Anifrolumab for refractory autoimmune hemolytic anemia in SPENCD-associated Lupus: a case-based review

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ABSTRACT

Spondyloenchondrodysplasia (SPENCD) is a rare monogenic interferonopathy caused by biallelic ACP5 mutations, characterized by skeletal dysplasia, neurological involvement and immune dysregulation frequently manifesting as lupus-like disease. Autoimmune cytopenias, particularly autoimmune hemolytic anemia (AIHA), are among the most severe and treatment-refractory manifestations. Anifrolumab, a monoclonal antibody targeting interferon alpha receptor subunit 1 (IFNAR1), blocks signaling by all type I interferons and is approved for moderate-to-severe systemic lupus erythematosus. We report a 50-year-old man with SPENCD-associated lupus and refractory, transfusion-dependent AIHA who achieved sustained hematologic remission following anifrolumab initiation. Using this case as a framework, we discuss the pathophysiological basis of SPENCD, the spectrum and treatment challenges of its associated autoimmune cytopenias, and the evolving role of targeted therapies in monogenic interferonopathies, with particular emphasis on SPENCD, and summarize the published experience with anifrolumab in these disorders. Collectively, this case and the available literature provide preliminary support for IFNAR1 blockade as a mechanism-based, steroid-sparing strategy for refractory autoimmune cytopenias in SPENCD.

KEYWORDS: Anifrolumab; Autoimmune Hemolytic Anemia; Spondyloenchondrodysplasia; systemic lupus erythematosus; interferonopathy.

KEY MESSAGES

1. Autoimmune cytopenias in SPENCD are often refractory, reflecting persistent type I interferon pathway activation.
2. This case supports anifrolumab as a promising mechanism-based, steroid-sparing therapeutic option for refractory AIHA in SPENCD-associated lupus.
3. Published cases support IFNAR1 blockade as a rational strategy for monogenic interferon-driven disease.

INTRODUCTION

Spondyloenchondrodysplasia (SPENCD) is a rare immuno-osseous disorder caused by biallelic loss-of-function mutations in ACP5, encoding tartrate-resistant acid phosphatase (TRAP)[1]. TRAP deficiency leads to accumulation of phosphorylated osteopontin and sustained activation of plasmacytoid dendritic cells, resulting in chronic overproduction of type I interferons (IFN-I) and upregulation of interferon-stimulated genes. SPENCD is therefore classified as a monogenic type I interferonopathy[2, 3].

Clinically, SPENCD is characterized by skeletal dysplasia (platyspondyly, metaphyseal enchondroma-like lesions, short stature), neurological involvement (intracranial calcifications, spasticity) and immune dysregulation[4, 5]. The immune phenotype frequently overlaps with systemic lupus erythematosus (SLE), and autoimmune cytopenias, particularly AIHA and immune thrombocytopenia, are among the most common and clinically challenging manifestations, often refractory to conventional immunosuppressive therapy[3, 6].

Anifrolumab is a fully human monoclonal antibody targeting IFNAR1 that blocks signaling by all type I interferons[7]. Its efficacy in moderate-to-severe SLE has been demonstrated, namely in the TULIP trials[8, 9]. Despite a strong pathophysiologic rationale, experience with anifrolumab in monogenic interferonopathies remains limited.

We report a patient with SPENCD-associated lupus and refractory AIHA who achieved sustained remission following anifrolumab initiation. To contextualize this case, we performed a targeted PubMed literature search for reports published up to March 2026 on anifrolumab use in monogenic interferonopathies, particularly SPENCD. Search was conducted using combinations of the terms "spondyloenchondrodysplasia", "SPENCD", "ACP5", "interferonopathy", "type I interferonopathy", "SAVI", "CANDLE", "Aicardi-Goutières syndrome" and "anifrolumab". Reference lists of relevant articles were also screened. Of note, conference abstracts were excluded because of limited patient-level data and potential overlap with subsequently published reports.

CASE REPORT

A 50-year-old Caucasian man, a former smoker with an 8-pack-year history who quit in 2019, has been followed in our Rheumatology department for several years for longstanding SPENCD-associated SLE. He was born to non-consanguineous parents, with no family history of SPENCD or autoimmune disease. He presented with typical skeletal abnormalities, including short

stature and widespread metaphyseal and vertebral enchondroma-like lesions with platyspondyly (Figures 1 and 2), but had no neurological or cognitive impairment. Genetic testing, performed 18 years after the diagnosis of SLE, confirmed a homozygous ACP5 c.325G>A (p.Gly109Arg) pathogenic variant.

Since his early thirties, he developed recurrent severe AIHA and persistent lymphopenia, with positive antinuclear antibodies, negative anti-double-stranded DNA antibodies and persistently low complement levels. AIHA was confirmed by anemia with elevated lactate dehydrogenase and bilirubin, low haptoglobin, reticulocytosis and a positive direct antiglobulin test. Hemolytic episodes required red blood cell transfusion on three occasions. Sequential immunosuppressive therapies, namely glucocorticoids, azathioprine, mycophenolate mofetil (MMF), and rituximab, failed to achieve sustained disease control, and the patient remained glucocorticoid-dependent (prednisolone >10 mg/day) with recurrent AIHA relapses.

In 2021, he developed progressive dyspnea. High-resolution computed tomography (HRCT) demonstrated bilateral interlobular septal thickening, intralobular reticulation and ground-glass opacities, predominantly in the subpleural regions, associated with bronchiectatic changes and features of fibrosis (Figure 3A). Pulmonary function tests showed reduced forced vital capacity (FVC) (71% predicted) and DLCO (57.3% predicted). Bronchoalveolar lavage, performed while the patient was receiving immunosuppressive therapy, showed a predominantly macrophagic profile (85%), with mild neutrophilia (6%), no lymphocytosis (6%), and CD8 predominance (CD4/CD8 ratio 0.45). Bacterial, fungal and mycobacterial cultures were negative, as was *Mycobacterium tuberculosis* PCR. Low-titre serum precipitins against pigeon antigens and Penicillium notatum were detected, although the absence of BAL lymphocytosis and the uncertain exposure history did not support a definite diagnosis of hypersensitivity pneumonitis. Follow-up HRCT approximately 1 year later showed persistent bilateral fibrotic interstitial abnormalities with a similar distribution, together with mild upper-lobe centrilobular emphysema (Figure 3B). Transbronchial lung cryobiopsy was deferred because of the patient's cytopenias and overall clinical condition. In January 2024, he developed acute respiratory failure with concurrent AIHA worsening (hemoglobin 7.3 g/dL), requiring high-dose prednisolone (60 mg/day). A second exacerbation two months later required oxygen therapy at 6 L/min, and he remained dependent on 4 L/min during ambulation thereafter. Microbiological investigations did not identify a causative pathogen. However, an infectious etiology could not be definitively excluded, as the patient received a 14-day course of levofloxacin concomitantly with an increase in the prednisolone dose, precluding attribution of the clinical improvement to either intervention alone. Repeat HRCT in May 2024 showed persistent bilateral, predominantly

subpleural inter- and intralobular reticulation with bronchiectatic changes and features of fibrosis, without substantial interval progression (Figure 3C).

Given persistent disease activity, recurrent AIHA and glucocorticoid dependence, anifrolumab (10) was initiated in July 2024, combined with MMF (3 g/day) and prednisolone (20 mg/day). After 3 months, hemoglobin normalized and hemolysis markers improved. After 18 months of continuous therapy, the patient remained in sustained remission with no further AIHA episodes, successful tapering to prednisolone 2.5 mg/day and MMF 2 g/day, and no treatment-related adverse events. Oxygen requirements also decreased, with supplemental oxygen currently required only during exertion at 1 L/min. Pulmonary function showed a modest early decline in FVC (71% to 66% predicted) during the first 6 months, followed by stabilization at 65% predicted, while DLCO improved from 49% to 57% predicted (Table I). Follow-up HRCT in June 2026 showed persistent fibrotic interstitial abnormalities without substantial radiological progression (Figure 3D).

DISCUSSION

Autoimmune cytopenias are among the most severe manifestations of SPENCD. In the largest survey of 26 molecularly confirmed patients, Briggs et al. reported autoimmune disease in 85%, with thrombocytopenia and SLE being most frequent[3]. AIHA, Evans syndrome and autoimmune neutropenia were also documented[3]. Sacri *et al.* highlighted that autoimmune cytopenia may be the presenting feature, preceding recognition of the skeletal phenotype[5]. More recent series have confirmed the severity and treatment-refractoriness of cytopenias in SPENCD[11-14]. Across these reports, autoimmune cytopenias are frequently refractory to glucocorticoids, azathioprine, MMF and rituximab, likely reflecting persistent upstream IFN-I pathway activation not adequately suppressed by downstream-targeted therapies[4].

The recognition that constitutive IFN-I signaling drives disease in interferonopathies has prompted the use of JAK inhibitors. In an open-label expanded-access program, Sanchez *et al.* treated 18 patients with CANDLE, SAVI and other interferonopathies with baricitinib, demonstrating significant reductions in symptom scores, glucocorticoid requirements and IFN biomarkers[15]. Consistent with this emerging evidence, the 2021 EULAR/ACR Points to Consider recommend JAK inhibitors as the primary targeted therapy for CANDLE/PRAAS, SAVI and AGS[16]. Further real-world evidence was provided by Li *et al.,* who reported clinical improvement with tofacitinib or ruxolitinib in a six-patient series encompassing SAVI, AGS and SPENCD, particularly

in febrile and cutaneous manifestations, together with reductions in corticosteroid exposure and IFN scores[17].

In SPENCD specifically, both patients included in the Li *et al.* cohort showed marked reductions in IFN scores after tofacitinib, although clinical responses were heterogeneous, with satisfactory disease control in one patient but persistent laboratory and neurological disease activity in the other[17]. Shimizu *et al.* had previously reported a child with steroid-dependent systemic inflammation, membranous nephropathy and thrombotic thrombocytopenic purpura who achieved sustained remission, glucocorticoid tapering and reductions in ferritin and IFN score following baricitinib treatment[18]. Gernez *et al.* later described two patients with refractory Evans syndrome responding to JAK1/JAK2 inhibition[6] and additional pediatric reports have also documented favorable responses to tofacitinib and ruxolitinib[19-21]. However, JAK inhibitors exert broad effects beyond IFN-I, leading to more general immunosuppression, prompting interest in more specific IFN-I pathway blockade[22].

Anifrolumab provides targeted IFN-I blockade by directly inhibiting IFNAR1[7]. Although current evidence is limited to case reports and small case series, anifrolumab has demonstrated encouraging efficacy across a spectrum of type I interferonopathies, including SAVI, CANDLE/PRAAS, DNASE2 deficiency and probable SPENCD (Table II)[23-28]. Across these reports, treatment was associated with normalization of the IFN-I transcriptional signature, improvement of systemic inflammatory and organ-specific manifestations, marked glucocorticoid sparing and reduced reliance on JAK inhibitors, with successful transition to anifrolumab monotherapy in selected patients[24-28]. Notably, the only previously published case of probable SPENCD reported normalization of the platelet count and complete glucocorticoid withdrawal following the addition of anifrolumab to baricitinib[27]. While viral infections have been observed during combination therapy[26] these findings collectively support IFNAR1 blockade as a promising therapeutic approach for interferon-mediated diseases and provide further rationale for its use in SPENCD.

The sustained hematologic remission observed in our case is notable for several reasons. First, it represents the first report of anifrolumab use in an adult with SPENCD and the first report specifically targeting refractory AIHA in this condition. Second, the durability of remission of 18 months without relapse after years of transfusion-dependent episodes despite multiple therapies, strongly supports a clinically meaningful contribution of IFNAR1 blockade. While concomitant MMF may have contributed, it had previously failed to prevent relapses, reinforcing the relevance of targeting the upstream interferon pathway. Third, the marked

glucocorticoid-sparing effect is consistent with benefits observed in both SLE trials and interferonopathy cases.

From a mechanistic perspective, the poor response of AIHA to conventional immunosuppression in SPENCD likely reflects persistent upstream IFN-I pathway activation[29]. Anifrolumab directly blocks IFNAR1, inducing receptor internalization and downregulating multiple IFN-induced gene modules, plasmablast differentiation and NETosis-associated pathways[30]. These effects are directly relevant to the pathogenesis of autoimmune cytopenias in SPENCD, where IFN-I-driven B-cell hyperactivity and loss of tolerance are central[3]. Across the published reports, anifrolumab has achieved marked IFN-I suppression and enabled reduction or discontinuation of JAK-inhibitor therapy. Notably, Kretzschmar *et al.* demonstrated sustained disease control with anifrolumab monotherapy in two patients[26].

Our case also reinforces that a subset of patients classified as SLE may represent monogenic interferonopathies with fundamentally different disease mechanisms[2, 4]. The present patient carried a diagnosis of SLE for nearly two decades before the monogenic etiology was identified. Genetic testing should be considered in patients with early-onset, familial or treatment-refractory lupus, particularly when accompanied by skeletal abnormalities, intracranial calcifications or short stature.

The pulmonary findings warrant cautious interpretation. Interstitial lung disease (ILD) is a major and well-recognized manifestation of SAVI, but it has not emerged as part of the established phenotypic spectrum of SPENCD in published cohorts, in which recurrent respiratory infections related to immune dysfunction are more commonly described[31]. Moreover, our literature search identified no previous report of ILD in a patient carrying the ACP5 p.Gly109Arg variant. The present case may therefore represent a previously unreported association, but the available evidence is insufficient to establish ILD as a manifestation of either this specific variant or SPENCD more broadly. In this patient, HRCT findings were consistent with chronic fibrotic ILD, but the etiological investigation remained inconclusive. Microbiological investigations did not identify a causative pathogen, although an infectious contribution could not be definitively excluded because levofloxacin and an increased prednisolone dose were administered concomitantly during the acute deterioration. Bronchoalveolar lavage findings and low-titre serum precipitins did not support a definite alternative diagnosis. Connective tissue disease-associated ILD and a possible relationship with the underlying interferonopathy were considered, but histopathological confirmation could not be obtained because transbronchial lung cryobiopsy was deferred owing to cytopenias and the patient's overall clinical condition. Respiratory symptoms and oxygen requirements improved after anifrolumab initiation. However, this occurred in parallel with correction of severe anemia and possible resolution of a

superimposed acute pulmonary process. Follow-up HRCT showed radiological stability rather than regression, while FVC declined modestly before stabilizing. DLCO increased from 49% to 57% predicted, although this may partly reflect the rise in hemoglobin if values were not corrected for hemoglobin concentration. In the absence of standardized serial exertional oximetry or arterial blood gas measurements, a specific therapeutic effect of anifrolumab on pulmonary involvement cannot be established.

This report has limitations inherent to a single case. Concomitant immunosuppression is a potential confounder. The IFN signature was not longitudinally assessed, precluding direct correlation between molecular and clinical responses. The summary of published cases (Table II) is limited by small numbers, heterogeneity in disease subtypes and incomplete reporting. Nevertheless, the durability of remission after prolonged disease activity and repeated therapeutic failures supports a true treatment effect.

CONCLUSION

This case demonstrates that IFNAR1 blockade with anifrolumab can achieve sustained control of severe, refractory AIHA in SPENCD-associated lupus. Although evidence remains limited to isolated cases across monogenic interferonopathies, the consistent pattern of clinical benefit supports a broader role for anifrolumab in genetically defined, interferon-driven disease. Prospective studies with longitudinal IFN signature monitoring are needed to further define the role of IFNAR1 blockade in SPENCD.

Tables and Figures

Figure 1. Clinical phenotype of spondyloenchondrodysplasia. Frontal **(A)** and lateral **(B)** views showing characteristic skeletal features, including short stature, disproportionate body habitus with relatively short limbs, and increased trunk-to-limb ratio, consistent with underlying metaphyseal and vertebral dysplasia.

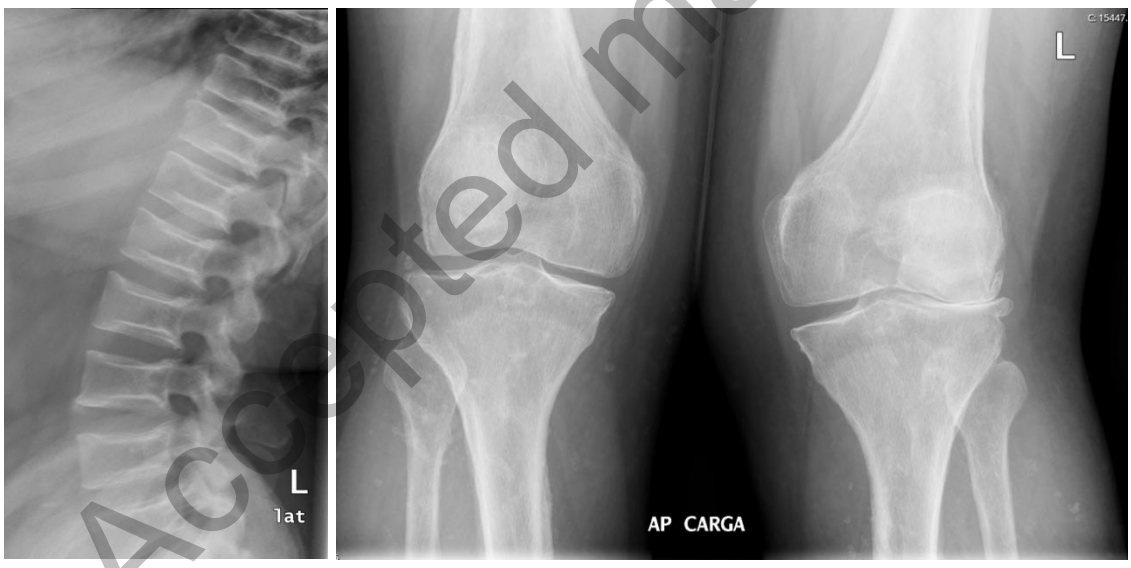
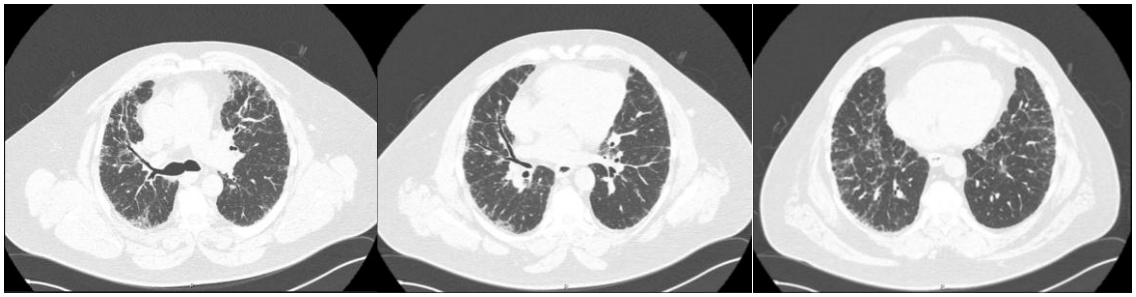
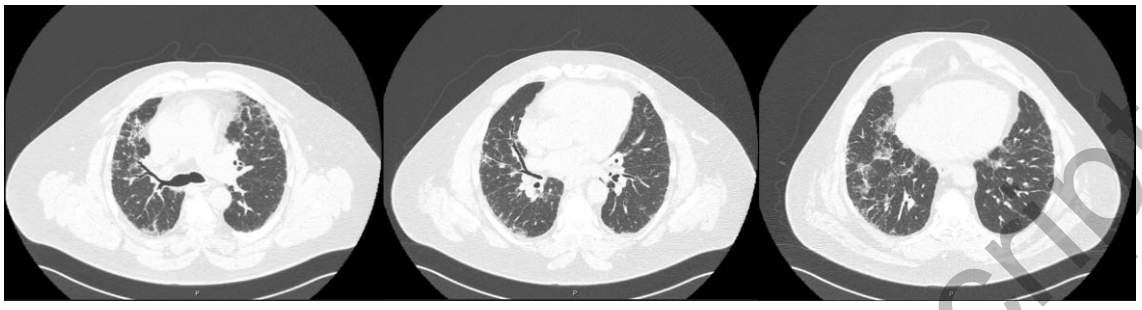


Figure 2. Skeletal imaging findings in spondyloenchondrodysplasia. **(A)** Lateral lumbar spine radiograph showing platyspondyly with vertebral body flattening and endplate irregularity. **(B)** Weight-bearing anteroposterior radiograph of both knees showing chronic osseous changes involving the tibial metaphyseal regions, together with bilateral femorotibial degenerative changes.

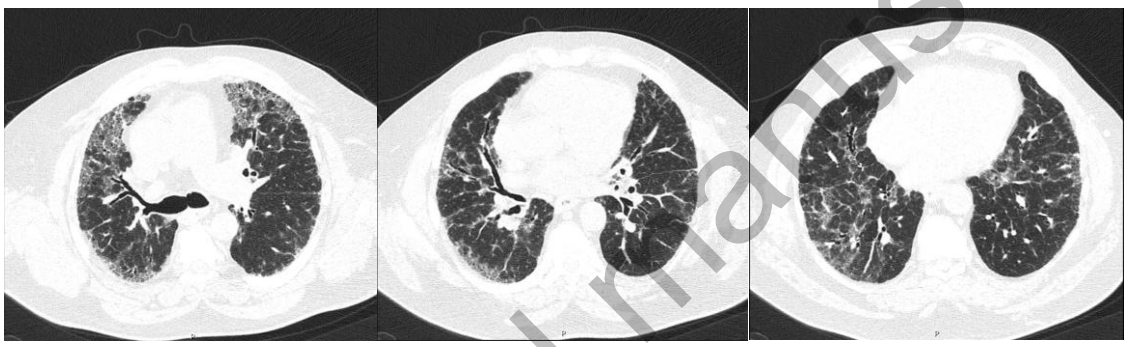
(A)



(B)



(C)



(D)

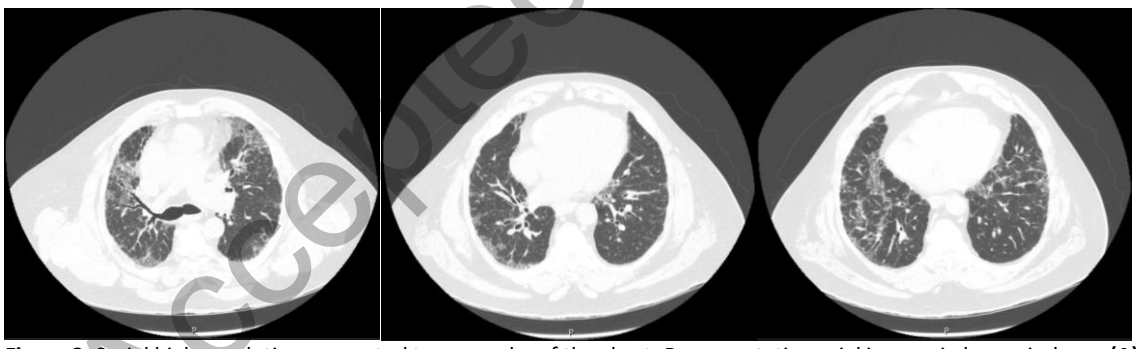


Figure 3. Serial high-resolution computed tomography of the chest. Representative axial images in lung windows. **(A) December 2021, initial evaluation of diffuse bilateral reticular pulmonary abnormalities:** bilateral, predominantly subpleural interlobular septal thickening, intralobular reticulation and ground-glass opacities, associated with bronchiectatic changes, consistent with fibrotic interstitial lung disease. **(B) November 2022, updated assessment before consideration of lung biopsy:** persistence of the bilateral subpleural fibrotic abnormalities, with reticulation and bronchiectatic changes, without substantial interval progression. **(C) May 2024, eassessment after infectious episodes, functional deterioration and new exertional oxygen requirement:** persistent bilateral inter- and intralobular reticulation, ground-glass opacities and bronchiectatic changes, without significant honeycombing. **(D) June 2026, longitudinal follow-up to assess stability of the fibrotic interstitial lung disease under immunosuppressive treatment:** overall stable fibrotic interstitial abnormalities, with coarse subpleural and peribronchovascular reticulation, traction bronchiectasis and limited ground-glass opacities, predominantly involving the mid-lung regions. No significant honeycombing was identified. The overall pattern remained indeterminate.

Table I. Clinical, laboratory, and respiratory evolution after initiation of anifrolumab 300 mg every 4 weeks.

		Anifrolumab 300 mg every 4 weeks				
	January/2024	**M0 (Jul 2024)**	**M3 (Oct 2024)**	**M6 (Jan 2025)**	**M12 (Jul 2025)**	**M18 (Dec 2025)**
Hemoglobin, g/dL	7.3	10	13.6	13.6	13.2	15.1
Reticulocytes, %	N. D.	2.3	2.9	4.1	2.3	2.1
Lymphocytes, % / $\times 10^9$/L	9.9/0.25	4.2/0.53	6.3/1.03	6.7/0.59	4.1/1.03	5.0/1.28
Platelets, $\times 10^9$/L	218	131	168	185	193	166
Haptoglobin, g/L	N. D.	1.53	1.05	1.06	1.35	1.13
LDH, U/L	327	212	253	266	260	290
C3/C4, g/L	0.80/0.20	0.87/0.31	1.02/0.20	1.0/0.26	1.20/0.35	1.16/0.32
Urine protein-to-creatinine ratio, mg/g	219	129	-	-	125	-
FVC, % predicted (z-score)	-	71% (-2.14)	-	66%	-	65% (-2.60)
DLCO, % predicted (z-score)	-	49% (-4.01)	-	50%	-	57% (-3.17)
Oxygen requirement, L/min	-	6 L/m	4 L/min *	2 L/min *	1 L/min *	1 L/min *
Prednisolone, mg/day	60	15	7.5	7.5/5	5	2.5
Mycophenolate mofetil, mg/day	3000	3000	3000	2500	2000	2000

N.D., not determined; C3/C4, complement fractions 3 and 4; LDH, lactate dehydrogenase; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide. * Oxygen supplementation required only during exertion.

Table II. Published cases of anifrolumab use in monogenic type I interferonopathies.

Study	Diagnosis	Age*	Key manifestations	Prior therapies	Therapeutic regimen	IFN signature	Clinical outcome	Follow-up
Doroudchi et al. 2024 (24)	**DNASE2 deficiency** (homozygous p.Cys347Tyr)	Paediatric (15 yr)	Cyclic fevers, severe non-haemolytic anemia, thrombocytopenia, systemic inflammation, growth failure, sensorineural hearing loss and mild splenomegaly	RBC transfusions (no prior immuno-suppression)	Anifrolumab 300 mg IV q4w	Trended to low/normal	Fever cessation; anemia resolved; no further transfusions; CRP decreased; 9kg weight gain; mild thrombocytopenia persisted	16 months
Mansilla-Polo et al. 2024 (25)	**SAVI** (TMEM173 c.497G>A, p.Gly166Glu)	Adult (≈30 yr)	Cutaneous vasculopathy, painful perniotic ulcers; nasal and auricular cartilage necrosis, exertional dyspnea with mild restrictive ventilatory defect and normal HRCT	GC, nifedipine, MTX and CYC	Anifrolumab 300 mg IV q4w	NR	>50% reduction in cutaneous lesions after 1 month and complete cutaneous response after 3 months; subjective improvement in exertional dyspnea; no significant adverse events; treatment suspended after the 6-month cold season	6 months
Kretzschmar et al. 2024 (26)	**SAVI** (STING1 p.Val155Met)	Paediatric (≈5 yr)	ILD, recurrent respiratory infections, reduced exercise capacity and mediastinal lymphadenopathy	Baricitinib, GC	Anifrolumab 5.5 mg/kg IV q4w + baricitinib + GC	Normalized	Reduced pulmonary inflammation and mediastinal lymphadenopathy; improved 6-minute walking distance without desaturation; GC and baricitinib discontinued.	15 months
	SAVI (STING1 p.Val155Met)	Adult (NR)	Chronic ILD with pulmonary cysts and fibrosis	Baricitinib, GC	Anifrolumab 5.5 mg/kg IV q4w + baricitinib	Normalized	GC and baricitinib discontinued	NR
	SAVI (STING1 p.Val155Met)	Paediatric (5 yr)	Vasculitic and pulmonary involvement	Baricitinib, RTX	Anifrolumab 5.5 mg/kg IV q4w + baricitinib	Normalized	Substantial reduction in baricitinib dose	11 months
	SAVI (STING1 p.Val155Met)	Adult (34 yr)	Chronic inflammatory joint and pulmonary disease	Sarilumab, Baricitinib, GC	Anifrolumab 3.75 mg/kg IV q4w + baricitinib + GC	Normalized	Baricitinib and GC doses reduced	3 months

	CANDLE / PRAAS (PSMB8 p.Gly209Arg and PSMB10 p.Gln170Ter)	Paediatric (2 yr)	Neonatal hyperinflammation, necrotic skin lesions, liver and kidney involvement, ascites, growth restriction and developmental delay	Baricitinib, GC	Anifrolumab 5.5 mg/kg IV q4w + baricitinib + GC	Reduced but fluctuating	Reduction of baricitinib and GC doses but discontinuation of both led to marked IFN-signature rebound and fever, requiring resumption of triple therapy	14 months
Pandurangi et al. 2025 (27)	**ACP5 deficiency/ probable SPENCD-I** (homozygous p.His205Tyr VUS)	Infant (≈9 mo)	Severe neonatal thrombocytopenia, autoimmune hepatitis, hepatosplenomegaly and markedly elevated IFN-I signature (no skeletal or neurological manifestations)	IVIG, Baricitinib, GC	5.5 mg/kg IV monthly + baricitinib + GC	Normalized	Normalization of platelet count and liver function; complete GC withdrawal; baricitinib discontinuation caused IFN-signature recurrence, requiring continued dual therapy; no adverse events	10 months
Alehashemi et al. 2025 (28)	**SAVI** (STING1 p.Asn154Ser	Adult (≈26 yr)	Refractory vasculitic ulcers, systemic inflammation, progressive osteolysis, anemia and minimal lung disease	Baricitinib, Dazukibart, Tocilizumab, GC	300 mg IV q4w + Tocilizumab + Baricitinib	Normalized	Complete healing of vasculitic ulcers with rare limited flares; viral reactivations resolved; baricitinib discontinuation; no adverse events	15 months
Present case	**SPENCD** (homozygous ACP5 c.325G>A (p.Gly109Arg)	Adult (50 yr)	Refractory AIHA, ILD, lymphopenia	RBC transfusions, GC, AZA, MMF, RTX	300 mg IV q4w + MMF + GC	NA	Sustained AIHA remission; GC taper to 2.5 mg/day	18 months

* Age at anifrolumab initiation. AZA: azathioprine; CYC: cyclophosphamide; GC: glucocorticoids; ILD: interstitial lung disease; IV: intravenous; MMF: mycophenolate mofetil; MTX: methotrexate; NA: not assessed; NR: not reported; q4w: every 4 weeks; RBC: red blood cell; RTX: rituximab.

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