Received: 31 May 2021 | Accepted: 27 July 2021

DOI: 10.1111/all.15047

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

LETTERS

A single dose of BNT162b2 vaccine elicits strong humoral response in SARS-CoV-2 seropositive individuals

To the Editor,

The high demand for COVID-19 vaccines, combined with a significant lack of supply, leaves smaller and developing countries behind in mass immunization. This prompts the question whether administering a single vaccine dose in SARS-CoV-2 seropositive individuals could be a method for rationing available vaccine doses.

We report results from a prospective study on Macedonian healthcare workers who received two doses of the Pfizer/BioNTech BNT162b2 mRNA vaccine, comparing antibody titres and frequency of side effects after vaccine administration between individuals who were SARS-CoV-2 seropositive (SeroPOS group) and seronegative (SeroNEG group) prior to immunization. The study included 226 participants recruited through convenience sampling, of whom 41 were SeroPOS (73.17% female; mean age 43 years, SD: 10.571), and 185 were SeroNEG (68.11% female, mean age 46 years, SD: 10.523). Baseline patients' characteristics are provided in the Supplementary Appendix (Table S1). Blood samples were collected 18–21 days after the first vaccine dose and 25–28 days after the second dose. Baseline antibody levels were obtained from patient records. All participants gave blood samples after the first dose and filed a questionnaire for side effects, and 189 participants (83.63%) returned for assessment four weeks after the second dose. Serological testing was performed using the commercially available quantitative CLIA anti-SARS-CoV-2 RBD kit (Snibe, Shenzhen, China),[1] which targets the S1 subunit of the viral spike protein. More details on methods are available in the Supplementary Appendix.

Anti-SARS-CoV-2 RBD IgG antibody levels after the first dose of BNT162b2 were on average 11.7-times higher in SeroPOS individuals (mean: 923.40 AU/ml, SD: 948.119, range 15.04–5034.70) compared to SeroNEG individuals (mean: 79.06 AU/ml, SD: 253.243, range 0.912–1867.30; Wilcoxon rank-sum test, $p < 2e\text{-}16$, Figure 1A). After the second dose, anti-SARS-CoV-2 RBD IgG antibody levels were still higher in SeroPOS individuals (mean: 602.59 AU/ml, SD: 511.545, range 25.41–1986.00) compared to SeroNEG individuals (mean: 375.567 AU/ml, SD: 437.088, range 9.617–3704.40; Wilcoxon rank-sum test, $p = 0.006$, Figure 1B). SeroNEG individuals had on average a 5.35-fold increase in anti-SARS-CoV-2 RBD IgG antibody levels after the second dose (Wilcoxon signed-rank test, $p < 2e\text{-}16$, Figure 1B), whereas SeroPOS individuals had no benefit of increased antibody levels after the second dose (Wilcoxon signed-rank test, $p = 0.529$, Figure 1B). SeroPOS individuals had higher antibody levels after the first dose than SeroNEG individuals after the second dose (Wilcoxon rank-sum test, $p = 0.0039$, Figure 1B). Exploratory analysis of the influence of sex and age on antibody response showed that older age had a reducing effect on antibody levels after the first and second vaccine dose (Supplementary Appendix, Table S2). The vast majority of the study participants reported at least one side effect after the first dose (91.15%, Figure 1C), mostly minor local pain (69.47%). A higher proportion of study participants reported at least one side effect after the second dose (97.35%, Figure 1D), again mostly minor local pain (53.97%).

Our findings are in line with previous reports of higher antibody levels in SeroPOS individuals after a single dose of BNT162b2 compared to SeroNEG individuals[2-5] and support the hypothesis that a single dose of BNT162b2 in SARS-CoV-2 seropositive individuals might provide sufficient humoral immunity towards SARS-CoV-2. These findings should be validated in a clinical trial setting as soon as possible, due to direct implications for public health policy in developing countries with limited access to vaccines. Future investigations should incorporate analyses of the cellular immunity and take into consideration the duration of the immune response, which have not been evaluated in this study. The more rational use of vaccines could accelerate the attainment of collective immunity at reduced costs.

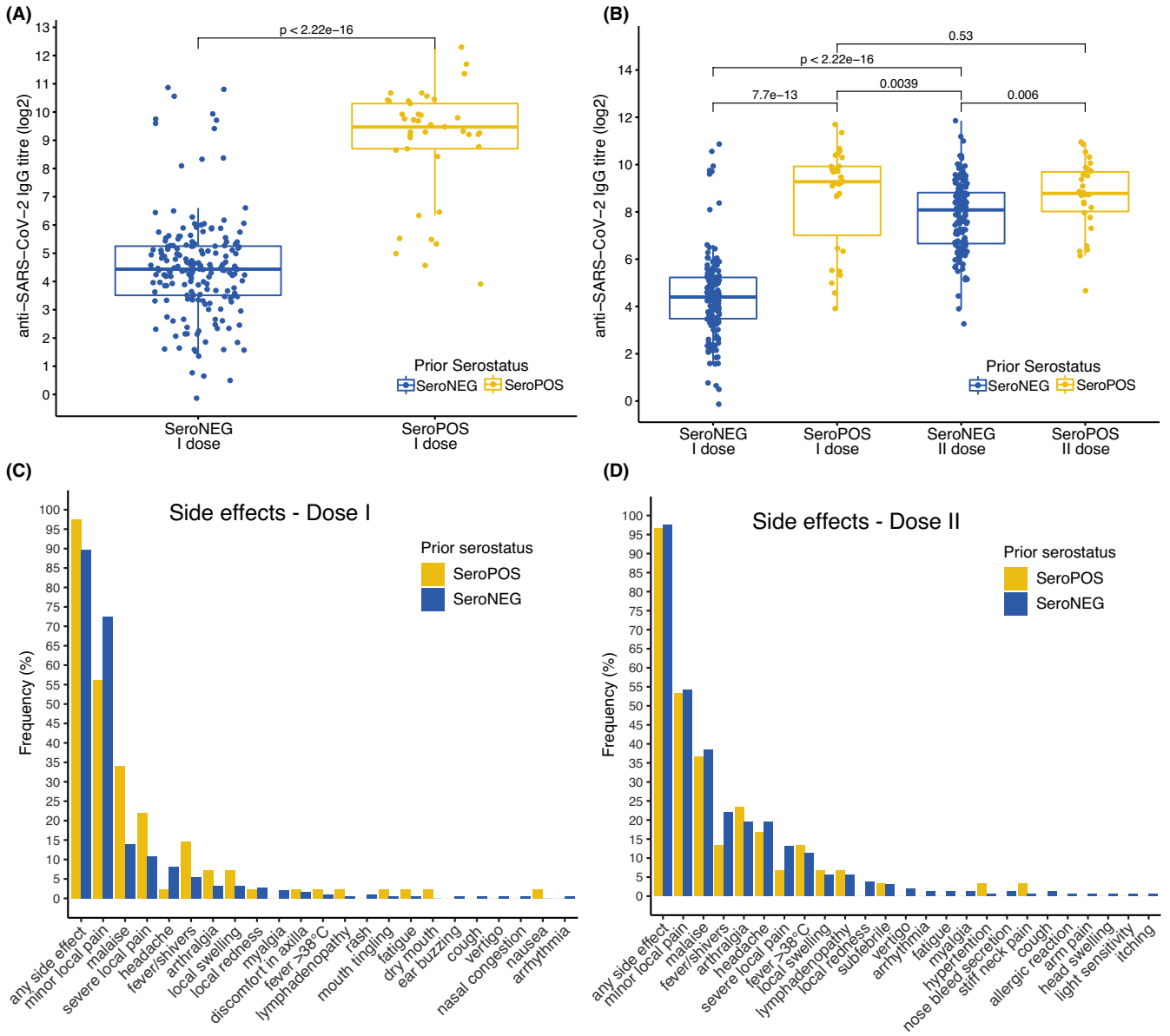

FIGURE 1 Antibody titres (log2-transformed) and side effects after the first and second dose of the Pfizer/BioNTech BNT162b2 vaccine in patients with (SeroPOS) and without (SeroNEG) anti-SARS-CoV-2 antibodies before vaccination. (A) Anti-SARS-CoV-2 RBD antibody titres after the first dose of BNT162b2 in SeroPOS individuals (n = 41) versus SeroNEG individuals (n = 185), full cohort. (B) Anti-SARS-CoV-2 RBD antibody titres after the first and second dose of BNT162b2 in SeroPOS individuals (n = 30) versus SeroNEG individuals (n = 159), participants who returned for analysis after the second dose. (C and D) Frequency of self-reported side effects in SeroPOS and SeroNEG individuals after the first and second dose of BNT162b2

FUNDING INFORMATION

Faculty of Medicine, University Ss Cyril and Methodius, Skopje, North Macedonia; National Health Insurance Fund and Ministry of Education and Science of North Macedonia

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

DOI: 10.1111/all.15048

Antiviral response in vernal keratoconjunctivitis may be protective against COVID-19

To the Editor,

Vernal keratoconjunctivitis (VKC) is a severe type 2 ocular eosinophilic inflammation with a proven IgE sensitization in about 50% of patients. Many Th2-type and proinflammatory cytokines have been found to be locally overexpressed in VKC patients, recalling a sort of local cytokine storm. Conjunctivitis is a common, self-limiting manifestation of COVID-19 with an incidence of 11% in affected patients,[1] but can be the first or the unique manifestation of SARS-CoV-2 infection. As a referral center for the diagnosis and treatment of VKC, so far, we observed only two VKC patient affected by COVID-19 without any ocular symptoms or consequences. The prevalence of VKC is estimated in our area 4/10.000 under 15 years of age.[2] Knowing that the prevalence of COVID-19 in pediatric population (0–14) in Padova great area is 6.4%, we calculated that the odds ratio (OR) for VKC to be associated with COVID-19 is OR = 0.88 (95% CI, 0.66–1.16), therefore, with a tendency for VKC to be protective. It has been suggested that a Th2-skewed immunity may be protective against severe COVID-19 disease.[3] For this reason, we investigated the conjunctival expression of genes related to the local defense immunity to virus that may play a relevant role in the response to SARS-CoV-2.

Conjunctival samples were collected from 15 VKC patients and 5 healthy age-matched control subjects (CTRL) using the Eyeprim™ device (OPIA Technologies SAS). Samples were immediately treated and stored at −80°C for subsequent RNA isolation and Affymetrix assay (see Appendix S1). Over the 21,448 tested expression probes, using the Gene Ontology Biological Process (GOBP) term "defense response to virus," 237 genes were selected (Figure S1). In addition, using bibliographic elements, we selected genes with SARS-CoV-2 receptor function and antiviral activity. The receptor angiotensin-converting enzyme 2 (ACE2), cellular transmembrane serine protease 2 (TMPRSS2), Basigin/CD147/EMMPRIN (BSG), cathepsin L (CTSL), and dipeptidyl peptidase (DPP4) were not overexpressed in VKC compared to CTRL. Conversely, FURIN (FC = 2.73, $p = 0.001$) and ADAM-17 (FC = 1.61; $p = 0.01$) were significantly higher in VKC. Thirty-eight genes involved in the defense response to virus, including bone marrow stromal antigen (BST2)/tetherin and MX Dynamin Like GTPase 2/myxovirus resistance protein 2 (MX2) and tumor necrosis factor-alpha-induced protein 3 (TNFAIP3) were overexpressed in VKC (Table 1 and Figure 1). Even though several members of the interferon regulatory and inducible proteins (Table 1) were overexpressed in VKC, genes encoding for interferons were not. Notably, interferon receptors IFNAR1 (FC = 1.88; $p = 0.003$), IFNGR2 (FC = 2.6; $p = 0.04$) were significantly overexpressed in VKC.

The meaning of the upregulation of all these antiviral genes in VKC is not clear. It has been shown that ACE2 is overexpressed in diseased conjunctiva compared to normal tissues and that conjunctival inflammation can enhance its expression.[4] Our results show that this is not the case for allergic inflammation. It has been suggested that type 2 immune response can provide certain protective effects against COVID-19 since asthma patients do not