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LETTER

Rescue combination treatment of anti-MDA5-associated ARDS with daratumumab

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Anti-MDA5 antibodies are associated with a variant of (often amyopathic) dermatomyositis and a rapidly progressive interstitial lung disease (ILD). In cases with severe MDA5-associated ILD aggressive immunosuppression is recommended; common treatment strategies include combinations of high-dose steroids, calcineurin inhibitors, cyclophosphamide as well as tofacitinib or rituximab.[1] Once the patients progress to an acute respiratory distress syndrome (ARDS) requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO), the prognosis is very limited.[2] In this letter, we report the successful treatment of an ECMO-dependent case of anti-MDA5-associated ARDS with the anti-CD38 monoclonal antibody daratumumab.

The 55-year-old female patient was transferred to our hospital, presenting with oligoarthritis, Gottron's papules and ARDS requiring mechanical ventilation and ECMO (figure 1A). Pulmonary imaging of the patient had initially shown signs of bilateral acute ILD with ground-glass opacities and progressed to complete 'white lung syndrome' (figure 1B). She was positive for anti-MDA5 and anti-Ro52 antibodies and diagnosed with anti-MDA5-associated dermato-pulmonary syndrome. She did not report muscular symptoms and the creatine kinase was normal. Combination immunosuppressive treatment with cyclophosphamide, tofacitinib (5 mg daily), ciclosporin (100 mg daily), intravenous immunoglobulins (IVIGs), high-dose steroids and prophylactic trimethoprim/sulfamethoxazole was initiated, however, her condition did not improve for 3 weeks.

As a rescue therapy, we started treatment with the anti-CD38 antibody daratumumab as four 1800 mg weekly subcutaneous injections on day 23 after admission. Treatment with tofacitinib, ciclosporin and steroids was continued. Over the next 2 months pulmonary improvement with reduced inflammatory infiltrates and reducible ECMO gas flow was noted, however, her clinical course was complicated by an ischaemic stroke and a bloodstream infection with enterococci, correlating with a renewed increase in ECMO gas flow (day 35–55 after daratumumab). Semiquantitative MDA5 and Ro52 antibody levels turned negative. After antibiotic treatment of the bloodstream infection, she continued to improve, allowing the explantation of the ECMO 70 days after the first dose of daratumumab and successful weaning from the mechanical ventilation a week later. (figure 1A)

Serum ferritin levels decreased from 3100 µg/L to a minimum of 1600 µg/L without normalising. We were able to taper the prednisolone dose from 50 mg/day to 10 mg/day. As her immunoglobulin levels dropped below normal range, she received supplemental IVIGs. At the time of discharge from our care, 108 days after admission to the ICU, she required only low-flow nasal oxygen, was able to walk unassisted for short distances and was transferred to rehabilitative care. At follow-up 6 months after her initial admission, she showed further pulmonary improvement and did not require supplemental oxygen.

In summary, treatment with daratumumab in this patient with MDA5-associated ARDS likely led to a stark clinical improvement despite a poor initial prognosis. Autoantibodies like those against MDA5 are produced both by B lymphocytes and plasma cells. Long-lived plasma cells play an important role in the pathogenesis of autoantibody-mediated autoimmune diseases and as conventional immunosuppressive agents are not able to deplete them, they have remained

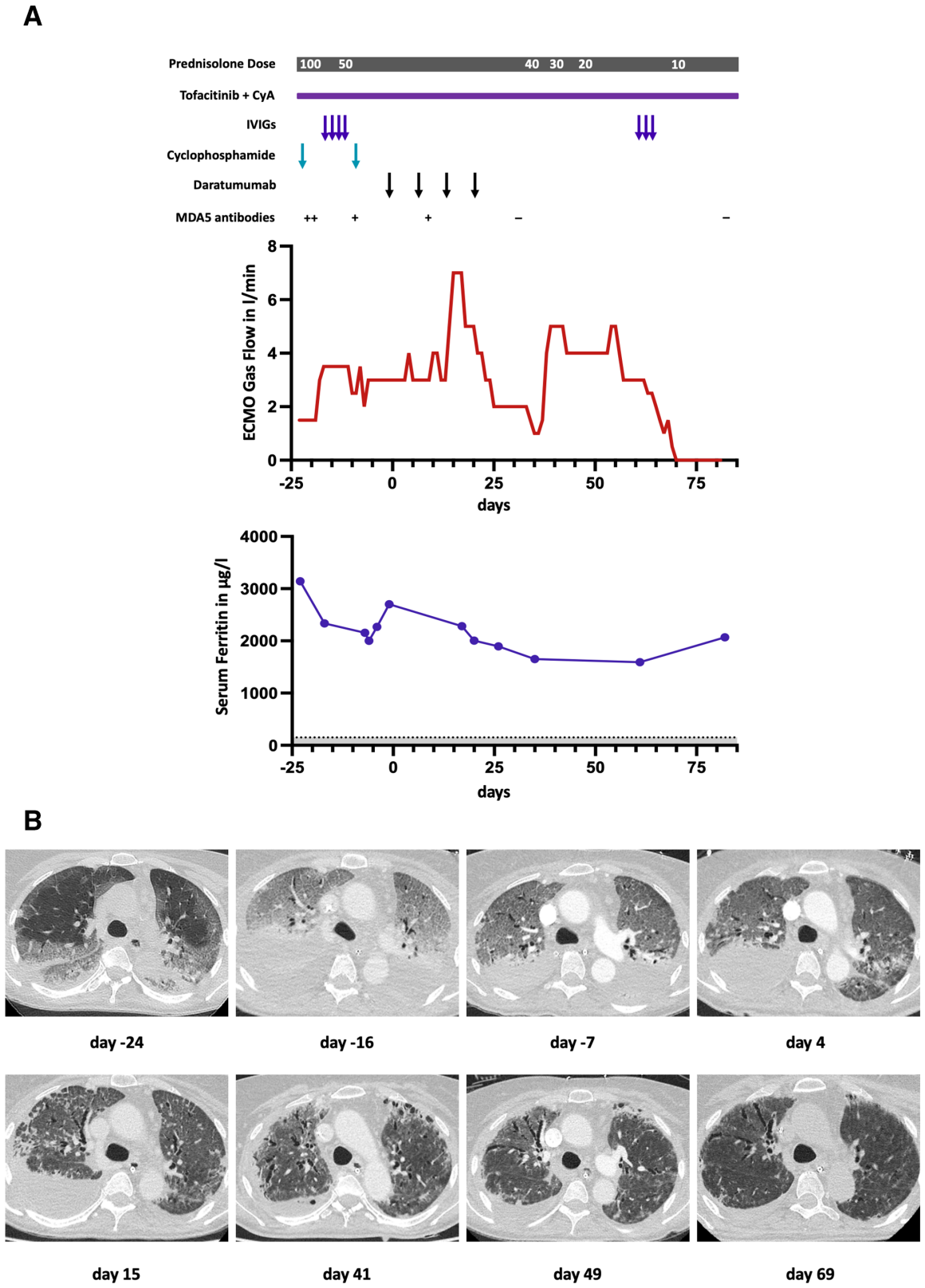

Figure 1 (A) Extracorporeal membrane oxygenation (ECMO) gas flow as a surrogate for acute respiratory distress syndrome (ARDS) severity and serum ferritin levels in a patient with MDA5-associated dermatomyositis treated with the anti-CD38 antibody daratumumab. The grey area indicates the range of normal for serum ferritin (15–150 µg/L). Day 0 indicates the first day of daratumumab treatment. The second increase in gas flow (starting at day 35) correlated with an enterococcal bloodstream infection. Prednisolone dose in mg/day. MDA5 antibody levels as detected by a semiquantitative immunoblot (Labor Berlin, Berlin, Germany). (B) Axial CT scans showing refractory ARDS and pleural effusion in MDA5-associated dermatomyositis and resolution after combination immunosuppressive treatment. CyA, ciclosporin A; IVIGs, intravenous immunoglobulins.

an elusive target for therapies.[3] Daratumumab is an anti-CD38 monoclonal antibody, licensed for the treatment of multiple myeloma, that has shown promise as a plasma cell-targeting agent in case reports of refractory autoantibody-mediated autoimmune diseases,[4] including one less severe case of anti-MDA5-associated ILD not requiring ventilation.[5] Additionally, the important role of type I interferons in the pathogenesis of anti-MDA5 disease led to the successful use of JAK inhibitors for this disease, which likely also played a role in this patient.[6]

Overall, due to the use of a combination immunosuppressive treatment, the contribution of daratumumab to clinical improvement cannot clearly be established. Prospective clinical trials will be needed to establish the safety and efficacy of daratumumab and combination regimens in MDA5-associated disease.

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