Anifrolumab in the management of lupus headaches: a case report

Sirs,

We present a 52-year-old woman with a 10-year history of systemic lupus erythematosus (SLE) characterised by systemic, articular, cutaneous, and neurological manifestations, including refractory lupus headache. Despite treatment with glucocorticoids, hydroxychloroquine, and belimumab, her headaches remained unresponsive to non-steroidal anti-inflammatory drugs (NSAIDs), triptans, and amitriptyline. After initiating anifrolumab 300 mg monthly, she experienced rapid and sustained symptom resolution, including significant improvement in her lupus headaches.

The patient was diagnosed with SLE in 2014, presenting with polyarthritis, photosensitive rash, recurrent oral aphthae, and pericarditis, alongside positive antinuclear antibodies (ANAs) and secondary Sjögren's syndrome (anti-Ro >320 U). Notably, there was no elevation of anti-double-stranded DNA (anti-dsDNA) antibodies or complement consumption. Her treatment history included variable doses of glucocorticoids, hydroxychloroquine, and methotrexate, discontinued in March 2020 due to ineffectiveness. Belimumab was added in 2018 for persistent polyarthritis.

Since 2022, the patient has reported left-sided headaches refractory to three migraine therapies including NSAIDs, triptans, amitriptyline (50 mg/day) and flunarizine (5 mg/day). Associated depressive symptoms were noted, while neurological evaluation, including MRI, was unremarkable. By April 2024, her SLE activity worsened with chronic fatigue, polyarthritis, and severe photosensitive rash (SLEDAI-2k 14, SLE-DAS 31.04), requiring oral and topical glucocorticoids. Laboratory tests showed lymphopenia (0.8 x 10^9/L), normal haemoglobin (14.6 g/dL), erythrocyte sedimentation rate (ESR) of 5 mm/h, C-reactive protein (CRP) of 0.07 mg/dL, normal anti-dsDNA levels (13.6 UI/mL) and normal complement levels (C3 122 mg/dL, C4 24 mg/dL). Belimumab was discontinued, and Anifrolumab 300 mg IV monthly was initiated.

After one month of Anifrolumab treatment, the patient reported a marked reduction in headache episodes and improvement in systemic and cutaneous symptoms. By month six, her symptoms resolved, including a significant reduction in headaches instensity and the associated cognitive fog. This allowed discontinuation of flunarizine and other migraine therapies. Laboratory results improved, showing lymphopenia recovery (1 x 109/L), stable haemoglobin (14.9 g/dL), CRP (0.05 mg/dL), ESR (9 mm/h), anti-dsDNA (14.2 UI/mL) and complement levels (C3 111 mg/dL, C4 24 mg/dL). SLE-DAI-2K and SLE-DAS scores fell to 0 and 0.37, respectively.

Anifrolumab, a human monoclonal antibody targeting type I interferon receptor, has demonstrated efficacy in SLE patients and is included in the updated 2023 EULAR recommendations for managing refractory to conventional therapy SLE (1). Phase 3 trials (TULIP 1 and TULIP 2) (2, 3) established its ability to reduce global and organ-specific disease activity and facilitate glucocorticoid tapering (4). Recent real-world data highlight its rapid effectiveness, particularly in those with cutaneous, joint, and haematological manifestations (5). However, evidence regarding its use in neuropsychiatric SLE, including lupus headache remains scarce.

Neurological manifestations in SLE encompass a wide range of neurologic and psychiatric symptoms with varying severity, often complicating the differentiation from unrelated conditions (6). Lupus headache, a severe headache attributed directly to SLE with no secondary cause, remains a challenging manifestation with poorly defined pathogenic mechanism (7, 8). Its prevalence ranges from 24% to 72%, with no clear association with disease activity, and the management typically involves a combination of treatments targeting both the neurological complications and the underlying SLE (7, 8). However, the efficacy of these treatment protocols has not been rigorously studied, highlighting the need for further investigation (8). To our knowledge, this is among the first cases demonstrating a positive and sustained response of lupus headaches to Anifrolumab.

In conclusion, our cases highlight the potential role of Anifrolumab in managing refractory neuropsychiatric manifestations, such as lupus headache, providing rapid symptom resolution and overall disease control. Further studies are warranted to validate these findings and explore the full spectrum of the efficacy of anifrolumab in neuropsychiatric SLE.

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References

1. FANOURIAKIS A, KOSTOPOULOU M, ANDERSEN J *et al.*: EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Ann Rheum Dis* 2024; 83(1): 15-29. https://doi.org/10.1136/ard-2023-224762
2. MORAND EF, FURIE R, TANAKA Y *et al.*: Trial of anifrolumab in active systemic lupus erythematosus. *N Engl J Med* 2020; 382: 211-21. https://doi.org/10.1056/nejmoa1912196 .
3. FURIE RA, MORAND EF, BRUCE IN *et al.*: Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. *Lancet Rheumatol* 2019; 1: e208-19. https://doi.org/10.1016/S2665-9913(19)30076-1
4. BRUCE IN, VAN VOLLENHOVEN RF, PSACHOULIA K, LINDHOLM C, MAHO E, TUMMALA R: Time to onset of clinical response to anifrolumab in patients with SLE: pooled data from the phase III TULIP-1 and TULIP-2 trials. *Lupus Sci Med* 2023; 10(1): e000761. https://doi.org/10.1136/lupus-2022-000761
5. CINGIREDDY AR, RAMINI N, CINGIREDDY AR: Evaluation of the efficacy and safety of anifrolumab in moderate-to-severe systemic lupus erythematosus. *Cureus* 2024; 16(7): e63966. https://doi.org/10.7759/cureus.63966
6. OTA Y, SRINIVASAN A, CAPIZZANO *et al.*: Central nervous system systemic lupus erythematosus: pathophysiologic, clinical, and imaging features. *Radiographics* 2022; 42(1): 212-32. https://doi.org/10.1148/rg.210045.
7. HANLY JG, UROWITZ MB, O'KEEFFE AG *et al.*: Headache in systemic lupus erythematosus: results from a prospective, international inception cohort study. *Arthritis Rheum* 2013; 65(11): 2887-97. https://doi.org/10.1002/art.38106.
8. SHABAN A, LEIRA EC: Neurological complications in patients with systemic lupus erythematosus. *Curr Neurol Neurosci Rep* 2019; 19(12): 97. https://doi.org/10.1007/s11910-019-1012-1