Case Reports in Women's Health 25 (2020) e00162

Contents lists available at ScienceDirect

Case Reports in Women's Health

journal homepage: www.elsevier.com/locate/crwh

Severe rebound disease activity after fingolimod withdrawal in a pregnant woman with multiple sclerosis managed with rituximab: A case study

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ARTICLE INFO

Article history:
Received 24 October 2019
Received in revised form 6 November 2019
Accepted 8 November 2019

Keywords:
Multiple sclerosis
Pregnancy
Rituximab
Fingolimod
Rebound

ABSTRACT

Although pregnancy is potentially protective against relapses of multiple sclerosis, severe rebound of disease activity after withdrawal of fingolimod may occur. We report a woman with multiple sclerosis who discontinued fingolimod in the first month of her pregnancy. She developed severe disease rebound which responded poorly to steroids. She was started on rituximab, which was continued during the rest of her pregnancy and beyond. Rituximab appeared safe and well tolerated by both mother and infant, and could be considered in pregnancy for those patients with multiple sclerosis who are at high risk of gestational and postpartum relapse.

1. Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory disorder of the central nervous system (CNS) characterized by relapses caused by a new or enlarging demyelinating plaque at the site of an inflammatory event within the CNS. These relapses are clinically defined as a new neurologic deficit or episode of neurologic worsening lasting longer than 24 h in the absence of fever or infection [1]. Although recovery to the pre-existing functional baseline is the usual outcome after a relapse, in many cases recovery is incomplete and relapses result in the accumulation of disability [1]. Disease-modifying drugs (DMDs) for MS reduce relapse rates and prevent progression.

However, in MS, withdrawal of certain DMDs, in particular, lymphocyte anti-trafficking therapies such as natalizumab and fingolimod, may result in severe disease reactivation or even rebound of disease activity [2,3]. Disease rebound is defined as newly occurring, severe polysymptomatic neurologic manifestations associated with significant new or enlarging T2-weighted or gadolinium-enhancing T1-weighted lesions exceeding the patient's pre-DMD baseline activity, on treatment discontinuation [2]. A recent study estimated the incidence of disease rebound after withdrawal of fingolimod at 5–10% [3,4]. This unexpected severe and potentially fatal reactivation of disease activity is particularly of concern to women on fingolimod who are planning a pregnancy. Despite the fact that pregnancy has classically been associated with a significant reduction in clinical relapse rate, there are several reports of dramatic disease rebound during pregnancy following withdrawal of fingolimod [5].

We report a case of severe disease rebound during the second trimester of pregnancy after withdrawal of fingolimod, which was managed with rituximab, and describe the safety and clinical outcome of B-cell-depleting therapy for both mother and newborn.

2. Case report

At the age of 32, the patient (G1P1A0) was diagnosed with MS and was started on disease-modifying therapy with interferon-β 1a (IFNβ) 30 μg once weekly. Over the course of 5 years she had several relapses (with recovery), mostly related to lack of adherence. She became pregnant with her first child 5 years after diagnosis. Consequently, her IFNβ therapy was discontinued. She resumed IFNβ after delivery, but again with poor compliance. Three years later, she experienced a new relapse. Her score on the Expanded Disability Status Scale (EDSS) was 3.0. (EDSS scores range from 0 to 10 in 0.5-unit increments, with higher scores representing higher levels of disability, and scores above 6.0 indicate that people with MS are in need of walking aids.) At that time, a brain MRI scan revealed already high levels of disease activity. Consequently, her treatment was escalated to fingolimod. While on fingolimod, she

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https://doi.org/10.1016/j.crwh.2019.e00162

had no clinical relapses. She expressed a wish to conceive another child 3 years after that. She was counseled about her treatment, wash-out period and potential alternative disease-modifying therapies during the pregnancy. Despite all this, she refused to take contraceptive measures during the fingolimod wash-out period. Seven months later, a pregnancy test indicated that she was 4 weeks pregnant. Without taking medical advice, she decided to discontinue fingolimod.

Two months later, after a relapse, consisting of left-sided hemiparesis, urinary incontinence, blurring of vision in the right eye, ataxia and presence of Lhermitte's sign, she sought medical attention. At that time, her lymphocyte count was $0.8 \times 10^3/\mu L$. An MRI scan revealed multiple new active lesions affecting the right corona radiata, the corpus callosum, brainstem, bilateral middle cerebellar peduncles, cerebellar white matter and the right cerebellar hemisphere (Fig. 1). In addition, there were multiple active lesions affecting the cervical and dorsal spinal cord. She was twice pulsed with 1 g of methylprednisolone for 5 days (EDSS 7.0) with one week interval but responded poorly. Therapeutic plasmapheresis was proposed but was refused because of her pregnancy. As she could not afford natalizumab, it was decided, after obtaining her informed consent, to start her (in week 22 of the pregnancy) off-label on rituximab (two 1 g infusions 15 days apart) and to re-evaluate her condition post-partum. This decision was based on the severity of her relapses and to protect her from further relapses during the rest of the pregnancy and post-partum. By the end of the pregnancy she had a partial recovery (EDSS 4.5) and the remainder of the pregnancy was uneventful. Under the care of a high-risk obstetrician she delivered a healthy boy (birth weight 2419 g) at 38 weeks of gestation via cesarean section.

APGAR scores were 9 at 1 min, and 10 at 5 min. At 3 months, no infections and normal development were reported, and the infant's % CD19+ count was 19.8%. The standard vaccinations were delayed till the third month.

Post-delivery, the mother developed no new relapses (EDSS 4) and her physical examination remained stable. She was continued on rituximab (1 g six-monthly). No neurologic or infectious sequelae at 6-month follow-up were reported.

3. Discussion

In this case no congenital malformations were detected related to the intake of fingolimod during the first 4 weeks of pregnancy, and rituximab had no adverse fetal or infant effects. The patient clearly presented with severe rebound and not a relapse: she had severe polysymptomatic deficits resulting from multiple new and enlarging MRI lesions (Fig. 1), her EDSS score (7.0) was significantly worse than her pre-fingolimod baseline score (EDSS 3.0) and, as frequently observed with fingolimod [2], there was poor response to methylprednisolone, leaving the patient severely disabled. The reason for her rebound was the cessation of fingolimod. Fingolimod causes nodal trapping of lymphocytes, which results in a significant decrease in peripherally circulating lymphocytes (lymphopenia), and which prevents autoaggressive lymphocytes from entering the CNS. After withdrawal of fingolimod, these lymphocytes were suddenly able to egress from the lymphoid organs and migrate to the CNS, causing this massive inflammatory reaction (rebound).

Our patient revealed the first symptoms of rebound 8 weeks after withdrawal of fingolimod, which is earlier than rebound described for natalizumab (8–24 weeks) [2]. In the study by Lapucci et al., 6 patients who had a wash-out of fingolimod developed severe withdrawal only 3–4 months after discontinuation of the drug [6]. The underlying mechanisms by which fingolimod causes such dramatic rebound phenomena in certain patients are elusive, but may include a prompt B cell reconstitution after cessation of the drug, the rapid influx and increase in self-reactive T cells, particularly central memory T cells, the activation of antibody production by T cells, and decrease of direct S1P receptor-mediated activity on astrocytes, oligodendrocytes, and neurons [7]. Similar to previous reported cases of rebound following fingolimod withdrawal, the response to high-dose steroid therapy in our patient was relatively poor [2,8].

Rituximab is an anti-CD 20 chimeric (human/mouse) monoclonal antibody which rapidly and profoundly depletes circulating but also centrally localized $CD20^+$ B cells [9]. In view of its good safety and efficacy profile, in addition to its affordable price, the drug is frequently used off-label in the management of MS and has become the DMD of choice for patients in our center who have limited financial means. Moreover, rituximab may offer distinct advantages in women with MS who wish to conceive [10]: firstly, its B-cell depleting effect extends beyond its pharmacokinetic half-life (minimal 3.6 months), providing a window for conception without risk of fetal exposure to the drug but offering protection against relapses during pregnancy; secondly, being a monoclonal antibody of the IgG1 isotype, rituximab does not cross the placenta during the first trimester of pregnancy. However, after the 16th week of gestation rituximab crosses the placenta and reduces B cell levels in the developing fetus.

Recently, Das et al. [10] reviewed a series of 11 patients who received rituximab within 6 months of conception. Seven of them were MS patients while the remainder had neuromyelitis optica. In all MS

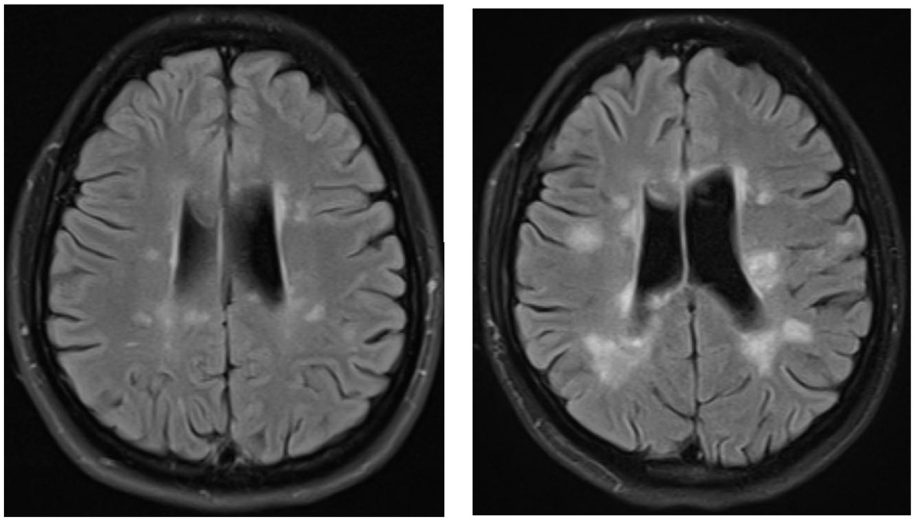

Fig. 1. Brain MRI before cessation of fingolimod (left panel) and at the time of rebound (right panel). Axial flair images at rebound show several new and enlarging hyperintense lesions.

cases, rituximab therapy was started prior to conception (1–6 months before). In 4 of them, fingolimod was the prior DMD, with a wash-out interval of 2–6 months. Their observations led them to conclude that rituximab was safe. Few data exist on rituximab administration during pregnancy. Three cases have been reported that featured the use of rituximab in the first trimester in patients suffering from hematological conditions. [11–13]. No negative safety signals were observed. The transient B cell depletion and peripheral lymphocytopenia reported in infants born of mothers treated with rituximab during pregnancy generally normalized within 3–6 months. [10]

Although the use of B cell depleting monoclonal antibodies during pregnancy is still controversial and relatively contraindicated because of potential harm to the developing fetus and infant, this case illustrates a favorable outcome in MS and for the newborn after initiation of rituximab in the second trimester. Although anecdotal, we suggest that B cell depleting therapy – in this case rituximab - could be considered as an alternative to natalizumab in MS during pregnancy following fingolimod withdrawal. In such cases, a highly specialized multidisciplinary team with high-risk obstetrician and pediatrician are essential for the close monitoring of the patient and infant.

Contributors

Beatriz Canibaño conceived the idea of the case report and wrote the manuscript.

Musab Ali collected the data.

Boulenouar Mesraoua contributed to the data and reviewed the manuscript.

Gayane Melikyan contributed to the data and reviewed the manuscript.

Hasan Al Hail collected the data.

Faiza Ibrahim contributed to the data and reviewed the manuscript.

Yolande Hanssens contributed to the data and reviewed the manuscript.

Dirk Deleu conceived the idea of the case report and wrote the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

Funding

The publication of this article was funded by the Qatar National Library.

Patient consent

The patient gave consent for the publication of the report and the associated images.

Provenance and peer review

This case report was peer reviewed.

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