A survey of hepatic impairment pharmacokinetic studies for new drug approvals and proposal for the setting of the criteria for hepatic impairment

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Background
Child-Pugh classification (C-Pc) is commonly used for the stratification index in hepatic impairment (HI) pharmacokinetic (PK) studies, as recommended in the FDA guidance (a). C-Pc has 3 stages according to the degree of progress, A (mild), B (moderate) and C (severe). However, due to the nature of C-Pc that categorizes by scores of clinical laboratory value and medical condition, C-Pc has the possibility that 'non-cirrhosis' such as healthy and hepatitis patients are also classified as C-Pc(A).

Meanwhile, drug clearance decreases depends on the progress of HI, and the effect of cirrhosis on PK is larger than that of hepatitis (b).

To enroll patients with cirrhosis is key evaluation factor in HI studies.

Objectives
Objectives are to investigate the inclusion criteria of published HI studies, to propose the criteria in order to evaluate the effect of HI on PK and to indicate it in package insert (PI) appropriately.

Methods
Scope was small-molecule drugs which were approved by Japanese Health Authority between 2013 and 2016 as initial new drugs except for anti-cancer or anti-hepatic disease drugs, and the results of HI studies are available. Inclusion criteria of HI studies was surveyed using published documents.

Results and discussion
30 drugs were surveyed. For 20/30 drugs, HI studies were including C-Pc(A) group. In 20 drugs, the number of drugs of which inclusion criteria for HI study including (1) diagnosed as 'cirrhosis', (2) NOT diagnosed as 'cirrhosis', and (3) unspecified, were 8, 4, 8, respectively. In type (2) and (3) drugs, no drugs showed the significant change of exposure in the C-Pc(A) group and PI cautioned the adjustment of dosage for mild HI patients.

These 12 drugs may be underestimated the effect of HI on PK, because we hypothesized some enrolled patients in C-Pc (A) group may not be 'cirrhosis'.

To set 'cirrhosis' as inclusion criteria or record the status of hepatic disease in HI studies is required, in order to evaluate the effect of HI on PK.

(a) Guidance for Industry-Pharmacokinetics in Patients with Impaired Hepatic Function (May 2003)
(b) Jpn J Clin Pharmacol Ther 36(5) sept.2005