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EDITORIAL

Anifrolumab: the new frontier in the treatment of genetic interferonopathies

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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 T1Is[10–14] 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

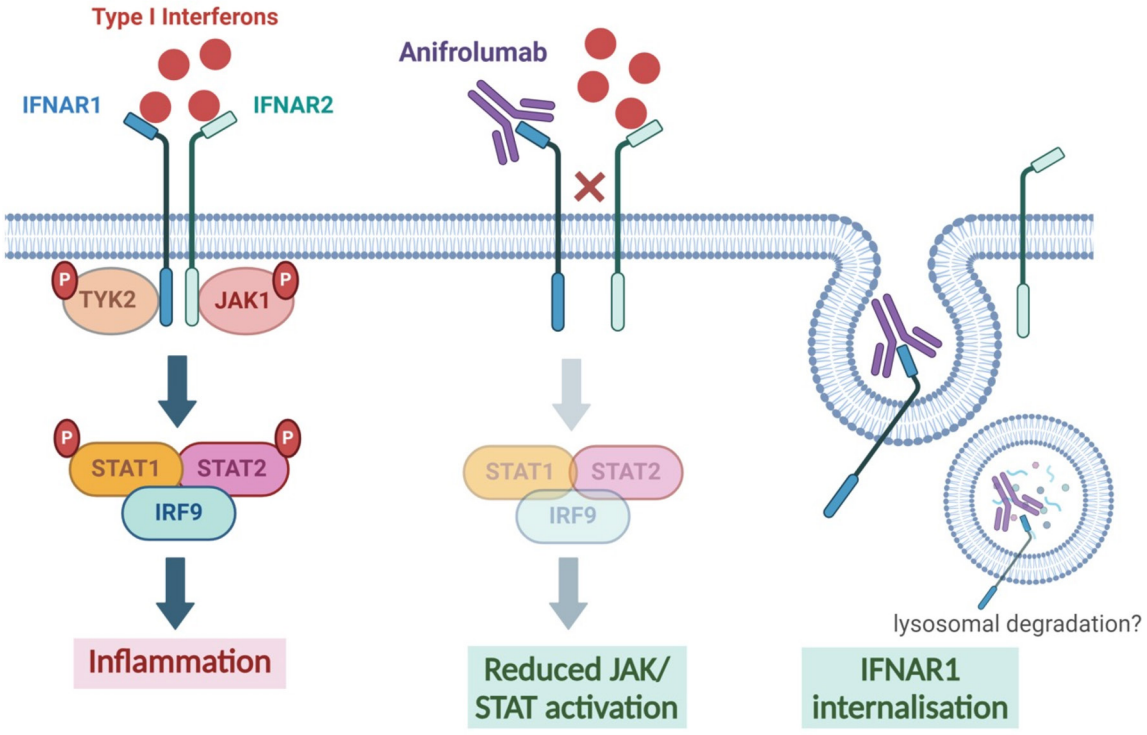

Figure 1 Effect of anifrolumab on the type I interferon pathway. Type I interferons are recognised by their specific receptor, IFNAR, which consists of two subunits, IFNAR1 and IFNAR2. Receptor binding leads to the activation of intracellular kinases, JAK1 and TYK2, that phosphorylate STAT1 and STAT2. 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 surface[19] (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 FcgR 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 T1Is has been reported in a few patients.[31 32] The team of Dr Raphaela 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.

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