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CORRESPONDENCE

Thromboembolic events in younger women exposed to Pfizer-BioNTech or Moderna COVID-19 vaccines

Maurizio Sessa^a, Kristian Kragholm^b, Anders Hviid^{a,c} and Morten Andersen^a

^aPharmacovigilance Research Center, Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark;

^bDepartment of Cardiology, Aalborg University Hospital, Aalborg, Denmark; ^cDepartment of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark

ABSTRACT

Introduction: Concerns about the increased risk of blood clots associated with the VAXZEVRIA (previously named Oxford-AstraZeneca COVID-19 vaccine) and Johnson & Johnson (Janssen) COVID-19 vaccines raises the question of the thrombotic safety of other COVID-19 vaccines such as Pfizer-BioNTech or Moderna, especially in younger women, who at the early stage of the pandemic was a priority group for vaccination.

Methods: Using the US-based Vaccine Adverse Event Reporting System (VAERS) and the FDA Event Reporting System (FAERS), we retrieved cases of thrombosis following vaccinations or hormonal contraceptive use in women aged ≤ 50 years. We used the reporting odds ratio (ROR) as a disproportionality measure.

Results: On 19 March 2021, out of 13.6 million women aged ≤ 50 exposed to at least one dose of Pfizer-BioNTech or Moderna COVID-19 vaccines in the US, only 61 cases were reported with a total of 68 thromboembolic events (1 case per 222,951 vaccinated). None of the thromboembolic events included in our analysis were disproportionately reported for the two COVID-19 vaccines.

Conclusion: Our results do support that, when compared to hormonal contraceptive use, the mRNA vaccines do not show disproportional reporting of thromboembolic events in younger women.

KEYWORDS

Vaccine; thrombosis; COVID-19; VAERS; FAERS

1. Introduction

The European Medicines Agency (EMA) recently concluded that blood clots in combination with thrombocytopenia can occur in less than 1 in 10,000 people exposed to VAXZEVRIA (previously named Oxford-AstraZeneca COVID-19 vaccine) [1]. Analogously, concerns about the increased risk of blood clots associated with the Johnson & Johnson (Janssen) COVID-19 vaccine also emerged. This raises the question of the thrombotic safety of other COVID-19 vaccines such as Pfizer-BioNTech or Moderna, especially in younger women working as frontline personnel, who in the early stage of the pandemic was a priority group for vaccination. Of note, these rare events are now well established also in older people and men.

2. Methods

We conducted an analysis of the reporting of thromboembolic events following vaccination with the Pfizer-BioNTech or Moderna COVID-19 vaccines compared to hormonal contraceptive use, which is known to be associated with an increased but acceptable risk of thromboembolic events. Using the US-based Vaccine Adverse Event Reporting System (VAERS) [2] and the Food and Drug Administration Adverse Event Reporting System (FAERS) [3], we retrieved all cases of

thrombosis reports following Pfizer-BioNTech/Moderna COVID-19 vaccinations or hormonal contraceptive use in women aged ≤ 50 years. We used the reporting odds ratio (ROR) to investigate disproportional reporting of thrombotic events between the mRNA vaccines and widely used hormonal contraceptives (gestodene, levonorgestrel, levonorgestrel/ethinyl estradiol, and progesterone). Thromboembolic events under investigation were thrombosis, cerebrovascular accident, myocardial infarction, and pulmonary embolism. Analyses were conducted using state-of-the-art methodological standards for disproportionality analysis [4]. Underreporting for thrombotic events associated with hormonal contraceptives in spontaneous reporting databases has been previously reported (reporting rate of 5.1/100,000 women-years versus 61/100,000 women-years observed in large phase-3 clinical trials) [5]. Therefore, we conducted a sensitivity analysis correcting the reporting odds ratio (ROR) for underreporting by multiplying the number of events by 1.932, which has been obtained as follows: $1 + (61 - 5.1)/61$.

3. Results

On 19 March 2021, out of 13.6 million women aged ≤ 50 exposed to at least one dose of Pfizer-BioNTech or Moderna

Table 1. Disproportionality analysis.

Adverse event of interest	Pfizer-BioNTech/Moderna – adverse event of interest	Pfizer-BioNTech/Moderna – all other events	Hormonal contraceptives *- event of interest	Hormonal contraceptives* – all other events	ROR	SE	Low 95% CI	High 95% CI
Thrombosis	14	77,668	303	454,086	0.27	0.27	0.14	0.50
Cerebrovascular accident	18	77,664	332	454,086	0.32	0.24	0.15	0.67
Myocardial infarction	11	77,671	165	454,061	0.39	0.31	0.24	0.64
Pulmonary embolism	25	77,657	458	454,086	0.32	0.21	0.13	0.79

95% CI = 95% Confidence Interval. ROR = reporting odds ratio. SE = Standard Error. *Gestodene, levonorgestrel, levonorgestrel/ethinyl estradiol, and progesterone.

Table 2. Sensitivity analysis accounting for under-reporting of thrombosis with hormonal contraceptives.

Adverse event of interest	Pfizer-BioNTech/Moderna – adverse event of interest	Pfizer-BioNTech/Moderna – all other events	Hormonal contraceptives *- event of interest	Hormonal contraceptives* – all other events	ROR	SE	Low 95% CI	High 95% CI
Thrombosis	14	77,668	581	453,505	0.19	0.23	0.09	0.42
Cerebrovascular accident	18	77,664	574	453,512	0.24	0.21	0.10	0.57
Myocardial infarction	11	77,671	581	453,505	0.23	0.22	0.10	0.53
Pulmonary embolism	25	77,657	765	453,321	0.25	0.18	0.09	0.70

95% CI = 95% Confidence Interval. ROR = reporting odds ratio. SE = Standard Error. *Gestodene, levonorgestrel, levonorgestrel/ethinyl estradiol, and progesterone.

COVID-19 vaccines in the US, only 61 cases were reported with a total of 68 thromboembolic events (1 case per 222,951 vaccinated). The median time-to-event was 3 days (interquartile range, IQR 1–6 days) and the median age of the cases was 42 years [IQR, 35–46]. Twenty-five out of 61 cases (41%) reported risk factors for thromboembolic events such as COVID-19 infection (4), hypertension (4), medical history of venous thrombosis (3), cancer (2), atrial fibrillation (1), diabetes mellitus (2), obesity (1), IgG deficiency requiring IgG infusion (1), protein-c-deficiency (1), systemic lupus (1), or exposure to hormonal contraceptive (3), ibuprofen (1), or phentermine (1). None of the thromboembolic events included in our analysis were disproportionately reported following the Pfizer-BioNTech or Moderna COVID-19 vaccines (Table 1). The results from the sensitivity analysis were in line with the results of the main analysis (Table 2). Based on the results of the main analysis, for hormonal contraceptives, the proportions of thrombotic events over the total number of adverse events reported during the study period were 0.07%, 0.07%, 0.04%, and 0.10% for thrombosis, cerebrovascular accident, myocardial infarction, and pulmonary embolism, respectively.

4. Discussion

In conclusion, while it is well known, that underreporting of adverse events is significant in pharmacovigilance, our results do support that, when compared to hormonal contraceptive use, the mRNA vaccines do not show disproportional reporting of thromboembolic events in younger women.

Authors' contributions

Dr Sessa had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Sessa, Hviid, Andersen, Kragholm.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Sessa.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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ORCID

Maurizio Sessa  <http://orcid.org/0000-0003-0874-4744>

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