Anifrolumab as maintenance therapy in a patient with haemophagocytic lymphohistiocytosis secondary to systemic lupus erythematosus

Sirs,

Anifrolumab, a type I interferon receptor inhibitor, is commonly used in systemic lupus erythematosus (SLE), particularly in cutaneous and musculoskeletal symptoms (1-5). However, its efficacy in patients with severe hematologic manifestations remains undocumented. We report a case of hemophagocytic lymphohistiocytosis (HLH) secondary to SLE, successfully managed with anifrolumab as maintenance therapy.

In February 2020, a 26-year-old male was diagnosed with SLE after presenting with symmetric polyarthritis, malar rash, alopecia, asthenia, and recurrent fever. Antinuclear antibodies (ANA) were positive, alongside anti-Ro52, anti-RNP, and anti-Sm antibodies. Treatment with hydroxychloroquine (HCQ) 400 mg/day and prednisone (PDN) 10 mg/day was initiated.

In August 2020, the patient developed oligoarthritis, high fever, and lymphadenopathy, with a 10 kg weight loss. Blood tests showed hypertransaminasaemia and elevated acute-phase reactants (APR) and lactate dehydrogenase (LDH), while complement levels and blood counts were normal. Despite intensifying therapy with PDN 20 mg/day and mycophenolate mofetil (MMF), he was hospitalised with vomiting, malar rash, night sweats, and foamy urine.

Further tests ruled out infection, but he exhibited leuconeutropenia, lymphopenia, hyperferritinaemia (6300 ng/mL), elevated LDH (660 U/L), and high APR. A PET-CT revealed hypermetabolic lymphadenopathy and splenomegaly. A cervical lymph node biopsy confirmed haemophagocytosis, leading to an HLH diagnosis. Treatment following the HLH-2004 protocol (high-dose dexamethasone, cyclosporine, and etoposide) resulted in improvement, allowing discharge with HCQ reintroduction.

He was readmitted shortly after with fever, inflammatory low back pain, and leg oedema. Blood tests revealed cytopenias, hyperferritinaemia (25000 ng/mL), elevated LDH (1100 U/L), and APR. Off-label anakinra (100 mg/day) was initiated, leading to clinical improvement. After discharge, dexamethasone was switched to PDN, and cyclosporine was replaced by tacrolimus (TAC) due to intolerance. MMF was continued, but tapering PDN was difficult, and anakinra withdrawal triggered relapses.

Subcutaneous tocilizumab (162 mg/week) replaced anakinra, allowing PDN reduction and withdrawal of TAC with clinical stability. However, attempts to discontinue tocilizumab led to HLH flares.

In April 2023, the patient presented with malar rash and chest skin lesions, suggestive of subacute cutaneous lupus, but no HLH relapse. Treatment with TAC and quinacrine was added, alongside PDN escalation. However, skin lesions recurred when PDN was reduced below 10 mg/day. Tocilizumab was replaced with intravenous anifrolumab (300 mg/4 weeks), leading to rapid cutaneous improvement without HLH recurrence. Within three months, PDN was reduced to 5 mg/day, and TAC, MMF, and quinacrine were discontinued. Fourteen months later, the patient remains free of SLE or HLH flares on monthly anifrolumab, HCQ, and PDN 5 mg/day.

The mechanism of anifrolumab involves blocking type I interferon, which is implicated in SLE pathogenesis. Anifrolumab is an IgG1κ humanised monoclonal antibody that binds to IFNα receptor (IFNAR) subunit 1, inhibiting all type I IFN signalling (1). Although trials have shown its efficacy in cutaneous and musculoskeletal SLE, there is limited evidence regarding its use in severe haematologic SLE.

In the MUSE study, anifrolumab achieved good clinical responses in patients with SLE, improving particularly lymphopenia and thrombocytopenia in patients with predominant type I IFN gene signature (IFNGS), probably because of its involvement in haematopoiesis alteration, changes in cell migration, and reduction of apoptosis and NETosis (1).

However, there is no evidence of its efficacy in patients with severe haematologic SLE manifestations. All clinical trials excluded patients with severe manifestations or with severe cytopenias (1, 2), or because the haematologic domain was not specifically evaluated (3, 4), neither in real-world studies (6). Also, HLH secondary to SLE which improved or maintained asymptomatic with anifrolumab treatment has not been described to date. It is remarkable to mention that HLH pathogenesis involves type II IFN signalling, with the role of type I IFN being unclear at the moment (7, 8). However, there is some evidence of effectiveness of anifrolumab in patients with severe haematologic conditions, as one patient with type I interferonopathy with haemophagocytosis in bone marrow improved after anifrolumab treatment (9).

While more data is needed, anifrolumab could be considered a viable maintenance therapy in SLE patients with severe hematologic manifestations, particularly if other domains are affected.

A. Mayo-Juanatey, *MD*
C. Valera-Ribera, *MD*
P. Andújar-Brazal, *MD*
P. León-Torralba, *MD*
I. Vázquez-Gómez, *MD*
J.J. Alegre-Sancho, *MD, PhD*

Rheumatology Department, Doctor Peset University Hospital, Valencia, Spain.

Please address correspondence to:
Adrián Mayo-Juanatey
Rheumatology Department, 2nd Floor,
Calle Juan de Garay 21,
46017, Valencia, Spain.
E-mail: adrianmayoju@gmail.com
ORCID iD: 0009-0008-5434-3021

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