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The Effect of Silymarin Treatment on the Oral Disposition of Rosuvastatin

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Background: Silymarin, a raw extract from the seeds of milk thistle(Silybum marianum), has been used as a supplementary treatment of liver diseases. Previous experiment demonstrated that silymarin was a potential human OATP1B1 modulator in vitro. This study is to evaluate the effect of silymarin treatment on the uptake of rosuvastatin, a substrate of OATP1B1, in OATP1B1-expressing xenopus oocytes and on the disposition of rosuvastatin in healthy subjects.

Methods: The uptake of rosuvastatin (10 uM) study in OATP1B1-expressing oocyte in the absence or presence of silymarin (50 uM) was performed. The clinical trial was designed as open, randomized, 2-way crossover study with 2 weeks washout and six healthy male volunteers were divided into 2 groups. In the silymarin phase, sujbects were treated with a single oral dose of 140 mg silymarin three times per a day for 5days. On day 4, after 1 hr of silymarin dosing at 8AM, 10 mg rosuvastatin was administered orally. In the control phase, rosuvastatin PK study was repeated using placebo pretreatment. Blood samples were serially taken up to 72hours. Assay of plasma rosuvastatin was conducted using a LC/MS/MS.

Results: In vitro, in OATP1B1-expressing xenopus oocyte, the silymarin (50 uM) produced significant decreases in rosuvastatin uptake. In clinical trial, in the silymarin phase, mean AUC and Cmax were 126.86±48.24 ng*hr/ml and 12.77±5.23 ng/ml respectively. In the control phase, those were 135.18±40.47 ng*hr/ml and 13.03±4.85 ng/ml respectively. There was no significant difference of rosuvastatin PK paramters in relation to silymarin treatment.

Conclusion: Silymarin strongly inhibited the OATP1B1-mediated uptake of rosuvastatin in vitro. On the other hand, there is no significant effect of silymarin treatment on disposition of rosuvastatin in vivo. Probably, the involvement of other drug transporters contributing to the disposition of rosuvastatin might mask the OATP1B1 mediated interaction effect of silymarin on the transporting rosuvastatin in vivo. Addtionally, flavonoids such as silymarin can work on the activity of transporters with one or more mechanism of action, therefore combined effect of these action mechanisms may produce the in vivo final outcome inconsistent with in vitro results.