Increased plasma exposure and toxicity to imatinib in chronically treated GIST patients with SARS-CoV-2 infection: a case-series

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Background: Maintaining imatinib exposure within the therapeutic range is crucial for the successful and safe treatment of patients with gastrointestinal stromal tumours (GIST). Imatinib plasma levels can be influenced by individual metabolic capacity, co-administered drugs, food or other patient's conditions. The release of inflammatory factors during severe SARS-CoV-2 infection was shown to influence cytochromes P450 metabolizing phenotypes, with consequences on drugs exposure. However, no data on the effect of mild COVID-19 on imatinib exposure are available. Here we describe the increased plasmatic concentrations of imatinib observed in a series of 4 GIST patients with mild COVID-19 symptoms.

Methods: Patients underwent routine pharmacologic monitoring, including therapeutic drug monitoring (TDM) of imatinib and pharmacogenetic analyses of polymorphisms in genes involved in its metabolism and transport (*CYP3A4*, *CYP3A5*, *ABCB1*, and *ABCG2*). Imatinib and norimatinib concentrations were determined at C_{trough} using a validated LC-MS/MS method. PGx analyses were performed by KASP genotyping assays on a Real-Time PCR system. All patients received imatinib 400 mg/day. Case 1 was prospectively monitored. Cases 2-4 were identified retrospectively.

Results: Case 1, a 50-year-old woman, few days after SARS-CoV-2 infection showed a 90% increase in imatinib C_{trough} (1260 ng/mL) compared to pre-COVID-19 levels (C_{trough} = 659 ± 7 ng/mL, mean of two evaluations). Concomitantly, imatinib typical side effects appeared. Imatinib concentrations remained higher than the baseline average during the subsequent 6-month follow-up (approximately +36% and +60%). No relevant polymorphisms were detected through PGx analysis. Cases 2-4 were males aged 45-71 years. Compared to the average imatinib plasma levels before COVID-19, case 2 showed an increase in imatinib concentration of 69% (994 vs. 588 ng/mL) and case 3 of 53% (2679 vs. 1751 ng/mL). Case 4, exhibiting the CYP3A5*1/*3 genotype consistent with a more efficient CYP3A5 metabolizer status, showed the smallest increase in imatinib exposure compared to the other cases (40%, 893 vs. 638 ng/mL).

Conclusions: Considering the herein reported increased exposure to imatinib as a consequence of mild COVID-19, attention should be paid to the clinical impact of this infection, even in its milder forms, on the management of GIST patients chronically treated with CYP450 substrates such as imatinib.

Key words: Imatinib, TDM, pharmacogenetics, COVID-19