ORIGINAL RESEARCH

Clinical Observational Study on the Therapeutic Efficacy of Pirfenidone in Sjögren's Syndrome Complicated with Nonspecific Interstitial Pneumonia

Wei Wei, MD; Wei Zou, BM; Wei Han, BM; Jingjing Liu, MM

ABSTRACT

Objective • This study aimed to evaluate the therapeutic impact of pirfenidone in patients with nonspecific interstitial pneumonia (NSIP) secondary to Sjögren's syndrome, comparing its effectiveness against conventional treatments.

Methods • A controlled clinical trial was conducted on a cohort of patients diagnosed with primary Sjögren's syndrome complicated by interstitial lung disease. The study included a total of 120 patients, divided equally into two groups: a control group comprising 60 patients and an observation group with another 60 patients. Random assignment placed patients in either a control group receiving hydroxychloroquine and prednisone or an observation group supplemented with pirfenidone. Pulmonary function parameters, Warrick scores from high-resolution CT scans, and Leicester Cough Quality of Life Questionnaire (LCQ) scores were assessed before and after treatment. Adverse reactions were monitored for treatment safety.

Results • Before treatment, no statistically significant differences in pulmonary function indicators (FVC%, FEV1%, DLco%) were observed between the groups ($P > .05$). Post-treatment, both groups showed significant improvements in these parameters ($P < .05$). Importantly, the observation group demonstrated superior improvements in pulmonary function compared to the control group ($P < .05$). Warrick's scores improved significantly in both groups after treatment, with the observation group achieving a more substantial reduction in scores compared to the control group ($P < .05$). LCQ scores showed no significant differences between the groups before treatment ($P > .05$). However, after treatment, both groups exhibited significant improvements, with the observation group consistently scoring higher ($P < .05$). Safety assessments revealed a slightly higher incidence of adverse reactions, including neurosensory abnormality and drowsiness, in the observation group compared to the control group.

Conclusions • This study suggests that adding pirfenidone to the treatment regimen for NSIP secondary to Sjögren's syndrome leads to significant improvements in pulmonary function, high-resolution CT scores, and quality of life compared to conventional treatments. (*Altern Ther Health Med.* [E-pub ahead of print.])

Wei Wei, MD, Chief Physician; School of Medicine, Tongji University, Shanghai, China; Yuyao People's Hospital of Zhejiang Province, Yuyao, China. **Wei Zou,** BM, Attending Doctor; **Wei Han,** BM, Resident Doctor; **Jingjing Liu,** MM, Associate Chief Physician; Yuyao People's Hospital of Zhejiang Province, Yuyao, China.

Corresponding author: Jingjing Liu, MM
E-mail: jiayi435@126.com

INTRODUCTION

Primary Sjögren's syndrome (pSS) is an autoimmune disease primarily impacting the salivary and lacrimal glands, resulting in symptoms such as dry mouth and dry eyes. In certain instances, individuals with pSS may experience lung involvement, including the development of interstitial pneumonia. Interstitial pneumonia is a lung disease characterized by inflammation and fibrosis of alveolar walls and interstitial tissue.[1,2]

While there is no unanimous agreement on the treatment of secondary interstitial pneumonia in pSS, steroids and immunosuppressants are frequently employed.[3] Among these, Cyclophosphamide (CTX) is the most utilized. However, the use of CTX is restricted in certain patients due to potential side effects, such as bone marrow suppression, liver function impairment, potential tumor risks, reproductive toxicity, and hemorrhagic cystitis.[3-5]

Recent studies indicated that pirfenidone serves as an effective cytokine inhibitor, which reduces the biological activity of fibroblasts by regulating or inhibiting specific factors. This regulation leads to a reduction in cell proliferation

and the synthesis of extracellular matrix collagen.[5] Pirfenidone is characterized by its immunomodulatory, anti-inflammatory, and anti-angiogenic properties, suggesting potential benefits in ameliorating clinical symptoms and enhancing lung function in patients with interstitial pneumonia.[6]

This study aims to assess the effectiveness of pirfenidone in the treatment of secondary mild-to-moderate NSIP following pSS. The objective is to improve the quality of life for patients and present a potential novel treatment option which carries positive clinical significance for both patients and healthcare.

MATERIALS AND METHODS

Study Design

A clinical controlled trial was conducted, and a total of 120 patients with pSS complicated with ILD treated at Yuyao People's Hospital between October 2016 and October 2018 were enrolled in this pilot study. All patients were confirmed to have pSS based on the 2002 American-European Consensus Group criteria (Rheumatism and Rheumatism classification criteria). High-resolution computed tomography (HRCT) imaging characteristics met the evidence-based guidelines for the diagnosis and management of ILD published by ATS/ERS/JRS/ALAT and the 2018 Chinese expert-based consensus statement regarding the diagnosis and treatment of interstitial lung disease associated with connective tissue diseases.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) Age ≥ 18; (2) Confirmed diagnosis of pSS; (2) Complete medical history and clear treatment records; (3) Ability to undergo HRCT examination during the study. Exclusion criteria were as follows: (1) Use of any immunosuppressant or glucocorticoids within the last 12 weeks; (2) Presence of other disorders, such as pulmonary tuberculosis, lung tumors, pneumonia, pleurisy, chronic obstructive lung disease, and long-term smoking; (3) Severe hypertension, diabetes, or liver, heart, or renal failure; (4) Presence of idiopathic interstitial lung disease.

Treatment Methods

Patients enrolled in the study refrained from using or had discontinued disease-modifying antirheumatic drugs and other medications affecting outcome assessment for at least 4 weeks before initiating treatment. In the control group, hydroxychloroquine was administered at a daily dose of 0.4 g, along with prednisone at a dose of 0.5 mg/kg. The prednisone dose was gradually tapered after 4 weeks and maintained at 10 mg daily after 12 weeks. In the observation group, pirfenidone was added at a daily dose of 50 mg to the control group regimen.

Clinical Effectiveness Assessment: Primary Outcome Measures

The primary study endpoints encompassed alterations in pulmonary function indicators and high-resolution CT scores of the lungs following 24 weeks of continuous treatment.

Pulmonary Function Indicators. (1) Forced Vital Capacity (FVC) as a percentage of the predicted value (FVC%); (2) Forced Expiratory Volume in one second (FEV1) as a percentage of the predicted value (FEV1%); (3) Carbon Monoxide Diffusing Capacity (DLco) as a percentage of the predicted value (DLco%).

Warrick Score for High-Resolution CT of the Lungs. Patients underwent supine position scans from the lung apex to the base with a slice thickness of 1 mm and an interslice gap of 10 mm. Specialized radiologists in CT evaluated the disease severity based on lung lesion manifestations, assigning scores as follows: ground-glass opacities (1 point), irregular pleural margins (2 points), linear opacities or subpleural curvilinear lines (3 points), honeycombing (4 points), and subpleural cysts (5 points).

Additionally, a score reflecting the extent of disease involvement, based on the number of bronchopulmonary segments affected (segments 1-18), was assigned: 1-3 segments (1 point), 4-9 segments (2 points), and >9 segments (3 points). The sum of both scores ranged from 0 to 30. The Warrick score was semiquantitatively graded as follows: 0 points for normal, < 8 points for mild, 8-15 points for moderate, and >15 points for severe.

Secondary Outcome Measures

The secondary study endpoint involved assessing the Leicester Cough Quality of Life Questionnaire (LCQ) score after 24 weeks of continuous treatment. The LCQ comprises 19 items categorized into three domains (physiological, psychological, and social impact of cough), each rated on a 7-point scale. Higher scores denote an enhanced quality of life.

Statistical Analysis

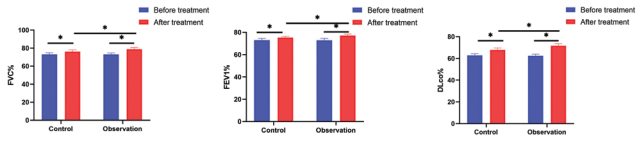
Statistical Package for Social Science (SPSS) 17.0 software (Chicago, IL, USA) was employed for statistical analysis. Continuous variables were presented as mean ± standard deviation ($\bar{x} \pm s$). Within-group comparisons were conducted using paired t tests, while between-group comparisons were analyzed using independent sample t tests. The χ^2 test was utilized for comparing categorical data between groups. A significance level of $P < .05$ was deemed statistically significant.

RESULT

Comparison of Lung Function Parameters Before and After Treatment in Two Patient Groups

Initially, there were no statistically significant differences in various pulmonary function indicators (FVC%, FEV1%, DLco%) between the two patient groups before treatment ($P > .05$). However, post-treatment, both groups exhibited a significant improvement in FVC%, FEV1%, and DLco% ($P < .05$). Notably, the observed group demonstrated a significantly superior enhancement in pulmonary function compared to the control group ($P < .05$), as illustrated in Figure 1.

Figure 1. Comparison of Lung Function Between the Two Groups Before and After Treatment



Note: The figure illustrates the comparison of lung function parameters before and after treatment in the two groups. FVC% is the forced vital capacity expressed as a percentage predicted; FEV1% is the forced expiratory volume in 1 second expressed as a percentage predicted; DLco% is the diffusing capacity for carbon monoxide as a percentage predicted. *$P < .05$.

Table 1. Comparison of Warrick's Score of Lung High-Resolution CT Between The Two Groups Before And After Treatment

Group	Before Treatment	After Treatment
Control (n = 60)	9.28±1.45	7.33±1.52*
Observation (n = 60)	9.49±1.55	5.85±1.84*#

Note: $P < .05$, vs. Before treatment; #$P < .05$, vs. Control. Warrick's score was semiquantitatively graded as follows: 0 points for normal, < 8 points for mild, 8-15 points for moderate, and> 15 points for severe. The asterisk (*) denotes statistical significance compared to the scores before treatment, and the hash (#) signifies statistical significance compared to the control group after treatment.

Table 2. Comparison of LCQ Scores Between The Two Groups Before And After Treatment

	Physiology		Psychology	
Group	Before Treatment	After Treatment	Before Treatment	After Treatment
Control (n = 60)	4.94±0.56	5.89±0.58*	5.10±0.66	6.15±0.58*
Observation (n=60)	5.09±0.60	6.53±0.28*#	5.00±0.60	6.52±0.28*#
	Sociology		Total Score	
Group	Before Treatment	After Treatment	Before Treatment	After Treatment
Control (n = 60)	4.99±0.61	6.01±0.62*	15.03±1.11	18.05±1.02*
Observation (n = 60)	4.94±0.56	6.48±0.30*#	15.03±0.93	19.53±0.42*#

Note: $P < .05$, vs. Before treatment; #$P < .05$, vs. Control. LCQ scores are presented as mean ± standard deviation. The asterisk (*) denotes statistical significance compared to the scores before treatment, and the hash (#) signifies statistical significance compared to the control group after treatment.

Table 3. Comparison of adverse reactions between the two groups after treatment [n (%)]

Group	Leukopenia	Stomach Upset	Neurosensory Abnormality	Constipation	Drowsiness
Control (n = 60)	0	2 (3.33)	1	2 (3.33)	1
Observation (n = 60)	1 (1.67)	2 (3.33)	3 (5.00)	3 (3.33)	5 (8.33)

Note: Adverse reactions are presented as the number and percentage (in parentheses) of affected individuals in each group.

Comparison of Warrick Scores on High-Resolution CT scans Before and After Treatment in Two Patient Groups

Prior to treatment, the control group exhibited an average Warrick's score of 9.28±1.45, while the observation group had a slightly higher score of 9.49±1.55. Following treatment, both groups demonstrated significant improvements in their Warrick's scores. In the control group, the score decreased to 7.33±1.52, marked by an asterisk (*) to indicate statistical significance ($P < .05$) compared to the scores before treatment.

On the other hand, the observation group exhibited a more substantial improvement, with their score decreasing to 5.85±1.84 after treatment. This change is denoted by an asterisk (*) and a hash (#), indicating a statistically significant difference ($P < .05$). This significance was observed compared to their baseline scores and also in comparison to the control group after treatment; refer to Table 1.

These findings suggest that the use of pirfenidone in the observation group led to a more significant reduction in Warrick's score on lung high-resolution CT, indicating a potentially superior therapeutic effect for patients with NSIP following Sjögren's syndrome when compared to traditional treatment methods involving the control group.

Comparison of LCQ Scores Before and After Treatment in Two Patient Groups

LCQ scores were assessed both before and after treatment in both patient groups. The results indicated no statistically significant differences in physiological, psychological, social, and total LCQ scores between the two groups before treatment ($P > .05$). However, post-treatment, all LCQ scores in both groups demonstrated a significant improvement compared to pre-treatment values ($P < .05$). Notably, the observational group consistently exhibited higher LCQ scores than the control group, and these differences were statistically significant ($P < .05$), as illustrated in Table 2.

Drug Safety Assessment

Table 3 provides a comparison of adverse reactions between the control group and the observation group post-treatment. The control group, comprising 60 patients, reported no cases of leukopenia. However, 2 patients (3.33%) experienced stomach upset, 1 patient (1.67%) reported neurosensory abnormality, 2 patients (3.33%) suffered from constipation, and 1 patient (1.67%) reported drowsiness.

In contrast, the observation group, also consisting of 60 patients, showed 1 case (1.67%) of leukopenia, 2 patients (3.33%) with stomach upset, 3 patients (5.00%) with neurosensory abnormality, 3 patients (3.33%) with constipation, and 5 patients (8.33%) experiencing drowsiness. These results suggest that the observation group exhibited a slightly higher incidence of adverse reactions compared to the control group, particularly in terms of neurosensory abnormality and drowsiness. Further investigation and monitoring of the treatment's safety and tolerability may be warranted.

DISCUSSION

Connective tissue disease (CTD) is a comprehensive term encompassing a diverse group of rheumatic diseases marked by chronic inflammation of connective tissues as their pathological foundation. This condition can impact various tissues and organs across the body. Interstitial lung disease (ILD) stands as a prevalent clinical manifestation of CTD, affecting the lungs and involving diseases characterized by inflammation and/or fibrosis.[7,8]

According to the classification criteria for idiopathic ILD established by the American Thoracic Society and the

European Respiratory Society in 2002, autoimmune-related ILD is categorized into distinct pathological subtypes. These subtypes include usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), lymphocytic interstitial pneumonia (LIP), cryptogenic organizing pneumonia (COP), and others. These diverse pathological subtypes exhibit different clinical prognoses.

UIP prevails in idiopathic ILD and exhibits lower responsiveness to treatment with steroids and immunosuppressants, resulting in a less favorable prognosis. In contrast, secondary ILD in pSS is primarily associated with LIP and NSIP pathology. It demonstrates good responsiveness to treatment with steroids and immunosuppressants, leading to an improved prognosis.[9,10]

CTX is a conventional medication employed in the treatment of secondary ILD in connective tissue diseases. However, it comes with side effects, including bone marrow suppression, liver function impairment, and increased susceptibility to secondary infections.[10] This is especially significant in patients with pSS, often in the middle-aged to elderly demographic, who may already exhibit leukocyte reductions and abnormal liver function. The low tolerance of CTX in this population restricts its use.[11] Therefore, discovering effective alternative treatments for secondary ILD in pSS has emerged as a challenge for rheumatologists in recent years.[11,12]

ILD often presents insidiously, with main symptoms including dry cough and progressive dyspnea, especially after physical activity. High-resolution CT scans of the lungs reveal linear, reticular, honeycombing, and ground-glass opacities, primarily in the peripheral areas of the lower and middle lung fields.[13] The typical pulmonary function changes include restrictive ventilatory impairment, with decreased FVC%, FEV1%, and DLco%, while the FEV1/FVC ratio remains normal or increases.[14]

Recent studies indicate a strong correlation between the classification of ILD derived from high-resolution CT lung imaging and the pathological classification obtained through open lung biopsy, providing a high level of reliability.[15] Therefore, high-resolution CT is considered sufficiently effective for clinically determining ILD types. In this study, we categorized the high-resolution CT indicators of ILD patients into three types based on the revised classification of idiopathic ILD introduced by the American Thoracic Society and the European Respiratory Society in 2013. These types include the following: (1) UIP, characterized by honeycombing and reticular patterns; (2) NSIP: marked by ground-glass opacities; and (3) unclassified: encompassing mixed or inconclusive findings.

Considering that individuals with NSIP type typically respond better to treatment, making efficacy observation more straightforward, and considering that ILD associated with pSS is mostly of the NSIP type, our study intentionally focused on patients exhibiting NSIP-like patterns in high-resolution CT scans. Patients with UIP or unclassified ILD were intentionally excluded. Additionally, recognizing the critical condition of patients with severe ILD (Warrick score > 15), our study exclusively included individuals with mild to moderate ILD for a more focused investigation.

For classification, two radiologists independently reviewed the images and reevaluated them in the event of disagreements until a consensus was achieved. Ultimately, 49 patients with pSS-associated ILD met the inclusion criteria, with 3 lost to follow-up, resulting in 46 patients completing the study. Following 24 weeks of steroid treatment, both patient groups exhibited significant improvement in lung function (FVC%, FEV1%, DLco%) and LCQ scores compared to their respective baseline values.

Furthermore, the Warrick scores on high-resolution CT scans decreased, indicating the effectiveness of combined steroid and immunosuppressant treatment for NSIP-type ILD secondary to pSS. Notably, patients in the group receiving steroids combined with pirfenidone treatment exhibited more significant improvements ($P < .05$) in lung function, LCQ scores, and Warrick scores. These results suggest that pirfenidone can enhance lung function, alleviate cough symptoms, and foster the absorption of lung lesions in patients with mild to moderate pSS-associated NSIP.

Considering the old age of patients within this group and aiming to mitigate adverse events, our study adopted a treatment regimen of 50 mg/day. Moreover, typical side effects associated with pirfenidone encompass indigestion, photosensitivity, and drowsiness. In the event of severe adverse reactions, such as rash, itching, or other symptoms, discontinuation of the medication should be promptly implemented. We believe that reducing the dose and incorporating combination therapy can effectively manage the disease while minimizing adverse reactions.

Study Limitations

This study has certain limitations that warrant acknowledgment. The relatively small sample size may impact the generalizability of the findings to a broader population. Additionally, the short duration of the research limits the ability to assess the long-term effects and sustainability of the observed outcomes. Future investigations should consider expanding the sample size, conducting extended follow-up periods, and investigating personalized approaches to pirfenidone treatment. Addressing these limitations would contribute to a more comprehensive understanding of the therapeutic potential of pirfenidone in the context of primary Sjögren's syndrome-associated interstitial lung disease.

CONCLUSION

This study highlighted the potential of pirfenidone to enhance lung function and alleviate cough symptoms in patients with mild to moderate primary Sjögren's syndrome-associated nonspecific interstitial pneumonia, contributing to an improved quality of life. Notably, the exclusion of patients with severe interstitial lung disease (Warrick score > 15) and the focus on the NSIP subtype limit the generalizability

of these findings. Additionally, the effectiveness of pirfenidone was not assessed in patients with pSS-associated ILD other than NSIP or ILD arising from other connective tissue diseases. Future research endeavors should explore these specific patient groups to ascertain the broader efficacy of pirfenidone in diverse ILD contexts.

ETHICAL COMPLIANCE

The research conducted in this study received approval from the Yuyao People's Hospital Ethics Committee under the reference Y2020-01-01. All participants involved in the study completed informed consent forms, ensuring their voluntary participation and understanding of the study's objectives. Furthermore, the study was officially registered in the National Record Information System for National Health Security at http://61.49.19.26, with the registration number MR-33-20-004439.

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DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are restricted by the Ethics Board of Yuyao People's Hospital of Zhejiang Province in order to protect patient privacy. Data is available from Jingjing Liu (jiayi435@126.com) for researchers who meet the criteria for access to confidential data.

CONFLICT OF INTERESTS

The authors declare that there were no conflicts of interest.

AUTHORS' CONTRIBUTIONS

WW and JL designed the study and performed the experiments, WZ collected the data, WH analyzed the data, and WW and JL prepared the manuscript. All authors read and approved the final manuscript.

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