Scandinavian Journal of Rheumatology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/irhe20

Tocilizumab and rituximab for anti-MDA-5 positive amyopathic dermatomyositis complicated with macrophage activation syndrome and progressive fibrosing interstitial lung disease

C-F Su, H-T Liao & C-Y Tsai

To cite this article: C-F Su, H-T Liao & C-Y Tsai (2021): Tocilizumab and rituximab for anti-MDA-5 positive amyopathic dermatomyositis complicated with macrophage activation syndrome and progressive fibrosing interstitial lung disease, Scandinavian Journal of Rheumatology, DOI: 10.1080/03009742.2021.1972519

To link to this article: https://doi.org/10.1080/03009742.2021.1972519

LETTER

Tocilizumab and rituximab for anti-MDA-5 positive amyopathic dermatomyositis complicated with macrophage activation syndrome and progressive fibrosing interstitial lung disease

C-F Su[1], H-T Liao[1,2,3], C-Y Tsai[1,2]

[1]Division of Allergy, Immunology and Rheumatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[2]School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
[3]Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

Anti-melanoma differentiation-associated protein-5 (MDA-5) antibody-positive dermatomyositis is frequently complicated by progressive fibrosing interstitial lung disease (PF-ILD), which is associated with acute respiratory failure, with an extremely high mortality rate (1). Macrophage activation syndrome (MAS) is a life-threatening condition in which uncontrolled activation of lymphocytes and macrophages, and thus the secretion of large amounts of inflammatory cytokines, leads to cytokine storm (2). Herein, we present the case of a patient with anti-MDA-5 amyopathic dermatomyositis patient with MAS and PF-ILD. After sequential treatment with tocilizumab and rituximab for MAS and PF-ILD, the patient no longer required oxygen supplementation and was discharged from hospital smoothly.

A 50-year-old man presented to our rheumatology clinic with a 1 month history of dyspnoea on exertion and skin eruptions in June 2017. Physical examination disclosed inverse Gottron's sign with painful purpuric flat skin lesions on the palmar aspect of the proximal and distal interphalangeal joints, scaling and ulcerations at the digital pulp (Figure 1A), and periungual erythema (Figure 1B). Serial evaluation disclosed high-titre MDA-5 antibody, elevated lactate dehydrogenase and alanine aminotransferase, and mild lymphocytic infiltration in muscle biopsy, but normal serum concentration of creatine phosphokinase. Pulmonary function tests revealed reduced forced vital capacity (FVC, 69% predicted value). Computed tomography (CT) of the chest found subpleural interlobular septal thickening (Figure 1E). A diagnosis of anti-MDA-5 antibody-positive amyopathic dermatomyositis with ILD was made. He received monthly steroid pulse therapy (methylprednisolone 1000 mg/day for 3 days) three times and one course of intravenous immunoglobulin (IVIG, 0.4 g/kg/day for 3 days), followed by maintenance prednisolone combined with one disease-modifying anti-rheumatic drug at a time, namely, hydroxychloroquine (400 mg/day), azathioprine (100 mg/day), or mycophenolic acid (360 mg/day). The skin lesions persisted, while lung function deteriorated gradually, warranting home oxygen therapy.

He was hospitalized in late July 2018 because of high fever and pancytopenia. The diagnosis of MAS was made based on fever, splenomegaly, elevated levels of ferritin and triglyceride, decreased level of fibrinogen, and evidence of haemophagocytosis in a bone marrow specimen. Infectious diseases, including cytomegalovirus and tuberculosis, were excluded after a comprehensive work-up. Extremely elevated ferritin (143 543 ng/mL), leucopenia (1200 cells/mm^3), anaemia (haemoglobin level of 7.2 g/dL), and thrombocytopenia (7000 cells/mm^3) developed despite steroid pulse therapy, mycophenolic acid, and IVIG. Tocilizumab 8 mg/kg was administered intravenously in four fractions as salvage therapy, followed by maintenance therapy with prednisolone and cyclosporine (100 mg/day). Cyclosporine was chosen as it was one of the main agents proposed by the HLH-2004 protocol (3). The medication dosage is shown chronologically in Figure 1H. Both haematological abnormalities and skin lesions dramatically improved (Figure 1C and D) and he was discharged on day 76.

Owing to increasing oxygen demand, CT of the chest disclosed progressive subpleural reticulation with traction bronchiectasis and patchy ground-glass opacities in January 2019 (Figure 1F). Pulmonary function tests revealed a further decline in FVC (42% of predicted value). Bronchoalveolar lavage fluid analysis showed lymphocytosis without micro-organisms. Anti-MDA-5 antibody-associated PF-ILD was diagnosed. Three doses of rituximab 1000 mg were administered, one each in January, February, and September 2019. The patient was weaned off home oxygen therapy from April 2019. The dosage of prednisolone was tapered to 5 mg/day in combination with cyclosporine from June 2019. The FVC increased to 49% in September 2019 and to 68% in December 2020. CT of the chest in October 2020 also showed dramatic regression of ILD (Figure 1G).

MAS is a life-threatening complication in patients with rheumatic diseases and has been reported in only six

DOI: https://doi.org/10.1080/03009742.2021.1972519

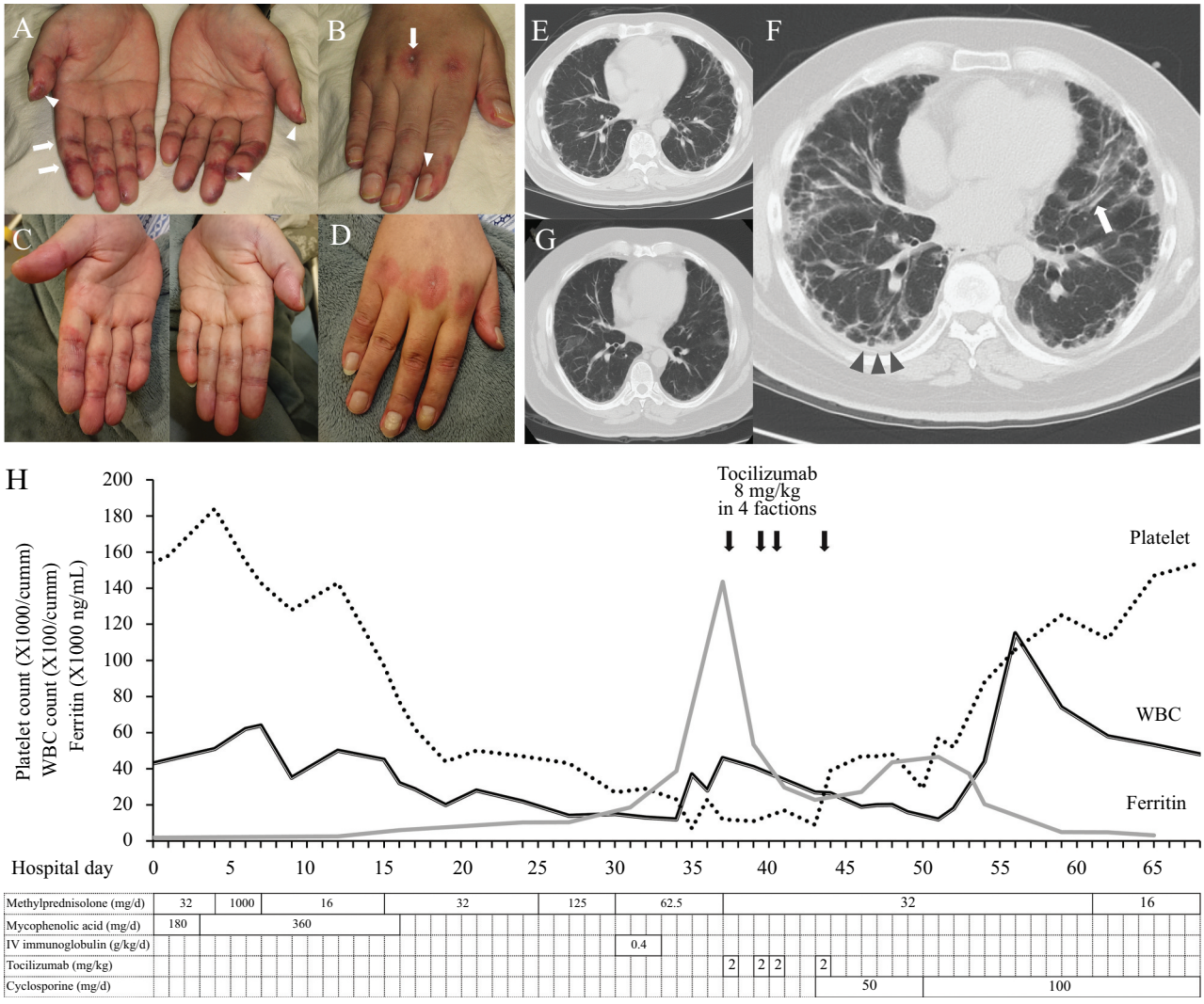

Figure 1. (A) Inverse Gottron's sign on the palmar aspect of the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints (arrows) and digital scaling with ulcerations (arrowheads). (B) Gottron's papules with ulcerations (arrows) and periungual erythema (arrowheads). (C, D) Regression of skin lesions after treatment with tocilizumab. (E) Computed tomography (CT) of the chest in April 2018. (F) Progression of subpleural reticulation (arrowheads) with traction bronchiectasis (arrows) with small patchy ground-glass opacities on CT of the chest in January 2019. (G) CT of the chest in October 2020 showed regression of interstitial lung disease after treatment with three doses of rituximab since January 2019. (H) Laboratory data and medications used during the hospital course from July to October in 2018 for macrophage activation syndrome. The hyperferritinaemia, leucopenia, and thrombocytopenia all improved after administration of tocilizumab.

patients with anti-MDA-5 antibody-positive dermatomyositis (4). Based on the experience in treating juvenile idiopathic arthritis and adult-onset Still's disease, interleukin-6 blockade with tocilizumab has been used in a limited number of patients with MAS (2, 5). In our patient, tocilizumab induced a rapid and sustained clinical remission of MAS and, surprisingly, the cutaneous lesions as well. Regarding PF-ILD in anti-MDA-5-positive dermatomyositis, combination therapy with high-dose glucocorticoids, a calcineurin inhibitor, and intravenous cyclophosphamide has been proposed by several study groups (1, 6). Rituximab has been used as an add-on therapy to glucocorticoid, mycophenolate, and/or cyclophosphamide, with varying response (1). Zhang et al suggested tocilizumab as a salvage therapy for refractory anti-MDA-5 antibody-associated ILD (7). In our patient, tocilizumab resolved MAS but not the process of PF-ILD. After adding rituximab, the radiological finding of ILD as well as lung function significantly improved.

To the best of our knowledge, this is the first report of the successful treatment of MAS and skin lesions with tocilizumab in a patient with anti-MDA-5-positive amyopathic dermatomyositis. The therapeutic effect of rituximab or sequential therapy with tocilizumab and rituximab in anti-MDA-5 antibody-associated PF-ILD warrants further investigation.

Acknowledgements

The authors thank the patient for the permission to report this case. The report was approved by the Institutional Review Board of Taipei

Veterans General Hospital (IRB-TPEVGH no 2019-07-008CC#2). The patient's written informed consent was obtained.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

1. Romero-Bueno F, Diaz Del Campo P, Trallero-Araguás E, Ruiz-Rodríguez JC, Castellvi I, Rodriguez-Nieto MJ, et al. Recommendations for the treatment of anti-melanoma differentiation-associated gene 5-positive dermatomyositis-associated rapidly progressive interstitial lung disease. Semin Arthritis Rheum 2020;50:776–90.
2. Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465–77.
3. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–31.
4. Kishida D, Sakaguchi N, Ueno KI, Ushiyama S, Ichikawa T, Yoshinaga T, et al. Macrophage activation syndrome in adult dermatomyositis: a case-based review. Rheumatol Int 2020;40:1151–62.
5. Gilboa M, Bornstein G, Ben-Zvi I, Grossman C. Macrophage activation syndrome complicating rheumatic diseases in adults: case-based review. Rheumatol Int 2020;40:663–9.
6. Tsuji H, Nakashima R, Hosono Y, Imura Y, Yagita M, Yoshifuji H, et al. Multicenter prospective study of the efficacy and safety of combined immunosuppressive therapy with high-dose glucocorticoid, tacrolimus, and cyclophosphamide in interstitial lung diseases accompanied by anti-melanoma differentiation-associated gene 5-positive dermatomyositis. Arthritis Rheumatol 2020;72:488–98.
7. Zhang X, Zhou S, Wu C, Li M, Wang Q, Zhao Y, et al. Tocilizumab for refractory rapidly progressive interstitial lung disease related to anti-MDA 5-positive myositis. Rheumatology 2021;60:e227–e228.

H-T Liao, Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Taipei Veterans General Hospital, No 201, Sec 2, Shih-Pai Road, Taipei 11217, Taiwan. E-mail: htliao@vghtpe.gov.tw

Accepted 23 August 2021