EVALUATION OF METHOD PERFORMANCE USING SELF-CONTROLLED CASE SERIES

Jasmanda Wu, PhD, MPH, Ling Zhang, MD, MS, Patrick Caubel, MD, MBA, Juhaeri Juhaeri, PhD

Global Pharmacovigilance and Epidemiology, Sanofi, Bridgewater, New Jersey

ABSTRACT

Background
Previous analyses conducted using a cohort study showed tricyclic antidepressant (TCA) users were 1.5 times more likely to develop acute myocardial infarction (AMI) than those who did not receive TCA. The TCA-AMI pair combination is considered as 'true positive' for evaluation of method performance. In this study, we examined the association between TCA and AMI using a self-controlled case series (SCCS).

Objectives
To compare analytical method performance using SCCS in a US claims database and Observational Medical Dataset Simulator (OSIM2) for examining the association between TCA and AMI.

Methods
The InVision DataMart ™ (United HealthCare, formerly LabRx™) database and OSIM2 were used. Study population included eligible participants who had an AMI diagnosis and were prescribed at least one TCA prescription during 01/01/2007-12/31/2011 and 01/01/2004-12/31/2008 for InVisonDataMart and OSIM2, respectively. Each individual's observation time was divided into exposure periods as follows: fully exposed periods, followed by 1-14, 15-30, 31-60 and 61-90 days after the end of a treatment period. All other periods of time were classified as unexposed periods. Rate ratios (RR) to compare the rate of events during exposed periods with the rate during unexposed periods were estimated using conditional Poisson regression.

Results
There were 1,193 and 3,094 TCA users identified for SCCS in the InVision DataMart and OSIM2 database, respectively. The RR for AMI among all patients prescribed TCA was 1.10 (95%CI 0.90-1.20), compared fully exposed with unexposed periods in the InVision DataMart. During 90 days periods after TCA treatment, the RRs were significant (for example, within 14 days after treatment, RR = 2.38 (95%CI 1.70-3.33). In the OSIM2, exposure to TCA did not have an increased risk of AMI during fully exposed and also during 90 days periods after treatment (for example, exposed vs. unexposed, RR=0.88, 95%CI 0.81-0.96). The results using SCCS from the two databases were not consistent.

PURPOSE

To compare analytical method performance for examining the association between tricyclic antidepressant (TCA) and acute myocardial infarction (AMI) using a self-controlled case series (SCCS) in a US claims database and Observational Medical Dataset Simulator (OSIM2).

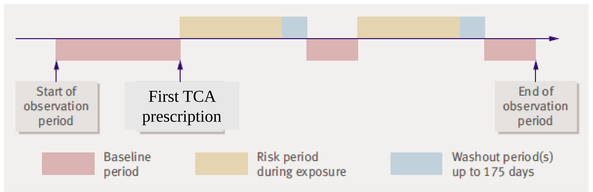
STUDY SUBJECTS

- Study population included eligible participants who had an AMI diagnosis and were prescribed at least one TCA prescription during 01/01/2007-12/31/2011 and 01/01/2004-12/31/2008 for InVisonDataMart™ and OSIM2, respectively.
- The InVision DataMart database is an integrated medical and prescription claims database augmented with partial laboratory data for an employed, commercially insured population of patients and their dependents.
- OSIM2 is an open-source software application, written in R, that allows users to create simulated datasets that conform to the OMOP Common Data Model. The simulation creates hypothetical persons with fictitious drug exposure and condition occurrence, with known characteristics that represent the types of scenarios expected in real observational sources.

METHODS

- Each individual's observation time was divided into exposure periods as follows: fully exposed periods, followed by 1-30, 31-60 and 61-90 days after the end of a treatment period. All other periods of time were classified as unexposed periods.
- Rate ratios (RR) to compare the rate of events during exposed periods with the rate during unexposed periods were estimated using conditional Poisson regression (proc genmod in SAS)

Exposure Period Definition



RESULTS

- There were 1,193 and 3,094 TCA users identified in the InVision DataMart and OSIM2 databases, respectively.
- The mean age was older in the InVision DataMart database (InVision DataMart, 59.6±12.7 yrs; OSIM2, 50.6±11.4 yrs).
- TCA users in the InVision DataMart database also had more comorbidities, including hypertension, diabetes, and coronary heart disease.

Demographics of Tricyclic Antidepressant Users in InVision DataMart and OSIM2

	InVision DataMart (n=1,193)	OSIM2 (n=3,094)
Age (yrs, mean ± std)	59.6±12.7	50.6±11.4
18-45	10.0%	25.4%
46-64	60.9%	70.1%
≥65	29.1%	4.5%
Gender (% female)	52.3%	40.1%

Demographics

Comorbid Conditions at Baseline

	InVision DataMart (n=1,193)	OSIM2 (n=3,094)
Coronary heart disease	54.4%	11.5%
Diabetes	29.5%	28.1%
Hypertension	75.7%	61.8%

Comorbidities

Case Series Analysis for Tricyclic Antidepressants between Exposure and Acute Myocardial Infarction - Rate Ratio (95% CI) in InVision DataMart and OSIM2

	InVision DataMart	OSIM2
Exposed vs. unexposed periods	1.10 (0.90-1.20)	0.88 (0.81, 0.96)
Days after treatment		
0-14	2.38 (1.70, 3.33)	0.58 (0.28, 1.2)
15-30	2.01 (1.41, 2.87)	0.54 (0.23, 1.28)
31-60	1.57 (1.14, 2.15)	0.41 (0.16, 1.07)
61-90	1.10 (0.75, 1.62)	1.00 (0.42, 2.39)

RESULTS

- In the Invision DataMart, the RR for AMI among all patients prescribed TCA was 1.10 (95%CI 0.90-1.20), compared fully exposed with unexposed periods.
- During 90 day periods after TCA treatment, the RRs were significant (for example, within 14 days after treatment, RR = 2.38 (95%CI 1.70-3.33).
- In the OSIM2, exposure to TCA did not increase the risk of AMI during fully exposed and also during 90 day periods after treatment (for example, exposed vs. unexposed, RR=0.88, 95%CI 0.81-0.96).

DISCUSSION

- The results using SCCS from the two databases in our analyses were not consistent. Overall, we did not observe a strong association between AMI and TCA use using SCCS.
- Published literatures also show inconsistent results for the TCA-AMI association using different methods. For instance, in the study by Tata et al. (2005), the case-control analysis found an initial increased risk of MI after TCA exposure (OR=1.90, 95%CI 1.15-3.14), however the associations were marginally significant in the self-controlled analysis.
- One explanation for our findings is that the TCA-AMI pair combination did not meet some SCCS assumptions, including:
  1) conditional independence between event occurrences - a patient who has a first AMI is at higher risk for a second AMI
  2) risk factors for the event are not fixed within individuals over the observation period.

CONCLUSIONS

- Overall, we did not observe a strong association between AMI and TCA use SCCS
- SCCS design may not be suitable for examining the TCA-AMI association.
- SCCS design is most valid when its assumptions are met.
- Careful evaluation of various characteristics of specific drug and event pair combinations and selection of the most appropriate design and analytical method suitable for a particular scenario are necessary for signal refinement and evaluation.

References

1. Whiaker HJ, Farrington CP, Spiessens B, et al. Tutorial in biostatistics: the self-controlled case series method. Statistics in Medicine 2006;25:1768-1797.
2. Tata LJ, West J, Smith C, et al. General population based study of the impact of tricyclic and selective serotonin reuptake inhibitor antidepressants on the risk of acute myocardial infarction. Heart 2005;91:465-471.

The study was sponsored by Sanofi

SANOFI