CASE REPORT

A Malaysian case series on anifrolumab treatment for haematological manifestations in systemic lupus erythematosus

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SUMMARY

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease often presenting with a wide range of manifestations, including haematological abnormalities. Anifrolumab, a first-in-class type I interferon receptor antagonist, was recently approved in Malaysia as an add-on treatment for moderate-to-severe active autoantibody-positive SLE in adult patients. Though the phase III TULIP trials demonstrated the efficacy of anifrolumab in improving disease activity and haematological parameters in SLE patients, real-world data on its haematological impact have been limited. This case series presents five Malaysian patients with moderate-to-severe SLE, all of whom had significant haematological manifestations and sub-optimal responses to conventional treatments. Each patient demonstrated marked clinical and laboratory improvements after initiating anifrolumab, including reductions in corticosteroid dosage. Two patients completely discontinued corticosteroids, while others significantly tapered their doses. Haematological parameters, such as haemoglobin level, white blood cell (WBC) count, and platelet count, improved consistently across the cases. This series highlights the potential of anifrolumab as an effective therapeutic option for managing haematological manifestations of SLE, particularly in patients struggling with the adverse effects of prolonged corticosteroid use. These findings contribute valuable real-world evidence supporting the use of anifrolumab in the broader management of SLE, addressing a critical gap in the current literature.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystemic disease which includes the presence of haematological manifestations. The haematological changes in SLE can be an initial manifestation and a predominant sign during the initial years. However, because haematological abnormalities can be found in a variety of medical conditions, the diagnosis of SLE may elude physicians, who often label them as idiopathic or primary conditions.[1] In Malaysia, 51.6% of SLE patients were reported to have haematological manifestations and was the third most common presentation following malar rash (61.3%) and arthritis (52.3%).[2]

Anifrolumab, a first-in-class type 1 interferon receptor antagonist, was approved in 2023 in Malaysia as an add-on therapy for adult patients with moderate to severe, active autoantibody-positive SLE despite standard therapy.[3] Currently, there is limited real-world evidence to demonstrate the effectiveness of anifrolumab in improving SLE haematological manifestations.[4] This case series presents five SLE patients with haematological manifestations treated with anifrolumab due to failure of disease control with standard treatment. A summary of the cases is presented in Table I.

CASE PRESENTATION

Patient 1

In 2017, VA, a 22-year-old woman, presented with autoimmune haemolytic anaemia (AIHA), fever, arthritis, malar rash, and oral ulcers. Her laboratory findings revealed low complements, elevated antinuclear antibody (ANA), elevated anti-double-stranded DNA (dsDNA) titres and a positive anti-Smith antigen (anti-Sm) and anti-Sjögren's-syndrome-related antigen A (SSA) antibody. Initial treatments included hydroxychloroquine, prednisolone >15 mg/day, with ciclosporin 75 mg twice daily. Ciclosporin was then discontinued due to hirsutism, and disease control needed to be maintained with high GC (glucocorticoid) doses.

While pursuing her PhD in July 2023, she presented with a stress-related SLE flare with arthralgia, oral ulcers, fatigue, alopecia, anaemia, and thrombocytopenia with a Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA)-Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of 15. At that time, her medications were hydroxychloroquine 200mg/day, prednisolone 20mg/day, and azathioprine 125 mg/day.

Due to longstanding steroid exposure, she had developed steroid-induced osteopenia and voiced concerns about inadequate disease control.

Laboratory analyses during the July 2023 flare revealed significant worsening of haematological parameters (Table II). The lactate dehydrogenase (LDH) level was 535 U/L (more than double the upper limit of normal [ULN]), indicating ongoing haemolysis. Given the ongoing active disease, poor quality of life, and inability to reduce GC despite optimum doses of azathioprine, a new treatment strategy was advocated.

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Table I: Summary of cases

Case study	Age	Features	Haematological parameters	Pre-anifrolumab steroid dose (duration)	Reasons for starting anifrolumab	Duration of anifrolumab	Post-anifrolumab steroid dose
Cases shared by the first author							
1	22	AIHA Fever Arthritis Malar rash Oral ulcers	Cytopenia Anaemia Thrombocytopenia WBC - normal	20 mg daily (6 years)	SLE flare with SLEDAI 15. Long-standing steroid-induced osteopenia. Rituximab not started as it is generally reserved as rescue and salvage treatment in the author's practice, while anifrolumab was chosen as it had a clear indication/approval for moderate-to-severe SLE and haematological manifestations of SLE.	6 months 9 months	7.5 mg daily 3 mg daily
2	31	Arthritis Malar rash Fatigue Alopecia Anaemia Leukopenia	Leukopenia Lymphocytopenia Anaemia Platelet - normal	12.5 mg daily (11 years)	Intolerance and failure to respond to SOC. Long-standing steroid-induced osteoporosis, weight gain, cataracts, fatty liver, lipidaemia, genital warts. Rituximab not started as it is generally reserved as rescue and salvage treatment in the author's practice, while anifrolumab was chosen as it had a clear indication/approval for moderate-to-severe SLE and haematological manifestations of SLE.	6 months	4 mg daily
Cases shared by the second author							
3	36	Arthritis Malar rash Fatigue Alopecia Anaemia Leukopenia	Anaemia Leukopenia Neutropenia	10-15 mg daily (1 year 7 months)	Active disease after tapering initial steroid dose to <7.5 mg daily. Chronic steroid dependence. Rituximab was not considered as it was during the peak of the COVID-19 pandemic.	4 months 6 months	5 mg daily 2.5 mg daily
4	39	Arthritis Malar rash Fatigue Alopecia Anaemia Leukopenia	Leukopenia	15-20 mg daily (1 year 5 months)	Inadequate response to Azathioprine. Failed response to 2 doses of rituximab with worsening biochemical parameters when prednisolone dosage was reduced to 10 mg daily. Significant dyspepsia and nausea with mycophenolate mofetil.	5 months	7.5 mg daily
5	36	MCTD with active SLE Skin rash Oral ulcers Alopecia Recurrent joint pain and swelling Raynaud's symptoms Fatigue	Anaemia (mild) Lymphopenia	15-20 mg daily (1 year 5 months)	Allergies to hydroxychloroquine and dapsone. Inadequate response to methotrexate. Though there was partial response to rituximab with some improvement in biochemical parameters such as complements and leucopoenia, skin rashes and alopecia began to worsen by four months post-rituximab. Persistent high-dose steroid requirement.	1 month 8 weeks	5 mg daily Discontinued

AIHA, autoimmune haemolytic anaemia; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SOC, standard of care; WBC, white blood cell.

Table II: Laboratory parameters, pre- and post-anifrolumab treatment

	Hb (g/dl)	WBC (x 10^9/L)	Lymphocyte (x 10^3/µl)	Platelet (x 10^3/µl)	ESR (mm/hour)	C3 (g/L)	C4 (g/L)	dsDNA (IU/ml)
Patient 1: VA								
Mar 2023	9.0	-	-	96	51	0.56	0.08	945
Jul 2023	8.8	-	-	90	60	0.53	0.05	2600
Aug 2023	9.0	-	-	110	45	-	-	-
Oct 2023	10.8	-	-	112	36	0.68	0.10	627
Jan 2024	12.1	-	-	147	18	0.87	0.14	496
May 2024	12.4	-	-	156	19	0.86	0.16	244
Patient 2: LPK								
Mar 2023	9.4	3.2	-	-	36	0.46	0.08	229
May 2023	9.5	3.3	-	-	46	0.44	0.06	302
Jun 2023	9.8	3.8	-	-	40	-	-	-
Aug 2023	10.4	4.1	-	-	28	0.78	0.12	160
Dec 2023	11.3	4.2	-	-	17	0.89	0.10	112
Mar 2024	10.8	3.9	-	-	32	0.80	0.08	216
June 2024	11.6	4.8	-	-	20	0.91	0.10	220
Patient 3: LKJ								
Jul 2023	11.7	6.2	0.93	268	6	0.67	0.09	189
Aug 2023	12.1	5.5	2.42	342	7	0.78	0.10	-
Oct 2023	11.9	11.9	1.50	295	2	0.71	0.09	-
Nov 2023	12.6	6.2	1.18	330	14	1.00	0.17	-
Jan 2024	11.9	4.9	1.76	324	2	0.71	0.10	-
Mar 2024	12.1	5.2	1.54	310	2	0.71	0.09	-
Patient 4: WMY								
Aug 2023	13.8	2.8	-	238	3	0.49	0.15	-
Nov 2023	15.1	10.2	-	269	4	0.59	0.20	-
Dec 2023	14.3	8.4	-	241	5	0.69	0.19	-
Feb 2024	14.5	5.9	-	274	4	0.67	0.16	-
Apr 2024	13.8	5.0	-	273	2	0.69	0.17	-
Patient 5: TSY								
Feb 2024 (baseline in 2020)	12.3	2.8	0.62	242	9	0.63	0.14	71.7
Mar 2024	12.1	5.4	0.97	365	12	0.70	0.13	-
Apr 2024	12.6	5.4	0.97	327	5	0.68	0.14	0.00

Anifrolumab initiation for Case 1 (VA): July 2023, Case 2 (LPK): May 2023, Case 3 (LKJ): July 2023 (dsDNA was only taken at baseline), Case 4 (WMY): November 2023, and Case 5 (TSY): February 2023. All patients had progressive improvements in their blood parameters post-treatment initiation.
C, complement; dsDNA, double-strand DNA; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; IU, international unit; WBC, white blood cells.

In 2023, VA was started on intravenous (IV) anifrolumab 300 mg every four weeks. After 6 months of anifrolumab, prednisolone was tapered to 7.5 mg/day, and azathioprine reduced to 100 mg/day. Her laboratory parameters improved significantly; haemoglobin, platelet count, erythrocyte sedimentation rate (ESR), and C3 and C4 levels almost normalised, while dsDNA levels decreased by nearly 80%. She reported reductions in pain, fatigue, and hair loss. Her clinical and laboratory parameters significantly improved (Table II) with a SELENA-SLEDAI score of 4 and with prednisolone reduced to 3 mg/day by May 2024.

Patient 2

LPK, a 31-year-old lady diagnosed with moderate SLE in September 2012, initially presented with arthritis, malar rash, fatigue, alopecia, anaemia and leukopenia. Treatment history between 2012 and 2023 included hydroxychloroquine, prednisolone >10 mg/day, azathioprine (stopped due to elevated liver enzymes), methotrexate (stopped due to gastrointestinal [GI] symptoms), and leflunomide. After 11 years on moderate-to-high doses of corticosteroids, LPK had developed long-term corticosteroid complications such as osteoporosis, weight gain, cataracts, fatty liver, lipidaemia, and genital warts. Due to her chronic joint inflammation, she also developed Jaccoud's arthropathy. At this time, her treatment encompassed hydroxychloroquine 200 mg/day, prednisolone 12.5 mg/day, leflunomide 20 mg/day, and denosumab 60 mg every six months.

Her laboratory results in May 2023 indicated persistently active disease (Table II), with high ANA titres (1:640), elevated anti-dsDNA, lymphocytopenia (0.73/ml), and anaemia (9.4 g/dl). Due to her suboptimal disease control, poor quality of life, complications from disease and treatment, and intolerance and failure to respond to standard of care (SOC), IV anifrolumab 300 mg every four weeks was initiated.

In December 2023, six months after anifrolumab, there were significant improvements in the resolution of rash and joint synovitis; prednisolone was reduced to 4 mg/day while leflunomide was discontinued. Her Hb, WBC, ESR, C3/C4, and dsDNA levels also improved (Table II).

However, the patient defaulted two subsequent anifrolumab infusions, resulting in a minor SLE flare affecting her skin and musculoskeletal system, and deterioration in blood parameters (Table II). Considering the resurgence in disease severity, anifrolumab was recommenced in April 2024, with a good clinical response seen after the first dose.

Patient 3

LKJ, a 36-year-old female with moderate SLE (based on SLEDAI-2000), presented in December 2021 with fever, joint pain, rash and oral ulcers. Investigations revealed low C3/C4 levels, anaemia and leukopenia. ANA, anti-dsDNA, and extractable nuclear antigen antibodies (ENA) were positive. She was initially treated with prednisolone 1 mg/kg/day with gradual tapering to <7.5 mg/day, hydroxychloroquine and azathioprine. In July 2023, she continued to exhibit active disease, with leukopenia, anaemia, skin rash, alopecia, oral ulcers, joint pain and vasculitis. This was complicated by fever, frequent infections secondary to oral immunosuppressants and chronic steroid dependence (GC < 10 mg/day). Her last findings revealed significantly high ANA and anti-dsDNA, positive ENA for SmD1, Ro-60, La and nucleosomes, low C3/C4 levels, leukopenia (2.4 x 10^9/L), neutropenia (1.01 x 10^9/L), anaemia (Hb 9.6 g/dL) and elevated LDH (567 U/L).

Considering LKJ's overall clinical picture, IV anifrolumab 300 mg every four weeks was added in July 2023. At nine months of anifrolumab, dose reductions were possible in her prednisolone, hydroxychloroquine 400 mg/day alternating with 200 mg/day to 200 mg/day, azathioprine 125 mg/day to 75 mg/day and prednisolone 10-15 mg/day to 2.5 mg/day. The prednisolone was successfully tapered to 5 mg/day by the fourth month and to 2.5 mg/day by the sixth month. Progressive improvements were seen in haematological parameters (resolved lymphopenia), except for the C3/C4 levels, which remained roughly the same (Table II). Clinically, LKJ experienced less fatigue and no frequent infections.

Patient 4

WMY, a 39-year-old woman, presented with SLE in June 2022. She had moderate disease based on SLEDAI-2000 with joint pain, skin rashes, and oral ulcers that had begun two months postpartum. Biochemical abnormalities included low complement levels and leukopenia. Intolerant to azathioprine (headaches and neutropenia,) she was started on IV rituximab, 1 g for two doses at two-week intervals, which led to a partial response (improved C3/C4 levels and leukopenia). However, tapering the prednisolone to <15 mg/day four weeks after rituximab therapy, she experienced joint pain and declining blood parameters. Mycophenolate mofetil up to 1 g twice daily was started, but she experienced constant dyspepsia and nausea. Other immunosuppressives were not prescribed as the patient had concerns about experiencing similar adverse events (AE). Optimising the prednisolone dose was challenging; she experienced constant fatigue when the dose was tapered but suffered from insomnia when it exceeded 10 mg/day.

Given her AEs to conventional immunosuppressive agents, persistent prednisolone dependency, constant disease activity, and poor well-being, IV anifrolumab 300 mg every four weeks was started in November 2023. At that time, her treatment regimen included hydroxychloroquine, 200 mg/day alternating with 400 mg/day, prednisolone 15-20 mg/day, and mycophenolate mofetil 1500 mg/day. After five months, her treatment regimen improved significantly: hydroxychloroquine was reduced to 200 mg/day, the prednisolone to 7.5 mg/day, and discontinued mycophenolate mofetil. Her blood parameters also showed improvement (Table II), as did her fatigue and insomnia.

Patient 5

In 2020, TSY, a 36-year-old woman, was diagnosed with mixed connective tissue disease (MCTD) with a predominant active lupus component. She initially presented with skin rashes, oral ulcers, increased hair fall, recurrent joint pain, swelling, Raynaud's (digital) symptoms, and fatigue. Her investigations revealed mild anaemia (Hb 11.7 g/dL), lymphopenia (0.9 x 10^9/L), low C3/C4, elevated ESR, and were positive for ANA (1:1280) and ENA (positive for U1-SmRNP, SmD1, PCNA, P0). Skin biopsy showed subacute cutaneous lupus erythematosus (SCLE) and was diagnosed with moderate SLE using the SLEDAI-2K score.

She was initially treated with hydroxychloroquine and methotrexate. However, she developed allergic reactions to hydroxychloroquine and had an inadequate response to methotrexate, which worsened her skin rash and caused cytopenia. Rituximab, administered at 1 g for two doses two weeks apart every six months, also proved inadequate after three doses, as she had persistently low C3/C4 levels, leukopenia (<4.0 x 10^9/L), and dependence on high-dose prednisolone (>10 mg/day). During multiple disease flare-ups on rituximab, she required intermittent pulses of IV methylprednisolone at 500 mg. Unfortunately, during the rituximab regimen, she experienced spontaneous pregnancy that resulted in intrauterine demise at eight weeks of amenorrhea.

Due to persistently active disease, intolerance, inadequate responses, worsening leukopenia, and low C3/C4 levels despite rituximab treatment, as well as persistent corticosteroid dependence, IV anifrolumab 300 mg every four weeks with prednisolone 10 mg/day was initiated in February 2024. In a month, prednisolone was tapered to 5 mg/day and discontinued within eight weeks. Her haematological parameters improved, except for C3/C4 levels, which remained stable (Table II). Clinically, she showed marked improvement after three months of anifrolumab therapy, with complete resolution of her cutaneous rash, alopecia, and oral ulcers.

DISCUSSION

The cases presented highlight the effectiveness of anifrolumab in treating SLE patients with sub-optimal responses, intolerable AEs with SOC, and who were on high GC doses. Fifty percent to 70% of SLE patients may present with anaemia, while leukopenia (65%) and lymphopenia (50%) are frequently observed. Although SLE-related thrombocytopenia is less common (10-25%), severe thrombocytopenia can result in morbidity and mortality.[5]

Current SOC includes corticosteroids, anti-malarial and immunosuppressants. GCs have potent anti-inflammatory effects, but long-term use of >5 mg/day prednisone equivalent may cause irreversible organ damage, prompting recommendations to taper and ultimately withdraw GC.[4,6]

With the availability of biologics like belimumab and anifrolumab, the 2023 European Alliance of Associations for Rheumatology (EULAR) SLE treatment guidelines recommended prompt biologic initiation, rather than after multiple SOC treatment failures, due to more robust clinical trial evidence to control disease and facilitate GC sparing. The guidelines also recommended anifrolumab as a second-line option for mild SLE patients and as first-line for moderate-to-severe SLE patients when the response to hydroxychloroquine is suboptimal or inability to taper GC doses to ≤5 mg/day prednisolone equivalent to control disease activity.[4]

Clinical trials show significantly more anifrolumab patients achieved a GC of ≤7.5 mg/day from weeks 40-52 compared to placebo (52% vs. 30%, p=0.01).[7] At year four, 36.4% of anifrolumab patients were free of GC (0 mg/day), while 74.4% received doses between 0 - <5 mg/day with an acceptable safety profile.

In all cases presented, the patients were on high GC doses that could not be reduced due to disease recurrence or flare-ups, and none was trialled with belimumab. However, with anifrolumab treatment, two patients reduced their GC doses to < 5 mg/day, two reduced their doses by more than 50%, and one discontinued GC within eight weeks. In real-world clinical practice, anifrolumab enabled GC-dependent patients to align with the EULAR 2023 SLE recommendations to lower the daily GC dose to ≤5 mg/day.[4]

In a post-hoc analysis of the TULIP long-term extension (LTE) trial, improvement in the SLEDAI-2K haematological domain was more frequent in the anifrolumab 300 mg group compared to placebo at Week 208. Patients receiving anifrolumab also showed improved haemoglobin, platelet, and lymphocyte counts compared to placebo over the 4-year TULIP LTE study period.[9]

All the patients in this case series exhibited improvements in their SLE symptoms including the haematological parameters. It should be noted that other causes of the haematological abnormalities were ruled out and generally mild-to-moderate but were considered significant as adding conventional immunosuppressants during treatment would potentially further deviate the value of the counts. Interestingly, patient 5 showed significant cytopenia improvement, with a marked increase in WBC counts within three cycles of anifrolumab. This patient, who presented with AIHA, demonstrated a substantial increase in haemoglobin levels, rising by 36% from 8.8 g/dl to 12.0 g/dl within six months. Additionally, the patient's platelet count increased from 96 to 146 x 10^3/L, and the erythrocyte sedimentation rate (ESR) decreased from 51 to 18 mm/hour. Patient 2 highlights the potential rebound effect of abruptly discontinuing anifrolumab and underscores the importance of treatment compliance. Reassuringly, disease activity improved upon recommencing treatment.

CONCLUSION

The presented cases reinforced the role of anifrolumab as a viable treatment option in improving haematological parameters and reducing corticosteroid dependence in patients with moderate-to-severe SLE. These findings align with clinical trial data, while further real-world studies will be beneficial in strengthening the evidence and ultimately guide optimal patient management.

DECLARATION

It is hereby confirmed that consent for publication has been obtained from the patient or their caregiver.

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