Effectiveness of combined therapy with pirfenidone and inhaled N-acetylcysteine for advanced idiopathic pulmonary fibrosis: A case–control study

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ABSTRACT

Background and objective: Treatment with pirfenidone may slow the decline in vital capacity and increase progression-free survival (PFS) in idiopathic pulmonary fibrosis (IPF). The effects of combination therapy with inhaled N-acetylcysteine (NAC) and pirfenidone are unclear. We assessed the effects of this combination therapy in patients with advanced IPF.

Methods: Patients with a diagnosis of advanced IPF (Japanese Respiratory Society stage III/IV IPF) and a relative decline in forced vital capacity (FVC) of ≥10% within the previous 6 (±2) months were enrolled. Outcomes were evaluated in a 12-month follow-up pulmonary function test. Treatment was considered ineffective if the decline in FVC was >10% and effective if the decline was <10%. We compared clinical characteristics, effectiveness and PFS between patients receiving inhaled NAC plus pirfenidone (n = 24) and those receiving pirfenidone alone (control; n = 10).

Results: Data from 34 IPF patients (age range, 59–82 years) were analysed. At the 12-month follow-up examination, treatment was deemed effective in 8 of 17 (47%) patients receiving NAC plus pirfenidone and in 2 of 10 (20%) receiving pirfenidone alone. The annual rate of change in FVC was −610 mL in the NAC plus pirfenidone group and −1320 mL in the pirfenidone group (P < 0.01). PFS was longer (304 days) in the NAC plus pirfenidone group than in the pirfenidone group (168 days; P = 0.016).

Conclusions: Combination treatment with inhaled NAC and oral pirfenidone reduced the rate of annual FVC decline and improved PFS in patients with advanced IPF.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a devastating, progressive and fatal disorder. Pirfenidone has anti-inflammatory, antioxidant and antifibrotic effects in experimental models of pulmonary fibrosis, and thus has therapeutic potential in human with IPF. It inhibits the transforming growth factor-β (TGF-β) in vitro and acts as an antifibrotic by directly altering expression, synthesis and possibly accumulation of collagen, and by inhibiting recruitment, proliferation and possibly expression of extracellular matrix-producing cells. Pirfenidone also has antioxidant properties due to its action in scavenging reactive oxygen species (ROS). Although pirfenidone was better than placebo in preserving forced vital capacity (FVC) and improving progression-free survival (PFS) in patients with mild-to-moderate IPF, its effects have not been thoroughly investigated among patients with advanced IPF (stage III or IV IPF, Japanese Respiratory Society (JRS) criteria).

N-acetylcysteine (NAC) is a tripeptide (γ-glutamylcysteinyl-glycine) that is a precursor of the antioxidant...
glutathione (GSH) and a scavenger of oxygen-free radicals. NAC also directly alters the structure of TGF-β, thus attenuating its possible profibrotic properties. NAC has been used as a mucolytic agent, in acetaminophen-induced liver failure, in the prevention of contrast-medium-induced nephropathy, in chronic obstructive pulmonary disease and in IPF.

Oxidant–antioxidant imbalance may contribute to IPF disease processes. NAC is a potentially effective therapeutic compound in the treatment of IPF, as it may replenish GSH stores and thus restore the natural oxidant/antioxidant balance and prevent oxidative injury that precedes fibroproliferation.

In the IPFGENIA study, a three-drug regimen comprising azathioprine, prednisone and acetylcysteine was better at maintaining FVC than a two-drug regimen consisting of azathioprine and prednisone. However, in the Panther trial, a 60-week regimen of acetylcysteine (600 mg t.i.d.) failed to maintain FVC when compared with matched placebo in patients with IPF and mild-to-moderate impairment in pulmonary function.

Orally administered NAC may not produce a sustained increase in GSH levels sufficient to increase the antioxidant capacity of the lungs, even when given orally in high doses (600 mg t.i.d.). In contrast, aerosol administration of NAC acts directly as an antioxidant in alveoli, in addition to its GSH-increasing effect. Administration of GSH aerosols can increase GSH levels in bronchoalveolar lavage fluid (BALF) in patients with IPF, which may in turn significantly reduce release of oxidants by alveolar macrophages. NAC inhalation might, therefore, be effective in reducing inflammation and lung fibrosis.

Although a randomized trial of aerosolized NAC by Homma et al. did not achieve the primary end-point in all subjects, post-hoc analysis showed significantly lower 48-week declines in FVC in a subset of patients with a mean baseline vital capacity (VC) of almost 80% and a carbon monoxide diffusing capacity (DLco) of almost 43% of the predicted value. Furthermore, we have shown that the clinical efficacy of NAC inhalation, including lung function, at the same dose used in this study correlated with improvement in redox imbalance in IPF patients.

The search for new therapies for IPF has intensified since the start of the 21st century. However, several drugs targeting only one or a few genes, such as interferon-γ and endothelin-receptor antagonists, have not resulted in a breakthrough. Therefore, international guidelines for IPF state that successful IPF therapy requires a combination of therapeutic modalities targeting the multiple pathways involved in fibroproliferation.

In this study, we assess the efficacy and safety of pirfenidone monotherapy or combination therapy with inhaled NAC in patients with deteriorated phase of advanced stage IPF.

**METHODS**

This case–control study (registered with the University Hospital Medical Information Network under registration number UMIN000016045) included patients with IPF who received pirfenidone (1200–1800 mg/day) during the period from February 2009 through September 2013. Diagnosis of IPF was made in accordance with the IPF guidelines of the American Thoracic Society/European Respiratory Society/JRS/Latin-American Thoracic Association (ALAT). The eligible patients were adults with a confirmed clinical and radiological diagnosis of stage III or IV IPF (advanced IPF), that is, an arterial oxygen partial pressure less than 69 Torr at rest, with or without desaturation during a 6-min walk distance test, according to the JRS criteria. The stages of IPF severity were determined according to an established severity classification. Patients with an oxygen partial pressure in resting arterial blood (PaO2) of ≥80 Torr were classified as stage I. Stage II was defined as ≥70 to <80 Torr, stage III as ≥60 Torr to <70 Torr, and stage IV as <60 Torr. Among patients with stage II– III IPF, if SpO2 during a 6-min walk test was less than 90%, then severity was increased by one stage. However, patients with a PaO2 < 60 Torr were not required to undergo measurement of SpO2 during a 6-min walk test (Table 1).

Of the 128 consecutive IPF patients treated during this period, advanced IPF was diagnosed in 65, and 34 of the 65 patients who had relative declines in FVC of 10% or more during the 6 (±2) months before the study were enrolled. Of the 34 patients with JRS stage III or IV IPF, 24 were treated with both inhaled NAC and oral pirfenidone and 10 patients were treated with pirfenidone only (pirfenidone group). Among the 24 patients treated with both inhaled NAC and oral pirfenidone, 7 were excluded for various reasons; thus, 17 patients were included in the analysed combination treatment group (NAC-pirfenidone group).

Serial pulmonary function test (PFT) trends at 12 (±2) months, expressed as percentages of the baseline values, were evaluated for FVC. The exclusion criteria were (i) clinical features of idiopathic interstitial pneumonia other than IPF, (ii) duration of pirfenidone therapy shorter than 1 month, due to adverse events, (iii) poor adherence to inhaled NAC therapy, (iv) an extent of emphysema greater than 10% or more during the 6 (±2) months before the study.

**Table 1** Idiopathic pulmonary fibrosis severity classification of the Japanese Respiratory Society

<table>
<thead>
<tr>
<th>Severity stage</th>
<th>Resting PaO2</th>
<th>SpO2 during a 6-min walk test</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>≥80 Torr</td>
<td>If &lt;90%, classified as stage III</td>
</tr>
<tr>
<td>II</td>
<td>≥70 Torr and &lt;80 Torr</td>
<td>(measurement not required if there is a risk to patient)</td>
</tr>
<tr>
<td>III</td>
<td>≥60 Torr and &lt;70 Torr</td>
<td>Measurement not required</td>
</tr>
<tr>
<td>IV</td>
<td>&lt;60 Torr</td>
<td></td>
</tr>
</tbody>
</table>
that of fibrotic change on high-resolution computed
tomography (HRCT), or physiological evidence of
airflow obstruction, defined as a ratio of forced
expiratory volume in 1 s (FEV_{1}) to FVC of <0.7, or a
residual volume >120%, and (v) evidence of coexisting
respiratory infection or lung cancer (Fig. 1).

This study was conducted with the approval of the
Institutional Review Board of Toho University Omori
Medical Center (Project Approval Number 21–64). All
patients, or their family members, provided written
informed consent, and the medical records were
reviewed with the approval of the institutional review
board.

Pulmonary function tests
Lung volume, FEV_{1}, and DLco were measured accord-
ing to standard methods using the Chestac 8800
(Chest Co Ltd, Tokyo, Japan) and expressed as a per-
centage of the predicted value. %FVC was calculated
according to the Baldwin formula, and %DLco was
calculated according to the Burrows formula.

Inhaled NAC treatment
Pretreatment for IPF was continued after the start of
pirfenidone therapy. Using Micro Air nebulizers and
vibration mesh technology (NE-U07, Omron, Tokyo,
Japan), patients receiving NAC were treated twice
daily with 352.4 mg of inhaled NAC, which was
diluted with saline to a total volume of 6 mL.

Pirfenidone treatment
Pirfenidone dose was increased in a stepwise manner,
as follows: one tablet orally three times a day for the
first 2 weeks (600 mg/day), then two tablets per dose
three times a day for the next 2 weeks (1200 mg/day),
and then three tablets three times a day for the
remaining weeks (1800 mg/day).

Determination of treatment effectiveness
The effectiveness of pirfenidone therapy was evalu-
ated at the 12-month follow-up PFT. Progressive
disease (treatment failure) was defined as a 10% or
greater decrease in FVC from baseline (e.g. a decrease
from 3000 mL to 2700 mL is a 10% decline in FVC),
and a decline less than 10% was defined as stable
disease (treatment success). Disease progression was
defined as death, a 10% decline in FVC or a 15%
decline in DLco from baseline. We used relative
decline in FVC, as it maximizes the chance of identi-
fying a 10% decline in FVC, without sacrificing prog-
nostic accuracy. Patients from whom FVC data could
not be obtained due to worsening of respiratory
symptoms, including acute exacerbation, were also
classified as having progressive disease. In analyses of
mean change in FVC, the principle of last observation
carried forward was adopted to address the issue of
missing values. Missing values due to patient deaths
were assigned the worst possible outcome (e.g.
FVC = 0). Missing values for disease progression other
than death were imputed as half the previous value.
We compared clinical features, effectiveness, inci-
dence of acute exacerbation and PFS between the
NAC plus pirfenidone group (n = 24) and the
pirfenidone group (control; n = 10) (Table 2).

Statistical analysis
All values are expressed as medians (range), and dif-
fences between the patients groups were analysed
using the Mann–Whitney nonparametric U-test or for
two independent samples. Analyses of change in FVC
from baseline were performed by two-way analysis of
variance, followed by multiple comparison using the
Bonferroni method. For time-to-event analyses, the
log–rank test was used to compare the pirfenidone
plus NAC group with patients receiving pirfenidone
alone. All reported P-values are two-sided and were
considered statistically significant when less than
All analyses were performed using the SPSS statistical software package (version 19; SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Seven of the 34 patients were excluded because of adverse events, lung cancer and poor adherence to inhaled NAC therapy (Fig. 1). Data from 27 patients (23 men and 4 women; age range, 59–82 years) with IPF who received pirfenidone with/without inhaled NAC therapy were reviewed. Table 1 shows the characteristics of the patients before the start of pirfenidone therapy. Baseline disease severity was determined according to JRS criteria, and was stage III in 6 patients and stage IV in 21 patients.

Pretreatment for IPF included inhaled NAC monotherapy in 19 patients, low-dose prednisolone (<20 mg/day) with inhaled NAC in 3 patients, and a combination immunosuppressive treatment, including low-dose prednisolone (<20 mg/day) with tacrolimus (2 mg/day), in 2 patients. Three patients did not receive pretreatment. There were no differences between the two groups in the frequency of acute exacerbation before pirfenidone therapy (0 vs 0). Clinical and laboratory parameters before the start of pirfenidone, with or without NAC therapy, including age, smoking status, estimated pulmonary artery pressure and serum levels of markers of damaged pneumocytes (KL-6, surfactant protein-D) did not significantly differ between the two groups. Baseline data from PFT performed before the start of pirfenidone therapy, including the FVC, % predicted FVC, % predicted DLco and FEV1%, did not significantly differ between the two groups (Table 2).

Decline in FVC during the 6 (±2) months before the start of pirfenidone therapy did not significantly differ between the two groups. The numbers of patients with a usual interstitial pneumonia (UIP) pattern and possible UIP pattern on HRCT were 15 and 2 in the NAC plus UIP group and 10 and 0 in the pirfenidone group (Table 2).

Overall effects

At the 12-month follow-up PFT, treatment was deemed effective in 8 of 17 patients (47%) in the NAC plus pirfenidone group and in 2 of 10 patients (20%) in the pirfenidone group. The proportion was higher among patients receiving NAC plus pirfenidone. FVC before and after 12 months of pirfenidone therapy in both groups is shown in Figure 2. Mean change in FVC at 6 months was −210 mL in the NAC plus pirfenidone group and −610 mL in the pirfenidone group (P<0.01). The annual rate of change in FVC was −610 mL in the NAC plus pirfenidone group and −1320 mL in the pirfenidone group (P<0.01) (Fig. 3).

### Table 2 Characteristics of the patients at baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NAC + PFD (n = 17)</th>
<th>PFD alone (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age–year</td>
<td>73.5 (64–82)</td>
<td>75.0 (59–82)</td>
</tr>
<tr>
<td>Male sex—no. (%)</td>
<td>14 (82.3)</td>
<td>9 (90.0)</td>
</tr>
<tr>
<td>Smoking status (never/former/current) smoking index</td>
<td>2/15/0 850</td>
<td>1/5/0 800</td>
</tr>
<tr>
<td>IPF stage (I/II/III/IV)</td>
<td>0/0/5/12</td>
<td>0/0/1/9</td>
</tr>
<tr>
<td>Use of supplemental oxygen—no. (%)</td>
<td>15 (88.2)</td>
<td>9 (90.0)</td>
</tr>
<tr>
<td>Past treatments (NAC/CS/immunosuppressant/none)</td>
<td>16/2/0/1</td>
<td>6/3/2/2</td>
</tr>
<tr>
<td>Concurrent treatments (NAC/CS/immunosuppressant/none)</td>
<td>17/2/0/0</td>
<td>0/3/2/2</td>
</tr>
<tr>
<td>Diagnostic findings on high-resolution computed tomography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible pattern of usual interstitial pneumonia† no. (%)</td>
<td>2 (11.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Definite pattern of usual interstitial pneumonia no. (%)</td>
<td>15 (88.2)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Combined with emphysema no. (%)</td>
<td>6 (35.2)</td>
<td>5 (50.0)</td>
</tr>
<tr>
<td>Surgical lung biopsy no. (%)</td>
<td>2 (11.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lung physiological features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forced vital capacity (FVC) (L)</td>
<td>1.82 (1.01–3.25)</td>
<td>2.20 (1.14–2.62)</td>
</tr>
<tr>
<td>FVC—% of predicted value</td>
<td>68.3 (41.8–105.2)</td>
<td>67.7 (38.6–80.7)</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>86.5 (72.4–98.5)</td>
<td>86.7 (71.5–96.9)</td>
</tr>
<tr>
<td>Carbon monoxide diffusing capacity—% of predicted value</td>
<td>40.3 (18.1–60.7)</td>
<td>29.6 (19.6–43.9)</td>
</tr>
<tr>
<td>Distance on 6-min walk test—m</td>
<td>252 (42–420)</td>
<td>235 (57–390)</td>
</tr>
<tr>
<td>Serum makers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krebs von den Lungen-6 (KL-6) (U/mL)</td>
<td>948 (324–2391)</td>
<td>1020 (414–12 100)</td>
</tr>
<tr>
<td>Surfactant protein-D (SP-D) (ng/mL)</td>
<td>278.5 (112–676)</td>
<td>329 (128–555)</td>
</tr>
<tr>
<td>Brain natriuretic peptide (BNP) (pg/mL)</td>
<td>30.5 (11.0–302.8)</td>
<td>21.2 (11.9–75.0)</td>
</tr>
<tr>
<td>Estimate pulmonary artery pressure (mm Hg)</td>
<td>39.4 (22.0–57.6)</td>
<td>33 (19.5–61.3)</td>
</tr>
<tr>
<td>Relative decline in FVC during previous 6 months (%)</td>
<td>−12 (−44–10)</td>
<td>−15 (−24–10)</td>
</tr>
<tr>
<td>Time since diagnosis (days)</td>
<td>973.5 (59–2765)</td>
<td>1261 (183–4726)</td>
</tr>
</tbody>
</table>

† The diagnosis was subsequently confirmed on surgical lung biopsy indicating a histological pattern of usual interstitial pneumonia.

CS, corticosteroids; FEV1, forced expiratory volume in 1 s; IPF, idiopathic pulmonary fibrosis; NAC, N-acetylcysteine; PFD, pirfenidone.
PFS was significantly longer in the NAC plus pirfenidone group than in the pirfenidone group (304 vs 168 days; \(P = 0.016\); Fig. 4). There was no difference between groups in the incidence of acute exacerbation (5(29%) vs 3(30%)).

**Safety**

Severity of adverse events was assessed using the grading scale of the Common Terminology Criteria for Adverse Events v3.0 (National Cancer Institute, http://ctep.cancer.gov). Although photosensitivity is a known major adverse effect of pirfenidone, only one patient developed photosensitivity but improved after treatment with steroid ointment and UV care and did not withdraw. Four patients discontinued therapy due to gastrointestinal discomfort, such as nausea and/or anorexia (grade 4). However, most adverse events resolved after a decrease in dose or temporary cessation of pirfenidone treatment.

A previous study found that the common adverse events of inhaled NAC were bacterial pneumonia, cough and sore throat. No adverse events in this study were attributed to inhaled NAC. Therefore, treatment with inhaled NAC was generally well tolerated.

All adverse events in this study, which were likely caused by pirfenidone, were in the group treated with NAC. Because of their longer survival, patients treated with NAC received pirfenidone for a longer period as compared with the control group. This may be a reason why adverse events appeared to be more frequent in the NAC plus pirfenidone group.

**DISCUSSION**

Although several large clinical trials of IPF treatments have been conducted during the past decade, IPF...
remains a progressive and fatal disease. The present results show that combination pirfenidone and inhaled NAC treatment improved FVC at 12 months in 47% of patients with advanced IPF. PFS was significantly better among patients receiving combined treatment than among those receiving pirfenidone alone. These results suggest that treatment with inhaled NAC and pirfenidone decreases the risk of poor outcomes in patients with advanced IPF. No significant differences were noted between the NAC plus pirfenidone and the pirfenidone groups in regard to pretreatment background factors, such as age, sex, smoking history, FVC and DLco. The annual rate of change in FVC was −610 mL in the NAC plus pirfenidone group and −1320 mL in the pirfenidone group ($P < 0.01$). These data suggest that combination therapy decreases the decline in FVC as compared with pirfenidone alone in some patients with rapidly progressive advanced IPF (decline in FVC >10% during the 6 months before treatment).

The present findings are supported by a phase 3 study of pirfenidone, which found that decline in VC was significantly reduced at week 52 in patients with IPF. Additionally, a Cochrane meta-analysis of all three phase 3 trials of pirfenidone in patients with IPF ($n = 1046$) showed significant improvements in PFS (hazard ratio: 0.70, 95% confidence interval: 0.56–0.88; $P = 0.002$), an end-point predominantly associated with a large decline in lung function. However, it is important to highlight that these phase 3 trials enrolled only patients with mild-to-moderate disease (FVC >50%, DLco >30%) and few comorbidities; thus, the results cannot necessarily be generalized to patients with advanced disease. However, our favourable results in patients with advanced IPF suggest that combination therapy with pirfenidone plus inhaled NAC was an effective treatment irrespective of disease severity. This study’s findings may show NAC-pirfenidone effectiveness in advanced disease, but this finding has not been confirmed by other research or prospective studies. In addition, it is only postulated that combination therapy may be effective in mild-to-moderate disease, but there is no available data to support this claim.

In this study, combination therapy with pirfenidone plus NAC was associated with favourable outcomes; therefore, this regimen may be effective in treating NAC- or pirfenidone-resistant IPF. Concomitant administration of inhaled NAC was generally well tolerated.

The use of acetylcysteine may benefit patients with IPF by favourably altering the oxidative state of the lung. In the IFIGENIA study, a three-drug regimen consisting of azathioprine, prednisone and acetylcysteine was better at maintaining FVC and DLco than a two-drug regimen consisting of azathioprine and prednisone. However, in the Panther trial, a 60-week regimen of acetylcysteine (600 mg t.i.d.) failed to maintain FVC better than matched placebo in patients with IPF and mild-to-moderate impairment in pulmonary function. However, it must be emphasized that these results are applicable only to patients with IPF who satisfied the inclusion criteria of the Panther trial and not to patients with more-advanced disease.

Acetylcysteine is a precursor of the antioxidant GSH, the level of which is reduced in the lungs of patients with IPF. NAC given at a dose of 352.4 mg b.i.d. resulted in few adverse effects and has been used for many years in Japan as a mucolytic agent via direct instillation or nebulization into the airway. Aerosol administration of NAC, as used in this study, is a rational approach for delivery of a pharmacological dose to the lung in IPF. GSH levels in sputum were significantly higher at 2 weeks after treatment with NAC 352.4 mg b.i.d. This increase was associated with clinical improvement in patients with IPF. Hagiwara et al. showed that NAC inhalation increased neutralization of oxygen radicals in an animal model of bleomycin-induced lung fibrosis. Furthermore, we have shown that the clinical efficacy of NAC inhalation, including lung function, at the same dose used in this study correlated with improvement in redox imbalance in IPF patients. However, NAC may not
produce a sustained increase in GSH levels sufficient to increase the antioxidant capacity of the lungs, even when given in high oral doses (600 mg t.i.d.).\textsuperscript{20} Furthermore, NAC itself is not detected in BALF when given orally (200 mg t.i.d.).\textsuperscript{21} In contrast, aerosol administration of NAC acts directly as an antioxidant in alveoli, in addition to its GSH-increasing effect.\textsuperscript{15} Therefore, inhaled NAC may be more effective in attenuating inflammation and lung fibrosis. The two drugs investigated in this study act at different points in ROS metabolism. Thus, there is a logical basis for combining them to reduce ROS.

Homma \textit{et al.} reported that inhaled NAC monotherapy was an effective treatment for IPE. Although not all participants in that study could be evaluated for the primary end-point, post-hoc analysis showed significantly lower 48-week declines in FVC (difference, 120–170 mL) in a subset of patients with a mean baseline VC of almost 80% of the predicted value and a DLco of almost 43% of the predicted value.\textsuperscript{22}

We previously reported findings from a retrospective study of the combined effects of pirfenidone and inhaled NAC for advanced IPE (stage III/IV). Patients receiving pirfenidone with NAC had more-stable FVC and better median survival as compared with patients not receiving NAC.\textsuperscript{23} This trend was confirmed in the present study. It should be noted, however, that this was a case–control study with a small number of patients and that the favourable results regarding the efficacy of combined therapy must be confirmed in a randomized controlled trial.

Further trials (e.g. to evaluate pirfenidone alone vs NAC combined with pirfenidone) are needed in order to guide the development of new therapies for IPE.

The present study has some limitations as it was a single-centre, case–control study with a small sample size. Patients who, due to adverse events, were unable to continue pirfenidone therapy for at least 1 month were excluded. Therefore, the enrolment and exclusion criteria may have biased the results. Whether NAC/pirfenidone combination therapy translates into clinical benefits in the quality of life or survival remains to be proven.

In conclusion, combined treatment with NAC and pirfenidone might improve the poor prognosis of patients with advanced IPE. Future large, placebo-controlled, randomized trials should investigate the efficacy of this treatment regimen at various stages of IPE.

\textbf{Acknowledgement}

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\textbf{REFERENCES}


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