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Letter

Risk factors for poor humoral response to primary and booster SARS-CoV-2 vaccination in hematologic and oncological outpatients—COVIDOUT study

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In the ongoing COVID-19 pandemic, patients with hematologic and oncological diseases represent a heterogeneous population at risk of severe course of infection (Kuderer et al., 2020; Pagano et al., 2021). Considering the broad spectrum of hematologic and oncological diseases and applied therapy modalities, vaccination efficacy for different patient groups could hardly be assessed by the comparison of reduction of infection, hospitalization, and mortality rates. Therefore, surrogate markers such as the SARS-CoV-2 spike-protein-specific IgG (anti-S) response, neutralizing antibody tests, and T cell assays have been used to characterize their immune response and to identify entity- or therapy-specific risk groups for whom there is insufficient vaccine protection. Several risk factors have already been identified: e.g., underlying multiple myeloma and lymphoma and treatment with anti-CD20- or anti-CD38-directed therapy (Addeo et al., 2021; Mairhofer et al., 2021; Thakkar et al., 2021; Van Oekelen et al., 2021). The aim of our prospective single-center COVIDOUT study was to investigate time-dependent humoral vaccine response in hematologic and oncological patients under treatment or active surveillance in the outpatient setting and to identify risk factors for an impaired serological response after vaccination.

In total, 653 consecutive hemato-oncological patients at the University Cancer Center Hamburg (UCCH) were screened for SARS-CoV-2 infection between December 2020 and January 2022, and 35 (5.4%) were identified positive, and 12 (1.8%) of those were identified incidentally via detection of SARS-CoV-2 anti-nucleocapsid IgG. 494 patients were primary vaccinated, as defined by homologous or heterologous two-time regimens in case of BNT162b2, mRNA-1273, and ChAdOx1 (95% of primary vaccinated patients), single-dose vaccination in case of A26.COV2-S (1%), and single- or two-dose vaccination in case of previous SARS-CoV-2 infection (4%). In 30% of these patients, the antibody response could also be analyzed after additional booster vaccination. Four patients had a SARS-CoV-2 infection after vaccination (two were homologous BNT-162b2 vaccinated and two were one-time ChAdOx1-S vaccinated). Patients had a median age of 62 years (range from 18 to 93), 41% were female, and patients were grouped into five classes of diagnosis: solid cancer (34%), myeloid malignancies (23%), plasma-cell dyscrasia (PCD, 23%), lymphoma (13%), and other hematologic diseases (8%). 17% received chemotherapy, 7% immunotherapy, 13% corticosteroids, and 41% antibody or inhibitor therapy. As a control cohort, data from 146 health care workers (HCWs) of the University Medical Center Hamburg-Eppendorf were used, and these HCWs exhibited significantly different demographic characteristics when compared to the patient cohort regarding sex (female 73%, $p < 0.001$), age (median 40 years, $p < 0.001$), and applied vaccination regimens (58% heterologous vaccination vs. 9% in the patient cohort, $p < 0.001$) (Tables S1A and S1B).

The predefined HCW and patient subgroups showed significant differences in terms of their anti-S response ($p < 0.001$), and the strongest response was observed in HCWs (median 8,253 binding antibody units [BAU]/ml), followed by myeloid malignancies (median 2,649 BAU/ml), solid cancers (median 760 BAU/ml), and PCDs (median 352 BAU/ml), and the weakest anti-S response was for lymphoma (median four BAU/ml). Except for the comparison of solid cancer vs. PCD, all between-group analyses were significantly different (Figure S1A). Within the different disease classes, no significant differences in anti-S levels after primary vaccination could be observed for the respective sub-entities except for acute leukemia and/or myelodysplastic syndrome vs. chronic myeloid leukemia ($p = 0.04$) (Figures S1A and S1B).

Serological response persistence over 5–7 months after primary vaccination was analyzed in a subgroup of 199 patients and evaluated in predefined categories (no seroconversion <0.8, poor response 0.9–99, reduced response 100–499, sufficient response >500 BAU/ml). There was a significant reduction of anti-S levels for solid cancer ($p = 0.03$, e.g., a decline in sufficient response from 64% [0–2 months] to 40% [5–7 months]) but not in the hematologic subgroups. Only in two of 199 cases did anti-S levels shift more than one anti-S category level (Figure S1C).

In the solid cancer patient cohort, patients who underwent chemotherapy had a significant reduction in anti-S levels compared to those who did not receive chemotherapy (median 439 vs. 1,015 BAU/ml, $p < 0.001$). In addition, patients treated with VEGF (vascular endothelial growth factor) inhibitor also showed reduced anti-S levels compared to the VEGF-inhibitor untreated group (median 231 vs. 872 BAU/ml, $p = 0.01$). For immunotherapy or EGFR (epidermal growth factor receptor) inhibitor treatment, no impact on anti-S levels was observed. In the group of myeloid malignancies, JAK (Janus kinase) inhibitor-treated patients had a significant reduction of anti-S levels (median 451 vs. 2,850 BAU/ml, $p = 0.02$); interferon was the only identified treatment with an increase of titers (median 4,040 vs. 2,293 BAU/ml, $p = 0.03$). No differences were observed for hydroxyurea or tyrosine kinase inhibitor (TKI) treatment. In PCD patients, significantly lower anti-S levels were observed for anti-CD38 antibody treatment (median 83 vs. 597 BAU/ml, $p = 0.02$), immunomodulatory imid drugs (IMiD) (median 149 vs. 597 BAU/ml, $p = 0.04$), and proteasome inhibitor treatment (median 18 vs. 535 BAU/ml, $p = 0.001$). The strongest negative impact on anti-S levels was observed in lymphoma patients treated with Bruton's tyrosine kinase (BTK) inhibitors (median 0 vs. 17 BAU/ml, $p = 0.02$) and/or anti-CD20 antibodies (median 0 vs. 101 BAU/ml, $p < 0.001$). In patients for whom anti-CD20 treatment was initiated right after or ended more than six months prior to the first vaccination, seroconversion was observed in half of the patients ($n = 3/6$), and similar results were recently reported in a larger lymphoma cohort (Shree et al., 2022). In an analysis of the whole patient cohort, corticosteroid treatment also resulted in reduced anti-S levels (median 150 vs. 1,110 BAU/ml, $p < 0.001$) (Figure S1D, Table S1C). Increasing age ($p < 0.001$), male sex ($p = 0.01$), cardiovascular comorbidity ($p = 0.03$), and CD19 cell count ($p < 0.001$, immune status obtained in 151/513 patients) were additionally identified as having a significant negative impact on anti-S levels after primary vaccination (Figure S1E and S1F).

Next, patients' characteristics (age, sex), disease groups, anti-neoplastic treatments, vaccination schemata, and SARS-CoV-2 infection statuses were included in multivariable analysis. Hereby, we could identify the diagnosis of lymphoma ($\beta_{log(anti\text{-}S)} = -2.1$ [reference HCW], $p < 0.001$) and treatment with chemotherapy ($\beta_{log(anti\text{-}S)} = -0.8$, $p = 0.002$), corticosteroids ($\beta_{log(anti\text{-}S)} = -0.5$, $p = 0.046$), BTK inhibitor ($\beta_{log(anti\text{-}S)} = -2.7$, $p < 0.001$), anti-CD20 antibody ($\beta_{log(anti\text{-}S)} = -3.5$, $p < 0.001$), anti-CD38 antibody ($\beta_{log(anti\text{-}S)} = -0.8$, $p = 0.007$), and proteasome inhibitor ($\beta_{log(anti\text{-}S)} = -1.6$, $p < 0.001$) as independent risk factors for poor vaccination response after primary vaccination (Table S1D).

To evaluate the effect of different vaccination strategies, we first directly compared the anti-S levels of BNT 162b2, mRNA-1273, and ChAdOx1-S after homologous immunization and of Ad26.COV2-S after one-time vaccination (limited cohort of $n = 4$), and we found no significant differences. Yet, in the multivariable analysis, Ad26.COV2-S vaccination showed significantly reduced anti-S levels ($p < 0.001$) and was therein similar in its effect to BNT162b2/mRNA-1273/ChAdOx1-S single-dose vaccination and SARS-CoV-2 infection without additional vaccination (multivariable analysis: $\beta_{log(anti\text{-}S)} = -3.8$ [Ad26.COV2-S] vs. −4.2 [BNT162b2/mRNA-1273/ChAdOx1-S single dose] vs. −3.6 [COVID-19]). These poor anti-S levels in SARS-CoV-2-infected patients could be distinctly increased by primary vaccination. Interestingly, no difference was observed in these patients regarding one or two additional vaccinations if applied within six weeks of the first vaccination (median anti-S 197 [COVID-19] vs. 18,268 [+1 vaccination] vs. 19,827 [+2 vaccinations] BAU/ml). Due to an adaption of European vaccination guidelines, 39 patients received a heterologous ChAdOx1-mRNA-based vaccination. This heterologous schedule showed an enhanced immune response compared to homologous vaccination (median anti-S 3,139 vs. 630 BAU/ml, $p = 0.01$). Likewise, the mRNA-based booster vaccination increased anti-S levels in hematologic and oncological patients compared to homologous primary two-time vaccination (median anti-S 9,185 vs. 630 BAU/ml, $p < 0.001$). There was no difference in anti-S levels after a booster vaccination when primary vaccination regimens (mRNA, vector, and heterologous) were compared. To test the effect of the established therapy-associated risk factors (chemotherapy, BTK inhibitor, anti-CD20 antibody, anti-CD38 antibody, and proteasome inhibitor) on anti-S levels after a booster vaccination, we compared patients with and without these risk factors, and we found that patients with a risk for poor vaccination response after primary vaccination again had significantly reduced anti-S levels compared to normal-risk hematologic and oncological patients (median 12,213 [no risk factors] vs. 907 BAU/ml [risk factors], $p < 0.001$) (Figure S1G).

The COVIDOUT cohort represents one of the largest cohorts of hematologic and oncological patients in which long-term SARS-CoV-2 vaccination response has been analyzed so far. In comparison to HCWs, patients from the hematologic and oncological disease groups showed a decreased humoral vaccine response, and there were large differences among these groups. Whereas myeloid malignancy patients still had a high vaccine-induced humoral response, and PCD and solid cancer patients had similarly reduced anti-S levels, only half of the lymphoma patients reached a seroconversion after primary vaccination. These findings strongly suggest that we should not group patients with PCD, myeloid malignancies, and lymphoid malignancies into one category of "hematologic patients," because they distinctly differ in their vaccination response. Furthermore, it was shown that therapy-caused impairment of anti-S response to vaccination exceeds the effect of the underlying disease. Except for lymphoma, the disease influence remained insignificant in the multivariable

analysis, whereas several treatment modalities were confirmed to be robust and independent negative factors (chemotherapy, steroids, anti-CD38 and anti-CD20 treatment, and proteasome and BTK inhibitors), of which not all have yet been consistently described as independent risk factors for an impaired SARS-CoV-2 vaccination response. In contrast, in patients who achieved adequate anti-S levels, only a mild regression over time was observed. Our data also demonstrate the need for vaccination in patients who previously underwent SARS-CoV-2 infection, because anti-S titers after infection were similarly poor to those in patients who were vaccinated only one time. Yet, when vaccinated after SARS-CoV-2 infection, these patients had distinctly higher anti-S titers than those without previous infection had. In addition, and as reported for healthy individuals (Pozzetto et al., 2021), our data show improved anti-S responses after heterologous ChAdOx1-mRNA-based vaccination. This is likely accompanied by complementary B and T cell effects, thus providing a potential future strategy for immunocompromised patients (Pozzetto et al., 2021). In line with other studies (Fendler et al., 2021; Shroff et al., 2021), booster vaccination also led to increased anti-S levels in the COVIDOUT cohort. However, patients with one of the identified therapy-associated risk factors benefited significantly less from booster vaccination. We recommend that these groups of patients should be considered for primary prophylactic measures like modification of social behavior, vaccination of contact persons, and treatment with anti-SARS-CoV-2 monoclonal antibodies in case of breakthrough infection, after high-risk exposure, or even for primary prevention. Despite a potentially weaker humoral response, these at-risk patients might profit from additional or even repetitive booster vaccinations, because their booster did show activity in our cohort.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2022.04.016.

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AUTHOR CONTRIBUTIONS

Conceptualization, M. Schönlein, V.W., S.M., W.A., P.S., and M.Sinn; formal analysis, M. Schönlein, V.W., G.S., and M.Sinn; investigation, M. Schönlein, V.W., S.G., and M.Sch.; methodology, M. Schönlein, V.W., G.S., and M.Sinn; project administration, M. Schönlein, V.W., D.P., and M.Sinn; resources, M. Schönlein, V.W., S.G., T.B., L.L., N.U., R.S., W.A., N.B., L.B., M. Schönrock, K.V., J.z.W, K.W., C.B., P.S., and M.Sinn; supervision, M.L., J.z.W., K.W., C.B., P.S., and M.Sinn; writing—original draft, M. Schönlein, V.W., S.M., and M.Sinn; writing—review and editing, all authors.

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