LUPUS SCIENCE & MEDICINE™

Targeting type I interferon in lupus autoimmune haemolytic anaemia: first report with anifrolumab

Fulvia Ceccarelli ,[1] Rossella De Angelis ,[2] Francesca Bottazzi,[3] Danila Madonna,[2] Melania Alessia Coscia,[4] Noemi Italiano,[4] Emanuela Praino,[5] Emanuela Sabatini,[6] Leonardo Santo,[5] Lorenzo Cavagna,[3] Fabrizio Conti[1]

To cite: Ceccarelli F, De Angelis R, Bottazzi F, *et al*. Targeting type I interferon in lupus autoimmune haemolytic anaemia: first report with anifrolumab. *Lupus Science & Medicine* 2026;**13**:e002063. doi:10.1136/lupus-2026-002063

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/lupus-2026-002063).

Received 27 March 2026
Accepted 3 July 2026

[1]University of Rome La Sapienza, Rome, Italy
[2]Polytechnic University of Marche, Ancona, Italy
[3]University of Pavia, Pavia, Italy
[4]Azienda Ospedaliera di Caserta Sant'Anna e San Sebastiano, Caserta, Italy
[5]Barletta Hospital, Barletta, Italy
[6]Ospedale Clinicizzato SS Annunziata, Chieti, Italy

Correspondence to
Dr Fulvia Ceccarelli; fulviaceccarelli@gmail.com

ABSTRACT

Objective Autoimmune haemolytic anaemia (AIHA) occurs in approximately 5–10% of patients with SLE and it is traditionally associated with higher disease activity, increased damage accrual and reduced survival. SLE management recommendations partially address disease-related haematological manifestations without specific indication for AIHA treatment. Indeed, therapeutic approaches are prevalently extrapolated from the haematology field. In the present report, we aimed at describing a case series of patients with SLE and AIHA successfully treated with anifrolumab (ANF).

Methods We described patients with SLE treated by ANF with active AIHA at the drug initiation. Clinical and laboratory data were reported in a standardised electronic form, including laboratory evidence of haemolysis. Overall disease activity was assessed by using the SLE Disease Activity Index 2000 (SLEDAI-2k). We collected patients data at baseline (T0), after 1 month (T1) and every 3 months thereafter.

Results We included seven patients (6F/1M, median age 61 years (IQR 33), median disease duration 48 months (IQR 72)). All the patients had a positive direct Coombs test and laboratory evidence of active haemolysis at ANF starting. During treatment, we observed a progressive increase in haemoglobin (Hb) levels, with a statistically significant difference compared with baseline after 3 months of treatment (p=0.02). In parallel we registered the increase in RBC count, without the need to perform RBC transfusions after ANF starting. Overall disease activity significantly improved during the follow-up, with significant reduction of mean SLEDAI-2k values after 6 months of treatment (p=0.01).

Conclusion In the present case-series study, we provide the first report about the benefit of ANF in the treatment of SLE-related AIHA, a rare but potentially severe manifestation associated with increased morbidity and mortality. In our cohort, ANF treatment was associated with a rapid and sustained increase in Hb levels, evident already at 1 month and progressively improving up to 6 months.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Autoimmune haemolytic anaemia is a rare but potentially severe manifestation associated with increased morbidity and mortality.

WHAT THIS STUDY ADDS

⇒ The present study is the first report about the efficacy of anifrolumab in the treatment of lupus-related autoimmune haemolytic anaemia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study provides novel insights into the potential role of anifrolumab in the management of lupus-associated autoimmune haemolytic anaemia.

INTRODUCTION

Haematological involvement represents a common manifestation in patients with SLE, occurring either at disease onset or during the disease course. It may present as thrombocytopenia, leucopenia and autoimmune haemolytic anaemia (AIHA), with different degrees of severity. While mild and asymptomatic cases may require only close monitoring, more severe presentations can develop and require urgent therapeutic intervention.[1] The clinical relevance of haematological manifestations is underscored by their inclusion in the SLE classification criteria.[2]

From a pathogenic perspective, multiple and potentially overlapping mechanisms could contribute to the development of SLE-related haematological features. First, the autoantibody-mediated destruction of red blood cells (RBCs) plays a central role. In addition, complement activation may promote RBC opsonisation and phagocytosis, while chronic inflammation could contribute to bone marrow suppression.[3] Acting simultaneously and not exclusively, these mechanisms likely account for the heterogeneity of haematological manifestations observed in patients with SLE.[1 3] Importantly, it is crucial to distinguish whether haematological abnormalities are directly attributable to SLE itself

or secondary to treatments administered for disease control.

AIHA occurs in approximately 5–10% of patients with SLE and it is traditionally recognised as an autoantibody-mediated manifestation. IgG autoantibodies target erythrocyte surface antigens, leading to complement activation and enhanced RBC phagocytosis.[4] The presence of AIHA has been clearly associated with higher disease activity, increased damage accrual and reduced survival. Available evidence suggests a distinct SLE phenotype, characterised by coexistence of AIHA, thrombocytopenia, renal involvement and an increased risk of thrombosis. These patients typically exhibit hypocomplementaemia and positivity for anti-double-stranded DNA and anti-phospholipid antibodies.[5]

With regard to management, AIHA should be considered a manifestation of systemic disease, therefore overall disease activity must be carefully assessed. Furthermore, the treatment should aim to achieve rapid AIHA control and to prevent complications and drug-related adverse events.

Current SLE management recommendations only partially address disease-related haematological involvement, primarily focusing on severe autoimmune thrombocytopenia, without indication for the treatment of AIHA.[6] Consequently, therapeutic approaches are largely extrapolated from the haematology field. Glucocorticoids (GCs) represent the first-line treatment for AIHA, whereas rituximab or immunosuppressant drugs may be considered in refractory cases. For severe cases requiring a rapid response, intravenous IgG could be considered and, where necessary, supportive management with RBCs transfusion.[7] However, although evidence supports the efficacy of rituximab in AIHA, no studies have specifically evaluated the role of biological agents approved for SLE in this setting.

Here, we report a case series of patients with SLE and AIHA successfully treated with anifrolumab (ANF).

METHODS

We described patients with SLE fulfilling the 2019 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria,[2] treated by ANF according to the current clinical practice, with active AIHA at the drug initiation. The drug was administered intravenously at a dose of 300 mg every 4 weeks.

First, before classifying anaemia as autoimmune, we have ruled out all other possible causes of anaemia (eg, iron deficiency, renal involvement).

Clinical and laboratory data were reported in a standardised electronic form, including medical history, laboratory evidence of haemolysis (elevated LDH (Lactate Dehydrogenase), indirect hyperbilirubinaemia, reticulocytosis, low haptoglobin and a positive direct antiglobulin (Coombs) test), previous and concomitant treatments. Overall disease activity was assessed by using SLE Disease Activity Index 2000 (SLEDAI-2k).[8]

We defined active AIHA as the presence of at least one abnormal marker of active haemolysis and/or the need for blood transfusion and/or PDN dose ≥7.5 mg/daily, with AIHA worsening below this cut-off.

We collected patients information at baseline (T0), after 1 month (T1) and every 3 months thereafter.

Normally distributed variables were summarised using the mean±SD, and non-normally distributed variables by the median and IQR. Frequencies were expressed by percentage. Wilcoxon's matched pairs test and the paired t-test were performed accordingly. GraphPad V.9.0 (La Jolla, California, USA) software was used for the statistical analysis.

RESULTS

We included seven patients with SLE fulfilling the 2019 ACR/EULAR classification criteria[2] (6F/1M, median age 61 years (IQR 33), median disease duration 48 months (IQR 72)).

Clinical, laboratory and therapeutic data are summarised in table 1. In detail, we included clinical and laboratory manifestations referring to overall disease history (according to 2019 ACR/EULAR classification criteria), together with active disease-related manifestations at the ANF beginning (according to SLEDAI-2k domains).[2 8]

With regard to the latter, three patients (42.8%) had additional haematological manifestations attributable to the disease, in particular one patient reported thrombocytopenia and leucopenia and the other two lymphocytopenia. The other active manifestations at ANF beginning were fever and skin and/or joint involvement, which were observed in 42.8% of patients.

Notably, AIHA was present at disease onset in four patients (57.1%).

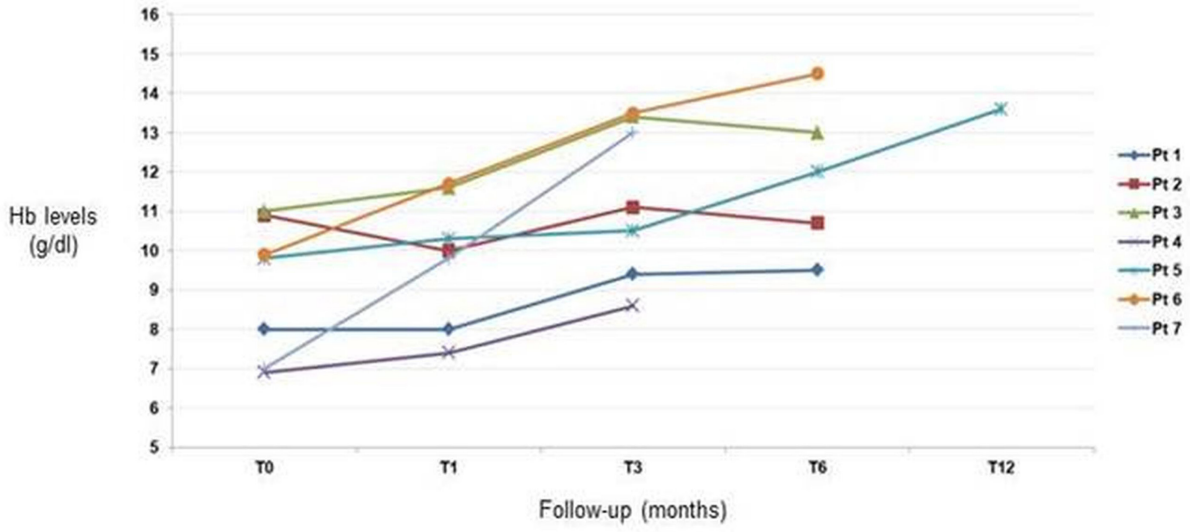
Before ANF treatment, five patients were treated by another biological drug; in detail, four patients (85.7%) by belimumab and one (14.3%) by rituximab. In all the patients, AIHA was refractory to previous biological drugs. Four patients (57.1%) had required at least one RBCs transfusion in the 3 months preceding ANF initiation. We registered data about concomitant treatments at the ANF starting: as reported in table 1, two patients were treated only by hydroxychloroquine, while the remaining five patients were taking immunosuppressant drugs. All the patients had a positive direct Coombs test and laboratory evidence of active haemolysis at ANF starting (for details see table 1).

Figure 1 illustrates the course of haemoglobin (Hb) levels during the follow-up (T0: 9.1±1.7 g/dL; T1: 9.8±1.6 g/dL; T3: 11.4±1.9 g/dL; T6: 11.9±1.9 g/dL). Median Hb levels progressively increased, with a statistically significant difference compared with baseline after 3 months of treatment (p=0.02). Notably, no patients required further RBCs transfusions after starting ANF.

Table 1 Overall information about described patients with SLE and AIHA

Pt	Sex	Age (years)	Disease duration (months)	Other SLE related manifestations (2019 ACR/EULAR) (ANA+)	Information about AIHA			Other active SLE related manifestations at ANF start	Previous SLE treatments	Concomitant SLE treatments
					AIHA at SLE onset	Direct Coombs test	Active haemolysis signs			
1	F	45	48	**Laboratory:** aDNA +, ↓C4, LAC+ **Clinical:** Arthritis, skin and lung involvement	YES	+	↑ LDH ↓ haptoglobin	Arthritis	HCQ, MMF, BLM	HCQ, MMF
2	M	74	12	**Laboratory:** aDNA +, ↓C3/C4 **Clinical:** Skin involvement, serositis, fever	YES	+	↑ LDH ↓ haptoglobin ↑ indirect bilirubin ↑ reticulocytes	Fever Skin involvement	HCQ, RTX, MMF	MMF
3	F	32	12	**Laboratory:** aDNA +, ↓C3 ENA +, aCL IgM+IgG+, aβ2GPI IgG+IgM+, **Clinical:** Haematological abnormalities (leucopenia, thrombocytopenia) inflammatory arthralgias	YES	+	↑ LDH ↓ haptoglobin ↑ indirect bilirubin	Skin involvement Leucopenia Thrombocytopenia	HCQ BLM	HCQ
4	F	65	84	**Laboratory:** aDNA +, ↓C4 **Clinical:** Skin involvement, haematological abnormalities (lymphocytopenia)	NO	+	↑ LDH ↓ haptoglobin ↑ indirect bilirubin	Joint involvement Lymphocytopenia	HCQ AZA, MMF BLM	HCQ, MMF
5	F	61	528	**Laboratory:** aDNA +, ↓C3/C4 **Clinical:** Skin involvement Lupus nephritis Inflammatory arthralgia Haematological abnormalities (lymphocytopenia)	NO	+	↓ haptoglobin	Lymphocytopenia	MMF, CY	MMF
6	F	65	48	**Laboratory:** aDNA +, aSm+ ↓C3/C4 **Clinical:** Arthritis, Fever, Skin involvement	NO	+	↑ LDH ↓ haptoglobin ↑ reticulocytes	Arthritis, Fever, Skin involvement	HCQ BLM	AZA
7	F	22	5	**Laboratory:** aDNA +, aSm+ ↓C3/C4 **Clinical:** Headache	YES	+	↑ LDH ↓ haptoglobin	Fever	HCQ	HCQ

LDH: Lactate Dehydrogenase
ACR, American College of Rheumatology; AIHA, autoimmune haemolytic anaemia; AZA, azathioprine; BLM, belimumab; EULAR, European Alliance of Associations for Rheumatology; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; RTX, rituximab.



	T0 (baseline) (N=7)	T1 (1 month) (N=7)	T3 (3 months) (N=7)	T6 (6 months) (N=5)	P
Hb levels (g/dl) mean±SD	9.1±1.7	9.8±1.6	11.4±1.9	11.9±1.9	T0 versus T3 p=0.02

Figure 1 Changes in Hb levels during treatment with anifrolumab. Hb, haemoglobin.

We evaluated the AIHA response to ANF treatment according to the recently published treatment response measure for SLE clinical trials.[9] This analysis could be performed in six patients who were eligible for scoring AIHA response. Accordingly, a clinically meaningful response (Hb increased >2 g/dL) was achieved in 50% of patients after 3 months of treatment and 60% after 6 months of treatment.

Online supplemental table S1 summarises changes in other haematological parameters and complement levels. We observed a progressive increase in mean RBCs count (T0: 2.8×10^6/µl±0.5; T1 3.0×10^6/µl±0.4; T3 3.8×10^6/µl±0.7; T6 3.8×10^6/µl±0.6). Given the stability of leucocytes and lymphocytes values, we observed an increase in platelet counts, which rose from a baseline value of 181.7±100.1×10^3/µl to 266.0±110.5×10^3/µl after 6 months of treatment. In particular, one patient who began ANF treatment with 46×10^3/µl platelets showed an increase after just 1 month of treatment, reaching a platelet count >100×10^3/µl, which remained stable thereafter.

Overall disease activity significantly improved during the follow-up. As reported in figure 2, mean SLEDAI-2k values decreased from 6.0±2.2 at baseline to 1.6±1.7 after 6 months (p=0.01). In parallel we registered the increase of C3 and C4 serum levels (see online supplemental table S1). In particular, mean C3 serum levels significantly increased after 6 months (T0: mean±SD 70.4±9.0; 6 months 97.2±8.5; p=0.01). Furthermore, PDN dosage progressively decreased, moving from a mean daily dose of 36.8±21.5 mg at baseline to 4.7±5.8 mg at 6 months.

Moving on safety, during the follow-up period covered by this study, no patients discontinued treatment and no significant adverse events were reported.

DISCUSSION

Real-world data on ANF have consistently demonstrated the excellent efficacy and rapidity in SLE-related skin manifestations, whereas evidence regarding the drug's effectiveness on other SLE-related domains remains limited. In the present case-series study we provide the first report about the efficacy of ANF in the treatment of SLE-related AIHA.

In our cohort, ANF treatment was associated with a rapid and sustained increase in Hb levels, evident already at 1 month and progressively improving up to 6 months. In parallel, we observed the increase of RBCs values, without the need for further RBCs transfusion after ANF starting. We also considered the recently published treatment response measure for SLE clinical trials, showing a clinically meaningful response in half of eligible patients already after 3 months.[9]

In our view, this is an important point, given that AIHA is not included in the SLEDAI-2k domains and is therefore not taken into account in the overall assessment of disease activity. This lack is certainly a limitation of the SLEDAI-2k.[8] Furthermore, overall disease activity significantly improved and a marked steroid-sparing effect was observed. Indeed, after 6 months the mean daily dosage

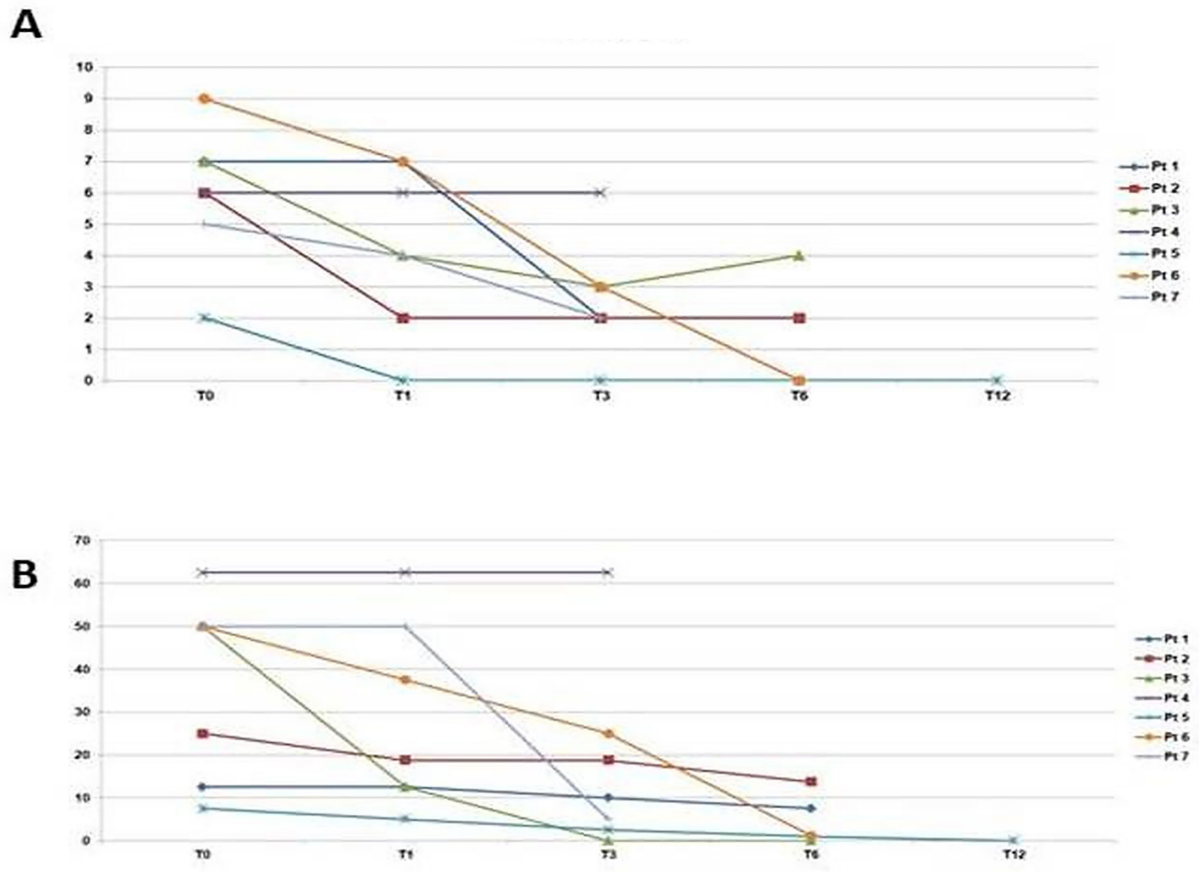


Figure 2 Changes in SLEDAI-2k values (A) and PDN dosage (mg/daily) (B) during treatment with anifrolumab. SLEDAI-2K, SLE Disease Activity Index 2000.

was lower than 5 mg, reaching the dosage suggested by the EULAR recommendations.[6]

In our opinion, despite the limited number of patients, our contribution provides very interesting data. Indeed, haematological involvement in patients with SLE has always been given little consideration in clinical studies and, as above-mentioned, only thrombocytopenia was considered in the latest recommendations.[6] Therefore, the management of patients with haematological involvement remains an unmet clinical need.[1] Focusing on AIHA, specific evidence for this potentially severe manifestation is still limited, probably because this is a rare feature and severe active haematological lupus was not well represented in clinical studies.

Drawing on the haematological experience of patients with primary AIHA, GCs, frequently with high dosage, remains the first-line treatment also in SLE-related cases, followed by immunosuppressant drugs and/or rituximab for refractory patients.[7]

The potential role of type I interferon (IFN) in AIHA pathogenesis is supported by reports of AIHA developing during IFN therapy for other conditions, such as haematological malignancies or multiple sclerosis, with haemolysis resolution on treatment discontinuation and starting of immunosuppressant drugs.[8] These observations suggest that IFN, in particular IFN-α, may trigger AIHA through mechanisms including antibody-mediated RBC destruction or induction of autoreactive B-cells.[10] Furthermore, experimental models indicate that IFN may modulate antibody-mediated haemolysis by regulating the expression of Fcγ receptor on RBC surface.[11]

ANF, a fully human monoclonal antibody targeting the type I IFN receptor subunit 1, has been approved to treat extrarenal SLE manifestations, based on positive results deriving from TULIP 1 and TULIP 2 randomised controlled trials.[12 13] Emerging real-world data confirm its efficacy and rapidity in SLE-related manifestations, such as musculoskeletal involvement, with very encouraging results.[14] Indeed, interim results from REVEAL study have also suggested benefit across multiple SLEDAI-2k domains, including haematological features.[15] Furthermore, Bottazzi and colleagues described the efficacy of ANF as a first-line therapy for the treatment of patients with SLE and thrombocytopenia.[16]

Our contribution, made in a real-life scenario, provides preliminary evidence supporting the efficacy of ANF in SLE-related AIHA, a rare but potentially severe manifestation associated with increased morbidity and mortality. In our cohort, ANF was able to improve Hb levels, without flare in the observation period and a substantial steroid-sparing effect.

The main limitation of our paper is certainly the number of patients, but it should also be borne in mind that AIHA is a rare disease-related manifestation.

Furthermore, the observation period is too short for conclusive evidence. Finally, the effect of background therapy in AIHA response cannot be evaluated due to the real-life setting of this clinical cases collection. Therefore, the effect of background therapy should be assessed in dedicated clinical trials.

In conclusion, while confirmation in larger cohorts with longer follow-up is warranted, our study provides preliminary evidence into the potential role of ANF in the management of SLE-associated AIHA.

Acknowledgements We would like to thank our patients for their cooperation.

Contributors FCe and FCo conceived and designed the study. All the authors participated in the recruitment of patients. FCe and FCo wrote the paper. All the authors revised the paper and approved the last version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval We requested the informed consent directly from the patients.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to this study have been included in the manuscript. The data code supporting the findings of this study is available from the corresponding author on reasonable request.

ORCID iDs

Fulvia Ceccarelli https://orcid.org/0000-0001-5026-8783

Rossella De Angelis https://orcid.org/0000-0001-5169-3511

REFERENCES

1 Yuce Inel T, Uslu S, Demirci Yildirim T, *et al*. Hematologic Involvement in Systemic Lupus Erythematosus: Clinical Features and Prognostic Implications in a Hematology-Referred Cohort. *J Clin Med* 2025;14:7304.
2 Aringer M, Costenbader K, Daikh D, *et al*. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheumatol* 2019;71:1400–12.
3 Hair P, Goldman DW, Li J, *et al*. Classical complement activation on human erythrocytes in subjects with systemic lupus erythematosus and a history of autoimmune hemolytic anemia. *Lupus* 2020;29:1179–88.
4 Kokori SI, Ioannidis JP, Voulgarelis M, *et al*. Autoimmune hemolytic anemia in patients with systemic lupus erythematosus. *Am J Med* 2000;108:198–204.
5 Sultan SM, Begum S, Isenberg DA. Prevalence, patterns of disease and outcome in patients with systemic lupus erythematosus who develop severe haematological problems. *Rheumatology (Oxford)* 2003;42:230–4.
6 Fanouriakis A, Kostopoulou M, Andersen J, *et al*. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Ann Rheum Dis* 2024;83:15–29.
7 Murakhovskaya I, Yazdanbakhsh K. Warm autoimmune haemolytic anaemia: Clinical considerations. *Br J Haematol* 2026;208:841–4.
8 Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;29:288–91.
9 Connelly K, Morand E, Koelmeyer R, *et al*. Measurement of haemolytic anaemia in a novel treatment response measure for SLE clinical trials. *Lupus Sci Med* 2026;13:e001830.
10 Rönnblom L. Systemic lupus erythematosus: from an adverse event of interferon administration to a disease with new treatment options. *Ups J Med Sci* 2025;130.
11 Giannouli S, Voulgarelis M, Ziakas PD, *et al*. Anaemia in systemic lupus erythematosus: from pathophysiology to clinical assessment. *Ann Rheum Dis* 2006;65:144–8.
12 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.
13 Morand EF, Furie R, Tanaka Y, *et al*. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. *N Engl J Med* 2020;382:211–21.
14 Ceccarelli F, Ciancarella C, Natalucci F, *et al*. Rapid response to anifrolumab in lupus related joint involvement as assessed by ultrasonography: A case series study. *Joint Bone Spine* 2025;92:105830.
15 Tani C, Cardelli C, Moroni L, *et al*. Patient profiles and early response in patients with systemic lupus erythematosus initiating anifrolumab: interim analysis from the ongoing multicentre observational REVEAL study. *Lancet Rheumatol* 2026;8:e181–91.
16 Bottazzi F, Manna E, Codullo V, *et al*. Efficacy of anifrolumab as a first-line therapy for the treatment of thrombocytopenia in systemic lupus erythematosus: a case report. *Clin Exp Rheumatol* 2025;43:1364.