have an antigen receptor, the B cell receptor. Once the B cell receptor recognizes an antigen, the B cell is activated and undergoes proliferation and subsequent

differentiation, leading to the secretion of specific antibodies [63]. B cells with autoreactive properties undergo a process of regulation during early development, leading to central tolerance and a process of regulation during later stages of maturation in peripheral lymphoid organs, leading to peripheral tolerance. A disorder in central tolerance leads to the development of autoimmune and some immunodeficiency disorders [63]. Autoimmune disease evolves when affected individuals develop aberrant T and/or B cell responses against self-proteins. It is hypothesized that responses are targeted to single immunogenic epitopes on the self-proteins. Data from animal models of autoimmunity show that the targets of immune responses in autoimmune phenomena may not remain fixed but can be extended to include cryptic epitopes on the same protein or other proteins. This procedure is called epitope spreading [64]. In the case of tissue damage, epitope spreading also occurs when tissue damage from a primary inflammatory process causes the release and exposure of a previously cryptic antigen, leading to a secondary autoimmune response against the newly released antigen. B cell epitope spreading may be involved in the pathogenesis and progression of SLE [64–66]. Cell surface markers such as CD19 and CD20 are expressed on B cells depending on the stage of maturation, CD19 observed on B cells from the stage of pre-B cell to plasmablast [62,67].

B lymphocytes are critically involved in SLE pathogenesis. Epstein–Barr virus has been implicated in the pathogenesis of SLE [68] and the virus infects B lymphocytes, where its genome may persist as an episome and may shift between a latent and a lytic phase [69]. Hence, modes of treatment targeting B lymphocytes (Figure 2) have shown beneficial effects in the treatment of SLE [70]. Modes of treatment targeting B cells utilize either the inhibition of B cells via the blockade of BAFF (B cell-activating factor) and APRIL (a proliferation-inducing ligand) [71] and B cell depletion through the application of monoclonal antibodies against B cell surface molecules, namely CD19, CD20, or CD22 [72,73]. Rituximab, an anti-CD20 monoclonal antibody; ocrelizumab, another anti-CD20 monoclonal antibody; obinutuzumab, a fully humanized anti-CD20 monoclonal antibody; and epratuzumab, a recombinant humanized anti-CD22 monoclonal antibody, have been used in lupus treatment with varied success. Rituximab induces B cell depletion via the CD20 molecule [74]. However, tissue resident B cells [75] as well as cells not expressing the CD20 molecule evade depletion, leading to incomplete response to treatment [76,77]. Ocrelizumab has been administered in lupus nephritis with partial success; however, its administration led to serious infections [78]. Obinutuzumab has been administered to patients with lupus [79], renal and non-renal patients, patients unresponsive to second-line rituximab, and patients with lupus nephritis [80]. Epratuzumab, a recombinant monoclonal antibody targeting the CD22 molecule (Figure 3) on B cells, has also been administered to lupus patients [81]. Belimumab was the first biologic agent approved for the treatment of SLE [82]. It inhibits BAFF, which is important for B lymphocyte survival [83]. Belimumab improved disease activity and flare rates [84] and was effective in renal lupus [85]. Tabalumab and blisibimod are BAFF inhibitors that have also been applied in lupus [86–88]. Atacicept, which aims to achieve the inhibition of both APRIL and BAFF, has also been applied in lupus cases with efficacy and no serious adverse effects [89–91]. Bispecific monoclonal antibodies are also applied in the treatment of SLE [28]. Cases refractory to this type of treatment exist as well as cases that respond exhibiting adverse effects.

The therapeutic approaches applied so far suggest that targeting the B lymphocyte is a fruitful approach in the management of SLE. In addition, this approach has so far been fraught with the emergence of refractory cases as well as adverse effects. Thus, novel methods targeting the B lymphocyte in the treatment of SLE have been investigated. The successful application of chimeric antigen receptor (CAR) T lymphocytes in the treatment of B cell lymphomas has led to the observation that coexistent autoimmune diseases im-

proved [92–94]. Thus, the application of CAR T lymphocytes engineered to target the CD19 molecule on B lymphocytes was initiated. The aim was to target the CD19 molecule on the B lymphocyte in SLE patients and the subsequent depletion of B lymphocytes, suppressing the autoimmune process and disease remission. The application of anti-CD19 CAR T lymphocytes in a murine model of SLE indicated that this treatment modality had a preventive as well as a therapeutic efficacy as far as SLE was concerned [95]. The anti-CD19 CAR T cell treatment was administered to a female patient with active lupus nephritis refractory to treatment. The treatment led to seroconversion, i.e., anti-dsDNA antibodies were negative post treatment, and complement levels increased to normality [96]. Similar results were obtained by Taubmann et al. [97]. In a larger trial involving five patients, four female and one male, with severe refractory SLE, Mackensen et al. [98] administered anti-CD19 CAR T lymphocytes. B cell depletion occurred in all patients following treatment along with drug free remission in all eight patients. The B cell population re-emerged in the course of time following treatment. However, the re-emerging B cell population had a different non-pathogenic phenotype, indicating an immune system reset [98]. In another series of SLE patients, the administration of chimeric antigen receptor T cell treatment led to disease remission [99]. A disease activity index (SLEDAI) of 0 was observed following treatment in the lupus cohort. Anti-CD19 CAR -T cell therapy was administered to a 15-year-old female patient with lupus nephritis who was on haemodialysis [100]. The patient improved remarkably as creatinine levels decreased to normal, the glomerular filtration rate increased, proteinuria improved, and seroconversion was observed. The patient was not in need of hemodialysis following CAR-T cell treatment, and anti-hypertensive treatment was withdrawn. A double-target CAR T cell infusion harboring both BCMA (B cell maturation antigen) and CD19 molecules on CD19 B cells and plasma cells with BCMA surface antigen has been applied in patients with SLE and lupus nephritis in an open-label clinical trial [101]. The severity of lupus nephritis is related to an increased expression of BCMA in plasma cells with a long half-life [102,103]. Two patients suffering both from SLE and lymphoma achieved medication-free remission [101]. A group of nine patients suffering from lupus nephritis had symptom- and medication-free remission with a follow-up post infusion of up to 46 months. Complement levels increased to normal, and renal function and SLE disease activity index improved. Treatment was well tolerated, and the cytokine release syndrome observed was mild. B cell receptor deep sequencing was performed post infusion, revealing a complete immune reset. Through the use of specific molecular methods, it has been further shown that selective B cell depletion via CAR-T cell therapy reduces the interferon signature in SLE [104]. CAAR-T cell therapy is a further adaptation of CAR-T cell therapy that aims to deplete B cells producing specific sets of pathogenic antibodies and is now being further tested in neuroimmunology [105]. CAR-T cell therapy is accompanied by deep B cell depletion as the infused cells act autonomously, as opposed to monoclonal antibodies against B cells, which require natural killer cells, macrophages, or the complement to achieve their goal [74]. CAR therapy with alternative cells such as natural killer cells or macrophages is being evaluated [106,107].

CAR T cell therapy is a novel method, initially applied successfully in patients with B cell lymphoma and leukemia [108–111]. The treatment is accompanied by toxicity, including cytokine release syndrome (CRS) or, alternatively, cytokine-associated cytotoxicity [112], immune effector cell-associated neurotoxicity syndrome (ICANS) [113], anemia, leukopenia, thrombocytopenia [114], immunogenicity leading to anaphylaxis [115], and oncogenesis [116]. CRS is an inflammatory response that results from the activation of T lymphocytes. It complicates CAR-T cell therapy in a proportion of 42% to 93% of patients subjected to this type of treatment. It is an inflammatory response resulting from the activation of T lymphocytes and the release of IL-6 [112]. CRS is considered a consequence

of the efficacy of CAR T cell infusion; however, it may be associated with undesirable outcomes [117–119]. CRS may manifest itself in the initial 1 to 4 days of CAR-T cell administration and may vary in severity. Severe episodes tend to occur earlier after the infusion. The levels of laboratory indicators of the acute inflammatory response, such as of C-reactive protein and ferritin, are elevated in parallel with cytokine levels, including those of IL-6 and IFN-γ [120]. CRS may vary in severity from mild, with only fever and myalgia, to severe, manifesting with cardiorespiratory dysfunction [121]. CRS has been classified into five levels of severity [117]. CRS may need only symptomatic treatment. However, more severe cases may require the administration of tocilizumab to manage [122,123]. ICANS is another complication of CAR-T cell therapy and may follow CRS, manifesting with delirium, seizures, and aphasia. Its severity is not related to CRS severity. Corticosteroids are the best treatment modality for ICANS in the context of CAR-T cell treatment [119]. Immunogenicity leading to allergic reactions may also be observed [115,124]. CAR-T cells are generated through the genomic integration of a viral vector into the genome of the recipient. Therefore, long-term oncogenicity is a concern leading to the necessity of long-term follow-up of the recipient for any malignancy. Secondary malignancies after CAR-T cell treatment have been described [116,125].

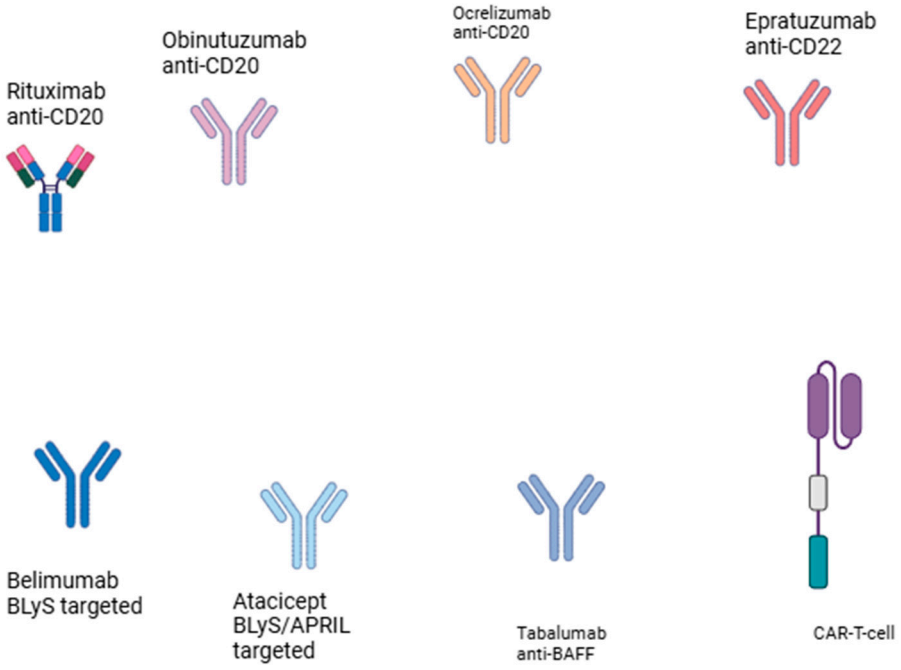

Figure 2. B cell-targeted treatment modalities in systemic lupus erythematosus.

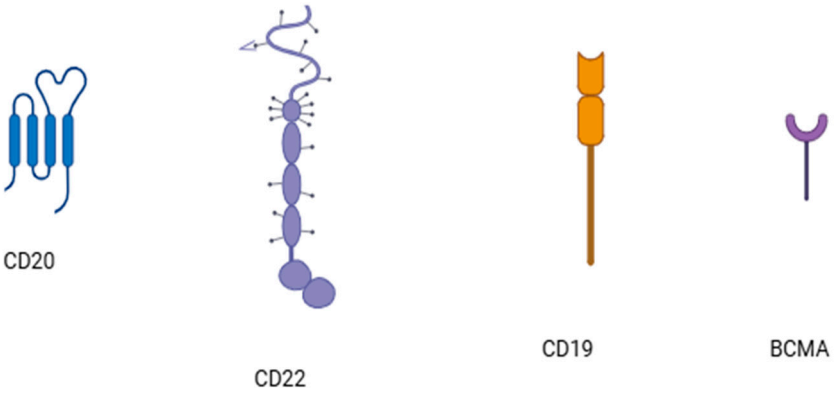

Figure 3. Molecular targets on B lymphocytes.

CAR-T cell therapy may be autologous or heterologous, meaning that the infused cell line may be derived from the patient's own T lymphocytes or from the lymphocytes of an unrelated donor. Autologous CAR-T cell therapy can avoid the adversity of immunological rejection, but it requires a lengthy production, and this may be critical in severely ill patients. However, the adverse effects of host versus graft and graft versus host reactions may be avoided [126]. CAR-T cell therapy involving a rapid manufacturing protocol has been applied successfully to patients with SLE [127,128]. Sequential lymph node biopsy performed before and after CD-19 CAR T cell therapy in patients with autoimmune rheumatic diseases, including a group of patients with SLE, indicated complete B cell depletion in the lymph nodes, while T cells, macrophages, and plasma cells remained intact [129].

Treatment with CAR T cells offers a possibility of lengthy sustained remission in cases of SLE refractory to conventional modes of treatment such as treatment with biological agents or monoclonal antibodies targeting B lymphocytes. This treatment modality is characterized by cumbersome logistics, requires specialized facilities, and is accompanied by adverse effects such as cytokine release syndrome. In addition, CAR T cells are not readily available and require quite a lengthy period of production of about 4 weeks, as opposed to monocolonal antibodies or biological agents, which are ready to be administered. It should be noted that protocols with shorter production periods as well as allogeneic CAR T cell products have been tested [130]. CAR T cell therapy is investigated because it holds the potential to be a one-stop therapeutic procedure to induce permanent remission in SLE patients, refractory to standard treatment modalities. Thus, CD-19-targeted CAR-T cells from a brave new world [131] may be the future in the treatment of refractory lupus [132].

5. Conclusions

The prototype systemic autoimmune disease SLE may be considered a stem cell disease, and B lymphocytes are critically involved in its pathogenesis. Various drugs are available for the treatment of SLE. These include immunomodulating agents, corticosteroids, monoclonal antibodies targeting B lymphocytes, and biological agents. However, cases refractory to these treatment modalities as well as adverse effects necessitate the evolution of alternative modes of treatment. Nowadays, there are alternative treatment modalities for treating refractory lupus. These include HSCT, mesenchymal cell transplantation, and CAR-T cell therapy. Autologous HSCT has been the procedure of choice in patients with SLE, with allogeneic stem cell transplantation being reserved only for pediatric cases. Remission and, in some cases, long-term remission have been achieved following stem cell transplantation. However, infections, which are in some cases fatal, have emerged. In addition, secondary autoimmune phenomena complicate the procedure. Mesenchymal cell transplantation is another stem cell procedure that has been tested in SLE. The procedure of choice has been allogeneic mesenchymal cell transplantation. However, the procedure has not entered clinical practice successfully. CAR-T cell therapy was applied successfully in patients with hematologic malignancies such as leukemia, lymphoma, and myeloma. CAR-T cell therapy targeting CD-19 on B lymphocytes proved successful in cases with hematologic malignancies. In addition, it was noted that autoimmune conditions went into remission. As B cell-targeted monoclonal antibodies proved therapeutically successful, targeting the B lymphocyte with CD-19-targeted CAR-T cells has been a promising approach for the treatment of SLE patients refractory to standard treatment. Thus, CD-19-targeted CAR T cell therapy has been administered to patients with SLE. The procedure was followed by long-lasting remission, and adverse events such as cytokine release syndrome and immune effector cell neurotoxicity syndrome were manageable. CAR-T cell therapy with alternative targets as well as CAR therapy with alternative cell types are being

investigated. CAR-T cell therapy with preparations for ready administration to recipients is also under research in an effort to provide a readily prepared off-the-shelf treatment.

In conclusion, cell therapy is an option for SLE refractory to standard treatment. CAR-T cell therapy holds a major promise for the achievement of sustained remission over older methods such as hematopoietic stem cell transplantation or mesenchymal cell transplantation.

Author Contributions: Conceptualization, P.A., L.A., I.K.-A. and Y.S.; methodology, P.A.; software, P.A., L.A., I.K.-A. and Y.S.; validation, P.A., L.A., I.K.-A. and Y.S.; formal analysis, P.A., L.A., I.K.-A. and Y.S.; investigation, P.A., L.A., I.K.-A. and Y.S.; resources, P.A.; data curation, P.A., L.A., I.K.-A. and Y.S.; writing—original draft preparation, P.A., L.A., I.K.-A. and Y.S.; writing—review and editing, P.A., L.A., I.K.-A. and Y.S.; visualization, P.A., L.A., I.K.-A. and Y.S.; supervision, P.A.; project administration, P.A., L.A., I.K.-A. and Y.S.; funding acquisition, P.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Grigoriou, M.; Banos, A.; Filia, A.; Pavlidis, P.; Giannouli, S.; Karali, V.; Nikolopoulos, D.; Pieta, A.; Bertsias, G.; Verginis, P.; et al. Transcriptome reprogramming and myeloid skewing in haematopoietic stem and progenitor cells in systemic lupus erythematosus. *Ann. Rheum. Dis.* **2020**, *79*, 242–253. [CrossRef]
2. Boddu, P.C.; Zeidan, A.M. Myeloid disorders after autoimmune disease. *Best. Pract. Res. Clin. Haematol.* **2019**, *32*, 74–88. [CrossRef] [PubMed]
3. Snowden, J.A.; Saccardi, R.; Allez, M.; Ardizzone, S.; Arnold, R.; Cervera, R.; Denton, C.; Hawkey, C.; Labopin, M.; Mancardi, G.; et al. Haematopoietic SCT in severe autoimmune diseases: Updated guidelines of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* **2012**, *47*, 770–790. [CrossRef]
4. Vasconcelos, C.; Kallenberg, C.; Shoenfeld, Y. Refractory disease in autoimmune diseases. *Autoimmun. Rev.* **2011**, *10*, 653–654. [CrossRef] [PubMed]
5. Marinho, A.; Delgado Alves, J.; Fortuna, J.; Faria, R.; Almeida, I.; Alves, G.; Araújo Correia, J.; Campar, A.; Brandão, M.; Crespo, J.; et al. Biological therapy in systemic lupus erythematosus, antiphospholipid syndrome, and Sjögren's syndrome: Evidence- and practice-based guidance. *Front. Immunol.* **2023**, *14*, 1117699. [CrossRef]
6. Aranow, C.; Allaart, C.F.; Amoura, Z.; Bruce, I.N.; Cagnoli, P.C.; Chatham, W.W.; Clark, K.L.; Furie, R.; Groark, J.; Urowitz, M.B.; et al. Efficacy and safety of sequential therapy with subcutaneous belimumab and one cycle of rituximab in patients with systemic lupus erythematosus: The phase 3, randomised, placebo-controlled BLISS-BELIEVE study. *Ann. Rheum. Dis.* **2024**, *83*, 1502–1512. [CrossRef]
7. Nikolopoulos, D.; Lourenço, M.H.; Depascale, R.; Triantafyllias, K.; Parodis, I. Evolving Concepts in Treat-to-Target Strategies for Systemic Lupus Erythematosus. *Mediterr. J. Rheumatol.* **2024**, *35* (Suppl. 2), 328–341. [CrossRef] [PubMed]
8. Alexander, T.; Greco, R.; Snowden, J.A. Hematopoietic Stem Cell Transplantation for Autoimmune Disease. *Annu. Rev. Med.* **2021**, *72*, 215–228. [CrossRef] [PubMed]
9. Muraro, P.A.; Martin, R.; Mancardi, G.L.; Nicholas, R.; Sormani, M.P.; Saccardi, R. Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis. *Nat. Rev. Neurol.* **2017**, *13*, 391–405. [CrossRef]
10. Balassa, K.; Danby, R.; Rocha, V. Haematopoietic stem cell transplants: Principles and indications. *Br. J. Hosp. Med.* **2019**, *80*, 33–39. [CrossRef]
11. Tyndall, A. Hematopoietic stem cell transplantation for autoimmune diseases: More than just prolonged immunosuppression. *Curr. Opin. Hematol.* **2018**, *25*, 433–440. [CrossRef] [PubMed]
12. Malmegrim, K.C.R.; Lima-Júnior, J.R.; Arruda, L.C.M.; de Azevedo, J.T.C.; de Oliveira, G.L.V.; Oliveira, M.C. Autologous Hematopoietic Stem Cell Transplantation for Autoimmune Diseases: From Mechanistic Insights to Biomarkers. *Front. Immunol.* **2018**, *9*, 2602. [CrossRef]

13. Atkins, H.L.; Muraro, P.A.; van Laar, J.M.; Pavletic, S.Z. Autologous hematopoietic stem cell transplantation for autoimmune disease--is it now ready for prime time? *Biol. Blood Marrow Transplant.* **2012**, *18*, S177–S183. [CrossRef] [PubMed]
14. Boffa, G.; Signori, A.; Massacesi, L.; Mariottini, A.; Sbragia, E.; Cottone, S.; Amato, M.P.; Gasperini, C.; Moiola, L.; Meletti, S.; et al. Hematopoietic Stem Cell Transplantation in People with Active Secondary Progressive Multiple Sclerosis. *Neurology* **2023**, *100*, e1109–e1122. [CrossRef]
15. Boffa, G.; Inglese, M.; Mancardi, G.L. Hematopoietic stem cell transplantation for multiple sclerosis. *Handb. Clin. Neurol.* **2024**, *202*, 153–167. [PubMed]
16. Genc, B.; Bozan, H.R.; Genc, S.; Genc, K. Stem Cell Therapy for Multiple Sclerosis. *Adv. Exp. Med. Biol.* **2019**, *1084*, 145–174. [PubMed]
17. Ross, L.A.; Stropp, L.M.; Cohen, J.A. Autologous Hematopoietic Stem Cell Transplantation to Treat Multiple Sclerosis. *Neurol. Clin.* **2024**, *42*, 165–184. [CrossRef] [PubMed]
18. Di Benedetto, P.; Ruscitti, P.; Cipriani, P.; Giacomelli, R. Haematopoietic stem cell transplantation in systemic sclerosis: Challenges and perspectives. *Autoimmun. Rev.* **2020**, *19*, 102662. [CrossRef]
19. Van Laar, J.M.; Farge, D.; Sont, J.K.; Naraghi, K.; Marjanovic, Z.; Larghero, J.; Schuerwegh, A.J.; Marijt, E.W.; Vonk, M.C.; Schattenberg, A.V.; et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: A randomized clinical trial. *JAMA* **2014**, *311*, 2490–2498. [CrossRef] [PubMed]
20. Reider, S.; Binder, L.; Fürst, S.; Hatzl, S.; Blesl, A. Hematopoietic Stem Cell Transplantation in Refractory Crohn's Disease: Should It Be Considered? *Cells* **2022**, *11*, 3463. [CrossRef]
21. Wang, R.; Yao, Q.; Chen, W.; Gao, F.; Li, P.; Wu, J.; Yu, J.; Cao, H. Stem cell therapy for Crohn's disease: Systematic review and meta-analysis of preclinical and clinical studies. *Stem Cell Res. Ther.* **2021**, *12*, 463. [CrossRef] [PubMed]
22. Hawkey, C.J. Hematopoietic Stem Cell Transplantation in Crohn's Disease: State-of-the-Art Treatment. *Dig. Dis.* **2017**, *35*, 107–114. [CrossRef]
23. Ruiz, M.A.; Kaiser Junior, R.L.; Piron-Ruiz, L.; Peña-Arciniegas, T.; Saran, P.S.; De Quadros, L.G. Hematopoietic stem cell transplantation for Crohn's disease: Gaps, doubts and perspectives. *World J. Stem Cells.* **2018**, *10*, 134–137. [CrossRef] [PubMed]
24. Leone, A.; Radin, M.; Almarzooqi, A.M.; Al-Saleh, J.; Roccatello, D.; Sciascia, S.; Khamashta, M. Autologous hematopoietic stem cell transplantation in Systemic Lupus Erythematosus and antiphospholipid syndrome: A systematic review. *Autoimmun. Rev.* **2017**, *16*, 469–477. [CrossRef] [PubMed]
25. Sui, W.; Hou, X.; Che, W.; Chen, J.; Ou, M.; Xue, W.; Dai, Y. Hematopoietic and mesenchymal stem cell transplantation for severe and refractory systemic lupus erythematosus. *Clin. Immunol.* **2013**, *148*, 186–197. [CrossRef] [PubMed]
26. Marmont du Haut Champ, A.M. Hematopoietic stem cell transplantation for systemic lupus erythematosus. *Clin. Dev. Immunol.* **2012**, *2012*, 380391. [CrossRef] [PubMed]
27. Alexander, T.; Arnold, R.; Hiepe, F. Autologous hematopoietic stem cell transplantation in systemic lupus erythematosus. *Z. Rheumatol.* **2016**, *75*, 770–779. [CrossRef] [PubMed]
28. Askanase, A.; Khalili, L.; Tang, W.; Mertz, P.; Scherlinger, M.; Sebbag, E.; Chasset, F.; Felten, R.; Arnaud, L. New and future therapies: Changes in the therapeutic armamentarium for SLE. *Best. Pract. Res. Clin. Rheumatol.* **2023**, *37*, 101865. [CrossRef] [PubMed]
29. Arruda, L.C.; Clave, E.; Moins-Teisserenc, H.; Douay, C.; Farge, D.; Toubert, A. Resetting the immune response after autologous hematopoietic stem cell transplantation for autoimmune diseases. *Curr. Res. Transl. Med.* **2016**, *64*, 107–113. [CrossRef] [PubMed]
30. Swart, J.F.; Lindemans, C.A.; van Royen, A.; Boelens, J.J.; Prakken, B.J.; Wulffraat, N. Changing winds in refractory autoimmune disease in children: Clearing the road for tolerance with cellular therapies. *Curr. Opin. Rheumatol.* **2012**, *24*, 267–273. [CrossRef]
31. Snowden, J.A.; Badoglio, M.; Labopin, M.; Giebel, S.; McGrath, E.; Marjanovic, Z.; Burman, J.; Moore, J.; Rovira, M.; Wulffraat, N.M.; et al. Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. *Blood Adv.* **2017**, *1*, 2742–2755. [CrossRef] [PubMed]
32. Alexander, T.; Badoglio, M.; Henes, J.; Heesen, C.; Arnold, R.; Radbruch, A.; Snowden, J.A.; Hiepe, F. Autologous hematopoietic stem cell transplantation for autoimmune diseases: Current indications and mode of action, a review on behalf of the EBMT Autoimmune Diseases Working Party (ADWP). *Z. Rheumatol.* **2020**, *79*, 419–428. [CrossRef]
33. Kelsey, P.J.; Oliveira, M.C.; Badoglio, M.; Sharrack, B.; Farge, D.; Snowden, J.A. Haematopoietic stem cell transplantation in autoimmune diseases: From basic science to clinical practice. *Curr. Res. Transl. Med.* **2016**, *64*, 71–82. [CrossRef] [PubMed]
34. Doglio, M.; Alexander, T.; Del Papa, N.; Snowden, J.A.; Greco, R. New insights in systemic lupus erythematosus: From regulatory T cells to CAR-T-cell strategies. *J. Allergy Clin. Immunol.* **2022**, *150*, 1289–1301. [CrossRef]
35. Snowden, J.A.; Sánchez-Ortega, I.; Corbacioglu, S.; Basak, G.W.; Chabannon, C.; de la Camara, R.; Dolstra, H.; Duarte, R.F.; Glass, B.; Greco, R.; et al. Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: Current practice in Europe, 2022. *Bone Marrow Transplant.* **2022**, *57*, 1217–1239. [CrossRef] [PubMed]

36. Faul, C.; Donnelly, M.; Merscher-Gomez, S.; Chang, Y.H.; Franz, S.; Delfgaauw, J.; Chang, J.-M.; Choi, H.Y.; Campbell, K.N.; Kim, K.; et al. The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat. Med.* **2008**, *14*, 931–938. [CrossRef] [PubMed]
37. Xiong, H.; Cui, M.; Kong, N.; Jing, J.; Xu, Y.; Liu, X.; Yang, F.; Xu, Z.; Yan, Y.; Zhao, D.; et al. Cytotoxic $CD161^{-}CD8^{+}$ T_{EMRA} cells contribute to the pathogenesis of systemic lupus erythematosus. *eBioMedicine* **2023**, *90*, 104507. [CrossRef] [PubMed]
38. Sureda, A.; Pereira, M.I.; Dreger, P. The role of hematopoietic stem cell transplantation in the treatment of relapsed/refractory Hodgkin's lymphoma. *Curr. Opin. Oncol.* **2012**, *24*, 727–732. [CrossRef] [PubMed]
39. Meloni, G.; Capria, S.; Vignetti, M.; Mandelli, F.; Modena, V. Blast crisis of chronic myelogenous leukemia in long-lasting systemic lupus erythematosus: Regression of both diseases after autologous bone marrow transplantation. *Blood* **1997**, *89*, 4659. [CrossRef]
40. Lowenthal, R.M.; Cohen, M.L.; Atkinson, K.; Biggs, J.C. Apparent cure of rheumatoid arthritis by bone marrow transplantation. *J. Rheumatol.* **1993**, *20*, 137–140.
41. Yin, J.A.; Jowitt, S.N. Resolution of immune-mediated diseases following allogeneic bone marrow transplantation for leukaemia. *Bone Marrow Transplant.* **1992**, *9*, 31–33.
42. Milanetti, F.; Bucha, J.; Testori, A.; Burt, R.K. Autologous hematopoietic stem cell transplantation for systemic sclerosis. *Curr. Stem Cell Res. Ther.* **2011**, *6*, 16–28. [CrossRef] [PubMed]
43. Burt, R.K.; Han, X.; Quigley, K.; Arnautovic, I.; Shah, S.J.; Lee, D.C.; Freed, B.H.; Jovanovic, B.; Helenowski, I.B. Cardiac safe hematopoietic stem cell transplantation for systemic sclerosis with poor cardiac function: A pilot safety study that decreases neutropenic interval to 5 days. *Bone Marrow Transplant.* **2021**, *56*, 50–59. [CrossRef] [PubMed]
44. Brierley, C.K.; Castilla-Llorente, C.; Labopin, M.; Badoglio, M.; Rovira, M.; Ricart, E.; Dierickx, D.; Vermeire, S.; Hasselblatt, P.; Finke, J.; et al. Autologous Haematopoietic Stem Cell Transplantation for Crohn's Disease: A Retrospective Survey of Long-term Outcomes From the European Society for Blood and Marrow Transplantation. *J. Crohns Colitis.* **2018**, *12*, 1097–1103. [CrossRef] [PubMed]
45. Bregante, S.; Gualandi, F.; van Lint, M.T.; Schenone, A.; Bacigalupo, A.; Marmont, A.M. Sjögren's syndrome associated chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) treated with autologous and subsequently allogeneic haematopoietic SCT (HSCT). *Bone Marrow Transplant.* **2013**, *48*, 1139–1140. [CrossRef]
46. Loh, Y.; Oyama, Y.; Statkute, L.; Quigley, K.; Yaung, K.; Gonda, E.; Barr, W.; Jovanovic, B.; Craig, R.; Stefoski, D.; et al. Development of a secondary autoimmune disorder after hematopoietic stem cell transplantation for autoimmune diseases: Role of conditioning regimen used. *Blood* **2007**, *109*, 2643–2648. [CrossRef] [PubMed]
47. Bohgaki, T.; Atsumi, T.; Koike, T. Multiple autoimmune diseases after autologous stem-cell transplantation. *N. Engl. J. Med.* **2007**, *357*, 2734–2736. [CrossRef] [PubMed]
48. Daikeler, T.; Labopin, M.; Di Gioia, M.; Abinun, M.; Alexander, T.; Miniati, I.; Gualandi, F.; Fassas, A.; Martin, T.; Schwarze, C.P.; et al. Secondary autoimmune diseases occurring after HSCT for an autoimmune disease: A retrospective study of the EBMT Autoimmune Disease Working Party. *Blood* **2011**, *118*, 1693–1698. [CrossRef]
49. He, J.; Li, Z. Dilemma of immunosuppression and infection risk in systemic lupus erythematosus. *Rheumatology* **2023**, *62* (Suppl. 1), i22–i29. [CrossRef] [PubMed]
50. Burt, R.K.; Han, X.; Gozdziak, P.; Yaung, K.; Morgan, A.; Clendenan, A.M.; Henry, J.; Calvario, M.A.; Datta, S.K.; Helenowski, I.; et al. Five year follow-up after autologous peripheral blood hematopoietic stem cell transplantation for refractory, chronic, corticosteroid-dependent systemic lupus erythematosus: Effect of conditioning regimen on outcome. *Bone Marrow Transplant.* **2018**, *53*, 692–700. [CrossRef] [PubMed]
51. Jayne, D.; Tyndall, A. Autologous stem cell transplantation for systemic lupus erythematosus. *Lupus* **2004**, *13*, 359–365. [CrossRef] [PubMed]
52. Huang, X.; Chen, W.; Ren, G.; Zhao, L.; Guo, J.; Gong, D.; Zeng, C.; Hu, W.; Liu, Z. Autologous Hematopoietic Stem Cell Transplantation for Refractory Lupus Nephritis. *Clin. J. Am. Soc. Nephrol.* **2019**, *14*, 719–727. [CrossRef] [PubMed]
53. Daikeler, T.; Tichelli, A.; Passweg, J. Complications of autologous hematopoietic stem cell transplantation for patients with autoimmune diseases. *Pediatr. Res.* **2012**, *71 Pt 2*, 439–444. [CrossRef]
54. Jasim, S.A.; Yumashev, A.V.; Abdelbasset, W.K.; Margiana, R.; Markov, A.; Suksatan, W.; Pineda, B.; Thangavelu, L.; Ahmadi, S.H. Shining the light on clinical application of mesenchymal stem cell therapy in autoimmune diseases. *Stem Cell Res. Ther.* **2022**, *13*, 101. [CrossRef]
55. Sun, L.; Akiyama, K.; Zhang, H.; Yamaza, T.; Hou, Y.; Zhao, S.; Xu, T.; Le, A.; Shi, S. Mesenchymal stem cell transplantation reverses multiorgan dysfunction in systemic lupus erythematosus mice and humans. *Stem Cells.* **2009**, *27*, 1421–1432. [CrossRef]
56. LLiang, J.; Zhang, H.; Hua, B.; Wang, H.; Lu, L.; Shi, S.; Hou, Y.; Zeng, X.; Gilkeson, G.S.; Sun, L. Allogenic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: A pilot clinical study. *Ann. Rheum. Dis.* **2010**, *69*, 1423–1429. [CrossRef] [PubMed]

57. Sun, L.; Wang, D.; Liang, J.; Zhang, H.; Feng, X.; Wang, H.; Hua, B.; Liu, B.; Ye, S.; Hu, X.; et al. Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus. *Arthritis Rheum.* **2010**, *62*, 2467–2475. [CrossRef] [PubMed]
58. Li, A.; Guo, F.; Pan, Q.; Chen, S.; Chen, J.; Liu, H.F. Mesenchymal Stem Cell Therapy: Hope for Patients with Systemic Lupus Erythematosus. *Front. Immunol.* **2021**, *12*, 728190. [CrossRef] [PubMed]
59. Xia, Y.; Ye, H.; Li, K.; Shi, B.; Sun, X.; Wu, J. Efficacy of Mesenchymal Stem Cell Therapy on Lupus Nephritis and Renal Function in Systemic Lupus Erythematosus: A Meta-Analysis. *Clin. Investig. Med.* **2023**, *46*, E24–E35. [CrossRef]
60. Wang, D.; Niu, L.; Feng, X.; Yuan, X.; Zhao, S.; Zhang, H.; Liang, J.; Zhao, C.; Wang, H.; Hua, B.; et al. Long-term safety of umbilical cord mesenchymal stem cells transplantation for systemic lupus erythematosus: A 6-year follow-up study. *Clin. Exp. Med.* **2017**, *17*, 333–340. [CrossRef] [PubMed]
61. Liang, J.; Zhang, H.; Kong, W.; Deng, W.; Wang, D.; Feng, X.; Zhao, C.; Hua, B.; Wang, H.; Sun, L. Safety analysis in patients with autoimmune disease receiving allogeneic mesenchymal stem cells infusion: A long-term retrospective study. *Stem Cell Res. Ther.* **2018**, *9*, 312. [CrossRef] [PubMed]
62. Oh, S.; Payne, A.S. Engineering Cell Therapies for Autoimmune Diseases: From Preclinical to Clinical Proof of Concept. *Immune Netw.* **2022**, *22*, e37. [CrossRef] [PubMed]
63. Nemazee, D. Mechanisms of central tolerance for B cells. *Nat. Rev. Immunol.* **2017**, *17*, 281–294. [CrossRef]
64. Cornaby, C.; Gibbons, L.; Mayhew, V.; Sloan, C.S.; Welling, A.; Poole, B.D. B cell epitope spreading: Mechanisms and contribution to autoimmune diseases. *Immunol. Lett.* **2015**, *163*, 56–68. [CrossRef] [PubMed]
65. Carl, P.L.; Temple, B.R.; Cohen, P.L. Most nuclear systemic autoantigens are extremely disordered proteins: Implications for the etiology of systemic autoimmunity. *Arthritis Res. Ther.* **2005**, *7*, R1360–R1374. [CrossRef] [PubMed]
66. Monneaux, F.; Muller, S. Epitope spreading in systemic lupus erythematosus: Identification of triggering peptide sequences. *Arthritis Rheum.* **2002**, *46*, 1430–1438. [CrossRef]
67. Kochenderfer, J.N.; Rosenberg, S.A. Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. *Nat. Rev. Clin. Oncol.* **2013**, *10*, 267–276. [CrossRef] [PubMed]
68. Draborg, A.H.; Duus, K.; Houen, G. Epstein-Barr virus and systemic lupus erythematosus. *Clin. Dev. Immunol.* **2012**, *2012*, 370516. [CrossRef] [PubMed]
69. Kerr, J.R. Epstein-Barr virus (EBV) reactivation and therapeutic inhibitors. *J. Clin. Pathol.* **2019**, *72*, 651–658. [CrossRef] [PubMed]
70. Nashi, E.; Wang, Y.; Diamond, B. The role of B cells in lupus pathogenesis. *Int. J. Biochem. Cell Biol.* **2010**, *42*, 543–550. [CrossRef] [PubMed]
71. Samy, E.; Wax, S.; Huard, B.; Hess, H.; Schneider, P. Targeting BAFF and APRIL in systemic lupus erythematosus and other antibody-associated diseases. *Int. Rev. Immunol.* **2017**, *36*, 3–19. [CrossRef] [PubMed]
72. Lee, W.S.; Amengual, O. B cells targeting therapy in the management of systemic lupus erythematosus. *Immunol. Med.* **2020**, *43*, 16–35. [CrossRef]
73. Lee, D.S.W.; Rojas, O.L.; Gommerman, J.L. B cell depletion therapies in autoimmune disease: Advances and mechanistic insights. *Nat. Rev. Drug Discov.* **2021**, *20*, 179–199. [CrossRef] [PubMed]
74. Weiner, G.J. Rituximab: Mechanism of action. *Semin. Hematol.* **2010**, *47*, 115–123. [CrossRef] [PubMed]
75. Anolik, J.H.; Barnard, J.; Owen, T.; Zheng, B.; Kemshetti, S.; Looney, R.J.; Sanz, I. Delayed memory B cell recovery in peripheral blood and lymphoid tissue in systemic lupus erythematosus after B cell depletion therapy. *Arthritis Rheum.* **2007**, *56*, 3044–3056. [CrossRef] [PubMed]
76. Forsthuber, T.G.; Cimbora, D.M.; Ratchford, J.N.; Katz, E.; Stüve, O. B cell-based therapies in CNS autoimmunity: Differentiating CD19 and CD20 as therapeutic targets. *Ther. Adv. Neurol. Disord.* **2018**, *11*, 1756286418761697. [CrossRef] [PubMed]
77. Merrill, J.T.; Neuwelt, C.M.; Wallace, D.J.; Shanahan, J.C.; Latinis, K.M.; Oates, J.C.; Utset, T.O.; Gordon, C.; Isenberg, D.A.; Hsieh, H.J.; et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: The randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum.* **2010**, *62*, 222–233. [CrossRef] [PubMed]
78. Mysler, E.F.; Spindler, A.J.; Guzman, R.; Bijl, M.; Jayne, D.; Furie, R.A.; Houssiau, F.A.; Drappa, J.; Close, D.; Maciuca, R.; et al. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: Results from a randomized, double-blind, phase III study. *Arthritis Rheum.* **2013**, *65*, 2368–2379. [CrossRef]
79. Arnold, J.; Dass, S.; Twigg, S.; Jones, C.H.; Rhodes, B.; Hewins, P.; Chakravorty, M.; Courtney, P.; Ehrenstein, M.; Yusof, Y.M.; et al. Efficacy and safety of obinutuzumab in systemic lupus erythematosus patients with secondary non-response to rituximab. *Rheumatology* **2022**, *61*, 4905–4909. [CrossRef] [PubMed]
80. Furie, R.A.; Aroca, G.; Cascino, M.D.; Garg, J.P.; Rovin, B.H.; Alvarez, A.; Fragoso-Loyo, H.; Zuta-Santillan, E.; Schindler, T.; Brunetta, P.; et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: A randomised, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.* **2022**, *81*, 100–107. [CrossRef] [PubMed]

81. Clowse, M.E.B.; Wallace, D.J.; Furie, R.A.; Petri, M.A.; Pike, M.C.; Leszczyński, P.; Neuwelt, C.M.; Hobbs, K.; Keiserman, M.; Duca, L.; et al. Efficacy and Safety of Epratuzumab in Moderately to Severely Active Systemic Lupus Erythematosus: Results From Two Phase III Randomized, Double-Blind, Placebo-Controlled Trials. *Arthritis Rheumatol.* **2017**, *69*, 362–375. [CrossRef] [PubMed]
82. Dubey, A.K.; Handu, S.S.; Dubey, S.; Sharma, P.; Sharma, K.K.; Ahmed, Q.M. Belimumab: First targeted biological treatment for systemic lupus erythematosus. *J. Pharmacol. Pharmacother.* **2011**, *2*, 317–319. [CrossRef]
83. Wallace, D.J.; Ginzler, E.M.; Merrill, J.T.; Furie, R.A.; Stohl, W.; Chatham, W.W.; Weinstein, A.; McKay, J.D.; McCune, W.J.; Petri, M.; et al. Safety and Efficacy of Belimumab Plus Standard Therapy for Up to Thirteen Years in Patients with Systemic Lupus Erythematosus. *Arthritis Rheumatol.* **2019**, *71*, 1125–1134. [CrossRef] [PubMed]
84. Manzi, S.; Sánchez-Guerrero, J.; Merrill, J.T.; Furie, R.; Gladman, D.; Navarra, S.V.; Ginzler, E.M.; D'Cruz, D.P.; Doria, A.; Cooper, S.; et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: Combined results from two phase III trials. *Ann. Rheum. Dis.* **2012**, *71*, 1833–1838. [CrossRef] [PubMed]
85. Furie, R.; Petri, M.; Zamani, O.; Cervera, R.; Wallace, D.J.; Tegzová, D.; Sanchez-Guerrero, J.; Schwarting, A.; Merrill, J.T.; Chatham, W.W.; et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum.* **2011**, *63*, 3918–3930. [CrossRef]
86. Merrill, J.T.; van Vollenhoven, R.F.; Buyon, J.P.; Furie, R.A.; Stohl, W.; Morgan-Cox, M.; Dickson, C.; Anderson, P.W.; Lee, C.; Berclaz, P.-Y.; et al. Efficacy and safety of subcutaneous tabalumab, a monoclonal antibody to B-cell activating factor, in patients with systemic lupus erythematosus: Results from ILLUMINATE-2, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. *Ann. Rheum. Dis.* **2016**, *75*, 332–340.
87. Merrill, J.T.; Shanahan, W.R.; Scheinberg, M.; Kalunian, K.C.; Wofsy, D.; Martin, R.S. Phase III trial results with blisibimod, a selective inhibitor of B-cell activating factor, in subjects with systemic lupus erythematosus (SLE): Results from a randomised, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.* **2018**, *77*, 883–889. [CrossRef]
88. Petri, M.A.; Martin, R.S.; Scheinberg, M.A.; Furie, R.A. Assessments of fatigue and disease activity in patients with systemic lupus erythematosus enrolled in the Phase 2 clinical trial with blisibimod. *Lupus* **2017**, *26*, 27–37. [CrossRef] [PubMed]
89. Isenberg, D.; Gordon, C.; Licu, D.; Copt, S.; Rossi, C.P.; Wofsy, D. Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE): 52-week data (APRIL-SLE randomised trial). *Ann. Rheum. Dis.* **2015**, *74*, 2006–2015. [CrossRef] [PubMed]
90. Merrill, J.T.; Wallace, D.J.; Wax, S.; Kao, A.; Fraser, P.A.; Chang, P.; Isenberg, D.; ADDRESS II Investigators. Efficacy and Safety of Atacicept in Patients with Systemic Lupus Erythematosus: Results of a Twenty-Four-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm, Phase IIb Study. *Arthritis Rheumatol.* **2018**, *70*, 266–276. [CrossRef] [PubMed]
91. Wallace, D.J.; Isenberg, D.A.; Morand, E.F.; Vazquez–Mateo, C.; Kao, A.H.; Aydemir, A.; Pudota, K.; Ona, V.; Aranow, C.; Merrill, J.T. Safety and clinical activity of atacicept in the long-term extension of the phase 2b ADDRESS II study in systemic lupus erythematosus. *Rheumatology* **2021**, *60*, 5379–5389. [CrossRef]
92. Bachanova, V.; Nachman, P.H. Two for one? CAR-T therapy for lymphoma benefits concurrent autoimmune disorders. *Bone Marrow Transplant.* **2023**, *58*, 1175–1176. [CrossRef]
93. Sheng, L.; Zhang, Y.; Song, Q.; Jiang, X.; Cao, W.; Li, L.; Yi, H.; Weng, X.; Chen, S.; Wang, Z.; et al. Concurrent remission of lymphoma and Sjögren's disease following anti-CD19 chimeric antigen receptor-T cell therapy for diffuse large B-cell lymphoma: A case report. *Front. Immunol.* **2023**, *14*, 1298815. [CrossRef]
94. Wang, J.; Alkrekshi, A.; Dasari, S.; Lin, H.C.; Elantably, D.; Armashi, A.R.A. CD19-targeted chimeric antigen receptor T-cell therapy in patients with concurrent B-cell Non-Hodgkin lymphoma and rheumatic autoimmune diseases: A propensity score matching study. *Bone Marrow Transplant.* **2023**, *58*, 1223–1228. [CrossRef] [PubMed]
95. Jin, X.; Xu, Q.; Pu, C.; Zhu, K.; Lu, C.; Jiang, Y.; Xiao, L.; Han, Y.; Lu, L. Therapeutic efficacy of anti-CD19 CAR-T cells in a mouse model of systemic lupus erythematosus. *Cell Mol. Immunol.* **2021**, *18*, 1896–1903. [CrossRef]
96. Mougiakakos, D.; Krönke, G.; Völkl, S.; Kretschmann, S.; Aigner, M.; Kharboutli, S.; Böltz, S.; Manger, B.; Mackensen, A.; Schett, G. CD19-Targeted CAR T Cells in Refractory Systemic Lupus Erythematosus. *N. Engl. J. Med.* **2021**, *385*, 567–569. [CrossRef]
97. Taubmann, J.; Müller, F.; Mutlu, M.Y.; Völkl, S.; Aigner, M.; Bozec, A.; Mackensen, A.; Grieshaber-Bouyer, R.; Schett, G. CD19 Chimeric Antigen Receptor T Cell Treatment: Unraveling the Role of B Cells in Systemic Lupus Erythematosus. *Arthritis Rheumatol.* **2024**, *76*, 497–504. [CrossRef] [PubMed]
98. Mackensen, A.; Müller, F.; Mougiakakos, D.; Böltz, S.; Wilhelm, A.; Aigner, M.; Völkl, S.; Simon, D.; Kleyer, A.; Munoz, L.; et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. *Nat. Med.* **2022**, *28*, 2124–2132. [CrossRef] [PubMed]
99. Müller, F.; Taubmann, J.; Bucci, L.; Wilhelm, A.; Bergmann, C.; Völkl, S.; Aigner, M.; Rothe, T.; Minopoulou, I.; Tur, C.; et al. CD19 CAR T-Cell Therapy in Autoimmune Disease—A Case Series with Follow-up. *N. Engl. J. Med.* **2024**, *390*, 687–700. [CrossRef]
100. Krickau, T.; Naumann-Bartsch, N.; Aigner, M.; Kharboutli, S.; Kretschmann, S.; Spoerl, S.; Vasova, I.; Völkl, S.; Woelfle, J.; Mackensen, A.; et al. CAR T-cell therapy rescues adolescent with rapidly progressive lupus nephritis from haemodialysis. *Lancet.* **2024**, *403*, 1627–1630. [CrossRef]

101. Wang, W.; He, S.; Zhang, W.; Zhang, H.; DeStefano, V.M.; Wada, M.; Pinz, K.; Deener, G.; Shah, D.; Hagag, N.; et al. BCMA-CD19 compound CAR T cells for systemic lupus erythematosus: A phase 1 open-label clinical trial. *Ann. Rheum. Dis.* **2024**, *83*, 1304–1314. [CrossRef] [PubMed]
102. Salazar-Camarena, D.C.; Palafox-Sánchez, C.A.; Cruz, A.; Marín-Rosales, M.; Muñoz-Valle, J.F. Analysis of the receptor BCMA as a biomarker in systemic lupus erythematosus patients. *Sci. Rep.* **2020**, *10*, 6236. [CrossRef]
103. Martin, J.; Cheng, Q.; Laurent, S.A.; Thaler, F.S.; Beenken, A.E.; Meinl, E.; Krönke, G.; Hiepe, F.; Alexander, T. B-Cell Maturation Antigen (BCMA) as a Biomarker and Potential Treatment Target in Systemic Lupus Erythematosus. *Int. J. Mol. Sci.* **2024**, *25*, 10845. [CrossRef] [PubMed]
104. Wilhelm, A.; Chambers, D.; Müller, F.; Bozec, A.; Grieshaber-Bouyer, R.; Winkler, T.; Mougiakakos, D.; Mackensen, A.; Schett, G.; Krönke, G. Selective CAR T cell-mediated B cell depletion suppresses IFN signature in SLE. *JCI Insight* **2024**, *9*, e179433. [CrossRef] [PubMed]
105. Haghikia, A.; Schett, G.; Mougiakakos, D. B cell-targeting chimeric antigen receptor T cells as an emerging therapy in neuroimmunological diseases. *Lancet Neurol.* **2024**, *23*, 615–624. [CrossRef]
106. Maalej, K.M.; Merhi, M.; Inchakalody, V.P.; Mestiri, S.; Alam, M.; Maccalli, C.; Cherif, H.; Uddin, S.; Steinhoff, M.; Marincola, F.M.; et al. CAR-cell therapy in the era of solid tumor treatment: Current challenges and emerging therapeutic advances. *Mol. Cancer* **2023**, *22*, 20. [CrossRef] [PubMed]
107. Pan, K.; Farrukh, H.; Chittepu, V.; Xu, H.; Pan, C.X.; Zhu, Z. CAR race to cancer immunotherapy: From CAR T, CAR NK to CAR macrophage therapy. *J. Exp. Clin. Cancer Res.* **2022**, *41*, 119. [CrossRef]
108. Denlinger, N.; Bond, D.; Jaglowski, S. CAR T-cell therapy for B-cell lymphoma. *Curr. Probl. Cancer* **2022**, *46*, 100826. [CrossRef] [PubMed]
109. Westin, J.; Sehn, L.H. CAR T cells as a second-line therapy for large B-cell lymphoma: A paradigm shift? *Blood* **2022**, *139*, 2737–2746. [CrossRef] [PubMed]
110. Haslauer, T.; Greil, R.; Zaborsky, N.; Geisberger, R. CAR T-Cell Therapy in Hematological Malignancies. *Int. J. Mol. Sci.* **2021**, *22*, 8996. [CrossRef]
111. Cook, M.R.; Dorris, C.S.; Makambi, K.H.; Luo, Y.; Munshi, P.N.; Donato, M.; Rowley, S.; Saad, A.; Goy, A.; Dunleavy, K.; et al. Toxicity and efficacy of CAR T-cell therapy in primary and secondary CNS lymphoma: A meta-analysis of 128 patients. *Blood Adv.* **2023**, *7*, 32–39. [CrossRef] [PubMed]
112. Maude, S.L.; Barrett, D.; Teachey, D.T.; Grupp, S.A. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer J.* **2014**, *20*, 119–122. [CrossRef] [PubMed]
113. Jain, M.D.; Smith, M.; Shah, N.N. How I treat refractory CRS and ICANS after CAR T-cell therapy. *Blood* **2023**, *141*, 2430–2442. [PubMed]
114. Sun, S.; Hao, H.; Yang, G.; Zhang, Y.; Fu, Y. Immunotherapy with CAR-Modified T Cells: Toxicities and Overcoming Strategies. *J. Immunol. Res.* **2018**, *2018*, 2386187. [CrossRef]
115. Maus, M.V.; Haas, A.R.; Beatty, G.L.; Albelda, S.M.; Levine, B.L.; Liu, X.; Zhao, Y.; Kalos, M.; June, C.H. T cells expressing chimeric antigen receptors can cause anaphylaxis in humans. *Cancer Immunol. Res.* **2013**, *1*, 26–31. [CrossRef]
116. Verdun, N.; Marks, P. Secondary Cancers after Chimeric Antigen Receptor T-Cell Therapy. *N. Engl. J. Med.* **2024**, *390*, 584–586. [CrossRef] [PubMed]
117. Lee, D.W.; Gardner, R.; Porter, D.L.; Louis, C.U.; Ahmed, N.; Jensen, M.; Grupp, S.A.; Mackall, C.L. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* **2014**, *124*, 188–195. [CrossRef]
118. Hay, K.A. Cytokine release syndrome and neurotoxicity after CD19 chimeric antigen receptor-modified (CAR-) T cell therapy. *Br. J. Haematol.* **2018**, *183*, 364–374. [CrossRef]
119. Maude, S.L.; Frey, N.; Shaw, P.A.; Aplenc, R.; Barrett, D.M.; Bunin, N.J.; Chew, A.; Gonzalez, V.E.; Zheng, Z.; Lacey, S.F.; et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N. Engl. J. Med.* **2014**, *371*, 1507–1517. [CrossRef] [PubMed]
120. Zhao, J.L.; Ma, C.; O'connell, R.M.; Mehta, A.; DiLoreto, R.; Heath, J.R.; Baltimore, D. Conversion of danger signals into cytokine signals by hematopoietic stem and progenitor cells for regulation of stress-induced hematopoiesis. *Cell Stem Cell.* **2014**, *14*, 445–459. [CrossRef]
121. Brentjens, R.; Yeh, R.; Bernal, Y.; Riviere, I.; Sadelain, M. Treatment of chronic lymphocytic leukemia with genetically targeted autologous T cells: Case report of an unforeseen adverse event in a phase I clinical trial. *Mol. Ther.* **2010**, *18*, 666–668. [CrossRef]
122. Kotch, C.; Barrett, D.; Teachey, D.T. Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome. *Expert. Rev. Clin. Immunol.* **2019**, *15*, 813–822. [CrossRef]
123. Frey, N.; Porter, D. Cytokine Release Syndrome with Chimeric Antigen Receptor T Cell Therapy. *Biol. Blood Marrow Transplant.* **2019**, *25*, e123–e127. [CrossRef] [PubMed]
124. Lamers, C.H.J.; Willemsen, R.; van Elzakker, P.; van Steenbergen-Langeveld, S.; Broertjes, M.; Oosterwijk-Wakka, J.; Oosterwijk, E.; Sleijfer, S.; Debets, R.; Gratama, J.W. Immune responses to transgene and retroviral vector in patients treated with ex vivo-engineered T cells. *Blood* **2011**, *117*, 72–82. [CrossRef] [PubMed]

125. Levine, B.L.; Pasquini, M.C.; Connolly, J.E.; Porter, D.L.; Gustafson, M.P.; Boelens, J.J.; Horwitz, E.M.; Grupp, S.A.; Maus, M.V.; Locke, F.L.; et al. Unanswered questions following reports of secondary malignancies after CAR-T cell therapy. *Nat. Med.* **2024**, *30*, 338–341. [CrossRef] [PubMed]
126. Mansouri, V.; Yazdanpanah, N.; Rezaei, N. The immunologic aspects of cytokine release syndrome and graft versus host disease following CAR T cell therapy. *Int. Rev. Immunol.* **2022**, *41*, 649–668. [CrossRef] [PubMed]
127. Ghassemi, S.; Durgin, J.S.; Nunez-Cruz, S.; Patel, J.; Leferovich, J.; Pinzone, M.; Shen, F.; Cummins, K.D.; Plesa, G.; Cantu, V.A.; et al. Rapid manufacturing of non-activated potent CAR T cells. *Nat. Biomed. Eng.* **2022**, *6*, 118–128. [CrossRef] [PubMed]
128. Dickinson, M.J.; Barba, P.; Jäger, U.; Shah, N.N.; Blaise, D.; Briones, J.; Shune, L.; Boissel, N.; Bondanza, A.; Mariconti, L.; et al. A Novel Autologous CAR-T Therapy, YTB323, with Preserved T-cell Stemness Shows Enhanced CAR T-cell Efficacy in Preclinical and Early Clinical Development. *Cancer Discov.* **2023**, *13*, 1982–1997. [CrossRef] [PubMed]
129. Tur, C.; Eckstein, M.; Velden, J.; Rauber, S.; Bergmann, C.; Auth, J.; Bucci, L.; Corte, G.; Hagen, M.; Wirsching, A.; et al. CD19-CAR T-cell therapy induces deep tissue depletion of B cells. *Ann. Rheum. Dis.* **2024**, *84*, 106–114. [CrossRef]
130. Mougiakakos, D.; Sengupta, R.; Gold, R.; Schroers, R.; Haghikia, A.; Lorente, M.; Pendleton, M.; Register, A.; Heesen, C.; Kröger, N.; et al. Successful generation of fully human, second generation, anti-CD19 CAR T cells for clinical use in patients with diverse autoimmune disorders. *Cytotherapy* **2024**, *27*, 236–246. [CrossRef] [PubMed]
131. van Leuven, S.I.; Duivenvoorden, R. CAR-T cell therapy in systemic lupus erythematosus and beyond: A brave new world? *Rheumatology* **2024**, *63*, 1192–1194. [CrossRef] [PubMed]
132. Kambayana, G.; Surya Rini, S. Autologous CD19-Targeted Chimeric Antigen Receptor (CAR)T-Cells as the Future of Systemic Lupus Erythematosus Treatment. *Curr. Rheumatol. Rev.* **2023**, *19*, 260–269. [CrossRef] [PubMed]