Case Study

international lactation consultant association®

Journal of Human Lactation
1–4

DOI: 10.1177/08903344221076539
journals.sagepub.com/home/jhl
SAGE

Remdesivir and Human Milk: A Case Study

Yuka Sano Wada, MD, PhD[1], Jumpei Saito, PhD[2], Yuko Hashii, PhD[3], Tomomi Kishi, MD[4], Masayuki Kobayashi, MD, PhD[4], Taro Kamiya, MD, PhD[5], and Katsumi Mizuno, MD, PhD[5]

Abstract

Introduction: Remdesivir was originally developed to treat Ebola hemorrhagic fever, and its efficacy in treating coronavirus disease 2019 was detected during a preliminary analysis of a randomized controlled trial. It is known that Severe Acute Respiratory Syndrome Coronavirus 2 is not transmitted through human milk, but data about the presence of remdesivir in human milk have been lacking.

Main issue: In this case study, we determined the human milk-to-serum drug concentration ratio and the relative dose of Remdesivir in one participant.

Management: The participant, a 28-year-old primipara, was found to have Coronavirus 2 infection in 2019, 2 days after delivery. She was given Remdesivir. The Remdesivir concentration in maternal serum and human milk was measured, and the milk-to-serum drug concentration ratio was found to be low (0.089), as was the relative infant dose (0.0070). The participant could not breastfeed her infant during her Coronavirus 2 infection treatment because in Japan anyone with COVID-19 was completely quarantined. However, she was able to resume breastfeeding after discharge and breastfed her infant for 6 months with supplements.

Conclusion: Given the low amount of Remdesivir in the participant's milk, the inclusion of antibodies to Severe Acute Respiratory Syndrome Coronavirus 2, which can be expected to protect the infant from infection, and various other benefits of human milk, suggests that breastfeeding is safe during treatment with Remdesivir.

Keywords

breastfeeding, case study, COVID-19, human milk, relative infant dose, remdesivir, SARS-CoV-2

Introduction

Remdesivir was originally developed for the treatment of Ebola hemorrhagic fever, and its efficacy in treating coronavirus disease 2019 (COVID-19) was detected in a preliminary analysis of a randomized controlled trial (Beigel et al., 2021; Pan et al., 2021; Wang et al., 2020). It is currently approved for the treatment of COVID-19 in several countries, including Japan.

Remdesivir has a molecular weight of 602.8, a pH of 3.0–4.0, and is a prodrug of adenosine nucleoside whose chemical name is 2-ethylbutyl *N*-{(S)-[2-C-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2,5-anhydro-D-altrononitril-6-O-yl]phenoxyphosphoryl}-L-alaninate. In vivo, Remdesivir becomes activated by hydrolysis; this metabolite has antiviral activity that inhibits ribonucleic acid (RNA)-dependent RNA polymerase required for RNA virus replication (Fact Sheet for Healthcare Providers, 2020, available at https://www.gilead.com/remdesivir).

After giving birth, or during lactation, some women have contracted COVID-19. In Japan, they are administered Remdesivir as a treatment. Breastfeeding is recommended

[1]Division of Neonatology, Center for Maternal-Fetal, Neonatal, and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan
[2]Department of Pharmaceuticals, National Center for Child Health and Development, Tokyo, Japan
[3]Department of Pharmacy, the Japan Baptist Hospital, Kyoto, Japan
[4]Division of Internal Medicine, the Japan Baptist Hospital, Kyoto, Japan
[5]Department of Pediatrics, Showa University School of Medicine, Tokyo, Japan

Date submitted: September 4, 2021; Date accepted: December 24, 2021.

Corresponding Author:
Yuka Sano Wada, MD, PhD, Division of Neonatology, Center for Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan.
Email: wada-y@ncchd.go.jp

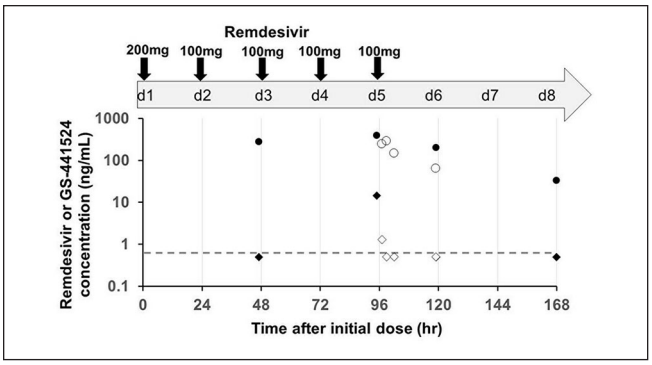

Figure 1. Case Study Timeline.
Note. The mother received 200 mg of remdesivir on Day 1 and 100 mg from Day 2 to Day 5. Milk and maternal serum concentration–time profile for remdesivir is represented by squares, and that for GS-441524 is represented by circles. Closed and opened makers represent the serum and milk levels, respectively. Relevant dose times are indicated by the arrows. The horizontal dashed line indicates the lower limit of quantification (LLOQ; 0.5 ng/ml).

by institutions (e.g., the WHO and the United Nations International Children's Emergency Fund). It is known that the virus that causes COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is not transmitted through human milk (Zhu et al., 2021). However, the safety of human milk for infants of those who receive Remdesivir is not clear. We report a case in which Remdesivir was administered to a Japanese mother, after which we analyzed her milk. This study was approved by the Ethics Committee of the National Center for Child Health and Development (No. 2020-103). We obtained the participant's written informed consent to publish her data.

History and Observational Assessment

The participant was a 28-year-old primipara (52 kg) and had no underlying illness. She was admitted to the hospital for premature rupture of the membranes at 38 weeks and 1 day of gestation. The next day, she gave birth vaginally to a healthy boy weighing 2758 g. Two days after delivery, she was febrile (39℃) and had fatigue, joint pain, and myalgia. The polymerase chain reaction (PCR) test for SARS-CoV-2 yielded a positive result, and COVID-19 was diagnosed. Her infant, being considered a close contact, was transported to the neonatal intensive care unit in another hospital and therefore could not be breastfed; it is a common practice in Japan for those who have COVID-19 to be completely quarantined. Worsening symptoms in the participant were considered an indication for administration of Remdesivir, to which she consented. She received 200 mg of Remdesivir on Day 1 and 100 mg from Day 2 to Day 5 (Figure 1). She recovered, and her infant was not infected. She was able to resume breastfeeding after discharge and continued to breastfeed her infant to 6 months with supplements.

Management

Breastfeeding was interrupted; therefore, the participant pumped her milk to maintain her milk production. Her milk was collected to determine the amount of Remdesivir present. On Days 3 and 5, her serum was collected just before Remdesivir administration, then 24 hr and 72 hr after the end of Remdesivir administration. On Day 5, milk was collected just before and 1, 3, 6, and 24 hr after the end of Remdesivir administration (Figure 1). The level of remdesivir (CAY30354; Cayman Chemical, Ann Arbor, MI, USA) was measured, and the level of GS-441524 (HY-103586; MedChemExpress, Monmouth Junction, NJ, USA), which is a metabolite of Remdesivir, was also measured because the half-life of this drug is short (0.90–0.96 hr) while the half-life of GS-441524 is as long as 27.4 hr. The 6,7-dimethyl-2,3-di \(2-pyridyl) quinoxaline was used as the internal standard (126462-5G; MilliporeSigma, St. Louis, MO, USA), and was also measured. A previously reported liquid chromatography–tandem mass spectrometry method (Avataneo et al., 2020) was used to quantify Remdesivir and GS-441524 levels in milk and serum. Briefly, 0.05 ml aliquots of milk or serum were added to 1 ml of a methanol/acetonitrile 50/50 (v/v) mixture with the internal standard to precipitate proteins. The filtrated supernatant with a 0.22 μm filter (0.01 ml) was injected onto an Acquity® Premier HSS T3, 3.0 μm, 2.1 × 50 mm column (Waters, Tokyo, Japan), using a mobile phase of 0.1% formic acid in water and 0.1% formic acid in methanol at 0.4 ml/min. Positive electrospray ionization was used for all the analytes. Multiple reaction monitoring traces were quantified as mass-to-charge ratios of 603.2 > 200.0 for Remdesivir, 292.0 > 163.0 for GS-441524, and 313.2 > 78.1 for the internal standard. Interday and intraday relative standard deviations for the method were < 10.0% at all evaluated concentrations (0.5–500.0 ng/ml) for both milk and serum.

Outcomes

The concentration of Remdesivir in the participant's serum was below detection sensitivity in three of four samples, and the concentration before administration on Day 5 was 14.4 ng/ml. The concentration of Remdesivir in human milk was below detection sensitivity in three of four samples, and the concentration at 1 hr before administration on Day 5 was 1.29 ng/ml (Figure 1). The milk-to-serum drug concentration ratio (so-called milk/plasma or serum ratio [M/P]) of Remdesivir was 0.089 when calculated from the detected concentration. The relative infant dose (RID) in the 3 kg infant, who took 160 mg/kg of human milk daily, was extremely low (0.0070%).

The concentration of the nucleoside analog GS-441524, a metabolite of Remdesivir, in maternal serum was 33.1–389.9 ng/ml. The concentration of GS-441524 in human milk was 13.50–284.9 ng/ml (Figure 1). The concentration

of GS-441524 before and 24 hr after administration on Day 5 in serum was 389.9 ng/ml and 201.1 ng/ml, respectively, and in human milk was 13.5 ng/ml and 64.34 ng/ml respectively. Calculated from these data, the maximum M/P is 0.32. The RID of GS-441524 was 1.55% when calculated from the detected concentration in the manner wherein Remdesivir was calculated. The half-lives for GS-441524 in maternal serum and milk were 25.1 and 9.3 hr, respectively.

The participant was pleased with her COVID-19 treatment and her ability to resume breastfeeding after discharge by maintaining breastfeeding via pumping, although she was unable to breastfeed during the treatment.

Discussion

The M/P of Remdesivir and GS-441524 was < 1, and the RID was $< 10\%$, which was within the range considered safe for breastfeeding (Hale, 2021). Furthermore, the bioavailability of GS-441524, which is a metabolite of Remdesivir, is 57% (Xie & Wang, 2021); thus, the RID is considered 0.89%, even if the concentration in human milk is estimated to be the maximum value, which is 284.9 ng/ml. Hence, it is considered safe.

The infant in this case did not actually breastfeed. Therefore, his blood concentration of Remdesivir and its effect on him are unknown, which is a limitation of this study. However, remdesivir was administered at 10 mg/day to a neonate with Ebola hemorrhagic fever (birth weight, 2800 g) for 12 days, without any drug-related toxicity (Dörnemann et al., 2017). Because the administration of a therapeutic amount of Remdesivir to a neonate caused no side effects, a small amount—as in our case—would most likely not have affected the infant even if the infant consumed human milk containing Remdesivir. However, further research is needed to determine the blood concentration of Remdesivir in breastfed infants whose mothers are receiving Remdesivir, along with its effects on the infant.

Infants may already be infected when their mothers become infected with SARS-CoV-2. SARS-CoV-2–specific immunoglobulin A and G antibodies were present in the human milk of mothers with COVID-19 (Zhu et al., 2021), which neutralized SARS-CoV-2 infectivity in vitro (Pace et al., 2021). Additionally, human milk contains other components related to infection protection (e.g., immunoglobulins, lactoferrin, and oligosaccharides). Thus, human milk most likely protects infants from SARS-CoV-2 infection. Based on these clinical findings, we suggest that the milk of women administrated with Remdesivir is safe for infant consumption.

Acknowledgments

The authors would like to thank Enago (www.enago.jp) for the English language review.

Author Contributions

Yuka Sano Wada, MD, PhD: Conceptualization; Investigation; Methodology; Project administration; Supervision; Visualization; Writing – original draft; Writing – review & editing.
Jumpei Saito, PhD: Data curation; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.
Yuko Hashii, PhD: Data curation; Investigation; Resources; Writing – original draft; Writing – review & editing.
Tomomi Kishi, MD: Data curation; Resources; Writing – original draft.
Masayuki Kobayashi, MD, PhD: Data curation; Investigation; Resources; Writing – review & editing.
Taro Kamiya, MD, PhD: Conceptualization; Data curation; Investigation; Resources; Supervision; Writing – review & editing.
Katsumi Mizuno, MD, PhD: Conceptualization; Funding acquisition; Investigation; Project administration; Supervision; Writing – review & editing.

Disclosures and Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by Health and Labor Sciences Research Grant (No. 20DA1008, address; 1-2-2, Kasumigaseki, Chiyodaku, Tokyo, Japan). The funder had no role in study design, data collection, data analysis, or the writing of this report.

ORCID iDs

Yuka Sano Wada https://orcid.org/0000-0001-5277-9624
Katsumi Mizuno https://orcid.org/0000-0002-6983-8851

References

Avataneo, V., de Nicolò, A., Cusato, J., Antonucci, M., Manca, A., Palermiti, A., Waitt, C., Walimbwa, S., Lamorde, M., di Perri, G., & D'Avolio, A. (2020). Development and validation of a UHPLC-MS/MS method for quantification of the prodrug remdesivir and its metabolite GS-441524: A tool for clinical pharmacokinetics of SARS-CoV-2/COVID-19 and Ebola virus disease. *Journal of Antimicrobial Chemotherapy*, *75*(7), 1772–1777. https://doi.org/10.1093/jac/dkaa152

Beigel, J. H., Tomashek, K. M., Dodd, L. E., Mehta, A. K., Zingman, B. S., Kalil, A. C., Hohmann, E., Chu, H. Y., Luetkemeyer, A., Kline, S., Lopez de Castilla, D., Finberg, R. W., Dierberg, K., Tapson, V., Hsieh, L., Patterson, T. F., Paredes, R., Sweeney, D. A., Short, W. R., . . .Nayak, S. (2021). Remdesivir for the treatment of Covid-19—Final report. *New England Journal of Medicine*, *383*(19), 497–511. https://doi.org/10.1056/NEJMoa2007764

Dörnemann, J., Burzio, C., Ronsse, A., Sprecher, A., De Clerck, H., Van Herp, M., Kolié, M. C., Yosifiva, V., Caluwaerts, S., McElroy, A. K., & Antierens, A. (2017). First newborn baby to receive experimental therapies survives Ebola virus disease.

Journal of Infectious Diseases, *215*(2), 171–174. https://doi.org/10.1093/infdis/jiw493

GILEAD. https://www.gilead.com/remdesivir

Hale, T. W. (2021). *Hale's medications and mothers' milk 2021: A manual of lactational pharmacology* (19th ed.). Springer Publishing Company.

Pace, R. M., Williams, J. E., Järvinen, K. M., Belfort, M. B., Pace, W., Lackey, K. A., Kanagaiah, P., Fitzgerald, T., Ferri, R., Young, B., Rosen-Carole, C., Diaz, N., Meehan, L. C., Caffé, B., Sangster, M. Y., Topham, D., McGuire, M. A., Seppo, A., & McGuire, M. K. (2021). Characterization of SARS-CoV-2 RNA, antibodies, and neutralizing capacity in milk produced by women with COVID-19. *mBio*, *12*(1), e03192–20. https://doi.org/10.1128/mBio.03192-20

Pan, H., Peto, R., Henao-Restrepo, A. M., Preziosi, M. P., Sathiyamoorthy, V., Abdool Karim, Q., Alejandria, M. M., Hernández García, C., Kieny, M. P., Malekzadeh, R., Murthy, S., Reddy, K. S., Roses Periago, M., Abi Hanna, P., Ader, F., Al-Bader, A. M., Alhasawi, A., Allum, E., Alotaibi, A., Alvarez-Moreno, C.A., Swaminathan, S.. . .World Health Organization Solidarity Trial Consortium. (2021). Repurposed antiviral drugs for Covid-19—Interim WHO solidarity trial results. *New England Journal of Medicine*, *384*(6), 497–511. https://doi.org/10.1056/NEJMoa2023184

Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., Fu, S., Gao, L., Cheng, Z., Lu, Q., Hu, Y., Luo, G., Wang, K., Lu, Y., Li, H., Wang, S., Ruan, S., Yang, C., Mei, C., . . .Wang, C. (2020). Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*, *395*(10236), 1569–1578. https://doi.org/10.1016/S0140-6736(20)31022-9

Xie, J., & Wang, Z. (2021). Can remdesivir and its parent nucleoside GS-441524 be potential oral drugs? An in vitro and in vivo DMPK assessment. *Acta Pharmaceutica Sinica. B*, *11*(6), 1607–1616. https://doi.org/10.1016/j.apsb.2021.03.028

Zhu, F., Zozaya, C., Zhou, Q., De Castro, C. D., & Shah, P. S. (2021). SARS-CoV-2 genome and antibodies in breastmilk: A systematic review and meta-analysis. Archives of Disease in Childhood. *Fetal and Neonatal Edition*, *106*(5), 514–521. https://doi.org/10.1136/archdischild-2020-321074