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CAR-T cell therapy for juvenile-onset autoimmune diseases: a promising future?

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Abstract

Chimeric antigen receptor (CAR) T-cell therapy targeting B cells has shown promising results, including drug-free remission, in adult-onset autoimmune diseases. Extending this therapeutic approach to the pediatric population, particularly for juvenile autoimmune diseases, presents an exciting opportunity. However, challenges specific to juvenile-onset autoimmune conditions, such as long-term adverse events, heightened disease activity, and the imperative to reduce steroid exposure, must be considered. While this strategy appears viable for these severe conditions, the limited data available for this population and the absence of evidence on cases with a high genetic component, such as monogenic lupus, represent significant challenges. Most monogenic lupus cases are associated with innate immune defects, and the involvement of B cells in these genetic anomalies remains poorly understood. In this review, we examine the potential indications, current knowledge, and limitations of CAR-T cell therapy in juvenile-onset autoimmune diseases, extending the discussion beyond early-onset lupus.

Keywords Lupus, Juvenile dermatomyositis, Monogenic lupus, CAR-T cells, CD19, B cells, Children, Autoimmunity

Introduction

Early-onset autoimmune diseases exhibit distinct characteristics, often manifesting with greater severity compared to their adult-onset counterparts. Juvenile systemic lupus erythematosus (jSLE) typically presents with a more aggressive phenotype characterized by heightened disease activity and earlier onset of organ damage, with a frequent contribution of lupus nephritis and neurological involvement [1]. Severe forms of juvenile dermatomyositis (JDM) can evolve into chronically active diseases, with persistent disease activity extending years beyond the initial diagnosis. The identification of myositis-specific autoantibodies over the past decade has facilitated the classification of sub-phenotypes, each associated with specific clinical outcomes [2]. Patients with jSLE and JDM commonly experience a marked decline in quality of life [3, 4]. The management of autoimmune disease with juvenile-onset is particularly challenging, often requiring the use of combination therapies and prolonged corticosteroid. This approach can lead to significant

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immunosuppression, life-threatening complications, and an increased risk of infections and organ damage, all contributing to long-term disability [5–7].

While treatment strategies are frequently extrapolated from guidelines for adult-onset SLE and dermatomyositis, the management of these juvenile conditions requires specialized expertise tailored to the unique needs of younger patients. Achieving optimal disease control critical to support normal development, facilitate uninterrupted schooling and minimize long-term disease sequelae [8].

B cells play a pivotal role in the pathophysiology of SLE by presenting autoantigens to T cells and secreting proinflammatory cytokines [9] while plasmablasts contribute by generating autoantibodies. Immune complex deposits are critical in the development of renal pathology. Similarly, B lymphocytes are central in dermatomyositis evidenced by the significant reduction in regulatory B cells and the expansion of CD19 + B lymphocytes, which are activated via type-I interferons (IFN-I). These abnormalities in B cell compartments are closely correlated with clinical disease activity in JDM [10–12].

Targeting B lymphocytes with anti-CD20 therapies such as Rituximab, Obinutuzumab, and Ocrelizumab, has yielded variable results in SLE and JDM [13–15]. The limited efficacy observed may be due to the predominance of pathogenic B cells being plasmablasts, which express CD19 but not CD20, and the incomplete depletion of B cells in tissues achieved by monoclonal antibodies, particularly with rituximab [16].

Chimeric antigen receptor (CAR) T-cells represent an innovative approach in cellular therapy wherein T-cells are genetically engineered to express a chimeric antigen receptor that targets a specific membrane antigen. Specifically, anti-CD19 CAR T-cells are activated upon recognition of their target antigen, leading to their proliferation and potent cytotoxic action against CD19 + B cells. This cytotoxicity is mediated through various mechanisms, including perforin/granzyme and cytokine-induced cytotoxicity [17].

CAR-T cells targeting CD19 have been developed for the treatment of refractory or relapsed B cell malignancies in pediatric patients, with remarkable success [18]. Recently, anti-CD19 CAR-T cells have been used to treat adult patients with refractory auto-immune diseases such as SLE and DM [19]. This therapy can induce long-term drug-free remission, eliminate autoantibodies, and reset the B cell repertoire [19–21].

In early 2024, the first case reports emerged of children with refractory jSLE and JDM achieving similar remarkable results, including sustained remission following a few months of follow-up and without significant adverse effects [22–24].

The aim of this review is to provide a comprehensive overview of the use of CAR-T cells therapy for juvenile autoimmune diseases, to discuss current and future limitations, and to advocate for the advancement of these innovative approaches in pediatric rheumatology.

Specificities of the pediatric-onset autoimmune diseases

Juvenile systemic lupus erythematosus

JSLE is defined as lupus with onset before 18 years of age. The most common jSLE manifestations include hematological, cutaneous, musculoskeletal and renal symptoms [25–27]. Additionally, severe pulmonary, and life-threatening neuropsychiatric manifestations are also reported in jSLE [28, 29]. These patients are particularly susceptible to mental health issues, displaying a higher prevalence of fatigue, pain, anxiety, and depressive symptoms compared to the general population [30]. Compared to adults, jSLE is more frequently associated with hematological and renal complications; thrombocytopenia, hemolytic anemia, and lupus nephritis which are significantly more prevalent in this population [26, 31]. A large meta-analysis found that anti-dsDNA antibodies were more common in jSLE and disease activity, as measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), was higher in children than in adults at disease onset [32].

Clinical complications often develop within two years of diagnosis, and drug-free remission is rarely achieved in these patients. As they transition into adulthood, individuals with jSLE frequently experience impaired health-related quality of life, significantly impacted by changes in physical appearance. By their 20 s, approximately half of young adults with jSLE develop significant organ damage, including cerebrovascular accidents, renal transplants, replacement arthropathies, and myocardial infarctions (6). Standardized mortality rates among SLE patients, particularly those under 18, are higher than those of the general population, with mortality risk increasing with the duration of the disease [27, 33]. In the juvenile population, severe infections are the most common cause of death, whereas adults with SLE often succumb to cardiovascular events, renal failure, infections, or cancers [27, 34–36]. Furthermore, jSLE is more frequently associated to single gene mutations, defining the field of Mendelian lupus [37]. At least 7% of jSLE are monogenic, predominantly involving innate immune anomalies linked to complement defects or interferon dysregulation [38].

Various combination therapies have been recommended for jSLE, with new therapeutics recently entering the market. The Pediatric Rheumatology European Society (PreS) international task force now recommends the application of a'treat-to-target'strategy in jSLE to ensure long-term survival, prevent organ damage, and optimize

health-related quality of life [39]. The treatment target should be disease remission, with low disease activity being acceptable in refractory cases, achieved with the lowest possible dosage of glucocorticoids.

The cornerstone of maintenance therapy in jSLE remains hydroxychloroquine often combined with Disease-Modifying Antirheumatic Drugs (DMARDs) such as methotrexate, mycophenolate mofetil and azathioprine despite the challenge of maintaining daily medication adherence in this population [40]. Severe forms of lupus (class III/IV or refractory lupus nephritis, neurolupus or pulmonary involvement) may require cyclophosphamide treatment, raising concerns about reproductive toxicity in pediatric patients [41–46]. Additionally, the long-term use of immunosuppressive treatments increases the risk of non-melanoma skin cancers and lymphomas [47, 48].

Therapeutic options for jSLE are limited, with only one biologic treatment (belimumab) approved, while rituximab is used off-label for refractory cases. Janus Kinase (JAK) inhibitors should be considered in cases of monogenic lupus, depending on the presence of specific mutations [39, 49–52] (Table 1). Novel therapeutics, such as obinutuzumab, voclosporine [53] and anifrolumab [54]. Have recently emerged for adult-onset SLE, although these medications are not yet approved for patients under 18 years of age. Despite advancements in treatment, a large number of children treated for jSLE continue to present with severe and refractory forms of the disease. No immunosuppressive treatment has been able to achieve both clinical and biological remission, which is why autologous hematopoietic stem cell transplantation (HSCT) is now being considered for refractory SLE [55].

Autologous HSCT, aimed at achieving broad immune depletion through conditioning treatments (e.g., antithymocyte globulin and cyclophosphamide or alemtuzumab), has been used in the treatment of SLE for the past 20 years. Between 1994 and 2018, 107 cases were reported in the European Society for Blood and Marrow Transplantation (EBMT) registry, including 18 patients

Table 1 Treatment recommendation for juvenile SLE

Treat-to-target recommendations for juvenile SLE (SHARE/PreS/EULAR)
1. Hydroxychloroquine
○ 5 mg/kg/day
2. Glucocorticoid
• at the lowest dosage
○ initially 1–2 mg/kg/day or in case of severe disease: intravenous pulse therapy 30 mg/kg/dose three consecutive days
○ 10%–20% at 1-week or 2-week interval based on clinical improvement
3. Methotrexate
• skin and joint involvement
4. Azathioprine/mycophenolate mofetil
• Class II, III, IV, V lupus nephritis
5. Tacrolimus, ciclosporine
• Pure class V lupus nephritis in selected case (nephrotoxicity)
Then, in addition of DMARDs
6. Belimumab
• Class III, IV lupus nephritis
• skin and joint involvement
○ 10 mg/kg/month
7. Rituximab
• Refractory lupus nephritis
○ 4 × 375 mg/m^2/week
○ 2 × 750 mg/m^2/14 days
8. Cyclophosphamide
• class III/IV or refractory lupus nephritis
• Severe neurolupus
○ 6 × 500 mg or 500 mg/1,73 m^2 every 2 weeks for three months EURO-LUPUS
○ 0,75–1 g/m^2 monthly for 6–9 months NIH lupus regimen
JAK inhibitors could be a valuable option in monogenic lupus with specific mutations

SHARE Single Hub and Access point for pediatric Rheumatology in Europe, *PreS* Paediatric Rheumatology European Society, *EULAR* European Alliance of Associations for Rheumatology, *NIH*: National Institutes of Health

under 18 years of age at the time of transplantation [56]. Auto-HSCT has been shown to enable the discontinuation of immunosuppressive treatment and achieve both clinical and serological remission. However, it is associated with significant risks and potential complications, including secondary autoimmune disorders and gonadotoxicity, with an estimated mortality rate of around 5% [57, 58]. Therefore, auto-HSCT is indicated only in the most severe and life-threatening cases. Allogeneic HSCT has been proposed for five patients (two children and three adults) with successful outcomes [59].

Juvenile dermatomyositis

Juvenile dermatomyositis (JDM) is the most prevalent idiopathic inflammatory myopathy in childhood, characterized by involvement of both muscle and skin with significant heterogeneity in clinical presentation and disease progression. JDM can manifest as monophasic, polycyclic, or persistently active disease [60], with severe cases leading to profound muscular deficits, respiratory dysfunction and swallowing disorders. associated with JDM can also cause gastrointestinal dysfunction, potentially escalating to life-threatening complications. A subgroup of patients with MDA5-positive antibody JDM and rapidly progressive interstitial lung disease (RP-ILD) may have a particularly severe prognosis [61]. The overall mortality rate is estimated at 3%, with variation among subgroups depending on autoantibodies [62].

The juvenile form is characterized by more pronounced vasculopathy, calcinosis, telangiectasias, and ulcerative skin disease at presentation compared to the adult form. Additionally, younger age at onset is associated with a trend toward more intensive treatment approaches in younger children with JDM [63].

Data from a large multicenter study conducted by UK specialists on over 500 patients with JDM suggests that the majority of patients (approximately 89%) show an overall improvement in disease activity over time. However, a smaller subgroup (around 11%) presents with more persistent disease activity lasting up to 10 years post-diagnosis [64]. Baseline factors associated with this more severe disease trajectory include higher levels of baseline disease activity, abnormal respiration, lipodystrophy, and a longer time from symptom onset to diagnosis. Muscle weakness, despite treatment and remission of other symptoms, is a common issue, leading to functional impairments in muscle strength and physical activity levels. These physical limitations can impact daily activities and overall quality of life [65].

The primary treatment for JDM relies on corticosteroid, often combined with immunosuppressants. Methotrexate is commonly used in conjunction with steroids (Table 2). As second-line treatment option, other DMARDs such as mycophenolate mofetil (MMF) and cyclosporine may be considered. In severe cases, intravenous immunoglobulins may be employed, particularly for managing swallowing difficulties [66]. The efficacy of Rituximab has been investigated in juvenile dermatomyositis, and its use is endorsed by experts [14, 67, 68].

Observations from retrospective case series have underscored the effectiveness of JAK inhibitors, such as baricitinib, which enable the tapering or discontinuation of steroids and other immunosuppressive agents [69–71]. Abatacept has shown improvement in disease activity in an open-label study [72]. Although rare, cases of autologous hematopoietic stem cell transplantation have suggested efficacy, though the data remain limited compared to those for jSLE [73].

Table 2 Treatment recommendation for juvenile dermatomyositis (SHARE/PRES)

Treat-to-target recommendations for dermatomyositis (SHARE/PreS)
1. Glucocorticoids
• Start high dose with intravenous pulse therapy 15–30 mg/kg/dose three consecutive days
• Followed by 1–2 mg/kg/day
2. Methotrexate
• 15–20 mg/m^2
3. Azathioprine/mycophenolate mofetil
• In case of refractory evolution or intolerance
4. Intravenous Immunoglobulins
• Severe forms
5. Rituximab
• 750 mg/m^2 up to a maximum of 1 g per infusion, once a week for 2 weeks
Alternatives: JAK inhibitors, adalimumab, infliximab, abatacept, plasma exchanges: there is a need to define indication for these therapies

In summary, jSLE and JDM are two pediatric diseases with significant unmet therapeutic needs. From a pathogenesis standpoint, B cells are considered a promising therapeutic target; however, the results of B-cell depletion using monoclonal antibodies have been inconsistent. This highlights the urgent need for the development of novel anti-B-cell therapies.

CAR T cells as an anti-B cell therapy

Chimeric antigen receptors are human-made receptors that combine two essential elements of the adaptive immune response: an antibody fragment combined with motifs involved in intracellular signaling so that induces a TCR-like antigen-specific and costimulation response [74, 75]. CARs consist of several parts. The first is the single-chain variable fragment (ScFv), which fuses the variable regions of heavy (VH) and light (VL) immunoglobulin chains that provide antigen specificity and are connected by a linker peptide. The ScFv is then linked to a hinge region (typically from CD8a or CD28) and a transmembrane domain (also CD8a or CD28). The presence or absence of additional co-stimulatory molecules (CD28 or 4- 1BB) upstream of the CD3z chain distinguishes CAR generations [76]. These domains are absent in first-generation CARs, whereas second- and third-generation CARs possess one or two co-stimulatory domains, respectively [76]. To date, six CAR T-cell products have been authorized in France and Europe for use in hematologic B cells malignancies [77]. All commercial CAR-T-cells in the European Union are autologous and second-generation cells. The production process of autologous CAR-T cells is lengthy and complex [78]. The first step involved isolating the patient's leukocytes via apheresis. After transfer to production units, lymphocytes are sorted magnetically, activated with beads coated with anti-CD3 and CD28 antibodies and cytokines, and exposed to a viral vector that delivers the genetic sequence necessary for CAR expression in T cells. While various techniques exist for integrating Deoxyribonucleic acid (DNA) sequences into T cells [79], the most widely used for CAR-T generation employs lentiviral particles, which are known for their high transduction efficiency and low toxicity. After activation and transduction, the cells are maintained in culture for the expansion phase and then prepared for infusion. The main regulatory release controls are viability, CAR expression measurement, potency tests against antigen-expressing cells, and vector copy number (VCN) determination.

As previously mentioned, the recognition of a target expressing the antigen recognized by CAR mimics TCR-mediated activation [80]. This activation leads to the proliferation of CAR-T-cells and the secretion of cytokines (IL- 2, IFN-γ, and TNF-α), increasing their number and cytolytic effector functions [81]. The main pathway of cytotoxicity is the perforin/granzyme pathway [82]. In tumor models, it has also been shown that CAR-T-induced apoptosis can involve interactions between death receptors and their ligands (TRAIL, Fas-FasL) [83].

Targeting CD19 + B cells with CAR T cells in juvenile-onset autoimmune disease: evidence to date

Clinical presentation of adolescents treated with anti-CD19 CAR T cells therapy

On July 2024, it was reported that 11 patients with SLE had received treatment with anti-CD19 CAR T cells and one had received CD19-BCMA compound CAR. Of these patients, 10 were over 18 years old and 2 were under 18. All patients had severe and refractory disease, characterized by skin involvement and proliferative kidney nephritis (WHO grade III and IV). Notably, most of the adult patients experienced their first manifestations of the disease before the age of 18 (5 out 10 of adult patients) [19, 22, 23, 84–86]. Recently, a satisfactory response to anti-CD19 CAR T-cell therapy has been recently reported in four adults with inflammatory myositis, which included myositis and interstitial lung disease, with a maximum follow-up period of 12 months [19, 21].

Two adolescents with refractory jSLE have been treated with CAR T cell infusions. The first case, involving a 15-year-old girl with refractory jSLE, was reported in April 2024 by the Erlangen team [22]. A second patient was reported by the medical team at Bambino Gesu Children's Hospital in Rome, Italy [23]. Additionally, a 12-year-old Caucasian boy with severe chronic JDM was successfully treated with CAR T cells [24]. The characteristics of all patients are detailed in Table 3.

The median age at the administration of CAR-T cell infusion was 15 years [range 12–15]. All patients exhibited multiple clinical manifestations including severe renal and/or pulmonary complications in SLE and severe skin and muscular involvement in cases of JDM.

Patients with jSLE had extremely elevated activity scores, with a median SLEDAI of 22.5 (range 22–23), which exceeded the median SLEDAI of 16 (range 8–16) observed in the adult cohort treated with CAR-T cells [21, 87]. These patients were refractory to both conventional and combination therapeutic regimens. All patients had previously undergone B-cell-targeted therapy with rituximab or belimumab, which yielded limited efficacy. Additionally, cyclophosphamide was

Table 3 Clinical characteristics of pediatric patients treated by CD19 CAR T cells [20–22]

Patients	Disease	Sex	Age at the CAR-T cells infusion	Clinical manifestations	Activity score	Biological markers	Treatments Previously used	Side effects of conventional treatments	Follow-up duration	Outcome	Side effects of CAR-T cells
Patient 1 Krickau and al. (20)	jSLE	female	15	Class IV lupus nephritis with chronic renal disease requiring dialysis, rash, fever, arthritis	SLEDAI score of 23	High anti-dsDNA, high ANA with anti-nucleosome and anti-histone antibodies	High doses of GC AZA MMF Belimumab	Not reported	6 months	Drug-free Remission with SLEDAI score of 0 Mild residual kidney damage Resolution of arthritis Return to school 4 months after infusion	Mild cytokine release syndrome (grade 1) Transient anemia (grade 2) Neutropenia (grade 4) Malaise between days 3 and 7
Patient 2 Marasco and al. (21)	jSLE	female	15	hemolytic anemia, thrombocytopenia, rash, class II/V lupus nephritis, interstitial lung disease, pulmonary hypertension, pericardial effusion	SLEDAI score of 22	High anti-dsDNA, high ANA, hypo-complementemia High NT-pro BNP	High doses of GC, HCQ, MMF, Rituximab and CYC	Osteoporosis Arterial hypertension Severe systemic infections	10 weeks	Drug-free remission SLEDAI score of 2 at 6 weeks anti-DsDNA titers significantly decreased Normalization of NT pro- BNP	Mild cytokine release syndrome (grade 1) Transient anemia (grade 2) Neutropenia (grade 3)
Patient 3 Nicolai and al. (22)	JDM	male	12	Severe muscle weakness, skin rashes, severe ulcerations, calcinosis	CMAS 36/52 CAT-BM 9/17	ANA 1:320 No positivity for myositis autoantibodies Elevated interferon (INF) signature BUT normal CK	High doses of GC MMF, HCQ, MTX, cyclosporin, IVIG, CYC, Rituximab, plasmapheresis	Osteoporosis with vertebral fractures Arterial hypertension Infectious complications	8 months	Drug-free remission CMAS 50/52, CAT-BM 2/7 normalization of muscle strength in 4 weeks Resolution of skin ulceration and calcinosis. Persistent minimal Gottron's sign Normalization of IFN signature	Mild cytokine release syndrome (grade 1) Transient anemia (grade 2) Neutropenia (grade 4)

CMAS Childhood Myositis Assessment Scale, *CAT -BM* Cutaneous Assessment Tool (CAT) in the shortened Binary Method version (CAT-BM), *CK* Creatine kinase, *GC* Glucocorticoids, *HCQ* Hydroxychloroquine, *MMF* Mycophenolate mofetil, *MTX* Methotrexate, *CYC* Cyclophosphamide

administered to patients 2 and 3, but it failed to achieve clinical remission.

Treatments modalities

The washout period, defined as the discontinuation of immunosuppressive drugs, for juvenile patients ranged from 3 to 7 days prior to leukapheresis, accompanied by a reduction in corticosteroid dosage. This washout period aimed to optimize T cell harvesting and subsequent ex vivo expansion. Its duration was necessarily limited due to the severe and life-threatening nature of the patients'disease manifestations in the absence of treatment. Notably, the washout period was shorter than that used in the adult population (median of 3 weeks) but did not adversely affect the expansion or efficacy of the CAR-T cells. All patients'autologous T cells were transduced with a second-generation lentiviral anti-CD19 CAR vector and infused at a uniform dosage of 1×10^6 CAR cells/kg, consistent with the protocol for patients with B cell malignancies and most reported autoimmune patients [19]. The lymphodepletion regimen varied, with differences in the duration and intensity of cyclophosphamide and fludarabine administration (Table 4). A"higher intensity"cyclophosphamide regimen was preferred in patients without renal failure. Despite the relatively short washout period, the procedure was successfully completed.

Table 4 Lymphodepletion regimen in adolescents

Regimen for lymphodepletion	
Patient 1 (with severe renal insufficiency) Krickau and al. [22]	Fludarabine 12.5 mg/m^2/d over 3 days cyclophosphamide 500 mg/m^2 once
Patient 2 Marasco and al. [23]	Fludarabine 90 mg/m^2 (the duration of treatment was not reported) Cyclophosphamide 1500 mg/m^2 (the duration of treatment was not reported)
Patient 3 Nicolai and al. [24]	Fludarabine 90 mg/m^2 over 3 days Cyclophosphamide 1000 mg/m^2 over 2 days

The follow-up duration for each patient was respectively 6 months, 10 weeks and 8 months (median: 8 months) after infusion

B Cell depletion and reconstitution

Peripheral B cell aplasia was observed between days 5 and 7 in all patients. Bone marrow aspirates at weeks 2 and 4

confirmed complete tissular B-cell depletion in patients 2 and 3. Patient 1 experienced persistent B cell aplasia for a period of 6 months, whereas patient 3 exhibited detectable B cells 8 weeks post-infusion. These B cells exhibited a phenotype of naïve mature cells with low levels of memory B cells, plasmablasts and mature B cells by week 18. Throughout the follow-up period, Patient 3's IgG and IgM levels remained within normal limits. Unfortunately, no information regarding B-cell reconstitution was available for patient 2.

Clinical improvement

Patient 1, who had severe renal disease, was able to discontinue dialysis on day 17, and exhibited a significant improvement of estimated glomerular filtration rate (eGFR) (only mild persistent proteinuria, resolution of oedema, significant decrease of proteinuria). Additionally, the patient experienced normalized appetite, gained muscle mass, and saw a complete resolution of arthritis, with the SLEDAI score reaching 0 a few weeks after CAR-T cell infusion. Patient 2 showed normalization of cardiac function and renal markers, with the SLEDAI score decreasing to 2 after 6 weeks of treatment. The patient with dermatomyositis initially experienced a worsening of skin and muscular symptoms due to the tapering of immunosuppressants. However, by week 4 post-infusion, the disease activity score began to decrease, eventually leading to the normalization of muscle strength and resolution of cutaneous manifestations, including calcinosis and skin ulcerations. By the last follow-up, all patients had successfully discontinued all immunosuppressive therapies.

Biological assessment

All patients ($n = 3$) exhibited normalization of laboratory parameters, including the dramatic decrease or disappearance of anti-double-stranded DNA antibodies. The IFN score normalization in the patient with dermatomyositis was observed as early as week 24 and was sustained thereafter. As mentioned above, CK levels were already at the baseline before the CAR-T cell infusion and did not increase after discontinuation of corticosteroids/immunosuppressive drug.

Side effects

All juvenile patients ($n = 3$) experienced similar side effects, including neutropenia ($n = 1$ grade 3, $n = 2$ grade 4), transient anemia ($n = 3$ grade 2), and mild cytokine release syndrome (CRS, $n = 3$ grade 1). One patient required a single infusion of Tocilizumab (8 mg/kg) for grade 1 CRS management. None of the patients exhibited signs of infections or immune effector cell-associated neurotoxicity syndrome (ICANS) (Fig. 1).

Challenges in pediatric CAR-T cell use

Children who received CAR-T cell therapy had particularly severe and refractory autoimmune diseases, unresponsive to conventional therapies. These patients also suffered severe complications related to intensive immunosuppressive therapies and high-dose corticosteroids, including arterial hypertension, osteoporosis, and infections. Prior treatment with the B-cell-depleting anti-CD20 monoclonal antibody Rituximab provided only partial and transient benefits. However, anti-CD19 CAR T-cell therapies appeared to be more effective (albeit with short follow-up), achieving B-cell clearance in the bone marrow. Notably, a dramatic response was observed in cases of severe renal disease in SLE and calcinosis in JDM, highlighting the therapeutic potential of CAR-T cells in these challenging complications.

Despite the promising outcomes, the limited number of treated patients and the short duration of follow-up necessitate confirmation through larger cohorts and randomized studies.

Conventional treatments have failed to achieve persistent normalization of biological markers such as anti-dsDNA antibodies and the type I interferon signature. The significant reduction in the IFN-I signature following CAR-T cell therapy suggests that IFN-I signaling may be a consequence, rather than a cause, of autoreactive B cell activation.

The hypothesis that CAR-T cell therapy resets the B-cell compartment, potentially eliminating autoreactive pathogenic B-cell clones, may explain the observed dramatic response observed. Post-treatment, a virtual disappearance of IgG and IgA expressing B cells are observed while IgM and IgD expressing B cell clone are expanded [88]. Interestingly, preexisting humoral immunity to vaccine related antigens can persist in adult patients suggesting a persistence of long-lived plasma cells and humoral immunity [89]. Additionally, repertoire analysis showed that CD19 CAR-T cell therapy did not affect the T cell receptor (TCR) repertoire allowing a normal T cell response [88].

The observed efficacy in a young patient with seronegative juvenile dermatomyositis, who had no detectable autoantibodies, suggests a role for B-cells or the presence of undetectable autoantibodies in this patient.

Leukapheresis can be challenging due to high disease activity and severe lymphopenia resulting from both the disease and prior immunosuppressive treatments. It is noteworthy that the washout period was shorter in

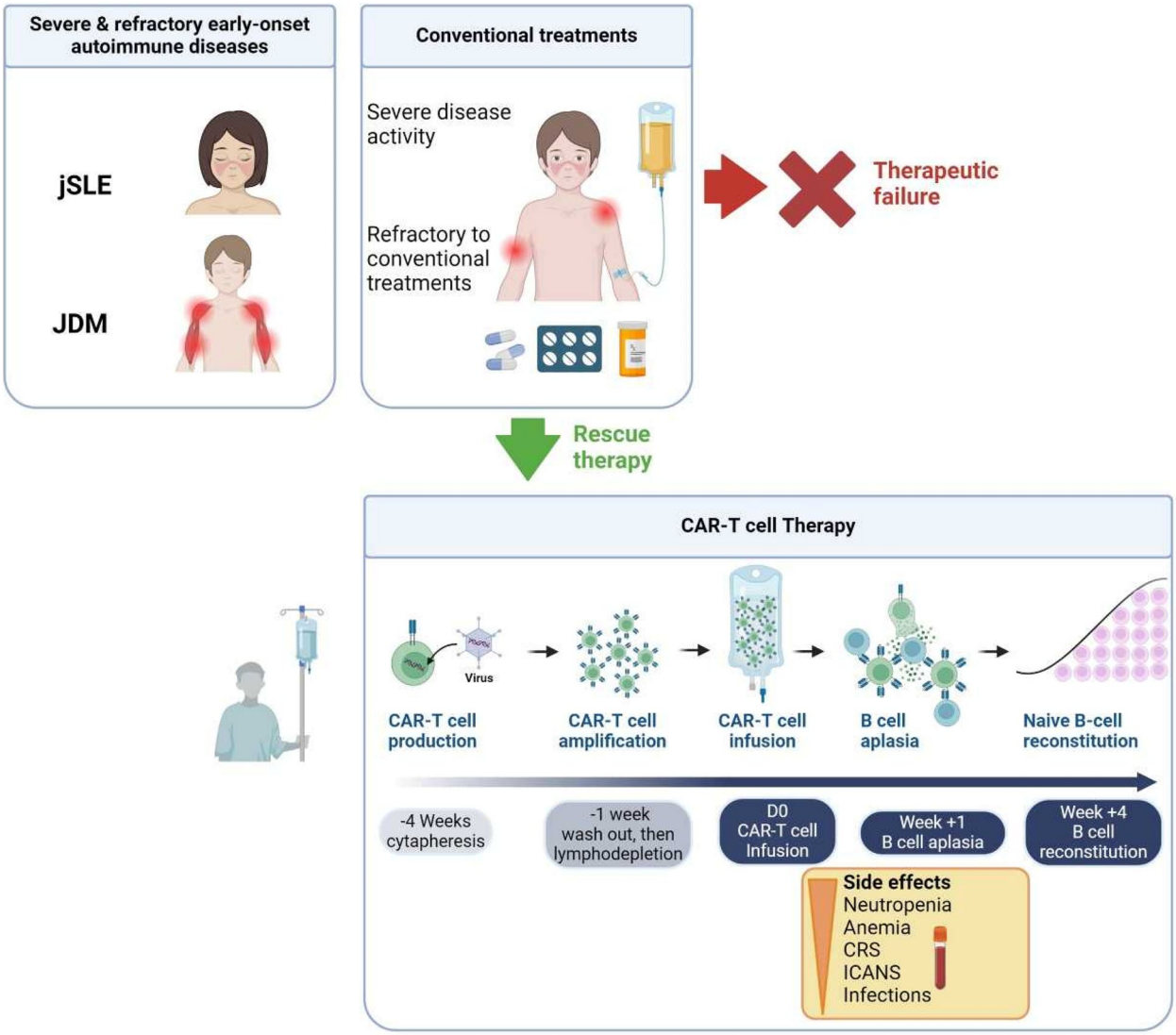

Fig. 1 Illustration of the treatment pathway for patients with severe early-onset autoimmune diseases that are refractory to conventional treatments, with CAR-T cell therapy serving as a salvage option. To optimize CAR-T cell expansion, lymphodepletion is induced using fludarabine and cyclophosphamide which carries a risk of disease exacerbation. Following CAR-T cell infusion, patients commonly experience a transient period of bone marrow aplasia, increasing susceptibility to infections. The expansion of CAR-T cells leads to the targeted depletion of autoreactive B lymphocytes. However, this process may also trigger the release of cytokines, potentially leading to cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Lymphocyte reconstitution occurs progressively over the course of several weeks, though the timeline may vary among patients. The reconstituted B cells are naive and no longer produce autoreactive antibodies, leading to both clinical and biological remission, thereby eliminating the need for ongoing immunosuppressive therapy. *Figure created with Biorender.com*

juvenile patients compared to the adult population without compromising the efficacy of CAR-T cell therapy. Determining the optimal duration of the washout period will be critical for future pediatric studies.

While lymphodepletion with fludarabine and cyclophosphamide may have contributed to initial outcomes, the doses were lower than those used in previous treatments (e.g., plasmapheresis, cyclophosphamide), which had proven ineffective.

Given the heightened risk of infections, side effects, and treatment burdens, exploring reduced conditioning regimens is worthwhile. However, lymphodepletion remains necessary to induce CAR-T cell expansion. Although reducing the intensity of lymphodepletion may lessen side effects, such as ICANS, it could also reduce efficacy. Lymphodepletion might be particularly beneficial in conditions like myositis and scleroderma, where

T-cell activation during CAR-T cell expansion could temporarily worsen disease activity.

Conditioning regimens were adjusted according to renal function, indicating a tailored approach to patient safety. Recent data regarding ovarian dysfunction with intravenous cyclophosphamide used for 6 months at the NIH regimen (0.5–0.75 g/m2 monthly) minimally impacts fertility, suggesting that fertility concerns related to CAR-T cell therapy, which involves even lower doses of cyclophosphamide, are likely minimal [90].

The persistence of CAR-T cells for six months in the bloodstream of the pediatric patient from Erlangen, is notably longer than observed in adults. However, in autoimmune diseases, prolonged CAR-T cell persistence or extended B-cell aplasia may not be necessary, as immune system resetting appears to induce prolonged remission in adults effectively. The reconstitution of the naive B-cell population aims to restore humoral immunity and enable vaccine protection. Notably, remission persisted in the juvenile dermatomyositis patient even after B-cell reconstitution at eight months, without the need for ongoing immunosuppression.

No deaths were reported in either the adult or juvenile cohorts during CAR-T cell therapy. The survival rate appears notably higher than with autologous or allogeneic HSCT for autoimmune diseases, although further studies are needed to confirm this, given the limited number of patients treated with CAR-T cells. Additionally, no severe side effects were reported, even in patients with end-stage kidney failure. In the juvenile population, mild cytokine release syndrome (CRS) occurred but resolved quickly with a single dose of Tocilizumab in one patient. Adults with anti-synthetase syndrome experienced some ICANS, but symptoms were effectively managed with a short course of dexamethasone [20]. The use of corticosteroids or Tocilizumab does not seem to affect the efficacy of CAR-T cell therapy in the treatment of hematological conditions [91].

CRS is a systemic condition characterized by a high cytokines production that can mimic infectious conditions, leading to fever, tachycardia, tachypnea, and hypotension. Following lymphodepletion, which induces profound neutropenia and B-cell depletion, along with the use of steroids or biologics (such as Tocilizumab), patients are at an increased risk of infectious complications [92]. The duration of B-cell aplasia varies and can last for several months. No infections have been reported in the juvenile population, but preventive measures, such as immunoglobulin replacement therapy starting one month after infusion, are recommended to avoid complications. Vaccine guidelines for children post-CAR-T cell therapy established in oncological indications, advise against administering live or attenuated vaccines during B-cell depletion due to reactivation risks, while inactivated vaccines should generally be postponed during B-cell aplasia. However, the influenza vaccine can be administered one month after CAR-T cell therapy [92].

Concerns have been raised regarding the safety of CAR-T cell therapies, particularly in relation to secondary malignancies and potential impacts on future pregnancies. The hypothesis that genetic modifications of T lymphocytes could induce T-cell neoplasms emerged following a Food and Drug Administration (FDA) warning about secondary T-cell malignancies in patients with hematologic disorders treated with CAR-T cells [93]. However, it is important to note that the adult population had significant prior exposure to chemotherapeutic agents, and pre-cancerous cells with clonal hematopoiesis were detected before CAR-T cell infusion, a condition likely less prevalent in the pediatric auto-immune population. Additionally, T-cell malignancies did not consistently express the CAR transgene [94]. A global survey on the risk of secondary malignancies after CAR-T cells therapy in pediatric oncology published reassuring data with only one patient identified to develop T cell lymphoma without retroviral transgene in the clonal population. No insertional mutagenesis was reported in pediatric patients [95] though further long-term studies are necessary to fully assess the enduring safety profile of CAR-T cell therapies.

The sustained drug-free remission observed after a single infusion strongly suggests a causal effect of CAR T-cell therapy, positioning the pediatric population as a promising candidate for future studies. The therapy has demonstrated a favorable safety profile and efficacy, with manageable side effects. Further research involving larger patient cohorts will be necessary to confirm these findings and refine treatment protocols.

Multidisciplinary teams, including pediatric rheumatologists and hematologists, are crucial for managing these severe conditions with multi-organ involvement and tailoring treatments to meet the specific needs of each patient.

To our knowledge, none of the patients treated with CD19-targeted therapy currently described have undergone genetic exploration. The early onset of the disease and its severity suggest that genetic factors might be implicated. JSLE cases have been linked to single gene mutations, defining the concept of monogenic or Mendelian lupus. Genes associated with monogenic lupus can be classified into at least five functional categories: complement deficiency, interferonopathies driven by defective nucleic acid metabolism or innate sensor overactivity, tolerance breakdown of the adaptive immune

system, JAK-STAT pathway abnormalities, apoptosis dysregulation, and TLR-mediated autoimmunity [96, 97].

Notable differences can be observed between monogenic and polygenic lupus. Apart from complement deficiencies, certain mutations in lupus patients lead to immune deficiencies such as IKAROS, RAG2, while others are commonly associated with lymphoproliferative diseases like PRKCδ. PKCδ deficiency is the first identified B cell–related form of monogenic lupus [98]. Some mutations, such as those in *C1q*, *C1R*, *C1S*, *PRKCD*, *UNC93B1*, and *TLR7*, are more frequently associated with glomerulonephritis [96, 97, 99]. In monogenic lupus associated with B cells genetic defects, the strategy might be harmful, although the risk of relapse is likely higher than in adult-onset non-genetic lupus. Some monogenic interferonopathies have been described with an increase in lupus-like phenotype as a direct consequence of excessive production of IFN-I [100]. The penetrance is variable, suggesting that constitutive expression of IFN-I alone is not sufficient to drive the autoimmunity. Consequently, resetting B cells in these patients may still represent an option to cure a flare and delay disease progression.

The duration of remission achieved through CAR-T cell therapy in patients with monogenic lupus remains unclear. In the worst-case scenario, genetic factors may facilitate early relapses. However, it is also recognized that additional external environmental factors likely contribute to the onset of clinical manifestations. Given the severity of these clinical manifestations, achieving multiple years of remission without any treatment would be considered a significant success. In the event of a relapse, a second infusion could be a viable option.

In March 2024, the first CAR T-cell trial in children with lupus gets FDA go-ahead. This marks the first CAR T-cell trial for pediatric lupus in the United States, with Seattle Children's planning to enroll patients in the summer of 2024 [101].

Simultaneously, a prospective open-label single-arm study is underway in China to evaluate the efficacy of anti-CD19 CAR-T cells in children aged 5 to 18 years with refractory SLE (NTC06222853). This trial, spanning 24 months, consists of two phases for dose exploration and expansion to determine a safe and effective dose, with an expected enrollment of 10 to 19 patients. Further clinical trials are essential to develop a treatment algorithm that enables the timely and optimal utilization of CAR T-cell therapies.

CAR-T cell therapies have been used in a limited number of pediatric patients with SLE and JDM, selected based on disease activity and severity. Early-onset SLE is often complicated by neurolupus, while JDM is associated with interstitial lung disease and gastrointestinal vasculopathy. To date, CAR-T cells have not been applied to these specific complications. Further exploration of CAR-T cell therapy in these indications and in other autoimmune diseases, such as systemic scleroderma, is warranted.

CAR-T cell therapies offer significant advantages over conventional treatments, offering impressive clinical outcomes with drug-free remission, and potentially reducing long-term health complications and the economic burden associated with managing chronic conditions in patients with early-onset disease. Treatment adherence, a significant challenge in adolescents, is effectively addressed with CAR-T therapies. The ability to return to school within a few months after infusion is another significant benefit. However, the high cost of manufacturing CAR-T cells restricts their widespread use. Therefore, conducting economic studies valuating the long-term benefits of clinical remission for severe patients are essential.

Although short-term safety data are encouraging, long-term safety evaluations remain crucial. New strategies utilizing allogeneic CAR (T or NK) cells could enhance the accessibility of such therapies. Additionally, non-cellular therapies, such as bispecific T cell engagers (BiTEs), are currently being investigated in adult autoimmunity and may potentially be adapted for pediatric use.

Conclusions

CAR-T cells represent a significant breakthrough in pediatric rheumatology, offering the potential for curative treatments for autoimmune diseases. This new era in patient care has brought forth novel questions and challenges, particularly regarding outcomes in patients with specific genetic backgrounds. Coordinated translational and clinical research is essential to deepen our understanding and expand access to CAR-T cell therapies for children with severe and refractory conditions. Understanding and expand access to CAR-T cell therapies for children with severe and refractory conditions. While most of the efforts currently focus on adult-onset autoimmune diseases, the high burden and severity in children make this population of particular interest. Consequently, there is an urgent need to offer CAR-T cell therapy to severe pediatric patients, ideally through clinical trials, or the least, through compassionate use.

Abbreviations

BiTEs	Bispecific T cell Engagers
CAR	Chimeric Antigen Receptor
CAT	Cutaneous Assessment Tool
CAT -BM	Cutaneous Assessment Tool in the shortened Binary Method version
CK	Creatine Kinase
CMAS	Childhood Myositis Assessment Scale
CRS	Cytokine Release Syndrome
CYC	Cyclophosphamide
DMARD	Disease-Modifying Antirheumatic Drugs

DNA	Deoxyribonucleic Acid
EBMT	European Society for Blood and Marrow Transplantation
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
GC	Glucocorticoids
HCQ	Hydroxychloroquine
HSCT	Hematopoietic Stem Cell Transplantation
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
IFN-I	Type-I Interferons
JAK	Janus Kinase
JDM	Juvenile Dermatomyositis
jSLE	Juvenile Systemic Lupus Erythematosus
MMF	Mycophenolate Mofetil
MTX	Methotrexate
NIH	National Institutes of Health
PRES	Pediatric Rheumatology European Society
RP-ILD	Rapidly progressive interstitial lung disease
ScFv	Single-chain variable Fragment
SLEDAI	Systemic Lupus Erythematosus Disease Activity
SHARE	Single Hub and Access point for pediatric Rheumatology in Europe.
TCR	T Cell Receptor
VCN	Vector Copy Number
VH	Variable regions of Heavy immunoglobulin
VL	Variable regions of Light immunoglobulin

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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