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Short Communication

Does smoking have an impact on the immunological response to COVID-19 vaccines? Evidence from the VASCO study and need for further studies

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ABSTRACT

Objectives: The aim of this study was to investigate the possible impact of smoking on the humoral response to the BNT162b2 mRNA COVID-19 vaccine (also known as the BioNTech-Pfizer COVID-19 vaccine).
Study design: A longitudinal sero-epidemiological study was conducted in sample of Italian healthcare workers (HCWs).
Methods: HCWs who were administered two doses of the BNT162b2 mRNA vaccine, 21 days apart, between December 2020 and January 2021, were invited to undergo multiple serology tests to identify SARS-CoV-2 S-RBD-specific immunoglobulin G (IgG) antibodies. Participants also responded to questions about their smoking status (i.e. current smokers vs non-smokers) in a survey.
Results: Sixty days after the completion of the vaccination cycle, serological analyses showed a difference in vaccine-induced IgG titre between current smokers and non-smokers, with median antibody titres of 211.80 AU/mL (interquartile range [IQR] 149.80–465.50) and 487.50 AU/mL (IQR 308.45–791.65) [*P*-value = 0.002], respectively. This significant difference in vaccine-induced IgG titres between current smokers and non-smokers remained after adjusting for age, sex, and previous infection with SARS-CoV-2.
Conclusions: This study observed that vaccine-induced antibody titres decrease faster among current smokers than non-smokers. Further research to investigate the impact of smoking on the immunological response to COVID-19 and non-COVID-19 vaccines is required.

Introduction

Monitoring the level and time trend of the humoral response to COVID-19 vaccines represents an essential tool in the study of immunological response and enables a greater understanding of the protection offered by the vaccination during the SARS-CoV-2 pandemic.[1] This study presents a subanalysis of the VASCO project ('Monitoraggio della risposta al Vaccino Anti-SARS-CoV-2/COVID-19 negli operatori sanitari del Pineta Grande Hospital'), an ongoing longitudinal study that investigates the effectiveness, immunogenicity, and safety of the BNT162b2 mRNA COVID-19 vaccine (also known as the BioNTech-Pfizer COVID-19 vaccine) in a sample of healthcare workers (HCWs).[1,2] The study includes an analysis of the dynamics of antibody response to BNT162b2 mRNA COVID-19 vaccine at monthly intervals over a period of 6 months. A decrease in vaccine-induced anti-S-RBD immunoglobulin G (IgG)

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antibodies was seen at the second month (i.e. Sixty days) after the completion of the vaccination cycle.[1]

Methods

Complete cohort characteristics and study methods have been described in previous articles.[1,2] In brief, HCWs who were administered two doses of the BNT162b2 mRNA vaccine, 21 days apart, between December 2020 and January 2021, underwent multiple quantitative serology tests to identify SARS-CoV-2 S-RBD-specific IgG. Participant HCWs also responded to questions about their smoking status (i.e. current smokers vs non-smokers). This study focused on the differences in SARS-CoV-2 S-RBD IgG dynamics according to smoking status. Antibody level was assessed using the Snibe–Maglumi® SARS-CoV-2 S-RBD IgG chemiluminescent immunoassay, with a reactivity cutoff of 1.0 AU/mL.[1] A Mann–Whitney U test was used to assess differences of median IgG levels between current smokers and non-smokers. A multivariate linear regression model was built to investigate the association between IgG level and smoking status, adjusting for possible covariates, namely, age, sex, and previous infection with SARS-CoV-2.

Results

Overall, 162 HCWs participated in this study; the majority were women (58.0%), with a mean age of 42.5 years (±11.9 standard deviation). In total, 28 participants had a history of previous SARS-CoV-2 infection. Sixty days after the completion of the vaccination cycle, serological analyses of 63 participants (19 current smokers and 44 non-smokers; 30.2% vs 69.8%) showed a difference in vaccine-induced IgG titre, with median antibody titres of 211.80 AU/mL (interquartile range [IQR] 149.80–465.50) and 487.50 AU/mL (IQR 308.45–791.65) [*P*-value = 0.002], respectively. This significant difference in vaccine-induced IgG titres between current smokers and non-smokers remained after adjusting for age (mean: 41.4 ± 11.8 years), sex (female: 65.1%), and previous SARS-CoV-2 infection (in 11.1% HCWs). The results from the multivariate regression models showed that the β coefficient is equal to −335.62 (95% confidence interval: −557.41 to −113.83; $P = 0.004$) for current smokers (Fig. 1). Differences in IgG titres between current smokers and non-smokers were not significant one month after the completion of the vaccination cycle; in addition, the differences were no longer significant at the serological analyses after the second month.

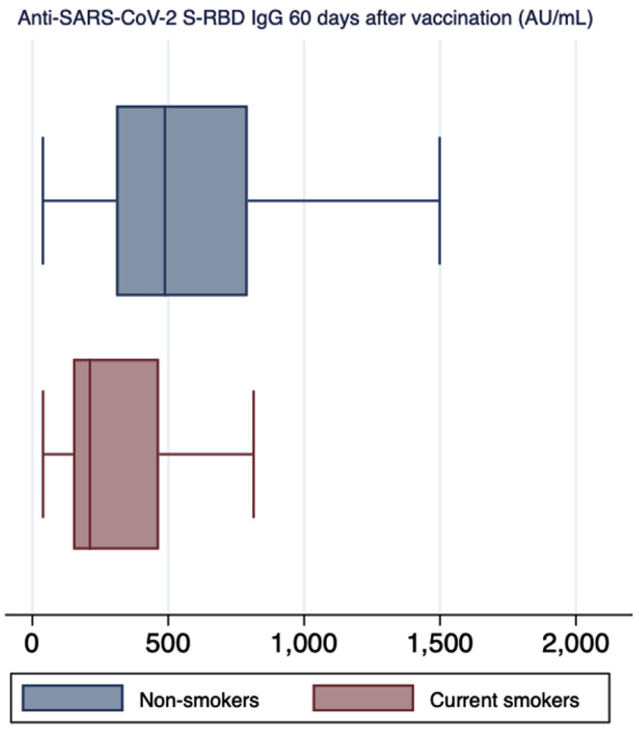

Fig. 1. Difference in vaccine-elicited SARS-CoV-2 S-RBD IgG between current smokers and non-smokers 60 days after vaccination with BNT162b2 COVID-19 vaccine.

Conclusions

This study showed that smoking may result in the rapid decrease in vaccine-induced IgG antibody levels. Emerging evidence has described lower antibody levels in response to COVID-19 mRNA vaccine in smokers, irrespectively of duration of smoking or number of cigarettes per day.[3] However, the pathophysiological basis for the impact of smoking on the dynamics of vaccine-elicited anti-SARS-CoV-2 antibodies have not yet been suggested. Previous literature observed that smoking may impact the immune response after vaccinations other than anti-COVID-19, such as hepatitis B and influenza vaccines, with a more rapid decrease in postvaccination antibodies in smokers.[4] Exposure to cigarette smoking impairs the immune system and thus the ability to form memory cells that are critical to the maintenance of the protective immune response induced by vaccines.[4,5] It is important to note that human IgG subclasses and specific antibodies generally have a half-life of approximately 3–4 weeks, depending on IgG isotype and attributes. Cigarette smoking is associated with increased monocyte-macrophage counts, which may influence the clearance of circulating antibodies.[5]

The present analysis shows that antibody titres decrease faster among current smokers than non-smokers. The mechanisms by which tobacco smoke decreases the immunological responses to COVID-19 vaccines deserve further research.

To date, the IgG threshold below which the risk of breakthrough infections is not yet known;[1] therefore, it is important to determine possible factors that may impair or decrease vaccine immunological response.[1] In this context, the findings from this study could be used to promote smoking cessation with the additional benefit of improving vaccine effectiveness. The results of the present study may also be used as a reference for further research on the impact of smoking on vaccine response.

It is worth noting that this study relies on observational data and used a specific and sensitive antibody test, which precisely correlates with vaccine-elicited humoral response. However, when interpreting the results, the small sample size must be taken into consideration, and the involvement of any undetected confounders of the vaccine-induced humoral response cannot be completely excluded.

Author statements

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Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki. The VASCO project was approved by the

Institutional Review Board - Comitato Etico Campania Nord, with referral number CECN/1614/2021. All participants provided written informed consent before enrollment into the study.

Funding

This research received no external funding.

Competing interests

R.P. is a full tenured professor of Internal Medicine at the University of Catania (Italy) and Medical Director of the Institute for Internal Medicine and Clinical Immunology at the same University. In relation to his recent work in the area of respiratory diseases, clinical immunology, and tobacco control, R.P. has received lecture fees and research funding from Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, MSD, Boehringer Ingelheim, Novartis, Duska Therapeutics, and Forest Laboratories. Lecture fees from a number of European EC industry and trade associations (including FIVAPE in France and FIESEL in Italy) were directly donated to vaper advocacy no-profit organizations. R.P. has also received grants from European Commission initiatives (U-BIOPRED and AIRPROM) and from the Integral Rheumatology & Immunology Specialists Network (IRIS) initiative. He has also served as a consultant for Pfizer, Global Health Alliance for treatment of tobacco dependence, CV Therapeutics, Boehringer Ingelheim, Novartis, Duska Therapeutics, ECITA (Electronic Cigarette Industry Trade Association, in the UK), Arbi Group Srl. and Health Diplomats. R.P. has served on the Medical and Scientific Advisory Board of Cordex Pharma, Inc., CV Therapeutics, Duska Therapeutics Inc, Pfizer and PharmaCielo. R.P. is also founder of the Center for Tobacco Prevention and Treatment at the University of Catania and of the Center of Excellence for the acceleration of Harm Reduction at the same University, which has received support from Foundation for a Smoke-Free World to conduct eight independent investigator-initiated research projects on harm reduction. R.P. is also currently involved in the following pro bono activities: scientific advisor for LIAF, Lega Italiana Antifumo (Italian acronym for Italian Anti-Smoking League), the Consumer Advocates for Smoke-free Alternatives, and the International Network of Nicotine Consumers Organizations; Chair of the European Technical Committee for standardization on 'Requirements and test methods for emissions of electronic cigarettes' (CEN/TC 437; WG4). All other authors declare no conflicts of interest.

Authors' contributions

P.F. and D.P. conceived and designed the VASCO study. P.F. and R.P had the idea for this Short Communication. P.F. led the statistical analyses and wrote the first draft of the article. All authors contributed to data collection and acquisition, database development, discussion and interpretation of the results, and writing the article. All authors have read and approved the final article.

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