Evaluation of atherosclerotic lesions by BCR/ABL1 tyrosine kinase inhibitor effects in a familial type Ⅱ$_a$ model mouse.

Masamitsu Takaba[1], Takayuki Iwaki[2], Takaaki Ono[1], Yuji Matsumoto[2], Kazuo Umemura[2]

[1]Third Division, Department of Internal Medicine, Hamamatsu University School of Medicine, [2]Pharmacology, Hamamatsu University School of Medicine

[Introduction] BCR/ABL1 tyrosine kinase inhibitors (TKIs) have improved the treatment of chronic myeloid leukemia. However, it becomes widely known that treatment with TKIs increases vascular adverse events (VAEs) and the detailed mechanism for VAEs is unknown. We hypothesized that TKIs accelerate atherosclerotic lesions and studied atherosclerotic lesions by TKIs in a familial type II a model mouse.

[Methods] In order to evaluate atherosclerotic lesion by TKIs, *Ldlr*$^{-/-}$and *Apobec1*$^{-/-}$($L^{-/-}/A^{-/-}$) mice were used. $L^{-/-}/A^{-/-}$ mice have a high plasma LDL levels and more pronounced development of atherosclerosis. 8-week-old male $L^{-/-}/A^{-/-}$ mice were randomized in 4 groups (n=10 per group) and received oral gavage with DMSO, imatinib(50mg/kg), nilotinib(45mg/kg), ponatinib(10mg/kg) for 16 weeks. Thereafter, mice were sacrificed to evaluate atherosclerotic lesions and plasma cholesterol levels.

[Results] There were no significant differences in atherosclerotic lesions and plasma cholesterol levels between 4 groups.

[Discussion] We could not find an association between atherosclerosis and TKIs in this study. The onset of VAEs by TKIs is very complex and it may be difficult to explain solely by atherosclerosis.