CORRESPONDENCE

JAK Inhibition in STAT1 Gain-of-Function–Mediated Treatment-Resistant Autoimmune Hepatitis

TO THE EDITOR: Autoimmune hepatitis responds well to long-term immunosuppression with low-dose glucocorticoids with added azathioprine or mycophenolate in approximately 80 to 90% of treated children. In children with treatment-resistant disease, cyclosporine, tacrolimus, rituximab, and biologic agents have been tried with varying success.[1]

Here, we report a case of a 21-month-old girl who presented with jaundice, fatigue, and abnormal aminotransferase levels and had received a diagnosis of type II autoimmune hepatitis and autoimmune hypothyroidism (titer of liver–kidney microsomal [LKM] antibodies, 1:10,520; and a positive test for antithyrotropin receptor autoantibodies). Results on the initial liver biopsy suggested autoimmune hepatitis (Fig. 1A). She began receiving prednisolone at a dose of 2 mg per kilogram of body weight but did not have a biochemical response after 6 weeks of therapy. She then began receiving azathioprine (2 mg per kilogram), which was eventually replaced by mycophenolate (40 mg per kilogram). After 6 months of therapy, the patient had three further episodes of severe biochemical relapse, for which she received high-dose glucocorticoids. Interim liver biopsies revealed incompletely treated autoimmune hepatitis (Fig. 1B and 1C).

The patient was found to have a heterozygous c.821G→A p.(Arg274Gln) pathogenic variant in the gene encoding signal transducer and activator of transcription 1 (*STAT1*), as previously reported (ClinVar number, VCV000030085.35).[2] Functional assays in the patient repeatedly showed abnormally high *STAT1* phosphorylation as compared with healthy controls (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org) — findings that confirmed an autosomal dominant *STAT1* gain-of-function defect. Fourteen months after the patient received the diagnosis of autoimmune hepatitis, treatment with baricitinib, an inhibitor of Janus kinase 1 (JAK1) and 2 (JAK2), was started (4 mg per day) for glucocorticoid-sparing effects, on the basis of previous reports of JAK inhibition for *STAT* mutations.[3] Baricitinib was chosen over other JAK inhibitors owing to minimal hepatic metabolism and predominantly renal excretion. Within weeks, the patient's aminotransferase levels normalized.

At 44 months after diagnosis, results on liver biochemical testing were normal, and the patient's spleen had reduced from 11.0 cm to 7.1 cm in diameter; however, testing for anti-LKM antibodies remained strongly positive. A liver-biopsy sample that was obtained 4 months after the initiation of baricitinib therapy showed an absence of appreciable inflammation with residual mild fibrosis (Fig. 1D). She was weaned off mycophenolate and is continuing to receive daily baricitinib (8 mg) and prednisolone (2.5 mg) along

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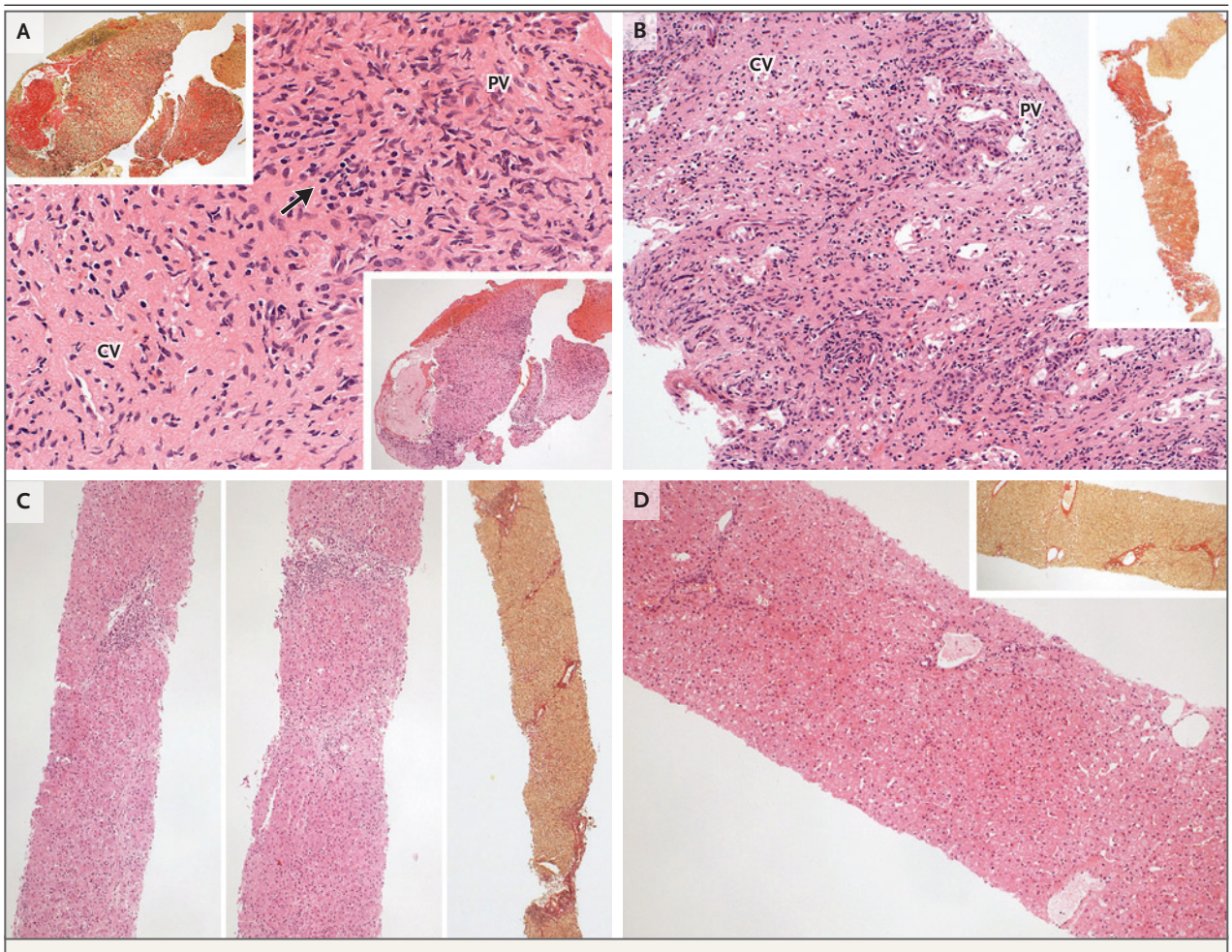

Figure 1. Biopsy Samples Obtained from a Patient with Autoimmune Hepatitis.

A biopsy sample that was obtained at presentation, when the patient was 21 months of age, showed chronic cholestatic hepatitis with interface activity featuring lymphocytes and plasma cells (Panel A, arrow; hematoxylin and eosin stain). Panacinar confluent necrosis was present; the central vein (CV) and portal vein (PV) are labeled to provide histologic landmarks. There was established postnecrotic bridging fibrosis (Panel A, upper inset [picrosirius red stain]; the lower inset shows equivalent upper-inset detail with hematoxylin and eosin stain). A follow-up biopsy sample obtained 8 months later showed ongoing chronic portolobular hepatitis with areas of panacinar confluent necrosis and areas of fibrosis similar to findings in the biopsy sample obtained at presentation (Panel B, main image [magnification, 100×] and inset [magnification, 40×]; picrosirius red stain). An additional follow-up biopsy sample obtained 6 months later showed ongoing chronic hepatitis with foci of bridging fibrosis (Panel C, left and center images [showing different locations of patchy fibrosis in the liver; hematoxylin and eosin stain] and right image [picrosirius red stain]). A biopsy sample obtained after the initiation of baricitinib therapy showed no appreciable inflammation (Panel D, main image; hematoxylin and eosin stain) and mild portoseptal and perivenular fibrosis (Panel D, inset; picrosirius red stain).

with fluconazole and azithromycin for infection prophylaxis.

The JAK-dependent *STAT* apparatus constitutes essential intracellular signaling pathways that induce phosphorylation and stimulation of various proinflammatory cytokines, interleukins, and growth factors. The proportion of interleukin-17–producing and interleukin-22–producing T cells is markedly decreased in patients with *STAT1* gain-of-function mutations,[4] which may relate to classic immunopathological observations of reduced numbers and impaired function of regulatory T cells in patients with untreated or relapsed autoimmune hepatitis.[5]

Autoimmune hepatitis has a complex genetic and environmental pathogenesis, but there is a possibility of an underlying genetic variant of immune regulation in a proportion of treat-

ment-resistant cases. Such patients would benefit from genetic analysis and more targeted immune treatments, rather than from nonselective enhancement of antiinflammatory response.

Nedim Hadžić, M.D.
Maesha Deheragoda, M.D., Ph.D.
King's College Hospital
London, United Kingdom
nedim.hadzic@kcl.ac.uk

Austen Worth, M.D., Ph.D.
Great Ormond Street Hospital
London, United Kingdom

Sanjay Bansal, M.D.
Marianne Samyn, M.D.
King's College Hospital
London, United Kingdom

Maaike Kusters, M.D., Ph.D.
Great Ormond Street Hospital
London, United Kingdom

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Patisiran in Patients with Transthyretin Cardiac Amyloidosis

TO THE EDITOR: The primary end point in the APOLLO-B trial conducted by Maurer et al. (Oct. 26 issue)[1] was the change from baseline in the distance covered on the 6-minute walk test at 12 months. The decline in the distance was lower in the patisiran group than in the placebo group (median difference, 14.69 m; 95% confidence interval [CI], 0.69 to 28.69; P=0.02). However, the minimal clinically important difference in the distance on 6-minute walk test for adults with pulmonary arterial hypertension is approximately 33 m.[2] The first secondary end point was the change in score on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS), on which scores range from 0 to 100, with higher scores indicating better health status. The KCCQ-OS score increased in the patisiran group and decreased in the placebo group (mean between-group difference in the change in score, 3.7 points; 95% CI, 0.2 to 7.2; P=0.04). This difference is again below the minimal clinically important difference, which is approximately a 5-point change in the KCCQ-OS score.[3] Significant benefits were not observed for the second and third secondary end points. Arthralgia and muscle spasms occurred more often among the patients in the patisiran group than among those in the placebo group (arthralgia in 8% vs. 4% and muscle spasms in 7% vs. 2%). The authors conclude that patisiran therapy resulted in preserved functional capacity, health status, and quality of life. In my opinion, the conclusions should be different.

Manuel Martínez-Sellés, M.D., Ph.D.
Hospital Universitario Gregorio Marañón
Madrid, Spain
mmselles@secardiologia.es

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

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THE AUTHORS REPLY: What constitutes a meaningful change is determined by many factors, including the condition being studied and the study duration. Transthyretin cardiac amyloidosis is a progressive condition in which declines in func-