Peri-pregnancy safety of monoclonal antibodies inhibiting PCSK9: a pharmacovigilance study using VigiBase®

Roberta Noseda [1], Francesca Bedussi [1], Alice Panchaud [2,3], Alessandro Ceschi [1,4,5,6]

1. Division of Clinical Pharmacology and Toxicology, Institute of Pharmacological Sciences of Southern Switzerland, Ente Ospedaliero Cantonale, Lugano, Switzerland
2. Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
3. Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland
4. Clinical Trial Unit, Ente Ospedaliero Cantonale, Lugano, Switzerland.
5. Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland
6. Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, Switzerland

Introduction

- Alirocumab and evolocumab are fully humanized monoclonal antibodies that inhibit free plasma proprotein convertase subtilisin/kexin type 9 (PCSK9), thereby promoting the recycling of low density lipoprotein receptor (LDL-R) to the surface of hepatocytes and the reduction of plasma LDL-cholesterol (LDL-C) levels [1].
- They are approved for use of primary hyperlipidaemia, secondary prevention of cardiovascular events and familial hypercholesterolemia and are overall well tolerated [2,3].
- During the first and second trimester of pregnancy, LDL-C levels increase up to 50% to ensure placental hormone production and fetal fatty acid synthesis [4].
- PCSK9 is known to play a role in placental lipid (including LDL-C) metabolism and fetal growth [5].
- As immunoglobulin G antibodies, monoclonal antibodies inhibiting PCSK9 cross the placenta through the neonatal Fc receptor that appears after the first 20-22 weeks of pregnancy [6].
- Available safety data on exposure to alirocumab and evolocumab in the peri-pregnancy period (i.e. before, during and after pregnancy) are scarce and limited to one clinical case [7]. Accordingly, alirocumab and evolocumab are labelled as contraindicated in pregnancy by manufacturers.

Aim

To describe the largest-to-date case series of exposures to alirocumab and/or evolocumab in the peri-pregnancy period with or without pregnancy outcomes

Methods

Pharmacovigilance study in VigiBase®, the World Health Organization's global database of spontaneous safety reports, based on case-by-case assessment

➢ Safety reports included (n=95):

- collected in VigiBase® as of 31.12.2022
- reporting as suspected drug alirocumab and/or evolocumab
- concerning pregnancy, therefore captured by the standardized query "pregnancy and neonatal topics" from the Medical Dictionary for Regulatory Activities (MedDRA®)

➢ Safety reports excluded (n=57, 60%):

- those for which it was not possible to ascertain drug exposure in the peri-pregnancy period because lacking specific terms referring to pregnancy

Results

The study cohort consisted of 38 safety reports

1. Demographic and clinical characteristics of safety reports, n (%)	
Country of origin	22 (57.9) from Europe 9 (23.7) from United States of America 6 (15.8) from Asia 1 (2.6) from South America
Type of reporter	22 (57.8) physicians 8 (21.1) other healthcare professionals 8 (21.1) patients/consumers
Patient sex	32 (84.2) females 2 (5.3) males[1]
Patient age	18 (47.4), median 36.5 years, 25th-75th percentiles, 31-41 years
Suspected drug	25 (65.8) evolocumab 13 (34.2) alirocumab
Indication	10 (26.3) familial hypercholesterolemia 7 (18.4) hypercholesterolemia 2 (5.3) hyperlipidaemia 2 (5.3) familial hyperlipidaemia 17 (44.7) not reported
Time of drug exposure in the peri-pregnancy period	31 (81.6) maternal exposure during pregnancy 3 (7.8) paternal exposure 2 (5.3) during lactation 2 (5.3) not reported

[1] One safety report referred to paternal exposure to alirocumab; one involved a male neonate

2. Safety profile, n (%)	
Nr. of safety reports reporting only drug exposure in the peri-pregnancy period	20 (52.6)
Nr. of safety reports reporting drug exposure in the peri-pregnancy period AND pregnancy outcomes	18 (47.4)

3. Safety reports with pregnancy outcomes, n (%)	
Only maternal toxicities	4 (10.5) • Deep vein thrombosis • Gestational diabetes • Fatigue and peripheral oedema • Vascular stent thrombosis, myocardial ischemia, cardiac arrest and death
Maternal toxicity and foetal death	1 (2.6) • Prosthetic cardiac valve thrombosis, myocardial ischemia, cardiac arrest, back pain / foetal death
Only foetal/neonatal outcomes	13 (34.2) • 8 spontaneous abortions* • 2 live new-borns • 1 foetal death • 1 premature baby* • 1 congenital central nervous system anomaly*

* Presence of alternative causes among maternal age >35 years, co-reported drugs beside the suspected monoclonal antibody targeting PCSK9 and the underlying comorbidities (for which co-reported drugs were indicated)

Conclusions

➢ **No specific maternal toxicities or patterns of birth defects were observed**

➢ **Spontaneous abortion was the most frequently reported adverse pregnancy outcome, however with causal relationship with respect to use of alirocumab or evolocumab in the peri-pregnancy period been unlike**

As the number of safety reports in VigiBase® increases over time, it will be possible to re-assess in the future the series of safety reports of spontaneous abortion with alirocumab and evolocumab and eventually perform disproportionality analyses to promptly detect signals of disproportionate reporting

References [1] Shimada YJ et al., *Eur Heart J.* 2015; [2] Sabatine MS et al., *N Engl J Med.* 2017; [3] Schwartz GG et al., *N Engl J Med.* 2018; [4] Herrera E. *Endocrine.* 2002; [5] Cantin C et al., *Antioxidants (Basel).* 2022; [6] Simister NE et al., *Eur J Immunol.* 1996; [7] Vuignier Y et al., *Birth Defects Res.* 2021