

Case study of tocilizumab in the treatment of dermatomyositis-associated interstitial lung disease

Zhimin Wang, Zheng Zhang, Caixia Sun*

The Affiliated Hospital of Hebei University, Baoding, China

*Corresponding author: bdsuncaixia@163.com

Abstract: Dermatomyositis (DM) complicated by rapidly progressive interstitial lung disease (RP-ILD) is a type of connective tissue disease (CTD) with rapid disease progression and high mortality. Traditional treatment regimens such as glucocorticoids, cyclophosphamide, and calcineurin inhibitors are available, and some of them are not effective. Tocilizumab is an IL-6 receptor (IL-6R) antagonist that is widely used to improve the symptoms and signs of autoimmune diseases as a commonly used drug in the treatment of connective tissue diseases such as rheumatoid arthritis and Takayasu's arteritis. Related studies have shown that it has a certain efficacy in alleviating the acute response of connective tissue disease-associated interstitial lung disease (CTD-ILD). This may be related to the increased levels of IL-6, KL-6, and serum ferritin in ILD. In this paper, we report two cases of successful treatment of dermatomyositis complicated with interstitial lung disease with tocilizumab, and review the literature to explore the diagnosis and treatment experience of DM ILD and further explore its potential mechanism.

Keywords: Dermatomyositis; Pulmonary interstitial fibrosis; Tocilizumab

1. Introduction

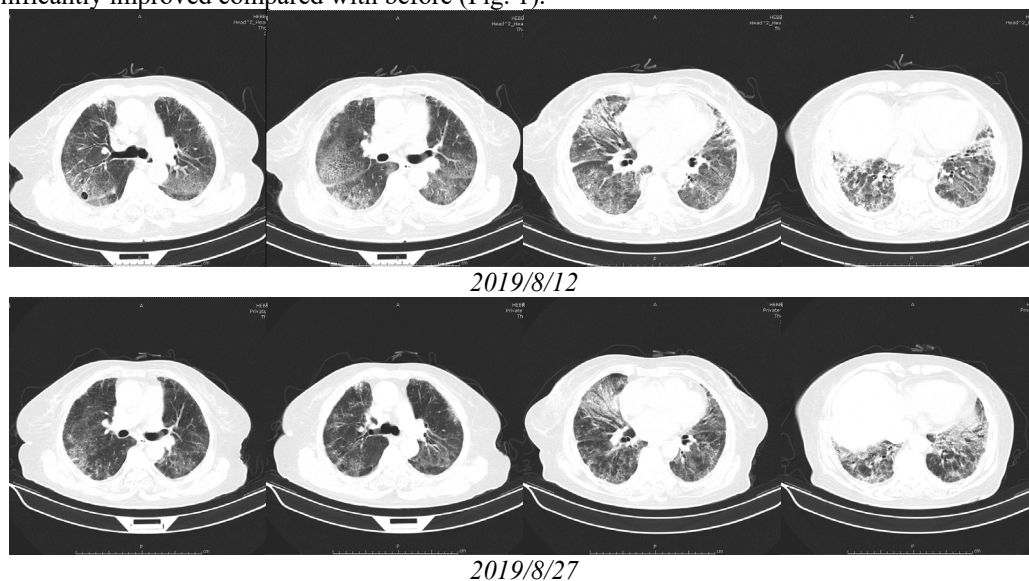
Dermatomyositis (DM) is a common inflammatory myopathy in clinical practice, which often manifests as purple-red skin edematous rash, myalgia, muscle weakness, arthralgia, fever, etc., which can involve multiple organs and have a high risk of tumors [1]. Interstitial lung disease (ILD) is the most common complication in patients with dermatomyositis, with an incidence of about 23.1% to 65% [2] and is an important factor affecting the prognosis. Most patients with DM have a chronic onset (> 3 months), some patients have an acute onset, and a small number of patients have a rapid and progressive exacerbation of lung imaging within 3 months, accompanied by progressive dyspnea, hypoxemia, and even acute respiratory failure, which is called rapidly progressive ILD (RP-ILD). Patients with DM and RP-ILD have a poor prognosis, with more than half of patients dying within three months of onset, even with high-dose corticosteroids combined with cyclophosphamide and calcineurin [3,4]. Early identification of disease conditions and early detection of clinical changes are crucial, and exploring feasible treatment options are urgent problems to be solved in clinical work. In this paper, two successful cases of tocilizumab in the treatment of DM ILD are introduced, and the purpose of this article is to explore the experience of diagnosis and treatment of DM and further explore its potential mechanism.

2. Case data

2.1 Case 1

The patient, a 73-year-old female, was admitted to the Department of Cardiology of the Affiliated Hospital of Hebei University on August 11, 2019 due to shortness of breath for more than 20 days after activity. In mid-July 2019, the patient had suffocation and shortness of breath after activity without obvious causes, could not tolerate general physical activity, accompanied by cough and sputum production, and self-administration of "isosorbide dinitrate" was not relieved. Laboratory tests on admission showing Cardiac enzymes: LDH 269U/L, CK, CK-MB were normal; TG 2.67mmol/L; Normal renal function and electrolytes; Fasting blood glucose 10.7mmol/L; FIB 5.52g/L, D-dimer in 1.09mg/L; NTproBNP 707pg/ml; Ferritin: 354.2ng/ml; Cardiac ultrasound: left atrial enlargement, slightly widening of the ascending aorta, aortic valve degeneration with a small amount of regurgitation, small amount of regurgitation of the mitral and tricuspid valves, pulmonary hypertension (about 40 mmHg). Left ventricular diastolic function is reduced. Cardiac CTA: multiple calcified plaque formations in the coronary arteries. Pulmonary artery CTA: no clear signs of embolism. Multiple lesions in both lungs.

Pulmonary function: The patient did not cooperate well, and the pulmonary diffusion function could not be measured by repeated measurements. (1) Moderate to severe restrictive ventilatory dysfunction, (2) Small airway ventilatory dysfunction, (3) Severe decline in MVV. CT of the chest: interstitial fibrosis of both lungs with infection, pericardial thickening, multiple lymph nodes in the mediastinal space, partial enlargement, follow-up is recommended. Bilateral pleural thickening, bilateral pleural effusion. ECG: sinus rhythm, normal electrical axis. Blood gas analysis: PH 7.43, PCO₂ 38mmHg, PO₂ 56mmHg, SAT 90%, BE 0.9mmol/L, LAC(T) (1) 1mmol/L (oxygenation index 266.7mmHg). Consider (1) Pulmonary embolism? (2) For coronary atherosclerotic heart disease, ceftriaxone sodium, low molecular weight heparin, aspirin and other treatments are given. The patient's shortness of breath symptoms worsened after activity, and the antinuclear antibody was further tested positive cytoplasmic granule type 1:320, anti-RO-52 antibody positive, IgG 16.60g/L; Complement assay, ASO, and RF were normal; Negative for ANCA and autoantibodies. Combined with rheumatology consultation, the patient has been diagnosed DM, with rough skin on the extensor side of the proximal interphalangeal joints of both hands and elbows for more than 10 years. He was transferred to the Department of Rheumatology for further treatment on 14 August 2019. Physical examination: P 104 times/min, R 26 times/min, BP 165/83mmHg, SPO₂ 55%, poor mental health, rough radial surface of both hands, suspicious Gottron rash on both proximal interphalangeal joints, extensor sides of both elbows, strained breathing, The lips are slightly cyanotic, the breath sounds in both lungs are low, fissures can be heard, the muscles of the joints are not tender, the muscle strength test of the limbs cannot be cooperated, and the muscle tone is normal. On August 14, blood gas analysis (oxygen mask 10L/min) was :P CO₂ 35mmHg, PO₂ 67mmHg, SAT 94%, and LAC(T) 2.7 mmol/L. Complete blood count::WBC 15.34*10⁹/L,HGB 85g/L,PLT 444 *10⁹/L;Further tests showed ESR 127mm/h, CRP 133.1mg/L, myositis antibody spectrum, positive anti-EJ antibody, positive anti-PL-12 antibody, positive anti-SSA/Ro antibody, and positive anti-SAE1 antibody. Modified diagnosis: dermatomyositis pulmonary interstitial fibrosis with infection type I respiratory failure, the following course of treatment is given: methylprednisolone (MP) 40 mg, once a day (1 day), adjusted to 40 mg twice a day (for 13 days), as well as meropenem, low molecular weight heparin, ambroxol and other treatments, the patient's chest tightness and shortness of breath still progressively worsened, and the resting state felt suffocation, and the oxygenation index was reduced to 78.7mmHg at the lowest, and he refused to be transferred to the ICU. On August 21, 2019, Professor Tian Xinping of Peking Union Medical College Hospital was invited to consult, and recommended the addition of tocilizumab, intravenous human immunoglobulin, and tacrolimus for treatment. On August 22, 2019, tocilizumab 480 mg (8 mg/kg) intravenously and tacrolimus 3 mg orally once a day, and on August 23, 2019, intravenous human immunoglobulin 20 g was given once a day (for 5 consecutive days). The patient's suffocation and shortness of breath gradually improved, and the oxygenation index rose to 172mmHg on August 27, 2019. On August 27, chest CT showed that the changes in the lung interstitium were better than before, and the dose of methylprednisolone was reduced to 48mg orally once a day on August 28. Subsequently, the patient was treated with tocilizumab 480mg on August 29, September 5, and September 16, respectively, and the inflammatory indicators gradually decreased. In September 2019, pirfenidone was added, and the patient continued to take oral methylprednisolone (reduced to 8 mg once a day) and tacrolimus, and her condition was stable, and the lung CT lesions were significantly improved compared with before (Fig. 1).



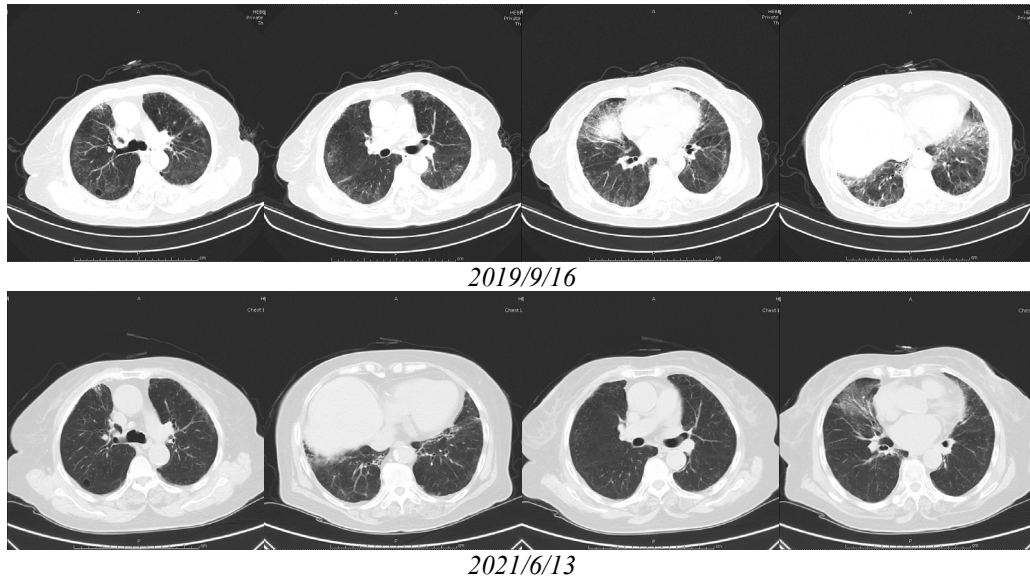


Figure 1: Case 1: Changes in chest CT images

2.2 Case 2

The patient, a 30-year-old male, was admitted to the hospital on April 8, 2021 due to skin rash for 4 months, pain and weakness all over the body, weakness for more than 3 months, and shortness of breath for 1 month. The patient had no obvious cause of rash 4 months before admission, manifested as patchy congestive rash on the extensor side of the proximal interphalangeal joints of both hands, extensor joints of both elbows, and lateral thighs on both sides, slightly higher than the skin surface, covered with scales, partially ulcerated, without obvious pain and itching, accompanied by hoarseness, and anti-allergic treatment (specifics unknown) was given by the hospital, and the effect was not good. Half a month later, he developed multi-joint pain, accompanied by muscle soreness and weakness in the limbs, and slight restriction of heavy lifting. On January 29, 2021, he was admitted to a hospital in Baoding City, and chest CT was examined: multiple small lymph nodes in the mediastinum and bilateral axilla. Diagnosis of "psoriatic arthritis", given "methotrexate 10mg once a week, hydroxychloroquine sulfate 0.2g twice a day, diclofenac sodium enteric-coated tablets 25mg 3 times a day" treatment, the patient's joint pain and rash slightly improved. At the beginning of February 2021, his hands turned purple when exposed to cold, flaky erythema on his face, and obvious hair loss. In early March, he developed dysphagia, worsening muscle weakness in the limbs, difficulty raising his head and getting up when lying flat, accompanied by intermittent cough, palpitations, shortness of breath, and limited brisk walking on flat ground. On April 1, he had intermittent fever, with a maximum body temperature of 39.0 °C, accompanied by chills and excessive sweating, and the clinic kept "azithromycin" for 6 days, but there was no improvement. He was admitted to our hospital for further diagnosis and treatment. On admission examination: T 38.2°C, hoarseness, puffiness of both eyelids, (Fig. 2) patchy congestive rash on the extensor side of the 2nd and 3rd metacarpophalangeal joints of both hands, extensor joints of both elbows, and lateral thighs on both sides, slightly higher than the skin surface, covered with scales, and partially ulcerated. Pharyngeal congestion, weak breath sounds in both lungs, no dry and wet rales, positive tenderness in the metacarpophalangeal joints of both hands, proximal interphalangeal joints, and metatarsophalangeal joints of both wrists, knees, and feet, no obvious swelling, and no edema in both lower limbs. Mild tenderness in the proximal muscles of the limbs, V-level muscle strength in the limbs. Laboratory tests on admission: Liver function + cardiac enzymes:CK 415U/L,HBDH 346U/L,LDH 566U/L,GGT 116U/L,AST 123U/L,ALT 76U/L,ALB 29g/L;Arterial blood gases:PH 7.45,PCO₂ 27mmHg,PO₂ 110.0mmHg,SaO₂ 98.5%,LAC 0.9mmol/L;ESR 91mm/h;CRP 28.5mg/L;Complement, RF, and anti-CCP antibodies were normal;ANCA negative; ANA spectrum: ANA positive, nuclear granular type 1:100, cytoplasmic granular type 1:100, anti-R0-52 antibody positive, remaining negative; Electromyography: bilateral deltoid polyphasic narrow potentials, denervation potentials in the left deltoid muscle, and no obvious abnormalities were found. CT chest (13 April 2021): interstitial changes in both lungs. Exudation from both lungs. Fatty liver. Myositis antibody spectrum: anti-MDA-5 antibody IgG positive (53AU), anti-SSA/RO52 antibody IgG positive (100AU), remaining negative. Diagnosis: dermatomyositis (positive anti-MDA5 antibody) pulmonary interstitial fibrosis with infection, methylprednisolone 80mg once a day intravenous point, ceftazidime, oxygen and other treatments. The

patient's appetite improved, dysphagia, limb weakness, rash, and shortness of breath were all improved, but the new oral mucosal leukoplakia further improved the sputum culture: *Pseudomonas aeruginosa*+, *Candida albicans* growth+; PJT 220.10pg/ml, blood culture, T-SPOT negative. On April 12, intravenous human immunoglobulin 20 g was given intravenously once a day (for 3 days), tacrolimus 1 mg orally twice a day on April 19, fluconazole 0.4 g once a day, and tocilizumab 480 mg on April 15 and April 29, respectively. Chest CT was re-examined on April 30: 1. Interstitial changes in both lungs. 2. Exudation from both lungs. 3. Gas in the mediastinum. 4. Pneumosis in the soft tissues of the neck and bilateral thoracic cage. 5. Fatty liver. Compared with 2021-4-19, the mediastinum and the new gas density shadows in the neck and bilateral thoracic soft tissues were compared. The partial pressure of oxygen was rechecked at 70mmHg, and treatment such as symptomatic oxygen inhalation was followed, followed by tocilizumab 480mg (a total of 5 times) on May 13, June 10, and August 8, respectively, and pirfenidone 400mg 3 times a day on May 14, 2021. At present, the patient's methylprednisolone dose was reduced to 6 mg once a day, and oral tacrolimus and other treatments were continued, and the chest CT showed that the lung lesions were significantly reduced compared with the previous (Fig. 3).



Figure 2: Cutaneous manifestations

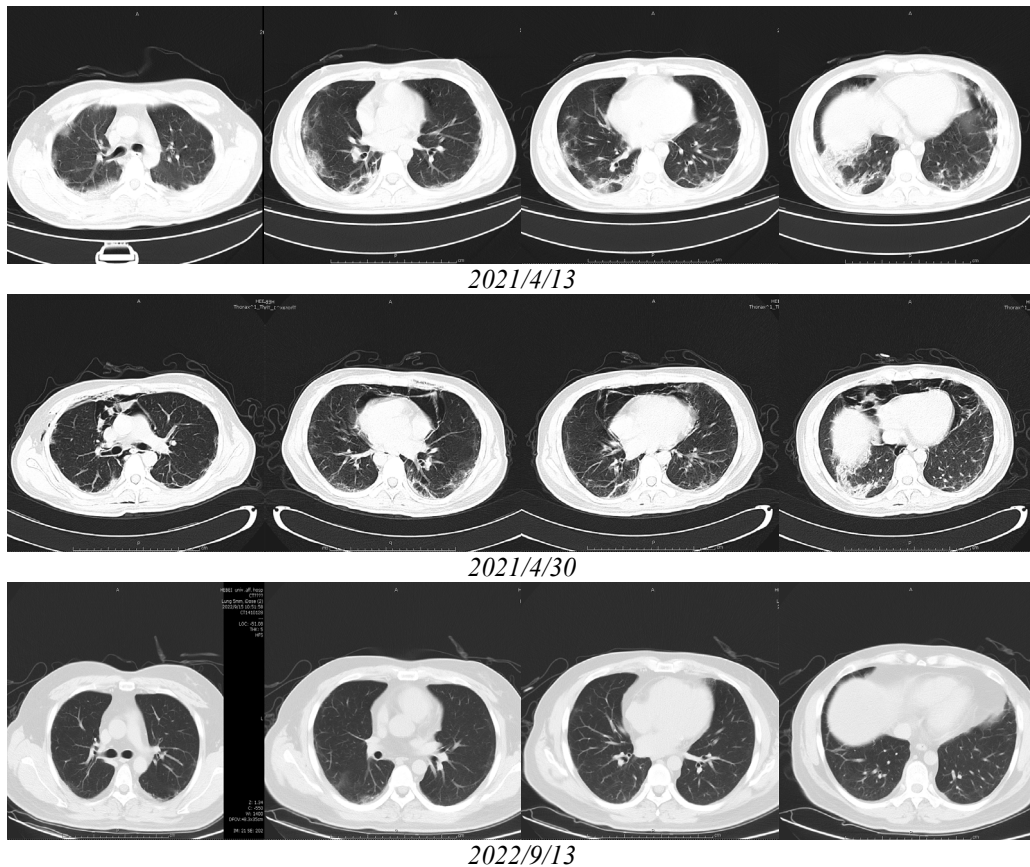


Figure 3: Case 2: Chest CT image changes

3. Discuss

DM is easy to misdiagnose and miss, and the first department may be dermatology, neurology, respiratory, cardiology, etc. The first department of the above two cases was in another department, and there was a misdiagnosis at first. After rheumatology consultation, combined with clinical manifestations, it is recommended that further examination of myositis antibody profiling confirm the diagnosis. Myositis autoantibodies are important indicators for predicting the course of DM, the probability of interstitial pneumonia and the prognosis of the disease. Different antibodies predict different clinical manifestations, among which autoantibodies closely related to the development of ILD in dermatomyositis include anti-aminoacyl tRNA synthetase (ARS) antibody and anti-melanoma differentiation-related gene 5 (MDA-5) antibody. Anti-ARS antibodies include anti-Jo-1, anti-OJ, anti-EJ, anti-PL-7, anti-PL-12, anti-KS and other antibodies. Among them, anti-MDA5 antibodies are associated with rapidly progressive lung stromal lesions and severe skin lesions (skin ulcers), which are often associated with poor prognosis, and prominent imaging features are ground-glass changes, consolidation, and mediastinal emphysema [5]. Hospitalization and mortality rates are 94 percent [2], and patients should be closely monitored for lung imaging changes during treatment. This case was positive for anti-EJ antibody, anti-PL-12 antibody and anti-MDA-5 antibody, respectively. The rapid development of interstitial lung lesions and severe disease led to the development of emphysema in case 2, a rare but fatal complication of DM-associated ILD, caused by the spread of ruptured air in the alveoli along the lungs to the mediastinum and subcutaneous tissues. It is more common in patients with dermatomyositis who do not respond well to conventional treatments. Kono et al. [6] analyzed alveolar rupture in cases of mediastinal emphysema that may be associated with vasculitis, as patients who develop mediastinal emphysema tend to have severe skin lesions. Treatment is mainly active treatment of the primary disease and interstitial pneumonia, requiring high-dose corticosteroids combined with immunosuppressants, such as cyclosporine, and immunoglobulin (IVIG) if necessary. Patients with high volume of gas can die due to acute cardiac insufficiency and should be treated surgically. In this case, the patient had dermatomyositis combined with mediastinal emphysema, with mild clinical symptoms and stable vital signs, so the treatment was mainly given bed rest, oxygen inhalation, and treatment of the underlying disease, and the emphysema was gradually absorbed and improved. In addition, it has been reported in the literature [7] that several biomarkers, including ferritin, IL-6, IL-18, and KL-6 levels, can be used as indicators of disease activity and can be monitored during clinical diagnosis and treatment.

In the treatment of dermatomyositis, glucocorticoids and immunosuppressants (including methotrexate, cyclophosphamide, tacrolimus, azathioprine, etc.) are preferred, and the initial treatment regimen is combined with a strengthening regimen. For MDA5+ dermatomyositis-ILD, a "triple therapy" is advocated, in which high-dose glucocorticoids, calcineurin inhibitors, and intravenous cyclophosphamide are combined, and JAK inhibitors combined with glucocorticoids are the mainstream therapies [5]. It has a certain effect on the prognosis of patients, but the risk of secondary infection and leukopenia is high, and patients are often prone to co-infection with pulmonary interstitial lesions when they are hospitalized, which increases the difficulty of treatment. For patients with refractory cases or co-infection, the addition of IVIG therapy may be an option. In addition to the use of immunosuppressants, antifibrotic drugs (eg, pirfenidone, nintedanib) have potential benefits for patients [8]. However, a high level of evidence is urgently needed for more effective and safe regimens for refractory cases, especially rapidly progressive pulmonary interstitial lesions.

The pathogenesis of dermatomyositis-related interstitial pneumonia is still unclear, and the combined effects of multiple factors such as genetic basis, autoantibodies, immune cells, and cytokines may be involved in the pathogenesis of DM-ILD. Serum levels of ferritin, IL-6, IL-8, IL-10, and KL-6 have been reported to be higher in RP-ILD than in non-rapidly progressive pulmonary interstitial lesions [7,9]. Activation of pro-inflammatory cytokines provides new therapeutic targets. Biologics for DM-ILD have been reported to include JAK inhibitors, anti-CD20 monoclonal antibodies, anti-IL-1, TNF antagonists, and anti-IL-6 [10-14].

IL-6 is a pleiotropic cytokine that regulates immune response and inflammatory response, and regulates the proliferation and differentiation of a variety of immune cells. IL-6 induces increased leukocyte and platelet production in the bone marrow, stimulates the release of C-reactive protein (CRP) and acute-phase markers from hepatocytes, increases erythrocyte sedimentation rate (ESR), activates neutrophils and macrophages, and leads to the differentiation of T helper cells into type 17 T helper cells (Th17) [15]. It is a useful target for a variety of autoimmune diseases and plays a role in inducing and maintaining immune inflammation in autoimmune diseases [16]. Tocilizumab is an IL-6 receptor antagonist, and many studies have shown that tocilizumab blocking the treatment of IL-6R can not only significantly improve the symptoms and signs of autoimmune diseases, but also alleviate its acute

reactions. At present, tocilizumab has been approved for rheumatoid arthritis, juvenile idiopathic arthritis, Takayasu's arteritis, etc., and has achieved good results [17], and the exploration, promotion and application of tocilizumab are ongoing. Khanna D et al. [18], a phase III clinical trial, confirmed the long-term safety and efficacy of tocilizumab in the treatment of interstitial lung disease associated with early systemic sclerosis. Tocilizumab for the treatment of dermatomyositis-related pulmonary interstitial lesions is an off-label drug and is rarely reported. According to the literature, Kondo M et al. [19] successfully treated a 32-year-old female with refractory dermatomyositis complicated with RA by tocilizumab, which not only had a significant effect on joint swelling and pain, but also alleviated the symptoms of rash and myalgia, and the muscle enzymes were also reduced to normal. Lu Z et al. [20] reported a case of NXP2-positive dermatomyositis that was significantly reduced by tocilizumab treatment. Fei Teng et al. [21] reported that tocilizumab was successfully applied to a 63-year-old female with anti-MDA5-positive rapidly progressive pulmonary interstitial lesions, and the patient was intubated to assist breathing due to pulmonary lesions. Zhang X et al. [22] also summarized that 6 patients with anti-mda5-positive DM with RP-ILD who did not respond well to conventional combination immunosuppressant therapy and recovered after tocilizumab (TCZ) treatment. C-F Su et al. [23] reported a case of anti-MDA5+ dermatomyositis complicated with macrophage activation syndrome, which was treated with tocilizumab, which not only relieved the symptoms of MAS, but also significantly improved the rash. Based on the above literature reports, the treatment of tocilizumab in the above two cases showed significant improvement in lung interstitial lesions.

4. Conclusions

In patients with symptoms such as muscle weakness, rash, and dyspnea, it is recommended to check creatine kinase, myositis antibody spectrum, chest CT, etc., to screen for dermatomyositis as soon as possible and diagnose and treat it as soon as possible. For interstitial lung disease associated with dermatomyositis, tocilizumab may be a salvage treatment option when traditional glucocorticoids and immunosuppressants are not effective, and the long-term clinical efficacy and adverse reactions need to be further observed, and more clinical trials are needed to verify it.

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