Treatment of a patient with severe systemic sclerosis (SSc) using CD19-targeted CAR T cells

Several lines of evidence suggest a role of B cells in severe systemic sclerosis (SSc) pathophysiology: elevated levels of B-cell stimulating factors, disturbed B-cell homeostasis with expansion of naïve and decrease of memory B cells, and anti-fibrotic effects of B-cell depletion in murine fibrosis models. First randomised controlled trials showed promising efficacy of the CD20-targeting antibody rituximab (RTX)\(^4\); however, therapeutic efficacy of RTX in SSc remains controversial: while one trial demonstrated significant skin improvement,\(^5\) RTX slowed forced vital capacity (FVC) decline in another fibrotic effects of B-cell depletion in murine fibrosis models.\(^6\) First randomised controlled trials showed promising efficacy of the CD20-targeting antibody rituximab (RTX)\(^4\); however, therapeutic efficacy of RTX in SSc remains controversial: while one trial demonstrated significant skin improvement,\(^5\) RTX slowed forced vital capacity (FVC) decline in another fibrotic effects of B-cell depletion in murine fibrosis models.\(^6\)

Of note, autologous stem cells targeted via CD20 expanded in SSc, and plasmablasts, which may be responsible for autoantibody production, are not targeted via CD20 treated mortality is high. Hence, a more tolerable treatment with deep and broad CD19+ B-cell depletion may be more effective. Recently, CD19-chimeric antigen receptor (CAR) T cells showed remarkable effects in refractory SLE\(^3\) and first evidence of efficacy in a patient with antisynthetase syndrome,\(^6\) suggesting the principle feasibility to intercept B cell depletion in murine fibrosis models.\(^5\) Several lines of evidence suggest a role of B cells in severe systemic sclerosis (SSc) pathophysiology: elevated levels of B-cell stimulating factors, disturbed B-cell homeostasis with expansion of naïve and decrease of memory B cells, and anti-fibrotic effects of B-cell depletion in murine fibrosis models. First randomised controlled trials showed promising efficacy of the CD20-targeting antibody rituximab (RTX)\(^4\); however, therapeutic efficacy of RTX in SSc remains controversial: while one trial demonstrated significant skin improvement,\(^5\) RTX slowed forced vital capacity (FVC) decline in another fibrotic effects of B-cell depletion in murine fibrosis models.\(^6\)

Here, we report for the first time the treatment of a patient with severe, treatment refractory SSc with CD19-CAR T cells. A 60-year-old man presented with diffuse cutaneous SSc with first non-Raynaud’s disease manifestation (skin, lung and heart fibrosis) 22 months before baseline and onset of Raynaud’s phenomenon 28 months before baseline. At baseline, the patient presented with diffuse myocardial fibrosis (cardiac MRI), lung fibrosis (high-resolution computed tomography), pulmonary hypertension (class I with combined precapillary and postcapillary pulmonary hypertension based on the results of right heart catheterisation: mean pulmonary arterial pressure of 33 mm Hg (>20), pulmonary arterial wedge pressure of 18 mm Hg (>14) and pulmonary vascular resistance of 3 Wood units (>2)), Raynaud’s phenomenon and carpal arthritis. He had positive anti-nuclear antibody titres and anti-RNA polymerase III autoantibodies (subunit RP11). Previously failed immunosuppressants included methotrexate (15 mg/week, treatment duration 3 months) and mycophenolate (dose 2 g/day for 23 months). Cyclophosphamide was not used due to inefficacy for arthritis and concerns regarding cardiac involvement. Immunosuppression was tapered before lymphodepletion and stopped 4 weeks before CAR T-cell infusion. CAR T cells were produced from autologous T cells obtained by leucapheresis. T cells were transduced by a lentiviral vector (Miltenyi) and expanded through the automated system (ClinicMACS Prodigy).\(^3\) After dose-reduced lymphodepletion (50%) due to renal impairment with fluoradine (12.5 mg/m\(^2\); days −5, −4 and −3) and cyclophosphamide (500 mg/m\(^2\); day −3), 1 × 10\(^6\) CAR T cells/kg were administered. CAR T cells rapidly expanded from day 3 (total: 0.3 cells/μL, 0.1% CARs of CD3+ T cells) until day 9 (1275/μL; 66.35% CARs of CD3+ T cells; figure 1A,B). CAR T cells then rapidly decreased but were still detectable (1%) on day 119 after infusion. Full B-cell depletion was reached on day 7 (figure 1B).

CAR T-cell therapy was well tolerated. Following CAR T-cell infusion, the patient had mild fever for less than 24 hours (Cytokine Release Syndrome (CRS) grade 1) and no signs of immune effector cell-associated-neurotoxicity syndrome. No anti-interleukin-6 receptor antibody treatment was given as there was no higher-grade CRS. Immune cells reconstituted quickly: CD4+ T cells were above 200/μL on day 37 and cells reoccurred on day 77. IgG levels remained above 700 mg/dL in the following 6 months, while ANA reactivity (titre 1:320 at baseline, speckled pattern) was abrogated, and RP11 auto-antibodies were no longer detectable (figure 1C) on follow-up of 3 and 6 months. Seroconversion was paralleled by reduced molecular fibroblast activation particularly in the myocardium by 32.6% as determined by \(^6\)Ga-FAPi-04 positron emission tomography—CT (septal basal myocardial uptake value prior to CAR T cell therapy: 8.6, on follow-up: 5.8)\(^7\) (figure 1D). Pulmonary fibrosis remained stable as assessed by CT on follow-up of 3 months and pulmonary function tests (figure 1H) on follow-up of 3 and 6 months. Echocardiography was performed at baseline and 6 months after CAR T-cell therapy as part of the non-invasive PAH screening: left ventricular ejection fraction remained stable, while signs of right ventricular strain showed a tendency of improvement (figure 1I). Carpal arthritis improved 3 months after CAR T-cell therapy (figure 1E). Consistently, tender joint counts improved from n=22 at baseline to n=3. Tendon friction rubs were no longer detectable on follow-up of 3 months as reflected in the European Scleroderma Trials and Research Group (EUSTAR)-activity index (figure 1F) at three and six months follow-up. Skin fibrosis showed a tendency of improvement as analysed by two independent assessors (figure 1G) during three and six months follow-up. Moreover, the patients subjectively reported less frequent and less severe attacks of Raynaud’s phenomenon.

These data provide first evidence that CD19-targeting CAR T-cell treatment might be effective in severe SSc. The fast improvement of heart, joint and skin manifestations paralleled by seroconversion supports a central role of B cell-mediated autoimmunity in SSc. It cannot be completely ruled out that conditioning therapy contributed to the short-term effects of CAR T-cell therapy in this patient, and further observation of the drug-free course of SSc is warranted. Level of immunosuppression is limited with the current conditioning therapy as low doses are used compared with standard SSc treatment regimens. Thus, future controlled studies, if not done in life-threatening disease, may include an arm with conditioning therapy only in order to tease out the effect of conditioning therapy. Moreover, SSc patients with other known risk factors for a poor prognosis, such as positivity for anti-Scl antibodies, will need to be studied.

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Figure 1 Patient with severe diffuse systemic sclerosis treated with CD19-CART cells. (A) Dot plot showing expression of CD3 (y-axis) and CD19-CAR (x-axis) quantifying the circulating CD19-CART cells by FACS on days 3 and 9 after infusion. (B) Time course of absolute and relative numbers of circulating CD19-CART cells and CD19+ B cells; d0=01.080.2022. (C) Densitometric analysis of autoantibodies against RNAPIII, subunit RP11 at baseline (1 month prior to CAR T-cell infusion) and 3 months after CAR T-cell therapy. (D) PET showing resolution of fibroblast activation protein inhibitor (68Ga-FAPI-04) tracer accumulation in the heart at baseline and 3 months after CAR T-cell therapy. (E) Axial and coronal sections of T1-weighted contrast-enhanced MRI of the hands at baseline and 3 months after CAR T-cell therapy. (F) EUSTAR activity index, (G) mRSS and (H) lung function parameters at baseline and 3 months after CAR T-cell therapy. mRSS changes (G) were visualised using a modified version of the scheme described in Khanna D, Furst de, et al. J scleroderma relat Disord.2017 Jan-Apr;2 (1):11–18.doi:10.5301/jsrd.5000231. CAR, chimeric antigen receptor; CRP, C reactive protein; DLCO, diffusing capacity or transfer factor of the lung for carbon monoxide; EF, ejection fraction; FACS, fluorescence-activated cell scanner; KCO, carbon monoxide transfer coefficient; mRSS, modified Rodnan Skin Score; PASP, pulmonary artery systolic pressure; PET, positron emission tomography; PFT, pulmonary function tests; RA, right atrium; SUV, standard uptake value; TFR, tendon friction rubs; TTE, transthoracic echocardiography.
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