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Intravenous Cyclophosphamide Infusion Effects on Skin Fibrosis, IL-6, and TGF-β1 Responses in Systemic Sclerosis with Interstitial Lung Disease

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A B S T R A C T

Background: Systemic sclerosis (SSc) is a chronic multisystem disease characterized by organ fibrosis, microvascular damage, and immunological dysregulation. This study aimed to evaluate the effects of intravenous cyclophosphamide (CYC) infusion on skin fibrosis severity, interleukin-6 (IL-6), and transforming growth factor-beta 1 (TGF-β1) levels in patients with SSc-associated interstitial lung disease (SSc-ILD), compared to conventional disease-modifying antirheumatic drug (DMARD) therapy. **Methods:** This study included patients meeting the 2013 ACR/EULAR classification criteria for SSc. Thirty-two patients (47.8%) received intravenous CYC, while 35 patients (52.2%) received conventional DMARDs. Skin fibrosis severity, assessed by the modified Rodnan skin score (mRSS), alongside serum IL-6 and TGF-β1 levels, were measured at baseline and after six months of therapy. Efficacy was evaluated by comparing post-treatment values to baseline measurements. **Results:** Both CYC and conventional DMARDs achieved significant reductions in mRSS and serum TGF-β1 levels. Although both treatments effectively suppressed serum IL-6 levels, the inter-group difference regarding this reduction exhibited a trend toward statistical significance ($p = 0.051$). **Conclusion:** Intravenous CYC therapy substantially reduces skin fibrosis (mRSS) and serum TGF-β1 levels in patients with SSc-ILD.

1. Introduction

Systemic sclerosis (SSc) is a connective tissue disorder characterized by fibrosis of the skin and internal visceral organs.[1] The clinical characteristics of SSc include vasomotor abnormalities, fibrosis, and atrophy affecting the skin, subcutaneous tissue, muscles, and internal organs (including the vascular system, lungs, heart, and, kidneys, alongside immunological alterations.[2,3] SSc is associated with a high mortality rate, primarily driven by the progression of interstitial lung disease (ILD) and SSc-associated pulmonary arterial hypertension.[4,5]

The pathophysiology of SSc involves abnormal microvascular responses, genetic risk factors, and epigenetic modifications that lead to immune dysregulation, inflammation, micro vasculopathy, and fibrosis. During this disease stage, the immune activation of T cells and B cells triggers the fibrotic cascade.[6] Cytokine release resulting from T and B cell activation induces the trans differentiation of endothelial cells into myofibroblasts and promotes fibroblast activation, leading to excessive collagen production and extracellular matrix accumulation.[6,7] Immune system activation in SSc is notably characterized by B cell activation and autoantibody production.[8]

Skin manifestations are the most common signs of SSc and occur in most patients.[9] Cutaneous

manifestations in SSc are driven by inflammatory vasculopathy, myofibroblast accumulation, and dermal sclerosis. The interplay of cytokines and growth factors—predominantly transforming growth factor-beta (TGF-β)—stimulates mesenchymal cell activation and excessive extracellular matrix deposition. This cascade increases the biomechanical rigidity of the skin, ultimately producing the hallmark clinical features of SSc.[10] The modified Rodnan skin score (mRSS) is a rapid, reliable, and validated assessment tool used to evaluate disease activity and the extent of skin thickness.[11] The measurement of skin thickness serves as a surrogate for disease severity, an increased risk of internal organ involvement, and heightened mortality.[12]

Therapeutic strategies for SSc aim to reduce immune system activity, particularly that of B lymphocytes, to induce remission and control disease manifestations resulting from inflammatory processes. The use of immunosuppressive therapy in SSc is based on the involvement of both the innate and adaptive immune systems in its pathogenesis.[13] Agents such as methotrexate (MTX), azathioprine, glucocorticoids, cyclophosphamide, and mycophenolate mofetil are employed to treat specific manifestations, including skin thickening, alveolitis, and musculoskeletal symptoms.[14] However, SSc presents with significant variations in disease onset, progression rate, and organ involvement, necessitating individualized therapeutic approaches.[15]

Cyclophosphamide (CYC) is a cytotoxic alkylating agent, available in both oral and intravenous formulations, that exerts immunosuppressive effects by modulating lymphocyte activity, attenuating inflammation, and mitigating fibrosis. In patients with SSc, treatment induces an initial depletion of B lymphocytes, followed by a subsequent reduction in both T and B cell populations. Preclinical models suggest that the B-cell compartment is particularly sensitive to cyclophosphamide compared to T cells[14]. Unchecked B-cell proliferation and ongoing fibrogenesis ultimately drive irreversible organ damage and mortality in SSc.[16] Clinically, cyclophosphamide has demonstrated substantial efficacy in improving pulmonary function and quality of life in patients with SSc-associated interstitial lung disease (SSc-ILD).[17] Furthermore, clinical investigations evaluating a six-month regimen of intravenous cyclophosphamide (500 mg/m2/month) in early SSc have confirmed its utility in managing cutaneous thickening in diffuse disease, with 43% of treated patients achieving clinically meaningful improvements in their mRSS.[18]

Fibrotic progression in SSc is primarily mediated by a complex network of profibrotic cytokines, including TGF-β, IL-4, IL-13, IL-6, and IL-33.[6,19] Specifically, IL-6 acts as a pivotal driver in SSc pathogenesis by bridging immune activation with extracellular matrix overproduction. High expression of IL-6 promotes the differentiation of fibroblasts into myofibroblasts, and its serum concentration is a recognized predictor for worse skin involvement, pulmonary function decline, and mortality.[20] Working synergistically with this IL-6–driven environment, TGF-β become the regulator of ongoing tissue remodelling, particularly in pulmonary fibrosis.[21] Derived from platelets, macrophages, T cells, and fibroblasts, TGF-β signalling activates both canonical Smad pathways. This cytokine-driven fibrosis is further amplified by the innate immune system via Toll-like receptor 4 (TLR4).[22]

Despite the known clinical efficacy of immunosuppressive therapies, the precise molecular mechanisms—specifically how cyclophosphamide comparatively influences circulating fibrotic biomarkers like IL-6 and TGF-β1 in SSc-ILD patients—remain inadequately characterized. Previous studies have primarily focused on clinical parameters or pulmonary function outcomes, leaving an unmet need to understand the molecular alterations parallel to clinical improvements. Clarifying these biomarker responses is crucial for identifying objective indicators of treatment efficacy and bridging the knowledge gap regarding the molecular down-regulation of fibrosis in a real-world clinical setting. Therefore, this study aimed to evaluate the effects of intravenous cyclophosphamide infusion on skin fibrosis severity (mRSS), IL-6, and TGF-β1 levels in patients with SSc-ILD compared to

conventional disease-modifying antirheumatic drugs (DMARDs).

2. Methods

Study Design and Participants

This was a quasi-experimental study (non-randomized controlled design) conducted at the Division of Rheumatology, Department of Internal Medicine, Dr. Kariadi Hospital/Faculty of Medicine, Diponegoro University, Semarang, Indonesia, between December 2022 and July 2024. A total of sixty-seven patients diagnosed with SSc-ILD who met the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria were enrolled. Baseline demographic and clinical characteristics, including disease duration, were recorded at the time of initial blood collection.

Intervention and Treatment Allocation

In accordance with the quasi-experimental design, treatment allocation was not randomized; rather, patients received treatment based on standard clinical practice and physician judgment regarding disease severity. Specifically, patients presenting with a higher baseline mRSS, indicative of more severe and rapidly progressive diffuse cutaneous disease or advanced interstitial lung involvement, were preferentially allocated to receive intravenous cyclophosphamide (CYC). The CYC group (n = 32, 47.8%) received monthly intravenous infusions at a dose of 500 mg/m². Conversely, the conventional DMARD group (n = 35, 52.2%) consisted of patients prescribed oral immunosuppressants, primarily including Mycophenolate Sodium, Mycophenolate Mofetil, Methotrexate, Cyclosporin A, and Azathioprine, administered at standard clinical doses for a continuous duration of six months.

Clinical and Laboratory Measurements

The primary parameters evaluated at baseline and after six months of treatment included skin fibrosis severity, IL-6, and TGF-β1 levels. Skin fibrosis was assessed clinically using the mRSS. Serum levels of IL-6 and transforming growth factor-beta 1 (TGF-β1) were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits, specifically the Quantikine® Human IL-6 Immunoassay and Quantikine® Human TGF-β1 Immunoassay (R&D Systems, Minneapolis, MN, USA), according to the manufacturer's protocols. The assay sensitivity (minimum detectable dose) for IL-6 was 0.7 pg/mL with a detection range of 3.13 – 300 pg/mL. Meanwhile, the assay sensitivity for TGF-β1 was 15.4 pg/mL with a detection range of 31.2 – 2,000 pg/mL. Absorbance was read using a microplate reader (Bio-Rad Model 680, Hercules, CA, USA) with TaqMan™ assays.

Statistical Analysis

The normality of continuous data distribution was assessed using the Shapiro-Wilk test. To evaluate changes from baseline to six months post-treatment within the same group, the paired t-test or Wilcoxon signed-rank test was utilized. For comparisons between the two independent treatment groups, the independent t-test or Mann-Whitney U test was applied. Multiple group comparisons were performed using a one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, followed by Dunn’s post hoc analysis. Relationships between variables were evaluated using Pearson's or Spearman's correlation tests. All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA), and a p-value < 0.05 was considered statistically significant.

Ethical Clearance

The study protocol was reviewed and approved by the Health Research Ethics Committee of Dr. Kariadi General Hospital/Faculty of Medicine, Diponegoro University (Ethical Clearance Number: 1310/EC/KEPK-RSDK/2022; Date of Approval: November 17, 2022). The research was conducted in strict accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants prior to their inclusion in the study. All patient data were anonymized and managed with strict confidentiality.

3. Results

Baseline Demographic and Clinical Characteristics

The demographic profile and baseline clinical parameters of the 67 SSc-ILD patients participating in this study are summarized in Table 1. The cohort was stratified into two intervention arms: the intravenous cyclophosphamide group (CYC, n = 32) and the conventional DMARD group (n = 35). Comparative analysis confirmed no statistically significant disparities between the two groups at baseline, including gender distribution (p = 0.068), history of prior immunosuppressant use (p = 0.132), mean age (p = 0.313), and disease duration (p = 0.548).

Evaluation of Skin Fibrosis Severity

The median mRSS at baseline was significantly higher in the CYC group [25 (range: 9–44)] compared to the conventional DMARD group [13 (range: 3–41)] (p = 0.000). Post-treatment, the median mRSS in the CYC group [12 (range: 2–33)] remained significantly higher than that in the conventional DMARD group [6 (range: 2–21)] (p = 0.022). However, the median reduction in skin thickness (Δ mRSS) was significantly more profound in the CYC group [-11 (range: -27 to -2)] than in the conventional DMARD group [-4.0 (range: -36 to 3)] (p = 0.000) (Table 2).

Changes in Serum IL-6 Levels

At baseline, the median serum IL-6 level was higher in the CYC group [11.08 (range: 1.5–63.6) pg/mL] than in the conventional DMARD group [6.35 (range: 2–51.4) pg/mL], though this difference was not statistically significant (p = 0.127). Post-treatment, the median IL-6 level in the CYC group [6.16 (range: 1.5–24.2) pg/mL] also showed no significant variance compared to the conventional DMARD group [5.46 (range: 1.2–50.6) pg/mL] (p = 0.656). The median change in IL-6 levels (Δ IL-6) from baseline to post-therapy was -4.04 (range: -44.1 to 15.5) pg/mL in the CYC group and -1.0 (range: -34.1 to 29.5) pg/mL in the conventional DMARD group, demonstrating a borderline statistically significant difference between the two arms (p = 0.051). Intra-group analysis showed that both treatment groups effectively reduced IL-6 levels. The CYC group showed a significant decrease from baseline to post-therapy (p = 0.001) with a median reduction of -4.04 pg/mL, whereas the conventional DMARD group also achieved a significant reduction (p = 0.019) with a median decrease of -1.0 pg/mL (Table 3).

Suppression of Serum TGF-β1 Levels

The immunomodulatory effects of the interventions on serum TGF-β1 levels are presented in Table 3. A significant baseline variation was noted, with the mean TGF-β1 level in the CYC group (87,022.19 ± 23,252.97 pg/mL) being significantly higher than the median level in the DMARD group [67,186 (range: 30,236–120,000) pg/mL] (p = 0.003). At six months post-therapy, a significant suppression of TGF-β1 levels was observed in both groups (both p < 0.001). Comparative analysis of the absolute reduction (Δ TGF-β1) demonstrated the superior efficacy of CYC infusion; the CYC arm induced a significantly more profound depletion of TGF-β1 [median reduction: -18,791 pg/mL] compared to the conventional DMARD arm [median reduction: -8,000 pg/mL] (p = 0.004).

4. Discussion

The demographic profile of the subjects recruited from the Rheumatology Outpatient Clinic and Inpatient Wards of Dr. Kariadi General Hospital predominantly consisted of female, aligning with the well-established epidemiology of SSc. The baseline characteristics of this study population, including mean age and disease duration, are highly consistent with previous study from Asian populations, such as those from Hong Kong and Japan.[12] Systemic sclerosis is universally recognized as a female-predominant autoimmune condition, with the incidence typically peaking during the reproductive years and gradually declining post-menopause.[23]

The evaluation of cutaneous involvement revealed that patients allocated to the CYC group presented with a substantially higher baseline mRSS compared to those receiving conventional DMARDs. This discrepancy reflects standard clinical practice and patient stratification, wherein patients presenting with more severe, rapidly progressive diffuse cutaneous disease—and likely concurrent interstitial lung

involvement—are preferentially managed with aggressive immunosuppressive agents like CYC. Following therapy, while both therapeutic groups exhibited significant intra-group clinical improvements, the absolute reduction in mRSS was remarkably more pronounced in the CYC group.

The mRSS serves as a highly reliable surrogate marker for dermal fibroblast activation, extracellular matrix (ECM) deposition, and overall fibrotic burden.[12,24] The marked post-therapeutic attenuation of the mRSS observed in this study reflects a concurrent reduction in both local tissue inflammation and fibrogenesis. Despite the superior absolute reduction achieved by CYC, the post-treatment mRSS in this group remained higher than that of the DMARD group. This outcome highlights the clinical complexity of advanced SSc, extensive cutaneous sclerosis requires prolonged intervention, and complete structural reversal of the dermal matrix may extend well beyond a standard six-month observational window.[25] Furthermore, the wide variability in therapeutic responses across both groups underscores the clinical heterogeneity of SSc, which is largely determined by disease duration and the initial fibrotic burden. The pronounced regression of skin involvement observed in the CYC group suggests its potential utility in managing advanced cutaneous disease, whereas conventional DMARDs appear to be a viable and effective option for patients with milder manifestations. However, these observations should be interpreted with caution given the quasi-experimental design and the lack of treatment randomization, which resulted in significant baseline disparities between the two groups.

Beyond clinical assessment, the systemic inflammatory profile was evaluated through serum interleukin-6 (IL-6) levels. Baseline analyses demonstrated a trend toward higher IL-6 concentrations in the CYC group, biologically mirroring their more severe clinical phenotype. IL-6 acts as a pivotal pro-inflammatory cytokine that bridges the innate and adaptive immune responses; it drives T-cell differentiation, promotes B-cell hyperactivity, and directly stimulates fibrogenic pathways by inducing fibroblast-to-myofibroblast transition.[20,26,27] Post-treatment evaluations revealed a significant reduction in IL-6 across both therapeutic groups, resulting in comparable post-therapy systemic levels.

Although the absolute reduction in IL-6 was numerically greater in the CYC group—suggesting a potentially more robust initial suppression of early inflammatory cascades—both therapeutic modalities effectively downregulated this cytokine. The post-therapeutic decline in IL-6 underscores the capacity of both CYC and conventional DMARDs to dampen the underlying inflammatory drive that precedes irreversible tissue remodelling. Notably, the early suppression of IL-6 is clinically critical, as persistently elevated baseline IL-6 has been independently associated with rapid early progression of both skin thickening and pulmonary function decline in SSc-ILD.[28] These outcomes validate IL-6 as an inflammatory biomarker highly sensitive to therapeutic response, even if its utility in differentiating the absolute efficacy between these two specific regimens remains limited within a short-term timeframe.

Downstream of this inflammatory phase, the evaluation of TGF-β1—the primary molecular mediator of fibrogenesis—revealed distinct treatment responses. Baseline TGF-β1 levels were significantly elevated in the CYC group, further indicating the presence of pronounced profibrotic activity in these patients. Following intervention, both groups demonstrated a significant intra-group reduction in TGF-β1. However, the absolute decrease was significantly greater in the CYC group. Despite this substantial decline, post-therapy TGF-β1 levels in the CYC group did not decrease to match those of the DMARD group, reflecting a more persistent and chronic fibrotic drive in patients with severe diffuse disease.

The greater reduction of TGF-β1 by cyclophosphamide is consistent with the clinical improvements observed in the mRSS. TGF-β1 regulates fibrogenesis by stimulating fibroblast proliferation, driving myofibroblast differentiation, and upregulating the transcription of extracellular

matrix proteins such as type I collagen and fibronectin. The ability of cyclophosphamide to suppress this pathway reflects its mechanism as an alkylating immunosuppressant capable of depleting the immune cells (particularly B and T lymphocytes) responsible for producing this profibrotic cytokine. These clinical observations align with established experimental models, which demonstrate that cyclophosphamide therapy reduces myofibroblast populations—accompanied by an upregulation of E-cadherin and a downregulation of N-cadherin expression—via the suppression of the TGF-β signaling cascade and its associated receptors.[29] Consequently, the significant reduction of TGF-β1 highlights its potential value as a biomarker for monitoring fibrotic activity and suggests that the downregulation of this pathway is a key downstream effect of immunosuppressive therapy in SSc-ILD. Nevertheless, definitive causal inferences should be drawn cautiously due to the methodological limitations inherent in this quasi-experimental study.

Table 1. Baseline Demographic and Clinical Characteristics of the Patients

Variable	Cyclophosphamide (n= 32)		DMARD (n= 35)		Total (n = 67)	*p* Value
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)		
Sex						0.068†
Female	32 (100%)		31 (88.6%)		63 (94.0%)	
Male	0 (0%)		4 (11.4%)		4 (6.0%)	
Age (years)	42.13±12.66	43 (21-70)	45.37±13.04	47 (19-75)	43.82 ± 12.87	0.313‡
Immunosuppressants						0.132§
Azathioprine	2 (6.3%)		2 (5.7%)		4 (6.0%)	
Mycophenolate Sodium	22 (68.8%)		19 (54.3%)		41 (61.2%)	
Mycophenolate Mofetil	2 (6.3%)		0 (0%)		2 (3.0%)	
Cyclosporin A	4 (12.5%)		6 (17.1%)		10 (14.9%)	
Methotrexate	2 (6.3%)		8 (22.9%)		10 (14.9%)	
Disease durations (years)#	4.09 ± 2.93	3 (1-12)	4.8 ± 3.38	4 (1-14)	4.46 ± 3.17	0.548‡
mRSS	25.53 ± 8.07	25 (9-44)	15.37±11.45	13 (3-41)	20.22 ± 11.15	0.000*‡

*****Significant (p ≤0.05); †Chi-Square; ‡Independent-t; §Mann Whitney, DMARD: Disease-Modifying Antirheumatic Drugs; mRSS: modified Rodnan skin score; SD: Standard deviation.

Table 2. Comparative Analysis of mRSS Before and After Treatment with Cyclophosphamide versus DMARDs

Variable	Cyclophosphamide (n= 32)		DMARD (n= 35)		*p* Value
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	
MRSS Pre#	25.53 ± 8.07	25 (9-44)	15.37 ± 11.45	13 (3-41)	0.000*§
MRSS Post#	12.34 ± 7.32	12 (2-33)	8.29 ± 6.05	6 (2-21)	0.022*§
p Value	0.000*¶		0.000*II		
Δ MRSS#	-13.19 ± 7.04	-11 (-27-(-2))	-7.09 ± 9.51	-4.0 (-36-3)	0.000*§

*****Significant (p ≤0.05); §Mann Whitney; "test, ¶Pair t test, DMARD: Disease-Modifying Antirheumatic Drugs; mRSS: modified Rodnan skin score; SD: Standard deviation

Table 3. Comparative Analysis of IL-6 and TGF-β1 level Before and After Treatment with Cyclophosphamide versus DMARDs

Variable	Cyclophosphamide (n = 32)		DMARD (n = 35)		*p* Value
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	
IL-6					
IL-6 Pre (pg/mL)#	16.03 ± 16.10	11.08 (1.5-63.6)	10.74 ± 12.17	6.35 (2-51.4)	0.208‡
IL-6 Post (pg/mL)#	9.15 ± 6.16	6.16 (1.5-24.2)	8.66 ± 10.15	5.46 (1.2-50.6)	0.656‡
p Value	0.001*II		0.019*II		
Δ IL-6 (pg/mL)#	-6.88 ± 11.8	-4.04 (-44.1-15.5)	-2.08 ± 9.25	-1.0 (-34.1-29.5)	0.051§
TGF-β1					
TGF-β1 Pre (pg/mL)#	87,022.19 ± 23,252.97	87,765.5 (49,250-120,168)	69,171.49 ± 23,053.62	67,186 (30,236-12,000)	0.002*‡
TGF-β1 Post (pg/mL)#	71,565.34 ± 20,476.48	65,891.5 (29,083-108,670)	60,658.03 ± 21,783.05	54,119 (28,235-119,457)	0.026*‡
p Value	0.000*¶		0.000*II		
Δ TGF-β1 (pg/mL)#	-15,456.84 ± 15,633.18	-18,791 (-49,535-33,141)	-8,513.6 ± 6,723.73	-8,000 (-23,946 - (-22,600))	0.004*§

*Significant (p ≤0.05); ‡Independent-t; §Mann Whitney; IIWilcoxon test, ¶Pair t test, DMARD: Disease-Modifying Antirheumatic Drugs; SD: Standard deviation

Study Limitations

Several limitations of this study should be acknowledged. First, the six-month observation period may be insufficient to detect significant structural changes or radiographic regression of pulmonary fibrosis via high-resolution computed tomography (HRCT). Second, this was a single-center study with a relatively small sample size (n = 67), which may limit the generalizability of the findings to a broader population. Finally, there were baseline disparities in disease severity between the treatment arms—particularly regarding initial mRSS and TGF-β1 levels—which could potentially confound the comparative therapeutic outcomes.

Clinical Implications

Our findings support the use of intravenous cyclophosphamide as a primary induction therapy for severe SSc-ILD. While a six-month observation period may not reveal structural recovery on HRCT, CYC effectively prevents further clinical deterioration and yields significant improvements in skin fibrosis severity. Additionally, the marked downregulation of serum TGF-β1 underscores its potential as an objective biomarker to monitor fibrotic activity and guide early therapeutic decisions in clinical settings.

Future Directions

Future investigations should prioritize longitudinal studies with extended follow-up periods (e.g., 12 to 24 months) to evaluate whether the initial functional and molecular stabilization observed with CYC therapy ultimately leads to radiographic improvements in lung fibrosis. To further confirm our findings, large-scale, multi-centre randomized controlled trials are recommended. Furthermore, subsequent research should investigate sequential or combination therapeutic regimens. Evaluating a CYC induction phase followed by maintenance immunosuppression (such as mycophenolate mofetil) or targeted antifibrotic agents (like nintedanib) will be crucial for developing comprehensive management strategies for SSc-ILD.

5. Conclusion

Within the limitations of this quasi-experimental study, intravenous cyclophosphamide is associated with a significant reduction in skin fibrosis severity and the suppression of profibrotic pathways in patients with SSc-ILD. While both CYC and conventional DMARDs demonstrate clinical benefits and decrease serum IL-6 levels, CYC therapy showed a more profound reduction in mRSS and serum TGF-β1 levels. These findings suggest the potential efficacy

of CYC as an induction therapy for severe SSc-ILD and highlight TGF-β1 as a promising biomarker for monitoring antifibrotic treatment response. However, these conclusions must be interpreted with caution due to the non-randomized treatment allocation and baseline clinical disparities between the groups; further randomized controlled trials are needed to definitively establish comparative efficacy.

Conflicts of Interest

The authors have disclosed no conflicts of interest or personal relationships that could have influenced the findings or interpretation of this study.

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Author Contributions

Rakhma Yanti Hellmi: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft preparation, and Writing – review & editing. Bambang Satoto: Investigation (radiological assessment and scoring of lung fibrosis), and Data curation. Harry Isbagio: Validation, Supervision, and Writing – review & editing. Suharyo Hadi Saputro: Validation, Supervision, and Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

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