JAK inhibition in the type I interferonopathies

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The type I interferonopathies (T1Is) are Mendelian inborn errors of immunity characterized by upregulated type I interferon (T1IFN) signaling.1 The most frequently recognized disorders within this grouping are Aicardi-Goutières syndrome (AGS), STING-associated vasculopathy with onset in infancy (SAVI), COPA syndrome, the proteasomal-related autoinflammatory syndromes (PRAAS), and signal transducer and activator of transcription (STAT) 1 gain-of-function (Table I). On the premise that enhanced T1IFN signaling represents both a disease biomarker and a driver of pathology, attention has turned to the use of drugs inhibiting Janus kinase (JAK) 1, a component of the T1IFN receptor complex, as a treatment strategy in this group of severe disorders.

On ligand stimulation, receptor-associated JAKs become activated, and phosphorylate both each other and the intracellular tail of their receptors, thereby creating docking sites for latent, cytoplasmic transcription factors (signal transducers and activators of transcription), which in turn bind DNA to regulate gene expression.2 The selective interaction of different receptor chains with 1 of 4 JAKs (JAK1, JAK2, JAK3, TYK2) confers distinct functions in vivo, with T1IFN receptor engagement of JAK1 and TYK2 leading to activation of a transcription factor complex comprising STAT1, STAT2, and IRF9 (referred to as ISGF3) (Fig 1).

Although first described in 1984, the potential of immunomodulatory therapy in AGS, primarily a neurological disease, was not appreciated until recently. Rather, it was the definition of SAVI, 30 years later in a pediatric rheumatology context, that heralded the trailblazing of directed biologics in the T1Is.3 Importantly, patients subsequently identified to represent cases of PRAAS and SAVI were noted to respond poorly to drugs targeting the proinflammatory cytokines IL-1, TNF, and IL-6, prompting Goldbach-Mansky and colleagues, in 2012, to initiate a protocol of transcription (STAT) 1 gain-of-function. However, the interpretation of these data is not straightforward because of the small number of patients treated with 1 of 3 first-generation JAK inhibitors (ruxolitinib, baricitinib, and tofacitinib).

The first published description of the use of a JAK inhibitor in a T1I indicated a favorable, albeit partial, clinical response to ruxolitinib in 3 children with SAVI treated over a period of 6 to 18 months.4 Improvements in the skin, pulmonary, and systemic features of the disease were mirrored by a decrease in steroid dependency, improved hematological indices, and a reduction in laboratory markers of inflammation and T1IFN signaling. A number of subsequent case reports have suggested similarly favorable effects in SAVI, AGS, PRAAS, COPA syndrome, and STAT1 gain-of-function. However, the interpretation of these data is not straightforward because of the small number of patients treated, the different drugs and dosing regimens used, and variability in length of follow-up.

To date, the largest reported series are those of Sanchez et al,5 Forbes et al,6 Frémond et al,7 and Vanderver et al (Table II). Sanchez et al treated 10 patients with PRAAS, 4 with SAVI, and 1 with AGS using baricitinib over a mean duration of 3 years. A particularly favorable response was seen in PRAAS, where 50% of patients achieved durable clinical remission off steroids, with normalization of inflammatory markers. Forbes et al treated 11 patients with STAT1 gain-of-function with ruxolitinib, and Frémond et al treated 8 patients with SAVI (including the 3 patients from their initial report), also with ruxolitinib, both reporting good clinical efficacy relating to cardinal disease features. Meanwhile, the treatment of 35 patients with AGS using baricitinib over a period of 12 to 44 months was described by Vanderver et al.8 Although improvements were seen in the context of the skin phosphorylation in patient T and B cells), tens of individuals across a number of different T1I-related genotypes have now been treated with 1 of 3 first-generation JAK inhibitors (ruxolitinib, baricitinib, and tofacitinib).

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TABLE I. Summary of the major clinical features of the T1Is discussed in the article

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<th>Major clinical features</th>
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<td>AGS</td>
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<td>PRAAS</td>
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GOF, Gain-of-function.
and systemic manifestations of AGS, in this report, as in others, assessing treatment efficacy at the level of the neurological system has proven difficult. The limited developmental gains observed might be explained by the presence of already-established brain damage at treatment initiation. However, Neven et al \(^9\) described the onset of AGS at the age of 15 months, despite treatment with ruxolitinib started at age 5 months when the child was asymptomatic. Of possible note, the authors observed concentrations of ruxolitinib in the cerebrospinal fluid to be only 10% of those in blood, suggesting the importance of central nervous system drug penetration. The observation of apparent neurological benefit in a child with biallelic mutations in USP18 following an increase in the dose of ruxolitinib from 5 mg to 10 mg twice daily might relate to this same point. \(^10\)

The use of the JAK inhibitors in the T1Is has to be considered carefully, taking into account clinical status and the need to monitor for potentially serious side effects. The natural history of these disorders suggests that life-long therapy might be necessary, the risks of which, particularly considering the onset of disease in childhood and the potential effect of treatment on growth and bone remodeling, are unclear. Generally, these drugs have been reasonably well tolerated, but can be associated with enhanced rates of infection, anemia, lymphopenia, and thrombosis, all of these features having been reported in patients with T1Is. Because of a recognized risk of rebound cytokine storm, it is important never to stop treatment abruptly, tapering any cessation of therapy with steroid cover.

Clinical improvements with the use of JAK inhibition, the first directed therapy in the T1Is, might represent evidence of the pathological role of T1IFN in these disorders. However, the fact that all of the currently used JAK inhibitors target more than 1 JAK, and that JAK1 is not exclusive to the T1IFN receptor, limits the security of such an interpretation. Currently, there is no evidence to favor one JAK inhibitor over another on a clinical basis. However, second-generation JAK inhibitors with increased specificity, including JAK1-specific inhibitors, are entering the market or are under investigation, and may allow for more targeted therapy, presumably with a reduced side-effect profile.

Summarizing, given the small number of patients treated, and variability in the protocols used, assessing the effect of JAK inhibitors in the T1Is is challenging. Further studies are needed to better understand the role of JAK inhibition in these disorders.
inhibition in the T1Is remains challenging. Although, overall, early results are encouraging (with efficacy dependent, at least in part, on disease genotype/phenotype), the data are not commensurate with the use of IL-1-β blockade in systemic diseases related to enhanced IL-1-β activity, a criterion standard in the autoinflammatory field. Notably, treatment appears to be associated with only a partial, and sometimes minimal, reduction in interferon signaling measured in blood. However, increases in dose and dosing frequency are possibly limited by side-effect profiles. Thus, although representing an important advance, we believe that there remains a need for other treatments, perhaps used in combination, for this set of devastating disorders.

REFERENCES