World Academy of Science, Engineering and Technology
International Journal of Pharmacological and Pharmaceutical Sciences
Vol:15, No:05, 2021

Predictors of Post-marketing Regulatory Actions Concerning Hepatotoxicity

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Abstract : Background: Hepatotoxicity is a major reason for medication withdrawal from the markets. Unfortunately, serious adverse hepatic effects can occur after marketing with limited indicators during clinical development. Therefore, finding possible predictors for hepatotoxicity might guide the monitoring program of various stakeholders. Methods: We examined the clinical review documents for drugs approved in the US from 2011 to 2016 to evaluate their hepatic safety profile. Predictors: we assessed whether these medications meet Hy's Law with hepatotoxicity grade ≥ 3, labeled hepatic adverse effects at approval, or accelerated approval status. Outcome: post-marketing regulatory action related to hepatotoxicity, including product withdrawal or updates to warning, precaution, or adverse effects sections. Statistical analysis: drugs were included in the analysis from the time of approval until the end of 2019 or the first post-marketing regulatory action related to hepatotoxicity, whichever occurred first. The hazard ratio (HR) was estimated using Cox-regression analysis. Results: We included 192 medications in the study. We classified 48 drugs as having grade ≥ 3 hepatotoxicities, 43 had accelerated approval status, and 74 had labeled information about hepatotoxicity prior to marketing. The adjusted HRs for post-marketing regulatory action for products with grade ≥ 3 hepatotoxicity was 0.61 (95% confidence interval [CI], 0.17-2.23), 0.92 (95%CI, 0.29-2.93) for a drug approved via accelerated approval program, and was 0.91 (95%CI, 0.33-2.56) for drugs with labeled hepatotoxicity information at approval time. Conclusion: This study does not provide conclusive evidence on the association between post-marketing regulatory action and grade ≥ 3 hepatotoxicity, accelerated approval status, or availability of labeled information at approval due to sampling size and channeling bias.

Keywords : accelerated approvals, hepatic adverse effects, drug-induced liver injury, hepatotoxicity predictors, post-marketing withdrawal

Conference Title : ICPDS 2021 : International Conference on Pharmacovigilance and Drug Safety

Conference Location : London, United Kingdom

Conference Dates : May 24-25, 2021