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LETTER TO THE EDITOR

Physiologically Based Pharmacokinetic Model for Prediction of Leflunomide and Teriflunomide: Should Consideration Be Given to Cannalicular Efflux Transporters?

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Given the growing importance of leflunomide in rheumatoid arthritis therapy, it is essential to understand its disposition by considering physiological processes such as CYP enzymes (intestine and liver), transporters (mostly efflux), and systemic conversion (blood). This has led to the development of an impressive semiphysiologically based pharmacokinetic (semi-PBPK) model by Hopkins *et al.* ("Semiphysiologically Based Pharmacokinetic Model of Leflunomide Disposition in Rheumatoid Arthritis Patients").[1]

Examination of the plasma curves suggested that the RUN8 model described the pharmacokinetics of teriflunomide in close proximity to the original data in many instances.[1] The model fit with intravenous data was excellent, suggesting that the presystemic component was vital for model prediction.[3] There were a few instances where the model fit was less than ideal for oral dosing.[3] In spite of the caveat that this may be difficult to judge from the plots, the following observations are put forward aimed to help in a more refined PBPK model development: (i) lower oral doses of leflunomide under fed/fasting conditions tended to be overpredicted by the model in healthy subjects; (ii) with the exception of a single study in multiple sclerosis (MS) patients, where there was an underprediction, the model described the data satisfactorily in other studies that used a dose range similar to that of healthy subjects. These observations lead to the following questions: Would polypharmacy in MS patients or the disease itself have an effect on leflunomide disposition? Should a differential conversion factor of leflunomide to teriflunomide be considered (healthy vs. MS patients)? Among the covariates tested, alanine aminotransferase (ALT) showed a greater influence with an inverse correlation with CLINT.[1] There is a suggestion that increased ALT may be associated with lowered expression of cannalicular efflux transporters and uptake transporters.[2] The gradual fall in the expressions of Mrp2 and Oatp1b2 were directly correlated with the rise in the ALT levels.[2] In another study, the acetaminophen disposition was characterized in Mrp3+/+ and Mrp3−/− mice.[3] There was a 20-fold higher liver accumulation of acetaminophen glucuronides in Mrp3−/− as compared with Mrp3+/+ mice, leading to lower circulatory acetaminophen glucuronide.[3] As a result, Mrp3−/− mice showed lower ALT levels and were less prone to hepatotoxicity as compared to Mrp3+/+ mice.[3] In another study, the protective role of Mrp2 in preserving the liver function test was explored using arsenic in a rat model.[4] Arsenic-treated rats displayed higher expression of Mrp2 as compared with controls, which lasted for several weeks. This enabled a greater biliary excretion of arsenic and restored the elevated ALT to normalcy.[4]

In light of the above findings, it is well established that both leflunomide and teriflunomide are high-affinity substrates of BCRP (ABCC2).[5] Would this mean that consideration may be given to the quantitative expression levels of cannalicular efflux transporters such as Mrp2 (ABCC2), BCRP (ABCC2) etc., to improve the model fit for leflunomide and teriflunomide?

Conflict of Interest. The author has no conflicts of interest to declare.

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