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Comparative analysis of humoral responses to BNT162b2 vaccine among patients with hematologic disorders and organ transplant recipients.

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ABSTRACT

Vaccination against SARS-COV-2 is considered the most promising approach to curbing the pandemic. Patients with an immunocompromised state, such as those with hematological malignancies and organ transplantation recipients, are considered more susceptible to infection, but these at-risk patients were underrepresented in early clinical trials for vaccination. Although a growing body of studies suggests that the humoral response to COVID-19 vaccination in each of these at-risk groups of patients may be suboptimal in comparison to healthy controls, a clinical and strategic information for the further comparative analysis among these groups is not fully described. The humoral responses after two doses of BNT162b2 vaccination were evaluated in a total of 187 patients either with allogeneic hematopoietic transplantation, with renal transplantation, with anti-CD20 antibody therapy, or with anti-CD38 antibody therapy, and in 66 healthy controls. The early response at one to three months after vaccination was significantly inferior among patients with renal transplantation, patients with anti-CD20 antibody therapy, and patients with anti-CD20 antibody therapy in comparison to healthy controls. But the patients with allogeneic hematopoietic transplantation showed early humoral response comparable to healthy control. The late response at 6 months after vaccination was still suboptimal among patients with renal transplantation and patients with anti-CD20 therapy. Among our patient group, renal transplant recipients had the lowest antibody titers after vaccination regardless of timing of vaccination. Patients who had received allogeneic hematopoietic transplantation showed early humoral response comparable to healthy control. The late response at 6 months after vaccination was still suboptimal among patients with renal transplantation and patients with anti-CD20 therapy. Our results may provide policy makers with critical information for the further stratification of at-risk groups, helping contribute to a better allocation of resources, including additional booster vaccination.

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1. Introduction

Vaccination against SARS-Cov-2 (COVID-19) is considered the most promising approach for curbing the pandemic [1]. Its high effectiveness in prevention is durable and is still pertinent in the face of widespread dissemination of the delta variant [2,3]. As of March 10, 2022, >10,704 million vaccine doses have been administered to 4964 million individuals worldwide [4], and there have been multinational efforts to increase vaccination coverage that is broad enough to result in herd immunity and slow community transmission. In Japan, a total of 237 million vaccine doses have been administered as of March 10, 2022. This includes 79.3% of the total national population, with 92.4% of individuals of ≥65 years of age having been vaccinated twice [5].

Patients with an immunocompromised state, such as those with hematological malignancies and organ transplantation recipients, are considered to be more susceptible to COVID-19 infection and have higher morbidity and mortality rates in comparison to the general population [6–9]. Although these at-risk patients were underrepresented in early clinical trials for vaccination [2,3], vaccines have been expected to offer them immunological protection and early vaccination to these at-risk individuals has been prioritized in many countries, including Japan [10–16]. On the other hand, a growing body of studies suggests that the humoral response to COVID-19 vaccination may be suboptimal among a group that include people with hematological malignancies [1,17–20], chronic kidney failures [21,22], and organ transplant recipients [23–27]. Moreover, the degrees of impairment of the serological response within an at-risk group are often dependent on the treatment status and timing of vaccination [28–31], implying that risk-based vaccination is required. Although many of these studies help raise the alert to the poorer humoral response of at-risk individuals in comparison to healthy individuals, comparative risk analyses between the high-risk groups seems to be rather limited.

We herein describe a comparative analysis of the humoral responses across patients with different underlying medical conditions: hematological malignancies, allogeneic hematopoietic stem cell transplantation (allo-HCT) and renal transplantation. Our results may provide policy makers with critical information for the further stratification of at-risk groups, contributing to the discussion about the allocation of resources, including additional booster vaccination.

2. Methods

2.1. Patients and controls

Patients with hematologic diseases and allo-HCT recipients were prospectively recruited at one of the three transplantation centers in Nagano Prefecture, Japan, after providing their informed consent at each participating center. The inclusion criteria were ≥20 years of age and eligibility for COVID-19 vaccination. Renal transplant recipients were also retrospectively recruited at Shinshu University Hospital. Those with a history of PCR-confirmed COVID-19 infection were excluded. The decision regarding the timing of a treatment or a transplantation for an individual patient was made by the primary physician based on their clinical necessity. A retrospective chart review was performed to collect pertinent parameters for all participants. Controls were recruited among the healthcare workers at Shinshu University Hospital.

2.2. Vaccinations

All vaccinations were performed under the national immunization program empowered by the Immunization Act, Supplementary Provisions, enacted in Japan on December 9th, 2020 [32]. With a legal duty to endeavor to receive vaccination, multiple injection projects were launched across the country, and injections were started with those with higher priority, after which it was expanded to other groups of individuals who consented to vaccination: first, medical personnel in February 2021; second, at-risk individuals, including the elderly in April 2021; and then, other individuals under 65 years of age in June 2021.

For vaccination under the program, three vaccine preparations have been granted emergency use authorization by Japan’s Ministry of Health, Labor and Welfare (MHLW): BNT162b2 (Pfizer) was the only preparation that was widely available at the time of this study. While all the vaccinations for the controls were performed at Shinshu University Hospital, patients were to receive injections at a local hospital, at a medical office, or at a community site, to which each individual patient was allocated by a local government. The interval between the two vaccination series and treatment/transplantation was automatically determined by an availability of vaccines, rather than by the individual preference of the physician or patient. The dose and interval of the two vaccines doses were in accordance with the BNT162b2 protocol, two intramuscular injections of 30 μg, administered 3 weeks apart. As a third dose was not approved in Japan as of November 21; it is not included in the present result.

2.3. Assay for humoral response

The peripheral blood of both patients and controls was collected after the second dose. The periods between the second dose and sampling were one to three months (early-phase sample) and six months (late-phase sample). The samples were centrifuged within 6 h from blood collection and the separated sera were stored at −80 °C until the day of measurement. All samples were anonymized before storage.

The serum IgG fraction of a neutralizing antibody (NA) against the receptor binding domain in the S protein was measured with an Abbott ARCHITCT analyzer i2000SR (Abbott, Tokyo, Japan): a two-step fully automated, chemiluminescent microparticle indirect immunoassay for qualitative detection of the IgG [33]. The qualitative results and index values were reported by the ARCHITCT platform and were used in the analysis. The lowest detection limit was 6.8 AU/mL. A cut-off value of 50.0 AU/mL was adopted according to the manufacturer’s protocol, and a test result of NA ≥50.0 AU/mL was classified as positive.

2.4. Safety assessment

Information about adverse events (AEs) after vaccination in patients was obtained during a regular medical interview at a hospital visit. Questions of interest included timing and events, such as local symptoms (pain, erythema, swelling, or local myalgia at the injection site) and systemic reactions (fever, fatigue, headache) after vaccination. Abnormal laboratory data that were not attributable to underlying diseases or treatment, if any, were documented by the local physicians.

2.5. Statistical analyses

For statistical analyses, we used EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Fisher’s exact test was used to compare categorical variables, and the Kruskal-Wallis test or Mann-Whitney U test were used to compare continuous variables. Graphs were created with the Prism v9.0 software program (GraphPad Software, San Diego, CA, the USA).

2.6. Ethical approval

This study was conducted in accordance with the Declaration of Helsinki, and was approved by the Institutional Review Board of Shinshu University School of Medicine (approval number 5174, June 6, 2021).
3. Results

3.1. Demographics of the patients and controls

A total of 187 patients were included. Among these 119 had a recent history of anti-CD20 antibody treatment, 6 had a history of anti-CD38 antibody treatment, 23 had a history of hematopoietic stem cell transplantation and 39 had a history of renal transplantation (Table 1). More specifically, hematopoietic transplantation was performed to treat malignant lymphoma (n = 5), acute or chronic leukemia (n = 10) and other myeloid malignancies (n = 7). The allograft source was cord blood (n = 6, 27.3%) or bone marrow (n = 16, 72.7%). Indications for the renal transplantation included IgA nephropathy (n = 11), renal sclerosis (n = 6), diabetic nephropathy (n = 3), nephritis including lupus nephritis (n = 6) and congenital disorders (n = 5). Sixty-six individuals were recruited as a control group. The median age (range) of the patient and control groups was 66 (20–91) years and 36 (24–60) years, respectively (p = 2.71×10^{-21}). Seventy-six patients (40.1%) and 37 controls (56.1%) were female (p = 0.032). The median age did not differ to a statistically significant extent between the sexes in either the controls (p = 0.609).

3.2. Vaccination and the time period from treatment / transplantation

All patients and controls received the BNT162b2 mRNA COVID-19 vaccine. Of the 187 patients, 70 received vaccination within 300 days after the completion of last treatment/transplantation, 30 were vaccinated at 300–600 days after treatment, and 84 completed vaccination ≥600 days after the last treatment. The median time period (range) between the last treatment/transplantation to vaccination was 454 (–90–4740) days. More specifically, it was 583 (107–2880) days for allo-HCT recipients, 1440 (30–4740) days for renal transplant recipients, 339 (–90–1267) days for anti-CD20 treatment recipients and 0 (0–780) days for anti-CD38 treatment recipients. Three of 119 patients who had received anti-CD20 therapy had completed vaccination prior to treatment, while 20 were vaccinated during treatment. Four of the six patients with multiple myeloma were vaccinated during anti-CD38 antibody therapy.

| Characteristics | Patients | Control |
|----------------|----------|---------|
| median (range) of age (years old) | 66 (20–91) | 36 (24–60) |
| female (%) | 76 (40.1) | 37 (56.1) |
| anti CD20 therapy | n = 119 | n = 119 |
| underlying disease | | |
| non-Hodgkin lymphoma | n = 115 | |
| autoimmune thrombocytopenia | n = 4 | |
| anti CD38 therapy | n = 6 | |
| underlying disease | | |
| multiple myeloma | n = 6 | |
| hematopoietic cell transplant recipient | n = 23 | |
| underlying disease | | |
| acute or chronic leukemia | n = 10 | |
| malignant lymphoma | n = 5 | |
| other myeloid malignancy | n = 7 | |
| allograft source | | |
| adult bone marrow | n = 17 | |
| cord blood | n = 6 | |
| kidney transplant recipient | n = 39 | |
| underlying disease | | |
| IgA nephropathy | n = 11 | |
| renal sclerosis | n = 6 | |
| diabetic nephropathy | n = 3 | |
| nephritis including lupus nephritis | n = 6 | |
| congenital disorders | n = 5 | |
| BNT162b2 (Pfizer) | n = 187 | n = 66 |

3.3. Neutralizing antibody titers

The neutralizing antibody (NA) titers are summarized in Fig. 1. The median (range) NA titer at the early phase was 4840 (474–27,800) AU/mL in the control group and 322.5 (6.8–57,100) AU/mL in the patient group, with the patient group showing a significantly inferior NA titer (p = 1.44E-10) (Fig. 1a). The median (range) NA titer at the late phase was 1080 (218 to 4000) AU/mL in the control group and 141 (6.8–3690) AU/mL in the patient group, and the difference was statistically significant (p = 3.25×10^{-7}) (Fig. 1b). More specifically, patients who had received renal transplantation (p = 5.73×10^{-3}) or anti-CD20 antibody therapy (p = 1.75×10^{-6}) or anti-CD38 antibody therapy (p = 3.55×10^{-3}) showed significantly inferior NA responses in comparison to the control group in the early phase, while a significant difference was not observed between the allo-HCT group and the control group (p = 1.00) (Fig. 1c). The significantly inferior serological response among patients who had received renal transplantation (p = 7.98×10^{-4}) and anti-CD20 antibody therapy (p = 9.85×10^{-4}) in comparison to the control group was also reiterated in the late phase (Fig. 1d).

The lower serological response of patients varied between the subgroups (p = 5.56×10^{-3}). Those with allo-HCT showed superior humoral responses to the renal transplantation subgroup (p = 1.51×10^{-4}) and the anti-CD20 antibody therapy subgroup (p = 4.4×10^{-3}) at the early phase (Fig. 1c). These significant differences among patient subgroups were not observed in the late phase (Fig. 1d).

A comparative analysis of the interval between the recent treatment/transplantation and vaccination shows that the serological response was poorer if patients were vaccinated within 300 days after the last treatment/transplantation (p = 9.35×10^{-11}) (Fig. 2). Specifically, among those who had received anti-CD20 therapy, the humoral response in the early phase was significantly lower if the patient was vaccinated within 300 days after treatment (p = 8.0×10^{-4}), while it was not significantly different from that of the control group if the patient was vaccinated >300 days after transplantation (p = 0.197). Among allo-HCT recipients, the humoral response at the early phase was not significantly different with those of control group notwithstanding that the time period between the vaccination and vaccination was within 300 days (p = 0.183) or longer than 300 days (p = 0.852). But among kidney transplant recipients, the humoral response at the early phase was significantly lower in comparison to the control group, whether the period between vaccination and vaccination was within 300 days (p = 0.0181) or longer (p = 1.66×10^{-10}). The serological response did not differ regardless of the WBC levels of the patients at the time of vaccination, while there was a significant difference difference in the lymphocyte level at the time of first vaccination (p = 0.000032).

3.4. COVID-19 infection

None of the patients in our cohort have reported PCR-proven COVID-19 infection as of April 16, 2022. In fact, a total of 7.3 million cases of infection and 28,000 deaths were caused by COVID-19 in Japan. In Nagano Prefecture, where the present study was undertaken, 54,000 patients with COVID-19 infection and 169 deaths [34]. The population of Nagano Prefecture accounts for 2% of the total population of Japan.

3.5. Vaccination safety

Information about adverse events after vaccination were available from n = 42 patients. A total of 33 patients (78.6%) reported any adverse events, including fever (16.7%, CTCAE grade ≤ 2), local pain (54.8%, grade ≤ 1), rash (7.1%, grade ≤ 1) and general fatigue (9.5%, grade ≤ 1). Patients younger than 60 years of age experienced fever more frequently than those over 60 years of age; however, the difference was not statistically significant (p = 0.0635). There were no grade ≥ 3 adverse events. These reported events were not as severe as those described in a previous survey among 19,000 medical personnel
conducted by the Japanese government in September 2021, which reported fever (38.1%), local pain (89.5%), rash (15.9%) and general fatigue (68.8%) as adverse events [34].

4. Discussion

This is a comparative analysis of the humoral response to COVID-19 vaccination among those with different immunocompromising states, including allo-HCT, renal transplantation, anti-CD20 antibody treatment and anti-CD38 antibody treatment. A suboptimal response, in
comparison to healthy controls, was frequently described for each of these groups [19,24,35], but an inter-group comparison, such as the present study, may provide valuable clinical and strategic information for the further stratification of at-risk groups, for identifying patients who require stricter infection control. A suboptimal response in the early phase after COVID-19 vaccination among patients receiving anti-CD20 antibody therapy (rituximab or obinutuzumab) was confirmed in our results. This was consistent with previous studies. However, patients who were vaccinated >300 days after the most recent therapy might be expected to achieve a humoral response that is comparable to that of normal controls, which suggests that a patient may benefit from withholding vaccination for at least 10 months after the recent treatment with anti-CD20 antibody. In fact, three of the patients in our patient cohort had been vaccinated one- to three-months prior to anti-CD20 therapy, and they attained a response comparable to normal controls. Despite the small sample size, this might support a strategic option to vaccinate a patient well before the initiation of anti-CD20 antibody therapy.

Our results also imply an inferior response among anti-CD38 therapy recipients. A negative impact of anti-CD38 therapy on vaccine efficacy was previously described by some studies [29,36,37] and denied by another [38]. However, it may be difficult to draw either conclusion from our results due to the underrepresentation of multiple myeloma in our cohort and because other effects of concomitant treatments, such as immunomodulatory drugs were not analyzed. One of the patients with multiple myeloma in our cohort also had a history of renal transplantation 30 years prior to vaccination and was still on cyclosporin A, despite his obsolete renal function, which may have affected his inferior humoral response after vaccination.

Previous studies demonstrated that an inferior antibody response to vaccination among allo-HCT recipients, the existence of chronic GVHD and immunosuppressive therapy were confounding factors that portend a poorer response [25,26,39]. However, the serological response among allo-HCT recipients in our cohort was less severe and comparable to the control group. The favorable result was consistent, whether the donor source was bone marrow or umbilical cord, and there was no significant difference in titers of the bone marrow and umbilical cord subgroups (p = 0.74). A previous study reported that cord blood transplant recipients and adult donor allograft recipients showed a similar response to protein-conjugated vaccines (e.g., tetanus, diphtheria, pertussis, Hae-
mophilus influenzae, polio, measles, mumps and rubella) [40]. Our result implies that the same is true for RNA vaccines, such as BNT162b2. The favorable response of allo-HCT recipients in our cohort may be due to the low prevalence of patients with immunosuppressant and steroid therapies (Table 2). The serological response may have to be monitored more carefully when an allo-HCT recipient is still on immunosuppressants.

On the other hand, a significantly lower humoral response was observed among kidney transplant recipients. Sattler et al. attributed insufficient immunization among renal transplant recipients to their suppressed humoral and cellular immunity [23]. Although we did not analyze cellular immunity in our study, a higher prevalence (95%) of current immunosuppressive therapy among renal transplant recipients may explain their inferior responses to vaccination. Our results imply that, solid organ transplant recipients, who have to continue immunosuppressant therapy for their lifetime, may be much more vulnerable than allo-HCT recipients, for whom immunosuppressive therapy is likely to be eventually withdrawn. Anti-CD20 antibody therapy recipients should also be considered vulnerable in the period soon after the completion of therapy.

The present study was associated with some limitations, including the fact that we did not analyze the cellular response of the study subjects. Cellular immunity may be highly variable among patients, especially between those with chronic immunosuppression after kidney transplantation and patients with immunological reconstitution after allo-HCT. It is, however, widely accepted that the humoral response is a predictor of vaccine effects, especially in immunocompromised patients [36]. Thus, our results, which are based on a direct comparison of the humoral response between these patient groups, may still be valid.

While multiple studies on third vaccination have been performed [41–43], our results may help clinicians identify individuals with greater vulnerability in this pandemic, and may contribute to a discussion among policy makers on the allocation of resources, including the subsequent series of vaccines. A risk-adopted approach may be warranted for more efficient vaccination. In addition, the NA titer that we utilized in the present study is only a surrogate marker of immunization and no threshold has been established for protective immunity [24]. Beyond the present study, there may be a question about the type of humoral and cellular immune response required for clinical protection against COVID-19 infection, and which test systems provide most relevant information for these groups of patients.

In summary, patients who had recently received anti-CD20 therapy showed suboptimal humoral responses to the BNT162b2 vaccine; however, their responses were less severe in comparison to renal transplants. Allo-HCT recipients are expected to have an optimal response if they stop immunosuppressive therapies.

### Authorship contributions

Conceptualization by HN; Data curation by HN, KS, YS, RI, HS, SN, TK, FK, SM, TI, MK, TU, AU, SK, HT and FJ; Visualization by HN and KS; Writing-original draft by HN and KS; Writing-review by HN. HK and KS equally contributed as first authors.

### Conflict of interest disclosures

The authors declare no competing financial interests.

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### Table 2

| Prednisolone and Immunosuppressive Therapies | n | Prednisolone (mg/day) | Number of other immunosuppressants |
|--------------------------------------------|---|----------------------|-----------------------------------|
| allogenic transplantation                   | 23 | 22 | 0 | 1 | 15 | 8 | 0 | 0 |
| kidney transplantation                      | 39 | 4 | 13 | 22 | 2 | 0 | 35 | 2 |
| anti-CD20 antibody therapy                 | 119 | 119 | 0 | 0 | 119 | 0 | 0 | 0 |
| anti-CD38 antibody therapy                 | 6 | 1 | 0 | 5 | 5 | 1** | 0 | 0 |

** Patients were treated dexamethasone-containing regimen.

† One patient had a history of renal transplantation 30 years ago, and was now on hemodialysis.
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