Efficacy and safety of abatacept for interstitial lung disease associated with antisynthetase syndrome: a case series

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Abstract

Objective

This study investigated the efficacy and safety of abatacept (ABA) in interstitial lung disease (ILD) associated with antisynthetase syndrome (ASS).

Methods

Eight patients were identified through retrospective analysis of the medical records of our centre. All patients fulfilled the Solomon criteria and had a disease complicated with ILD. Lung function, imaging, serum markers, clinical evaluation indicators of ILD, peripheral blood cell classification, cytokines, and prednisone doses were analysed.

Results

Seven of the eight patients were female. The mean age was 54.4 (standard deviation [SD] 6.0) years. Antibodies against Jo-1, PL-12, and PL-7 were present in three, three, and two patients respectively. At baseline, the mean diffusing lung capacity for carbon monoxide (DLCO) was 53.8% (SD 9.2%), the mean score of King's Brief Interstitial Lung Disease (KBILD) was 40.6 (SD 13.8), the median Krebs Von den Lungen-6 (KL-6) was 1612.5 (interquartile range [IQR] 1180.5-2431.5) U/ml. All patients experienced symptom alleviation after ABA therapy. The mean and median changes in DLCO percentage, KBILD, and KL-6 were 12.3% ($p<0.05$), 21.4 ($p<0.01$), and 174.5U/ml ($p<0.01$), respectively. No obvious adverse events related to ABA were observed during the treatment.

Conclusion

Our study offers preliminary, but encouraging, clinical evidence in favour of ABA as a therapy for ASS-ILD. ABA demonstrated favourable effects on ILD and was well-tolerated. Well-designed randomised controlled studies are required to confirm the efficacy and safety of this strategy.

Key words

abatacept, antisynthetase syndrome, interstitial lung disease

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Introduction

Interstitial lung disease (ILD) is one of the most prevalent and clinically significant manifestations of connective tissue disease (CTD) (1). ILD is present in most CTD, including systemic sclerosis (SSc), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjögren's syndrome (SS), and idiopathic inflammatory myopathy (IIM) (2). In recent years, many patients with IIM-associated ILD have been identified because myositis-specific antibodies have been widely used in clinical settings. Among the various subtypes of IIM, antisynthetase syndrome (ASS) is found to be the most prone to be accompanied by ILD, which occurs in up to 67–100% of cases, higher than that of non-ASS IIM. A retrospective study of 202 ASS cases showed that 49% (32/66) of the deaths were due to pulmonary fibrosis (3).

Following the appreciation of ILD as a major clinical challenge in ASS, new treatment strategies need to be introduced. The T lymphocyte inhibitors tacrolimus and cyclosporin A (CsA) have shown efficacy in some patients, confirming the role of T-cell activation in IIM-ILD pathogenesis; however, better therapeutic alternatives are still needed.

Abatacept (ABA), which consists of cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and an Fc portion of immunoglobulin G1, is a biological agent that inhibits T-cell activation by competing with CD28 to bind to their shared ligands, CD80 and CD86 (4), and by inducing regulatory T-cell (Treg) development and function (5). It is approved for RA treatment and appears to have better results than other biologicals for treating RA-ILD (6, 7). Although the pathophysiological role of T-cells as causative agents of myositis and pulmonary fibrosis is not fully understood (8, 9), the potential of T-cell inhibition therapy in ASS-ILD has been demonstrated. Treg dysfunction has been reported to be closely correlated with the severity of idiopathic pulmonary fibrosis, indicating a potential role for Tregs in the fibrotic process (10). Furthermore, ABA considerably suppresses the expression of most inflammatory genes, particularly interferon-γ (IFN-γ) (11), which is markedly up-regulated in ASS-ILD (12). A randomised pilot trial assessing the effect of ABA in treating antisynthetase autoantibody-positive patients is underway, but no results have been published yet. Single case reports and a phase IIb clinical trial also indicate that ABA affects disease activity in patients with IIM (13-17). We retrospectively analysed clinical data from our centre to further explore the potential role of ABA in ASS-ILD.

In this case series, we report the characteristics of eight patients with ASS-ILD and their response to ABA therapy in the pulmonary condition when they were refractory to conventional therapeutic agents.

Methods

We conducted a retrospective study of consecutively enrolled adults (≥ 18 years of age) who were diagnosed with ASS-ILD and treated with ABA between January 2021 and March 2022 at the Department of Rheumatology at Renji Hospital, Shanghai Jiao Tong University School of Medicine. Data were obtained from medical records at our centre. All the participants fulfilled Solomon's criteria (18). Respiratory symptoms, high-resolution computed tomography (HRCT) results, and clinical manifestations were used to diagnose ILD (19). Eligible patients had obvious or worsening respiratory symptoms. Patients with coexisting autoimmune inflammatory diseases such as SLE, SS, RA, autoimmune hepatitis (AIH), or infection were excluded. Additionally, patients who required daily doses of prednisone greater than 100 mg because of other problems outside the lungs were also excluded.

All patients were treated with ABA 250 mg via subcutaneous injection once every other week. We only included patients who had received ABA for at least 3 months. Previous therapy including glucocorticoids and immunosuppressive agents was continued and recorded.

We analysed the medical documentation of patients with ASS-ILD before and after ABA treatment. We assessed Krebs Von den Lungen-6 (KL-6), in-

terleukin-6 (IL-6), interleukin-8 (IL-8), helper T-cell (Th) absolute counts, pulmonary function tests (PFTs), modified Medical Research Council (mMRC), King's Brief Interstitial Lung Disease (KBILD), HRCT findings, and prednisone dose.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Renji Hospital, Shanghai, China (2013-216). All participants provided written informed consent to participate in the study.

Statistical analysis

Statistical analysis was performed using the SPSS Statistics 26 software and GraphPad Prism 8 software. Continuous data with a normal distribution are summarised as means and standard deviation (SD), non-normally distributed data with medians and interquartile range (IQR), and categorical variables are shown as numbers and percentages. The paired t-test or Wilcoxon signed-rank sum test was used for continuous variables, and Fisher's exact test was used for categorical variables. *p*-values (where set) <0.05.

Results

A total of 10 patients were found, but two patients were excluded due to only 1 month of ABA treatment. (They all reported that they subjectively felt the same as before). Thus, eight patients remained in the study. In this study, there were mostly females (7/8), with a mean age of 54.4 (SD 6.0) years. The median disease duration was 6.5 (IQR 3.3-14.8) months. Among these patients, three (37.5%) had anti-Jo-1 antibodies, three (37.5%) had anti-PL-12 antibodies, and two (25%) had anti-PL-7 antibodies. At the inception of the study, the mean diffusing lung capacity for carbon monoxide (DLCO) was 53.8% (SD 9.2%) and the mean forced vital capacity (FVC) was 66.3% (SD 12.9%) of the prediction. All patients had experienced respiratory symptoms, with 87.5% (7/8) of patients considered to have dyspnoea (mMRC grade ≥1) and a mean baseline KBILD score of 40.6 (SD 13.8). The median KL-6 was 1612.5U/ml (IQR 1180.5–2454.8). Creatine kinase (CK), an indicator related to disease activity(20), was within the normal range (49 [IQR 41.8–87.8] U/L) in all patients. Before ABA treatment, patients were administered prednisone (Pred), tacrolimus (Tac), mycophenolate mofetil (MMF), hydroxychloroquine (HCQ), and CsA. The dosage of prednisone and immunosuppressants in all participants was stable for at least one month before ABA treatment. Detailed demographic and clinical characteristics and laboratory parameters of all participants are summarised in Table I.

Table I. Demographic, clinical characteristics and laboratory parameters.

Variable	Pre-abatacept	Post-abatacept	*p*-value
Sex, n (%)			
Female	7 (87.5)		
Male	1 (12.5)		
Age, mean (SD), years	54.4 (6.0)		
Serum antibody, n (%)			
Jo-1	3 (37.5)		
PL-7	2 (25		
PL-12	3 (37.5)		
Disease duration, median (IQR), months	6.5 (3.3-14.8)		
Smoking, n (%)			
Clinical manifestation, n (%)	1 (12.5)		
Skin rash	6 (75)	3 (37.5)	0.315
Gottron's sign	3 (37.5)	1 (12.5)	0.569
Mechanic's hands	2 (25)	2 (25)	1.000
Joint pain	3 (37.5)	0 (0)	0.200
Raynaud syndrome	1 (12.5)	0 (0)	1.000
Myalgia	2 (25)	0 (0)	0.467
Weakness	4 (50)	1 (12.5)	0.282
Dyspnea	7 (87.5)	2 (25)	0.041*
Cough	8 (100)	2 (25)	0.007*
Expectoration	4 (50)	1 (12.5)	0.282
Shortness of breath			
Laboratory parameters	6 (75)	1 (12.5)	0.020*
CK, median (range), U/L	54.0 (41.8-87.8)	62.0 (38-78)	0.844
Ferritin, mean (SD), μg/L	172.4 (166.9)	192.6 (104.9)	0.415
LDH, mean (SD), U/L	255.4 (61.5)	253.0 (49.9)	0.688
WBC, mean (SD), $\times10^9$/L	9.3 (1.9)	8.3 (1.5)	0.240
RBC, mean (SD), $\times10^{12}$/L	4.6 (0.2)	4.4 (0.4)	0.047*
PLT, mean (SD), $\times10^9$/L	267.6 (59.4)	255.8 (70.6)	0.124
NEUT, median (IQR), $\times10^9$/L	5.6 (5.1-7.7)	5.2 (4.9-5.5)	0.195
LYM, mean (SD), $\times10^9$/L	2.1 (0.8)	2.1 (0.9)	0.919
ALT, median (IQR), U/L	26.5 (18-32.5)	19 (17.5-24.3)	0.195
Cr, mean (SD), μmol/L	59.0 (11.4)	62.0 (13.3)	0.345
CRP, mean (SD), mg/L	2.5 (2.6)	2.4 (1.7)	0.959
Concomitant medication			
Prednisone, mean (SD), mg/day	25.6 (10.1)	13.76 (5.4)	0.004*
Tacrolimus, n (%)	3 (37.5)	3 (37.5)	1.000
Mycophenolate mofetil, n (%)	2 (25)	1 (12.5)	1.000
Hydroxychloroquine, n (%)	1 (12.5)	1 (12.5)	1.000
Cyclosporin A, n (%)	0 (0)	1 (12.5)	1.000

SD: standard deviation; IQR: inter quartile range; CPK: creatine kinase; LDH: lactic dehydrogenase; WBC: white blood cell; RBC: red blood cell; PLT: platelet; NEUT: neutrophil; LYM: lymphocyte; Cr: creatinine; CRP: C-reaction protein.

Following ABA treatment, all patients improved their clinical state, especially in terms of alleviating symptoms related to interstitial lung disease. The essential parameters related to pulmonary function improved or remained stable (Table II). After ABA treatment, the mean improvement in DLCO percentage was 12.3% ($p<0.05$) (Fig. 1A), and the mean improvement in FVC percentage was 6.9% ($p=0.13$) (Fig. 1B). It seems that ABA is more effective in pulmonary carbon monoxide

Table II. Parameters along with follow-up.

Patients/parameter	Pre-abatacept n / %	Post-abatacept n / %	Change n / %
Patient 1			
DLCO	47%	86%	+76.6%
FVC	57%	90%	+57.9%
KL-6	2408	2377	-31
KBILD score§	39.1	41.9	+2.8
mMRC grade†	1	0	-1
Patient 2			
DLCO	57%	54%	-5.3%
FVC	81%	79%	-2.5%
KL-6	2595	1934	-661
KBILD score	52.4	64.8	+12.4
mMRC grade	0	0	0
Patient 3			
DLCO	70%	76%	+8.6%
FVC	68%	74%	+8.8%
KL-6	1325	1290	-35
KBILD score	35.2	64.8	+29.6
mMRC grade	2	1	-1
Patient 4			
DLCO	63.4%	77.9%	+22.9%
FVC	89.6%	90.6%	+1.1%
KL-6	1044	818	-226
KBILD score	25.7	61.9	+36.2
mMRC grade	1	0	-1
Patient 5			
DLCO	50%	54%	+8.0%
FVC	46%	51%	+10.9%
KL-6	992	987	-5
KBILD score	24.8	38.1	+13.3
mMRC grade	2	0	-2
Patient 6			
DLCO	38.7%	49.5%	+27.9%
FVC	58.2%	54.1%	-7.0%
KL-6	1900	1025	-875
KBILD score	61.9	75.2	+13.3
mMRC grade	1	0	-1
Patient 7			
DLCO	49%	69%	+40.8%
FVC	64%	70%	+9.4%
KL-6	5224	4557	-667
KBILD score	57.1	80	+22.9
mMRC grade	2	0	-2
Patient 8			
DLCO	55.2%	62.4%	+13.0%
FVC	66.5%	77.1%	+15.9%
KL-6	1226	1103	-123
KBILD score	28.6	69.5	+40.9
mMRC grade	1	1	0

DLCO: diffusing lung capacity for carbon monoxide; FVC: forced vital capacity; KL-6: Krebs Von den Lungen-6; KBILD: The King's Brief Interstitial Lung Disease; mMRC: Modified Medical Research Council.

§The King's Brief Interstitial Lung Disease is a tool to measure the impact of ILD.

†Modified Medical Research Council is a tool to demonstrate degree of baseline functional disability due to dyspnoea.

diffusion function than in ventilation function. The MRC grade was reduced by one or more in 62.5% (5/8) patients. For monitoring the impact of ILD, KBILD showed a mean improvement of 21.4 (p<0.01) (Fig. 1C). Improvement of KBILD above the minimum clinically important difference (MICD) (3.9) (21) in 87.5% (7/8) of the patients. All patients successfully decreased the dose of prednisone, with a mean decrease of 11.3 mg/day (p<0.01) (Fig. 1D). KL-6 showed a median decrease of 174.5U/ml (p<0.01) (Fig. 1E). Creatine levels in all patients remained within the normal range (p=0.653), and there were no significant differences in other indicators related to disease activity, such as lactic dehydrogenase (LDH) and ferritin (Table I). Two patients underwent HRCT before and after ABA treatment, and their HRCT improved compared to that of the previous patients (Fig. 1F). Interestingly, following ABA administration, IL-6 and IL-8 levels that were elevated before ABA treatment in three patients dropped sharply, with most returning to the normal range (Fig. 2). Considering that ABA is a CTLA4 fusion protein that mainly inhibits T-cell activation, we examined the peripheral blood cell classification of patients with decreased levels of IL-6 and IL-8 after ABA therapy. This demonstrates that the absolute counts of helper T-cells (Th) decreased or remained within the normal range after ABA treatment (Fig. 2).

Although two patients were excluded from the study for receiving only one month of ABA treatment, we recorded their outcomes after ABA treatment. One patient was a 37-year-old female with an anti-PL-7 antibody who had Gottron's sign and cough as the manifestation. Her HRCT showed ILD with a non-specific interstitial pneumonia (NSIP) pattern, and PFT showed that the predicted FVC and DLCO were 78% and 67%, respectively. After one month of therapy, this patient withdrew from treatment because she felt her rash did not improve significantly, although her respiratory symptoms were stable. Another patient was a 53-year-old female with anti-PL-12 antibodies who complained of significant cough and shortness of breath. Her HRCT demonstrated ILD with a usual interstitial pneumonia (UIP) pattern, and PFT showed that the predicted FVC and DLCO were 77.4% and 44.8 %, respectively. After one month, she withdrew from treatment because she felt her respiratory symptoms did not improve significantly. Therefore, we lacked clinical data on their lung condition after one month of ABA treatment.

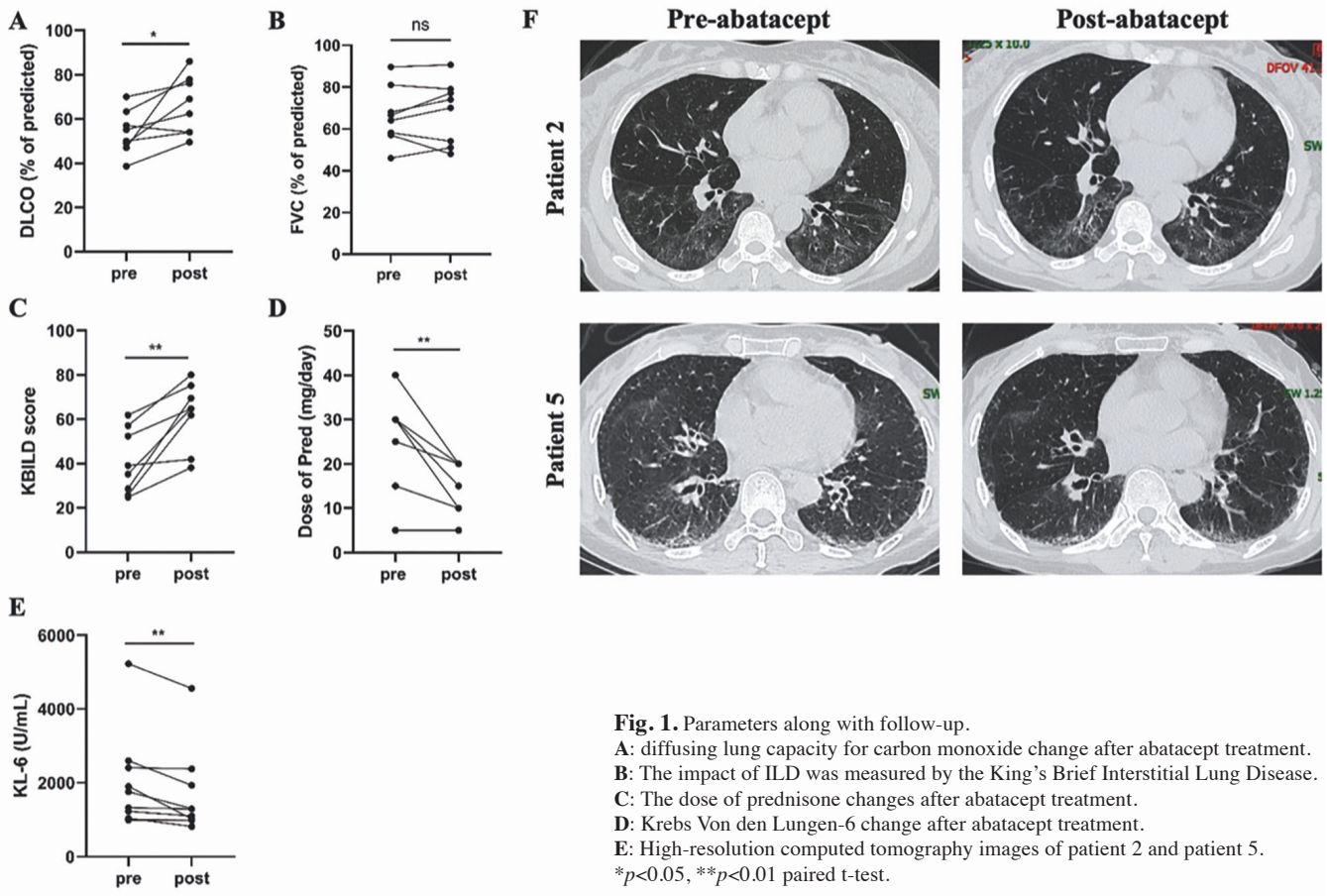

Fig. 1. Parameters along with follow-up.
A: diffusing lung capacity for carbon monoxide change after abatacept treatment.
B: The impact of ILD was measured by the King's Brief Interstitial Lung Disease.
C: The dose of prednisone changes after abatacept treatment.
D: Krebs Von den Lungen-6 change after abatacept treatment.
E: High-resolution computed tomography images of patient 2 and patient 5.
**p*<0.05, ***p*<0.01 paired t-test.

Although we retrospectively analysed only eight patients in this study, we found that all patients responded well to ABA treatment. It is important to note that ABA treatment was unexpectedly well-tolerated by all patients. None of the patients experienced serious adverse events that could be linked to ABA during treatment, such as infections requiring hospitalisation.

Patient 1. A 51-year-old female non-smoker diagnosed with ASS-ILD two years prior. During the past year, she had been treated regularly with oral prednisone to control the disease. She had slowly progressive dyspnoea, cough, expectoration, hoarseness, and sensation of a foreign body in the pharynx for an unknown reason for 1 month and, unfortunately, did not show sufficient improvement after taking 25 mg/day prednisone for 1 month. When enrolled, she had recurrent cough with expectorating white phlegm, which was usually worse at night. After 3 months of ABA treatment, her cough significantly reduced, and she was able to sleep well at night. The steroid treatment was changed to prednisone (20 mg/day).

Patient 2. A 50-year-old female non-smoker diagnosed with ASS-ILD 10 months prior. She was treated with oral prednisone 5 mg/day and HCQ 0.2 g twice daily for at least 5 months. She slowly developed shortness of breath, arthralgia, and a red rash on her lower back. HRCT showed an NSIP pattern with fibrous cords, multiple interstitial thickening, and traction bronchiole within the area of ground-glass opacity shadows in both lungs, with lower lung zone predominance. She was started on a subcutaneous injection of ABA and was maintained on 5 mg/day prednisone. Her symptoms improved, and HRCT revealed fewer fibrous cords and ground-glass opacity after 3 months of treatment, with a slight decrease in DLCO and FVC.

Patient 3. A 45-year-old female non-smoker diagnosed with ASS-ILD 10 years previously. She had been treated with oral prednisone and azathioprine for a long time. Five months prior, she had relapsed with myalgia and dry cough, with no fever or arthralgia. The treatment was adjusted to 30 mg/day prednisone and 0.75g/day MMF for about 5 months. Unfortunately, she was still coughing and had dyspnoea, which led her to walk up to 200 meters on flat ground. After 3 months of ABA treatment, she experienced less coughing and could climb five flights of stairs without dyspnoea. In addition, the dosage of prednisone was successfully decreased to 15 mg/day without obvious uncomfortable symptoms.

Patient 4. A 66-year-old female non-smoker diagnosed with ASS-ILD 5 months previously. She had a history of hypertension and coronary artery disease (CAD). Nine months prior, she first experienced shortness of breath and weakness for unknown reasons. She developed progressive resting dyspnoea within 3 months. After relapse, she

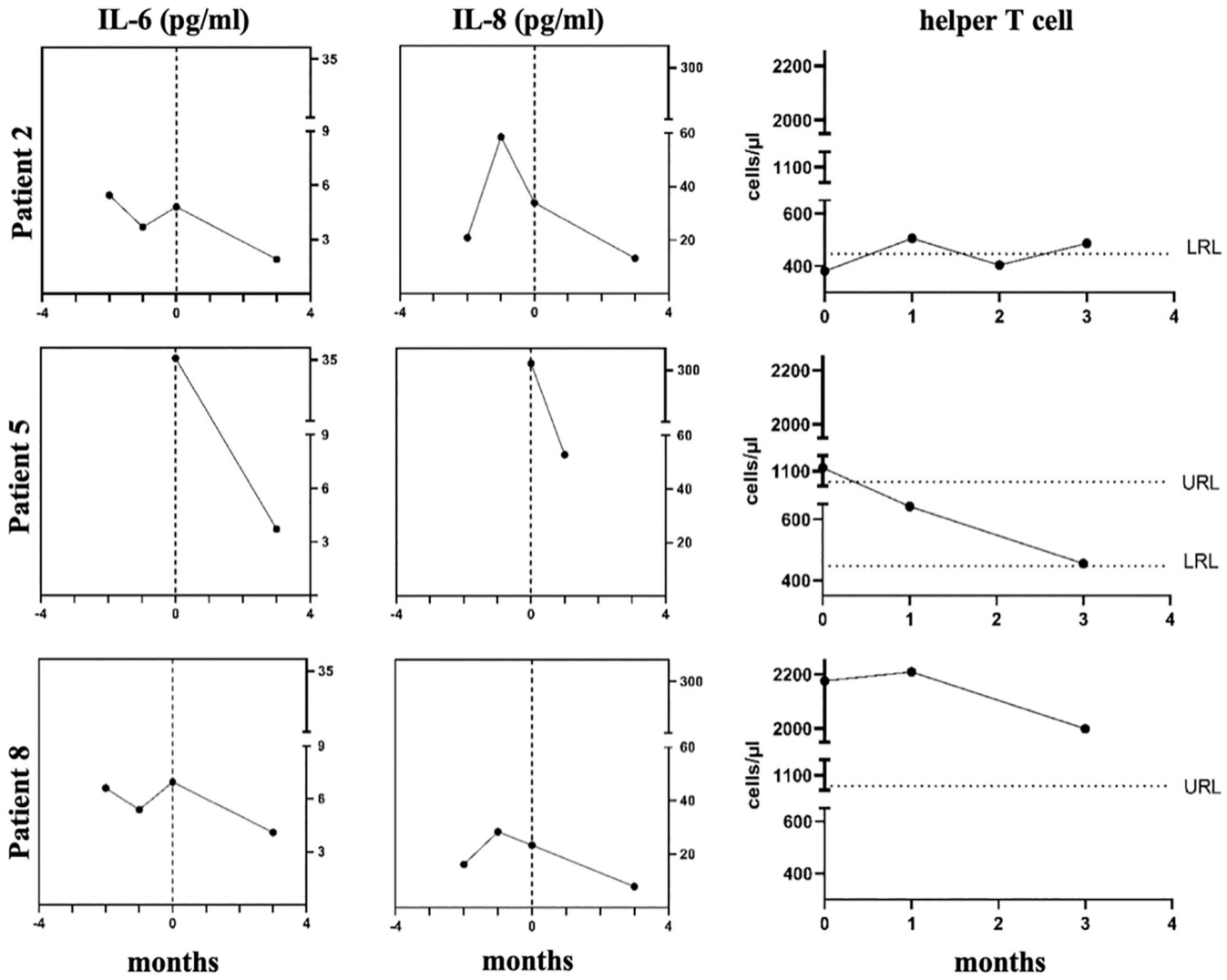

Fig. 2. Longitudinal development of IL-6, IL-8, and helper T cell absolute counts in patients 2, 5, and 8 before and after treatment with abatacept. The dotted line represents the time of treatment. The horizontal dotted line indicates the lower or upper limit. The normal ranges for IL-6 and IL-8 are 0-5.3pg/ml and 0-20.6pg/ml, respectively. The normal range for helper T cell absolute count is 447-1030cells/ul.
LRL: lower range limit; URL: upper range limit.

received 40mg/day prednisone, which was slowly decreased to 15 mg/day and maintained for one month. However, she still experienced shortness of breath with coughing and weakness after the activity. After 3 months of ABA therapy, her shortness of breath and cough markedly improved, and her PFT parameters and KL-6 levels improved significantly. The prednisone dosage was reduced to 10mg with no relapse.

Patient 5. A 53-year-old female nonsmoker diagnosed with ASS-ILD 4 months previously. Her symptoms initially presented as Raynaud's phenomenon and she was admitted for shortness of breath and weakness after activity in our outpatient clinic. The patient was treated with oral prednisone 30mg/day and tacrolimus 2 mg/day to control the disease. However, the patient's condition did not improve after 2 months of treatment. Initial HRCT demonstrated an NSIP pattern with infiltration and scattered patchy high-density shadows and sac lucency shadows in the bilateral lungs, with a preference for the lower lung zone. After three months of ABA treatment, her shortness of breath was alleviated, and her weakness improved. The key index of her PFT was increasing, and her HRCT showed less scattered, patchy high-density shadows than before. The prednisone dosage was changed to 10 mg/day.

Patient 6. A 60-year-old male with a more than 30-year smoking history (one cigarette per day on average) and a history of diabetes mellitus. He had been diagnosed with ASS-ILD one month previously. His clinical symptoms mainly included shortness of breath and rashes on his lower legs and anterior skin. After 1 month of treatment with 30mg prednisone, his symptoms did not improve significantly. He was started on a subcutaneous injection of 250 mg ABA along with oral 30 mg/day prednisone to control his disease. His rashes subsided after 1 month of treatment, and dyspnoea and shortness of breath improved after 3 months. Although his FVC decreased by 7.04%,

his DLCO improved by 27.91%, and his KL-6 level decreased substantially. The prednisone dosage was reduced to 20 mg/day.

Patient 7. A 55-year-old female nonsmoker diagnosed with ASS-ILD 4 months previously. She had developed a skin rash 4 months prior and slowing progressive shortness of breath after 2 months of activity. One month prior, she was hospitalised in an external hospital for severe dyspnoea, cough, and expectoration for a week and was diagnosed with "community-acquired pneumonia". She was maintained on 40 mg/day prednisone for 1 month and did not show obvious improvement. At enrolment, her main manifestations were dyspnoea, cough, mechanic's hands, and elbow rash. Her initial treatment consisted of 250 mg of ABA subcutaneously every fortnight and prednisone (40 mg/day) orally. After 3 months of ABA treatment, her skin rash subsided and was able to climb three flights of stairs without dyspnoea. She successfully reduced the prednisone dosage to 10mg/day. There was also a significant improvement in the PFT, with a 40.8% improvement in DLCO.

Patient 8. A 55-year-old female nonsmoker diagnosed with ASS-ILD 1 month previously. She reported obvious dyspnoea, shortness of breath, cough, and expectoration, which worsened with activity. She was treated with 40 mg prednisone per day and 1mg tacrolimus twice daily for illness control. After 1 month of treatment, there was no improvement in symptoms. She started treatment with ABA subcutaneously, and after three months of treatment, her cough, expectoration, and shortness of breath decreased. Her pulmonary ventilation and diffusion function improved, with a 13.0% improvement in FVC and a 15.9% improvement in DLCO. The prednisone dose was successfully reduced to 15 mg/day.

Discussion

To our knowledge, this is the first case series to demonstrate the efficacy and safety of ABA treatment in patients with ILD-associated ASS. Our data suggest the beneficial effects of ABA therapy on ASS-ILD, particularly ILD, for which our data indicate that ABA could improve pulmonary function.

In this cohort, all patients had ILD at the time of ASS diagnosis. Among these patients, shortness of breath after activity and paroxysmal cough were common symptoms, whereas muscle weakness and myalgia were rare. Our data demonstrated that 7/8 patients had improved DLCO and 6/8 patients had improved FVC, and the improvement rate of DLCO with ABA appeared to be higher than that with FVC. It is also worth mentioning that KL-6, KBILD scores and corticosteroid dosage were reduced in all patients.

Some patients underwent both peripheral blood cell classification and cytokine assays. These individuals had decreased or were within the normal absolute values of Th cells after ABA treatment. Additionally, we observed a notable increase in IL-6 and IL-8 levels in these patients at baseline, and an unexpected decrease after ABA treatment. Several studies revealed that serum IL-6 and IL-8 can be used as biomarkers to reflect the disease activity of IIM and are also associated with the combination of ILD (22-24). Serum IL-6 and IL-8 also play a role in other CTD-associated ILD. In early SSc, IL-6 is an essential contributor to developing lung fibrosis (26), and IL-8 levels are higher in SSc-ILD patients than in healthy controls(26). According to a phase 3 randomised controlled trial, anti-IL-6 treatment protected lung function and slowed FVC deterioration in patients with SSc-ILD (27). The serum IL-6 and IL-8 are highly correlated with the ILD in pSS patients (28). Several studies revealed the ability of ABA to reduce elevated IL-6 levels in RA patients (29-31). Bozec *et al*. (32) showed that ABA blocks antibody-mediated cytokine production, such as IL-6 and IL-8, which is attributed to the high expression of ABA binding to CD80/86 in monocytes, affecting their ability to produce pro-inflammatory cytokines. Our results also support the potential of ABA to influence the production of proinflammatory cytokines.

Biological DMARD ABA, a recombinant fusion protein, selectively modulates the co-stimulatory signal necessary for T-cell activation (33). CTLA-4 negatively regulates T-cell activation. On the one hand, CTLA-4 downregulates T-cell activation by competing with CD28 to bind their common ligands CD80 and CD86, which results in the marked blocking activity of several key transcription factors, including AP-1(34). Fra-2 and c-JUN are components of the AP-1 transcription complex. Several animal experiments have shown that lung fibrosis is attenuated by inactivation of Fra-2 and aggravated by overexpression of Fra-2 (35, 36). A previous study found that c-JUN expression is increased in many human fibrotic diseases, and that systemic induction of c-Jun in mice resulted in the development of fibrosis in multiple organs (37). Additionally, in patients with IIM, B- and $CD4^+$ T-cells are dominant in the inflammatory infiltrate on muscle biopsy, and CD28 expression has been discovered on the cell surface of myocytes in individuals with IIM, indicating that these cells may have a particular antigen-presenting role in IIM progression (38).

On the other hand, the CTLA-4 regulatory mechanism is also provided by the induction of Treg development and inhibition of Th17 differentiation (5, 39). Takei *et al*. (40) attenuated lung fibrosis in BLM-treated mice by increasing the number of Tregs and reducing inflammatory T-cell subsets, such as $CD4^+IFN\gamma^+$ T-cells and $\gamma\delta^+IL\text{-}17A^+$ T-cells. A study investigating the changes in peripheral lymphocytes in IIM patients revealed that Treg cell deficiency was associated with ILD occurrence in patients with myositis (41). Besides, CTLA-4-Ig infusion reduces the frequency of IFN-γ-producing cells and increases the ratio of Th2:Th1 lines, which means ABA can skew the immune response toward Th2 in Th1-mediated diseases (42). Galindo-Feria *et al*. (43) revealed that in the bronchoalveolar lavage fluid, $CD4^+$ T-cells from patients with ASS had a distinct Th1 phenotype and produced a large amount of IFN-γ after stimulation. However, the precise processes for controlling the immune system remain ambiguous

(44). A deeper understanding of CTLA-4 function is required to develop an effective strategy for autoimmune therapy and other immune-mediated diseases.

Although ABA appears to be an effective therapeutic agent in terms of its mechanism of action, there are no reports of ABA against ASS-ILD. According to a review related to the efficacy and safety of ABA in RA-ILD (45), under ABA treatment, DLCO showed a better response than FVC, with an improvement or stabilisation of DLCO and FVC in 88.9% to 90.6% and 86.1% to 87.7% of patients, respectively. This is consistent with our data showing a more pronounced improvement in DLCO of ASS-ILD patients with ABA. In the treatment of RA, ABA has the lowest risk of infection compared to other biologics and a good safety profile (46, 47). Additionally, it has been associated with the improvement and stabilisation of lung function in patients with RA-ILD in a small case series (48, 49). Several case reports have shown that ABA treatment is associated with favourable outcomes in IIM patients with refractory myositis, intramuscular calcification, ulcerative skin disease, and oesophageal disease (13-16). In addition, a retrospective study suggested that calcineurin inhibitors appear to be a good therapeutic option for managing ILD associated with ASS for refractory cases and as first-line treatment (50), suggesting a role for T-cell activation in ASS-ILD. In a randomised phase IIb clinical trial, ABA was successful in treating 20 patients with IIM, particularly in improving muscle performance (17). However, no statistically significant differences in disease activity indicators, such as CK, LDH, and ferritin, were found in our patients, contradicting previous findings. This might be because these patients had little muscle involvement, and their levels of disease-related indices at baseline were in the normal range or close to normal. Despite this, previous studies and our data suggest that ABA may not only be effective for ASS, but also for ILD, with a safety profile similar to that of RA-ILD.

Despite the limited size of our cohort, to the best of our knowledge, this is the largest case series to date to use ABA in ASS-ILD and highlight the potential role of ABA in improving the lung condition of ASS. It is worth noticing that all the patients tolerated ABA therapy unexpectedly well. The use of immunosuppressive medications and prednisone before ABA administration was a confounding factor in this study. We were unable to exclude the effects of these medications completely. According to a report on ASS-associated ILD, glucocorticoids plus calcineurin inhibitors significantly improved progression-free survival (51). Given the state of our patients, we considered waiting or washing out to be relatively risky. As a result, the concurrent use of prednisone and immunosuppressants is an unavoidable primary confounder.

In conclusion, our study provides preliminary but encouraging clinical evidence in favor of ABA in treating ASS-ILD. Well-designed randomised controlled studies are required tosconfirm the efficacy and safety of this strategy.

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