Fostamatinib Induced Hepatomegaly: A Novel Signal Identified Through US Food and Drug Administration Adverse Event Reporting System (FAERS) Database

The authors declare that there are no conflicts of interest related to this research.

Akshay Rajendra Gawai[1]
[1]MS Ramaiah University of Applied Sciences, Bangalore

INTRODUCTION

- Fostamatinib is an oral prodrug and spleen tyrosine kinase (SYK) inhibitor, approved for chronic immune thrombocytopenia (ITP) in adults.[Attachment]
- Its mechanism involves reducing platelet destruction and modulating immune activity.[Attachment]
- While generally effective, rare and unexpected adverse reactions like hepatomegaly may be detected only via pharmacovigilance studies and post-marketing surveillance.[Attachment]
- Analysis of the FAERS database helps uncover novel or under-recognized drug reactions.
- Hepatomegaly may represent a previously unidentified adverse reaction to fostamatinib, emphasizing the importance of ongoing safety monitoring and research.

Objective

- To identify and evaluate the signal of hepatomegaly related to fostamatinib using the FAERS (USFDA Adverse Event Reporting System) database.

METHODS

- Retrospective case-non-case disproportionality analysis was performed using the FAERS database for Fostamatinib.
- All Fostamatinib-related reports in FAERS were analyzed to identify adverse events
- The OpenVigil platform was utilized for FAERS data analysis and signal computation

U.S. FOOD & DRUG ADMINISTRATION

OpenVigil — a pharmacovigilance data analysis tool

- **Signal Detection:** employed two widely used pharmacovigilance data mining algorithms (1.Reporting Odds Ratio **(ROR)** 2. Proportional Reporting Ratio **(PRR)**)
- **Calculations for Positive Signal Used Criteria:**
  - *PRR* ≥ 2 and *ROR*- 1.96SE ≥ 2

RESULTS

Background and Significance

- Among 30,668,520 reports in the FAERS database, 4,685 were related to fostamatinib use, with 4,487 classified as serious events and many involving fatal outcomes.

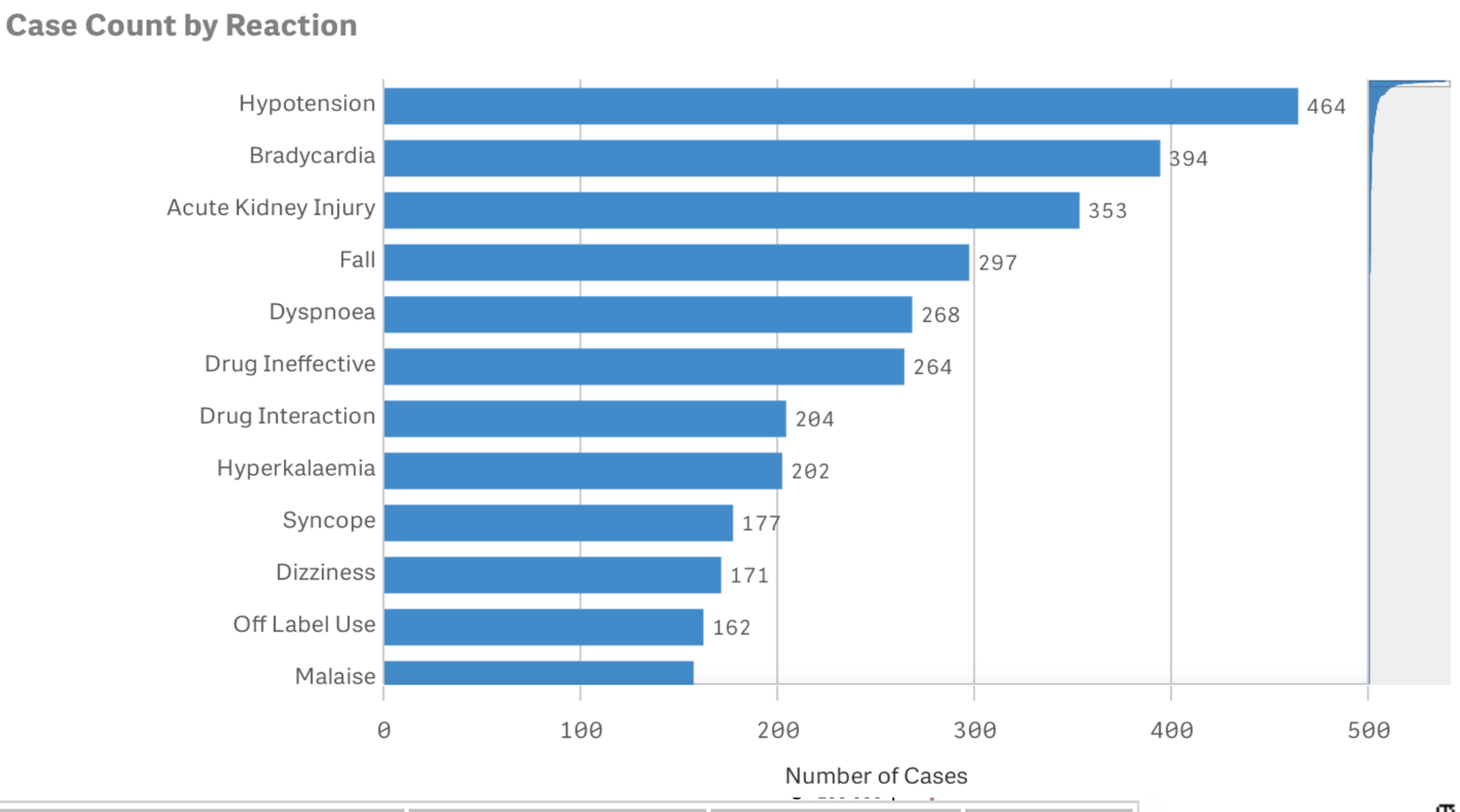
Among these, 6 adverse event reports specifically documented hepatomegaly in patients taking fostamatinib, highlighting a notable concern for gastrointestinal bleeding as a serious adverse reaction associated with this medication.

Disproportionality analysis using data mining algorithms showed strong signal detection:

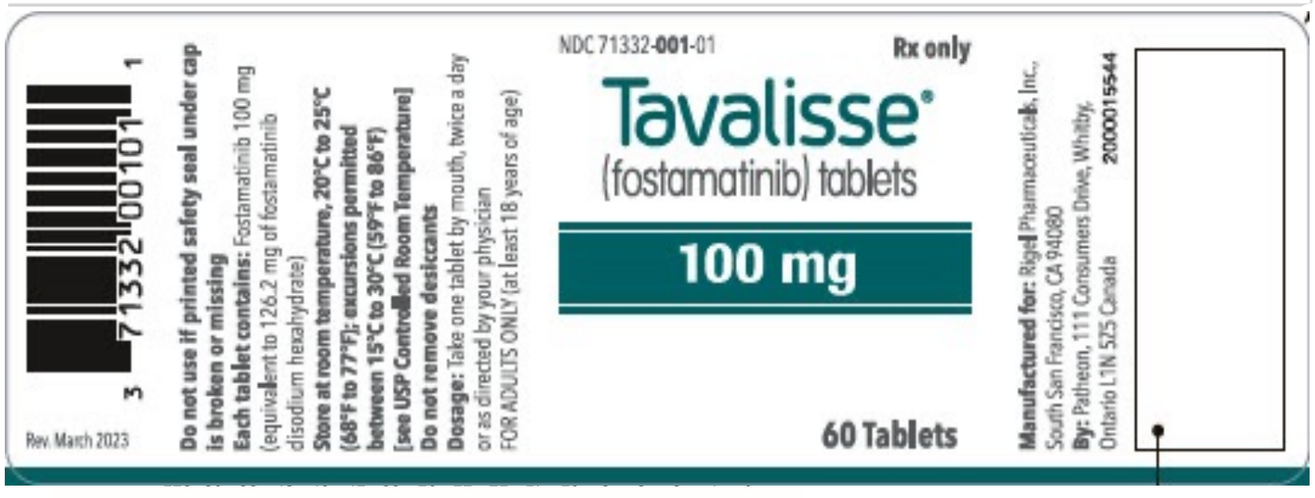
- Reporting Odds Ratio (ROR) was 3.043 (1.366 ; 6.779), indicating that the occurrence of hepatomegaly in fostamatinib users is over six times higher than in users of other drugs.
- Disproportionality analysis conducted using the Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR) demonstrated statistically significant signals: ROR was 3.043 (95% CI: 1.366–6.779) and PRR was 3.04 (1.366 ; 6.768). These elevated ratios indicate that reports of hepatomegaly were considerably higher in fostamatinib users compared to other drugs, suggesting a potential causal association.
- Both ROR and PRR values surpassed the positive signal threshold, indicating hepatomegaly as a potential safety signal with fostamatinib use
- Overall, these results emphasize the pivotal role of pharmacovigilance and real-world data in detecting rare but serious adverse events that may not be identified during pre-approval clinical trials, thereby improving patient safety and informing risk management strategies.

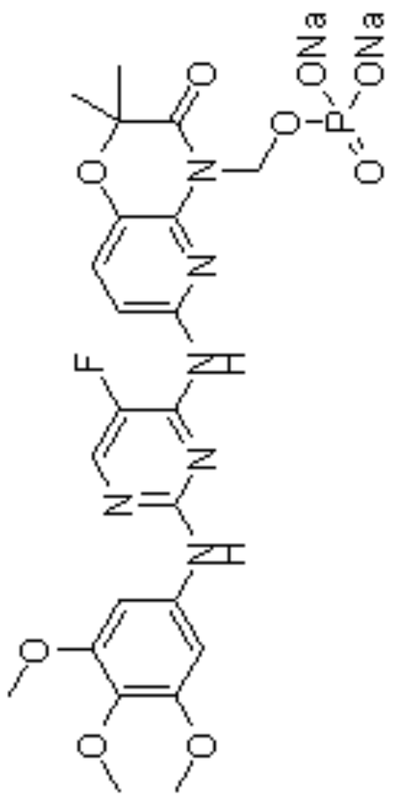
Parameter	Value	Interpretation
fostamatinib-related reports	4,685	Volume
hepatomegaly adverse events	97	Cases
Disproportionality signals	ROR: 3.043 (95% CI 1.366–6.779), PRR: 3.04 (95% 1.366-6.768), Signal threshold: PRR ≥ 2, ROR-1.96SE ≥ 2	Significant

Table 2. Distribution of Reported Adverse Drug Reactions Associated with fostamatinib in the FAERS Database



	Drug(s) of interest	All other drugs	Σ
Adverse event(s) of interest	6	5428	5434
All other adverse events	5013	13799751	13804764
Σ	5019	13805179	13810198





According to the criteria of Evans 2001 (n > 2, chisq > 4, PRR > 2) this combination of drug(s) and adverse event(s) is considered: **likely an adverse reaction**

Funding
This study did not receive any sponsorship or financial support from any organization or agency.

References
1. Kantarjian H, et al. *Blood* Cancer J. 2021;11(2):41; 2. Daver N, et al. *Leukemia* 2019;33(2):299–312.

RAMAIAH UNIVERSITY OF APPLIED SCIENCES