Treatment of Interstitial Lung Disease in Anti-MDA5-Positive Dermatomyositis: A Retrospective Study of 87 Patients

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Research Article

Keywords: anti-melanoma, interstitial lung disease, dermatomyositis, Corticosteroid

DOI: https://doi.org/10.21203/rs.3.rs-744940/v1

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Abstract

**Objectives:** The prognosis of anti-melanoma differentiation-associated gene (MDA5) antibody-positive dermatomyositis (DM)-interstitial lung disease (ILD) (anti-MDA5-positive DM-ILD) is often poor, especially in rapidly progressive interstitial lung disease (RPILD). So far there is no established therapy. This study evaluated the efficacy and safety of pharmacological treatments for anti-MDA5-positive DM-ILD.

**Methods:** This retrospective study comprised 87 anti-MDA5-positive DM-ILD patients. We reviewed the clinical characteristics, laboratory findings, lung function treatments, and outcomes of the 87 patients. Cox regression analysis was used to identify predictors of 6-month survival. The association between different combined immunosuppressive regimen and 6-month survival were evaluated.

**Results:** High level of CYFRA21-1 and low PaO2/FiO2 ratio were associated with poor prognosis. Corticosteroid (CS) alone treatment group with higher CYFRA21-1 and lower PaO2/FiO2 ratio showed worse 6-month survival than the combination of CS with immunosuppressants group (p<0.01). In addition, tacrolimus/cyclosporine-treated anti-MDA5-positive DM Non-RPILD exhibited a better survival, comparing with tacrolimus/cyclosporine combined intravenous cyclophosphamide (IVCY)-treated patients (p<0.05).

**Conclusion:** Addition of immunosuppressants to CS, were associated with better 6-month survival in anti-MDA5-positive DM-ILD. The triple regimen (CS, tacrolimus/cyclosporine and IVCY) was not superior to duple one (CS, tacrolimus/cyclosporine) in anti-MDA5 positive DM Non-RPILD.

**Key Messages**

1. A combined immunosuppressive regimen is more effective for anti-MDA5-positive DM-ILD than corticosteroid alone.

2. No difference was observed in anti-MDA5-positive DM-RPILD patients with triple intensive immunosuppressive regimen or duple regimen.

3. The duple regimen (CS and tacrolimus/cyclosporine) is more effective and safe than the triple regimen in anti-MDA5 positive DM Non-RPILD.

**Introduction**

Dermatomyositis is a kind of autoimmune inflammatory disease, that characterized by muscle weakness, skin lesions, arthralgia and internal organs damaged, including heart, lungs [1]. Interstitial lung disease (ILD) is a severe complication of DM patients that is associated with poor prognosis of DM patients, especially rapidly progressive interstitial lung disease (RPILD). Myositis specific antibodies (MSAs) are observed in 30–40% myositis/DM patients which are reported to be associated with different phenotypes of PM patients in terms of distinct clinical manifestations [2]. Among the MSAs, anti-melanoma
differentiation-associated gene (MDA5) auto-antibodies, are recently reported to be closely associated with the development of RPILD, especially in patients with typical skin lesions, which is one of the most prognostic factors in DM-ILD patients [3–7]. RPILD has been characterized by accelerated progressive deterioration of respiratory symptom and pulmonary function in three months, that is an important cause of substantial mortality [8, 9]. In previous study, we have observed that the serum CYFRA21-1 level was higher in anti-MDA5-positive DM-ILD, especially in RPILD patients, that was a prognostic factor and also associated with disease prognosis [10]. Evidence for the effectiveness of pharmacological treatment for anti-MDA5-positive DM-ILD is limited. Recently, the effective treatments mainly include corticosteroid (CS), calcineurin inhibitors, intravenous cyclophosphamide (IVCY) and plasmapheresis, etc. The conventional treatment including CS alone or a combination of CS and immunosuppressants, is applied to 28–66% of Asia patients with anti-MDA5-positive DM-ILD [11–13]. In clinical practice, CS is given at the beginning of diagnosis of anti-MDA5-positive DM-ILD, often in high doses, to most patients who demonstrate RPILD. Calcineurin inhibitors (tacrolimus or cyclosporine) are usually administered in combined with CS. In addition, a combined immunosuppressive therapy including high-dose CS, calcineurin inhibitors, and IVCY might be efficacious [14, 15].

Calcineurin inhibitors are the drug with strong immunosuppressive effect, that can down-regulate the production of cytokines in T lymphocytes by inhibition of calcineurin activation, and then suppress the function of T lymphocytes [16]. As a potent immunosuppressive agent, calcineurin inhibitors had been widely used for autoimmune diseases including DM, rheumatoid arthritis (RA) etc. Cyclophosphamide (CTX) as a kind of common immunosuppressive drugs, mainly inhibits immune responses mediated by T and B lymphocytes, and then reduces the inflammatory response induced by a variety of adhesion molecules, chemokines and cytokines. IVCY is given for treatment of progressive interstitial pneumonia in patients with DM, that had a good therapeutic effect [17]. Although CS, calcineurin inhibitors, IVCY, etc are very important for the treatment of anti-MDA5-positive DM-ILD, overtreatment would increase the risk of opportunistic infections to accelerate the death of patients. Few studies investigate the associations of various pharmacological treatments with survival in anti-MDA5-positive DM-ILD patients in China. Therefore, we conducted this retrospective study in an interstitial lung disease center, to investigate the relationship of immunosuppressive treatment with 6-months survival in anti-MDA5-positive DM patients.

Patients And Methods

2.1. Study subjects

This study investigated data from 87 anti-MDA5-positive DM-ILD patients admitted to Nanjing Drum Tower Hospital between December 2016 and February 2020. DM was diagnosed according to the criteria of Bohan and Peter [18]. Patients with overlap syndromes, including systemic sclerosis (SSC) and Sjogren's syndrome (SS), and following conditions were excluded: cancer, hepatitis B virus infection, active tuberculosis.

2.2. Diagnosis of ILD
ILD was diagnosed according to respiratory symptoms, physical examinations, lung function tests and chest high-resolution CT (HRCT) findings. HRCT was defined as organizing pneumonia (OP) pattern, nonspecific interstitial pneumonia (NSIP) pattern and others [19], that were reviewed by the chest radiologist. The patients had a follow-up period for 6 months.

2.3. Data collection

Clinical data were obtained from the electronic medical records to determine the characteristics of anti-MDA5-positive DM-ILD patients. We also collected information of lung function and laboratory tests at initial diagnosis. Written informed consents were obtained from all patients prior to the study, and all participants gave the permission for the use of their serum for research purposes. This study was conducted in accordance with the principles of the Declaration of Helsinki (1989) and approved by the Ethics Committee at Nanjing Drum Tower Hospital.

2.4. Therapeutic regimen of anti-MDA-positive DM-ILD

All patients were treated with CS therapy (prednisolone initially administered 500 mg/day for 3 days or 1 mg/kg/day). CS dose was tapered during treatment courses (20% decreased every 4 weeks when the dose was higher than 30mg daily, and 8 weeks when it was lower than 30mg daily). Tacrolimus (1-4mg/day) or cyclosporine (100-300mg/day) was combined with CS. Tacrolimus or cyclosporine was adjusted to maintain blood concentration within the range of 10–12 ng/mL or 100–150 ng/mL. CTX was started intravenously at a dose of 400 mg biweekly. IVCY was extended to 400 mg every 4 weeks after the six times.

Statistical analysis

Descriptive statistics for the clinical characteristics are expressed as counts (percentage) and median range. Continuous variables were compared between different groups using the Mann-Whitney U test. Univariate and multivariate Cox regression were performed to establish predictors of survival in anti-MDA5 positive DM-ILD. The cumulative survival rates were calculated by the Kaplan-Meier test. The log-rank test was also used to compare the survival rates in each group. The statistical analyses were performed using SPSS for Windows version 19 (IBM Corp. GraphPad Prism Version 6(GraphPad Software, San Diego, CA, USA). A p value < 0.05 was considered statistically significant.

Results

3.1. Clinical characteristics of 87 patients with anti-MDA-positive DM-ILD

There were 49 males (56.3%) and their median age was 53.0 [IQR: 47.0–63.0] years. Most of patients (71.3%) had skin rash (Gottron sign), and some patients (40.2%) were simultaneously accompanied by
fever, and only a few patients (23.0%) had muscle weakness. Laboratory findings showed that lactate dehydrogenase (LDH), c-reactive protein (CRP), and Cytokeratin 19 fragment (CYFRA21-1) levels were elevated and median PaO2/FiO2 ratio was low. The HRCT imaging showed OP/OP-NSIP pattern (78.2%) and NSIP pattern (21.8%). Median forced vital capacity (FVC% predicted) and diffusing capacity of the lung for carbon monoxide (DLCO% predicted) were 61.2% and 55.5% (Table 1).

Table 1
Characteristics of patients with Anti-MDA5-positive DM-ILD

| Clinical Characteristics of Anti-MDA5-positive DM-ILD patients | n = 87 |
|---------------------------------------------------------------|-------|
| Age, yr                                                      | 53.0(47.0–63.0) |
| Male                                                        | 49(56.3%) |
| **Clinical findings**                                         |       |
| fever                                                       | 35(40.2%) |
| Heliotrope rash                                              | 35(40.2%) |
| Gottron’s sign                                               | 62(71.3%) |
| Muscle weakness                                              | 20(23.0%) |
| **Laboratory findings**                                      |       |
| CPK(U/L)                                                     | 47.5(27.7–102.0) |
| LDH (U/L)                                                    | 363.5(270.0-502.8) |
| CRP (mg/L)                                                   | 15.2(4.7–35.8) |
| ESR(mm/h)                                                   | 33.0(18.3–59.0) |
| CYFRA21-1(ng/ml)                                             | 6.7(4.2–12.8) |
| PaO2/FiO2 ratio                                              | 208.0(142.8-300.3) |
| **HRCT patterns**                                            |       |
| OP/OP-NSIP                                                   | 68(78.2%) |
| NSIP                                                        | 19(21.8%) |
| **Lung function**                                            |       |
| FVC% predicted                                               | 61.2(48.3–73.0) |
| DLCO%predicted                                               | 55.5(45.3–67.9) |

CRP, C-reactive protein; LDH, lactate dehydrogenase; DLco, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; OP, organized pneumonia; NSIP, Non Specific Interstitial Pneumonia;
Figure 1 showed the details of therapeutic regimen for anti-MDA5-positive DM-ILD patients. Twenty-eight patients (32.1%) had received CS pulse therapy (500mg), initial CS dose (1mg/kg) was performed in 59 patients (67.8%). Forty-four patients (50.6%) had received tacrolimus, and 27 (31.0%) had received cyclosporine. Twenty-six (29.8%) underwent IVCY. (Fig. 1)

### 3.2. Predictors of 6-month survival

During the treatment period, 48 of 87 patients (55.2%) died. Univariate and Multivariate cox regression analyses showed that use of CS alone (HR, 1.971, 95% CI 1.012–3.838, p < 0.05) was associated with worse 6-month survival. High level of CYFRA21-1 (HR, 1.056; 95% CI, 1.029–1.084, p < 0.001) and low PaO2/FiO2 ratio (HR, 0.990, 95% CI 0.986–0.994, p < 0.001) were associated with poor outcome. In clinical practice, all the patients received CS treatment. In fact, the group treated with CS combined with immunosuppressors, which was associated with an obviously higher PaO2/FiO2, lower CYFRA21-1 level, had better outcomes. (Table 2)
Table 2
Results of univariate and multivariate COX analysis for 6-month survival in Anti-MDA5 positive DM-ILD patients

| Anti-MDA5-positive DM-ILD | Hazard ratio | 95%CI          | p value  |
|--------------------------|--------------|----------------|----------|
| **Univariate analysis**  |              |                |          |
| Age(years)               | 1.048        | 1.019–1.079    | < 0.01** |
| HRCT pattern (OP/OP-NSIP)| 1.311        | 0.682–2.521    | 0.417    |
| **Laboratory findings**  |              |                |          |
| PaO2/FiO2 ratio          | 0.990        | 0.986–0.993    | < 0.001***|
| WBC                      | 1.084        | 1.114–1.170    | < 0.05*  |
| CPK                      | 1.001        | 0.998–1.004    | 0.513    |
| LDH                      | 1.000        | 1.000–1.001    | 0.144    |
| CRP                      | 1.018        | 1.007–1.029    | < 0.01** |
| ESR                      | 1.011        | 0.999–1.022    | 0.073    |
| CYFRA21-1                | 1.067        | 1.042–1.091    | < 0.001***|
| FVC(%)                   | 1.021        | 0.968–1.076    | 0.448    |
| DLCO(%)                  | 1.005        | 0.944–1.070    | 0.866    |
| **Treatment**            |              |                |          |
| CS alone                 | 2.416        | 1.272–4.592    | < 0.01** |
| **Multivariate analysis**|              |                |          |
| PaO2/FiO2 ratio          | 0.990        | 0.986–0.994    | < 0.001***|
| CYFRA21-1                | 1.056        | 1.029–1.084    | < 0.001**|
| CS alone                 | 1.971        | 1.012–3.838    | < 0.05*  |

CRP, C-reactive protein; LDH, lactate dehydrogenase; DLco, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; OP, organized pneumonia; NSIP, Non Specific Interstitial Pneumonia; CS: corticosteroid

3.3. Survival analyses according to different treatment

Kaplan-Meier survival method were used to assess the prognosis of patients underwent different treatment. 6-month survival of CS alone-treated was significantly lower than those treated with CS combined immunosuppressors (p < 0.01; Fig. 2A). Compared with patients treated with CS combined tacrolimus/cyclosporine and IVCY, survival at 6 months was significantly better in the patients treated with CS combined tacrolimus/cyclosporine (p < 0.01; Fig. 2B).
Table 3 showed the clinical features of anti-MDA5-positive DM-ILD patients in CS alone-treated and CS combined immunosuppressors groups. A similar age, gender distribution, PaO2/FiO2 ratio, and other serological indicators (CPK, LDH, CRP, ESR) were found between these two groups. Patients with CS alone-treated had higher CYFRA21-1 level than patients with CS combined immunosuppressors (13.1 [6.6, 22.6] vs. 5.9 [3.9, 12.1], p = 0.008). Table 4 showed the clinical characteristics of anti-MDA-positive DM-ILD patients in CS combined tacrolimus/cyclosporine-treated and triple regimen group. Patients treated with CS combined tacrolimus/cyclosporine and IVCY, had worse PaO2/FiO2 ratio (158.0 [96.0, 259.0] vs 231.0 [177.0, 371.5], p = 0.018), and higher CYFRA21-1 level (9.1 [6.2, 13.7] vs 4.4 [3.1, 9.2], p = 0.002) than duple regimen group. (Table 3, 4)

Table 3
Patients characteristics of MDA5-DM-ILD in the CS alone and CS combined Immunosuppressors groups

| Clinical Characteristics | CS alone n = 16 | CS combined Immunosuppressors n = 71 | p value |
|--------------------------|----------------|-----------------------------------|---------|
| Age(years)               | 58.0(45.3–66.8) | 53.0(48.0–62.0)                   | 0.569   |
| Male                     | 8(50.0%)        | 30(42.3%)                         | 0.575   |
| HRCT pattern(OP/OP-NSIP) | 13(81.3%)       | 55(77.5%)                         | 0.742   |
| CPK(U/L)                 | 84.0(34.3-137.5)| 42.0(27.0-91.3)                   | 0.079   |
| LDH(U/L)                 | 420.0(322.5–499.0) | 344.5(266.3-502.8)               | 0.310   |
| CRP (mg/L)               | 20.3(6.1–35.9)  | 13.9(4.7–35.5)                    | 0.369   |
| ESR (mm/h)               | 40.5(18.8–60.8) | 31.0(18.3–58.8)                   | 0.520   |
| CYFRA21-1(ng/ml)         | 13.1(6.6–22.6)  | 5.9(3.9–12.1)                     | 0.008** |
| PaO2/FiO2 ratio          | 164.5(86.5-271.3)| 213.5(146.8-341.5)               | 0.124   |

*p< 0.05, **p< 0.01

CRP, C-reactive protein; LDH, lactate dehydrogenase; OP, organized pneumonia; NSIP, Non Specific Interstitial Pneumonia;
Table 4
Patients characteristics of MDA5-DM-ILD receiving CS combined different Immunosuppressors groups

| Clinical Characteristics | Tacrolimus/Cyclosporine n = 45 | Tacrolimus/Cyclosporine combined IVCY n = 26 | p value |
|--------------------------|---------------------------------|---------------------------------------------|---------|
| Age(years)               | 53.0(48.0–62.0)                 | 52.5(48.0-62.5)                             | 0.943   |
| Male                     | 21(46.7%)                       | 9(34.6%)                                    | 0.325   |
| HRCT pattern(OP/OP-NSIP) | 34(75.6%)                       | 21(80.8%)                                   | 0.615   |
| CPK(U/L)                 | 42.0(27.5–93.0)                 | 42.0(23.5–84.0)                             | 0.677   |
| LDH (U/L)                | 319.0(255.0-500.0)              | 429.0(309.0-583.0)                          | 0.190   |
| CRP (mg/L)               | 12.7(4.5–35.1)                  | 15.4(4.9–37.2)                              | 0.611   |
| ESR(mm/h)                | 28.5(14.5–49.5)                 | 38.0(23.0-59.8)                             | 0.135   |
| CYFRA21-1(ng/ml)         | 4.4(3.1–9.2)                    | 9.1(6.2–13.7)                               | 0.002** |
| PaO2/FiO2 ratio          | 231.0(177.0-371.5)              | 158.0(96.0-259.0)                           | 0.018*  |

*<p < 0.05, **<p < 0.01

CRP, C-reactive protein; LDH, lactate dehydrogenase; OP, organized pneumonia; NSIP, Non Specific Interstitial Pneumonia;

Most of the patients died during the first 6 months from respiratory failure caused by RPILD. Figure 3 showed Kaplan-Meier survival curves for the tacrolimus/cyclosporine-treated and tacrolimus/cyclosporine combined IVCY-treated in RPILD and Non-RPILD patients. Survival at 6 months in Non-RPILD patients was significantly better in the tacrolimus/cyclosporine-treated group than in the tacrolimus/cyclosporine combined IVCY-treated group (p < 0.05; Fig. 3A). No difference was observed in 6 months survival of RPILD patients between two groups (p = 0.138; Fig. 3B).

Table 5 showed the detailed features of anti-MDA5-positive DM-Non-RPILD patients. ESR and CYFRA21-1 levels were obviously higher in those receiving triple intensive immunosuppressive therapy. Table 6 showed the characteristics of anti-MDA5-positive DM-RPILD patients in the tacrolimus/cyclosporine-treated and tacrolimus/cyclosporine combined IVCY-treated group. There was no significant difference between two groups. (Table 5,6)
Table 5
Characteristics of Non-RPILD patients receiving CS combined different Immunosuppressors therapy

| Non-RPILD Clinical Characteristics | Tacrolimus/Cyclosporine n = 24 | Tacrolimus/Cyclosporine combined IVCY n = 9 | p value |
|-----------------------------------|---------------------------------|---------------------------------|---------|
| Age (years)                       | 52.5 (43.3–60.0)                | 50.0 (46.5–53.0)               | 0.512   |
| Male                              | 13 (54.2%)                      | 2 (22.2%)                      | 0.166   |
| HRCT pattern (OP/OP-NSIP)         | 19 (79.2%)                      | 7 (77.8%)                      | 0.953   |
| CPK (U/L)                         | 47.5 (28.5–160.8)               | 32.0 (20.5–56.0)               | 0.121   |
| LDH (U/L)                         | 278.0 (234.8–350.5)             | 343.0 (260.0–964.5)            | 0.370   |
| CRP (mg/L)                        | 8.2 (4.8–33.4)                  | 4.7 (2.7–8.5)                  | 0.054   |
| ESR (mm/h)                        | 26.0 (16.0–43.0)                | 59.0 (29.7–71.0)               | 0.030*  |
| CYFRA21-1 (ng/ml)                 | 3.9 (2.9–4.6)                   | 7.4 (3.8–15.0)                 | 0.026*  |
| PaO2/FiO2 ratio                   | 356.0 (224.3–386.8)             | 270.0 (200.0–355.8)            | 0.480   |

*p < 0.05

CRP, C-reactive protein; LDH, lactate dehydrogenase; OP, organized pneumonia; NSIP, Non Specific Interstitial Pneumonia;
Table 6
Patients characteristics of MDA5-DM-RIILD patients receiving CS combined different Immunosuppressors therapy

| Clinical Characteristics | Tacrolimus/Cyclosporine | Tacrolimus/Cyclosporine combined IVCY | p value |
|--------------------------|-------------------------|--------------------------------------|---------|
|                         | n = 21                  | n = 17                               |         |
| Age(years)              | 54.0(50.5–63.0)         | 56.0(49.5–66.0)                      | 0.663   |
| Male                    | 8(38.1%)                | 7(41.2%)                             | 0.885   |
| HRCT pattern(OP/OP-NSIP)| 15(71.4%)               | 14(82.4%)                            | 0.581   |
| WBC(counts/mm3)         | 6.4(3.9–8.3)            | 6.6(4.4–10.6)                        | 0.352   |
| CPK(U/L)                | 39.0(27.0-62.5)         | 52.0(26.0-158.0)                     | 0.323   |
| LDH (U/L)               | 448.0(227.5–833.0)      | 433.5(340.8-496.5)                   | 0.916   |
| CRP (mg/L)              | 15.0(4.2–37.0)          | 27.8(12.7–45.8)                      | 0.123   |
| ESR(mm/h)               | 33.0(13.5–55.0)         | 31.0(23.0-56.5)                      | 0.940   |
| CYFRA21-1(ng/ml)        | 9.2(4.2–13.8)           | 9.4(6.7–13.8)                        | 0.350   |

CRP, C-reactive protein; LDH, lactate dehydrogenase; OP, organized pneumonia; NSIP, Non Specific Interstitial Pneumonia;

Safety

Some adverse events happened in patients treated with CS combined immunosuppressive regimen during the observation period. Hyperglycemia, opportunistic infections and liver and renal dysfunction were frequently observed. Hyperglycemia developed in 52 patients, which improved within a few days after therapy of antidiabetics. There were several kinds of opportunistic infections, including CMV and or EB virus reactivation (21 patients), Pneumocystis carinii pneumonia (PCP) (10 patients). Three patients developed pulmonary embolism, 5 patients developed pneumonia.

Discussion

Although a number of the combined immunosuppressive regimen have been used for anti-MDA5-positive DM-ILD, the efficacy of such pharmacological treatments have not been confirmed in large prospective studies. This study evaluated the associations of 6-month survival with CS alone or use of immunomodulatory therapy (tacrolimus/cyclosporine, IVCY), which are administered in combination with CS in Chinese anti-MDA5-positive DM-ILD patients. The present study clearly indicated that early combined immunosuppressive regimen was better than CS alone for improving 6-month survival of anti-MDA5-positive DM-ILD patients. This finding was consistent with the prior report that in DM-ILD patients, the early combination of CS with immunosuppressants obtained better outcome, compared the other
patients who were administered with CS alone [20, 21]. In this study, the patients treated with CS alone - which was correlated with a higher CYFRA21-1 level - leaded to worse prognosis.

It is well known that DM associated ILD can be divided into RPILD and Non-RPILD based on its pathological progression [22, 23]. The prognosis of a subset of patients with RPILD complicating anti-MDA5-positive DM, is extremely poor, compared with Non-RPILD [24–27]. In clinical practice, intensified immunomodulators including CS pulsed doses in combination with tacrolimus/cyclosporine and/or IVCY, are sometimes used in DM-ILD patients, especially in RPILD [28, 29].

Tacrolimus/cyclosporine as calcineurin inhibitor suppresses expression of interleukin (IL)-2 to reduce the activation of T cells [30]. T cells and alveolar macrophages play an important role in anti-MDA5-positive DM-ILD pathogenesis [10, 31]. CTX mainly suppresses the function of B cells for treatment of DM-ILD [32]. Thus, a combined therapy of various immunomodulators can significantly increase the risk of infection. Although intensified immunosuppressive therapy is considered as necessary for RPILD complicating DM, the evidence of benefit is not conclusive. A previous study showed that early commencement of a regimen therapy including CS, cyclosporine and IVCY may be more efficacious for those patients with RPILD [33]. Early treatment of cyclosporine should be effective to control disease progression of HRCT and improve the survival in DM-ILD [21]. A previous study demonstrated that intensified immunosuppressive treatment with CS, tacrolimus, and IVCY improve survival of anti-MDA5-positive DM/CADM-ILD patients with well-tolerated adverse events [27]. However, our results indicated that anti-MDA5-positive DM-RPILD patients couldn’t obtain better efficacious with a combined regimen (CS, tacrolimus/cyclosporine and IVCY). There was no difference at 6-month survival between treatment with tacrolimus/cyclosporine and combination therapy with tacrolimus/cyclosporine and IVCY in anti-MDA5-positive DM-RPILD patients. In contrast, combination therapy with tacrolimus/cyclosporine and CS was shown to be superior to the combination of tacrolimus/cyclosporine, IVCY and CS in Non-RPILD patients. Non-RPILD patients administered with tacrolimus/cyclosporine, which was associated with a significantly lower ESR and CYFRA21-1 levels, -had better prognosis. Furthermore, such patients using single agent such as tacrolimus or cyclosporine, in addition CS, could reduce long-term adverse reactions and obtained better outcome. Thus triple intensive immunosuppressive therapy was not necessary in anti-MDA5-positive DM Non-RPILD in our study.

Overall, we assessed the relationship between intensive immunosuppressive regimen and 6-months survival in anti-MDA5 positive DM-ILD patients. However, there were several limitations in our study. First, other therapies such as plasmapheresis could not be applied generally in subjects due to rarity of plasma. Second, our ability to perform serial analysis of immunosuppressive regimen was limited due to the small study cohort, which was understandable in view of the rarity of anti-MDA5 positive DM-ILD. Third, this was a retrospective single-center study, so it was uncertain whether or not our results could be generalised to the entire population of patients with anti-MDA5 positive DM-ILD. A large-scale prospective trial would be helpful to confirm our results.
Summary, we showed the early administration of immunosuppressants was important in anti-MDA5 positive DM-ILD. The triple regimen (CS, tacrolimus/ cyclosporine and CTX) were not necessary in Chinese anti-MDA5-positive DM Non-RPILD patients. Further investigations were needed to find an additional effective and safe therapy.

**Abbreviations**

Anti-MDA5: anti-melanoma differentiation-associated gene; RP-ILD: rapidly progressive interstitial lung disease; CS: Corticosteroid; IVCY: intravenous cyclophosphamide HRCT: High-Resolution CT; OP: organizing pneumonia

**Declarations**

**Ethics approval and consent to participate:**

Not applicable.

**Consent for publication:**

All author give consent to publish.

**Availability of data and material:**

The data used to support the findings of this study are available from the corresponding author upon request

**Competing interests:**

The authors have declared no conflicts of interest.

**Funding**

Not applicable.

**Authors’ contributions:**

Yonglong Xiao conceived and designed the study. Xianhua Gui, ShenyunShi and Tingting Zhao collected and analyzed the data. Yuying Qiu and Min Yu contributed to analysis tools. Xianhua Gui wrote the paper. Xiaoyan Xin was a radiologist. The diagnosis of ILD patterns of interstitial pneumonia was based on radiological assessment of the chest HRCT results in the manuscript.

Miao Ma, Jingjing Ding, Lulu Chen, Xiaohua Qiu, Yingwei zhang, Min Cao and Mei Huang were responsible for the data collection in the manuscript.
Mengshu Cao, Jinghong Dai and Hourong Cai assisted with revising our poor language in the manuscript carefully.

All authors reviewed the manuscript critically and agreed upon publication.

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**Figures**

![Proportions of patients receiving various treatments](image)

**Figure 1**

Proportions of patients receiving various treatments (%) CS: corticosteroid; IVCY: intravenous cyclophosphamide
Figure 2

Kaplan-Meier survival method were used to assess the prognosis of patients underwent different treatment. 6-month survival of CS alone-treated was significantly lower than those treated with CS combined immunosuppressors (p<0.01; Fig. A). Compared with patients treated with CS combined tacrolimus/cyclosporine and IVCY, survival at 6 months was significantly better in the patients treated with CS combined tacrolimus/cyclosporine (p<0.01; Fig. B).

Figure 3

Kaplan-Meier survival curves for the tacrolimus/cyclosporine-treated and tacrolimus/cyclosporine combined IVCY-treated in RPILD and Non-RPILD patients. Survival at 6 months in Non-RPILD patients was significantly better in the tacrolimus/cyclosporine-treated group than in the tacrolimus/cyclosporine
combined IVCY-treated group ($p<0.05$; Fig. A). No difference was observed in 6 months survival of RPILD patients between two groups ($p=0.138$; Fig. B).

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