

Diamond-Blackfan anemia in remission for 2 years on valproic acid

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Dear editor, Diamond-Blackfan anemia (DBA) is a congenital macrocytic anemia characterized by defective erythroid progenitor maturation with normal megakaryocytic and granulocytic differentiation.¹ There is also reticulocytopenia and increased red blood cell (RBC) fetal hemoglobin (HbF).¹ About 25% of patients have a mutation on chromosome 19 that involves the gene encoding ribosomal protein S19 (RPS19).¹ The link between defective erythropoiesis and RPS19 is not clear yet.

We read with interest the recent study by Chiocchetti et al. in which the authors found that RPS19 binds a ubiquitous serine-threonine kinase PIM-1. The PIM-1/RPS19 interaction can phosphorylate RPS19 *in vitro* and may play a role in translational control.² PIM-1 is expressed through the JAK/STAT mediated mitogenic response to erythropoietin.² We reported a case of DBA that responded to valproic acid treatment.³ The patient is still in remission for more than two years while maintained only on valproic acid. She is a 23 year old woman with history of DBA since the age of 16 months. She had received different treatment regimens including prednisone for 13 years, methotrexate and cyclosporine for 3 years, and metoclopramide for 4 months. She developed autoimmune hemolytic anemia, underwent splenectomy, and had frequent blood transfusions including least incompatible blood. Despite this, the mean hemoglobin level remained at 6.4 g/dL and reticulocytes 0.1%. More than two years ago, she started taking valproic acid for generalized tonic-clonic seizures at a dose of 30 mg/kg per day with good seizure control. Blood valproic acid levels were therapeutic. Since then, the patient has required no further blood transfusions. Hemoglobin stabilized at a mean value of 12.6 g/dL, and reticulocytes count increased to 4%. Serial HbF levels have been 1.1% to 1.4%, and mean corpuscular volume, 92 to 96.

Many DBA patients initially respond to corticosteroids, but others require lifelong RBC transfusions. Other therapeutic modalities include androgens, cyclosporine, inter-

leukin-3, metoclopramide, and bone marrow transplantation.¹ We report here remission of DBA on valproic acid for more than 2 years. Valproic acid is structurally related to butyrates, and is shown to increase the concentration of HbF and the percentage of red blood cells that contained HbF^{4,5} through modulation of the mitogen-activated protein kinase signal transduction system.⁶

It is not clear how valproic acid worked in this patient but it didn't affect HbF levels. We postulate that valproic acid might have modulated the expression of PIM-1 and thus the translational control. Other mechanisms independent of RPS19 are also possible. We recommend considering the use of valproic acid in treating DBA if there is no response to other therapies. Further studies are needed to explore the potential benefits of this drug or other butyrates in treating DBA.

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