A patient with relapsing-remitting MS who received ocrelizumab monotherapy.

Results | A 44-year-old white woman with relapsing-remitting MS received 600 mg of ocrelizumab intravenously every 24 weeks for 4.5 years as part of the OPERA II trial. At screening, the patient tested positive for anti-hepatitis B virus (HBV) core and surface antibodies, while serum HBV surface antigen and HBV DNA test results were negative. Serum immunoglobulin levels were repeatedly found to be normal.

In July 2017, the patient and a person in close contact with her developed watery diarrhea. While the other person recovered quickly, the patient reported persistent febrile diarrhea (2 to 4 episodes/day) associated with a self-limiting maculopapular rash. For fever control, patient took 1000 mg of acetaminophen per day for 10 days. Two weeks thereafter, she was hospitalized. Blood tests showed increased alanine aminotransferase and aspartate aminotransferase levels (1847 and 2484 U/L, respectively; to convert either value to microkatal per liter, multiply by 0.0167), without cholestasis. An abdomen ultrasonographic examination and computed tomographic scan were normal.

Three days later, her liver enzyme levels markedly improved (alanine aminotransferase, 954 U/L; aspartate aminotransferase, 281 U/L), despite remitting fever and persistent diarrhea. On day 7 after admission, alanine and aspartate aminotransferase levels peaked to 6241 U/L and 9799 U/L, respectively, with increased bilirubin (total, 4 mg/dL; direct, 2.9 mg/dL; to convert either value to micromoles per liter, multiply by 17.104) and signs of coagulopathy (prothrombin time, 24%; international normalized ratio, 2.95). Owing to progression to liver failure, she received a liver transplant 11 days after admission.

The main infectious causes of acute liver failure were excluded. Reactivation of resolved HBV infection was ruled out by the negative serum HBV surface antigen and HBV DNA test results.

Serological and serum molecular tests excluded hepatitis A, C, and E; herpesviruses 6, 7, and 8; and HIV, cytomegalovirus, Epstein-Barr virus, parvovirus B19, and adenovirus. Stool samples tested negative for hepatitis A, adenovirus, rotavirus, and norovirus. Autoimmune hepatitis, suspected because of positive test results for antinuclear and antismooth muscle antibodies, was unlikely owing to the absence of liver or kidney failure.

### Ventricular Enlargement

**Introduction** | Ocrelizumab (Ocrevus [Roche-Genentech]), a second-generation humanized anti-CD20 antibody, has been recently approved for multiple sclerosis (MS). Echoviruses and other enteroviruses have been associated with life-threatening infections in patients receiving anti-CD20 antibodies other than ocrelizumab. In this case study, we report a case of fulminant echovirus 25-associated hepatitis in a patient with relapsing-remitting MS who received ocrelizumab monotherapy.

**Results** | A 44-year-old white woman with relapsing-remitting MS received 600 mg of ocrelizumab intravenously every 24 weeks for 4.5 years as part of the OPERA II trial. At screening, the patient tested positive for anti-hepatitis B virus (HBV) core and surface antibodies, while serum HBV surface antigen and HBV DNA test results were negative. Serum immunoglobulin levels were repeatedly found to be normal.

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microsomal antibodies and antisoluble liver antigen and liver pancreas antibodies.

Acetaminophen-associated toxic effects were excluded because severe liver damage usually occurs with administration of more than 4000 mg per day. Other toxic causes were excluded based on the patient’s history. A direct liver adverse event associated with ocrelizumab was unlikely, since the patient had been treated for more than 4 years.

The possibility of an enterovirus infection was investigated. Two plasma samples collected 8 days apart (11 and 2 days before the transplant procedure) tested positive for enterovirus RNA, and this was subsequently identified as echovirus 25. Stool samples tested negative for enteroviral RNA.

In the patient’s native liver tissue, an HBV DNA test result was negative, while a test result for enterovirus RNA was positive. A phylogenetic analysis revealed that both serum and native liver samples harbored echovirus 25.

Up to 12 months after the transplant, no relapse of echovirus 25 infection was observed clinically or in molecular test results. Although ocrelizumab was permanently withdrawn, the patient did not show signs of MS activity or disability progression, possibly owing to the immunosuppressive effects of basiliximab and tacrolimus, which were given to prevent liver rejection.

**Discussion** | We report what is, to our knowledge, the first case of fulminant hepatitis owing to echovirus 25 in a patient with MS who was treated with ocrelizumab. A few severe enteroviral infections were previously reported after B-cell depletion, mainly in patients with hematological conditions. While meningencephalitis was the most common manifestation, 3 cases of fulminant hepatitis were reported, of which 2 involved bimodal liver enzyme elevation, as this case did (Table). Because ocrelizumab is a novel, high-efficacy disease-modifying therapy for MS, it will probably be extensively used. However, it may impair clearance of enterovirus infections via B-cell depletion. Thus, in the case of compatible symptoms, tests should be conducted for enteroviruses. Given the bimodal clinical presentation (ie, the patient had a severe rebound of liver enzyme levels after initial improvement), patients receiving ocrelizumab with enteroviral infection need close follow-up.

Laura Ambra Nicolini, PhD
Paola Canepa, BI
Patrizia Caligiuri, BI
Malgorzata Mikulska, PhD
Giovanni Novi, MD
Claudio Viscoli, MD
Antonio Uccelli, MD

**Author Affiliations:** Department of Health Sciences, University of Genoa, Genoa, Italy (Nicolini, Canepa, Caligiuri, Mikulska, Viscoli); Infectious Diseases Unit, Ospedale Policlinico San Martino–Istituto Di Ricovero e Cura a Carattere Scientifico, Genoa, Italy (Nicolini, Mikulska, Viscoli); Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health and Center of Excellence for Biomedical Research, University of Genoa, Genoa, Italy (Novi, Uccelli); Ospedale Policlinico San Martino–Istituto Di Ricovero e Cura a Carattere Scientifico, Genoa, Italy (Uccelli).

**Corresponding Author:** Laura Ambra Nicolini, MD, PhD, Department of Health Science, University of Genoa, Ospedale Policlinico San Martino–Istituto Di Ricovero e Cura a Carattere Scientifico, Largo Rosanna Benzi, 10, 16132 Genoa, Italy (nicolini.la@gmail.com; lauraambra.nicolini@hsanmartino.it); and Antonio Uccelli, MD, Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health and Center of Excellence for Biomedical Research, University of Genoa, Via Balbi, 5, 16126 Genoa, Italy (uccelli@neurologia.unige.it).

**Published Online:** April 8, 2019. doi:10.1016/j.jamaneurol.2019.0522

**Author Contributions:** Drs Nicolini and Uccelli had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Viscoli and Uccelli are co-first authors. Concept and design: Nicolini, Mikulska, Viscoli, Uccelli. Acquisition, analysis, or interpretation of data: Nicolini, Canepa, Caligiuri, Novi, Uccelli. Drafting of the manuscript: Nicolini, Canepa, Caligiuri, Mikulska, Uccelli. Critical revision of the manuscript for important intellectual content: Novi, Viscoli, Uccelli.

**Conflict of Interest Disclosures:** Dr Uccelli reports receiving honoraria for speaking and consulting for Biogen, Genzyme, Merck, Novartis, Roche, and Teva and research grants from Biogen, Merck, and Novartis. Dr Novi received honoraria from Biogen and Novartis and received travel grants from Merck. No other disclosures were reported.

**Additional Contributions:** We thank the patient for granting permission to publish this information. Enzo Andorno, MD, Hepato-biliary-pancreatic Surgical Unit, Department of Surgery, and Simonna Marenco, PhD, Ospedale Policlinico San Martino–Istituto Di Ricovero e Cura a Carattere Scientifico, and Antonino Picciotto, MD, Department of Internal Medicine, University of Genoa and Ospedale Policlinico San Martino–Istituto Di Ricovero e Cura a Carattere Scientifico, contributed to the manuscript as members of the Liver Transplant Study Group. Bianca Brunozone, MD, Hygiene Unit, Ospedale Policlinico San Martino–Istituto Di Ricovero e Cura a Carattere Scientifico contributed interpretation of data, and Domenico Pinelli, MD, Department of Surgery and Transplantation, ASST Papa Giovanni XXIII, contributed technical support. These individuals were not compensated for their contributions.


**COMMENT & RESPONSE**

**Autoantibodies at the Center of (sub)Classification—Issues of Detection**

To the Editor | It was with interest that we read the article by Marimpiella et al describing a new classification approach for idiopathic inflammatory myopathies (IIM) based on clini-