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Porphyria Reply

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Porphyria

TO THE EDITOR: In their review article, Bissell and colleagues (Aug. 31 issue)[1] discuss porphyria. In the same issue, Reilley and Leston provide a timely Perspective article on the treatment of hepatitis C virus (HCV) infection, and they highlight discrepancies in the treatment of this infection in the United States.[2] Bissell et al. cite a case report that suggests possible resolution of porphyria cutanea tarda with treatment of HCV infection,[3] which affects two thirds of patients with porphyria cutanea tarda.

In Australia, highly effective direct-acting antiviral therapy has been available without restriction since March 2016. Through the oversight of a multidisciplinary clinic for patients with porphyria, eight patients with porphyria cutanea tarda (six men and two women; median age, 59 years) have been treated and cured of HCV infection. None of the patients had cirrhosis or severe fibrosis on assessment. The median ferritin level decreased from 516 μg per liter to 63 μg per liter (P=0.02) (reference range, 15 to 200 μg per liter) without the need for further venesection, while the uroporphyrin level decreased from 3430 nmol per liter to less than 300 nmol per liter after eradication of HCV (P=0.02) (normal value, <40 nmol per liter).

In many parts of the world, direct-acting antiviral therapy has been limited to or prioritized in patients with clinically significant hepatic fibrosis. However, direct-acting antiviral therapy offers important and probably curative benefits in patients with porphyria cutanea tarda and should be available despite an absence of clinically significant fibrosis in this cohort.

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Dr. Sood reports receiving speaking fees from Bristol-Myers Squibb and fees for serving on an advisory board from AbbVie Australia. No other potential conflict of interest relevant to this letter was reported.

1. Bissell DM, Anderson KE, Bonkovsky HL. Porphyria. N Engl J Med 2017;377:862-72.
2. Reilley B, Leston J. A tale of two epidemics — HCV treatment among Native Americans and veterans. N Engl J Med 2017;377:801-3.
3. Sheikh MY, Wright RA, Burruss JB. Dramatic resolution of skin lesions associated with porphyria cutanea tarda after interferon-alpha therapy in a case of chronic hepatitis C. Dig Dis Sci 1998;43:529-33.

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TO THE EDITOR: Bissell et al. provide an overview of acute porphyrias. However, little is known about the care of patients with porphyria in developing countries that have limited health care systems.

In Colombia, acute attacks of porphyria are predominantly identified by means of qualitative tests, and the results of these tests can take more than 3 weeks to arrive.[1] Thus, delayed diagnoses are common. In addition, physicians have little knowledge of how to interpret these tests, and misdiagnosis frequently occurs. In a retrospective study, 32.4% of symptomatic patients received misdiagnoses of porphyria attacks even though they had normal or unmeasured levels of urinary porphobilinogen.[2] Furthermore, intravenous heme is sometimes impossible to obtain, and patients die without receiving treatment.[3] Consequently, the mortality from porphyria is approximately 48%.[4]

These deficiencies probably occur in most developing countries that do not have specialized porphyria centers, since physicians and laboratories see patients with porphyrias only sporadically and never become proficient in managing these disorders. Hence, the centralization of care for patients with porphyria in these countries is important to ensure an adequate volume of patients that would allow the development of medical and analytic expertise in these conditions. Such development may improve the quality of care and prognosis of porphyrias, as it did in the United States and Europe.

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

1. Buitrago J, Santa SV. Acute intermittent porphyria presenting as spontaneous hemothorax. Biomedica 2009;29:339-47. (In Spanish.)

2. Latorre Sierra G, Muñoz Berrio A. Acute intermittent porphyria: San Vicente de Paul University Hospital (1974-1987). Acta Med Colomb 1988;13443-51. (In Spanish.)
3. Lozano A, Tovar OJ, Ortíz CA. Acute porphyria: case report and topic review. Revista Med. 2008;16:106-14. (In Spanish).
4. Argüello M, Vergara I, Mora MC, et al. Acute intermittent porphyria: a study of 23 cases. Acta Med Colomb 1978;3:217-40. (In Spanish.)

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THE AUTHORS REPLY: Sood et al. describe a small series of patients with porphyria cutanea tarda and chronic HCV infection. In these patients, porphyria responded to the sole treatment of eradication of HCV. An interesting observation is the decrease in the ferritin level in these patients. Excess iron is a major pathogenic factor in porphyria cutanea tarda, and 50% of the cases are associated with a gene mutation for hemochromatosis.[1]

Jaramillo-Calle highlights the challenges associated with the diagnosis and management of porphyria in developing countries. The porphyrias occur worldwide, and their prevalence in Latin America is probably similar to that in the United States and Europe. In South America, the problem may be in part a dearth of trained specialists, but it is also clearly aggravated by poor access to diagnostic tests such as a test to detect urinary porphobilinogen. Access to intravenous heme, the only currently approved treatment for acute porphyria, is also poor. In the United States, the American Porphyria Foundation is an effective advocate for patients and families with porphyria. The foundation also works with developing countries through an international alliance that encourages the creation of support groups for patients. Colombia is a member of this international alliance (www.porphyriafoundation.com/get-involved/global-porphyria-alliance). With regard to treatment, the Recordati Group, which manufactures both Panhematin and Normosang (two forms of intravenous heme), recently established an office in Mexico City and probably would consider expanding into other Latin American countries with a documented need.

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

1. Jalil S, Grady JJ, Lee C, Anderson KE. Associations among behavior-related susceptibility factors in porphyria cutanea tarda. Clin Gastroenterol Hepatol 2010;8(3):297-302.e1.

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More on Anti-CD19 CAR T Cells in CNS Diffuse Large-B-Cell Lymphoma

TO THE EDITOR: Abramson et al. (Aug. 24 issue)[1] report on an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy–mediated complete response of a refractory diffuse large-B-cell lymphoma (DLBCL) of the central nervous system, followed by a relapse that subsequently receded after a biopsy and concurrently with a CAR (mainly CD4) T-cell expansion. The patient had complete donor chimerism after allogeneic stem-cell transplantation at the time of CAR T-cell therapy. We can therefore surmise that the CAR T cells were of donor origin (i.e., potentially alloreactive in addition to having anti-CD19 specificity).

Potent graft-versus-tumor effects can occur after allogeneic stem-cell transplantation as well as after donor-lymphocyte infusion in the absence of graft-versus-host disease (GVHD),[2,3] especially when alloreactive CD4 T cells are involved.[4] Furthermore, such alloreactivity is sensitive to inflammation,[5] which is potentially induced locally by the biopsy procedure. Therefore, an immune response, mediated by alloreactive donor T cells within the CAR T cells, might have contributed in an important way to the clinical response and concurrent CAR T-cell expansion in the patient described by Abramson and colleagues. Confirmation of the donor origin of the CAR T cells