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Running head: tofacitinib in MDA5-ILD

A Retrospective Analysis of Outcome in MDA5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus

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Conflicts of interest

The authors have declared no conflicts of interest

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OBJECTIVES: The efficacy of tofacitinib in early diagnosis of MDA5-ILD has been described. But whether tofacitinib exposure is associated with a reduced one-year mortality remains undetermined.

METHODS: Patients diagnosed as MDA5-ILD receiving tofacitinib or tacrolimus treatment were included. Cox proportional hazards model adjusted for age, sex, smoking history, anti-MDA5 antibody titers, concurrent use of other steroids sparing agents was performed to compare all-cause mortality and to investigate the risk factors predicting 1-year mortality in the two treatment groups.

RESULTS: During the study period, twenty-six patients were treated with tofacitinib and thirty-five with tacrolimus. The 6-month and 1-year mortality in tofacitinib group were significantly lower than those in tacrolimus group(38.5% vs. 62.9%, p=0.028; 44.0% vs. 65.7%, p=0.031， respectively). There were thirteen patients diagnosed as rapidly progressive-ILD(RPILD) in tofacitinib group and twenty-two in tacrolimus group. The majority of death occurred in patients with RPILD. The 6-month and 1-year mortality of patients with RPILD in tofacitinib group were also lower than those in tacrolimus group(76.9% and 95.5%, p=0.021; 84.6% and 100.0%, p=0.017). The adjusted model showed tofacitinib exposure was associated with a lower risk for 1-year mortality (HR0.438, 95%CI0.200-0.960, p=0.039). While the incidence of adverse events and medication discontinuation rates between the two groups were similar (73.1% and 74.3%, p=1.000; 23.1% and 14.3%, p=0.504).

CONCLUSIONS: Our observational study showed tofacitinib use might have a potential impact on improving the outcomes of MDA5-ILD. Future clinical trials are needed to assess the long-term efficacy and tolerability of tofacitinib.

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1.Introduction

Idiopathic inflammatory myopathies(IIM) are a heterogeneous spectrum of systemic autoimmune diseases which affect multiple organs other than skeletal muscle[1,2]. Interstitial lung disease (ILD) is the most common and severe extra-muscular manifestation contributing significantly to morbidity and mortality in patients with IIM[3,4]. Typically, the adult-onset IIM phenotypes encompass polymyositis (PM), dermatomyositis(DM), amyopathic DM(ADM) and antisynthetase syndrome(ASS). Advancement in the knowledge of myositis-specific auto-antibodies(MSAs) had enabled clinicians better understanding IIM patients with distinctive clinical phenotypes [5]. For instance, patients with ASS have similar clinical presentations, including myositis, ILD, arthritis, mechanic's hands, and Raynaud's phenomenon; however, recent studies suggested heterogeneity in clinical features among different aminoacyl tRNA synthetases antibody-positive patients. Anti-Jo-1 antibody-positive patients have more myositis and arthritis, whereas anti-PL7 or anti-PL12 antibody-positive patients have a higher rate of ILD and higher mortality[6,7]. Anti-Mi-2 is associated with classic DM skin rash, good response to steroid treatment and good prognosis[8]. In recent years, much attentions have been focused in anti-melanoma differentiation-associated gene 5(MDA5) antibody for its closely associations with a rapidly progressive ILD(RPILD), a life-threatening phenotype which was resistant to conventional therapy[9-11].

The management of MDA5-related interstitial lung disease(MDA5-ILD) is a huge challenging. High-dose glucocorticoids, calcineurin inhibitors cyclosporine or tacrolimus, combined with cyclophosphamide was recommended as the first choice to treat MDA5-ILD[12]. Despite the aggressive therapy, the short-term mortality of MDA5-ILD was up to 50%[13]. Tofacitinib, a Janus kinase(JAK) inhibitor, has exhibited an excellent response in early-stage anti-MDA5-positive AMD-ILD in a single-center, open-label clinical study[14]. Prior literature also reported its efficacy as a rescue option for patients at high-risk ADM related ILD(ADM-ILD) refractory to conventional treatment[13] . However, to date, few studies investigated the impact of tofacitinib on survivals in patients with MDA5-ILD. We performed this retrospective study to determine the relationships of tofacitinib exposure with one-year mortality in MDA5-ILD. Patients with MDA5-ILD who were seen in our center and treated with tofacitinib were recruited. Patients treated with tacrolimus during the study period were served as a comparator control. Moreover, we investigated the risk factors predicting the mortality in patients with MDA5-ILD in two treatment group.

2.Method

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2.1Subjects

The medical records of patients diagnosed as anti-MDA5 autoantibody positive IIM-ILD in Nanjing University medical school affiliated Drum Tower Hospital from October 2017 to December 2020 were reviewed. Patients who received a combination treatment of systemic corticosteroids and Tofacitinib or Tacrolimus for at least 6 months were identified. Switching from another immunosuppressant to tofacitinib or adding tofacitinib to the initial treatment was allowed if it occurred within 1month from the therapy initiation. Patients who concurrently received tofacitinib and tacrolimus treatment were excluded. All patients were diagnosed with ILD for less than 6 months. IIMs were diagnosed according to 2017 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria[15]. ILD was diagnosed based on a combination of clinical manifestations, physical examination and high-resolution computed tomography(HRCT) abnormalities according to the guideline[16]. RPILD was defined when worsening of respiratory symptoms combined with new emerging of radiologic interstitial abnormalities in chest HRCT within 1 month with exclusion of an identified causes such as acute heart failure or pulmonary embolisms in the first 12 months from diagnosis[17,18].This study was approved by the Ethics Committee of Nanjing University Medical School Affiliated Drum Tower Hospital according to the policy. (protocol number 2022-067-02, March 28, 2022).

2.2 Clinical data

The clinical data including demographics, laboratory examinations, radiographic findings and treatments were extracted from reviewing the medical records. The demographic information included age of onset, gender and smoking history. Laboratory examinations included PaO2, PaO2/FiO2, the counts of white blood cell(WBC), the counts of neutrophil, neutrophil percentage, the counts of lymphocyte, lymphocyte percentage, the counts of red blood cell(RBC), hemoglobin, the counts of platelet(PLT), alanine aminotransferase(ALT), aspartate aminotransferase(AST), lactate dehydrogenase (LDH), albumin, globulin, urea nitrogen, serum creatinine, the values of C-reactive protein(CRP), creatine kinase(CK), creatine kinase isoenzyme(CKMB), ferritin, erythrocyte sedimentation rate(ESR), D-dimer, etc. Baseline pulmonary function tests(PFTs) if available were recorded including forced vital capacity(FVC), FVC% predicted, diffusing capacity of the lung for carbon monoxide(DLCO) and DLCO% predicted.

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All patients were performed myositis-associated antibodies profiles detection and had anti-MDA5 antibody positivity. In our center, the following antibody were routinely measured including anti-MDA5, anti-Mi-2α, anti-Mi-2β, anti-TIF1γ, anti-NXP2, anti-SAE1, anti-Ku, anti-PM-Scl100, anti-PM-Scl75, anti-SRP, anti-RO-52 and anti-synthetase antibody including anti-Jo1, anti-PL7, anti-PL12, anti-EJ and anti-OJ. The titers of anti-MDA5 antibody were detected by Western blotting; the detection film strip was placed in the result judgment template, and LineScan software was used to evaluate the gray values. The results were defined as negative with gray value of 6-15; weak positive, 15-50; moderate positive, 50-100; and strong positive, >100. Medications were recorded including systemic corticosteroids and other immunosuppressants including cyclophosphamide, hydroxychloroquine, azathioprine and tripterygium wilfordii and so on.

Chest HRCT were performed in 59 patients in supine position at diagnosis and two patients underwent chest HRCT at other hospitals within one week before admission. All images were reviewed independently by one experienced radiologist and one pulmonary specialist. Based on the proposed guidelines[16,19], HRCT appearances were mainly described as usual interstitial pneumonia(UIP) pattern, nonspecific interstitial pneumonia(NSIP) pattern, organizing pneumonia(OP) pattern, and diffuse alveolar damage(DAD) pattern.

Adverse events(AEs) that occurred after 5 days of tacrolimus or tofacitinib treatment were recorded as therapies related adverse events, which included cytopenia, digestive tract reactions, liver and renal dysfunction, infections, thrombosis and so on.

2.3 Follow-up data

The vital status was obtained through review of medical records and telephone follow-up. The survival time was calculated from the first HRCT indicating the diagnosis of ILD to all-cause deaths. Clinical outcomes including 6-month and 1-year mortality were recorded. The follow-up was ceased until December 2021.

2.4 Statistical analysis

Statistical analysis was performed by SPSS software version 22.0 and Graphpad Prism 8.0. All analysis were two-sided, and the level of significance was set at $P<0.05$. Qualitative data were presented as numbers and percentage, and quantitative data as mean and standard deviation(SD) or median and interquartile range(IQR). The normality of the data was assessed by the Shapiro-Wilk. For comparison clinical data, Student's t test, Chi-square analysis, Fisher's exact test and the Mann-

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Whitney U test were conducted as appropriate. The Kaplan–Meier curve with log rank test was used to access differences in survival. Two treatment groups were compared using a Cox proportional hazards model adjusted for confounding factors(time-to-event analyses). The following confounding factors were taken into account in comparisons between groups: age of onset, sex, smoking history, anti-MDA5 antibody titers, and concurrent use of other steroid-sparing agents. Cox proportional hazards model was also performed to assess the risk factors predicting the mortality in two treatment groups.

3.Results

3.1 Baseline characteristics

Through reviewing the medical records, 26 patients who received tofacitinib treatment were identified. 35 patients who received initial treatment with tacrolimus during the study period were served as a comparator group. The demographic and baseline clinical features were presented in Table 1. No significant differences were observed regarding age, gender, and smoking history. The mean age in tacrolimus group was 55.94±1.72 years old while in tofacitinib group was 55.42±2.20 years old. 15(57.7%) patients were female in tofacitinib group and 22(62.9%) in tacrolimus group. There were 4 (15.4%) and 7(20.0%) patients reported having a smoking history in tofacitinib and tacrolimus group, respectively. No significant differences were observed in the baseline laboratory examinations including PaO2/FiO2, LDH, CRP, CK, ferritin, ESR and so on. And the baseline pulmonary function testing including FVC, FVC% predicted, DLCO and DLCO% predicted also had no differences. 13(50.0%) patients were diagnosed with RP-ILD in tofacitinib group and 22(62.9%) in tacrolimus group. At treatments initiation, the constitution of anti-MDA5 antibody titers differed between the two groups, with more weak positive patients (16/26, 61.5%) in tofacitinib group than in tacrolimus group (9/35, 25.7%, p=0.002). The number of patients with weak, moderate, and strong positive anti-MDA5 antibody titers in tofacitinib group were 16, 6, and 4, and in tacrolimus group were 9, 9 and 17, respectively. There were 18(69.2%) patients concomitantly positive for anti-RO52 antibody in tofacitinib group and 17(48.6%) in tacrolimus group(p=0.124). In both groups, the most common HRCT findings was OP pattern(61.5% and 69.7%).

3.2 Treatment information

The initial glucocorticoids doses had no differences in the two groups(p=0.882). In tofacitinib group, the initial glucocorticoids dose was 152.88±19.04 mg/d(range 35-500 mg/d), and in tacrolimus

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group was 185.86±26.05 mg/d(range 15-500 mg/d). The tofacitinib dose was 5 mg once in two patients and twice daily in 24 patients. Tacrolimus was administered orally 2-4 mg daily. The concurrent use of other steroid-sparing agents had no significant difference(61.5% and 65.7%, p=0.792). The mean maintenance glucocorticoid dose in tofacitinib group was 6.69±1.49 mg daily, and in tacrolimus group was 5.42±1.06 mg daily(p=0.497). The duration of glucocorticoids tapering from the initial treatment to a maintenance dosage was 12.06 ± 1.74 months in tofacitinib group and 15.96 ± 2.36 months in tacrolimus group(p=0.196). The medication discontinuation rate due to adverse sides in tofacitinib group was 23.1%(6/26) and in tacrolimus group was 14.3%(5/35)(p=0.504).

3.3 Survival analysis

The mean follow-up time was 11.62±1.72(range 0.23-48.60) months. There were 23(65.7%) deaths in tacrolimus group with a mean survival of 11.52±2.65(range 0.23-48.60) months, compared with 12(46.2%) deaths in tofacitinib group with a mean survival 11.76±1.95(range 0.27-28.07) months. The 6-month all-cause mortality in tofacitinib group and tacrolimus group were 38.5% and 62.9% (p=0.028), and the 1-year mortality were 44.0% and 65.7%(p=0.031), respectively. (Figure 1). After adjustment for age, sex, smoking history, anti-MDA5 antibody titers, and concurrent use of other steroid-sparing agents, Cox proportional hazards model showed tofacitinib exposure was associated with a lower risk of 1-year mortality(Hazard Ratio[HR]0.438, 95% confidence interval[CI]0.200-0.960, p=0.039).

We compared the mortalities in the RPILD patients in both treatment groups(Table 2). There were 22 patients diagnosed with RPILD in tacrolimus group and 13 in the tofacitinib group, respectively. RPILD patients in tofacitinib group had higher PLT(p=0.040) and ESR levels(p=0.014) than those in tacrolimus group. The proportion of patients with weak anti-MDA5 antibody positive(8/13, 61.5%) was more in tofacitinib group than that in tacrolimus group(6/22, 27.3%, p=0.010). No differences were found in other baseline laboratory examinations, PFTs, initial glucocorticoids dosages, and concurrent use of other steroid-sparing agents. Both the 6-month and 1-year all-cause mortality of patients with RPILD in tofacitinib group were significantly reduced compared to those in tacrolimus group were(76.9%(10/13) vs 95.5%(21/22) p=0.021; 84.6%(11/13) vs. 100.0%(22/22) p=0.017, respectively). After adjusted for confounding factors, Cox proportional hazards model showed tofacitinib exposure was associated with a lower risk of 1-year mortality (HR 0.248, 95% CI 0.068-

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0.905, p=0.035).

3.4 Comparison between survivors and non-survivors in two treatment groups

We further performed subgroup analysis between survivors and non-survivors in two treatment groups(Supplemental table S1 and S2). In tofacitinib group, the non-survivors were older than the survivors(p=0.040); and PaO2/FiO2(p=0.003), lymphocyte percentage(p=0.037) and albumin(p=0.049) were significantly lower in non-survivors group than those in survivors group, while WBC(p=0.024), neutrophils(p=0.016), PLT(p=0.012), CRP(p=0.019) and ESR(p=0.001) were significantly higher in non-survivors than those in survivors. All the non-survivors were RPILD. There was no significant difference in anti-MDA5 antibody titers(p=1.000) and concurrent use of other steroid-sparing agents (8/12,66.7% and 8/14,57.1%) between the two groups(p=0.701). In tacrolimus group, compared to the survivors, non-survivors were older(p=0.001), had higher neutrophils percentage(p=0.012), ALT (p=0.019), AST(p=0.028), CKMB(p=0.006), D-dimer(p=0.012) and ferritin(p=0.044) levels at baseline, and reduced PO2(p=0.049), PaO2/FiO2(p=0.001), lymphocyte percentage(p=0.003), lymphocytes (p=0.001), albumin(p<0.001) and globulin(p=0.041) levels. NSIP was more common in survivors(4.8% vs 33.3%, p=0.047). 95.7%(22/23) of non-survivors were RPILD. There were no significant differences in anti-MDA5 antibody titers(p=0.418) and concurrent use of other steroid-sparing agents(15/23, 65.2% and 8/12, 66.7%) between the two groups(p=1.000).

Among non-survivors in tofacitinib group, the mean survival time was 2.18±0.57(range 0.27-12.73) months. Univariate analysis showed that older age(HR 1.073, 95%CI 1.010-1.039), decreased PaO2/FiO2 ratio(HR 0.989, 95%CI 0.982-0.996), increased WBC(HR 1.277, 95%CI 1.056-1.543), increased neutrophils(HR 1.305, 95%CI 1.065-1.599), decreased lymphocyte percentage(HR 0.889, 95%CI 0.796-0.993), increased CRP(HR 1.028, 95%CI 1.008-1.047), increased ESR(HR 1.045, 95%CI 1.018-1.073), and presence of RPILD(HR 184.488, 95%CI 1.065-31961.148) were predictors of mortality. Among non-survivors in the tacrolimus group, the mean survival time was 1.67±0.48 (range 0.23-11.03) months. Univariate analysis showed that older age(HR 1.039, 95%CI 1.007-1.072), decreased PaO2/FiO2 ratio(HR 0.993, 95%CI 0.989-0.997), decreased lymphocyte percentage(HR 0.878, 95%CI 0.0.810-0.951), decreased albumin(HR 0.803, 95%CI 0.707-0.913), increased CKMB (HR 1.041, 95%CI 1.001-1.082), increased ferritin(HR 1.006, 95%CI 1.001-1.011) and presence of RPILD(HR 41.127,95%CI 5.244-322.561) were predictors of mortality. Due to the large number of covariates and the small sample size, multivariate analysis could not be achieved for both groups.

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3.6 Adverse events

The overall incidences of adverse events had no significant differences between the two groups (19/26, 73.1% and 26/35, 74.3%, p>0.050). The observed adverse events included liver and kidney dysfunction, lymphocytopenia, anemia, diarrhea, reactivation of cytomegalovirus(CMV) and Epstein-Barr virus(EBV), herpes zoster, sepsis, pulmonary fungal infections, pulmonary bacterial infections, intermuscular vein thrombosis and pulmonary thrombosis. The most common adverse event was liver damage in both two groups (16/26, 61.5% and 23/35, 65.7%).

The detailed therapies related infections were described in Table 3 and 4. In tacrolimus group, there were eleven(31.4%) patients detected the evidence of infection. The blood 1,3-β-D glucan tests (referred to as G test)(>151.5pg/ml) were positive in five patients (patient 1, 2, 4, 7 and 8). Among them, three patients had new emerging HRCT abnormalities and blood galactomannan antigen detection (referred to as GM test)(>0.5) was also positive in one patient(patient 7). Sputum culture showed candida in two patients with abnormal chest images(patient 6 and 9). All these seven patients had received antifungal therapy including fluconazole, voriconazole and sulfamethoxazole(SMZ) and three of them were required tacrolimus discontinuation(patient 2, 4 and 7). Besides, Pseudomonas aeruginosa in patient 10, Acinetobacter baumannii in patient 11, had been found in sputum culture accompanied with abnormal chest images and both of patients received broad-spectrum antibiotics treatment, neither survived. Three patients were diagnosed with oral Candida infection based on oral leukoplakia and candida in sputum culture(patient 2, 4 and 5). EBV DNA was positive(>500IU/ml) in four patients(patient 5, 6, 7 and 8) and one patient had shingles(patient 3).

In tofacitinib group, there were eleven(42.3%) patients detected the evidence of infection. Five patients were clinically considered to have pulmonary fungal infection(patient 1, 5, 9, 10 and 11). Two patients had a positive G or GM test with the evidences of tissue biopsy or high-throughput sequencing of bronchoalveolar lavage fluid results proven the fungal infection(patient 1 and 9). Two patients had a positive G or GM test with new emerging HRCT abnormalities(patient 5 and 11). Patient 10 had a sputum culture of Aspergillus fumigatus with abnormal chest images. All five patients had received antifungal therapy including fluconazole, voriconazole, SMZ, caspofungin, posaconazole, amphotericin B and three of them discontinued tofacitinib treatment(patient 1, 5 and 9). Among them, one patient survived and four patients died. Additionally, oral Candida infection were diagnosed in two patients (patient 2 and 7) and EBV reactivation occurred in two patients(patient 1 and 3) and CMV reactivation

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(confirmed by blood detection of CMV DNA over 500IU/ml) in three patients(patient 1, 4 and 6). Two patients had herpes zosters(patient 2 and 4). One patient(patient 8) had developed pulmonary infection which progressed to severe sepsis and died despite combined antibacterial therapy with Imipenem/Cilastatin and Vancomycin. The mean duration from treatment initiation to occurrence of infection was 30.50±7.66 days(range 5.50-43.50 days) in tofacitinib group and 53.18±25.57 days(range 7.00-74.00 days) in tacrolimus group($p>0.050$).

Patients in tofacitinib group more likely had lymphocytopenia(10/26, 38.5%) compared to patients in tacrolimus group(5/35, 14.3%)($p=0.039$). And one case of renal dysfunction was noted in each group. Two cases of diarrhea and one case of anemia were observed in the tacrolimus group. One case of pulmonary embolism was observed in the tacrolimus group and one case of intermuscular vein thrombosis of both lower extremities was observed in tofacitinib group. Non-AEs were observed in 7(26.9%) and 9(25.7%) patients in tofacitinib group and tacrolimus therapy group, respectively.

4.Discussion

This observational study showed that the 6-month and 1-year all-cause mortality of MDA5-ILD patients treated with tofacitinib were significantly lower than those treated with tacrolimus. Adjusted Cox proportional hazards model showed tofacitinib exposure was associated with a lower risk of 1-year mortality. This therapeutic effect maintained in patients with RPILD. While the incidence of adverse events and the medication discontinuation rates were similar. To our knowledge, this study had the largest cohort to assess the impact on survival and adverse events of tofacitinib in patients with MDA5-ILD.

Anti-MDA5 antibody-positive IIM-ILD is a challenging disease with impressively high short-term mortality[10,11]. Ochi et al. found that tacrolimus was markedly effective in decreasing the serum KL-6 level and radiographic improvement[20]. In a retrospective study, tacrolimus usage was associated with the decrease dose of both glucocorticoids and other disease-modifying antirheumatic drugs[21]. A multicenter, single-arm, 52-week-long clinical trial showed that initial treatment with tacrolimus and glucocorticoids may improve short-term mortality of PM/DM-ILD patients with a 52-week survival rate of 88%[22]. Furthermore, tacrolimus had up to 100-fold stronger inhibitory effect on T cell proliferation and cytokine production than cyclosporine in vitro studies[23]. Another Japanese study also showed that the addition of tacrolimus could significantly prolonged the event-free survival in PM/DM-ILD patients[24]. Recently, in a prospective multicenter, open-label, randomized, 52-week phase

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2 trial, of 58 PM/DM-ILD patients, 30 patients received glucocorticoids plus tacrolimus treatment and 28 patients received glucocorticoids plus cyclosporine treatment, the final progression-free survival rate at 52 weeks was 87% in the tacrolimus group, that was significant higher compared to 71% in the cyclosporine group and the FVC % increased significantly in both groups[25].

Tofacitinib has been used in several autoimmune diseases[26] including rheumatoid arthritis[26], inflammatory bowel disease[27], psoriasis[28], vitiligo[29] and etc. Many studies had reported its roles in improving the symptoms of skin, muscles, and joints in patients with dermatomyositis[30-32]. In a recent clinical trial[14], all 18 patients with MDA5-ILD receiving a glucocorticoid combined with tofacitinib had an overwhelming survival advantage compared to patients who received conventional therapy. Further, the ferritin level, PFTs and HRCT findings in tofacitinib group were also considerably improved over time with the low grade adverse events. In another study, additional tofacitinib were prescribed to five patients with MDA5 -ILD who failed to respond to conventional triple therapy, three of them survived and two died[13]. Consistently, our study showed that tofacitinib was beneficial for the 6-month and 1-year survivals even in patients with RPILD. More patients with weak positive were in tofacitinib compared to those in tacrolimus group, which could partly explain our results. In addition, the small sample sizes between the two groups did not matched owing to the retrospective nature. Moreover, because patients with anti-MDA5 antibody combined with anti-RO52 antibody positivity had more severe clinical phenotypes and worse prognosis compared to those who had an isolated anti-MDA5 antibody positive[33], but in our study the frequency of anti-RO52 antibody in two treatment groups had no differences. Further well-designed multi-centers study is indeed anticipated to confirm the efficiency of tofacitinib and to identify the subtype patients who could best benefit from the treatment of tofacitinib.

A number of case series have been published reporting the beneficial effects of biological agents and small molecules in MDA5-ILD. Yamaguchi et al. reported one case with anti-MDA5 positive RP-ILD who failed to conventional immunosuppressive treatment responded to rituximab[34]. In another study, four patients with anti-MDA5 positive RPILD received additional rituximab after failed to respond to combination immunosuppressant therapy[35], all 4 patients had survived with their respiratory symptoms and lung function improvements. The HRCT findings had improved in three of them and remained stable in one patient. Plasmapheresis and polymyxin B hemoperfusion may also be used as rescue options to treat refractory cases[36,37]. A study[36] reported that six patients who received

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plasmapheresis had significantly better one-year survival than those who did not(100% and 25%). Plasmapheresis was also performed to patients with active infectious disease who were immunocompromised by intensive immunosuppressive therapy[36]. In our study, one RPILD survivor in tofacitinib group underwent four plasmapheresis sessions successfully and was discharged. Moreover, Veno-venous extracorporeal membrane oxygenation(VV-ECMO) was considered in critical cases to win the opportunity for lung transplantation[38,39].

The study had several limitations including the retrospective nature, the indication bias, which might lead to overestimating or underestimating the efficacy of the medication. Besides, few patients had re-performed lung function tests due to the short follow-up time, which could not demonstrate the longitudinal changes of physiology. And the concurrent use of other steroids-sparing agents precluded an evaluation of the specific benefit of tofacitinib or tacrolimus as monotherapy. In spite of these limitations, because a majority of fatalities may occur within one year from the onset of ILD and the disease trend to stabilize after one year, we assessed the impact of tofacitinib on six-month and one-year all-cause mortality of MDA5-ILD patients.

In conclusion, this observational study showed that tofacitinib use was associated with a benefit of six-month and one-year survival in MDA5-ILD patients and even in MDA5-RPILD patients while not increasing the risks of adverse effects. Future well-designed multi-centers randomized control trials are anticipated to assess the long-term efficacy and tolerability of tofacitinib in MDA5-ILD.

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Table1. Baseline characteristics and differences between tofacitinib group and tacrolimus group

	Tofacitinib group （n=26）	Tacrolimus group （n=35）	*P* value
Age of onset(mean±SD)-yr	55.42±2.20	55.94±1.72	.853
Female sex-n(%)	15(57.7%)	22(62.9%)	.793
History of smoking-n(%)	4(15.4%)	7(20.0%)	1.000
CADM-n(%)	17(65.4%)	26(74.3%)	.572
RPILD-n(%)	13(50.0%)	22(62.9%)	.600
Laboratory findings			
PO2(mean±SD)-mmHg	77.28±4.16	74.28±3.68(n=33)	.680
PaO2/FiO2(mean±SD)	265.77±19.01	277.57±18.49(n=33)	.658
LDH (mean±SD)-U/L	354.85±20.44	388.62±24.81(n=34)	.298
CRP (mean±SD)-mg/L	20.89±5.17(n=25)	18.60±4.65(n=33)	.744
CK (mean±SD)-U/L	70.62±9.53	74.88±11.30(n=32)	.774
ESR (mean±SD)-mm/h	44.36±5.05(n=25)	37.53±4.04(n=30)	.296
Ferritin level (median, IQR)-ng/ml	1425.90(764.00-1650.00)(n=8)	1305.55(508.63-1641.38)(n=10)	.549
D-dimer (median, IQR)-ng/ml	0.64(0.43-1.21)	0.96(0.48-1.60) （n=31）	.186
Constitution of Anti-MDA5 antibody titers			.002
Weak positive-n (%)	16(61.5%)	9(25.7%)	
Moderate positive-n (%)	6(23.1%)	9(25.7%)	

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Strong positive-n (%)	4(15.4%)	17(48.6%)	
Anti-Ro52 antibody positivity-n (%)	18(69.2%)	17(48.6%)	.124
Pulmonary function tests			
FVC (mean±SD)	2.20±0.35(n=12)	1.91±0.19(n=16)	.475
FVC-% of predicted value(mean±SD)	60.41±5.60(n=12)	57.16±4.42(n=16)	.654
DLCO (mean±SD)	4.65±0.87(n=9)	3.98±0.49(n=13)	.509
DLCO-% of predicted value(mean±SD)	59.86±9.76(n=9)	54.55±6.39(n=13)	.656
HRCT findings			
OP pattern-n(%)	16(61.5%)	23(69.7%)(n=33)	.585
NSIP pattern-n(%)	2(7.7%)	5(15.2%)(n=33)	.449
UIP pattern -n(%)	0(0.0%)	1(3.0%)(n=33)	1.000
DAD pattern-n(%)	2(7.7%)	0(0.0%)(n=33)	.190
DAD/OP overlapping pattern-n(%)	5(19.2%)	4(12.1%)(n=33)	.488
OP/NSIP overlapping pattern-n(%)	1(3.8%)	0(0.0%)(n=33)	.441
Therapy			
Initial GC dosage (mean±SD)-mg/d	152.88±19.04	185.86±26.05	.882
Maintenance dose of GC (mean±SD)-mg/d	6.69±1.49(n=14)	5.42±1.06(n=12)	.497
The duration of GC tapering(mean±SD)-months	12.06±1.74	15.96±2.36	.196
Concurrent use of other steroid-sparing agents -n(%)	16(61.5%)	23(65.7%)	.792
Tac and Tof discontinuation-n(%)	6(23.1%)	5(14.3%)	.504

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6-month mortality	10(38.5%)	22(62.9%)	.028
1-year mortality	11(44.0%)	23(65.7%)	.031

CADM: clinical amyopathic dermatomyositis; RP-ILD: rapidly progressive interstitial lung disease; LDH: lactate dehydrogenase; CRP: C-reactive protein; CK: creatine kinase; ESR: erythrocyte sedimentation rate; MDA5: anti-melanoma differentiation-associated gene 5; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; OP: organizing pneumonia, UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; DAD: diffuse alveolar damage; GC: glucocorticoids; Tac: tacrolimus; Tof: tofacitinib. Statistical significance was set at p-value < 0.05.

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Table 2. Baseline characteristics and differences between tofacitinib group and tacrolimus group with RPILD

	Tofacitinib group （n=13）	Tacrolimus group （n=22）	*P* value
Age of onset(mean±SD)-yr	59.23±10.75	60.05±9.10	.821
Female sex-n(%)	8(61.5%)	13(59.1%)	1.000
History of smoking-n(%)	2(25.4%)	6(27.3%)	.680
CADM-n(%)	8(61.5%)	15(68.2%)	.726
Laboratory findings			
PO2(median, IQR)-mmHg	64.00(48.00-101.00)	70.00(50.00-93.00) （n=21）	.937
PaO2/FiO2(mean±SD)	202.45±85.73	240.13±96.63(n=21)	.246
PLT (mean±SD)-*10^9/L	247.85±84.61	185.18±79.02	.040
LDH (mean±SD)-U/L	400.92±118.49	416.95±105.42	.691
CRP (median, IQR)-m/L	20.30(1.60-92.00)	9.65(2.10-107.90)	.200
CK (median, IQR)-U/L	57.00(20.00-169.00)	62.00(20.00-346.00)(n=20)	.993
ESR (median, IQR)-mm/h	64.00(23.00-95.00)	30.00(8.00-80.00)(n=19)	.014
Ferritin level (median, IQR)-ng/ml	1421.95(354.00-1650.00)(n=6)	1464.50(617.70-1650.00)(n=8)	.950
D-dimer (median, IQR)-ng/ml	0.89(0.25-2.18)	1.29(0.42-8.15)	.209

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Constitution of Anti-MDA5 antibody titers			.010
Weak positive-n (%)	8(61.5%)	6(27.3%)	
Moderate positive-n (%)	4(30.8%)	4(18.2%)	
Strong positive-n (%)	1(7.7%)	12(54.6%)	
Anti-Ro52 antibody positivity-n (%)	9(69.2%)	11(50.0%)	.312
Pulmonary function tests			
FVC (mean±SD)	1.85±0.94(n=4)	1.99±0.83(n=6)	.819
FVC-% of predicted value(mean±SD)	52.68±14.89(n=4)	56.73±20.07(n=6)	.724
DLCO (mean±SD)	6.22±1.51(n=2)	3.61±1.50(n=5)	.183
DLCO-% of predicted value(mean±SD)	80.40±21.35(n=2)	51.60±20.37(n=5)	.257
HRCT findings			
OP pattern-n(%)	5(38.5%)	14(70.0%)	.148
NSIP pattern-n(%)	1(7.7%)	1(5.0%)	1.000
UIP pattern -n(%)	0(0.0%）	1(5.0%）	1.000
DAD pattern-n(%)	2(15.4%)	0(0.0%)	.148
DAD/OP overlapping pattern-n(%)	4(30.8%）	4(20.0%）	.681
OP/NSIP overlapping pattern-n(%)	1(7.7%)	0(0.0%)	.394
Therapy			
Initial GC dosage (median, IQR)-mg/d	160.00(40.00-500.00)	160.00(20.00-500.00)	.424
Concurrent use of other steroid-sparing agents -n(%)	8(61.5%)	14(63.6%)	1.000

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Tac and Tof discontinuation-n(%)	2(15.4%)	3(13.6%)	1.000
6-month mortality	10(76.9%）	21(95.5%）	.021
1-year mortality	11(84.6%)	22(100.0%)	.017

RPILD: rapidly progressive interstitial lung disease; CADM: clinical amyopathic dermatomyositis; PLT: platelets; LDH: lactate dehydrogenase; CRP: C-reactive protein; CK: creatine kinase; ESR: erythrocyte sedimentation rate; MDA5: anti-melanoma differentiation-associated gene 5; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; OP: organizing pneumonia, UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; DAD: diffuse alveolar damage; GC: glucocorticoids; Tac: tacrolimus; Tof: tofacitinib. Statistical significance was set at p-value < 0.05.

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Table3. The therapy related infections in patients with MDA5-ILD treated with tacrolimus

patients	Age-years	initial GC dose(mg/d)	Tacrolimus dose(mg/d)	Other treatments	infection	Anti-infective therapy	Tac discontinuation	outcome
Patient 1/M	54	80	2	IVIG	Pulmonary fungal infection	fluconazole	N	Died
Patient 2/F	60	40	2	-	Oral candida infection、Pulmonary fungal infection	SMZ、fluconazole	Y	Died
Patient 3/F	70	80	2	-	Herpes zoster	-	N	Alive
Patient 4/F	48	160	4	IVIG	Oral candida infection、Pulmonary fungal infection	SMZ、Caspofungin、fluconazole	Y	Died
Patient 5/F	86	20	2	-	Oral candida infection、EBV DNA（+）	fluconazole	N	Died

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Patient 6/M	57	500	2	IVIG	Pulmonary fungal infection、EBV DNA（+）	Caspofungin、Ganciclovir	N	Died
Patient 7/F	56	160	3	-	Pulmonary fungal infection、EBV DNA（+）	voriconazole	Y	Died
Patient 8/M	49	500	4	IVIG	Pulmonary fungal infection、EBV DNA（+）	SMZ	N	Died
Patient 9/F	54	160	4	IVIG	Pulmonary fungal infection	fluconazole	N	Died
Patient 10/F	74	160	2	-	Pulmonary bacterial infection（pseudomonas aeruginosa）	Imipenem/Cilastatin	N	Died
Patient 11/F	68	240	4	PE、IVIG	Pulmonary bacterial infection（Acinetobacter baumannii）	Imipenem/Cilastatin 、linezolid	N	Died

IVIG: intravenous immunoglobulin; PE: plasma exchange; SMZ: sulfamethoxazole; Tac: tacrolimus; GC: glucocorticoids.

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EBV DNA positivity was referred as the detection of more than 500IU/ml of DNA of Epstein-Barr virus in the blood.

Pulmonary fungi infection was defined as a new high-resolution computed tomography(HRCT) abnormality (new pulmonary nodules) plus an elevated G test or GM test of blood or fungi in sputum culture, with or without histopathological biopsy.

Oral candida infection was defined as an oral leukoplakia plus candida in sputum culture.

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Table4. The therapy related infections in patients with MDA5-ILD treated with tofacitinib

patients	Age-years	initial GC dose(mg/d)	Tofacitinib dose(mg/d)	Other treatments	infection	Anti-infective therapy	Tof discontinuation	outcome
Patient 1/M	53	160	10	-	Pulmonary fungal infection 、 CMV DNA（+）、 EBV DNA（+）	Ganciclovir、Caspofungin、 voriconazole、posaconazole、 amphotericin B	Y	Alive
Patient 2/F	67	80	10	-	Oral candida infection、 Herpes zoster	-	N	Alive
Patient 3/F	45	160	10	-	EBV DNA（+）	Ganciclovi	N	Alive
Patient 4/M	47	40	5	PE、IVIG	CMV DNA （＋）、 Herpes zoster	Ganciclovi	N	Alive
Patient	41	160	5	IVIG	Pulmonary fungal	SMZ	Y	Died

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5/M					infection			
Patient 6/F	58	80	10	-	CMV DNA（+）	-	N	Alive
Patient 7/M	57	35	10	-	Oral candida infection	fluconazole	N	Alive
Patient 8/M	46	240	10	PE、IVIG、pirfenidone	Sepsis (Hemolytic staphylococcus)	Imipenem/Cilastatin、vancomycin	N	Died
Patient 9/M	65	80	10	IVIG	Pulmonary fungal infection	voriconazol	Y	Died
Patient 10/F	68	160	10	IVIG	Pulmonary fungal infection	voriconazol	N	Died
Patient 11/M	48	240	10	-	Pulmonary fungal infection	voriconazol	N	Died

IVIG: intravenous immunoglobulin; PE: plasma exchange; SMZ: sulfamethoxazole; Tof: tofacitinib; GC: glucocorticoids.

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CMV DNA positivity was referred as the detection of more than 500IU/ml of DNA of cytomegalovirus in the blood.

EBV DNA positivity was referred as the detection of more than 500IU/ml of DNA of Epstein-Barr virus in the blood.

Pulmonary fungi infection was defined as a new HRCT abnormality (new pulmonary nodules) plus an elevated G test or GM test of blood or fungi in sputum culture, with or without histopathological biopsy.

Oral candida infection was defined as an oral leukoplakia plus candida in sputum culture.

Sepsis was defined as bacteremia plus clinically systemic infectious manifestation.

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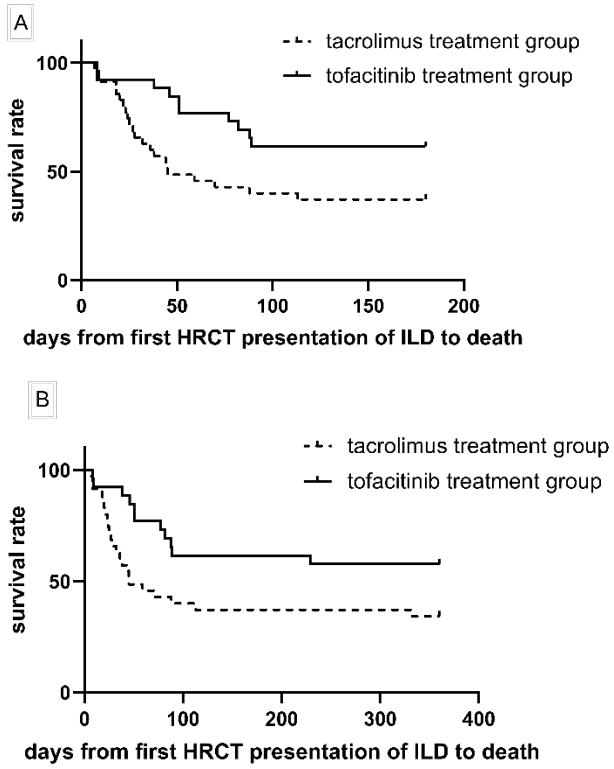

Figure1. The 6-month and 1-year survival curves of patients with MDA5-ILD treated with tofacitinib or tacrolimus.

(A)The 6-month mortality in tofacitinib group was 38.5% and in tacrolimus group was 62.9% (log-rank, p=0.028). (B)The 1-year mortality in tofacitinib group were 44.0% and in tacrolimus group was 65.7% (log-rank, p=0.031). Time was represented in days. HRCT: high-resolution computed tomography; ILD: interstitial lung disease.

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