Response to: 'JAK inhibition in STING-associated interferonopathy' by Crow *et al*

We appreciate the comments by Crow *et al* on our report of a gain-of-function mutation in *STING* in familial chilblain lupus and the effect of the JAK inhibitor tofacitinib.¹ In a concurrent study,² Crow *et al* reported a marked clinical improvement in three patients with stimulator of interferon genes (STING)-associated vasculopathy³ using the JAK inhibitor ruxolitinib. This was accompanied by an incomplete reduction in the expression of interferon (IFN)-stimulated genes (ISGs) in blood raising the question as to the IFN signature as a read-out of clinical efficacy. This is a very important question that we cannot

answer with regard to tofacitinib as we have no long-term experience with this JAK inhibitor in patients with type I interferonopathies. However, we have used ruxolitinib in two patients with Aicardi-Goutières syndrome (AGS), an inflammatory encephalopathy characterised by chronic type I IFN activation.⁴ Both patients carried biallelic *RNASEH2B* mutations and suffered from severe developmental delay. They received no other medications, when treatment with ruxolitinib (0.2 mg/kg increased to 0.5 mg/kg over 1 week) was started at the age of 23 months. Ruxolitinib was well tolerated without any signs of myelosuppression. Both patients responded with a marked reduction in ISG expression within 2 weeks (figure 1). Shortly after entering nursery, patient 1 presented with three episodes of upper respiratory infections accompanied by leucocytosis,

Figure 1 Interferon (IFN) score of patients with Aicardi-Goutières syndrome (AGS) treated with ruxolitinib. (A) IFN score calculated from the median fold change in relative mRNA for seven IFN-stimulated genes (ISGs) (*IFIT1*, *ISG15*, *RSAD2*, *SIGLEC1*, *IFI27*, *IFI44*, *IFI44L*) normalised to glyceraldehyde 3-phosphate dehydrogenase. Negative scores are those <3488 (mean of control IFN score plus 2 SD). IFN scores of patient 1 (n=2) and patient 2 (n=3) before treatment with ruxolitinib show increased expression of ISGs ($p \leq 0.001$ vs controls; Wilcoxon-Mann-Whitney test). (B) IFN score during treatment with ruxolitinib. # indicates upper respiratory infections.

Figure 2 Expression of *IFNB* gene and interferon (IFN)-stimulated genes (ISGs). Quantitative reverse transcription PCR of *IFNB* and seven ISGs in whole blood measured in 47 patients with molecularly defined type I interferonopathies and 13 healthy controls. The relative abundance of each target transcript was normalised to the expression level of glyceraldehyde 3-phosphate dehydrogenase and relative to a single calibrator. Each sample was run in triplicate. Horizontal bars denote median relative mRNA expression value. NS, not significant. Wilcoxon-Mann-Whitney test. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

elevated C reactive protein and an increased IFN score. The clinical course was uneventful. Because infections were attributed to environmental exposure, rather than immunosuppression, ruxolitinib was continued. After infections resolved, his IFN score gradually decreased (figure 1). Overall, patient 1 showed some developmental progress regarding his exploratory behaviour and feeding skills along with a decline of dystonic movements, although we cannot state with certainty whether this is due to ruxolitinib. Patient 2 exhibited a sustained reduction in ISG expression at 3 months of ruxolitinib treatment.

Clearly, conclusive evidence regarding the benefit of JAK inhibition in patients with AGS must await further clinical investigations. However, the differences in ISG responses in patients treated with ruxolitinib observed by the two groups might be related to differences in dosing, age or the underlying molecular pathology. Of note, all three patients in the study by Crow *et al* received steroids, one patient additionally hydroxychloroquine, while treated with ruxolitinib.² These immunomodulatory compounds may have influenced the metabolism of ruxolitinib by cytochrome P450 as well as immune responses.

In their letter, Crow *et al* also state *IFNA* and *IFNB* mRNA in blood of their patients to be absent. While we have no data on the expression of the large *IFNA* gene family in our patients, we routinely measured the expression of the *IFNB* gene alongside ISGs. In contrast to ISGs, we noted an extraordinary variability in *IFNB* expression over several orders of magnitude both among healthy controls and patients (figure 2), in agreement with a highly complex and dynamic regulation of *IFNB* gene expression.⁵

Notably, the exaggerated ISG response observed in AGS patient 1 during infection might reflect an overprimed IFN axis and is consistent with the clinical observation that the onset of AGS commonly coincides with an infection or a vaccination. While JAK inhibition appears to be of clinical benefit in patients with type I IFN-driven disease, complete inhibition of the IFN axis that could impede antiviral defence is undesirable. Thus, further investigations are necessary to identify the most appropriate set of ISGs to monitor and/or predict clinical responses to JAK inhibition.

Victoria Tüngler,¹ Nadja König,¹ Claudia Günther,² Kerstin Engel,¹ Christoph Fiehn,³ Martin Smitka,⁴ Maja von der Hagen,⁴ Reinhard Berner,⁵ Min Ae Lee-Kirsch¹

¹Molecular Pediatrics, Department of Pediatrics, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

²Department of Dermatology, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

³ACURA Akutklinik für Rheumatologie Baden-Baden, Baden-Baden, Germany

⁴Abteilung Neuropaediatric, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

⁵Pediatric Infectious Diseases and Rheumatology, Department of Pediatrics, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

Correspondence to Professor Min Ae Lee-Kirsch, Department of Pediatrics, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Fetscherstr. 74, 01307 Dresden, Germany; minae.lee-kirsch@uniklinikum-dresden.de

VT and NK contributed equally.

Contributors VT, NK, CG and MAL-K drafted the letter. VT, CF, MS, MvdH and RB collected and evaluated clinical data. NK, CG and KE performed and analysed experiments. All authors critically reviewed and approved the letter. MAL-K supervised the study.

Funding Deutsche Forschungsgemeinschaft (GU1212/1-1 and GU 1212/1-2 to CG, TU 421/1-2 to VT, LE 1074/3-1 and LE 1074/4-1 to MAL-K).

Competing interests None.

Ethics approval Technische Universität Dresden.

Provenance and peer review Commissioned; internally peer reviewed.

CrossMark

To cite Tüngler V, König N, Günther C, *et al*. *Ann Rheum Dis* 2016;**75**:e76.

Received 7 October 2016

Accepted 13 October 2016

► <http://dx.doi.org/10.1136/annrheumdis-2016-210504>

Ann Rheum Dis 2016;**75**:e76. doi:10.1136/annrheumdis-2016-210565

REFERENCES

- König N, Fiehn C, Wolf C, *et al*. Familial chilblain lupus due to a gain-of-function mutation in STING. *Ann Rheum Dis* Published Online First: 26 Aug 2016. doi: 10.1136/annrheumdis-2016-209841
- 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* Published Online First: 20 Aug 2016. doi: 10.1016/j.jaci.2016.07.015
- Liu Y, Jesus AA, Marrero B, *et al*. Activated STING in a vascular and pulmonary syndrome. *N Engl J Med* 2014;371:507–18.
- Lee-Kirsch MA, Wolf C, Kretschmer S, *et al*. Type I interferonopathies: an expanding disease spectrum of immunodysregulation. *Semin Immunopathol* 2015;37:349–57.
- Mostafavi S, Yoshida H, Moodley D, *et al*. Parsing the interferon transcriptional network and its disease associations. *Cell* 2016;164:564–78.