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Bevacizumab induced pulmonary embolism: A Disproportionality Analysis in US Food And Drug Administration Adverse Event Reporting System (FAERS) Database

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Introduction

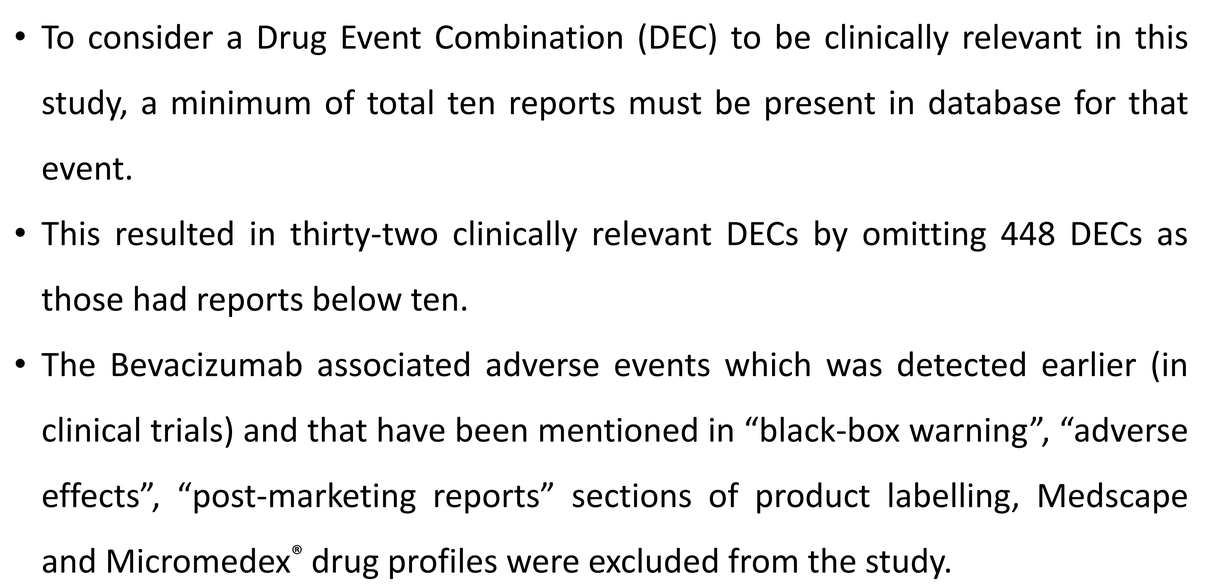
- Vascular endothelial growth factor (VEGF)/ vascular endothelial growth factor receptor (VEGFR) inhibitors are agents that inhibit the activity of VEGF and VEGFR which are known to modulate the angiogenesis .
- So, this class of drugs inhibit the abnormal angiogenesis in cancer and are used in treatment of various types of cancer.
- Bevacizumab is a anti-VEGF monoclonal antibody approved by the US Food and Drug Administration (FDA) in 2004 for the treatment of metastatic colorectal cancer.
- Data mining is defined as the use of statistical techniques, such as disproportionality measures for database or large information sources for extracting an unknown information
- Data Mining Algorithms (DMAs) are the rapidly emerging computer-assisted technique used to assess the degree of association between the reported adverse drug reaction (ADR) and the suspected drug compared to other drugs in the database.

Methodology

- This quantitative analysis was initiated after the approval from the Institutional Human Ethics Committee
- Publicly available FDA AERS database was downloaded from FDA AERS website
- AERS is a spontaneous reporting system that contains data on AEs and medication errors

Study Procedure

- To consider a Drug Event Combination (DEC) to be clinically relevant in this study, a minimum of total ten reports must be present in database for that event.
- This resulted in thirty-two clinically relevant DECs by omitting 448 DECs as those had reports below ten.
- The Bevacizumab associated adverse events which was detected earlier (in clinical trials) and that have been mentioned in “black-box warning”, “adverse effects”, “post-marketing reports” sections of product labelling, Medscape and Micromedex® drug profiles were excluded from the study.
- The reports were considered for analysis, only if they were reported as primary or secondary suspect for the drug of interest.
- The ROR and PRR as a measure of disproportionality, were used to assess the association between the drug of interest and event of interest



Formulae for computing signal

Data Mining Algorithm	Computation	Threshold
ROR	$\mathbf{ROR} = (\mathbf{A}/\mathbf{B})/(\mathbf{C}/\mathbf{D})$ $\mathbf{S.E} = \sqrt{\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}$	ROR-1.96SE>1
PRR	$\mathbf{PRR} = \mathbf{A(A+C)}/\mathbf{B(B+D)}$ $\mathbf{SE} = \sqrt{(\frac{1}{A}-\frac{1}{A+C}+\frac{1}{B}+\frac{1}{B+D})}$	PRR≥2 χ^2>4 ≥ 3 cases reported

Results

- A total of 52,770 reports for pulmonary embolism have been reported in the FDA database as on December 2018. Amongst which 1,264 reports were associated with Bevacizumab.
- The mean age was 27.70 (95% CI,) with a minimum age of 1 and a maximum age of 96 years, though age was not mentioned in 692 reports.
- The female to male ratio was 1.01:1, however gender was not mentioned in 155 reports.

Signal Strength of Clinically Relevant Reaction of Bevacizumab

Pulmonary embolism	
ROR- 1.96SE	PRR
3.40	3.42

Bevacizumab associated pulmonary embolism: A total 1,264 reports were associated with Bevacizumab.The DMA values for the mentioned DEC was found to be ROR : 3.40 and PRR : 3.42

Conclusion

- Signal detection is a propitious technique that aids in the early identification of new, rare reactions (desired or undesired) of a drug. Bevacizumab associated potential signal were generated by data mining in the FDA AERS database. Further clinical surveillance is required for the validation of this adverse event reported for Bevacizumab.

Reference

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