More on STAT1 Gain of Function, Type 1 Diabetes, and JAK Inhibition

TO THE EDITOR: Chaimowitz et al. (Oct. 8 issue)[1] report diabetes remission following ruxolitinib treatment in a patient with a signal transducer and activator of transcription 1 (*STAT1*) gain-of-function mutation.[1] This work is exciting and important, but we believe the authors were incorrect in referring to the diabetes in this monogenic autoimmune syndrome as type 1 diabetes.

Although both type 1 diabetes and diabetes in monogenic autoimmune syndromes are autoimmune diseases, with the associated islet autoantibodies, there is a crucial difference in their genetic susceptibility and hence their cause. Type 1 diabetes is a polygenic autoimmune disease with well-described associations with common variants in the HLA locus.[2] In contrast, the diabetes described by Chaimowitz et al. is caused by a highly penetrant variant in a single gene in a monogenic autoimmune form of diabetes and is not associated with HLA.[3,4] Specific immunomodulatory therapy can be chosen on the basis of the specific gene or pathway involved in monogenic autoimmunity, as shown by the authors, but the difference in causation means it is unlikely that the same therapy will prevent the development of the far more common type 1 diabetes.[5] We believe that diabetes in any monogenic autoimmune condition should be referred to as monogenic autoimmune diabetes and should include its gene name — in this case, *STAT1*-monogenic autoimmune diabetes — rather than being referred to by the term "type 1 diabetes."

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Our use of the term "type 1 diabetes" in this report aligns with published guidelines that define type 1 diabetes as insulin deficiency with loss of proper beta-cell function and the presence of islet autoantibodies.[1] Currently, the definition of type 1 diabetes is broad and includes both autoimmune and idiopathic diabetes. An increasing number of rare genetic mutations, such as the *STAT1* gain-of-function mutation, are strongly associated with autoimmune diabetes.[2] However, we would note that the association is incomplete and probably involves genetic interactions with other risk variants present in polygenic autoimmune diabetes that include the HLA locus.[3] Thus, autoimmune islet destruction in both polygenic and monogenic forms of diabetes may not be distinct but rather share commonalities, including a similar repertoire of autoreactive T cells and B cells. Accordingly, we believe that this particular report of diabetes reversal may be instructive beyond the rare constellation of findings in our patient. Nonetheless, we agree that a more refined definition of type 1 diabetes is important given the overall umbrella of autoimmune diabetes, which could be further subdivided into polygenic and monogenic subtypes.

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Since publication of their letter, the authors report no further potential conflict of interest.

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