Interaction between rosvastatin and ticagrelor resulting in rhabdomyolysis

Viola Macolic Sarinic, Lovisa Sandberg, Jenny Hartman, Pia Caduff-Janosa

Background
A signal screening focusing on drug-drug interactions in VigiBase, the WHO global database of individual case safety reports, identified a case series pointing to an interaction between the platelet aggregation inhibitor ticagrelor and the statin rosvastatin leading to rhabdomyolysis. Rhabdomyolysis is a well-known adverse drug reaction of statins. The risk of developing rhabdomyolysis is concentration dependent and is increased in elderly patients and in patients with renal and/or hepatic impairment[1].

Aim
To explore a possible interaction between rosvastatin and ticagrelor leading to rhabdomyolysis.

Methods
Clinical review of reports with rhabdomyolysis and concurrent use of rosvastatin and ticagrelor, included in VigiBase up to October 2016.

Results
VigiBase contained five unique cases reporting rhabdomyolysis with ticagrelor and rosvastatin as suspected medications. The reports originated from five countries in North America and Europe (including one literature case[2]). Patient ages, daily doses of rosvastatin and the time relationship between rhabdomyolysis and exposure of rosvastatin and ticagrelor are presented in the time lines below. In two cases the patient had used rosvastatin for years without complaints before ticagrelor was added. Two cases reported concurrent use of ezetimibe, which increases the AUC of rosvastatin 1.2 time[1]. Two cases reported concurrent use of ACE-inhibitors, which can cause renal dysfunction[3]. After discontinuation of both ticagrelor and rosvastatin in two cases, the symptoms regressed or disappeared.

Conclusions
The reports in VigiBase presented one or more risk factors for rhabdomyolysis: old age, higher than recommended rosvastatin dose, and/or concurrent use of drugs that may affect rosvastatin concentration. In these cases, the start of ticagrelor seems to have added an additional risk, raising rosvastatin concentration to critical levels, resulting in rhabdomyolysis. This is supported by a plausible temporal association in three cases. Rosuvastatin is mainly eliminated by biliary excretion, and to a lesser extent by renal excretion[1]. An interaction with ticagrelor possibly includes mechanisms affecting both elimination pathways:

i) Renal impairment caused by ticagrelor, leading to decreased renal excretion of rosvastatin

ii) Competition on transporter level (OATP1B1), leading to decreased biliary excretion of rosvastatin

iii) Genetic polymorphism (OATP1B1 and/or UGT2B7), leading to increased competition on transporter level [1,4,5]

In conclusion, the reports in VigiBase, together with plausible mechanisms, support a signal for an interaction between ticagrelor and rosvastatin especially in high-risk patients.

References

Disclosure
The authors are indebted to the national centres that contribute data to the WHO Programme for International Drug Monitoring. However, the opinions and conclusions in this study are not necessarily those of the various centres, nor of WHO.