Poster

[P27-9] P27-9: Pharmacokinetics and PK/PD

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[P27-9-6] Febuxostat exposure-response model in patients with renal dysfunction

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Background

Hyperuricemia causes not only gout arthritis, but also cardiovascular events. To reduce the risk, controlling serum uric acid level under 6.0 mg/dL is recommended. Febuxostat has been used as an antihyperuricemic agent for patients with renal dysfunction in clinical practice since febuxostat is well tolerated by patients with mild and moderate renal dysfunction as well as by those with normal renal function. Our previous study revealed that febuxostat is also well tolerated by patients with severe renal dysfunction (Hira *et al, Pharmacology*, 2015). There is, however, a wide inter-individual variability in the pharmacokinetics and the therapeutic efficacy. In the present study, we constructed a population pharmacokinetic-pharmacodynamic model to characterize the febuxostat exposure-response relationship and to explore patient's characteristics which influence serum uric acid levels.

Methods

Trough plasma concentrations of febuxostat and genetic polymorphisms of *ABCG2* (ATP-binding cassette sub-family G member 2 protein/Breast Cancer Resistance Protein) obtained from 44 patients were available for this study. Serum uric acid levels (N=398 points) and other patients' characteristics were collected from electric medical records. Population pharmacokinetic-pharmacodynamics modeling for serum uric acid decreasing after the administration of febuxostat was performed using NONMEM (version 7.2). Previous allopurinol treatment history, renal function, and *ABCG2* polymorphisms were considered as potential covariates for pharmacodynamic parameters.

Results

The median (range) values for age, estimated glomerular filtration rate (eGFR, as an index of renal function), and trough febuxostat concentration were 67.5 (35-85 years), 30.6 (5.6-78.7 mL/min/1.73 m^2), and 27.4 (10.2-125 ng/mL), respectively. Twenty-five patients (56.8% of total patients) were prescribed allopurinol before the initiation of febuxostat therapy. The indirect response model with an inhibitory I_{max} on uric acid production well described the uric acid decreasing profile after the administration of febuxostat. Covariate analysis revealed previous allopurinol treatment as an influencing factor which decreased I_{max} of febuxostat by 39.6% ($p<0.05$).

Conclusions

This is the first report on the febuxostat exposure-response relationship in patients with renal dysfunction. Describing the relationship by an inhibitory I_{max} model of uric acid production looks pharmacologically

reasonable, since febuxostat inhibits uric acid production via xanthine oxidase inhibition. These findings would contribute to febuxostat dose optimization.