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Absent antibody production following COVID19 vaccination with mRNA in patients under immunosuppressive treatments

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Abstract

Patients undergoing immunosuppressive treatments have a higher need for protection against coronavirus disease (COVID19) that follows infection with the SARS-CoV-2 virus but their ability to respond sufficiently to COVID vaccines is uncertain.

We retrospectively evaluated SARS-CoV-2 spike subunit 1 (S1)-specific antibody levels after two mRNA doses in 242 patients with underlying chronic inflammatory, hematological or metabolic diseases and in solid organ transplant recipients. S1-specific antibodies were measured 30 days after the second dose.

In 15.9% of these patients, no S1-specific antibodies were detectable. Non-responsiveness was linked to administration of B-cell depleting therapies as well as to ongoing therapies that block lymphocyte trafficking (Fingolimod) or inhibit T cell proliferation (Tacrolimus).

Thus, it is important to inform immunosuppressed patients about the risk of vaccine non-responsiveness and the necessity to maintain non-pharmaceutical protection measures. In these risk patients antibody testing and cellular analysis are helpful to estimate the benefit/responsiveness to further booster vaccinations.

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Introduction

COVID19 mRNA vaccines consist of a lipid nanoparticle-formulated nucleoside-modified mRNA which encodes for the receptor-binding domain of the SARS-CoV-2 spike protein 1. In fully vaccinated healthy individuals, mRNA vaccines induce a robust anti-spike antibody response resulting in ~95% efficacy against COVID19 [1].

Considering the extent of the SARS-CoV-2 pandemic, such observations on vaccine efficacy in healthy individuals were of utmost importance, but information on efficacy in vulnerable populations has been largely lacking [2]. We wondered whether treatments known to directly reduce B-cell numbers or impair T-lymphocyte function would inhibit vaccine-induced antibody production.

Thus, we performed a retrospective study of S1-antibody production following mRNA vaccination in patients undergoing various immunosuppressive treatment regimens.

Methods

Study population

We analysed S1-specific antibody results in a total of 214 patients (117 females, 97 males; mean age: 53.4 (51.4–55.4 95% CI) at our outpatient vaccination clinic for high-risk patients after intramuscular administration of two doses BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna). Both vaccines contain mRNA encoding for the spike protein in lipid nanoparticles that were administered into the deltoid muscle with no other vaccines administered concomitantly. Among these were patients suffering from chronic inflammatory diseases (including rheumatoid arthritis, intestinal bowel disease or multiple sclerosis; n = 104), hematological disorders (n = 66); solid tumors (n = 14), patients with solid organ transplants (n = 22) or metabolic disorders (n = 8). Additionally, antibody results from 26 healthy individuals (50% females; mean age: 48.7 (41.5–55.9 95% CI) served as controls.

Serologic testing

S1-specific IgG titers were assessed by ELISA (Quantivac® Euroimmune) following the manufacturer’s instructions at an average of 31.7 (30.2–33.3 95% CI) days after the second dose. We included test results received between January 2021 and June 2021.

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23rd 2021. Ethics approval for this study was obtained from the Ethics committee of the Medical University of Vienna (EK 1586/2021).

Results & Discussion

In our study population, we were able to evaluate baseline S1-specific antibody titers prior to the first dose in 89.1% (191/214) of patients. Of those 1.05% (n = 2) were positive and 0.52% (n = 1) was in borderline range already before receiving the first dose of an mRNA vaccine indicating a prior asymptomatic infection. After the two dose vaccination schedule we observed that anti-SARS-CoV-2 antibodies were undetectable (i.e. < 25.6 BAU/ml) in 15.89% (34/214; mean age 56.3 (50.7–61.9 95 %CI); 58.8% females) of the mentioned entity of patients (Fig. 1; Table 1). Borderline titer results (i.e. 25.6–35.2 BAU/ml) according to the manufacturer’s reference values were obtained in 2.8% (6/214; mean age 64.9 (53.6–76.3 95 %CI); 16.7% females; Fig. 1, Table 2) of patients and positive antibody results were received in 81.31% (n = 174; mean age) of patients. In contrast, among the healthy individuals, that had requested an antibody titer measurement, all (n = 26) had positive antibody titer (i.e. > 35.2 BAU/ml) results after two doses of the mRNA vaccines. Furthermore, geometric mean titers were significantly higher in the healthy individuals compared to the seropositive patients (GMT 706.7 versus 517.1; p < 0.05, Students t-test).

Table 1

| Age band | gender | diagnosis | Immunosuppressive treatment | Last dose RTX before 1st mRNA in months | Vaccine | Interval between 1st and 2nd dose |
|----------|--------|-----------|-----------------------------|----------------------------------------|---------|----------------------------------|
| 1 21–30 m | Multiple sclerosis | Fingolimod | BNT162b2 | 21 |
| 2 31–40 f | Multiple sclerosis | Fingolimod | BNT162b2 | 21 |
| 3 31–40 f | Multiple sclerosis | Fingolimod | BNT162b2 | 21 |
| 4 41–50 f | Multiple sclerosis | Fingolimod | BNT162b2 | 21 |
| 5 41–50 m | Multiple sclerosis | Fingolimod | BNT162b2 | 21 |
| 6 51–60 f | Multiple sclerosis | Fingolimod | BNT162b2 | 24 |
| 7 51–60 f | Rheumatoid arthritis | Rituximab | BNT162b2 | 21 |
| 8 71–80 m | Rheumatoid arthritis | Methotrexate, Tofacitinib | BNT162b2 | 22 |
| 9 51–60 f | Myositis | Rituximab | 7 | BNT162b2 | 21 |
| 10 51–60 f | Myositis | Rituximab | BNT162b2 | 21 |
| 11 61–70 m | Vasculitis | Rituximab, cortisone, Mycophenolate Mofetil | 4 | BNT162b2 | 21 |
| 12 71–80 m | Myasthenia gravis | Mycophenolate Mofetil | BNT162b2 | 21 |
| 13 18–20 m | Goodpasture syndrome | Rituximab | 9 | BNT162b2 | 21 |
| 14 71–80 f | Vasculitis | Rituximab, cortisone, Mycophenolate Mofetil, cortisone | 12 | BNT162b2 | 21 |
| 15 61–70 m | Pemphigus | Mycophenolate Mofetil, cortisone | BNT162b2 | 21 |
| 16 61–70 f | Systemic lupus erythematosus | Mycophenolate Mofetil | BNT162b2 | 21 |
| 17 51–60 f | Scleroderma | Rituximab, Cortisone | 8 | BNT162b2 | 21 |
| 18 31–40 f | Collagenosis | Rituximab, Cortisone, Prednisolon | 12 | BNT162b2 | n.d. |
| 19 51–60 f | Sarcoid | Ebetrexat | BNT162b2 | 21 |
| 20 71–80 m | Multiple myeloma, autologous stem cell transplantation | Lenalidomide | BNT162b2 | 21 |
| 21 51–60 m | Multiple Myeloma, autologous stem cell transplantation | Pomalidomide, cortisone | BNT162b2 | 21 |
| 22 61–70 m | Stem cell transplantation 2.20 with GvHD | Ruxolitinib | BNT162b2 | 21 |
| 23 21–30 f | Kidney transplantation | Mycophenolate Mofetil, Tacrolimus | BNT162b2 | 21 |
| 24 31–40 m | Kidney transplantation | Sirolimus, Mycophenolate Mofetil, Prednisolon | BNT162b2 | 21 |
| 25 51–60 f | Kidney transplantation | Tacrolimus, Mycophenolate Mofetil, Prednisolon | BNT162b2 | 21 |
| 26 61–70 f | Kidney transplantation | Tacrolimus, Azathioprin, Prednisolon | BNT162b2 | 21 |
| 27 61–70 m | Kidney transplantation | Tacrolimus, Mycophenolate, cortisone | BNT162b2 | 21 |
| 28 51–60 f | Lung transplantation | Mycophenolate Mofetil | BNT162b2 | 21 |
| 29 61–70 f | Heart transplantation, multiple | Everolimus, Tacrolimus, | BNT162b2 | 21 |
n.d. not documented.

Table 2

| Age band | gender | diagnosis | Immunosuppressive treatment | Last dose RTX before mRNA in months | Vaccine | Interval between 1st and 2nd dose |
|----------|--------|-----------|-----------------------------|------------------------------------|---------|----------------------------------|
| 30       | 71–80 m| lymphoma  | Daratumumab,                | 8                                  | BNT162b2| 21                               |
| 31       | 81–90 f| Lymphoma  | Rituximab                   | 1                                  | BNT162b2| 22                               |
| 32       | 81–90 m| Lymphoma  | Rituximab, Bendamustin      | n.d.                               | BNT162b2| 21                               |
| 33       | 61–70 m| Chronic lymphocytic leukemia | anti-CD20                  | 8                                  | BNT162b2| 21                               |
| 34       | 21–30 f| aplastic anemia | (immunglobuline substitution) |                                    | BNT162b2| 21                               |

With regard to non-responsiveness, further analysis showed that a lack of antibody production was preferentially linked to an ongoing treatment with Rituximab in patients with B-cell malignancies or autoimmune disorders, Fingolimod in patients with multiple sclerosis or Calcineurine inhibitors (Tacrolimus) in renal transplant patients (Table 1). Due to the retrospective character of this study B and T cell counts are not available from all study participants, however, among 13 non-responders B and T cell counts between 34 days before and up to 115 days after the first mRNA dose were available and revealed that none of them showed normal B cell counts according to the reference values, irrespective of the type of immunosuppressive therapies (Fig. 2). Part of these patients displayed CD4+ T cell counts in normal range, however, we do not have further information on the functionality of these cells. It is proposed that various mechanisms seem to be involved in the inability to mount an antibody response which include B cell depletion (<1%) by Rituximab[3], prevention of lymphocyte trafficking from lymphoid tissue by Fingolimod[4] or inhibition of lymphocyte proliferation by Tacrolimus[5] thereby hindering also T-cell help for B-cell antibody production. The Rituximab-induced defect in antibody production persisted for at least 11 months after the termination of treatment and was normalized only after this period resulting in an antibody response in 4 out of 14 Rituximab-treated patients. Of note, two patients with the last Rituximab administration longer than 11 months ago were still not able to mount an antibody response and remained seronegative, indicating individual recovery rates after this treatment. Recent data now show that part of these B cell depleted patients and also other immunosuppressed patients are able to mount a cellular response to the COVID19 vaccine [6–9].

In the group of responders, the underlying treatment regimen was diverse (Fig. 3). The data further show that 2 out of 8 patients on Fingolimod were able to mount an antibody response. In SOT patients, particularly kidney-transplanted patients (as well as one with a heart and one with a liver transplant on Tacrolimus) did not show any antibody responses, whereas the other SOT patients - even when treated with Tacrolimus - mounted S1-specific antibody levels. This illustrates that immune responsiveness/non-responsiveness cannot easily be predicted in patients with high-grade immunosuppressive treatments, and therefore immunologic testing of antibodies and cellular responses may help to anticipate vaccine-responsiveness.

Conclusion

We conclude that both, patients undergoing such immunosuppressive treatments and physicians prescribing these therapies should be informed about the potential lack of anti-SARS CoV-2 antibody formation following vaccination. Patients with the mentioned diseases and treatments need counseling for alternative protection methods including social distancing, use of masks and – most importantly – the inclusion of their immediate contacts into vaccination programs. However, also in patients mounting an immune response, one should be aware of the fact that antibody titers are often lower than in the healthy population and it is necessary to follow the kinetics of these antibody levels over time as they may wane more quickly in the immunosuppressed. Application of additional vaccine doses seem justified if an immune response at least at the cellular level can be expected and has been shown promising in SOT patients to increase seroconversion rates and antibody levels [10,11]. Importantly, these doses should be discussed in relation to lymphocyte typing results, and whenever
applicable, by lymphocyte functionality tests as well as monitoring of humoral and cellular responses. Wherever feasible, the timing of the booster application should be planned to utilize therapeutic cycles/intervals with lower immunosuppressive drug levels.

Authors contributions:

Literature search: AW, CZ, UW; figures: AW, ET; study design: AW, CZ, UW; data collection: AW, ET, JJ, UW; data analysis: AW, ET, JJ, CZ, UW; writing: AW, CZ, UW

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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