Long-term Prospective Population PK Study in GIST Patients—Response

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We thank Chatelut and colleagues for their interest in our prospective population pharmacokinetic analysis of imatinib exposure in patients treated for gastrointestinal stromal tumor (1). In their letter to the editor, these authors suggested an alternative explanation for the approximately 30% decrease in imatinib exposure after a treatment duration of 3 months or longer. They hypothesized that this decrease in imatinib plasma concentrations resulted from a decrease in α1-acid-glycoprotein (AGP) levels with time. Because this theory could be plausible, at least as a factor contributing to the clearance of imatinib, we studied their hypothesis in the patients included in our study.

For a subset of patients (n = 22), we prospectively determined plasma AGP concentrations during the first year of imatinib treatment. On the first day of imatinib treatment, and also at months 1, 6, and 12, AGP concentrations were correlated to a WinNonlin-derived area under the curve (AUC) of imatinib, and the sum of imatinib and active metabolite CGP74588, respectively. This metabolite results from a CYP3A-mediated conversion of imatinib (2). Next, we plotted AGP levels against the AUC ratio of active metabolite and parent drug.

Interestingly, good correlations were found between AGP and imatinib, and the sum of imatinib and CGP74588, respectively. No correlation was seen for AGP and the AUC ratio. As we show in Fig. 1, a change in AGP resulted in a proportional change in drug AUC in many individual cases, although the magnitude of this change may differ substantially. Moreover, not only decreases in AGP over time were found but also substantial increases. This finding contrasts with the expectations mentioned in the letter. Although the correlation these authors found (Fig. 1) is quite good at first glance ($r^2 = 0.76; P < 0.001$), we may wonder whether this correlation is useful (yet) in daily clinical practice, as a single AGP measurement may not be implemented directly into a dosing algorithm for imatinib. In our opinion, Judson’s proposal (3), a scheme to integrate therapeutic drug monitoring in clinical practice, is probably more clinically applicable.

Still, the correlation between AGP and imatinib exposure is very interesting, as the mechanisms behind the changes in drug exposure with time are not elucidated yet. As AGP levels did not correlate with the AUC ratio of CGP74588/imatinib, a relationship between AGP and CYP3A metabolism is less likely. Therefore, more research is warranted to discover the mechanisms behind the time dependency of imatinib.

References


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