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Original Article

Efficacy of infliximab plus conventional therapy in dermatomyositis/polymyositis with interstitial lung disease: a prospective cohort study

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Abstract: Background: Lung involvement is one of the most common visceral damages of dermatomyositis/polymyositis (DM/PM) and influences the prognosis. Objective: To explore the efficacy and safety of infliximab (INF) plus conventional therapy on dermatomyositis/polymyositis (DM/PM) patients with interstitial lung disease (ILD). Methods: Forty DM/PM-ILD patients were included in the study at the beginning, while thirty-four patients finished this cohort study. According to patients received intravenous INF whether or not, they were assigned into INF group (n=14) and conventional therapy group (n=20) and received 16~24 weeks of treatment with conventional therapy plus INF or conventional therapy alone. Levels of serum muscle enzymes, pulmonary function, muscle strength and manual muscle testing (MMT) were determined and compared at baseline and after treatment. The adverse reactions and one-year survival rate were analyzed. Results: After treatment, levels of serum muscle enzymes, pulmonary function and muscle strength improved obviously than those at baseline in both groups, and levels of muscle enzymes (AST, LDH and CK), pulmonary function and muscle strength in INF group improved more significantly than those in the conventional therapy group ($P<0.05$). The incidence of adverse reactions of INF group was lower than that in the conventional therapy group with no significant difference, one-year survival rate of INF group was just higher than that of the conventional therapy group with no significant difference (85.7% *vs* 65.0%, $\chi^2=1.956$, $P=0.162$). Conclusion: In DM/PM-ILD patients, INF plus conventional therapy could significantly inhibit muscle inflammation/damage and improve the muscle strength and pulmonary function.

Keywords: Dermatomyositis, polymyositis, interstitial lung disease, infliximab, muscle enzymes

Introduction

Dermatomyositis/polymyositis (DM/PM) is an autoimmune disease showed mainly the affected skeletal muscle, which is characterized by the non-purulent inflammation of skin and striated muscle. Except for affecting the extremities proximal muscles and the skin, lung involvement is one of the most common visceral damages of DM/PM and also the key factor that influences the prognosis. The clinical manifestations of lung involvement are various, and therein interstitial lung disease (ILD) is the most frequent pulmonary manifestation whose incidence is 21.4%~70% [1-3]. In clinic, the curative effect of DM/PM complicated with ILD is not satisfactory, and therefore seeking the more effective treatment means is of great significance.

Tumor necrosis factor α (TNF-α) gene pathway has been shown to be activated in a subset of PM patients [4], and TNF-α has been shown to inhibit myoblast and myotube differentiation and directly inhibit the expression of the myogenic microRNAs, miR-1, -133 and -206, which are heavily involved in skeletal muscle differentiation and maintenance [5]. Anti-TNF-α therapy inhibits the cytotoxic T lymphocyte response that would normally suppress the autoreactive B-cell response, thus promoting humoral autoimmunity and increasing the type-I interferon system [6, 7]. Though TNF-α inhibitors have demonstrated efficacy in large, randomized controlled clinical trials in the treatment of chronic inflammatory immune-mediated disease [8-10], there are few of reports about the treatment of such agents on DM/PM with ILD. Infliximab (INF) is an anti-TNF-α monoclo-

nal antibody and mainly used in treating rheumatoid arthritis (RA), inflammatory bowel disease, ulcerative colitis and Crohn's disease [11-13]. In the present cohort study, we analyzed the case data of 34 DM/PM inpatients associated with ILD, according to whether or not they received INF therapy, patients were assigned into different groups and the changes of muscle strength and myositis activity were detected at baseline and after treatment, in order to evaluate the therapeutic effect and safety of INF combined with conventional therapy.

Materials and methods

General data

A total number of 40 patients admitted to our hospital from Jan. 2013 to Apr. 2015 were recruited in the study at the beginning of this prospective trial, while 34 of them finished the study except for 4 dropped out patients and 2 lost patients during one-year follow-up period. And the 34 patients were assigned into two groups according to the therapeutic regimen of their preference.

And all the recruited subjects met the diagnosis criteria in DM/PM proposed by Bohan and Peter's [14], patients with allergies, serious infection or hepatic disease and juvenile DM patients were excluded. The diagnosis criteria of complicating with ILD were as follows: (1) patients with clinical manifestation of dry cough, chest distress, progressive dyspnea and velcrorale ("velcro" crackles) in lung; (2) patients with pulmonary interstitial involvement in high-resolution CT (HRCT); (3) patients with restricted pulmonary ventilation disorder [15]. All the participated patients met the diagnostic criteria of ILD. Classification of ILD [16, 17]: Acute/subacute-ILD was defined as a progressive dyspnea that developed rapidly, over days to weeks, after the onset of respiratory symptoms; chronic ILD was defined as a progressive dyspnea that developed slowly, over months.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. And informed consent was obtained from all individual participants included in the study.

Grouping and treatment regimens

The patients were assigned into two groups based on the treatment protocol including or excluding INF. The conventional therapy group, as the control group, was defined as the patients treated with conventional therapy (corticosteroids in combination with immunosuppressive agents). The INF group was defined as the patients treated with conventional therapy plus INF. Patients in both groups received the conventional therapy of glucocorticoids with immunosuppressors. The initial dose of prednisone was 0.5~2 mg/kg/d, if ILD was alleviated after one month of initiating the treatment, the dosage of prednisone was gradually reduced; in serious cases, *i.v.* methylprednisolone pulse therapy (500~1000 mg/d for 3~5 days) was given. Meanwhile, all the patients received cyclosporine (CsA) orally (150~200 mg/d) or cyclophosphamide by intravenous injection (0.8~1.2 g/month) or azathioprine orally (75~150 mg/d). Besides the conventional therapy, in INF group, treatment was initiated with TNF-α inhibitor (INF 5 mg/kg) *i.v.*, given at 0, 2, 6 and 14 weeks and then bimonthly in addition to conventional therapy. The whole treatment regimen lasted for 16~24 weeks in both groups.

To guarantee safety, vital signs were assessed for each patient, and the liver function, blood routine, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) was determined; subjects who were infected or conceived or had cardiac failure were excluded. Informed consent was obtained from each patient prior to inclusion in the study. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration. The study's protocol had been approved by the local ethics committee of the hospital.

Observed indices

Serum muscle enzymes levels were observed at baseline (before treatment) and after treatment, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine phosphokinase (CK) and lactic dehydrogenase

Table 1. Baseline characteristics of patients

Characteristics	Control group	INF group	*P* value
No.	20	14	------
Age of onset, years	47.4±15.0	51.1±13.8	0.465
No. (%) female	14 (70.0)	9 (64.3)	0.726
DM/PM	8/12	6/8	0.868
Disease duration (month)	8.8±8.3	11.5±9.1	0.376
ILD subset			
AIP/SIP	7	3	0.393
CIP	13	11	
Whether received glucocorticoid pulse therapy or not			
Yes	4	2	0.667
No	16	12	
Clinical manifestations			
Proximal weakness	18	14	0.223
Dysphagia	7	4	0.693
Rash	13	9	0.966
Mechanic hands	6	4	0.928
Joints involvement	14	10	0.928
Fever	13	11	0.393
Gottron papules	12	10	0.493
Raynaud's phenomenon	2	1	0.773
Dry cough	7	4	0.693
Dyspnea	3	2	0.954
Laboratory findings			
Anti-Jo-1 antibody, no. (%) positive	3 (15.0)	3 (21.4)	0.628
Anti-EJ antibody, no. (%) positive	2 (10.0)	1 (7.1)	0.773
Anti-OJ antibody, no. (%) positive	1 (5.0)	2 (14.3)	0.347
Anti-KS antibody, no. (%) positive	1 (5.0)	0 (0)	0.396
Anti-ANA antibody, no. (%) positive	12 (60.0)	7 (50.0)	0.563
Anti-MDA5 antibody, no. (%) positive	2 (10.0)	1 (7.1)	0.773
ESR (mm/h)	39.37±17.88	37.79±14.51	0.962
CRP (mg/L)	8.20 (4.62~24.65)	8.45 (4.77~23.78)	0.823
KL-6 (U/ml)	681.7 (271.4~1518.9)	711.4 (298.0~1657.4)	0.861
IgA (g/L)	2.82±1.18	3.08±1.02	0.516
IgM (g/L)	2.02±1.14	1.89±0.97	0.723
IgG (g/L)	13.45±2.66	13.66±3.43	0.844
HRCT features			
Ground glass opacity	14	10	0.766
Reticular opacity	10	8	0.525
Honeycombing opacity	8	7	0.435
Patch clouding opacity and/or associated with hypertrophic pleura	7	5	0.966

Note: The disease duration was defined as the time between the appearance of DM/PM-associated symptoms and admission.

(LDH). To assess the strength of each muscle, manual muscle testing (MMT) was performed for the following 18 muscles: the flexor and extensor muscles of the neck, the bilateral side of the deltoid, biceps brachii, brachioradialis, triceps brachii, iliopsoas, gluteus maximus, quadriceps femoris and hamstring. Each muscle was scored on a scale of 0~5 and the maximal total score was 90. Each patient was evaluated before and after the treatment by the same physical therapist [18-20]. Other measured parameters included FVC, FEV_1, vital capacity (VC) and DL_{CO}, which were expressed as percentages of the predicted values.

All patients were observed and followed up for at least twelve months after hospital discharge. Patient's clinical data was collected at the time

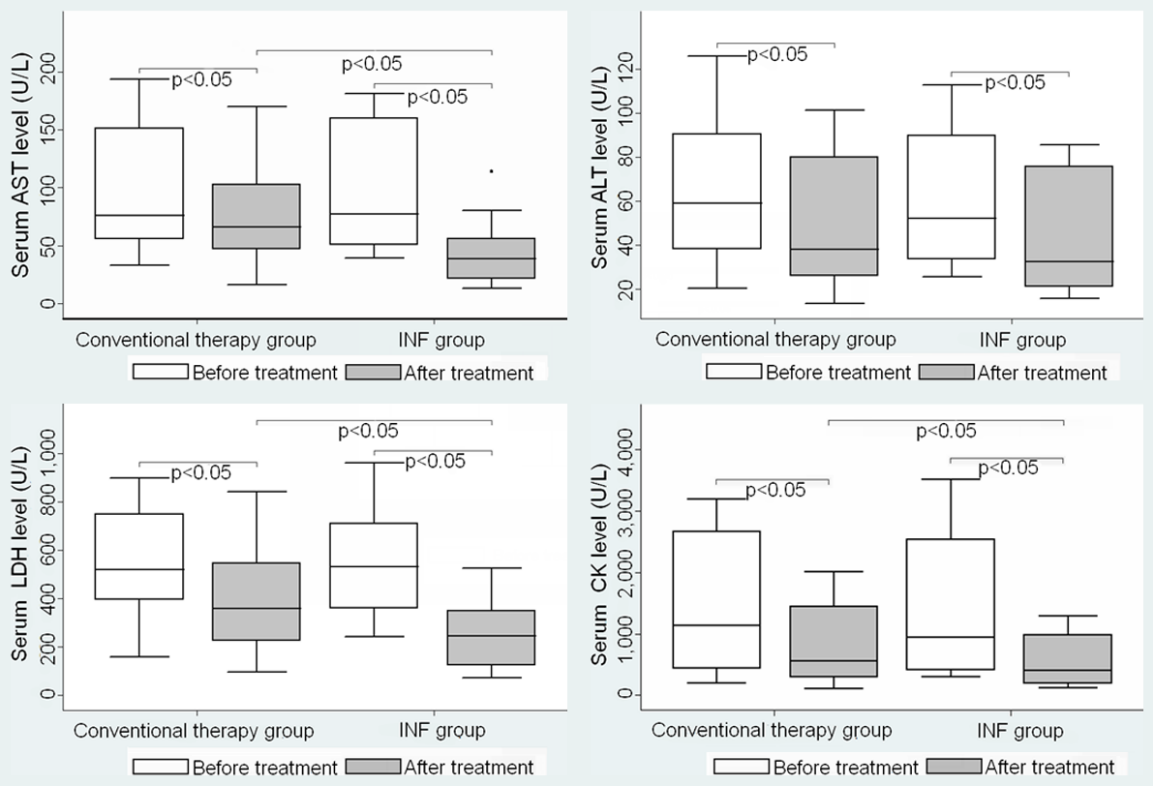

Figure 1. Levels of serum muscle enzymes in both groups before and after treatment.

of admission to hospital (baseline), hospital discharge, six months post-discharge and twelve months post-discharge. The adverse reactions and survival time were also observed and recorded.

Data statistics

Data in normal distribution was presented as mean ± SD, data in abnormal distribution was presented as the median (interquartile range). Demographic and clinical features and laboratory findings of both groups were compared using Student's *t*-test for continuous variables or Mann-Whitney *U*-test for discrete variables. For comparisons of muscle enzymes levels, independent-samples T test was used between groups, and to check the difference between before and after treatment, paired-samples T test was used. Pulmonary function and muscle strength was also compared between groups by independent-samples T test. Survival time was calculated by Kaplan-Meier method, and Log Rank test was conducted for comparing the survival rate and survivorship curve between groups. A p value of <0.05 was considered statistically significant.

Results

Baseline characteristics

In 34 inclusive DM/PM-ILD patients, male/female ratio was 11:23, age of onset was 19~73 years. There were 14 patients in INF group and 20 patients in conventional therapy group, the disease duration of conventional therapy group and INF group was 8.8±8.3 months and 11.5±9.1 months, respectively. ILD subsets included AIP/SIP and CIP, and there were 14 patients with AIP/SIP. Anti-melanoma differentiation-associated protein 5 (MDA5) antibody was detectable in 3 patients (2 patients in conventional therapy group and 1 patient in INF group), and all of them were DM-ILD patients. Of the 34 participants, 4 kinds of anti-aminoacyl-tRNA synthetase (ARS) antibodies were detected, including antihistidyl- (anti-Jo-1), antiglycyl- (anti-EJ), antiisoleucyl- (anti-OJ) and antiasparaginyl- (anti-KS) antibodies. Regarding the clinical manifestations, the baseline characteristics of conventional therapy group and INF group showed no significant difference (P>0.05, **Table 1**).

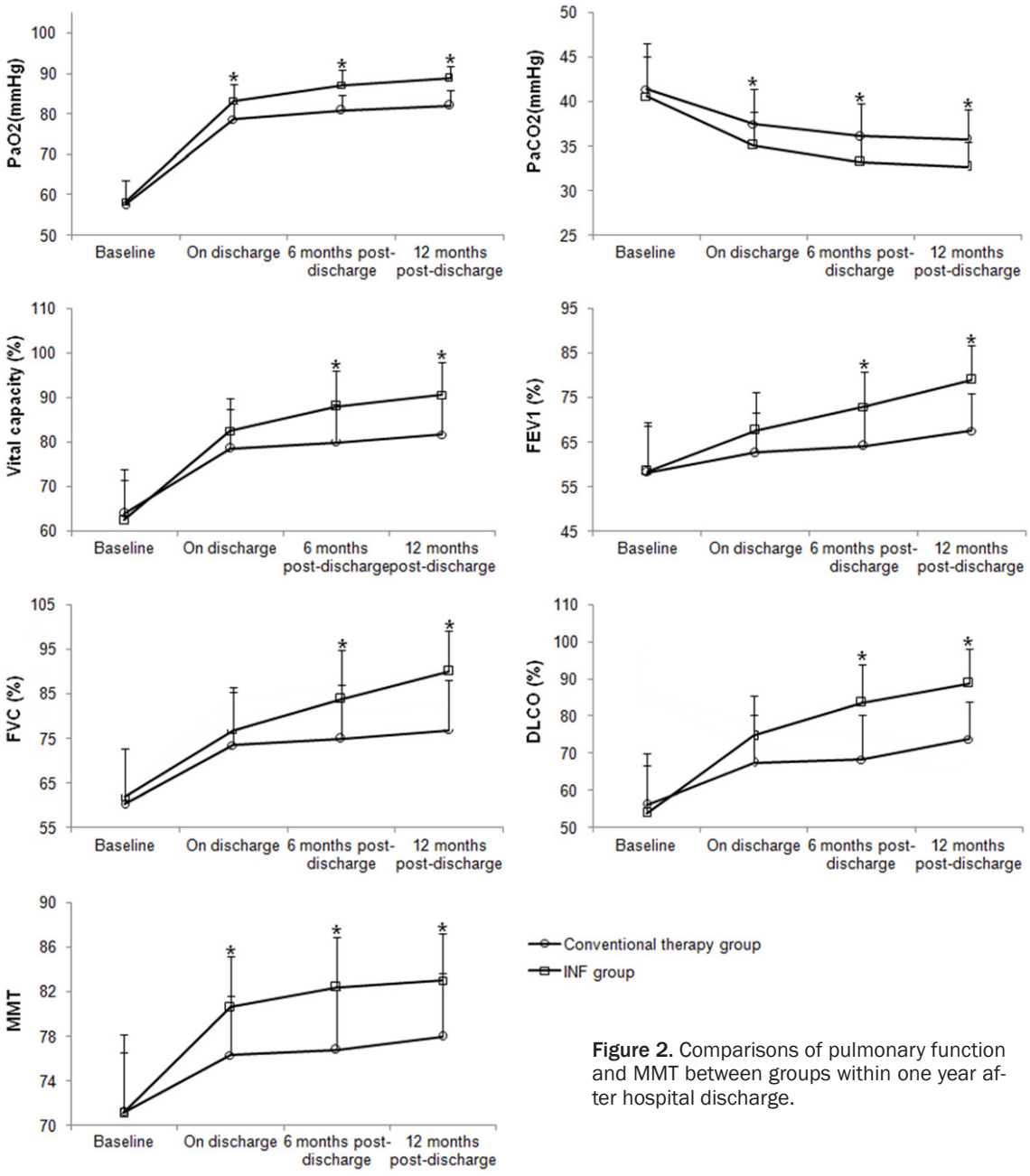

Figure 2. Comparisons of pulmonary function and MMT between groups within one year after hospital discharge.

Outcomes

Compared with the levels before treatment, **Figure 1** showed that after treatment serum muscle enzymes levels in both groups decreased obviously, and the levels of AST, LDH and CK in INF group decreased more obviously than conventional therapy group ($P<0.05$), which indicated that INF could obviously inhibit the inflammatory reaction and myositis damage.

We also tracked and analyzed the indices related to pulmonary function and muscle strength when patients were discharged from the hospital (after treatment), 6 months post-discharge and 12 months post-discharge. The results showed that the indices related pulmonary function and muscle strength (MMT) improved significantly after treatment in both groups ($P<0.05$); on discharge (when therapy was finished), levels of PaO_2, $PaCO_2$ and MMT in INF group improved more significantly than those in

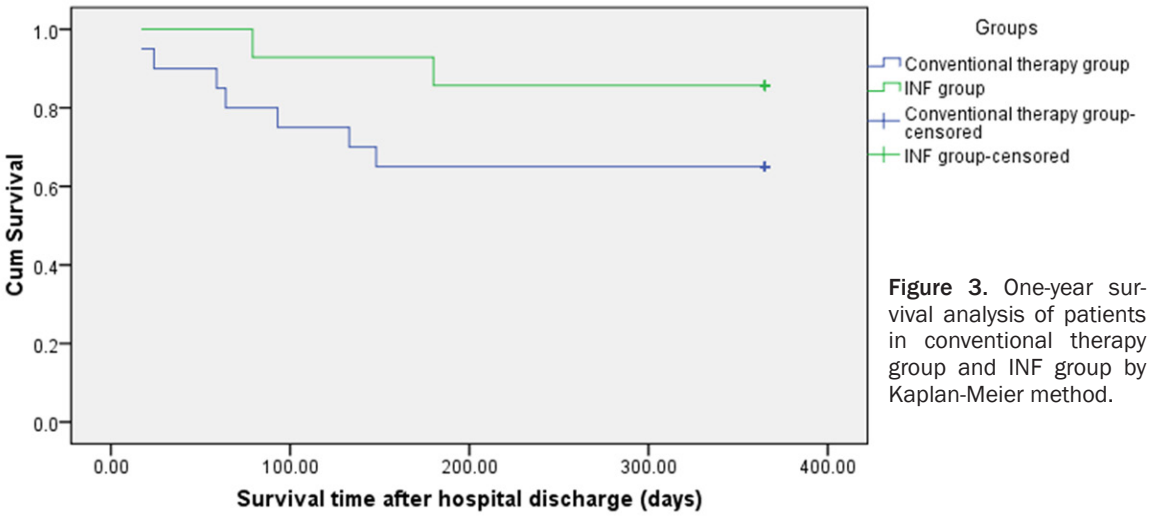

Figure 3. One-year survival analysis of patients in conventional therapy group and INF group by Kaplan-Meier method.

conventional therapy group (P<0.05); results of indices related to pulmonary ventilation function (VC, FEV_1, FVC and DL_{co}) showed INF group was also better than conventional therapy group since 6 months post-discharge (P<0.05) (**Figure 2**).

Adverse reactions and prognosis

There were 2 cases of osteoporosis, 4 cases of diabetes and 2 cases of granulocytopenia in conventional therapy group; there was 1 case of transfusion reaction, 1 case of secondary infection and 1 case of osteoporosis in INF group. The incidence of adverse reactions in INF group did not differ from that in conventional therapy group (21.4% *vs* 40.0%, P=0.255).

At the end of the follow-up period, there were 7 and 2 died cases in conventional therapy group and INF group, respectively. In conventional therapy group, 5 cases died of respiratory failure and 2 cases died of pulmonary infection; 2 cases of INF group died of respiratory failure. **Figure 3** showed that one-year survival rate of INF group was higher than conventional therapy group without significant difference (65.0% *vs* 85.7%, χ^2=1.956, P=0.162).

Discussion

When myositis is active, serum muscle enzymes of DM/PM patients usually elevate, therein the level of CK shows the highest sensitivity with relative specificity, which is important for the diagnosis, treatment guidance and prognosis. In patients with idiopathic inflammatory myopathies (IIM), the increase of serum CK is considered a hallmark of muscle inflammation/damage [21]. Transaminases levels often elevate in muscle injury and were observed concomitantly with the activity of myositis [22], though AST and ALT are not always considered indicators of muscle damage. Regarding the relationship between serum AST, ALT and CK levels at time of diagnosis of IIM, Mathur *et al*. found a strong correlation between CK and AST and ALT at initial presentation and also at the time of peak CK levels, respectively [23]. LDH is also one of the most important muscle enzymes that reflect muscle inflammation [24, 25]. In the present study, after the treatment, muscle enzymes levels of both groups decreased obviously, and the level of AST, LDH and CK of INF group decreased more than conventional therapy group. In addition to these clinical data, regarding on patients' pulmonary function and muscle strength, INF group also showed more obvious improvement than the other group after finishing the treatment. These results indicated that INF combined with conventional therapy could more effectively inhibit muscle inflammation/damage and improve pulmonary function, compared with conventional therapy alone.

There are few clinical trials in DM/PM-ILD, making it difficult to provide clear recommendations on the treatment of this rare disorder. In the report of Tosounidou and colleagues [26], the patient with systemic sclerosis/myositis overlap syndrome was affected by arthritis, myositis and moderate pulmonary fibrosis, and

INF transfusion therapy was given the patient after the failures of multiple therapeutic interventions, and then they found the calcification of the patient was reduced with the normalized level of CK and CRP, pulmonary fibrosis did not progress. In another report about juvenile dermatomyositis (JDM), intravenous INF was given for all five JDM patients, and the positive changes were also demonstrated in physician visual analogue scale (VAS), childhood myositis assessment score (CMAS), childhood health assessment questionnaire (CHAQ) and some regression of calcinosis and skin signs [27]. But in the treatment of refractory inflammatory myopathies, Dastmalchi *et al.* [28] pointed out that INF did not show obvious effectiveness in resistant myositis. In the present study, INF plus conventional therapy showed a better curative effect than conventional therapy alone, this might be attributed to the recruited participators, that most of them were not belonged to refractory DM/PM patients and they were able to respond to treatment with conventional therapy, such as the glucocorticoids or/and immunosuppressive agents.

As to the adverse reactions, except the common adverse reactions, transfusion reaction and secondary infection were usually observed during the delivery of INF. Therefore, infusion velocity must be controlled strictly and could be slowed or stopped for mild or moderate transfusion reaction. Regarding the secondary infection, it is mainly due to the inhibiting effect of INF on cytokines and immunocytes, which induces infection or aggravates the original infection [29].

Generally speaking, because of the destroyed pulmonary alveoli and interstitial fibrosis resulted from the concomitant ILD in DM/PM patients, patients usually show recession of respiratory system and other systems. Therefore, ILD is identified as the main reason of affecting the survival rate of DM/PM patients. In keeping with the previous studies, the main cause of death of both groups in the present study was respiratory failure [30, 31]. In addition, the use of glucocorticoid and immunosuppressors makes the reduction of immune function, which leads to be more likely to the occurrence of secondary infection, and then respiratory failure will happen. Therefore, during the nursing process, the clinical medical workers should adopt comprehensive and thoughtful nursing management and strengthen patients' respiratory training, in order to prevent pulmonary infection and respiratory failure.

However, because this study was a non-randomized control trial, the therapeutic regimen depended on patient's preference, so the bias from the subjects or/and investigators may be unavoidable to influence the results. Besides, this study was also limited by the small sample size.

In conclusion, INF plus conventional therapy could significantly inhibit muscle inflammation/damage and improve the muscle strength and pulmonary function in DM/PM-ILD patients, with no significant influence on the adverse reactions and one-year survival rate.

Disclosure of conflict of interest

None.

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