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Systemic sclerosis

Teclistamab induces rapid clinical response and deep tissue depletion in refractory systemic sclerosis—a case series

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ABSTRACT

Objectives: This study aimed to evaluate clinical outcomes, serologic changes, and immunologic effects induced by the bispecific B cell Maturation Antigen (BCMA)x Cluster of Differentiation (CD)3 T-cell-engaging antibody teclistamab in systemic sclerosis (SSc).
Methods: Patients with severe and treatment-refractory SSc were treated with teclistamab as off-label therapy. Blood and tissue samples from skin and bone marrow were analysed with immunohistochemistry and flow cytometry, serum antibodies were quantified by enzyme-linked immunosorbent assay (ELISA). Clinical efficacy was assessed using the American College of Rheumatology Composite Response Index in Systemic Sclerosis (ACR-CRISS) responses, among others.
Results: Ten patients with SSc (70% female; median age 51 years [IQR: 7]) completed 1 cycle of teclistamab. Two patients with advanced SSc heart involvement died shortly after treatment initiation. B-cells and plasma cells were almost completely eliminated from bone marrow and skin, accompanied by a median reduction of 70.6% (IQR: 39%) in antitopoisomerase antibody titres, decreases in serum IgG, and vaccination titres. After a median follow-up of 3.75 months (IQR: 2.5 months), 71% and 43% of patients achieved revised ACR-CRISS 25 and 50 responses, respectively. Among patients with interstitial lung disease, radiographic and functional improvement was observed by week 12 with a median increase in forced vital capacity of 7% (IQR: 15%). Skin fibrosis similarly improved, with a median decrease in the modified Rodnan skin score of 35.9% (IQR: 17.9%), accompanied by corresponding reductions in fibroblast activation protein (FAP)-alpha-positive fibroblasts in skin biopsy specimens.
Conclusions: Teclistamab induced deep tissue depletion of B-cells and plasma cells and rapid clinical and serological responses, with evidence for resolution of inflammation and potential modification of fibrotic processes. These data suggest the potential of BCMA-directed therapies to promote immune modulation and tissue remodelling.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Early findings from case reports and small case series suggest that BCMA-directed therapy with teclistamab may be effective and well tolerated in severe and refractory systemic sclerosis (SSc).

WHAT THIS STUDY ADDS

- Teclistamab treatment promoted profound depletion of B cells and plasma cells across peripheral blood, skin, and bone marrow samples, accompanied by marked reductions in disease-specific autoantibodies.
- Teclistamab led to rapid clinical improvement, suggesting reduction of inflammatory activity and potential modification of fibrotic processes in affected skin, lung, and cardiac tissue.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- BCMA-directed bispecific antibodies may provide substantial clinical benefit with improvement of organ functions and health-related quality of life in patients with treatment-refractory SSc.
- Findings warrant evaluation in prospective clinical trials with stringent patient selection, standardised safety monitoring, and assessment of durability of response.

INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune disease characterised by immune dysregulation, microangiopathy, and progressive fibrosis of skin and internal organs. Increasing evidence supports a B-cell-driven pathogenesis of SSc, in which autoreactive B-cells and plasma cells perpetuate autoantibody production, inflammation, and fibroblast activation [1]. Both B-cells and plasma cells have therefore emerged as promising therapeutic targets [2].

Despite an expanding armamentarium of immunosuppressive and targeted therapies, treatment options in SSc remain limited. Current therapeutic approaches primarily aim to attenuate inflammation and slow down the progression of fibrosis. SSc-associated interstitial lung disease (SSc-ILD), one of the leading causes of death, has been the focus of most therapeutic development. Antifibrotic agents, such as nintedanib [3], immunosuppressants such as mycophenolate mofetil [4], cyclophosphamide [5], and tocilizumab [6], as well as B-cell depletion with rituximab [7], have shown partial efficacy in the treatment of SSc-ILD [8,9]. Although established therapies can slow down disease progression, they have not been shown to support meaningful recovery of organ function. Autologous haematopoietic stem cell transplantation has demonstrated potential to induce long-term remission in selected cases [10,11], but its high toxicity limits broad application. The persistent gap between

high disease burden and limited therapeutic options highlights the unmet medical need for novel treatments in this devastating disease.

Recent guidelines emphasise the necessity for novel therapeutic approaches that go beyond transient immunosuppression toward durable immune reprogramming [12]. Novel B cell- and plasma cell-directed therapies, including anti-cluster of differentiation (CD)19 chimeric antigen receptor T-cells (CAR-T) [13–15], anti-CD19/B cell Maturation Antigen (BCMA) CAR-Natural Killer cells, and BCMA-directed bispecific antibodies such as teclistamab, have shown unprecedented results in early reports in SSc [16–20]. However, robust evidence from larger, multicentre cohorts and clinical trials is still lacking. The present multicentre case series therefore investigates the efficacy and safety of teclistamab in treatment-refractory SSc.

METHODS

Patients and treatment

Between June 2024 and September 2025, 10 patients who met the 2013 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria for SSc received teclistamab as an off-label therapy following a shared decision-making approach at Charité – Universitätsmedizin Berlin, University Medical Center Hamburg-Eppendorf, University Hospital Aarhus, and University Hospital Tübingen. Patients gave written informed consent and received teclistamab in compliance with the Declaration of Helsinki. The analysis was approved by the local Ethics Committee at Charité – Universitätsmedizin Berlin (EA1/002/24). All patients had progressive, treatment-refractory SSc and had failed at least 2 previous immunosuppressive treatments, as reflected by a revised American College of Rheumatology Composite Response Index in Systemic Sclerosis (rev ACR-CRISS [21]) score of 0 in response to their previous immunosuppressive treatment. Baseline immunosuppressive therapies were discontinued 2 weeks before therapy, except for patient 4, who continued tapering prednisone. Teclistamab was administered subcutaneously according to a step-up regimen identical to that approved for the treatment of relapsed and refractory multiple myeloma [22], with the target dose of 1.5 mg/kg being administered 2 to 4 times in all patients (see Supplementary Table S1 for details); median cumulative dose was 6.36 mg/kg (IQR: 0.35 mg/kg). All patients received antiviral and antimicrobial prophylaxis with acyclovir (400 mg twice daily) and cotrimoxazole (sulfamethoxazole/trimethoprim 800/160 mg 3 times per week), or atovaquone (250 mg/d). Intravenous immunoglobulin (IVIG) replacement therapy was initiated when serum immunoglobulin (IgG) levels fell <4 g/L.

We have previously reported part of the baseline and 3-month follow-up data of patient 1 [19].

Safety assessment

Patients were closely monitored for cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS) as recommended by the American Society for Transplantation and Cellular Therapy [23], as well as for infections, cytopenias, hypogammaglobulinaemia, and other adverse events. CRS was managed according to international standards using acetaminophen, glucocorticoids, and tocilizumab, as indicated.

Assessment of clinical, serological, and immunologic response

Only patients with ≥12 weeks of follow-up were included in the efficacy assessment. Depletion of B-cells and plasma cells was assessed in peripheral blood, skin, and bone marrow using established protocols (Supplementary Methods, Supplementary Tables S3, S4). Clinical disease activity assessments included the rev ACR-CRISS [21], assessed in a 2-step process excluding significant worsening or new end-organ damage in the first step and assessing all 5 parameters, showing improvement of 25% or 50% (except forced vital capacity [FVC], for which 5% improvement was calculated in all categories); only relapses as defined by the European Society for Blood and Marrow Transplantation [24] were able to transition patients to a lower category, and the revised European Scleroderma Trials and Research Group (EUSTAR) activity index (rev EUSTAR-AI [25]). Pulmonary function tests, including diffusion capacity for carbon monoxide, sequential chest computed tomography (CT) scans, and a visual analogue scale of patient-reported dyspnoea, were used to assess SSc-ILD. Cardiac involvement was evaluated by measuring troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP), and by transthoracic echocardiography and cardiac magnetic resonance imaging (MRI).

Patient and public involvement

Three patient research partners who are members of the Deutsche Rheumaliga were actively involved in all stages of the research project. They shaped both clinical research questions and output parameter selection to ensure that they were meaningful for their condition.

Statistics and graphical analysis

Analyses were conducted using all available data for each outcome measure. As a result, the number of evaluable patients varied across analyses. Organ-specific outcomes were assessed only in patients with the respective organ involvement at baseline. To improve interpretability, outcomes presented in the main figures were restricted to those available in >50% of the respective analysis population (either the overall cohort or the relevant disease subgroup). Analyses not meeting this threshold were considered exploratory and are reported in the supplementary material. Bone marrow analyses were retained in the main manuscript despite the limited sample size due to their mechanistic relevance and consistency across complementary methodologies; these analyses are explicitly labelled as exploratory. Statistical and graphical analysis and data visualisation were performed with GraphPad Prism, version 10.5. Data are presented as median (IQR) unless otherwise specified; categorical variables are presented as counts and percentages. Longitudinal data are displayed as individual patient trajectories. No formal hypothesis testing or statistical tests were performed due to the exploratory retrospective nature and limited sample size of this case series.

RESULTS

Patient characteristics

Ten patients with SSc (7 of 10 women), with a median age of 51 years (IQR: 7 years), were included in this case series (Table 1). Median disease duration was 2 years (IQR: 6), and median number of previous immunosuppressive treatments was

Table 1
Patient characteristics

Characteristics	Total, median (IQR)	Pat 1	Pat 2	Pat 3	Pat 4	Pat 5	Pat 6	Pat 7	Pat 8	Pat 9	Pat 10
Age (y)	51 (7)	48	55	49	48	35	55	63	39	57	53
Sex	70% f	f	f	f	m	f	m	m	f	f	f
Centre		BE	HH	HH	BE	BE	BE	BE	AA	AA	TU
Antinuclear antibody titre		1:1280	1:2560	1:640	1:1280	1:5120	1:1280	1:2560	1:1280	1:1280	1:1280
Autoantibody	60% Scl-70	Scl70	RNAP III	PM/Scl-75/-100, SSA	Scl70	Scl70	Scl70	RuvBL1/2	Scl70	Scl70	U1-RNP, SSA
CrP (<5 mg/L)	6.1 (18.2)	7.2	5	30	0.6	19.2	4.8	80.5	1	1	7.6
Disease duration, y	2 (6)	7	1	4	2	1	2	0.5	18	7	0.5
Follow-up duration, mo	3.75 (2.5)	17	8.5	5.5	1	4.5	4	3.5	3.5	3	1
Skin											
mRSS (0-51)	27.5 (11)	36	39	26	15	32	25	36	29	8	26
Lung											
Interstitial lung disease, N (%)	7/10 70%	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Duration of interstitial lung disease (y)	2 (3)	3		2			2	0.5	3.5	7	0.5
Dominant pattern of interstitial lung disease	NSIP	NSIP		NSIP			NSIP	NSIP	NSIP	NSIP	NSIP
Extent of reticulations, %	10 (7.5)	10		10			5	20	N.A.	N.A.	N.A.
Extent of ground-glass opacities, %	22.5 (12.5)	30		20			25	10	N.A.	N.A.	N.A.
FVC, % pred.	66 (34)	62		41			70	66	85	76	42
DLCOcSB, % pred.	42 (7)	36		40			44	42	25	43	43
DLCOcVA, % pred.	67 (27)	60		N.A.			67	74	33	73	N.A.
Heart											
SSc heart disease, N (%)	5/10 50%	Yes	No	No	Yes	Yes	No	Yes	No	No	Yes
Troponin T, ng/L (<14)	75.5 (147.5)	50			91	314		60			N.A.
NT-proBNP, ng/L	520 (9317.5)	375			5755	520		103			13358
LVEF, %	56 (19)	63			35	65		56			55
sPAP, mmHg	28 (12.5)	25			28	35		20			35
Pericardial effusion	60%	no			no	yes		yes			yes
Congestive heart failure	40%	no			yes	yes		no			no
Joints/muscle											
Arthritis	60%	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes
Tendon friction rubs	70%	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Contractures	80%	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
CK, U/L	129.5 (152)	50	203	137	73	332	33	362	51	130	129
Myalgias	100%	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vascular											
History of digital ulcers	50%	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Digital ulcers at baseline	40%	No	Yes	No	Yes	No	No	No	Yes	No	Yes
Pulmonary arterial hypertension	10%	No	No	No	No	No	No	No	No	No	Yes
Calcinosis cutis	20%	No	No	Yes	No	No	No	No	No	No	Yes
Telangiectasias	40%	Yes	No	No	Yes	No	Yes	No	No	No	Yes
Scleroderma renal crisis	0%	No	No	No	No	No	No	No	No	No	No
Gastrointestinal											
Reflux	90%	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dysphagia	70%	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes

(*continued on next page*)

Table 1 (*Continued*)

Characteristics	Total, median (IQR)	Pat 1	Pat 2	Pat 3	Pat 4	Pat 5	Pat 6	Pat 7	Pat 8	Pat 9	Pat 10
Early satiation	30%	No	Yes	No	No	No	No	No	Yes	Yes	No
Diarrhoea/constipation	40%	Yes	No	No	Yes	No	No	No	Yes	Yes	No
Previous therapies											
Immunosuppressive	3.5 (2)	HCQ, AZA, CYC, HSCT (CYC/ATG), **MMF, RTX**	CYC, **MMF, RTX**	CYC, **MMF, TAC, RTX**	**CYC, PRED**	**MMF, MTX**	CYC, **MMF, MTX**	**MMF, MTX**	PRED, CYC, ABT, MTX, ANI, **MMF, TOC, RTX**	PRED, CYC **MMF, RTX**	AZA, MMF, CYC, **RTX**
Vasoactive	100%	ILO	ILO, BOS	ILO, BOS	ILO	ILO	ILO, BOS	ILO	ILO, TAD	ILO, TAD, SIL, NIF	ILO, MAC, TAD
Antifibrotic	30%	NIN	No	No	No	No	No	No	**NIN**	**NIN**	No

AA, Aarhus; ABT, abatacept; ANA, antinuclear antibody; ANI, anifrolumab; ATG, antithymocyte globulin; AZA, azathioprine; BE, Berlin; BOS, bosentan; CK, creatine kinase; CrP, C-reactive protein; CYC, cyclophosphamide; DLCOcSB, diffusing capacity for carbon monoxide corrected for haemoglobin (single-breath); DLCOcVA, diffusing capacity for carbon monoxide corrected for alveolar volume; FVC, forced vital capacity; HH, Hamburg; HSCT, haematopoietic stem cell transplantation; ILD, interstitial lung disease; ILO, iloprost; IVIG, intravenous immunoglobulin; LVEF, left ventricular ejection fraction; MAC, macitentan; MMF, mycophenolate mofetil; mRSS, modified Rodnan skin score; MTX, methotrexate; N.A., not available. HCQ, hydroxychloroquine; NIF, nifedipine; NIN, nintedanib; NSIP, nonspecific interstitial pneumonia; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PM/Scl, Polymyositis/Scleroderma; PRED, prednisolone; RNAP, RNA polymerase; RTX, rituximab; SIL, sildenafil; sPAP, systolic pulmonary artery pressure; SSA, Sjögren's Syndrome Antigen A; SSc, systemic sclerosis; TAC, tacrolimus; TAD, tadalafil; TOC, tocilizumab; U1-RNP, U1 ribonucleoprotein.

Baseline characteristics are shown for all 10 patients with systemic sclerosis included in the study.

The last medical therapies before teclistamab was started is marked in bold.

3.5 (IQR: 2). All patients had diffuse skin disease with a median modified Rodnan skin score (mRSS) of 27.5/51 (IQR: 11) at baseline and a revised EUSTAR-AI score of ≥2.5 points, indicating highly active disease. Seven patients had ILD confirmed by high-resolution CT (HRCT) with a median baseline FVC of 66%/predicted (IQR: 34%) and a median baseline diffusing capacity for carbon monoxide corrected for haemoglobin (single-breath) (DLCOcSB) of 42%/predicted (IQR: 7%). Five patients had primary cardiac involvement, and 1 patient had concomitant pulmonary arterial hypertension (PAH). Six patients had anti-topoisomerase I (Scl-70) autoantibodies; anti-RNA polymerase III autoantibodies, anti-RuvB-like AAA ATPase 1/2 (RuvBL1/2), anti-Polymyositis/Scleroderma (PM/Scl)-75/-100, and U1 small nuclear ribonucleoprotein (U1-RNP) autoantibodies were present in 1 patient each.

Safety

CRS was common, occurring in 5 of 10 patients (50%). Events were mild, with 4 of 5 patients experiencing a maximum CRS of grade 1 and 1 patient experiencing grade 2 CRS. No ICANS occurred. Infections were common and diverse, ranging from viral to bacterial pathogens affecting the respiratory tract (n = 6), skin (n = 2), tonsils (n = 1), sinuses (n = 1), and urinary tract (n = 1). Details are summarised in Table 2. Only 2 patients (patient 6 with upper respiratory tract infection and patient 8 with bronchitis) required hospitalisation. All patients with a follow-up of ≥12 weeks developed severe hypogammaglobulinaemia (IgG <4 g/L; Fig 1D), requiring regular IVIG infusions (ranging between 20-70 g within the first 12 weeks; Supplementary Table S2) and a decline in vaccine titres that was partially mitigated by IVIG infusions (Fig 1E, Supplementary Fig S1).

Patient 6 developed severe, nonbloody diarrhoea (up to 30 stools/d) at week 6. Infectious work-up was negative, whereas faecal calprotectin was markedly elevated (>800 µg/g). Endoscopy demonstrated ulcerative proctitis with otherwise macroscopically normal ileum and colon. Histology of colonic biopsies showed features consistent with collagenous microscopic colitis, compatible with inflammatory bowel disease−like colitis with proctitis. Symptoms resolved under treatment with budesonide and mesalamine. Follow-up endoscopy at week 13 confirmed complete resolution of mucosal inflammation.

Two patients with advanced primary cardiac involvement died during follow-up. Patient 4 had rapidly progressive anti-Scl-70−positive SSc with severe primary cardiac involvement, recurrent ventricular tachycardia, pulmonary hypertension, and renal dysfunction. Left ventricular ejection fraction was reduced at 35%, and right ventricular (RV) ejection fraction was 24% with RV dilatation (right ventricular end-diastolic volume (RVEDV) 184 mL). Before teclistamab treatment, he was treated with pulse corticosteroids for severe myocardial inflammation and recurrent ventricular tachycardias, which his implantable cardioverter-defibrillator (ICD) failed to control due to the severe myocardial inflammation. Despite rapid improvement in skin fibrosis after teclistamab treatment, he developed multiorgan complications and died from diffuse alveolar haemorrhage and heart failure on day 20. Patient 10 had long-standing diffuse cutaneous SSc with PAH and primary cardiac involvement with reduced left ventricular function and atrial arrhythmias. She tolerated teclistamab without acute toxicity but died suddenly from presumed sudden cardiac death 12 days after the last dose (day 24). In both cases, death occurred in the context of severe preexisting SSc heart disease, and a definite causal relationship to teclistamab could not be

Table 2
Safety

Patient	CRS	CRS grade	CRS day (duration)	CRS symptoms	CRS treatment	ICANS	SAEs	Severe (<4 g/L) hypogamma-globulinaemia	Infections requiring treatment[a]
1	Yes	I I	d2 after 1st dose (1 d) d1 after 2nd dose (1 d)	Fever, nausea, diarrhoea Fever	PCM	No	No	Yes	4× bronchitis (weeks 20, 23, 32, 54; all CTCAE grade 2)
2	No	No	No	No	No	No	No	Yes	No
3	No	No	No	No	No	No	No	Yes	No
4	No	No	No	No	No	No	Death (diffuse alveolar haemorrhage)	Yes	No
5	Yes	I I	d1 after 1st dose (1 d); d1 after 2nd dose (1 d)	Fever Fever, nausea	PCM	No	No	Yes	1× tonsillitis (week 2; CTCAE grade 2)
6	Yes	I, II	d1 after 1st dose, (1 d); d1 after 2nd dose (1 d)	Fever Fever, hypotension	PCM, fluids	No	Hospitalisation for upper respiratory tract infection	Yes	1× upper respiratory tract infection (week 2; CTCAE grade 3)
7	Yes	I	d1 after 1st dose, (1 d)	Fever	PCM	No	No	Yes	1× phlegmone (week 1; CTCAE grade 2), 1× urine bacteraemia (week 3; CTCAE grade 2)
8	No	No	No	No	No	No	Hospitalisation for bronchitis	Yes	1× superinfection digital ulcer (week 1; CTCAE grade 2), 2× bronchitis (week 8; CTCAE grade 2; week 11; CTCAE grade 3)
9	Yes	I	d1 after 1st dose, (1 d)	Fever, diarrhoea	PCM	No	No	Yes	1× sinusitis (week 5; CTCAE grade 2),
10	No	No	No	No	No	No	Death (sudden cardiac death)	N.A.	No
Total, N (%)	5/10 (50)	I: 7/8 (87.5) II: 1/8 (12.5)	4/5 (80) d1 after 1st dose 1/5 (20) d2 after 1st dose 8/8 (100): 1 d duration	Fever: 8/8 (100) Hypotension: 1/8 (13) Nausea: 2/8 (25) Diarrhoea: 2/8 (26)	PCM: 8/8 (100); Fluids: 1/8 (13) TOC: 0/8 (0); GC: 0/8 (0)	0/10 (0)	2/10 (20)	8/8 (100)	6/8 (75)

2/2, secondary to; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; GC, glucocorticoids; ICANS, immune effector cell–associated neurotoxicity syndrome; N.A., not available; PCM, paracetamol; SAEs, serious adverse events; TOC, tocilizumab.
Table detailing the treatment-emergent adverse events observed in patients with SSc treated with teclistamab. Adverse events are presented for each patient; total frequencies and incidence rates are summarised in the final row.

[a] All infections resolved after treatment.

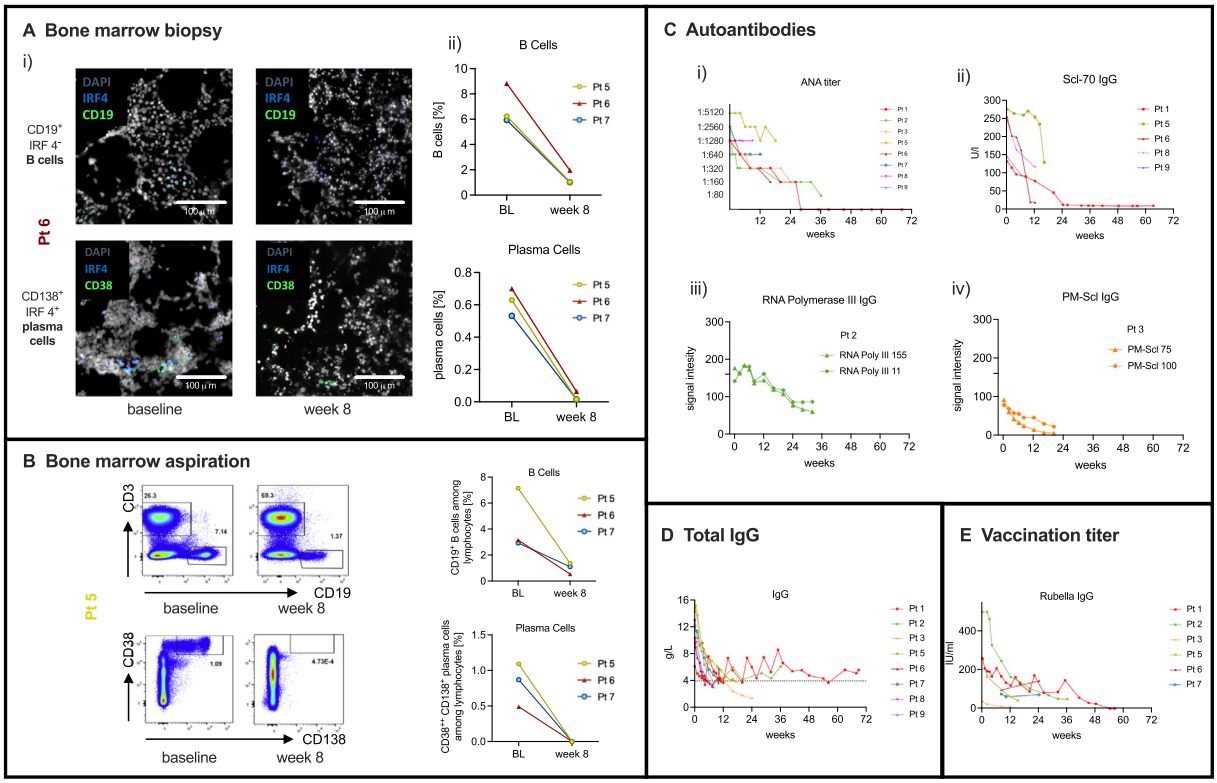

Figure 1. Teclistamab induces deep tissue depletion of B cells and plasma cells. (A) Plasma cell and B cell depletion in bone marrow biopsies (n = 3/8) at baseline (BL) and week 8 after teclistamab. (i) Multiplex immunofluorescence images showing dense infiltration of $CD19^{+}IRF4^{-}$ B cells and $CD38^{+}IRF4^{+}$ plasma cells at BL, followed by their (near-)complete absence at week 8. Staining includes CD19 (green, top row), CD138 (green, bottom row), IRF4 (blue), and DAPI (white). Scale bars 100 µm. (ii) Line graph depicting quantitative reductions in $CD19^{+}$ B cells and $CD38^{+}CD138^{+}$ plasma cells over time. (B) Plasma cell and B cell depletion in bone marrow aspirates (n = 3/8) at BL and week 8 after teclistamab (patients 5, 6, and 7). Representative flow cytometry plots and summary data for $CD19^{+}$ B cells (top row) and $CD38^{++}CD138^{+}$ plasma cells (bottom row) at BL and week 8. A marked reduction in $CD19^{+}$ B cells and complete loss of detectable plasma cells were observed. Cells were pregated on live lymphocytes. (C) Autoantibody titres. Antinuclear antibodies (ANAs), antitopoisomerase I (Scl-70), anti-RNA polymerase III, and anti-PM/Scl titres declined in all patients (n = 8/8). Patient 1 demonstrated complete and sustained seroconversion of ANA and Scl-70 beginning at week 24. (D) Total serum IgG levels after plasma cell depletion (n = 8/8). IgG concentrations decreased in all patients, most commonly to levels consistent with mild-to-moderate hypogammaglobulinaemia (4-7 g/L). All patients reaching week 12 (n = 8/8) developed severe hypogammaglobulinaemia (IgG <4 g/L), requiring IVIG substitution. (E) Vaccine-specific antibody titres (exemplified by rubella IgG; n = 6). Rubella IgG titres declined progressively in all evaluated patients for whom BL titres were available (n = 4/6) after teclistamab therapy. CD, cluster of differentiation; DAPI, 4′,6-diamidino-2-phenylindole; IgG, immunoglobulin; IRF, interferon regulatory factor; IVIG, intravenous immunoglobulin; PM/Scl Polymyositis/Scleroderma.

established. Detailed descriptions of the 2 fatal events are given in the Supplementary Case Descriptions.

Deep tissue depletion of B and plasma cells

Teclistamab induced profound depletion of B cells and plasma cells in peripheral blood, bone marrow, and skin (Fig 1A,B, Supplementary Fig S2; Supplementary Table S5). In peripheral blood, CD19+ B cells were depleted by week 8 in all patients (8/8; Supplementary Table S5). In bone marrow (3/8 patients were biopsied), plasma cells were almost completely eliminated by week 8, decreasing from a median of 0.629% at baseline to 0.016% in biopsy samples, and from 0.870% to 0.000% of lymphocytes in bone marrow aspirates. B-cells were markedly reduced (biopsy: 6.240% at baseline vs 1.036% at week 8; aspirate: 3.150% vs 1.110%; Fig 1A,B). Skin biopsies obtained at week 12 from 4 of 8 patients also confirmed depletion of plasma cells and B-cells (Supplementary Fig S2).

Notably, there was a concomitant decline in SSc-specific autoantibodies. Antitopoisomerase antibody titres decreased by a median of 70.6% (IQR: 39%) from baseline to last follow-up. Patient 1, who had the longest follow-up (68 weeks), achieved seroconversion for both antinuclear antibodies (ANAs) and antitopoisomerase antibodies at week 28 and remained seronegative thereafter (Fig 1C i-ii). Similarly, RNA polymerase III 11 antibodies decreased by 39% and RNA polymerase III 155 antibodies by 66% by the last follow-up (Fig 1C iii); PM/Scl-100 antibody levels declined by 71% and PM/Scl-75 antibodies by 93% (Fig 1C iv). In the patient with anti-RuvBL1/2 antibodies, ANA titres declined by 2 dilution steps at his last follow-up; cross-validation by ELISA or immunoblot was not available.

Peripheral B-cells returned in 3 of 10 patients after a median time of 20 weeks (week 20 in patients 1 and 3, week 36 in patient 2). In patient 1, the phenotype of returning B-cells developed from a predominantly transitional phenotype to a predominantly naïve phenotype (Supplementary Fig S3); in patients 2 and 3, B-cell numbers were too low for phenotyping at the last follow-up.

Teclistamab induced rapid clinical improvement

Eight of 10 patients completed follow-up of ≥12 weeks and were eligible for efficacy analysis. The rev ACR-CRISS was 0 at baseline in all patients, reflecting significant worsening, new end-organ damage, or no improvement in the assessed disease domains following previous medical therapies. Following teclistamab, the rev ACR-CRISS improved in 5 of 8 patients (62.5%, Fig 2A), and the revised EUSTAR-AI declined by a median of 39.1% (IQR: 33.3%) or 2.29 points (IQR: 2 points) within 12

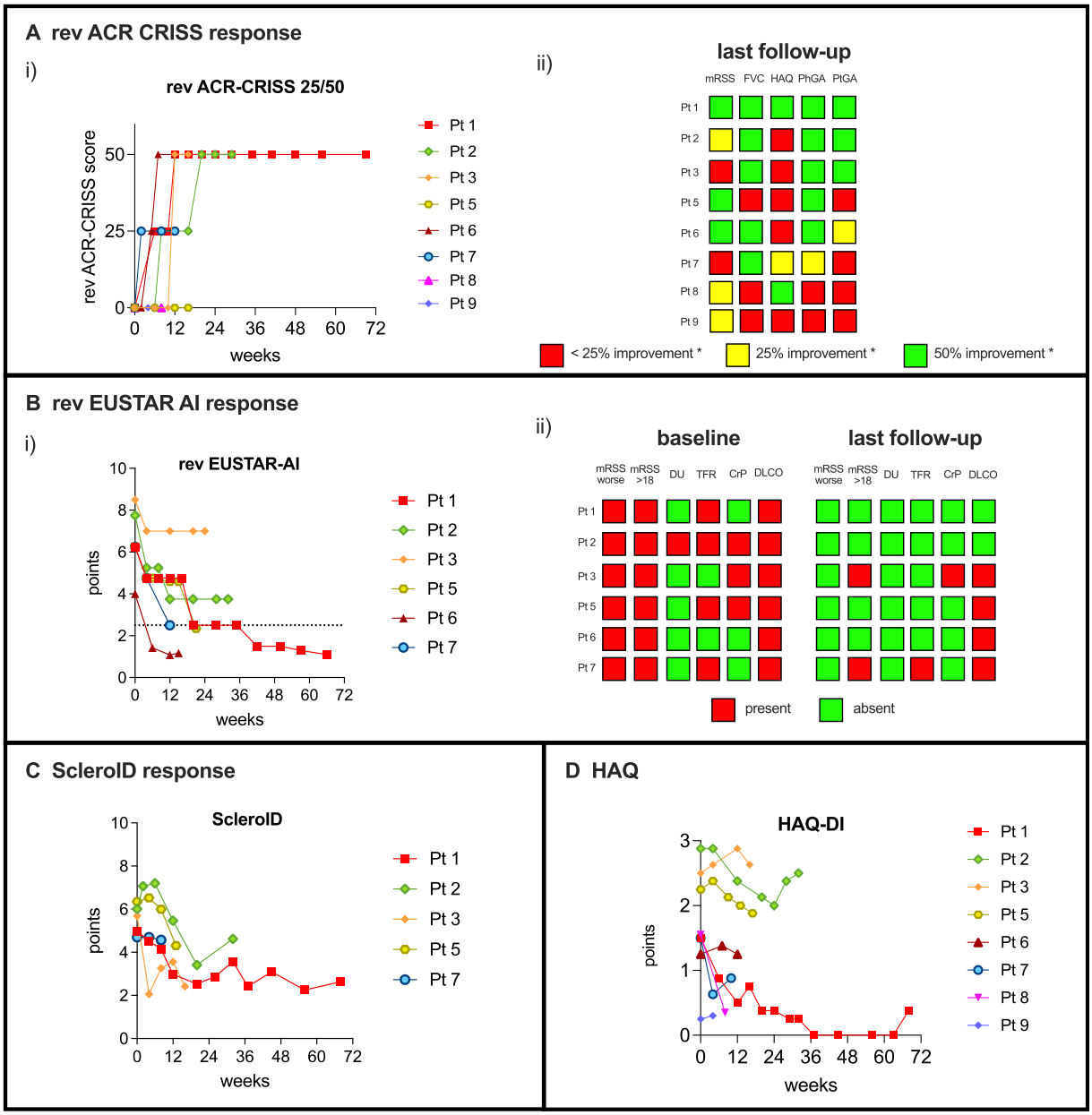

Figure 2. SSc disease activity and composite clinical response following teclistamab treatment. (A) Revised ACR-CRISS response (n = 8/8) (i) 5 of 7 patients demonstrated improvement in the revised ACR-CRISS score, with 4 of 5 achieving a revised ACR-CRISS 50 (3/5 domains) response by month 20. (ii) Percentage improvement (<25% marked in red, ≥25% marked in yellow, ≥50% marked in green) for individual patients at last follow-up (compared with baseline) across the components of the revised ACR-CRISS: modified Rodnan skin score (mRSS), forced vital capacity (FVC), health assessment questionnaire (HAQ), physician global assessment (PhGA), and patient global assessment (PGA). *For FVC, a percentage improvement of ≥5% was considered a response in all categories. (B) Revised EUSTAR Activity Index (AI) response (n = 6). (i) The revised EUSTAR-AI declined compared with baseline, with 33% of patients meeting the threshold for inactive disease (<2.5 points) at their last follow-up. (ii) Presence or absence of the EUSTAR-AI component items at baseline and last follow-up for each patient (mRSS worsening, mRSS >18, digital ulcers, tendon friction rubs, C-reactive protein elevation, and DLCO <70%) demonstrating marked clinical improvement at last follow-up. (C) ScleroID response (n = 5/8). Patient-reported disease burden, as assessed by the EUSTAR ScleroID questionnaire, showed substantial improvement from baseline to last follow-up. (D) HAQ scores (n = 8/8). Baseline functional status varied, with most patients falling into mild-to-moderate or severe-to-very severe impairment categories. Five of 8 patients showed marked improvement in HAQ scores, whereas 3 showed minimal change from baseline. ACR-CRISS, American College of Rheumatology Composite Response Index in Systemic Sclerosis; CrP, C-reactive protein; DLCO, diffusing capacity of the lungs for carbon monoxide; DU, digital ulcers; EUSTAR, European Scleroderma Trials and Research Group; ScleroID, Systemic Sclerosis Impact of Disease; SSc, systemic sclerosis; TFR, tendon friction rubs.

weeks compared with baseline (Fig 2B). At the last follow-up, 2 of 6 patients had reached inactive disease, defined as a rev EUSTAR-AI score <2.5. Improvement in overall disease activity was also confirmed by the EUSTAR Systemic Sclerosis Impact of Disease (ScleroID) questionnaire, with a marked median improvement of 32.2% (IQR: 24%) at last follow-up in all 5 patients (Fig 2C). Lower disease activity was accompanied by a reduction in functional disability, reflected by a decrease in the health assessment questionnaire (HAQ) score from a median of 1.53 points (IQR: 0.88 points) at baseline to 1.07 (IQR: 1.66) at the last follow-up (Fig 2D). A representative and exploratory whole-body fibroblast activation protein inhibitor (FAPI)-positron emission tomography (PET) scan from patient 1 demonstrates widespread fibroblast activation at baseline, with a marked reduction in tracer uptake at week 12 (Supplementary Fig S4). Interestingly, the rapid clinical improvement was

associated with a decline in C-reactive protein (CrP) levels. Of the 5 patients with elevated CrP at baseline, 4 achieved CrP normalisation during follow-up. The remaining patient (patient 3) had persistent CrP elevation, likely related to ongoing tissue injury from severe calcinosis with open wounds.

Notably, calcinoses improved over time, and no severe infections were observed. Similarly, digital ulcers in the 2 patients with appropriate follow-up also improved, allowing tapering of concomitant vasoactive therapy (tadalafil).

The 3 patients who did not achieve a rev ACR-CRISS 25 response within 12 weeks nonetheless demonstrated clinically meaningful improvement that was not fully captured by the composite index. Patient 5, who had cardiac involvement at baseline, recovered from congestive heart failure and showed a substantial improvement in skin fibrosis, with the mRSS decreasing from 32 of 51 to 16 of 51. Patient 8 experienced a marked symptomatic improvement by week 6, including near-complete resolution of fatigue and reduced dyspnoea. At week 8, she developed an influenza infection, which likely contributed to a transient decline in pulmonary function tests and confounded objective assessment of disease activity. Patient 9 did not have enough data available to calculate a rev ACR-CRISS response beyond week 4.

Improvement of pulmonary function and radiographic lung involvement

SSc-ILD was present in 7 of 10 patients (70%), and 6 of 7 completed a 12-week follow-up. At 3-month follow-up, a trend toward improvement in pulmonary function was observed, with median FVC increasing by 7% (IQR: 13%) and median DLCOcSB increasing by 12% (IQR: 15%) (Fig 3A). Patient 1, with the longest follow-up, showed an increase in FVC by 47% (equivalent to 29%/predicted) and in DLCOcSB by 158% (equivalent to 57%/predicted) at week 66, reflecting continuous improvement following 1 cycle of teclistamab. Consistent with these functional changes, HRCT images performed in 4 of 6 patients demonstrated resolution of ground-glass opacities (representative images in Supplementary Fig S5), with a median reduction of 50% (IQR: 13.8%) at week 12 among the 4 patients with paired scans (Fig 3B). Notably, patient 1 also exhibited regression of fibrotic reticulations (Fig 3B). Functional and radiological improvements were accompanied by patient-reported median improvement in dyspnoea scores of 75% (IQR: 6.3%) (Fig 3C), which was assessed in 4 of 6 patients.

Improvement of skin fibrosis and fibroblast activation

Skin disease was present in 10 of 10 patients, and 8 of 10 completed a 12-week follow-up. Skin disease improved in all 8 of 8 patients following teclistamab therapy, with a median mRSS reduction of 35.9% (IQR: 17.9%) or 12 points (IQR: 8.5 points) within 12 weeks, followed by further decreases in all patients throughout the follow-up period (Fig 4A). Improvement of skin disease was observed across all patients (Fig 4A) and anatomic regions assessed (Fig 4B, Supplementary Fig S6). Clinical findings were supported by histopathological analyses of skin biopsies from 4 of 8 patients, demonstrating a marked decrease in FAPalpha- and Leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5)-positive fibroblasts (Supplementary Fig S7).

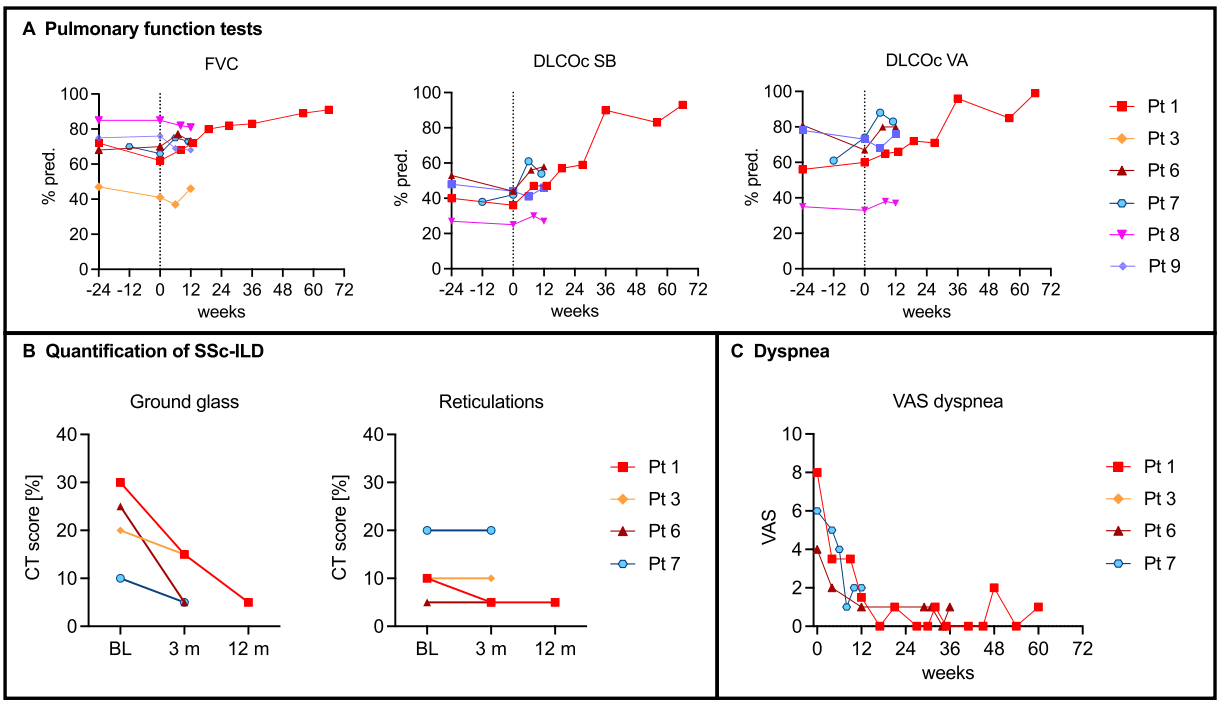

Figure 3. Interstitial lung disease following teclistamab treatment. (A) Pulmonary function tests in patients with SSc-associated interstitial lung disease (SSc-ILD; n = 6/6) and appropriate follow-up before and after therapy with teclistamab. Forced vital capacity (FVC% predicted) improved by a median of 6% (IQR: 2%) at 3-month follow-up in 5 of 6 tested patients (83%). Corrected diffusing capacity for carbon monoxide (DLCOc) measures demonstrated median improvement in both single-breath (DLCOcSB; left) and alveolar (DLCOcVA; right) diffusing capacity in all evaluated patients. (B) Quantification of ILD on HRCT in 4 of 6 patients at baseline (BL) and at 3- and 12-month follow-up, assessed by percentage of lung involvement with ground-glass opacities and fibrotic reticulations. Findings show a marked reduction in ground-glass opacities in all patients, a reduction of reticulations in 1 patient, and overall stabilisation of fibrotic reticulations, indicating decreased ILD burden. Additional images can be found in Supplementary Fig S3. (C) Visual analogue scale (VAS) for dyspnoea in 4 of 6 symptomatic patients with SSc-ILD reporting perceived breathlessness. Declining VAS scores indicate clinically meaningful improvement in dyspnoea. CT, computed tomography; HRCT, high-resolution CT; SSc, systemic sclerosis.

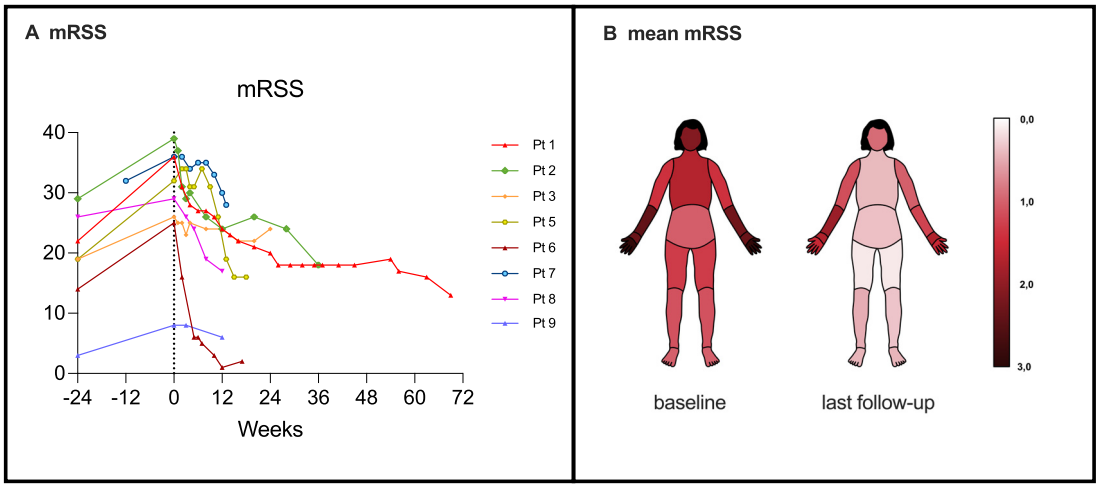

Figure 4. Skin disease following teclistamab treatment. (A) Modified Rodnan skin score (mRSS) in 8 of 8 patients with SSc-associated skin disease before and after teclistamab shows worsening before baseline and robust improvement in all patients at 3-month follow-up. (B) Schematic showing the distribution of skin disease severity by anatomical regions. SSc, systemic sclerosis.

Improvement of cardiac involvement

SSc heart disease was present in 5 of 10 patients (50%) at baseline, of whom 3 of 5 completed a 12-week follow-up. Disease severity ranged from elevated cardiac biomarkers (troponin T and NT-proBNP) in all 5 patients to pericardial effusion, clinically relevant cardiac arrhythmias, pericardial fibrosis, and congestive heart failure. Following treatment, cardiac biomarkers declined in all 3 patients included in the efficacy analysis, with median reductions of 72% (IQR 13%) in troponin T and 84% (IQR 18%) in NT-proBNP by week 12 (Supplementary Fig S8A). Cardiac imaging by echocardiography showed regression of SSc-specific cardiac disease, including pericardial effusion, heart failure, and diastolic dysfunction, in patient 5 (Supplementary Fig S8B) and no clinically relevant worsening in the other 2 patients (Supplementary Table S6). Accordingly, cardiac MRI showed improvement in pathological late gadolinium enhancement (LGE) and pathological T1 and T2 times in all 3 patients (Supplementary Table S6).

DISCUSSION

In this case series of patients with severe, highly active, and treatment-refractory SSc, treatment with teclistamab demonstrated substantial efficacy across organ systems, alongside a generally manageable safety profile, but with clinically relevant adverse events in this high-risk population.

No high-grade CRS or neurotoxicity was observed in this cohort, consistent with previous reports suggesting a favourable safety profile of teclistamab in autoimmune diseases compared with multiple myeloma [16–20,22,26–29].

Common treatment-related toxicities included severe hypogammaglobulinaemia (IgG <4 g/L), which occurred in all patients and required IVIG infusions. This is in line with the known on-target effects of BCMA-directed therapies reported in haematologic [22,30,31] and emerging autoimmune disease settings [16–20,26–28]. Severe hypogammaglobulinaemia persisted throughout the follow-up period of up to 68 weeks (in patient 1), but the rate of IgG decline slowed over time, resulting in less frequent IVIG transfusions (Supplementary Table S2). It is important to note that IVIG transfusions might have contributed to the observed clinical benefit in some patients. However, responses were generally observed before its initiation, suggesting that the primary effect is attributable to teclistamab. This interpretation is supported by the limited evidence for IVIG efficacy in SSc, with 1 randomised trial showing no significant improvement in mRSS despite higher cumulative doses [32].

Infectious complications were also frequent, often preceding severe hypogammaglobulinaemia (Table 2), but were generally controlled with standard antimicrobial treatment, consistent with previously published safety profiles [30]. Notably, 1 patient developed inflammatory bowel disease–like colitis with histopathological features of microscopic colitis, raising the possibility of gut-specific immunologic side effects of BCMA targeting, particularly in light of a prior report of Crohn's-like disease following teclistamab treatment in a patient with SLE [28].

Nevertheless, 2 deaths occurred during follow-up, both in patients with advanced, severe SSc heart disease (NT-proBNP >5000 ng/L), warranting particular attention. Both deaths occurred approximately 3 weeks after initiation of teclistamab therapy and were of uncertain relationship to the treatment; however, a treatment-related contribution cannot be excluded. Patient 4, who had received pulse corticosteroids for severe myocardial inflammation and recurrent ventricular tachycardia, developed progressive renal dysfunction, haemolytic anaemia, and thrombocytopaenia suggestive of microangiopathic haemolytic anaemia. The patient died on day 20 due to diffuse alveolar haemorrhage and heart failure, consistent with pulmonary-renal syndrome, a rare complication previously described in SSc [33]. Patient 10, with long-standing PAH and SSc heart disease, died from sudden cardiac death 12 days after the last teclistamab dose, without evidence of CRS or infection. Given the temporal dissociation from drug administration, absence of acute toxicity, and severe preexisting cardiac disease, a causal relationship with teclistamab cannot be established. These observations underscore the need for particular caution in patients with advanced cardiac involvement. In analogy to established cellular therapies such as HSCT and CAR T-cell approaches, careful patient selection based on comprehensive cardiac assessment and exclusion of patients with advanced cardiac involvement may be critical to mitigate treatment-related risk [8,11,34,35].

Notably, applying recently proposed risk stratification frameworks for cellular therapies [36,37], both patients who died would have met exclusion criteria, whereas the remaining patients would not. In contrast, patients with less advanced cardiac involvement showed favourable responses, supporting further evaluation of BCMA-directed therapies in earlier disease stages under controlled conditions.

Despite extensive clinical characterisation and tissue-level analyses, our study has several important limitations. The patient cohort, although the largest to date treated with BCMA×CD3 bispecific antibodies in SSc, remains small and clinically heterogeneous with respect to organ involvement, autoantibody profiles, and diagnostic assessments across centres. First, the retrospective, multicentre design, small sample size (n = 10, with 8 patients evaluable for ≥12 weeks), and off-label use in a highly selected population limit causal inference and generalisability. Clinical efficacy findings are therefore exploratory and susceptible to selection and survivorship bias. Second, outcome assessments were not standardised across centres, and data availability varied across outcome measures, resulting in differing numbers of evaluable patients for individual analyses. Analyses were conducted using all available data for each outcome measure. This particularly affects pulmonary assessments, where imaging protocols (including HRCT) and functional assessments (eg, 6-minute walk test and oxygen saturation) were inconsistently performed, limiting cross-patient comparisons. Imaging analyses were further constrained by the lack of standardised acquisition protocols and dedicated quantitative or AI-based tools. Third, cardiac assessments were heterogeneous and based on a limited number of evaluable patients. Differences in disease severity, timing of assessments, and the absence of predefined cardiac exclusion criteria limit the interpretation of cardiac risk. Fourth, several analyses, including bone marrow investigations and FAPI-PET imaging, were performed only in small subsets and should be considered exploratory. Finally, follow-up duration remains limited, precluding conclusions on long-term immune reconstitution, durability of response, and late safety signals.

Our findings confirm and extend emerging evidence for plasma cell-directed strategies in SSc [16–20]. BCMA targeting elicited a rapid, clinically meaningful response that translated into substantial improvements in health-related quality of life, with reproducible effects across multiple organ systems. Clinically, improvements were observed most pronounced in interstitial lung disease, for which actual reversal of established pathology has rarely been documented [38]. Skin involvement, tendon friction rubs, myocardial oedema, and fibrosis measured by LGE and T1 and T2 times on cardiac MRI and digital ulcers also improved rapidly and to an extent unexpected for treatment-refractory disease. Interestingly, although response rates varied across cohorts as reported by Düsing et al. [20], patients with SSc heart disease who survived teclistamab treatment in our cohort showed consistent improvements in cardiac biomarkers and MRI parameters. Notably, these findings suggest that established organ involvement in SSc may be reversible to an extent not previously appreciated [39,40]. Importantly, these organ-level improvements were paralleled by marked changes in patient-reported outcomes, including HAQ and ScleroID, indicating a clinically meaningful benefit from the patient perspective. The magnitude and consistency of these improvements are notable, particularly in a cohort with severe and refractory disease. Beyond established organ-based endpoints and composite scores, additional clinically relevant improvements were observed. Digital ulcers, for example, resolved in both patients who completed follow-up (patient 2 and patient 8; patient 4 and patient 10 died during teclistamab treatment) and skin lesions secondary to calcinosis improved in 1 patient who completed follow-up (patient 3; patient 10 died during teclistamab treatment). Consistently, the illustrative and exploratory FAPI-PET imaging of patient 1 demonstrated a global reduction in signal intensity across multiple organ systems, including lungs, skin, joints, and muscles, supporting the presence of broader treatment effects. These pronounced treatment effects might be because the majority of patients exhibited features of an early and inflammatory SSc phenotype, including elevated CrP levels and short disease duration. In line with previous observations from the Focused on Systemic Sclerosis - Study of Combined Efficacy of Drugs (focuSSced)/ Savety and Efficacy of Subcutaneous Tocilizumab in Adults with Systemic Sclerosis (faSScinate) and Safety and Efficacy of Rituximab in Systemic Sclerosis (DESIRES) trials [6,41,42], these patients appeared to show favourable clinical responses following immunosuppressive treatment, because organ damage might be reversible at this stage. Notably, many of our patients had previously received tocilizumab or rituximab without meaningful clinical improvement, supporting the refractory nature of this subgroup.

Our data indicate that, unlike established therapies, teclistamab achieves deep tissue depletion of autoreactive B cells and plasma cells in lymphatic organs and affected target tissues. We additionally provide direct tissue-level evidence that targeting BCMA is associated with depletion of B cells and plasma cells in fibrotic tissues and a reduction in FAPalpha expression, a marker of activated fibroblasts, across evaluable patients. However, fibroblast activation is a complex and heterogeneous process that cannot be fully captured by a single marker.

Our findings support a disease concept in which autoantibody-secreting cells may act as culprits, driving perivascular inflammation and endothelial dysfunction [43,44]. It may be hypothesised that deep tissue depletion of autoreactive B cells and plasma cells might be sufficient to break this vicious circle, improve microvascular perfusion and tissue oxygenation, and suppress profibrotic fibroblast activation, ultimately permitting tissue remodelling rather than continued scarring. However, at this stage, these hypotheses remain speculative and require further investigation.

Notably, the clinical effects of BCMA-directed therapy emerged rapidly, in several cases earlier than typically reported for CD19-directed CAR T-cell therapy in SSc [13–15]. Although these approaches are not directly comparable because of distinct targets, mechanisms, and therapeutic modalities, the present findings raise the hypothesis that plasma cell-directed T-cell engagement may enable a more rapid disruption of pathogenic immune circuits in SSc, possibly mediated by early and profound autoantibody depletion. In this context, recent data from Scherlinger et al. [45] on the CD19-directed T-cell engager blinatumomab in SSc may provide additional perspective. In that study, reductions in autoantibody titres and clinical responses appeared less pronounced, whereas effects on IgG levels and vaccination titres were also more limited. However, cross-study comparisons are inherently limited by differences in patient populations, targets, and treatment regimens. Lastly, the observed safety profile in our cohort, characterised by predominantly mild CRS and absence of neurotoxicity, may differentiate T-cell engager-based approaches from CD19-directed CAR T-cell therapies, although comparative data remain limited and should be interpreted with caution. In this context, an important question is whether BCMA targeting achieves a durable immunologic effect comparable to CD19 CAR T-cell therapy or instead functions solely as a potent but time-limited disease-modifying intervention; this remains to be determined.

Given the lack of effective alternatives in severe SSc, the observed benefit–risk profile appears to be justified in this high-risk population. Confirmation of safety and durability in larger, multicentre cohorts, along with registry-based long-term follow-up and harmonised outcome measures, will be essential to define the future role of teclistamab, either as a standalone approach, with the advantage of off-the-self and repeat dosing and easy scalability, or as a bridging or sequential therapy

within advanced or emerging treatment paradigms, such as haemopoietic stem cell transplantation or CAR-T cell therapy. In this context, comparative evaluation with other advanced therapeutic modalities remains an important objective. However, such comparisons are currently limited by the lack of harmonised datasets and standardised outcome measures across studies, precluding robust cross-modality analyses.

Despite its limitations, this study provides a proof-of-concept supporting the therapeutic potential of BCMA-targeting in SSc, extending prior case reports and case series with broader clinical evidence and mechanistic insights.

Competing interests

IM reports a relationship with AbbVie and Novartis that includes speaking and lecture fees. DaS reports relationships with AbbVie Inc, Bristol-Myers Squibb, Janssen-Cilag, Lilly, and Novartis that include board membership and speaking and lecture fees. DaS reports a relationship with Gilead Sciences that includes board membership. DaS reports a relationship with UCB that includes board membership and speaking and lecture fees. DaS reports relationships with Amgen and Alfasigma that include speaking and lecture fees. TA reports relationships with Abbvie, Amgen, AstraZeneca and GSK that include speaking and lecture fees; Johnson&Johnson that include research funding. AK reports relationships with AbbVie Inc, Bristol-Myers Squibb, Lilly, Novartis, UCB, and Janssen-Cilag that include board membership and speaking and lecture fees. AK reports a relationship with Gilead Sciences that includes board membership. AK reports a relationship with Alfasigma that includes speaking and lecture fees. ES reports a relationship with Janssen-Cilag that includes travel reimbursement. ES reports a relationship with Boeringer Ingelheim that includes board membership. JH reports relationships with AbbVie Inc, AstraZeneca, Boehringer Ingelheim, GSK, Johnson & Johnson, Lilly, Novartis, Pfizer, Roche, and UCB that include board membership and speaking and lecture fees. AT reports relationships with AstraZeneca and Roche that include board membership and speaking and lecture fees. MLH-K reports relationships with Amgen, Jazz Pharmaceuticals Inc, Novartis, Sanofi, and Sobi that include board membership and travel reimbursement. MK reports relationships with AbbVie Inc, Sobi, Novartis, Alfasigma, UCB, Lilly, Medac, GSK, and Bristol-Myers Squibb that include speaking and lecture fees. IH reports relationships with AbbVie Inc, AstraZeneca, Alfasigma, Boehringer Ingelheim, GSK, Johnson & Johnson, Medac, Novartis, UCB, and Lilly that include speaking and lecture fees. KS reports a relationship with Boehringer Ingelheim that includes board membership. PK reports a relationship with AbbVie Inc that includes travel reimbursement. PK reports a relationship with Alfasigma that includes speaking and lecture fees. All other authors declare they have no competing interests.

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Patient consent for publication

Explicit, written patient consent for publication was obtained from all patients.

Ethics approval

The analysis was approved by the local Ethics Committee (EA1/002/24).

Provenance and peer review

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Supplementary materials

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