TOFACITINIB-ASSOCIATED ADVERSE VASCULAR EVENTS REPORTED TO THE FEDERAL ADVERSE EVENT REPORTING SYSTEM (FAERS)

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Problem

Our group has previously shown that reporting interference is occurring with reports to the FDA Adverse Events Reporting System (FAERS). This practice was apparent after newly described adverse events (AES) from PPIs such as chronic kidney disease, cerebral vascular accidents, cardiovascular disease, and dementia appeared in the medical literature.

n the present study, we reviewed current trends on reporting interference in AE reports concerning Tofacitinib to the FAERS.

U.S. FOOD & DRUG ADMINISTRATION

TOFACITINIB (G); XELJANZ(P)

Case Count by Received Year

Category	Number of Cases
2021	24,371
2020	22,997
2019	17,961
2018	12,985
Totals	**78,314**

Data as of December 31, 2021

Introduction

Tofacitinib, an intracellular tyrosine kinase inhibitor, is approved by the U.S. FDA for active rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ulcerative colitis (UC).

In 2019 the FDA released a safety alert about an increased risk of blood clots and death in patients receiving treatment with tofacitinib. At this time, lawyers began accepting cases for patients who took the drug and had AES of pulmonary embolism (PE) and deep vein thrombosis (DVT).

In 2021, Black Box Warnings were issued for low dose (5mg BID) and high dose (10mg BID) tofacitinib, for increased risk of serious heart related AES and cancer.

Objective

Provide a summary on reporting trends concerning tofacitinib AES, in particular of cardiovascular nature, since the Black Box Warning was first introduced in 2021.

We aim to provide physicians with knowledge that allows them to more confidently manage clinical care for patient suffering form RA, PsA, and UC.

Methods

FAERS is a database of voluntarily reported AES used form post-marketing surveillance of medications.

8,867,077 FAERS reports from January 2018 to September 2021 were examined. There were 84,225 reports of tofacitinib-related AES.

Using MeDRA terminology, reports of cardiovascular (CV) AES emphasized in recent Black Box Warnings (PE, DVT, Cerebral Thrombosis, and Cerebral Vascular Occlusion) were reviewed.

There were 650 CV AES reported in the study period.

Demographics, cumulative dosage, indications for drug use, outcomes, reactions, and reporter trends were analyzed.

Reporting Odds Ratio (ROR) for all reporting groups (physicians, lawyers, community, pharmacists, etc.) were calculated. ROR >1 is elevated and indicates interference in reporting.

2021	Tofacitinib Reports with CV AES	Tofacitinib Reports excluding CV AES
Lawyer	A	B
Non-Lawyer	C	D

O1 = A/B, O2 = C/D; ROR = O1/O2

Results

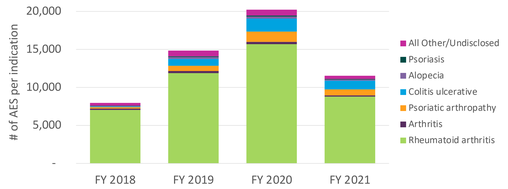
The most common indication for tofacitinib was RA 43,386 (52%) of reports.

There were 3,856 (5%) reports when tofacitinib was indicated for UC.

Hospitalization occurred in 10,182/84,225 (12%) of reports.

42,671 (51%) of AES occurred in subjects 36-64 years old. Females represented 65,806 (78%) of reports.

Top Tofacitinib AE Report Indications

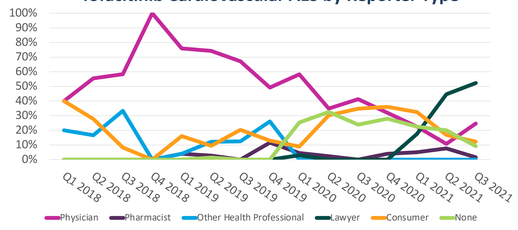


Physicians accounted for 13% of reporters while consumers consisted of 59% of reporters, (ROR = 1.52; 95%; CI – 1.49-1.54).

CV specific AES concerning tofacitinib accounted for 650/84,225 (0.77%) of reports.

Lawyer reporting demonstrated a sharp rise in 2021. Lawyer reports accounted for 70/170 (41%) CV AES in 2021 (ROR = 942; 95%; CI = 505-1757).

Tofacitinib Cardiovascular AES by Reporter Type



Discussion

Verden et al. investigated post market case reports to the FDA concerning DVT and PE AES of tofacitinib and ruxolitinib from their approval dates until 2017.

Jak inhibitors had elevated RORS >1 for certain thromboembolic AES indicating a trend toward higher-than-expected reporting rates.

Our post marketing safety review of FAERS reports concerning Tofacitinib showed elevated reporting for CV AES from physicians and lawyers.

Consumer reporters were found to have an elevated ROR for all AES concerning Tofacitinib.

Conclusions

Interference in the reporting of tofacitinib-related CV AES to FAERS appears be occurring, initially by excess consumer reporting and more recently by lawyers.

Lawyers reporting of CV AES concerning tofacitinib from 2018-2021 resulted in a signal for extremely high lawyer interference.

The effect of reporting bias on the use of tofacitinib in the clinical setting requires further investigation.

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