BLyS/APRIL dual inhibition for systemic sclerosis: a single-centre, single-arm, open-label clinical trial of telitacicept

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Abstract

Objectives

We aimed to explore the potential effectiveness and safety of telitacicept in the treatment of systemic sclerosis (SSc) and to investigate mechanisms such as B cell immune phenotypes.

Methods

This was a single-centre, single-arm, open-label study enrolling eight SSc patients inadequately responding to traditional immunosuppressants. All patients received telitacicept 160 mg weekly for 24 weeks in addition to their original stable immunosuppressive background treatment. The primary endpoint was changes in the median modified Rodnan skin thickness score (mRSS) at week 24.

Results

This study demonstrated that significant improvements were observed in the primary endpoints. Compared with the mean mRSS (18.9±5.8) at baseline, mRSS declined to 12.5±5.0 ($p=0.008$) and 10.8±5.8 ($p=0.003$) at weeks 12 and 24, respectively. SCTC-DI score, ScleroID questionnaire score, and SF-36 physical score at week 24 also improved ($p<0.05$). The CRISS score was 0.75, indicating clinical improvement, with higher scores reflecting better outcomes. Telitacicept as an add-on treatment significantly decreased CD19+ B cells from 10.2% to 4.3% ($p=0.006$), decreased transitional B cells from 6.8% to 1.4 % ($p=0.005$), decreased naive B cells from 8.9% to 3.0% ($p=0.001$), and increased immature B cells from 0.10 % to 0.24% ($p=0.03$). Telitacicept add-on treatment also decreased serum levels of immunoglobulins (IgG, IgA, IgM) ($p<0.05$) at week 24 and increased haemoglobin ($p=0.013$) at week 12. HRCT score for pulmonary fibrosis showed a decline at week 24 ($p=0.036$). A decrease in titer of SSc-specific antibodies was observed in six out of eight patients. No serious adverse events occurred. Adverse effects were mainly hypogammaglobulinemia, respiratory tract infection, urinary tract infections, and rash. No deaths occurred

Conclusions

Telitacicept has the potential to be a safe and effective treatment for patients with SSc; however, further studies with larger sample sizes are needed to confirm these findings and to better understand long-term safety and efficacy.

Key words

telitacicept, systemic sclerosis, B cell subsets, immunoglobulins

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Introduction

Systemic sclerosis (SSc), characterised by fibrosis, vasculopathy and autoimmunity, has limited treatment options (1), with an incidence of 3.0–24 per 100,000 people (2). Among connective tissue diseases in China, the incidence rate of SSc is second only to rheumatoid arthritis and systemic lupus erythematosus (3). However, the attributable mortality rate of systemic sclerosis is 64%, which is the highest among connective tissue diseases and has not decreased over the past 40 years (4). Thus, it remains urgent to develop new therapies targeting the pathogenesis of SSc with better effectiveness and safety.

Immune dysregulation in SSc is manifested by the presence of autoantibodies and alterations in the phenotype and activation levels of B cells, T cells, cytokines, and other components of the immune system (5). Compared to the healthy population, patients with SSc exhibit a marked imbalance in B-cell homeostasis. Specifically, there is an increase in transitional and naive B cells and a concomitant decrease in memory B cells. Additionally, these patients demonstrate abnormal expression of regulatory molecules involved in B-cell function (6, 7). Although memory B cells are reduced in number, they exhibit functional overactivation, leading to heightened antibody production (8). Elevated serum levels of B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) have been correlated with skin and lung fibrosis in SSc patients (9, 10). These observations underscore the pivotal role of B cells in the pathogenesis of SSc and suggest that B-cell-targeted biologic therapies could be a promising avenue for treatment.

Several studies have reported that B-cell-targeted therapies can ameliorate skin fibrosis and interstitial lung disease, as well as improve lung function in SSc patients (11-15). However, earlier B-cell-targeted therapies, such as rituximab, have been associated with significant adverse effects, including hypogammaglobulinemia, increased risk of severe infections, and elevated mortality rates (16). Telitacicept, a novel therapeutic agent designed to inhibit BAFF and APRIL activity involved in B cell function, has demonstrated safety and efficacy in B-cell-mediated diseases such as systemic lupus erythematosus and rheumatoid arthritis (17-19). Given its mechanism of action, telitacicept may hold therapeutic potential for SSc. Nevertheless, there is a paucity of data regarding the efficacy and safety of telitacicept in the context of SSc. Consequently, this exploratory pilot study aims to preliminarily evaluate the potential efficacy and safety of telitacicept as an add-on therapy in SSc patients with an inadequate response to conventional immunosuppressants, and to investigate its *in vivo* effects on B-cell homeostasis and related biomarkers.

Materials and methods

Study design and participants

This study was a single-centre, single-arm, open-label trial initiated by the researchers to evaluate the efficacy and safety of telitacicept in patients with SSc. Eight patients were enrolled in the Department of Rheumatology and Clinical Immunology, Ningbo Medical Center Lihuili Hospital, from December 2022 to June 2024.

Participants met the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) 2013 criteria for SSc (20). Eligible patients were aged 18 to 70 years and had been receiving stable doses of immunosuppressive therapy (mycophenolate mofetil ≥1.0 g/day, mycophenolate sodium ≥0.72 g/day, cyclophosphamide ≥0.5 g/m^2/month, tacrolimus ≥1.0 mg/day, methotrexate ≥10 mg/week, *tripterygium wilfordii* ≥40 mg/day, or azathioprine ≥50 mg/day) for a minimum of 24 weeks. Additionally, patients needed to have a baseline modified Rodnan skin score (mRSS) of ≥10 and were permitted to use low-dose prednisone (≤7.5 mg/day), provided the dose was stable for at least 12 weeks prior to randomisation.

Patients were excluded if their diffusing capacity for carbon monoxide (DLCO) was ≤30% predicted, their ejection fraction was ≤40%, they had received B-cell targeted therapies

or plasmapheresis within the past 6 months, had another autoimmune disease, or had a history of severe and uncontrolled comorbidities, infections, immunodeficiency, or malignancies.

The study intended to enrol eight subjects who would receive telitacicept (160 mg/week via subcutaneous injection) in conjunction with their existing stable immunosuppressive regimen. During the follow-up period, the dose of telitacicept could be reduced to 80 mg/week if immunoglobulin levels fell below the lower limits (IgG <6 g/L, IgM <0.4 g/L, IgA <0.76 g/L), with the possibility of discontinuation and withdrawal from the study if immunoglobulin levels continued to decline.

Participants were monitored every four weeks to assess and document clinical data, including adverse reactions, physical examinations, laboratory parameters, and medication usage. Comprehensive evaluations were conducted at baseline, 12 weeks, and 24 weeks. At the study's conclusion, baseline data and efficacy metrics were thoroughly reviewed. Statistical analysis was then performed to determine the therapeutic potential of telitacicept in treating SSc. In addition, infectious and non-infectious adverse events were recorded to evaluate drug safety.

Procedures

The mRSS, BNP, high-sensitivity cardiac troponin I, the NYHA heart function classification, 6-minute walking test (6MWT), capillaroscopic skin ulcer risk index (CSURI), derived from nailfold videocapillaroscopy (NVC), Short Form-36 (SF-36) score, the EULAR Systemic Sclerosis Impact of Disease (ScleroID) questionnaire score, Physician Global Assessment (PGA) score, Health Assessment Questionnaire Disability Index (HAQ-DI) score, University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT) 2.0 score, and B-cell subpopulations were assessed at baseline and weeks 12 and 24. Phenotypes of circulating B-cell subpopulations were analysed by flow cytometry (brand: BioLegend, product number: PCDBH0333).

Combined Response Index for Systemic Sclerosis (CRISS) score, high-resolution computed tomography (HRCT) score for pulmonary fibrosis, Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI) score, the titre of SSc-specific antibodies, as well as BAFF and APRIL levels were assessed at baseline and week 24. BAFF and APRIL were measured by ELISA (brand: PC-Biotech, product number: PCDBH0038). A high-resolution CT read, pulmonary function test, 12-lead electrocardiogram, and Doppler echocardiography were assessed at baseline and week 24 for all participants.

Complete blood count (CBC), urine routine examinations, liver function, kidney function, immunoglobulin levels, ESR (mm/h), CRP (mg/L), number of tender and swollen joints (/28), DAS-28 ESR/CRP scores, joint contractures and tendon friction rubs, visual analogue scale (VAS) and time for morning stiffness, VAS for articular pain, and adverse events were assessed at baseline and weeks 4, 8, 12, 16, 20, and 24.

Flow cytometry protocol

Peripheral blood samples were collected in ethylenediaminetetraacetic acid (EDTA)-coated tubes. Flow cytometry immunophenotyping was performed within 4 hours after blood sampling to identify and characterise peripheral blood mononuclear cell subpopulations. Healthy individuals, matched by age and sex, were analysed using the same flow cytometry conditions. One hundred microliters of whole blood were taken for each experiment, and a parallel control group was set. Erythrocytes were then lysed by incubation with 1 ml of lysing buffer for 15 min. Subsequently, samples were blocked with blocking buffer (BD Biosciences, 347530). Finally, surface marker staining was performed for 20 min to identify specific B cells, including CD19, CD20, CD27, IgD, and CD24. The gating strategy used included the following populations: immature B cells ($CD19^+$, $CD24^+$, IgD^-), transitional B cells ($CD19^+$, $CD24^+$, IgD^+), naive B cells ($CD19^+$, $CD20^+$, $CD27^-$, IgD^+), unswitched memory B cells ($CD19^+$, $CD20^+$, $CD27^+$, IgD^+), and switched memory B cells ($CD19^+$, $CD20^+$, $CD27^+$, IgD^-).

At least 30,000 gated cells were acquired in an 8-color BD FACSCanto™ II flow cytometer (BD Biosciences) using FACSDiva™ software (BD Biosciences). Flow cytometer technical parameters were automatically set with BD Cytometer Setup and Tracking Beads (BD Biosciences). The fluorescent channel 525/40 BP was used to detect fluorescein isothiocyanate (FITC) intensity for CD19; 780/60 BP was used to detect APC-Cy7 intensity for CD20; 585/42 BP was used to detect PE intensity for CD27; 610/20 BP was used to detect PE-Texas Red intensity for IgD; and 780/60 BP was used to detect PE-Cy7 intensity for CD24. Unstained and fluorescence-minus-one (FMO) control groups were included in each test to adjust compensation. Lymphocytes were initially distinguished from cell debris and monocytes based on their characteristic forward scatter (FSC) and side scatter (SSC) signals.

For gating naive B cells, unswitched memory B cells, and switched memory B cells, CD19 and CD20 were first used to identify B cells. Immature B cells and transitional B cells were initially gated by CD19 and CD24, then separated by IgD expression. Subsequently, unswitched memory B cells and switched memory B cells were gated by IgD expression, and naive B cells were gated by CD27 expression.

Outcomes

The primary endpoint was the change in mRSS at week 24. Secondary endpoints included CRISS score, changes in HRCT score for pulmonary fibrosis, FVC (% predicted), DLCO (% predicted), changes in 6MWT, VAS for morning stiffness and time for morning stiffness, DAS-28 ESR/CRP scores, VAS for joint pain, CSURI value for nailfold capillaroscopy, SCTC-DI score, SF-36 score, ScleroID questionnaire score, PGA score, HAQ-DI score, UCLA SCTC GIT 2.0 score, titres of SSc-specific antibodies, and immune parameters in peripheral blood.

Exploratory study endpoints included changes in the expression levels of pe-

Table I. Characteristics of patients at baseline.

Baseline characteristics	Patients enrolled (n = 8)
Demographics	
Female/male, n	6/2
Age at enrolment (years), mean ± SD	46 ± 13
Disease duration (months), mean ± SD	64 ± 43
SSc subsets	
dcSSc/lcSSc, n	6/2
Antibody	
ANA positivity, n (%)	8 (100)
ATA positivity, n (%)	3 (37.5)
ACA positivity, n (%)	3 (37.5)
ARA positivity, n (%)	2 (25.0)
Clinical manifestations	
mRSS, mean ± SD	18.88 ± 5.84
Skin involvement, n (%)	8 (100)
Raynaud's phenomenon, n (%)	8 (100)
Ischaemic digital ulcers, n (%)	3 (37.5)
Joint involvement, n (%)	5 (62.5)
Lung fibrosis, n (%)	6 (75.0)
Gastrointestinal involvement, n (%)	4 (50.0)
Haematological system, n (%)	2 (25.0)
Heart involvement, n (%)	0 (0)
Kidney involvement, n (%)	0 (0)
Previous treatment	
Prednisone, n (%)	3 (37.5)
Mycophenolate Sodium, n (%)	2 (25.0)
MMF, n (%)	4 (50.0)
MMF+HCQ, n (%)	2 (25.0)
MMF+MTX+HCQ, n (%)	1 (12.5)
CTX	2 (25.0)
Antifibrotic therapy	0 (0)

IQR: interquartile range; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; ANA: anti-nuclear antibody; ATA: anti-scleroderma-70 antibody; ACA: anti-centromere antibody; ARA: anti-RNA polymerase III antibodies; MMF: mycophenolate mofetil; HCQ: hydroxychloroquine; MTX: methotrexate; CTX: cyclophosphamide

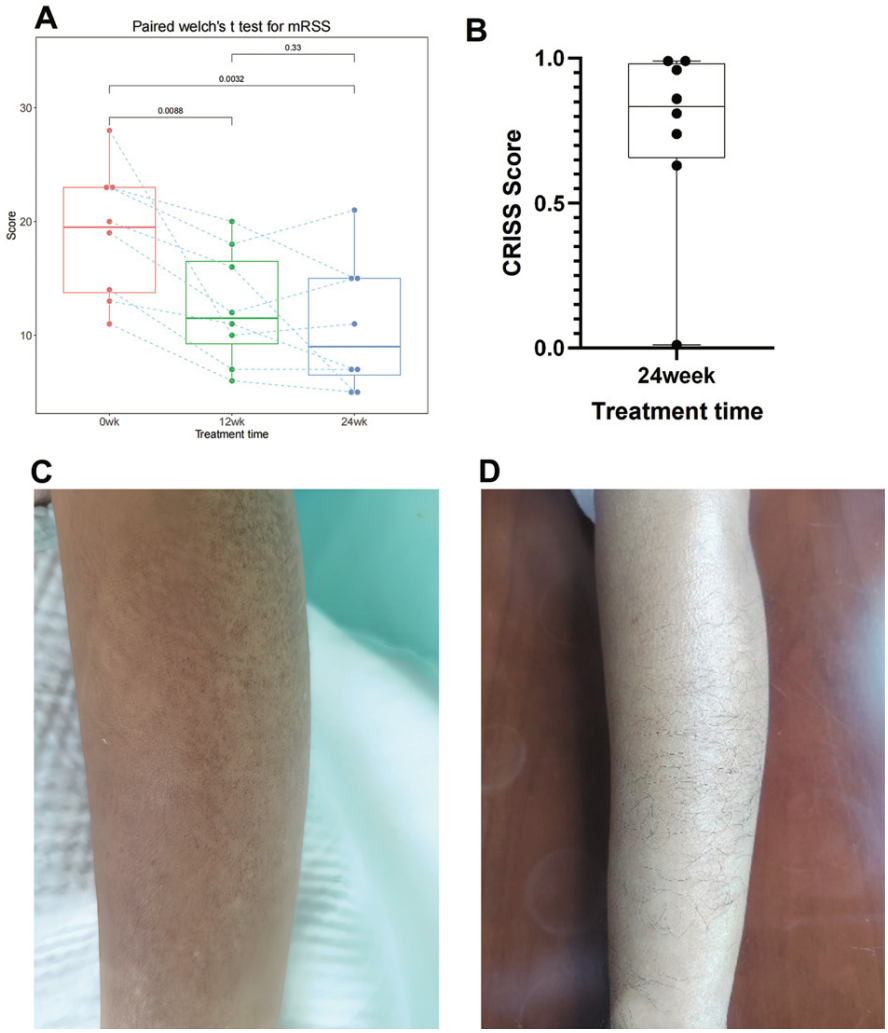

Fig. 1. Changes of mRSS and skin over time and CRISS score at week 24. **A**: mRSS at baseline, at week 12 and at week 24 in patients treated with telitacicept. **B**: CRISS score at week 24. **C-D**: the skin conditions of patient 2 (antibody: ARA, baseline immunosuppressive therapy: CTX) at baseline and at week 24. After treatment, the skin thickness, hardness and pigmentation were improved, and new hair appeared on the skin.

ripheral blood $CD19^+$ B cells, immature B cells, transitional B cells, naive B cells, unswitched memory B cells, and switched memory B cells at weeks 12 and 24, as well as changes in serum BAFF and APRIL levels at week 24. Additionally, all adverse events were recorded to evaluate drug safety.

Statistical analysis

This pilot trial was conducted to obtain initial safety and efficacy data to inform the sample size calculation for a future definitive randomized controlled trial. Therefore, no formal a priori power analysis was performed to determine the current sample size. For all continuous variables, normality of distribution was assessed using the Shapiro-Wilk test with significance set at $p<0.05$; this test was applied to baseline values and/or change-from-baseline values, as appropriate for paired analyses. Based on these assessments, variables that followed an approximately normal distribution (including mRSS, HRCT fibrosis score, FVC%, DLCO-SB%, DLCO-VA%, VAS for morning stiffness, DAS-28 ESR, SCTC-DI, SF-36 MCS, HAQ-DI) were summarized as mean ± standard deviation (SD) and analysed using the paired Student's t test for within-group changes from baseline to week 24. Variables that showed significant deviation from normality (including 6MWT, duration of morning stiffness, DAS-28 CRP, VAS for joint pain, CSURI capillaroscopy score, SF-36 PCS, ScleroID questionnaire score, PGA, and UCLA SCTC GIT 2.0 score) were summarized as median (interquartile range, IQR) and analysed using the Wilcoxon signed-rank test. Categorical variables were summarised as frequencies and percentages and compared using the Chi-squared test or two-tailed Fisher's exact test, as appropriate based on expected cell counts. To enhance interpretability of key efficacy outcomes, 95% confidence intervals (CIs) for the primary mRSS were calculated. A p value <0.05 was considered statistically significant. All statistical analyses were performed using R language version 4.3.0 and GraphPad Prism version 10.

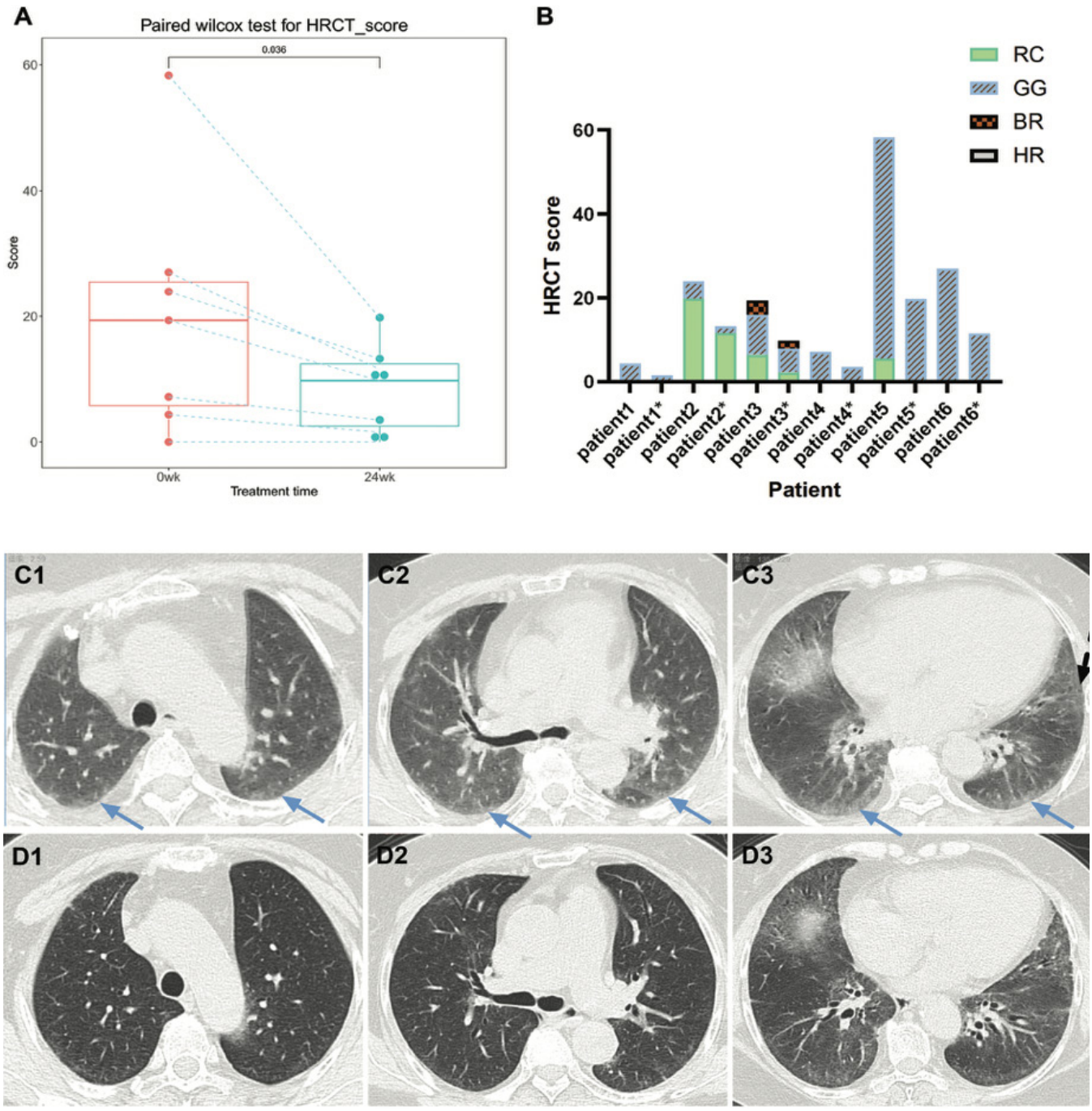

Fig. 2. A-B: HRCT score for pulmonary fibrosis at week 0 and 24. **C-D**: the CT transverse images of one patient's lungs over time; blue arrow, reticulation; black arrow, ground-glass opacity. **C**: the CT scans at baseline. **D**: the CT scans at week 24.
*: HRCT score at week 24.
BR: traction bronchiectasis, HR: honeycombing.

Standard protocol approvals, registrations, and patient consents

The study has been approved by the Ethics committee of Ningbo Medical Center Lihuili Hospital (NO. KY2022SL232-02). Written informed consent was obtained from all participants. The protocol was registered with Chictr.org.cn (ChiCTR2400085742).

Results

Baseline characteristics

A total of nine patients received telitacicept add-on treatment. One patient discontinued therapy after two weeks due to gastrointestinal adverse events, while the remaining eight patients successfully completed the 24-week treatment regimen. Of these eight patients, 75% were female (n=6), and 25% were male (n=2). The patients' ages ranged from 25 to 60 years, with a median age of 46 years. Detailed patient characteristics are provided in Table I.

Improvement in SSc by alleviating of skin fibrosis

Patients exhibited significant improve-

ments in their modified Rodnan skin score (mRSS). The mRSS decreased from 18.9±5.8 at baseline to 12.5±5.0 at 12 weeks (p=0.008) and further declined to 10.8±5.8 at 24 weeks (p=0.003) (Fig. 1A).

Improvement in SSc by composite response index scoring

For SSc, clinical improvement from baseline was primarily evaluated using the ACR-CRISS score, which includes the mRSS (21), FVC, HAQ-DI, PGA score, and patient global assessment score. An ACR-CRISS score >0.6 is considered an improvement, while a score <0.6 indicates no improvement (22). The response to telitacicept was assessed using the ACR-CRISS. Patients achieved an average ACR-CRISS score of 0.75 at week 24, indicating a positive clinical response (Fig. 1B).

Improvement in SSc by alleviating of lung fibrosis

Six patients had interstitial lung disease (ILD), and the severity of ILD was assessed by chest HRCT scans.

The HRCT score for pulmonary fibrosis is a quantitative assessment method that evaluates key imaging features representative of systemic sclerosis-associated interstitial lung disease (SSc-ILD), including ground-glass opacity, reticulations, traction bronchiectasis, and honeycombing. The scoring process involves the analysis of three anatomical levels of the thorax: the aortic arch, the carina, and the diaphragm. Advanced radiomics software is utilised to calculate the percentage area occupied by SSc-ILD lesions at each level. These level-specific scores are then aggregated to derive a comprehensive total chest HRCT score, reflecting the overall extent of pulmonary involvement in SSc-ILD.

The HRCT score for pulmonary fibrosis decreased from 27.5±19.6 to 7.5±7.2 at week 24 (p=0.036) (Fig. 2A). CT scans from one patient's lungs before and after treatment demonstrated improvement (patient 5) (Fig. 2C-D). However, there was no significant improvement in FVC% and DLCO% of lung function.

Improvement in SSc by decreasing levels of serum immunoglobulins and increasing of haemoglobin level

Significant reductions in serum immunoglobulin levels (IgG, IgA, IgM) were observed at week 4 in all patients and were sustained throughout the treatment period (all p<0.01) (Fig. 3A-C). By week 12, telitacicept add-on treatment also significantly increased haemoglobin levels (128.1 g/L *vs*. 136.8 g/L, p=0.013) (Fig. 3D), and this increase was sustained through week 24. However, no significant changes were observed in complement C3 and C4 levels (p>0.05).

Improvement in SSc by functional assessments

Several other secondary outcome measures were also evaluated (Table II). Significant improvements were observed in the duration of morning stiffness, SCTC-DI score, ScleroID questionnaire score, and SF-36 physical score (p<0.05). However, no significant differences were noted in DLCO-VA%, DLCO-SB%, FVC%, 6MWT, VAS for morning stiffness, VAS for joint pain, DAS-28 ESR/CRP score, UCLA SCTC GIT 2.0 score, SF-36 MCS score, PGA, HAQ-DI, or CSURI value.

Improvement in SSc by decreasing levels of serum BAFF/APRIL, CD19+ B cells, antibodies

To investigate the effects of telitacicept on BAFF and APRIL in patients with SSc, we first determined serum levels of BAFF and APRIL in 20 patients with SSc, as well as 20 healthy controls (HC). There were no significant differences in gender and age between the two groups. Compared with the HC group, SSc patients had higher circulating levels of BAFF (693 *vs*. 405.46 pg/ml, p=0.00044) and APRIL (967.10 *vs*. 536.39 pg/ml, p=0.01628). Following 24 weeks of telitacicept treatment, we observed that serum levels of BAFF and APRIL had significantly decreased in the eight enrolled SSc patients. Specifically, BAFF decreased from 839.69 to 561.00 pg/ml (p=0.016), and APRIL decreased from 967.10 to 368.05 pg/ml (p=0.0078) (Fig. 4 B1-2).

To better define the effects of telitacicept on B cells, we further explored B cell subpopulations using flow cytometry in the eight enrolled SSc patients and eight HC matched by gender and age. Compared with HC, the eight SSc patients had a higher proportion of unswitched memory B cells at baseline (p<0.05). There was also a decreasing trend in immature B cells (p=0.098) and increasing trends in transitional B cells (p=0.065) and naive B cells (p=0.065) at baseline, which indicates abnormality of B cell homeostasis. CD19+ B cells and switched memory B cells showed no significant change at baseline (Fig. 4D). Following telitacicept treatment, at both weeks 12 and 24, significant reductions were observed in CD19+ B cells, transitional B cells, and naive B cells (p<0.05), while immature B cells significantly increased (p<0.05). However, unswitched memory B cells and switched memory B cells showed no significant change (Fig. 4E). Additionally, antibody titres were quantitatively measured in six patients, with a decrease observed in four of them (Fig. 4C). The antibody types in the remaining two patients were ARA, which cannot be quantitatively detected. These results are consistent with the mechanism that telitacicept inhibits the increased concentration of circulating BAFF and APRIL, thereby rectifying disturbances of B cell homeostasis and suppressing autoantibody production in SSc.

Safety profiling following telitacicept treatment

In our study, one patient withdrew after two weeks due to intolerance of gastrointestinal reactions. The remaining eight patients completed the 24-week treatment; seven of them experienced no adverse reactions. One patient developed a local injection site reaction and experienced decreases in IgM and IgA levels beginning at week 8, reaching minimum levels of IgM, 0.18 g/L, and IgA, 0.69 g/L, at different times. This patient also exhibited minor lung inflammation on a CT scan at week 24 without accompanying symptoms and reported a one-month delay in her menstrual cycle compared to her normal cycle. Additionally, three patients suffered from upper respiratory tract infections.

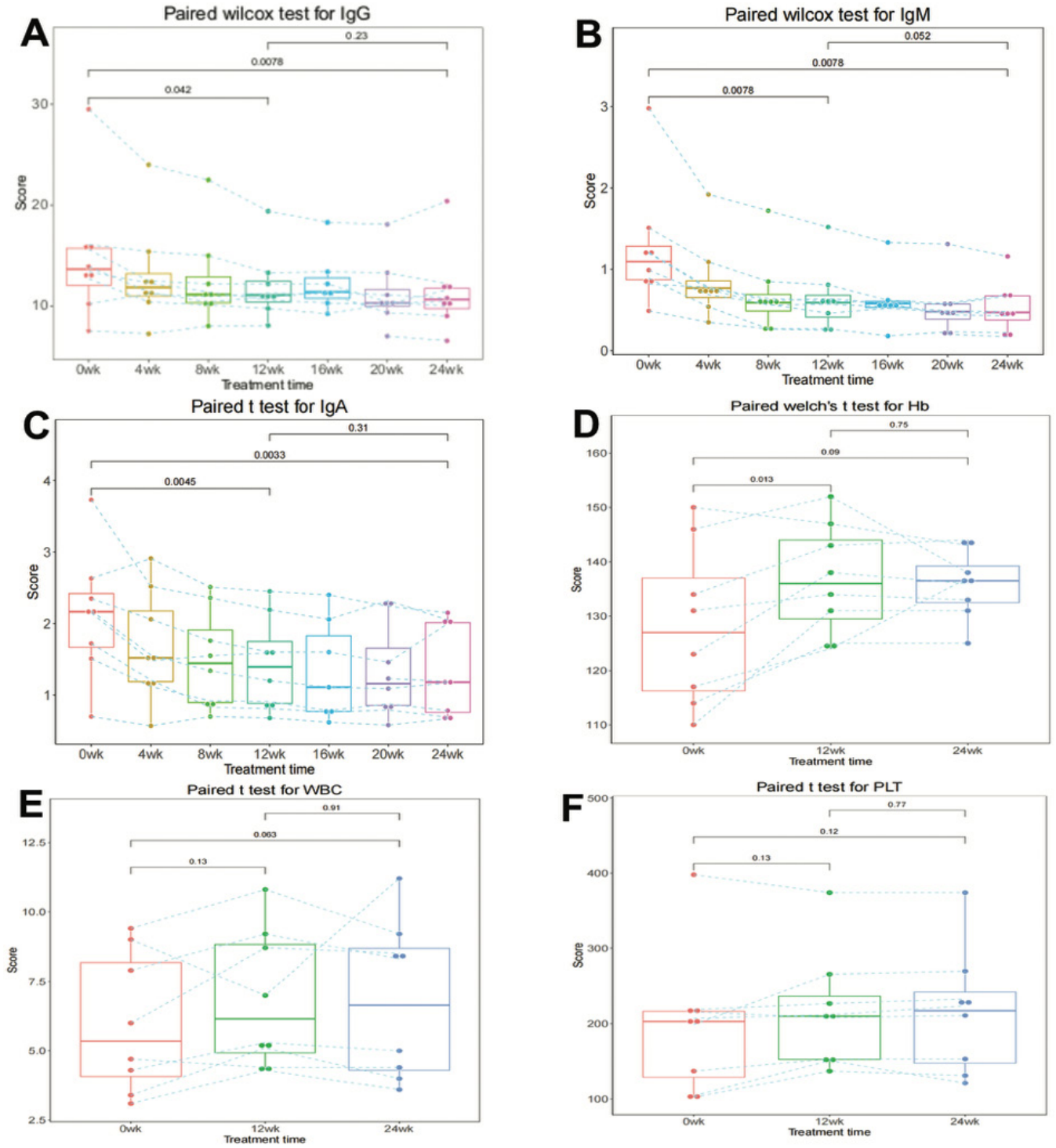

Fig. 3. Changes of serum immunoglobulins levels and complete blood counts over time. **A-C**: levels of IgG, IgM and IgA significantly decreased over time. **D**: Hb significantly increased at week 12. **E-F**: no significant changes were observed in white blood cell count and platelet count.

Discussion

This pilot study represents the first clinical investigation of the BLyS/APRIL dual inhibitor telitacicept for the treatment of SSc. Our findings suggested that telitacicept, as an add-on therapy, showed potential as a safe and effective treatment, demonstrating clinically significant improvements in skin and lung fibrosis, alongside a favourable immunomodulatory profile.

The therapeutic impact of telitacicept appears to extend beyond simple B-cell depletion. Transitional and naive B cells play multifaceted roles in immune regulation, including antigen presentation and T-cell activation (23). The upregulation of costimulatory molecules like CD80 and CD86 on these cells contributes to the activation of autoreactive T-cells and enhanced secretion of profibrotic cytokines in SSc (24). The observed reduction of these populations following telitacicept treatment

Table II. Change in primary and secondary endpoints at 24 weeks.

Index	baseline	24 weeks	*p*
mRSS, mean ± SD	18.9 ± 5.8	10.8 ± 5.8	0.003
mRSS change from baseline, mean (95% CI)	-	-8.1 (-12.4, -3.8)	0.003
CRISS score	NA	0.75	
HRCT score for pulmonary fibrosis, mean ± SD	27.5 ± 19.6	7.5 ± 7.2	0.003
FVC%, mean ± SD	89.4 ± 18.4	93.7 ± 20.3	0.203
DLCO-SB%, mean ± SD	55.8 ± 17.4	58.1 ± 19.3	0.367
DLCO-VA%, mean ± SD	65.5 ± 17.6	65.4 ± 19.5	0.963
6-minute walking test (6MWT), median (IQR)	525.5 (498.8, 575.0)	560.0 (518.0, 568.5)	0.500
VAS for morning stiffness, mean ± SD	3.8 ± 2.9	2.9 ± 1.9	0.195
Time for morning stiffness, median (IQR)	60 (47.5, 1440.0)	45 (4.75, 360.0)	0.022
DAS-28 ESR score, mean ± SD	2.4 ± 1.0	1.9 ± 1.0	0.240
DAS-28 CRP score, median (IQR)	1.7 (1.5, 2.7)	1.3 (1.0, 2.7)	0.109
VAS for joint pain, median (IQR)	0.5 (0, 3.5)	0 (0, 2)	0.174
CSURI value for nail fold capillary endoscopy, median (IQR)	6.3 (0, 14.1)	9.2 (1.5, 58.3)	0.330
SCTC-DI score, mean ± SD	3.1 ± 2.7	2.3 ± 2.3	0.041
SF-36 MCS score, mean ± SD	82.3 ± 23.3	78.8 ± 23.6	0.460
SF-36 PCS score, median (IQR)	78.5 (69.0, 93.0)	84.0 (74.5, 96.0)	0.015
ScleroID questionnaire score, median (IQR)	14.8 (9.8, 37.0)	10.5 (6.8, 35.0)	0.035
PGA score, median (IQR)	2.0 (1, 3)	1.0 (1, 3)	0.149
HAQ-DI score, mean ± SD	1.3 ± 1.4	0.5 ± 0.8	0.150
UCLA SCTC GIT 2.0 score, median (IQR)	0.02 (0, 0.42)	0.01 (0, 42)	1.000

CRISS: composite response index for systemic sclerosis; CSURI: capillaroscopic skin ulcer risk index; SCTC-DI: Scleroderma Clinical Trials Consortium Damage Index; SF-36: Short Form-36; ScleroID: the EULAR systemic sclerosis impact of disease; PGA: physician global assessment; HAQ-DI: Health Assessment Questionnaire Disability Index; UCLA SCTC GIT: University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract.

suggests a potential restoration of immune regulatory homeostasis, thereby disrupting a key pathway in the fibrotic process. This is further supported by the observed decrease in SSc-specific autoantibody titres in four out of six evaluable patients, linking the drug's mechanism to a reduction in hallmarks of B-cell hyperactivation.

Shifting focus to hematologic effects, another notable finding was the significant increase in haemoglobin (Hb) levels. Anaemia is a common comorbidity, found in 45.2% of patients in one SSc cohort, and is an independent prognostic factor for mortality and organ complications (25). The increase in Hb with telitacicept, a phenomenon also observed in a real-world study of SLE patients (18), suggested a potential benefit on SSc-related microangiopathy or gastrointestinal involvement. However, the exact mechanism warrants further investigation.

Regarding pulmonary and skin fibrosis, patients treated with telitacicept achieved a statistically significant improvement in mRSS and chest HRCT scores at 24 weeks. While the absence of a concurrent control group limits definitive conclusions, the magnitude and timing of the observed improvements warrant consideration. The mean reduction in mRSS of 8.1 points over 24 weeks in our cohort appears substantial when compared to the natural history of the disease and the effects typically seen with background immunosuppressants alone. For instance, Boulos *et al*. have reported mRSS reductions of approximately 3.7 after 1 year of mycophenolate mofetil therapy in diffuse SSc (26). The greater improvement observed here, coupled with the significant and rapid normalisation of pathogenic B-cell subsets and immunoglobulins suggests that the add-on therapy provided a benefit beyond that of background immunosuppression. Of note, given the natural history of SSc where skin involvement can spontaneously improve, randomised, placebo-controlled studies are required to confirm whether improvement can be attributed to telitacicept therapy. As research evolves, the combination of conventional immunosuppressive agents with targeted BAFF/APRIL dual inhibitors like telitacicept may offer a more comprehensive strategy for managing SSc. In our study, the pulmonary function parameters, such as FVC% and DLCO%, did not exhibit corresponding significant improvement. This dissociation between imaging and functional assessments is not uncommon in clinical trials of SSc-ILD. For example, weak associations between visual assessment of radiologic ILD and FVC at baseline and follow-up were found in a single-arm open-label clinical trial of dasatinib (p=0.14 and p=0.29, respectively) (27). One of the reasons for this is the inherent limitations of FVC in ILD, which may affect our ability to detect functional improvement. In a study evaluating the association of ILD and FVC through logistic regression, 62.5% of SSc patients with significant ILD on HRCT had a normal FVC value. Notably, 5 of 40 patients with a normal FVC value had severe, functionally occult lung fibrosis. In our patients, FVC was within the normal range at baseline, resulting in insufficient sensitivity to effectively reflect early, subtle physiological deterioration or improvement. Moreover, the measurement of pulmonary function tests itself is subject to variability due to factors such as patient effort and operator technique. Furthermore, the small sample size in this study (n=8) may have limited the statistical power to detect statistically significant differences in the pulmonary function data. Although the mean FVC% (p=0.203) showed an improving trend, it did not reach statistical significance due to inter-individual variability.

Regarding safety, telitacicept demonstrated an acceptable profile, consistent with its known effects in other autoimmune diseases (18, 28). The most common adverse events were upper respiratory tract infections and decreased immunoglobulin levels (IgG, IgA, IgM), which were manageable. One patient discontinued treatment due to gastrointestinal intolerance, but no serious adverse events or fatal infections were observed.

Despite these encouraging results, our study has several limitations. First and foremost, as an open-label, single-arm pilot study with a small sample size, the interpretation of efficacy is constrained by the lack of a control group. We cannot fully discount the

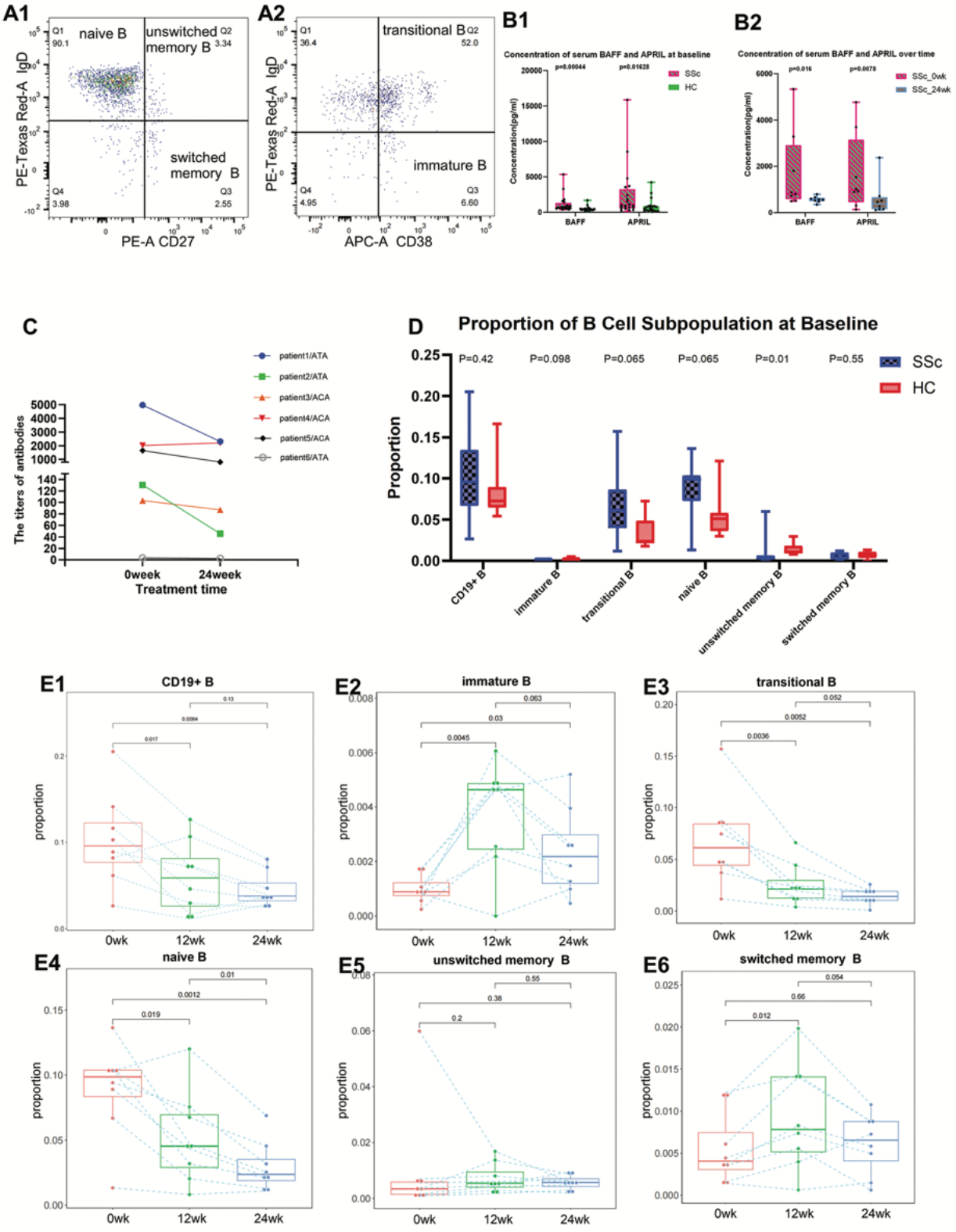

Fig. 4. The proportion of B cell subpopulations, serum BAFF and APRIL levers and titres of SSc-specific antibodies over time. **A1-A2**: flow cytometry of B cells in patients with SSc. **B1**: the baseline of BAFF and APRIL levels between 20 SSc patients and 20 healthy controls (HC). **B2**: the changes in BAFF and APRIL levels before and after telitacicept treatment in 8 SSc patients. **C**: the titres of SSc-specific antibodies at week 0 and 24. Patient 1, 2, 3 and 5 showed decrease in titres of antibodies compared to baseline. **D**: comparison of B cell subpopulations between healthy control group and SSc group at baseline. E, proportions of B cell subpopulations in SSc following telitacicept treatment. **E1-4**: Following telitacicept treatment, at both weeks 12 and 24, significant reductions were observed in CD19+ B cells, transitional B cells and naive B cells ($p<0.05$), while immature B cells had significantly increased ($p<0.05$). **E5-6**: unswitched memory B cells and switched memory B cells showed no trend.
ATA: anti-topoisomerase I antibody, ACA: anti-centromere antibody.

potential influences of placebo effects, regression to the mean, or the continued effect of established concomitant background therapies on the clinical outcomes. Similarly, the small sample size not only constrains efficacy interpretation but also precludes a definitive safety profile and limits the generalisability of our findings. However, these limitations are inherent to early-phase exploratory research. The primary value of our work lies in its role in generating robust hypotheses and providing crucial mechanistic insights and preliminary efficacy data to justify and inform the design of a larger, randomised, placebo-controlled trial.

In conclusion, this pilot study provides initial evidence that dual BLyS/APRIL inhibition with telitacicept can modulate the aberrant B-cell biology in SSc and translate into clinically meaningful improvements in fibrosis of the skin and lungs. Larger-scale, controlled clinical trials are warranted to confirm its efficacy and establish its role in the SSc treatment paradigm.

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