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Use of Ribavirin to Treat Influenza

TO THE EDITOR: Ribavirin, an antiviral drug with in vitro activity against both DNA and RNA viruses, is approved in the United States for the treatment of hepatitis C and respiratory syncytial virus.[1] Hepatitis C is treated with approved oral formulations in combination with interferon products; respiratory syncytial virus is treated with an aerosol formulation. Intravenous ribavirin is not currently approved in the United States.

With the current H1N1 influenza pandemic, questions have arisen regarding the potential for ribavirin as a treatment option. Possible reasons for interest in ribavirin may include resistance issues in drugs that are used to treat circulating human seasonal H3N2 virus (adamantanes) and H1N1 virus (oseltamivir), as well as pandemic H1N1 virus (adamantanes and potentially oseltamivir).[2] Although ribavirin shows in vitro activity against influenza viruses, clinical data are not consistent with in vitro data in many cases.[1,3] We reviewed published studies, using the search criteria "influenza" and "ribavirin," and identified 12 randomized, controlled clinical trials of ribavirin — equally divided between oral and aerosolized formulations — in subjects with influenza (either naturally acquired infection or challenge studies) (Table 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). In addition to having small sample sizes, these studies were limited by multiple factors, including differences in the subjects who were enrolled, the dose and duration of ribavirin treatment, the timing between the initiation of therapy and the onset of symptoms (or viral inoculation in challenge studies), and the reporting of clinical outcomes, microbiologic data, and adverse events. Reported adverse events were consistent with the labeling of approved aerosol and oral formulations.[4,5]

Since the late 1980s, clinicians have requested access to intravenous ribavirin from the manufacturer to treat patients with life-threatening conditions (including influenza) through an emergency investigational new drug (EIND) application. The Food and Drug Administration (FDA) grants EINDs on a case-by-case basis. We recently reviewed data on the use of intravenous ribavirin under EIND provisions.[3] From February 1997 through December 2008, the FDA granted 608 EIND requests for the use of intravenous ribavirin, of which 18 (3%) were for the treatment of influenza. Our analysis of EIND data focusing on the use of ribavirin to treat influenza was limited by the inadequate reporting of clinical outcomes and adverse events.

In our opinion, the studies that we identified in the published literature regarding the use of oral or aerosolized formulations of ribavirin and data on EIND use of intravenous ribavirin are inconclusive regarding the potential clinical benefit of the drug for the treatment of influenza. Substantial safety issues, such as the risk of hemolytic anemia and of teratogenicity, present further challenges to address if ribavirin is to be used for the treatment of influenza.[4,5] To further address these issues, formal trials of

ribavirin should be conducted to assess safety and efficacy.

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The views expressed in this letter are those of the authors and do not necessarily reflect the official position of the FDA.

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CORRECTIONS

The Serotonin Syndrome (March 17, 2005;352:1112-20). The fourth sentence in the penultimate paragraph of the Management section (page 1119) should have begun, "Bromocriptine, a dopamine agonist" instead of "Bromocriptine, a dopamine antagonist." The article has been corrected at NEJM.org.

Adjuvant Chemotherapy in Older Women with Early-Stage Breast Cancer (May 14, 2009;360:2055-65). In the author list (page 2055), "Gutav Magrinat, M.D." should have been "Gustav Magrinat, M.D." In the affiliations (page 2055) and in the Appendix (page 2064), the location of the Southeast Cancer Control Consortium of the Community Clinical Oncology Program should have been "Greensboro, NC" instead of "Goldsboro, NC." The article has been corrected at NEJM.org.

Artemisinin Resistance in *Plasmodium falciparum* Malaria (July 30, 2009;361:455-67). The support statement (page 467) should have read, "Supported by grants from the Wellcome Trust of Great Britain (Major Overseas Programme–Thailand Unit Core Grant) and the Li Ka Shing Foundation (B9RMXT0-2) and by the WHO through grants from the Bill and Melinda Gates Foundation (48821) and the U.S. Agency for International Development (umbrella grant AAG-G-00-99-00005)." The article has been corrected at NEJM.org.

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