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CORRESPONDENCE

Shorter duration of protection and lower geometric mean titers against A/H3N2 antigen of the quadrivalent influenza vaccine in children post-allogeneic hematopoietic stem cell transplantation

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TO THE EDITOR:

Children that have undergone hematopoietic stem cell transplantation (HSCT) are at a higher risk for complications from influenza and progression to severe disease [1]. Therefore, influenza vaccines are recommended starting post-transplant 6 months [2]. Previous studies have shown lower prevalence and hospital admission rates in post-HSCT adults immunized with the influenza vaccine compared to those unimmunized [3]. Although there is a lack of data on children that have undergone HSCT, one study showed superior serologic response compared to age-matched controls for all vaccine strains [4]. However, there remains a paucity of data on the effectiveness and duration of seroprotection of the influenza vaccine in children, especially those that have undergone HSCT or chemotherapy. Therefore, the primary aim of this study was to investigate immunogenicity and duration of seroprotection in children that have undergone HSCT compared to those that received chemotherapy and healthy age-matched controls.

We conducted a prospective study of patients below 18 years old that received HSCT or chemotherapy at the pediatric bone marrow center of Seoul St. Mary's hospital, South Korea. An age-matched control group of healthy subjects without any underlying immunocompromising disease or immunosuppressants and immunomodulator use within 4 weeks prior to vaccine administration were included. Participants below 18 years of age received either one dose or 2 doses of the quadrivalent influenza vaccine administered at least 4 weeks apart according the appropriate schedule for children during the 2020–2021 influenza season from October 2020 to January 2021 [5].

The inclusion criteria for the HSCT group were as follows: 1) received HSCT for underlying malignancy or primary immune deficiency, and 2) received the influenza vaccine at least 6 months post-transplant. For the chemotherapy group: 1) received chemotherapy for underlying malignancy, 2) 1st influenza vaccine after initiating chemotherapy, and 3) non-neutropenic at the time of influenza vaccination.

The Institutional Review Board of the Catholic University of Korea Seoul St. Mary's Hospital approved this study (IRB No. KT21TASI0182). All study participants and/or their legal guardians signed informed consent forms prior to the enrollment in this study.

The types of quadrivalent seasonal vaccines administered to the patients are on Supplementary Table 1, and influenza virus strains included in vaccines during the 2020–2021 Influenza season are on Supplementary Table 2.

Hemagglutination inhibition (HI) assay was performed according to the WHO manual [6]. Seropositive or seroprotection in an individual was defined as a post vaccination HI titer of ≥1:40. The seroprotection rate (SPR) was defined as the percentage of subjects with a post vaccination titer of ≥1:40. The HI antibody responses were described as geometric mean titers (GMT) and their 95% confidence intervals (CI) were calculated.

The chi square test was used to compare categorical variables. The Kruskal-Wallis One-Way ANOVA was used to determine any statistically significant differences in continuous variables between the three groups. The Mann-Whitney U test was used to compare the differences in the duration of antibody response within the groups, 3–6 months versus 7–8 months. All tests were two sided, and statistical significance was defined as $P < 0.05$.

A total of 77 study participants (control group, $n = 20$; chemotherapy group, $n = 24$; HSCT group, $n = 33$) were included in the study, and the median age of the patients was 8.9 (6.0–12.7) years old (Supplementary Table 3). According to the timing of blood sampling after vaccination, patients were categorized into the 3–6-month group or 7–8-month group (Supplementary Fig.). None of the study participants were confirmed with or had any flu-like symptoms prior to sampling (Supplementary Table 3).

None of the study participants in the control group had any underlying immunocompromising diseases, and all received blood sampling during routine follow up at the growth clinic. The underlying diseases of the patients are listed on Supplementary Table 4. The median interval of influenza vaccination after graft infusion of patients that received their first influenza vaccination post-HSCT ($n = 23/33$) was 17.8 months (IQR, 13.9–22.7 months), and 18.2% ($n = 6/33$) were on immunosuppressants when influenza vaccine was administered (Supplementary Table 5).

The SPR was found for each of the four antigens within the quadrivalent vaccine at 3–6 months versus 7–8 months post-vaccination in each group (Fig. 1a). Compared to the control group, no statistically significant difference in the SPR was observed in patients that received chemotherapy or HSCT except for in A/H3N2, where subjects in the HSCT group that received their 1st influenza vaccination post-HSCT had a significantly lower SPR at 7–8 months post-vaccination compared to the control group (50% vs. 100%, $P = 0.006$, respectively). Across all three groups, the SPR at 3–6 months and 7–8 months against both B strains were below 62%. Also, a trend towards lower SPR was observed in the HSCT group at 7–8 months post vaccination for B/

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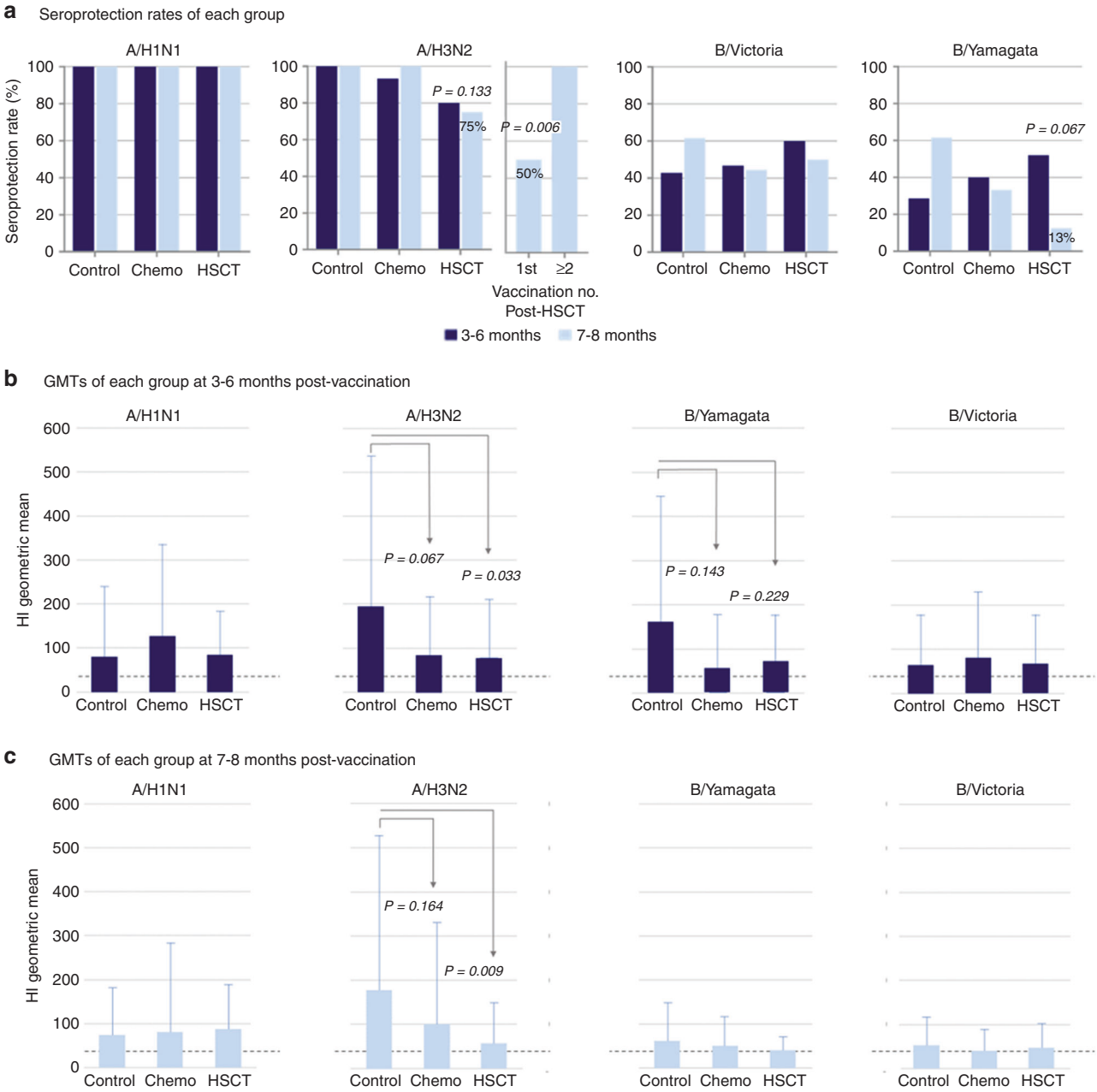

Fig. 1 Comparison of the seroprotection rates and geometric mean titers of the patients included in this study. (**a**) Seroprotection rate (SPR) (%) of the subjects in each group with a post vaccination titer of ≥1:40 for A/H1N1, A/H3N2, A/H3N2 (including subgroup analysis of patients that received their 1st influenza vaccination post-HSCT), B/Victoria, and B/Yamagata antigens at 3–6 months versus 7–8 months post-vaccination. Compared to the control group, no statistically significant difference in the SPR was observed in patients that received chemotherapy or HSCT except for A/H3N2, where subjects in the HSCT group that received their 1st influenza vaccination post-HSCT had a significantly lower SPR at 7–8 months post-vaccination compared to the control group. A trend towards lower SPR was observed in the HSCT group at 7–8 months post vaccination for B/Yamagata compared to the control group. (**b**), (**c**) Median HI response presented as GMT (+95% CI) of the seropositive samples (≥1:40) according to sampling time in each group. For A/H1N1, B/Victoria, and B/Yamagata, there were no significant differences in the GMT between the control, chemotherapy, and HSCT groups at (**b**) 3–6 months post-vaccination as well as (**c**) 7–8 months post-vaccination. However, for A/H3N2, at (**b**) 3–6 months post-vaccination, the GMT was lower in the HSCT group compared to the control group, as well as at (**c**) 7–8 months post-vaccination. To comply with licensure criteria (EMA CHMP, CBER) for CHMP the seroprotection rate must be >70%. CBER Center for Biologics Evaluation and Research, CHMP Committee for Medicinal Products for Human Use, CI Confidence interval, EMA European Medicines Agency's, GMT geometric mean titer, HI hemagglutination inhibition, HSCT Hematopoietic stem cell transplantation.

Yamagata compared to the control group (62% vs. 13%, $P = 0.067$, respectively).

The neutralizing GMT of the HI antibody response to the four antigens in seropositive subjects were compared between the groups at 3–6 months (Fig. 1b) and 7–8 months (Fig. 1c) post-vaccination. For A/H1N1, B/Victoria, and B/Yamagata, there were no significant differences in the GMT between the control, chemotherapy, and HSCT groups at 3–6 months post-vaccination as well as 7–8 months post-vaccination. However, for A/H3N2, at 3–6 months post-vaccination, the GMT was lower in

the HSCT group (77.63; 95% CI, 40.0–209.7) compared to the control group (195.0; 95% CI, 40.0–539.9) ($P = 0.033$), as well as at 7–8 months post-vaccination (HSCT group, 56.6; 95% CI, 40.0–146.7 vs control group, 178.0; 95% CI, 40.0–530.7) ($P = 0.009$). The chemotherapy group showed a trend towards a lower GMT (84.1; 95% CI, 40.0–216.0) compared to the control group (195.0; 95% CI, 40.0–539.9) ($P = 0.067$) at 3–6 months post-vaccination.

There is currently a lack of data on the immunogenicity, effectiveness, and duration of seroprotection of the quadrivalent influenza vaccine in children, especially those that have undergone HSCT. This study found that the control, chemotherapy, and HSCT group all had 100% SPRs for the A/H1N1 antigen up to 7–8 months post-vaccination. However, patients that received their first influenza vaccination after HSCT showed shorter duration of protection against A/H3N2, as only 50% of the recipients were seropositive after 6 months of vaccination (Fig. 1a). Also, the HI response of patients that received HSCT, regardless of previous influenza vaccination history, had lower HI GMTs compared to the control group at 3–6 months ($P = 0.033$) (Fig. 1b) and 7–8 months ($P = 0.009$) (Fig. 1c) post-vaccination for A/H3N2.

Observational studies have shown low vaccine effectiveness for the B lineages, even in immunocompetent subjects [7, 8]. Another study on children showed that in children aged 6 months to 3 years, post-vaccination SPR against B/Yamagata was 63.1% and 49.5% for B/Victoria, failing to meet the Korea Ministry of Food & Drug Safety (MFDS) standard of 70% [9]. Our study showed similar results, with study participants in all three groups showing below 60% SPRs at 3–6 months for B/Victoria and below 52% at 3–6 months for B/Yamagata.

There were several limitations in this study. The pre-vaccination HI titers were unavailable; therefore, the seroconversion rates could not be determined. However, none of the patients in the HSCT group received the influenza vaccine during the prior influenza season, therefore, patients in this group were most likely seronegative for the four antigens included in the quadrivalent influenza vaccine. Second, none of the patients in this study were infected with influenza during the 2020–2021 Influenza season regardless of low GMTs against vaccine strains, largely due to the missed influenza seasonal outbreak during 2020–2021 in South Korea because of social distancing and mandatory mask wearing in public as infection control precautions during the COVID-19 pandemic.

To conclude, children that received their first influenza vaccine after HSCT had a shorter duration of seroprotection against A/H3N2. The GMTs against A/H3N2 was lower in the HSCT group compared to the control group at 3–6 months and 7–8 months post-vaccination. There were no significant differences in the immunogenicity or duration of seroprotection against A/H1N1 and B lineages in children that underwent HSCT or chemotherapy compared to children without underlying diseases. The overall SPR and HI GMT against B lineages were low across all three groups. Solutions such as higher vaccine doses, 2-dose protocols, different adjuvants, etc. are imperative in improving the overall immunogenicity to better prevent Influenza in children, especially those immunocompromised.

Kyu Ri Kang[1], Ye Ji Kim[1,2], Moon Bae Ahn[2], Hyun Mi Kang[1,2]✉, Seong Koo Kim[2], Jae Wook Lee[2], Nack-Gyun Chung[2], Bin Cho[2], Dae Chul Jeong[2] and Jin Han Kang[1,2]
[1]*Vaccine Bio Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.* [2]*Department of Pediatrics, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.* ✉*email: pedhmk@catholic.ac.kr*

DATA AVAILABILITY

The hemagglutination inhibition assay titers (raw data) are available on Supplementary Table 5.

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AUTHOR CONTRIBUTIONS

HMK designed the study. KRK conducted the experiments. HMK analyzed the data. KRK, YJK, MBA, HMK, SKK, JWL, N-GC, BC, DCJ and JHK collected and retrieved the data. HMK, KRK and JHK wrote the manuscript. KRK, YJK, MBA, HMK, SKK, JWL, N-GC, BC, DCJ and JHK read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

The study was conducted in accordance with the Declaration of Helsinki.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41409-022-01768-6.

Correspondence and requests for materials should be addressed to Hyun Mi Kang.

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