

EDITORIAL

Anifrolumab: the new frontier in the treatment of genetic interferonopathies

Marie-Louise Frémond ^{1,2}, Clémence David,² Christophe Richez ^{3,4}

To cite: Frémond M-L, David C, Richez C. Anifrolumab: the new frontier in the treatment of genetic interferonopathies. *RMD Open* 2024;**10**:e004780. doi:10.1136/rmdopen-2024-004780

Received 17 July 2024
Accepted 16 August 2024



© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Department of Paediatric Hematology-Immunology and Rheumatology, Centre de Référence des Rhumatismes inflammatoires, maladies Auto-immunes et Interféronopathies Systémiques de l'Enfant RAISE, Necker-Enfants Malades Hospital, AP-HP, Paris, France

²Laboratory of Neurogenetics and Neuroinflammation, Imagine Institute, INSERM UMR1163, Paris, France

³Department of Rheumatology, Centre de référence des maladies auto-immunes systémiques rares RESO, Hôpital Pellegrin, Bordeaux, France

⁴ImmunoConcEpT, CNRS UMR 5164, University Bordeaux, Bordeaux, France

Correspondence to

Pr Marie-Louise Frémond;
marie-louise.fremond@aphp.fr

Pr Christophe Richez;
christophe.richez@chu-bordeaux.fr

Understanding the precise mechanisms of monogenic autoinflammatory diseases provides crucial insights into the complex pathophysiology of more common multifactorial diseases, while treatments developed for these prevalent conditions hold promising potential to tackle rare genetic disorders.

Type I interferons (IFN-I) are core antiviral cytokines of the innate immune system. Consisting mainly of IFN-alpha (13 subtypes) and IFN-beta, IFN-I play an important role in antitumour and viral defence and have anti-angiogenic effects. The resolution of the IFN-induced immune response is tightly regulated through feedback pathways, as evidenced by the minimal secretion of IFN-I by a healthy organism under basal conditions. IFN-I bind to a unique receptor, IFNAR (which has two subunits, IFNAR1 and IFNAR2), thereby activating the JAK-STAT pathway involving Janus kinases (JAK1 and TYK2) and STAT family molecules (STAT1 and STAT2). Activation of this signalling pathway leads to the formation of STAT1-STAT2 dimers, which bind to IRF9 (figure 1), forming the ISGF3 complex. This complex acts as a transcription factor that translocates to the nucleus and binds to the promoter regions of hundreds of genes, known as IFN-stimulated genes (ISGs).

The idea of a detrimental effect of IFN-I emerged in the 1970s when high levels of IFN-I were found in the blood of patients with systemic lupus erythematosus (SLE) compared with healthy individuals.¹ In the same decade, Gresser *et al* provided evidence of the toxic effect of IFN-I in mouse and rat models.^{2,3} These observations were further supported by the development of SLE following IFN-alpha therapy in patients with chronic hepatitis C or cancer.^{4,5} In human pathology, type I interferonopathies represent an emblematic genetic model of diseases due to an excess of IFN-I signalling. The term 'type I interferonopathy' (T1I) was coined by Yanick J Crow in 2011 to describe a group of autoinflammatory disorders associated

with an excess of IFN-I signalling relevant to the pathogenesis, with the hypothesis that targeting IFN-I signalling should improve the phenotype.⁶ T1Is are caused by genetic defects that result in either (i) increased production of IFN-I or (ii) impaired negative feedback in the IFN-I pathway.^{6,7} Most of the mutated proteins play a direct or indirect role in nucleic acid metabolism. Examples include gain-of-function mutations in a cytosolic receptor for RNA-type nucleic acids (*IFIH1* gene encoding MDA5) or in an adaptor protein of the cytoplasmic DNA recognition pathway (*STING1* gene encoding Stimulator of Interferon genes (STING)).

T1Is can affect several systems, primarily the brain and skin in the Aicardi-Goutières syndrome, and the lungs and joints, as seen in STING-associated vasculopathy with onset in infancy^{8,9} (SAVI) due to gain-of-function mutations in *STING1*. They are associated with high morbidity and mortality. In addition, they respond poorly to current conventional immunosuppressive drugs. Over the past decade, JAK inhibitors have been the most widely used targeted and compassionate therapeutic class in T1Is¹⁰⁻¹⁴ and are associated with an organ-specific response to the treatment, showing favourable efficacy in systemic, joint and cutaneous involvement. However, JAK inhibition did not prevent progression to pulmonary fibrosis in case of interstitial lung disease,^{13,15} and its effect on the brain remains uncertain.^{14,16} Notably, the dosage used to treat these genetic diseases, which are characterised by a constitutive excess of IFN-I pathway signalling, is much higher^{11,14,17} than that used in multifactorial conditions such as rheumatoid arthritis.¹⁸ At these higher doses, JAK inhibitors exhibit a pan-JAK inhibitory effect, dampening multiple signalling pathways, which is reflected in the occurrence of many side effects in the context of T1Is.^{11,14,17} These observations, combined with the incomplete response to JAK inhibition in

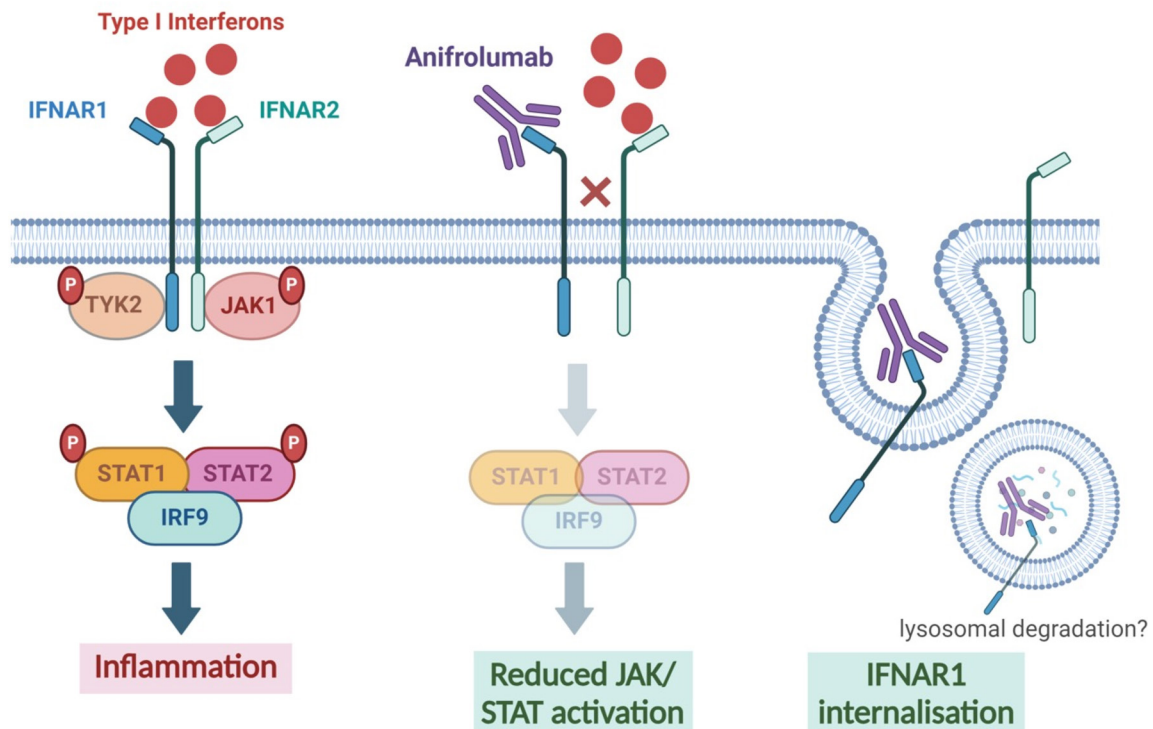


Figure 1 Effect of anifrolumab on the type I interferon pathway. Type I interferons are recognised by their specific receptor, IFNAR, which consists of two subunits, IFNAR1 and IFNAR2. Receptor binding leads to the activation of intracellular kinases, JAK1 and TYK2, that phosphorylate STAT1 and STAT2. On phosphorylation, STAT1 and STAT2 assemble with IRF9 to form a complex that translocates to the nucleus to act as a transcription factor for hundreds of interferon-stimulated genes. Anifrolumab specifically binds to IFNAR1 and prevents it from dimerising with IFNAR2 to limit the downstream signalling cascade. In addition, anifrolumab leads to IFNAR1 internalisation, which is thought to induce IFNAR1 degradation via the lysosomal machinery.

T1Is, highlight the need for combined and/or alternative targeted therapies.

Anifrolumab, a fully human monoclonal IgG1k that inhibits downstream IFN-I signalling and the expression of ISGs by binding to IFNAR, has been approved by the Food and Drug Administration and European Medicines Agency for the treatment of SLE in adults and has subsequently emerged as an interesting therapeutic option in T1Is. Anifrolumab induces internalisation of IFNAR1, reducing the number of receptors available on the cell surface¹⁹ (figure 1). It then disrupts the IFN-I self-amplification loop, particularly through its effect on plasmacytoid dendritic cells, suppressing type I IFN induction following stimulation with lupus immune complexes and preventing subsequent stronger responses to IFN-I.²⁰ The drug has been designed with a triple mutation in the heavy chain to reduce interaction with the cell surface receptor FcγR and its specific effector functions, mainly complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity.

In patients with SLE included in clinical trials of anifrolumab (mainly MUSE (A Phase II, Randomized Study to Evaluate the Efficacy and Safety of MEDI-546 in Subjects with Systemic Lupus Erythematosus) (phase IIb, 305 patients), TULIP (Treatment of Uncontrolled Lupus via the Interferon Pathway)-1 (phase III, 457 patients) and TULIP-2 (phase III, 362 patients),^{21–23} suppression of

blood IFN signatures following anifrolumab administration was achieved early (median suppression of a 21-gene type I IFN signature at week 12 was >80%) and maintained through week 52. Anifrolumab reversed many IFN-associated changes in SLE.²⁴ It significantly reduced levels of IFN-associated chemokines such as IP-10 (Interferon gamma-induced protein 10), ITAC (Interferon-inducible T cell alpha chemoattractant), CXCL13 (C-X-C motif chemokine ligand 13) or BAFF (B-cell activating factor).²⁴ At the cellular level, treatment with anifrolumab reversed lymphopenia and neutropenia and normalised the levels of several circulating T lymphocytes.²⁴ Of note, patients with SLE with high IFN signatures had significantly higher clearance of anifrolumab,^{20 21 23} which may be of concern in the context of T1I.

Tolerance was comparable and consistent across phase II and III studies in adults with SLE.^{21–23 25 26} Intravenous infusions are generally well tolerated, with only one case of anaphylaxis reported in TULIP-1.²² In the MUSE study, there was one death due to acute colitis in a patient receiving anifrolumab. In TULIP-1 and TULIP-2, one death related to pneumonia during anifrolumab treatment was reported in each study. Common adverse events included herpes zoster and upper respiratory tract infections.^{21–23 25} Most cases of herpes zoster were mild and responded well to antiviral therapy. Safety profiles were consistent across subgroups

in clinical trials.^{25–27} Data from the phase II open-label extension study (MUSE) over 3 years showed similar safety profiles.²⁸ Common adverse events included nasopharyngitis, urinary tract infections and upper respiratory tract infections, which decreased over time. Rates of non-opportunistic infection were similar between the anifrolumab and placebo groups, with the exception of latent tuberculosis. Herpes zoster infections remained more common in the anifrolumab group, although they decreased after the first year. COVID-19-related adverse events were higher with anifrolumab, resulting in three deaths during the first 6 months of the pandemic. No COVID-19-related adverse events were reported in fully vaccinated patients.^{29–30} The incidence of malignancies and major cardiovascular events was low and comparable to placebo.

The use of anifrolumab in genetic T1I has been reported in a few patients.^{31–32} The team of Dr Raphaëla Goldbach-Mansky (NIH, USA) reported their experience with the use of anifrolumab in 12 patients with genetic T1I,³¹ including 3 SAVI patients, 6 patients with T1I due to proteasome dysfunction (Proteasome-associated autoinflammatory syndrome (PRAAS)) and 3 patients with putative T1I. Patients received infusions of anifrolumab (300 mg or 5.5 mg/kg) every 4 weeks, either as monotherapy (n=1) or in combination with a JAK inhibitor (n=11). The median duration of treatment with anifrolumab was 8 months (range 2–20 months). All patients received varicella-zoster virus prophylaxis. Treatment with anifrolumab led to normalisation of the IFN signature in all patients. There were no clinical relapses and the dose of baricitinib was reduced from the initial dose in 10/11 patients. Corticosteroids, initially used in 9 patients, could be stopped (n=2) or reduced by 0.5 mg/kg (n=7). Inflammatory markers (C reactive protein (CRP) and erythrocyte sedimentation rate) improved significantly with anifrolumab (2/3 of SAVI patients still had elevated CRP). Anaemia resolved in all patients. Two patients treated with the combination of anifrolumab and JAK inhibitors developed systemic viral infections (enterovirus n=1, herpes virus-6 n=1 complicated by encephalopathy) and two patients developed chronic rhinovirus and parainfluenza infections, which resolved after dose reduction of the JAK inhibitor. Beyond this single-centre experience, the use and efficacy of anifrolumab have recently been reported in two patients with DNASE2 deficiency and SAVI, respectively.^{32–33} In addition, anifrolumab was successfully used to treat discoid lupus in an adolescent.³⁴ In five French patients with genetic T1Is, anifrolumab effectively treated SLE-like features such as chilblains and lupus-like glomerulonephritis in three patients and was well tolerated. However, despite complete dampening of systemic inflammation, its use in SAVI (n=2) was more challenging, as the treatment was initiated because of severe aspergillosis during JAK inhibition (personal observations). The IFN signature normalised in all patients tested. The promising efficacy of IFNAR blockade in these patients is consistent

with the concept of T1I and a toxic effect of IFN-I. This positions anifrolumab as a potential future therapeutic option in T1I, perhaps in combination with low doses of JAK inhibitors, to inhibit the whole inflammatory process involved in these diseases, especially when mediated directly by STING activation, given the multiple facets of STING biology.³⁵ However, several unanswered questions remain, such as the ability of anifrolumab to cross the blood-brain barrier—which is relevant in the context of Aicardi-Goutières syndrome and neuroinflammation in SLE—and the long-term safety profile of this treatment in children. Therefore, compassionate access to this treatment will require international collaboration, particularly in Europe, through the establishment of registries to document its efficacy and safety in this extremely rare condition.

In addition, the development of clinical trials to determine the optimal treatment strategy, whether anifrolumab alone or in combination with JAK inhibitors, is highly anticipated.

In conclusion, the availability of anifrolumab represents a tremendous opportunity for patients suffering from T1I, conditions for which more targeted and effective treatments are awaited, with the potential to significantly improve patients' quality of life.

X Marie-Louise Frémond @MLFrémond and Christophe Richez @crichez33

Acknowledgements The authors would like to thank Professor Bénédicte Neven and Professor Yanick Crow for insightful discussions.

Collaborators Not applicable.

Contributors M-LF and CR wrote the manuscript. CD created the figure. All authors read and agreed to the final version. M-LF is the guarantor.

Funding CD is supported by the Fondation pour la Recherche Médicale (grant: FDM202106013329).

Competing interests CR received travel support, consulting fees and honoraria from AstraZeneca. CR is listed as an inventor on US Provisional Patent Application No.: 62/933,672 and 63/031,848 for type I interferon inhibition in active systemic lupus erythematosus. M-LF and CD have no conflicts of interest to disclose.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Marie-Louise Frémond <http://orcid.org/0000-0002-2798-9141>

Christophe Richez <http://orcid.org/0000-0002-3029-8739>

REFERENCES

- 1 Hooks JJ, Moutsopoulos HM, Geis SA, *et al*. Immune interferon in the circulation of patients with autoimmune disease. *N Engl J Med* 1979;301:5–8.
- 2 Gresser I, Tovey MG, Maury C, *et al*. Lethality of interferon preparations for newborn mice. *Nature New Biol* 1975;258:76–8.
- 3 Crow YJ, Lebon P, Casanova J-L, *et al*. A Brief Historical Perspective on the Pathological Consequences of Excessive Type I Interferon Exposure In vivo. *J Clin Immunol* 2018;38:694–8.
- 4 Rönnblom LE, Alm GV, Oberg KE. Possible induction of systemic lupus erythematosus by interferon-alpha treatment in a patient with a malignant carcinoid tumour. *J Intern Med* 1990;227:207–10.

- 5 Fukuyama S, Kajiwara E, Suzuki N, *et al.* Systemic lupus erythematosus after alpha-interferon therapy for chronic hepatitis C: a case report and review of the literature. *Am J Gastroenterol* 2000;95:310–2.
- 6 Crow YJ. Type I interferonopathies: a novel set of inborn errors of immunity. *Ann N Y Acad Sci* 2011;1238:91–8.
- 7 Crow YJ, Stetson DB. The type I interferonopathies: 10 years on. *Nat Rev Immunol* 2022;22:471–83.
- 8 Liu Y, Jesus AA, Marrero B, *et al.* Activated STING in a vascular and pulmonary syndrome. *N Engl J Med* 2014;371:507–18.
- 9 Jeremiah N, Neven B, Gentili M, *et al.* Inherited STING-activating mutation underlies a familial inflammatory syndrome with lupus-like manifestations. *J Clin Invest* 2014;124:79100:5516–20.
- 10 Frémond M-L, Rodero MP, Jeremiah N, *et al.* Efficacy of the Janus kinase 1/2 inhibitor ruxolitinib in the treatment of vasculopathy associated with TMEM173-activating mutations in 3 children. *J Allergy Clin Immunol* 2016;138:1752–5.
- 11 Sanchez GAM, Reinhardt A, Ramsey S, *et al.* JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. *J Clin Invest* 2018;128:98814:3041–52.
- 12 Vanderver A, Adang L, Gavazzi F, *et al.* Janus Kinase Inhibition in the Aicardi-Goutières Syndrome. *N Engl J Med* 2020;383:986–9.
- 13 Frémond M-L, Hadchouel A, Berteloot L, *et al.* Overview of STING-Associated Vasculopathy with Onset in Infancy (SAVI) Among 21 Patients. *J Allergy Clin Immunol Pract* 2021;9:803–18.
- 14 Frémond M-L, Hully M, Fournier B, *et al.* JAK Inhibition in Aicardi-Goutières Syndrome: a Monocentric Multidisciplinary Real-World Approach Study. *J Clin Immunol* 2023;43:1436–47.
- 15 Berrada KR, Belot A, Neven B, *et al.* Lung Transplantation under a Janus Kinase Inhibitor in Three Patients with SAVI Syndrome. *J Clin Immunol* 2023;43:2156–64.
- 16 Neven B, Al Adba B, Hully M, *et al.* JAK Inhibition in the Aicardi-Goutières Syndrome. *N Engl J Med* 2020;383:2190–1.
- 17 Volpi S, Insalaco A, Caorsi R, *et al.* Efficacy and Adverse Events During Janus Kinase Inhibitor Treatment of SAVI Syndrome. *J Clin Immunol* 2019;39:476–85.
- 18 Richez C, Truchetet M-E, Kostine M, *et al.* Efficacy of baricitinib in the treatment of rheumatoid arthritis. *Expert Opin Pharmacother* 2017;18:1399–407.
- 19 Riggs JM, Hanna RN, Rajan B, *et al.* Characterisation of anifrolumab, a fully human anti-interferon receptor antagonist antibody for the treatment of systemic lupus erythematosus. *Lupus Sci Med* 2018;5:e000261.
- 20 Gensous N, Lazaro E, Blanco P, *et al.* Anifrolumab: first biologic approved in the EU not restricted to patients with a high degree of disease activity for the treatment of moderate to severe systemic lupus erythematosus. *Expert Rev Clin Immunol* 2024;20:21–30.
- 21 Furie R, Khamashta M, Merrill JT, *et al.* Anifrolumab, an Anti-Interferon- α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. *Arthritis Rheumatol* 2017;69:376–86.
- 22 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.
- 23 Morand EF, Furie R, Tanaka Y, *et al.* Trial of Anifrolumab in Active Systemic Lupus Erythematosus. *N Engl J Med* 2020;382:211–21.
- 24 Casey KA, Guo X, Smith MA, *et al.* Type I interferon receptor blockade with anifrolumab corrects innate and adaptive immune perturbations of SLE. *Lupus Sci Med* 2018;5:e000286.
- 25 Vital EM, Merrill JT, Morand EF, *et al.* Anifrolumab efficacy and safety by type I interferon gene signature and clinical subgroups in patients with SLE: post hoc analysis of pooled data from two phase III trials. *Ann Rheum Dis* 2022;81:951–61.
- 26 Tummala R, Abreu G, Pineda L, *et al.* Safety profile of anifrolumab in patients with active SLE: an integrated analysis of phase II and III trials. *Lupus Sci Med* 2021;8:e000464.
- 27 Tanaka Y, Takeuchi T, Okada M, *et al.* Safety and tolerability of anifrolumab, a monoclonal antibody targeting type I interferon receptor, in Japanese patients with systemic lupus erythematosus: A multicenter, phase 2, open-label study. *Mod Rheumatol* 2020;30:101–8.
- 28 Chatham WW, Furie R, Saxena A, *et al.* Long-Term Safety and Efficacy of Anifrolumab in Adults With Systemic Lupus Erythematosus: Results of a Phase II Open-Label Extension Study. *Arthritis Rheumatol* 2021;73:816–25.
- 29 Breillat P, Mathian A, Rozenberg F, *et al.* Is there an increased risk of severe COVID-19 among patients with systemic lupus erythematosus treated with anifrolumab? *Lupus (Los Angel)* 2023;32:453–5.
- 30 Kalunian KC, Furie R, Morand EF, *et al.* A Randomized, Placebo-Controlled Phase III Extension Trial of the Long-Term Safety and Tolerability of Anifrolumab in Active Systemic Lupus Erythematosus. *Arthritis Rheumatol* 2023;75:253–65.
- 31 ACR Meeting Abstracts. Anifrolumab normalizes the type i interferon signature in a cohort of patients with type i interferonopathies. Available: <https://acrabstracts.org/abstract/anifrolumab-normalizes-the-type-i-interferon-signature-in-a-cohort-of-patients-with-type-i-interferonopathies/>
- 32 Doroudchi A, Butte M. First reported use of anifrolumab to treat a monogenic interferonopathy (DNASE2 loss of function). *Clin Immunol* 2023;250:109593.
- 33 Mansilla-Polo M, Martín-Torregrosa D, Escutia-Muñoz B, *et al.* Successful Treatment of Stimulator of Interferon Genes-Associated Vasculopathy of Infantile Onset SAVI Syndrome With Anifrolumab. *JAMA Dermatol* 2024;160:899–901.
- 34 Shaw KS, Rajeh A, Le T, *et al.* Anifrolumab for Adolescent Discoid Lupus Erythematosus. *JAMA Netw Open* 2023;6:e2338200.
- 35 Balka KR, De Nardo D. Molecular and spatial mechanisms governing STING signalling. *FEBS J* 2021;288:5504–29.