OPEN

Evaluation of Neural Tube Defects (NTDs) After Exposure to Raltegravir During Pregnancy

Hala Shamsuddin, MD,[a] Casey L. Raudenbush, MSN,[a] Brittany L. Sciba, BSN,[a] Yun-Ping Zhou, MD, PhD,[a] T. Christopher Mast, PhD,[b] Wayne L. Greaves, MD,[c] George J. Hanna, MD,[c] Ronald Leong, MD,[a] and Walter Straus, MD[a]

Objective: To evaluate the risk of neural tube defects (NTDs) after exposure to raltegravir during pregnancy.

Methods: Exposures to raltegravir during pregnancy reported cumulatively through May 31, 2018, to the company safety database were reviewed to identify cases of NTDs. This database includes all reports of pregnancy from Merck-sponsored clinical trials, spontaneous postmarketing reports, and non-interventional data sources, including the Antiretroviral Pregnancy Registry (APR). Reports were classified as prospective (before knowledge of pregnancy outcome) or retrospective (after knowledge of pregnancy outcome). We also reviewed data from 2 ongoing pregnancy cohorts.

Results: A total of 2426 pregnancies with reported outcomes were identified among women exposed to raltegravir: 1238 from the Merck database and 1188 from United Kingdom/Ireland and French pregnancy cohorts. Among all 2426 reports, 1991 were prospective. No cases of NTDs were identified among the prospective pregnancy reports, of which 767 were first trimester, including 456 in the periconception period (at or within 28 days after conception). Among the 435 retrospective reports, 3 NTD cases per APR criteria were identified (anencephaly, and 2 meningomyelocele), of which only one (meningomyelocele) was among exposures in the periconception period. Given the inherent limitations and bias of retrospective reports, it is not appropriate to calculate an incidence rate.

Conclusions: Prospectively collected pregnancy outcome data do not suggest an association between raltegravir exposure in the periconception period and NTDs. The current data support the updated DHHS and EACS treatment guidelines for use of raltegravir as a preferred integrase inhibitor in all stages of pregnancy.

Key Words: raltegravir, pregnancy, neural tube defect, HIV infection, integrase inhibitor, dolutegravir

(*J Acquir Immune Defic Syndr* 2019;81:247–250)

INTRODUCTION

Current HIV-treatment guidelines recommend that all women living with HIV receive antiretroviral therapy.[1–3] For those diagnosed during pregnancy, HIV treatment should be initiated as early in pregnancy as possible, both to improve well-being and survival of mothers and infants and to prevent vertical transmission, regardless of maternal plasma viral load or $CD4^+$ T-cell count.[1–4] In 2007, raltegravir was the first integrase inhibitor approved by the US Food and Drug Administration in combination with other antiretroviral agents for the treatment of adults living with HIV-1. Available data have not identified a potential birth defect signal among infants of women treated with raltegravir 400 mg twice daily during pregnancy.[5]

Neural tube defects (NTDs) are birth defects of the brain, spine, or spinal cord that occur when the neural tube fails to close. Embryonic neural tube development occurs during the first 28 days after conception.[6] Although the prevalence of NTDs worldwide is highly variable, they rank among the most common categories of birth defects.[7,8] The causes of NTDs are not known, but genetic and environmental factors have been implicated, with up to 70% of the variance in prevalence attributed to genetic factors.[9] Risk factors for NTDs include exposure to certain medications in pregnancy, obesity, poorly controlled diabetes, and folate deficiency.[9]

Raltegravir and dolutegravir are both in the integrase strand transfer inhibitor class of antiretroviral drugs. In a recent birth outcome surveillance study in Botswana to evaluate the prevalence of NTDs associated with exposure to antiretroviral drugs from the time of conception, NTDs

Received for publication October 24, 2018; accepted December 17, 2018.

From the Departments of [a]Clinical Safety and Risk Management; [b]Pharmacoepidemiology; and [c]Global Clinical Development, Merck Sharp & Dohme Corp., North Wales, PA.

Supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ. Medical writing and editorial assistance was provided by Kim M. Strohmaier and Carol Zecca, employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ.

All authors are employees of Merck Sharp & Dohme, Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ.

H.S.: drafting of the manuscript and critical review/revision for intellectual content. C.L.R.: acquisition of data, analysis and interpretation of data, and critical review/revision of manuscript. B.L.S.: acquisition of data, and analysis and interpretation of data. Y.-P.Z.: critical review of the manuscript. T.C.M.: statistical analysis and critical review of the manuscript. W.L.G.: Study concept/design and critical review of the manuscript.

Correspondence to: Hala Shamsuddin, MD, Clinical Safety and Risk Management, 351 North Sumneytown Pike, P.O. Box 1000, North Wales, PA 19454-2505 (e-mail: hala.shamsuddin@merck.com).

were identified in 4 infants born to 426 women who had been receiving a dolutegravir-based regimen at conception (0.94%, 95% confidence interval: 0.37 to 2.4) and in early pregnancy.[10] In comparison, NTDs were identified in 14 infants born to 11,300 women who had been receiving non-dolutegravir–based regimens at conception (0.12%, 95% confidence interval: 0.07 to 0.21) and in no infants born to 2812 women who started a dolutegravir-based regimen later in pregnancy. To determine whether the observed NTDs associated with dolutegravir exposure at conception represent an integrase inhibitor class effect, we performed a review of the available data to assess whether NTDs have been observed among infants whose mothers received raltegravir during pregnancy.

METHODS

The Merck Adverse Event Review and Reporting System (MARRS), which includes reports from the Antiretroviral Pregnancy Registry (APR), and 2 active surveillance pregnancy cohorts were reviewed. The MARRS database contains all adverse events spontaneously reported to the company in the postmarketing period and in noninterventional studies, as well as all serious adverse events (including all pregnancies) reported in company-sponsored and company-supported investigator-sponsored investigational clinical trials. The APR is a voluntary prospective, exposure registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral products and to detect a potential increase in the risk of major birth defects. All congenital anomalies reported to the APR are evaluated by an Advisory Committee and are assessed by a teratologist.[5] All reports received from the APR are included in the MARRS database.

The MARRS database was queried cumulatively from June 19, 2001 (the earliest reported pregnancy exposure) to May 31, 2018, to identify all pregnancy reports associated with raltegravir exposure, using the Pharmacovigilance Analytics software (TIBCO Spotfire Software, Palo Alto, CA). The retrieved pregnancy reports with a documented first trimester of exposure were further manually reviewed to determine whether the earliest exposure was in the periconception period (at or within 28 days after conception), the period during which neural tube development and closure occurs.

Reports of exposure during pregnancy were further classified as either prospective or retrospective. Prospective reports document pregnancy exposures before the knowledge of the pregnancy outcome, or before the detection of congenital malformation at prenatal examination. Retrospective reports document pregnancy exposures to raltegravir after the outcome of the pregnancy is known, or after detection of a congenital malformation or any fetal event during prenatal testing. For reports received from the APR, the pregnancy report type of prospective or retrospective is captured in the safety database as designated by the APR.[5] To identify all possible reports of NTDs, a query of the High-Level Group Terms "Neurological Disorders Congenital" was performed using Medical Dictionary for Regulatory Affairs (MedDRA) version 21.0. The preferred terms identified were compared with the list of NTDs provided by the APR (consistent with Metropolitan Atlanta Congenital Defects Program criteria): anencephaly and meningomyelocele.

In addition to the MARRS database, 2 pregnancy cohorts for which data were presented publicly were also reviewed to identify cases of NTDs: the United Kingdom (UK)/Ireland Cohort [National Study of HIV in Pregnancy and Childhood (NSHPC)] and the French Perinatal Cohort (EPF). The NSHPC is an active national surveillance study established in the United Kingdom and Ireland in 1990 that monitors the prevalence of HIV infection in pregnant women and children and transmission of infection from mother to child. The EPF is a national multicenter prospective cohort that enrolls approximately 70% of HIV-infected pregnant women in 100 sites in France. Data from both cohorts had not been submitted to the MARRS database at the time of the review.

RESULTS

Overall, a total of 2426 pregnancies with reported outcomes were identified among women exposed to raltegravir: 1238 from the MARRS database [including 728 (59%) from APR] and 1188 from UK/Ireland (NSHPC) and French cohorts (EPF). In 927 (38%), exposure to raltegravir occurred during the first trimester, including 557 (23%) in the periconception period. The reports identified in the MARRS database were received from the United States (47%), the European Union (25%), African countries (7%), and rest of world countries (21%).

Of the 2426 pregnancy reports, 1991 were prospective pregnancy reports {803 from the Company's safety database [including 584 (73%) from APR] and 1188 from the NSHPC and EPF cohorts}. The earliest raltegravir exposure was in the first trimester in 767, including 456 in the periconception period. No NTDs were reported among the prospective reports. Among the 435 retrospective reports, 3 NTDs by APR classification were identified (anencephaly and 2 meningomyelocele), of which only one NTD (meningomyelocele) was associated with raltegravir exposure in the periconception period. Results are provided below, by source.

Company Safety Database

From the company database, a total of 1587 reports of exposure to raltegravir were identified, including all APR reports. Of these, 349 (295 prospective and 54 retrospective) lacked individual information necessary for evaluation including exposure history, gestational age, and pregnancy outcome. Of the remaining 1238 pregnancies that reported 1256 outcomes, initial raltegravir exposure was in the first trimester in 603 (49%), in the second/third trimester in 498 (40%), and unknown in 137 (11%). Of the 603 first trimester exposures, 396 (66%) were in the periconception period.

Of the 1238 pregnancies, the outcome was prospectively reported in 803 and retrospectively reported in 435.

Among the 803 prospective reports, 443 (55%) documented first trimester as the earliest exposure, 302 (38%) had second/third trimester exposure, and 58 (7%) had an unknown trimester of exposure. Of the 443 first trimester exposures (451 outcomes), 295 (66%) were in women receiving raltegravir during the periconception period. No reports of NTDs were identified among prospectively reported pregnancy outcomes, regardless of the earliest time of raltegravir exposure.

Among the 435 retrospective pregnancy reports, 3 NTDs as classified by the APR (anencephaly and 2 meningomyelocele) were identified, all from the APR. Of the 3, only one NTD (meningomyelocele) was identified among infants born to 101 women who received raltegravir in the periconception period. The meningomyelocele was initially diagnosed through prenatal ultrasound and confirmed at birth. The mother had been concomitantly exposed to emtricitabine/tenofovir disoproxil fumarate, ledipasvir/sofosbuvir, and valcyclovir in the periconception period; further information regarding maternal, family, or dietary history was not available. One additional report in the APR database noted a retrospective case with periconception exposure to raltegravir resulting in a spontaneous abortion. At outcome, encephalocele was noted; however, this is not classified as NTD by the APR and the Metropolitan Atlanta Congenital Defects Program.

For the 2 remaining retrospectively reported cases, the initial exposure to raltegravir occurred more than 28 days after conception, ie, after the period in which neural tube development occurs: one report (anencephaly) documented first trimester exposure at 6-week, 6-day gestation (corresponding to 34 days postconception), and one report (meningomyelocele) documented second trimester exposure.

Reports of Raltegravir Exposure in NSHPC and EPF Cohorts

In NSHPC, raltegravir exposure was reported in 709 (7%) of 10,144 pregnancies reported between 2008 and 2016.[11] Of the 709 pregnancies, the earliest time of exposure was during the first trimester in 184 (26.5%), of which 161 (23%) were conceived on antiretroviral regimens that included raltegravir. NTDs were not observed in this cohort.

In the EPF, there were 479 pregnancy exposures to raltegravir between 2008 and 2015.[12] The number of women exposed at conception was not reported; however, 140 (29%) were exposed during the first trimester. NTDs were not observed in this cohort.

DISCUSSION

The primary aim of the Botswana birth outcome surveillance study was to evaluate the prevalence of NTDs associated with exposure to antiretroviral drugs from the time of conception. In May 2016, Botswana changed first-line antiretroviral therapy from tenofovir emtricitabine–efavirenz to tenofovir–emtricitabine–dolutegravir for all adults. In an unplanned interim analysis, the rate of NTDs among infants born to women who were receiving a dolutegravir-based regimen at conception was higher compared with women receiving a non-dolutegravir–based regimen at conception.[10]

This comprehensive evaluation of pregnancy outcomes after exposure to raltegravir did not identify any reports of NTDs among 1991 prospective pregnancy exposure reports, of which 456 were in the periconception period. One case of meningomyelocele and one case of encephalocele (not considered NTD by APR classification) were identified among 101 retrospective periconception reports. Given the inherent limitations and biases of retrospective spontaneous reporting, these reports cannot be used to estimate incidence rates.[13] However, the number of NTD reports associated with raltegravir exposure in the periconception period or later in pregnancy received over more than a decade is numerically low, especially when taking into consideration that serious outcomes are more likely to be reported retrospectively than nonserious outcomes, and that NTDs are among the most common birth defects, accounting for estimated 18.6 per 10,000 live births globally.[14]

Dolutegravir and raltegravir target HIV-1 integrase, but the chemical structures of dolutegravir and raltegravir are different. In an assessment using Extended-Connectivity Fingerprints[15] and Tanimoto coefficient[16] to compare the structural similarity of dolutegravir and raltegravir, the 2 structures were considered structurally dissimilar. Although the potential mechanism for dolutegravir-associated NTDs is not known, one potential consequence of the structural dissimilarity is that dolutegravir and raltegravir may have different side effect profiles.

The strength of this review is that multiple prospective pregnancy outcome data sources are included. Potential limitations include those inherent in postmarketing adverse event reporting, which is voluntary in nature, may be biased toward reporting of more unusual or severe cases, and is influenced by the time a product has been marketed and publicity about an event.[13] Critical information, such as receipt of concomitant medications, timing of exposure, and presence of other risk factors for the event in question, may be missing or incomplete.[13] Another limitation is the predominance of reports from Western countries (United States, United Kingdom, Ireland, and France) that have different diets and lower incidence of NTDs compared with the rest of the world.[8]

The lack of association between periconception exposure to raltegravir and the occurrence of NTD has practical implications for the choice of antiretroviral therapy in HIV-1–infected pregnant individuals. Dolutegravir has been used in WHO programs for the treatment of HIV-1–infected pregnant women, largely due to twice daily dosing of raltegravir 400 mg; however, the recently updated treatment guidelines from the US Department of Health and Human Services and the European AIDS Clinical Society do not recommend use of dolutegravir during the first trimester of pregnancy, or for an individual of childbearing potential who is sexually active and cannot use effective contraception or is contemplating pregnancy. The guidelines now support raltegravir 400 mg twice daily as a preferred integrase strand transfer inhibitor option for nonpregnant women who are trying to conceive, and for initial therapy or continuing therapy during the first, second, or third trimester of pregnancy.[2,3]

REFERENCES

1. World Health Organization. *Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants - Guidelines on Care, Treatment, and Support for Women Living with HIV/AIDS and their Children in Resource-Constrained Settings*. Available at: https://www.who.int/hiv/pub/mtct/en/arvdrugsguidelines.pdf.
2. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women With HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States*. Available at: https://aidsinfo.nih.gov/guidelines. Accessed August 4, 2018.
3. European AIDS Clinical Society (EACS). *European Guidelines for Treatment of HIV-Positive Adults in Europe, Edition 9.1*. Available at: http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html. Accessed August 4, 2018.
4. Bailey H, Zash R, Rasi V, et al. HIV treatment in pregnancy. *Lancet HIV*. 2018;5:e457–e467.
5. Antiretroviral Pregnancy Registry Steering Committee. *Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 January 2018*. Wilmington, NC: Registry Coordinating Center; 2017. Available at: www.APRegistry.com. Accessed August 4, 2018.
6. Cavalli P. Prevention of Neural Tube Defects and proper folate periconceptional supplementation. *J Prenat Med.* 2008;2:40–41.
7. Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities. *Folic Acid: Birth Defects COUNT*. Available at: https://www.cdc.gov/ncbddd/birthdefectscount/index.html. Accessed August 4, 2018.
8. Zaganjor I, Sekkarie A, Tsang B, et al. Describing the prevalence of neural tube defects worldwide: a systematic literature review. *PLoS One.* 2016;11:e0151586.
9. Copp A, Stanier P, Greene P. Neural tube defects: recent advances, unsolved questions, and controversies. *Lancet Neurol.* 2013;12:799–810.
10. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. *N Engl J Med.* 2018;379:979–981.
11. Sconza R, Rasi V, Peters H, et al. Raltegravir in pregnancy: patterns of use and birth outcomes in the UK & Ireland. Poster [806] presented at: 25th Conference on Retroviruses and Opportunistic Infections (CROI); March 2018; Boston, MA.
12. Sibiude J, Warszawski J, Blanche S, et al. Evaluation of the risk of birth defects among children exposed to raltegravir in utero in the ANRS-French Perinatal Cohort EPF. Presented at: 9th IAS Conference on HIV Science (IAS 2017), July 2017, Paris, Europe [Abstract MOAB0204].
13. Center for Drug Evaluation and Research. Surveillance—FDA adverse event reporting system (FAERS) public dashboard. Available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm070093.html. Accessed August 4, 2018.
14. Blencowe H, Kancherla V, Moorthie S, et al. Estimates of global and regional prevalence of neural tube defects for 2015: a systematic analysis. *Ann N Y Acad Sci.* 2018;1414:31–46.
15. Willett P. Similarity-based virtual screening using 2D fingerprints. *Drug Discov Today.* 2006;11:1046–1053.
16. Jaccard/Tanimoto coefficient (online calculator). Available at: https://planetcalc.com/1664/. Accessed August 4, 2018.