

CASE REPORT

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Repeated cholestyramine washouts in a pregnant patient on leflunomide: A case report

Vanessa Ku, Srikanth Mukkera, Nathan Joshua Manales, Asley Sanchez, Kushal Gandhi

ABSTRACT

Introduction: Leflunomide is a disease modifying anti-rheumatic drug (DMARD) that is commonly used for the treatment of rheumatoid arthritis (RA). It is considered as a category X drug because it is contraindicated during pregnancy (studies in pregnant women have demonstrated a risk to the fetus, and/or human or animal studies have shown fetal abnormalities; risks of the drug outweigh the potential benefits). In women attempting to conceive, it is necessary to ensure that leflunomide levels are undetectable in plasma to prevent the risk of fetal malformations. An 11-day treatment of cholestyramine has been shown to lower leflunomide active metabolite levels to near undetectable levels.

Case Report: In this case report, we discuss an RA patient taking leflunomide, who had an unintended pregnancy requiring two treatment courses of cholestyramine for complete washout of leflunomide. A C-section was performed at 39 weeks and 3 days due to concerns about the fetus' health and was complicated by postpartum hemorrhage. The infant received Apgar scores of 9 and

9 at 1 and 5 minutes. The infant was also found with no birth anomalies and was deemed healthy at a check-up of nine months of age.

Conclusion: Although a single 11-day treatment is typically sufficient to safely lower the concentration of leflunomide, it is important to remeasure the leflunomide active metabolite levels after the treatment course of cholestyramine to ensure that levels have reached zero. When leflunomide levels remain significantly elevated, a second treatment course of cholestyramine is required, otherwise the fetus could potentially be exposed to its teratogenic properties.

Keywords: Cholestyramine, Leflunomide, Pregnancy, Rheumatoid arthritis

How to cite this article

Ku V, Mukkera S, Manales NJ, Sanchez A, Gandhi K. Repeated cholestyramine washouts in a pregnant patient on leflunomide: A case report. J Case Rep Images Obstet Gynecol 2022;8(1):10–13.

Article ID: 100117Zo8VK2022

doi: 10.5348/100117Zo8VK2022CR

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Received: 27 January 2022

Accepted: 03 March 2022

Published: 03 June 2022

INTRODUCTION

Leflunomide is a disease-modifying antirheumatic drug (DMARD) used in the treatment of rheumatoid arthritis (RA). It acts through reversible inhibition of dihydroorotate dehydrogenase (DHODH), an enzyme involved in the pyrimidine synthesis pathway. This leads to decreased synthesis of the pyrimidine precursors that are required for T cell replication in response to growth factor and cytokine stimulation (Figure 1) [1].

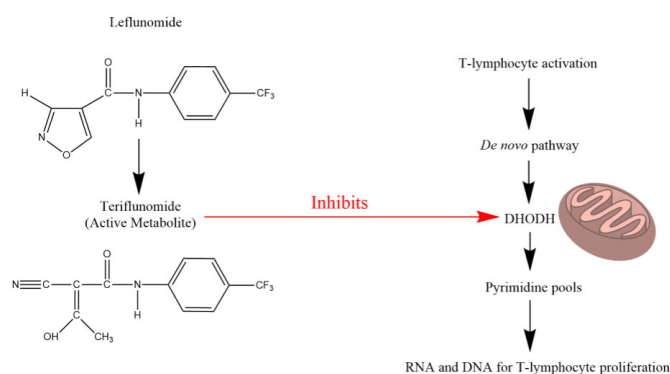


Figure 1: Diagram highlighting the mechanism of action for leflunomide, its active metabolite, and its inhibiting effect on dihydroorotate dehydrogenase (DHODH).

Leflunomide has been found to be embryotoxic and teratogenic in animals at similar therapeutic doses to those in humans [2]. In mice studies, offspring with leflunomide exposure in utero exhibited malformations such as neural tube defects, cleft palate, tail deformities, and cardiac defects [3]. Furthermore, because leflunomide has a long half-life of 14 to 15 days and undergoes enterohepatic circulation, its active metabolite, teriflunomide, can be detectable in plasma for up to two years after drug discontinuation [2]. Thus, due to the teratogenicity and long half-life of its active metabolite, leflunomide should be discontinued, and a drug washout procedure should be performed in women intending to conceive [4]. Oral cholestyramine has been shown to interfere with the enterohepatic recycling of leflunomide, leading to plasma leflunomide levels of less than 0.02 mg/L (0.02 ug/mL) in 11 days in women who plan to conceive or have an unplanned pregnancy [5].

In this case report, we discuss the importance of remeasuring plasma leflunomide levels after initiating cholestyramine therapy to ensure complete elimination of the active metabolite, because cholestyramine treatment may have to be repeated a second time in the setting of incomplete washout.

CASE REPORT

A 40-year-old female with seropositive rheumatoid arthritis (RA) presented to clinic with concern of fatigue and a missed period. She had a pregnancy test done in office which came back positive. At the time, she was taking Leflunomide 20 mg by mouth (PO) daily and subcutaneous (sub-Q) Enbrel 50 mg weekly for her RA. Follow-up ultrasound dated her pregnancy at six weeks and four days. This was an unintended pregnancy. She was advised to discontinue Leflunomide and Enbrel. We discussed starting Cimzia (Certolizumab) for her RA since it does not cross the placenta. The patient expressed her understanding, and she was started on Cimzia 200 mg sub-Q every two weeks. Additionally, she was given a

prescription for Cholestyramine 8 g TID (three times a day) for 11 days as part of the drug elimination procedure for leflunomide. A blood test for leflunomide levels was also ordered.

Table 1 demonstrates the leflunomide level before initiating treatment with cholestyramine and the leflunomide level after the 11-day treatment of cholestyramine. Leflunomide levels prior to initiating treatment with cholestyramine were 34,941 ng/mL. Since leflunomide levels were still elevated in serum at 546 ng/mL after the first treatment with cholestyramine, a second treatment course was prescribed. Leflunomide levels after completion of second trial of cholestyramine demonstrated undetectable levels in the serum.

Table 1: Leflunomide levels prior to starting treatment with cholestyramine for drug washout.

Leflunomide level (ng/mL)	Cholestyramine dose
34,941	8 g PO TID for 11 days
546	8g PO TID for 10 days

Follow-up and Outcomes

During the pregnancy, the patient tolerated Cimzia well with minimal RA disease activity. However, she stopped taking Cimzia after 30 weeks gestation due to an insurance change. Since she had no symptoms concerning for an RA flare-up throughout the pregnancy, the patient was not started on another medication. Instead, she was closely followed up with a plan to start oral prednisone if she started experiencing symptoms of a flare-up. The patient opted for an elective induction of labor at 39 weeks. She delivered via C-section at 39 weeks and three days due to non-reassuring fetal heart tones and arrest of descent after a planned induction of labor. The patient also had a bilateral tubal ligation during the procedure. C-section was complicated by a postpartum hemorrhage of 1135 mL, which did not require uterotonics or intervention. A male infant was born at 3415 g with Apgar scores of nine and nine at 1 and 5 minutes respectively, and had no birth anomalies noted upon physical exam. A check-up was performed at nine months of age with all regular milestones achieved for the infant's age.

DISCUSSION

Leflunomide, a commonly used DMARD for RA, has been classified as pregnancy category X by the U.S. Food and Drug Administration, and the manufacturer recommends that for women of childbearing age "treatment with Leflunomide must not be started until pregnancy is excluded and it has been confirmed that reliable contraception is being used" [5, 6]. Although current studies suggest that fetal exposure to leflunomide might not have a significant effect on pregnancy outcomes in humans, there is still not enough conclusive evidence [2,

6, 7]. It's important to note that in these studies a majority of the subjects undergo the cholestyramine washout procedure following discontinuation of leflunomide, with one study reporting that out of 64 women, 62 of them had at least one course of cholestyramine and 12 had more than one, up to six [6]. This means that actual fetal exposure to leflunomide is typically kept at the suggested 0.02 µg/mL or lower, and the effects of leflunomide on development above than concentration are not nearly as documented.

Regardless, these studies do not prove to be adequate enough to warrant any less caution, and women receiving treatment with leflunomide are still advised to follow the current standards: to use contraceptives, to avoid pregnancy, and to discontinue the use of leflunomide and undergo the drug elimination procedure if a pregnancy does occur [7, 8].

CONCLUSION

Although many leflunomide washouts require only one 11-day treatment of cholestyramine, the washout must be repeated if leflunomide levels remain elevated after the first treatment course. Leflunomide levels had not been repeated in this patient, her fetus may have been at increased risk for birth defects, such as cleft palate, axial skeleton anomalies, and defects of the heart and great vessels. Thus, it is important to remeasure leflunomide levels after cholestyramine washout to ensure that levels reach zero in the blood. Given the current working information we have about the teratogenicity of leflunomide, it's vital to err on the side of caution.

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Acknowledgements

We appreciate the Texas Tech University Health Sciences Center, Permian Basin, TX, and Evangelyna Nguyen at the TTUHSC-PB Research Lab for their assistance with submitting and revising this case report.

Author Contributions

Vanessa Ku – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Srikanth Mukkera – Conception of the work, Design of the work, Acquisition of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Nathan Joshua Manales – Design of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Asley Sanchez – Design of the work, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Kushal Gandhi – Design of the work, Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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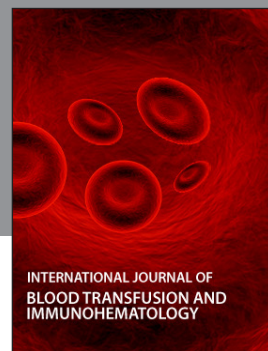
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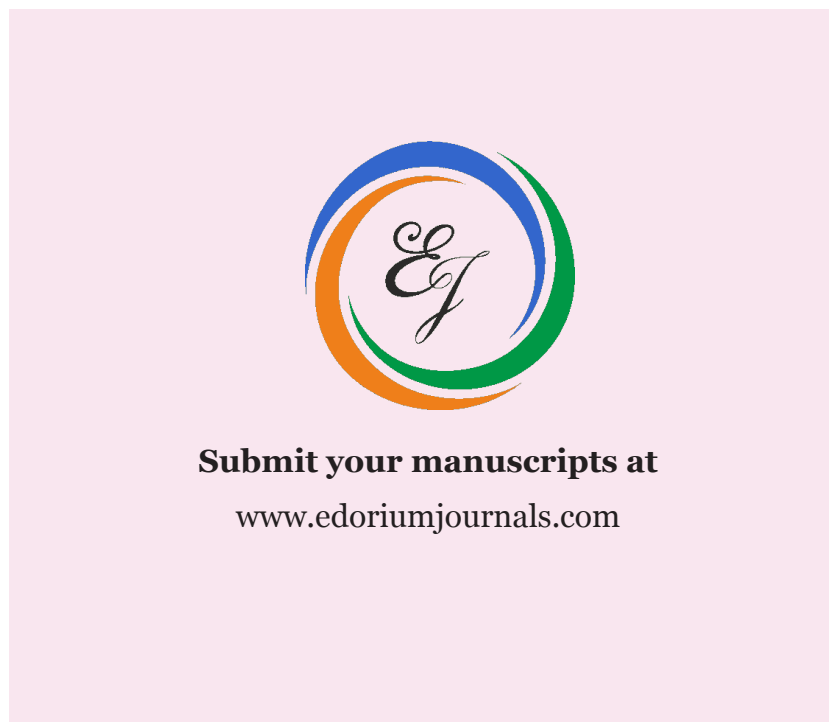
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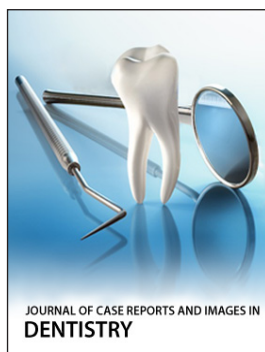
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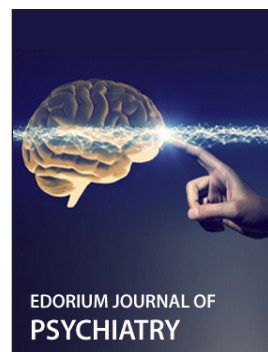
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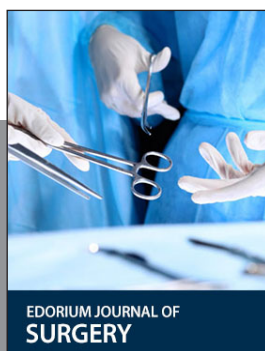
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