CORRESPONDENCE

Mutagenesis in Norovirus in Response to Favipiravir Treatment

TO THE EDITOR: Chronic norovirus infection in immunocompromised patients can lead to malabsorption and other complications[1]; currently, no treatment has proved to be effective. Favipiravir is an antiviral medication that has been approved for the treatment of influenza in Japan[2] and has been used by some as treatment for Ebola virus infection, with mixed results.[3] Preclinical data have shown that favipiravir can induce mutagenesis and impair norovirus infectivity in mice.[4] We used favipiravir to treat chronic norovirus infection in a 48-year-old man with common variable immunodeficiency.

The patient had a long history of common variable immunodeficiency enteropathy, a condition characterized by diarrhea, malabsorption, and duodenal villous atrophy with intraepithelial lymphocytosis; it had previously been treated with immunosuppressive agents, including infliximab. Administration of parenteral nutrition caused unacceptable side effects in this patient. Serial polymerase-chain-reaction–positive stool samples obtained in July 2014 led to a diagnosis of chronic norovirus infection. Six months later, *Mycobacterium avium*–associated bronchiolitis also developed and was treated with antimicrobial therapy and with oral glucocorticoids for airflow obstruction. Treatment with high-dose intravenous immune globulin, nitazoxanide, and ribavirin was ineffective against the norovirus infection.

We administered 6000 mg of favipiravir on day 1 in three divided doses, followed by 1200 mg twice daily. We used doses that had been evaluated in a trial of treatment for Ebola virus infection (higher doses than have been used for influenza), on the basis of the predicted 50% inhibitory concentration, the impaired enteral absorption in the patient, and the absence of serious adverse events attributed to the drug when given at these doses during the trial for Ebola.[3] Administration of favipiravir was approved by the Royal Free London NHS Trust Drug and Therapeutics Committee, and collection of records and samples for research was approved by the NHS Research Ethics Committee. Written informed consent from the patient was obtained for both the administration of the drug and the use of the data for this research.

With treatment, the patient's diarrhea and the use of adjunctive loperamide decreased, his body weight increased, and the norovirus viral

THIS WEEK'S LETTERS

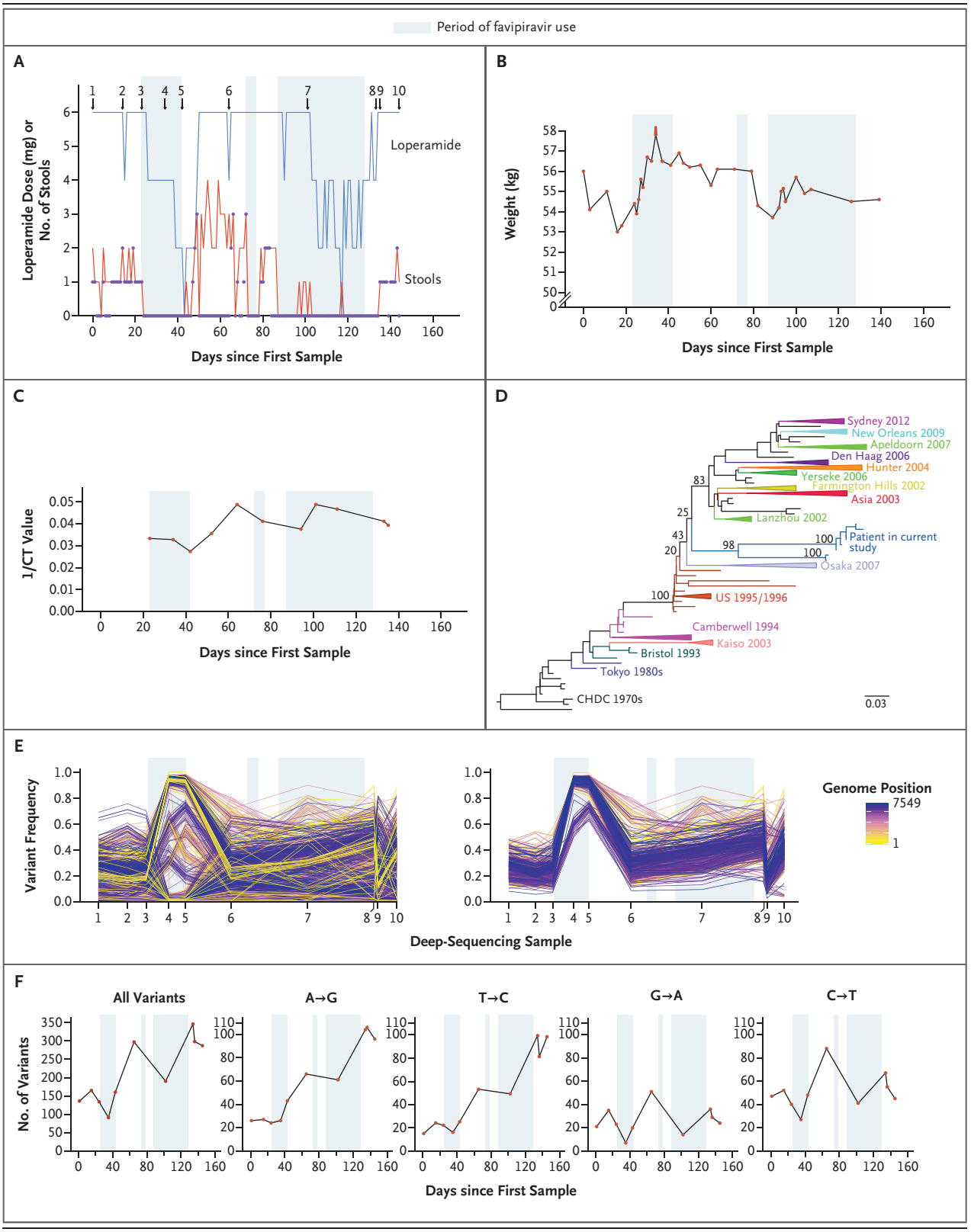

Figure 1 (facing page). Clinical Course and Laboratory and Molecular Results.

Panel A shows the dose of loperamide (blue line), numbers of stools per day that are of type 6 or 7 on the Bristol stool scale (orange line), and numbers of stools per day that are of type 7 on the Bristol scale (purple dots) over time (daily data for each measure), in relation to periods of favipiravir treatment (light blue shading). Numbered arrows indicate times at which stool samples were obtained for viral sequencing. Panels B and C show the patient's body weight (Panel B) and the inverse norovirus cycling threshold (CT) value (equivalent to viral load) (Panel C) from stool samples obtained over the same period. Panel D shows a reconstructed capsid nucleotide maximum-likelihood phylogenetic tree containing the 8 consensus sequences from our patient and 2198 reference sequences from all norovirus GII.4 strains. Samples 8 and 10 from the patient were not included in the phylogenetic trees because they contained a mixture of two variants at close to 50% frequency; therefore, a reliable sample consensus sequence could not be obtained. The sequences from our patient (in blue) form a single, well-supported monophyletic clade that contains very high diversity. Previously characterized GII.4 strains are colored to match the strain label and are collapsed where appropriate for clarity. We found a similar pattern in phylogenetic trees that were reconstructed on the basis of the nonstructural polyprotein and VP2. Bootstrap support values are shown at key nodes. The scale bar indicates the expected number of nucleotide substitutions per site. In Panel E, each line represents an individual nucleotide variant and indicates the frequency of that variant through time, colored according to the position of the site within the genome. In the graph on the left, all variants are plotted. In the graph on the right, only the dominant variants during favipiravir therapy are plotted; because these variants undergo similar changes in frequency through time, they are likely to be found on the same viral haplotype. For Panel F, we calculated the number of each mutation type present in each deep-sequencing sample and plotted the total number of variants and the number of mutation types (A→G, T→C, G→A, and C→T) through time in relation to the three periods of favipiravir treatment. The number of variants is the number of single-nucleotide variants present; therefore, an individual genome site can have up to three variants. The points represent the days on which deep-sequencing samples were obtained.

load decreased (Fig. 1A, 1B, and 1C). An increase in serum levels of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase on liver-function testing prompted a treatment interruption on day 19, and the patient's gastrointestinal symptoms promptly relapsed. Reintroduction of favipiravir was associated with rapid deterioration in liver-function test results and treatment interruption on day 6; on both occasions, he was also receiving intravenous levofloxacin. A third treatment course was attempted without a loading dose and after stopping treatment with levofloxacin. The symptomatic response was slower but notable (Fig. 1A), albeit without sustained weight gain, and the results of liver-function tests remained stable. Again, the patient had a relapse after discontinuation of favipiravir treatment due to a lack of available medication. Unfortunately, his pulmonary disease progressed, and he eventually died from respiratory failure.

Viral deep sequencing[5] and phylogenetic analysis of norovirus isolates obtained from the patient revealed a monophyletic clade containing substantial diversity (Fig. 1D). The divergence point from other GII.4 sequences suggested acquisition of the infection before 2002. During the first course of favipiravir treatment, there was apparent selection for a distinct viral variant (Fig. 1E); this variant also increased in frequency during the third course of treatment. At the consensus level, it differed from the dominant variant observed before or after treatment by 118 nonsynonymous substitutions throughout the genome. We also found increasing A→G and T→C minority single-nucleotide variants during favipiravir treatment (Fig. 1F), as has been described for murine norovirus.[4]

In summary, despite the presence of complex coexisting conditions, the patient in this case had some symptomatic response to favipiravir treatment, along with evidence for selective pressure on the infecting norovirus population. Further study of favipiravir for chronic norovirus infection should be considered.

Christopher Ruis, Ph.D.

University College London
London, United Kingdom

Li-An K. Brown, M.D.

Royal Free London NHS Foundation Trust
London, United Kingdom

Sunando Roy, Ph.D.
Claire Atkinson, Ph.D.
Rachel Williams, Ph.D.
Siobhan O. Burns, Ph.D.
Erika Yara-Romero, M.Sc.

University College London
London, United Kingdom

Michael Jacobs, Ph.D.

Royal Free London NHS Foundation Trust
London, United Kingdom

Richard Goldstein, Ph.D.
Judith Breuer, M.D.
David M. Lowe, Ph.D.

University College London
London, United Kingdom

Drs. Breuer and Lowe contributed equally to this letter.

Supported by a Wellcome Trust Collaborative Award (203268/Z/16/Z, to Dr. Breuer) and the University College London–University College London Hospitals Biomedical Resource Centre, National Institute for Health Research (to Dr. Breuer). Toyama Chemical provided favipiravir free of charge.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Brown LK, Clark I, Brown JR, Breuer J, Lowe DM. Norovirus infection in primary immune deficiency. Rev Med Virol 2017 March 8 (Epub ahead of print).
2. Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Japan. Report on the deliberation results: Avigan tablet 200 mg (favipiravir). March 4, 2014 (https://www.pmda.go.jp/files/000210319.pdf).
3. Sissoko D, Laouenan C, Folkesson E, et al. Experimental treatment with favipiravir for Ebola virus disease (the JIKI Trial): a historically controlled, single-arm proof-of-concept trial in Guinea. PLoS Med 2016;13(3):e1001967.
4. Arias A, Thorne L, Goodfellow I. Favipiravir elicits antiviral mutagenesis during virus replication in vivo. Elife 2014;3:e03679.
5. Brown JR, Roy S, Ruis C, et al. Norovirus whole-genome sequencing by SureSelect target enrichment: a robust and sensitive method. J Clin Microbiol 2016;54:2530-7.

DOI: 10.1056/NEJMc1806941

Olaparib Desensitization in a Patient with Recurrent Peritoneal Cancer

TO THE EDITOR: Olaparib, a poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitor, is a recommended and effective treatment option for patients who have relapsed, platinum-sensitive ovarian cancer, tubal cancer, or primary peritoneal cancer, regardless of *BRCA* mutation status.[1] Allergic reactions to olaparib have been reported in several patients worldwide. Urticaria developed in 10 of those patients, with one case being classified as severe.[2-4] In patients with drug allergy, desensitization can reduce or eliminate the allergic response to the drug and facilitate the continuation of a specific treatment. Owing to a paucity of information regarding desensitization to olaparib, we developed a desensitization protocol for the drug.

Table 1. Olaparib Desensitization Protocol.

Dose Day and No.	Daily Duration of Protocol	Interval since Previous Dose	Olaparib Dose	
			Single Dose	Cumulative Daily Dose
	hr:min	*min*	*mg*	
Day 1				
1	00:00	—	12.5	12.5
2	00:30	30	25	37.5
3	01:30	60	50	87.5
4	02:30	60	100	187.5
5	03:30	60	200	387.5
6	05:30	120	200	587.5
7	08:30	180	300	887.5
Day 2				
1	00:00	—	200	200
2	01:00	60	200	400
3	07:00	360	400	800

A 49-year-old woman presented with a platinum-sensitive relapse of a high-grade serous peritoneal cancer with extensive peritoneal and pleural carcinomatosis and effusions. Testing for a germline *BRCA1* mutation was positive. No second somatic mutation was found. The patient had a complete remission after the most recent platinum-based chemotherapy and then began receiving maintenance therapy with olaparib capsules at a dose of 400 mg twice daily. After the patient received the first dose, an allergic reaction developed that was characterized by angioedema and cutaneous wheals. This allergic reaction developed reproducibly within approximately 3 hours after each administration of olaparib and lasted for several hours. Three rechallenge attempts with preventive applications of clemastine (a first-generation H_1-antihistamine) or bilastine (a second-generation H_1-antihistamine), with or without the administration of omalizumab (a recombinant,