Clinical Case Report

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Pravastatin for prevention of HELLP syndrome

A case report

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Abstract

Rationale: Pravastatin has emerged for prevention and treatment of preeclampsia; no reports are available on pravastatin and HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome.

Patient concerns: The first pregnancy necessitated termination of pregnancy at gestational age (GA) 20+5 for HELLP. Intrauterine fetal death at GA 22+5 occurred in the second pregnancy, whilst on temporizing management of HELLP.

Diagnoses: Severe, recurrent early-onset HELLP syndrome.

Interventions: In her fourth pregnancy, pravastatin was commenced at GA 13.

Outcomes: The course of pregnancy was uncomplicated, and a healthy, appropriate for gestational age fetus was delivered at term.

Lessons: Pravastatin may be effective in prevention of HELLP. The hepatic uptake may be of particular advantage.

Abbreviations: AGA = appropriate for gestational age, ASA = acetylsalicylic acid, GA = gestational age, HELLP = hemolysis, elevated liver enzymes, and low platelets, HMG-CoA = hydrophilic 3-hydroxy-3-methylglutaryl-coenzyme A, HOMA = homeostasis model assessment, LMWH = low-molecular weight heparin, MTHFR = methylentetrahydrofolat-reductase, PlGF = placental growth factor, s-Flt = soluble fms-like tyrosine kinase-1 receptor.

Keywords: HELLP syndrome, HMG-CoA-reductase inhibitor, pravastatin

1. Introduction

The syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) is regarded as particularly severe form of preeclampsia, causing adverse pregnancy outcome for both the mother and the fetus.[1] Soluble fms-like tyrosine kinase-1 receptor (s-Flt) is involved in the pathogenesis by inactivation of vascular endothelial growth factor, resulting in angiogenic imbalance and endothelial dysfunction.[2]

Pravastatin, a hydrophilic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)-reductase inhibitor, has been shown to decrease levels of circulating s-Flt in animals.[3–6] Reassuring data on teratogenicity and promising results in preliminary clinical studies[7–10] prompted us to use pravastatin in a patient with a history of 2 pregnancies that had been complicated by severe, early-onset HELLP syndrome.

2. Case

In her first pregnancy (2012), the 36-year-old patient was referred to our unit at gestational age (GA) 20+3 with epigastric pain, nausea, and vomiting. Apart from a well-controlled Hashimoto thyreoiditis her medical history was noncontributory. The laboratory results were consistent with HELLP syndrome (Fig. 1); hypertension and proteinuria, not present initially, developed subsequently. Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and acute fatty liver of pregnancy were excluded. Obstetric ultrasound revealed an appropriate for gestational age (AGA) fetus with no obvious malformations; blood flow velocity waveform indices of the fetal and fetoplacental circulation were within normal range; the uterine arteries, however, had highly abnormal pulsatility indices and bilateral notching (Table 1). The maternal condition deteriorated and necessitated termination of pregnancy at GA 20+5 (female, weight: 330 g, 13th percentile). She made a rapid clinical recovery and was discharged on day 1 after termination.

One year later, in her second pregnancy, she was referred for severe fetal growth restriction and highly abnormal Doppler indices at GA 20+2 (Table 1). Because of first-trimester vaginal bleeding acetylsalicylic acid (ASA) had been withheld. Maternal symptoms were absent, and laboratory results were normal. She was monitored as outpatient until GA 22+2, when blood flow indices in the ductus venosus deteriorated; in addition, she developed symptoms of HELLP syndrome. The diagnosis was confirmed by laboratory results (Fig. 1). Temporizing management was initiated after extensive discussion; however, intrauter-

Editor: Daryle Wane.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:42(e8229)

Received: 10 May 2017 / Received in final form: 12 September 2017 / Accepted: 14 September 2017

http://dx.doi.org/10.1097/MD.0000000000008229

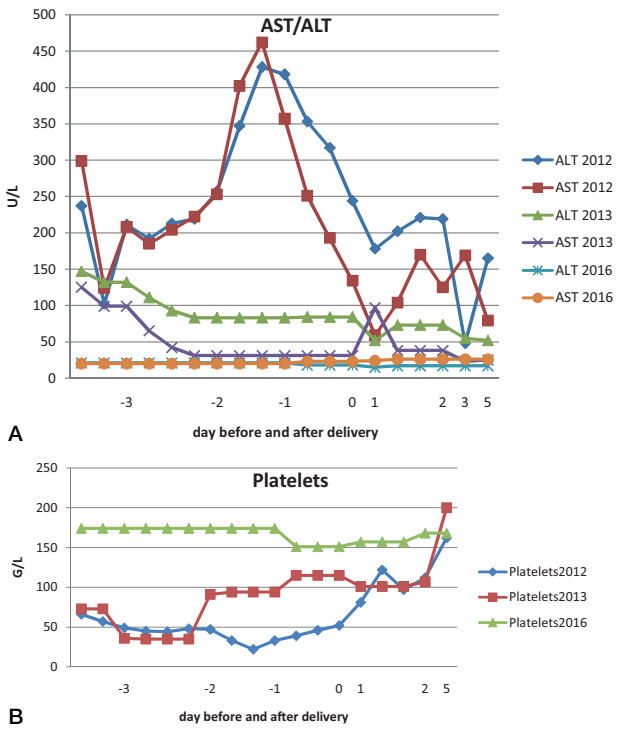

Figure 1. Liver function tests (A) and platelets (B) in the days before and after delivery. ALT = alanine aminotransferase, AST = aspartate aminotransferase.

ine fetal death occurred at GA 22+5 (female, weight: 325 g, <3rd percentile). Apart from a transient rise in blood pressure her postoperative course was uncomplicated.

Thereafter, the patient came for preconception counseling; she was informed about the high chance of another pregnancy failure and the substantial maternal risk, but she opted for another attempt. Her request for immunosuppressive/immunomodulatory treatment during her next pregnancy was denied because of lack of clinical and scientific evidence in HELLP syndrome; peripheral lymphocyte typing had revealed normal results.

Instead, an extensive diagnostic work-up for potential cofactors of recurrent HELLP syndrome was offered. It included parental karyotyping, 3-dimensional ultrasound of the uterine cavity to rule out genital malformations or secondary changes, repeated cervical swabs for chlamydia trachomatis, ureaplasma urealyticum, and mycoplasma hominis, all with negative results. The endocrinological work-up revealed normal early follicular phase hormones; autoimmune thyreoiditis (Hashimoto) was confirmed. Due to rising levels of anti-TPO antibodies, substitution with L-thyroxin (maximum dosage of 50 μg daily) and selen (200 μg daily) was initiated.

Table 1

Midtrimester pulsatility indices of the uterine arteries.

Pregnancy	GA*	Right PI†	Notching	Left PI†	Notching
1	20+3	2.11 (>95)	Yes	1.71 (>95)	Yes
2	22+2	2.55 (>95)	Yes	3.19 (>95)	Yes
4	20+4	0.71 (52)	No	1.40 (75)	No

* Gestational age: week plus day.
† PI = pulsatiliy index (percentile).

The HOMA (homeostasis model assessment) was slightly elevated, a subsequent glucose tolerance test showed a marginally abnormal 2-hour blood glucose concentration. The patient received nutritional advice; she declined treatment with biguanide derivatives.

Screening for thrombophilia did not reveal major inherited or acquired disorders except for homozygosity for the MTHFR (methylentetrahydrofolat-reductase) mutation C677T. Repeated controls for antiphospholipid antibodies remained negative. However, D-dimers were mildly elevated in several analyses.

In 2015, then 39 years old, she miscarried at 8 weeks' gestation; karyotyping revealed trisomy 22.

In early 2016, now 40 years old, the patient conceived again. She was commenced on prophylactic treatment with low-molecular weight heparin (LMWH) (enoxaparin 40 mg s.c. daily), ASA (100 mg daily), and natural progesterone (400 mg daily intravaginally). The preconception treatment with L-thyroxin (50 μg daily), selen (200 μg daily), myoinositol (1000 mg daily), and folic acid (2.5 mg daily) was continued. Pravastatin (10 mg daily) was started at GA 12. Institutional review board approval is not required for off-label use treatment. After extensive counseling about the medication, written consent was obtained from the patient. Close surveillance (clinical, laboratory, and ultrasound) was initiated. Throughout the entire course of pregnancy she was asymptomatic, and her laboratory results remained within normal range. The obstetric ultrasound revealed adequate growth of a fetus without major malformations, and normal Doppler indices of the fetal, fetomaternal, and uteroplacental vessels (Table 1). Gestational diabetes developed in the third trimester and was controlled with insulin. At GA 37 +1, elective cesarean delivery was performed (male; 2920 g, 31st percentile; Apgar scores 9/10/10 at 1, 5, and 10 minutes, respectively; umbilical artery pH 7.35). Both, patient and newborn, made an uncomplicated postoperative/postnatal course and were discharged on day 3.

3. Discussion

Pravastatin at a daily dosage of 10 mg, commenced early in the second trimester, in addition to ASA and LMWH, resulted in an uncomplicated pregnancy and term delivery of an AGA healthy neonate in a patient with a history of severe, early-onset, recurrent HELLP syndrome.

Presently, a HMG-Co-A-reductase-mediated decrease in s-Flt-1 synthesis is hypothesized to be the mechanism underlying the positive effect of pravastatin in preeclampsia; in addition, a rise in levels of circulating placental growth factor (PlGF) may contribute to the improvement of the proangiogenic profile and the reversion of sequelae of inflammation and endothelial dysfunction.[5,7,9] The effect of pravastatin on soluble endoglin, another cofactor of vascular homeostasis involved in the pathogenesis of preeclampsia, is less clear, and may include an organ-specific response.[8]

In contrast to preeclampsia, HELLP syndrome is characterized by hepatic and hematologic manifestations. Nevertheless, HELLP syndrome and preeclampsia share the same pathophysiology, and HELLP syndrome is considered a particular manifestation of preeclampsia, respectively.

We assume that the mechanism of action of pravastatin in HELLP syndrome is comparable to its effect in preeclampsia. The hepatic uptake of pravastatin may be of particular advantage in HELLP syndrome because 50% of the absorbed drug is lost by a first-pass effect.[11]

To our knowledge, this is the first report of pravastatin in severe, early-onset, recurrent HELLP syndrome; the positive outcome justifies further clinical trials in women at risk of developing HELLP syndrome.

References

[1] Mol BW, Roberts CT, Thangaratinam S, et al. Pre-eclampsia. Lancet 2016;387:999–1011.
[2] Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 2003;111: 649–58.
[3] Costantine MM, Tamayo E, Lu F, et al. Using pravastatin to improve the vascular reactivity in a mouse model of soluble fms-like tyrosine kinase-1-induced preeclampsia. Obstet Gynecol 2010;116:114–20.
[4] Fox KA, Longo M, Tamayo E, et al. Effects of pravastatin on mediators of vascular function in a mouse model of soluble Fms-like tyrosine kinase-1-induced preeclampsia. Am J Obstet Gynecol 2011;205: 366.e1–5.
[5] Kumasawa K, Ikawa M, Kidoya H, et al. Pravastatin induces placental growth factor (PGF) and ameliorates preeclampsia in a mouse model. Proc Natl Acad Sci USA 2011;108:1451–5.
[6] Bauer AJ, Banek CT, Needham K, et al. Pravastatin attenuates hypertension, oxidative stress, and angiogenic imbalance in rat model of placental ischemia-induced hypertension. Hypertension 2013;61: 1103–10.
[7] Nanovskaya TN, Patrikeeva SL, Paul J, et al. Transplacental transfer and distribution of pravastatin. Am J Obstet Gynecol 2013;209:373.e1–5.
[8] Brownfoot FC, Tong S, Hannan NJ, et al. Effects of pravastatin on human placenta, endothelium, and women with severe preeclampsia. Hypertension 2015;66:687–97.
[9] Costantine MM, Cleary K, Hebert MF, et al. Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial. Am J Obstet Gynecol 2016;214:720.e1–7.
[10] Lefkou E, Mamopoulos A, Dagklis T, et al. Pravastatin improves pregnancy outcomes in obstetric antiphospholipid syndrome refractory to antithrombotic therapy. J Clin Invest 2016;126:2933–40.
[11] Hatanaka T. Clinical pharmacokinetics of pravastatin: mechanisms of pharmacokinetic events. Clin Pharmacokinet 2000;39:397–412.