BCMA-Targeted T-Cell–Engager Therapy for Autoimmune Disease

TO THE EDITOR: The targeting of B cells and plasma cells is a key therapeutic strategy in patients with autoimmune diseases. Chimeric antigen receptor (CAR) T cells or T-cell engagers against CD19 have been effective in treatment-resistant autoimmune diseases.[1,2] However, in some patients, disease may be anchored in long-lived plasma cells that express B-cell maturation antigen (BCMA) but not CD19.[3] Thus, some autoantibodies (e.g., SS-A/Ro and polymyositis–scleroderma [PM-Scl]) remain stable even after CD19 CAR T-cell therapy.

The T-cell engager teclistamab acts on T cells through CD3 (the defining marker of T cells) and targets plasmablasts and plasma cells through BCMA. Teclistamab has been shown to be highly effective in patients with multiple myeloma.[4] Thus, we hypothesized that teclistamab may be effective for targeting severe autoimmune diseases, even after failure of conventional B-cell depletion.

We administered teclistamab subcutaneously to four patients with autoimmune diseases that were resistant to more than five immunosuppressants, including rituximab (Fig. 1A and Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Patient 1 had systemic sclerosis with calcinosis cutis and interstitial lung disease. Patient 2 had primary Sjögren's syndrome with xerostomia and xerophthalmia (dryness of mouth and eyes), arthritis, enthesitis, myositis, inflammatory rash, and interstitial lung disease. Patient 3 had MDA5-positive idiopathic inflammatory myositis with arthritis, inflammatory rash, digital ulcers, and interstitial lung disease. Patient 4 had seropositive rheumatoid arthritis.

The dose of teclistamab was incrementally increased in an inpatient setting as follows: day 1 (0.06 mg per kilogram), day 3 (0.3 mg per kilogram), and day 5 (1.5 mg per kilogram). One maintenance dose of 1.5 mg per kilogram was administered after 12 weeks in Patient 1 and after 4 weeks in Patients 2, 3, and 4 (Fig. 1B). All immunosuppressants were stopped and glucocorticoids were either discontinued (in Patients 1, 2, and 3) or tapered (in Patient 4) (Table S2). Teclistamab therapy had a good safety profile, with no neurotoxicity or myelotoxicity and only lower-grade cytokine release syndrome (Fig. 1C). Among the two patients with cytokine release syndrome, the symptoms were mild (grade 1 in Patient 1 and grade 2 in Patient 2). Four infections were reported in three patients (viral gastroenteritis in Patient 1, cutaneous infection in Patient 2, and herpes labialis and upper respiratory tract infection in Patient 4).

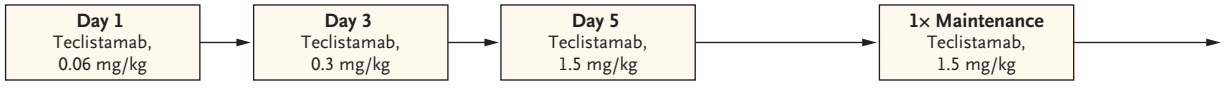
Teclistamab led to T-cell engagement with an acute-phase reaction with transient elevation in C-reactive protein and inflammatory cytokines, which peaked between days 2 and 5 (Fig. S1A and S1B). T-cell engagement led to transient T-cell consumption with rapid recovery (Fig. S1C). Concomitantly, circulating B cells were depleted (Fig. S1D) and free light chains (half-life, <6 hours) were reduced, which documented the targeting of plasma cells (Fig. S1E and S1F). Accordingly, levels of IgG, IgA, and IgM were decreased (Fig. 1D and Fig. S1G and S1H). Seroconversion of PM-Scl-75, PM-Scl-100, rheumatoid factor, and autoantibodies against mutated citrullinated vimentin was noted, and levels of antinuclear antibodies, MDA5, SS-A/Ro, SS-B/La, and PL-7 were decreased (Fig. 1E). B-cell levels recovered in Patient 1 after 12 weeks of therapy, and high-dimensional flow cytometry revealed a reduction in class-switched memory B cells and plasmablasts and an increase in non–class-switched, IgD-positive naive B cells (Fig. S2).

Teclistamab improved disease activity in all four patients. In Patient 1, skin disease (as measured by the modified Rodnan skin score) improved from 39 to 24. In Patient 2, the score on the EULAR Sjögren's Syndrome Disease Activity Index improved from 34 to 15. In Patient 3, the skin inflammation score on the Cutaneous Dermatomyositis Disease Area and Severity Index improved from 22 to 6 points, the arthritis score on the Disease Activity Score 28 for Rheumatoid Arthritis with CRP (DAS28-CRP) improved from

A Baseline Characteristics of Patients

Variable	Patient 1	Patient 2	Patient 3	Patient 4
Disease	Systemic sclerosis	Primary Sjögren's syndrome	Idiopathic inflammatory myositis	Rheumatoid arthritis
Age — yr	60	57	24	52
Sex	Female	Female	Female	Female
Disease duration — mo	108	20	29	336
Arthritis	No	Yes	Yes	Yes
Myositis	No	Yes	Yes	No
Skin manifestation	Yes	Yes	Yes	No
Interstitial lung disease	Yes	Yes	Yes	Yes
Small-vessel vasculitis	No	Yes	Yes	No
Antinuclear antibodies — titer	1:3200	1:10,000	1:100	<1:40
Specific autoantibodies	PM-Scl	Ro, La, PL-7	MDA5	CCP2, MCV
Teclistamab dose — mg	3.3/16.0/ 81.9/75.0	3.3/16.0/ 82.0/82.0	3.3/16.0/ 80.0/79.5	3.8/19.0/ 94.2/94.2
Length of follow-up after first dose — wk	22	18	12	12

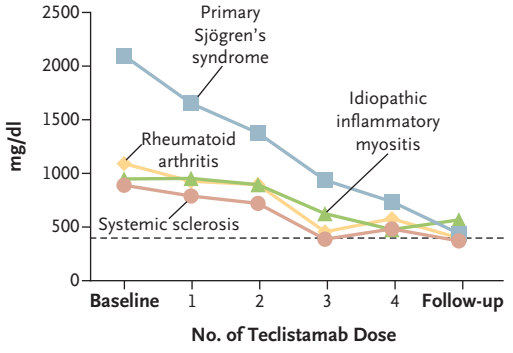
B Schematic Treatment Protocol



C Safety Analysis Results

	Patient 1 (systemic sclerosis)	Patient 2 (primary Sjögren's syndrome)	Patient 3 (idiopathic inflammatory myositis)	Patient 4 (rheumatoid arthritis)
CRS grade	1	2	0	0
ICANS grade	0	0	0	0
Myelotoxicity grade	0	0	0	0
Hypogammaglobulinemia (IgG, <4 g/liter)	No	No	Yes	No
Infections	GI	CUT	None	HSV, URTI

D IgG Levels in Serum



E Changes in Serum Autoantibodies at Latest Follow-up

	Autoantibody	Baseline	Follow-up
Patient 1 (systemic sclerosis)	ANA — titer	1:3200	1:100
	PM-Scl-75 — RU (normal <15)	30	1
	PM-Scl-100 — RU (normal <15)	35	3
Patient 2 (primary Sjögren's syndrome)	ANA — titer	1:10,000	1:3200
	SS-A/Ro-52 — U/ml (normal <25)	129.7	55.3
	SS-A/Ro-60 — U/ml (normal <25)	189.5	131.3
	SS-B/La — U/ml (normal <25)	222.5	165.2
	PL-7 — RU (normal <15)	122	91
Patient 3 (idiopathic inflammatory myositis)	ANA — U/ml (normal <25)	1:100	1:100
	MDA5 — RU (normal <15)	38	18
Patient 4 (rheumatoid arthritis)	RF — U/ml (normal <25)	507.2	18.4
	CCP2 — U/ml (normal <25)	2.7	0.9
	MCV — U/ml (normal <25)	82.9	3.0

F Clinical Efficacy Analysis

	Patient 1 (systemic sclerosis)		Patient 2 (primary Sjögren's syndrome)		Patient 3 (idiopathic inflammatory myositis)		Patient 4 (rheumatoid arthritis)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Visual analogue scale (patient global) — mm	90	50	50	10	50	20	60	40
Modified Rodnan skin score — units	39	24	N/A	N/A	N/A	N/A	N/A	N/A
ESSDAI (Sjögren's syndrome activity) — units	N/A	N/A	34	15	N/A	N/A	N/A	N/A
CDASI (skin inflammation) — units	N/A	N/A	N/A	N/A	22	6	N/A	N/A
MMT-8 (diffusion capacity of lung) — units	N/A	N/A	N/A	N/A	138	150	N/A	N/A
DAS28–CRP (arthritis) — units	N/A	N/A	N/A	N/A	3.6	1.6	5.6	1.9
Health assessment questionnaire — units	2.5	2.1	1.3	1.1	1.8	1.0	3.0	1.6
DLCOSB (single-breath diffusion capacity of lung for carbon monoxide) — percent of predicted	34	33	23	27	44	57	76	72

Figure 1 (facing page). Overview of Clinical Features and Laboratory Findings in the Study Patients Treated with Teclistamab.

Shown are the characteristics of the patients at baseline (Panel A), a schematic view of the treatment protocol (Panel B), safety results (Panel C), IgG levels in serum (Panel D), changes in serum autoantibodies at the latest follow-up (Panel E), and clinical efficacy (Panel F). ANA denotes antinuclear antibodies, CCP2 second-generation cyclic citrullinated peptide, CDASI Cutaneous Dermatomyositis Disease Area and Severity Index, CRS cytokine release syndrome, CUT cutaneous, DAS28 Disease Activity Score 28, ESSDAI EULAR Sjögren's Syndrome Disease Activity Index, GI gastrointestinal, HSV herpes simplex virus, ICANS immune effector-cell–associated neurotoxicity syndrome, MCV mutated citrullinated vimentin, MDA5 anti–melanoma differentiation-associated gene 5, MMT-8 manual muscle testing 8, N/A not applicable, PM-Scl polymyositis–scleroderma, PSS primary Sjögren's syndrome, RA rheumatoid arthritis, RF rheumatoid factor, RU relative units, and URTI upper respiratory tract infection.

3.6 to 1.6, and the lung diffusion capacity improved from 44% to 57%. In Patient 4, the arthritis score on the DAS28-CRP improved from 5.9 to 1.9 (Fig. 1F). In Patient 2, imaging performed with the use of positron-emission tomography–computed tomography with gallium 68–labeled fibroblast activation protein inhibitor (FAPI-PET-CT) revealed resolution of arthritis in the hands and knees (Fig. S1I). Skin inflammation and ulcerations were markedly reduced in Patient 3 (Fig. S1J). Taken together, these data show that the targeting of the plasma-cell compartment by a BCMA-targeted T-cell engager is feasible in patients with autoimmune disease. Whether such therapy results in sustained clinical remission warrants further study.

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