JAK inhibition in STING-associated interferonopathy

We read with interest the paper by Konig *et al*[1] describing a novel pathogenic mutation in *TMEM173*. This report is important in highlighting the stable segregation of a skin-restricted phenotype across four generations, thus expanding the clinical spectrum associated with gain-of-function mutations in stimulator of interferon genes (STING). These authors also report the use of the Janus kinase (JAK)1/3 inhibitor tofacitinib in two of their patients. Unfortunately, since the treatment period was limited to a total of 17 days, it was not possible to draw any conclusions as to therapeutic efficacy. However, we have recently described the use of an alternative JAK(1/2) inhibitor, ruxolitinib, in three STING-mutated patients treated for a period of up to 18 months.[2] Importantly, in this study, we observed a marked improvement in all three major aspects of the STING-associated phenotype so far described, that is, systemic inflammation, pulmonary involvement and skin disease. Indeed, continued follow-up, now beyond 2 years, and the treatment of further four patients with ruxolitinib (unpublished data), confirms the clinical efficacy of this approach. Relating to the sudden cessation of treatment at 17 days implied in the report of Konig *et al*, we observed a marked relapse following the withdrawal of ruxolitinib in one patient—likely reflecting a cytokine rebound effect and thus indicating the need for careful monitoring in the case of treatment interruption.

Of note, our encouraging clinical data have not been mirrored by the apparently marked reduction of interferon stimulated genes (ISGs) described by Konig *et al* after 14 days of tofacitinib. Rather, consistent with a recent description of the treatment of mice splenic B cells with that same drug,[3] our longer term experience has been of an, at best, incomplete inhibition of the interferon signature in the blood of patients with *TMEM173* mutations. This phenomenon is possibly explained by the induction of feedback loops subsequent to JAK inhibition, and by our demonstration of the transient effect of ruxolitinib on phosphorylated signal transducer and activator of transcription 1 inhibition in patients cells tested ex vivo. These data thus highlight that a reduction of interferon-induced gene transcripts cannot necessarily be used as a read-out of clinical efficacy. As an allied issue, we postulate that the partial inhibition of ISG transcription by ruxolitinib in our hands probably explains the very low incidence of infection in the patients whom we have treated.

Konig *et al* also describe elevated levels of interferon β gene transcript in their patients. We find this result somewhat unexpected since our experience of measuring interferon α/β mRNA expression in the peripheral blood of five untreated STING-mutated patients, and a much larger number of individuals with other type I interferonopathies, is of an absence of such transcripts. Consistent with its high potency, type I interferon mRNA is usually unrecordable in healthy individuals and, indeed, has recently been shown to be undetectable even after vaccination in the presence of a robust ISG response.[4] The above discrepancies between data sets might relate to technical issues, differences in disease-associated mutation, or the use of distinct JAK inhibitors. Thus, we have yet to ascertain a patient with the specific p.Gly166Glu mutation reported by Kenig *et al*, and we have no experience of the use of tofacitinib. More broadly, the question arises as to which JAK inhibitor would be most appropriate to use in STING-mutated patients. Indeed, in light of proven clinical efficacy for a disease associated with high childhood morbidity and mortality, and otherwise refractory to conventional immunosuppression (including steroids, methotrexate and anti-CD20 monoclonal antibodies),[5] the choice of appropriate therapeutic molecule and dosing regimen is now a matter of prime clinical importance. In terms of interferon signalling, the most logical approach to JAK inhibition would be with a JAK1-specific inhibitor. Thus, the field awaits the comprehensive evaluation of efficacy and side effect profile using treatments directly targeting type I interferon-driven pathology.

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