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Time to Onset Analysis of Ipilimumab Associated Hypophysitis Using Data from FDA Adverse Event Reporting System (FAERS) Database

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Introduction

- The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is a database containing reports regarding adverse event, medication error and product quality complaints submitted by manufacturers, health care professionals, or the public under the "MedWatch" program
- Ipilimumab, an inhibitor of cytotoxic T-lymphocyte antigen 4 (CTLA-4), as a single agent is used in the treatment of unresectable/metastatic melanoma in patients above the age of 12 or as an adjuvant treatment for cutaneous melanoma with regional lymph node involvement.
- Hypophysitis associated with the use of ipilimumab is established in the past. However, the time of onset of this event is relatively unexplored.

Objective

The aim of this study was to examine the onset profile of Ipilimumab Associated Hypophysitis using the FAERS database.

Methodology

- A systematic data mining was performed in the FAERS Database (2011Q2 to 2019Q4).
- To access the FAERS data, a pharmacovigilance analytical tool named OpenVigil 2.0 was utilized.
- The signal strength of ipilimumab induced hypophysitis was computed using Reporting Odds Ratio (ROR).
- A positive signal was considered to show a value ROR-1.96SE more than 1.
- The Weibull shape parameter (WSP) test was employed to analyze the time-to-onset profile, which is computed using (date of event) – (drug start date).
- The time-to-onset profile was defined by shape and scale parameters.
- A larger scale value stretches the distribution, while a smaller value shows distribution shrink.
- Shape parameter values of <1, ~1 and >1, attributes to early failure-type profile, random failure type profile and wear-out failure-type profile respectively.

FORMULA FOR ROR CALCULATION

	Drug of Interest	Other Drugs
ADR of interest	A	B
Other ADR	C	D

Computation	Threshold
$\mathrm{ROR} = AD/BC$ $\mathrm{S.E} = \sqrt{\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}$	ROR-1.96SE >1

A: The number of reports with both drug of interest and ADR of interest,

B: The number of reports with ADR of interest and other drugs,

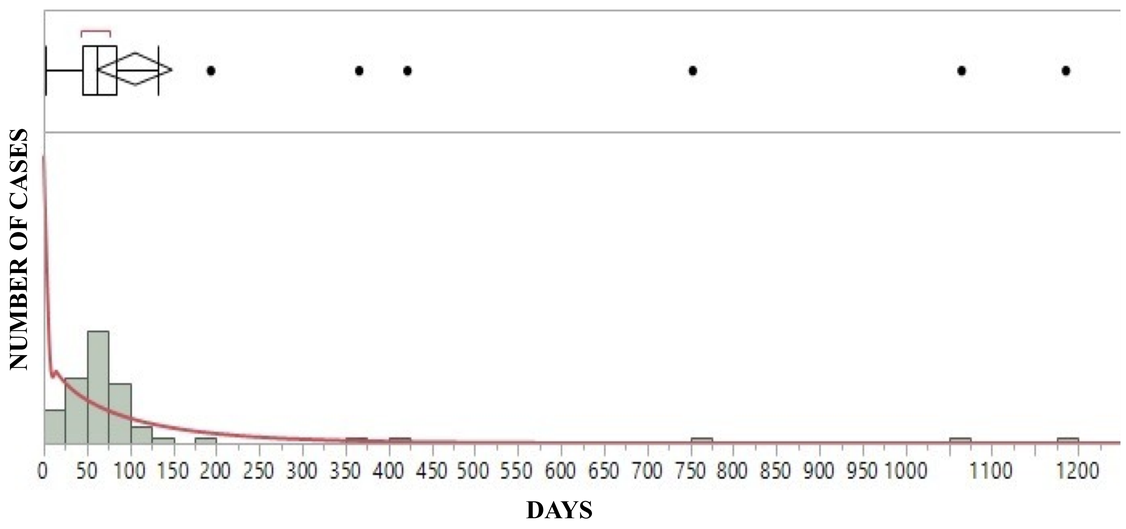
C: The number of reports with the drug of interest and other ADRs,

D: The number of reports with other drugs and other ADRs

Results

- A total of 700 reports was found for hypophysitis in FAERS database. Ipilimumab induced hypophysitis was associated with 551 (78.7%) reports.
- 48% of the reports from males, 30% from females and gender was not mentioned in the rest.
- The signal strength of ipilimumab induced hypophysitis was 2327.49 (1940.46 – 2791.71) which is above the threshold.
- The median time-to-onset of hypophysitis associated with ipilimumab use was 62 (range: 45-83) days.
- WSP test indicated early failure-type profile with shape parameter: 0.89 (95% C.I 0.76-1.02) and scale parameter**:** 97.79 (95% C.I 74.65-127.38).

WEIBULL DISTRIBUTION CURVE FOR IPILIMUMAB ASSOCIATED HYPOPHYSITIS



DRUG	MEDIAN	SCALE	SHAPE	TYPE
Ipilimumab	62 (range: 45-83)	97.79	0.89	Early-type failure

Conclusion

- Ipilimumab followed an early failure-type profile, suggesting requirement of close monitoring during first 90 days of treatment.
- However, due to widely distributed onset data, it is suggestive to monitor patients for hypophysitis throughout ipilimumab treatment.

Reference

- USFDA, 2018. FDA Adverse Event Reporting System (FAERS) public dashboard.
- Poluzzi E, Piccinni C, Raschi E, Dae Ponti F. Data mining techniques in pharmacovigilance: analysis of the publicly accessible FDA adverse event reporting system (AERS). UK: Intech Open Access Publisher; 2012
- BÖHM, R., VON HEHN, L., HERDEGEN, T., KLEIN, H.-J., BRUHN, O., PETRI, H. & HÖCKER, J. J. P. O. 2016. OpenVigil FDA–inspection of US American adverse drug events pharmacovigilance data and novel clinical applications. 11, e0157753.
- KINOSHITA, S., HOSOMI, K., YOKOYAMA, S., TAKADA, M. J. J. O. C. P. & THERAPEUTICS 2019. Time-to-onset analysis of amiodarone-associated thyroid dysfunction.

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