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Clinical Improvement with JAK2 Inhibition in Chuvash Polycythemia

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TO THE EDITOR

Chuvash polycythemia is a rare congenital polycythemia caused by a homozygous R200W (c.598C→T) germline mutation in the von Hippel–Lindau gene (*VHL*).^{1,2} Patients with Chuvash polycythemia present with erythrocytosis and symptoms such as headache, dizziness, dyspnea, and plethora.^{1,3} The disease is associated with an increased risk of hemorrhage, thrombosis, and early death.^{1,3,4} Intermittent phlebotomy has been used in the management of Chuvash polycythemia without clearly established efficacy.^{3,4} The VHL protein has been shown to target phosphorylated Janus kinase 2 (pJAK2) for ubiquitin-mediated degradation.⁵ Treatment of *Vhl*^{R200W/R200W}-knock-in mice with a JAK2 inhibitor (TG101209) led to normalization of the hematocrit and a reduction in splenomegaly.⁵ These findings provide a strong rationale for JAK2 inhibition as a therapeutic approach for Chuvash polycythemia.

We now report three patients with the disease who were treated with the JAK1 and JAK2 inhibitor ruxolitinib and who had symptomatic and hematologic improvement (Fig. 1A). Ruxolitinib was provided by Incyte, which was given access to the data and was allowed to review the manuscript before submission for publication; no specific modifications were requested by Incyte. Research samples were obtained through an institutional review board–

Drs. Zhou, Knoche, and Engle contributed equally to this letter.

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approved protocol in accordance with the principles of the Declaration of Helsinki. Each patient was confirmed to be homozygous for the *VHL* R200W mutation through direct sequencing (data not shown).

Patient CP-01 received a diagnosis of Chuvash polycythemia at 3 years of age and went on to have multiple thrombotic complications, including mesenteric-vein thrombosis and myocardial infarction by 27 years of age. He had chronic headaches and severe back pain and exhibited oscillations in his platelet count that were exacerbated after splenectomy. Ruxolitinib treatment was initiated at a dose of 5 mg twice daily, and the dose was gradually increased to 20 mg twice daily. At 69 weeks of treatment, he reported clinically significant improvement in his back pain and a reduction in phlebotomy frequency from weekly to less than once a month. His platelet-count oscillations also improved dramatically, which was associated with marked improvement in his headaches (Fig. 1B).

Patient CP-02 presented with erythrocytosis at 18 months of age. He had multiple thrombotic events, including deep-vein thrombosis, pulmonary embolism, and portal-vein thrombosis. He had severe abdominal pain that was attributed to his previous abdominal thrombosis. Ruxolitinib treatment was initiated at a dose of 10 mg twice daily, which was adjusted to 20 mg twice daily. This patient had a clinically significant decrease in phlebotomy requirement through 78 weeks of treatment (Fig. 1B) and reported marked improvement in his abdominal pain.

Patient CP-03 first presented with erythrocytosis at 5 years of age. Her symptoms included fatigue, plethora, and aquagenic pruritus, but she had no thrombotic complications. After starting ruxolitinib at a dose of 10 mg twice daily, she had improvement in her symptoms and a clinically significant decrease in phlebotomy requirement through 21 weeks of treatment (Fig. 1B).

Each patient had hematologic and symptomatic improvement, with no major safety issues or serious side effects to date. Correlative studies showed that clinical responses were associated with decreases in erythroid-colony formation and inflammatory cytokine levels (data not shown). On the basis of these findings, we believe that JAK inhibitors merit further testing in the treatment of patients with Chuvash polycythemia.

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Figure 1. Patient Characteristics at Baseline and Clinical Response to Ruxolitinib in Three Patients with Chuvash Polycythemia

Panel A shows laboratory values, phlebotomy requirement, and symptoms for all three patients before treatment and during ruxolitinib therapy. ND denotes not determined. Panel B shows the effects of ruxolitinib on platelet-count oscillations in Patient CP-01 and the effects of ruxolitinib on hematocrit levels and phlebotomy requirements in Patients CP-02 and CP-03.