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COMMENTARY

mRNA-1273 SARS-CoV-2 vaccine safety and COVID-19 risk perception in recently transplanted allogeneic hematopoietic stem cell transplant recipients

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Abstract

Purpose This study aims to describe the incidence and severity of adverse events (AEs) following the mRNA-1273 SARS-CoV-2 vaccine and explore the risk perception of COVID-19 in allogeneic hematopoietic stem cell transplant (HCT) recipients.

Methods We performed a single-center prospective study including recently transplanted (< 2 years post-infusion) allogeneic HCT recipients. AEs were assessed through phone calls and graded from 0 to 4, while COVID-19 risk perception was measured using the Brief Illness Perception Questionnaire (BIP-Q5).

Results Fifty-four HCT recipients were evaluated. Incidence and grades of AE (94.4% and 85.2% after the first and second dose, respectively) were similar to those described in the general population. The most common AE was pain at the site of injection. Three patients (5.6%) developed a grade ≥ 3 AE. Vaccine-related cytopenias and graft-versus-host disease flares were not observed. Female sex (OR 3.94, 95% CI 1.14–13.58, $p = 0.03$) and time since HCT (per month since HCT: OR 1.09, 95% CI 1.01–1.18, $p = 0.04$) were associated with the occurrence of any AE. The patients' risk perception level of COVID-19 decreased over time ($p < 0.05$).

Conclusion Our study confirms that the mRNA-1273 SARS-CoV-2 vaccine is safe in recent HCT recipients and suggests that the perceived risk of COVID-19 decreases over time.

Keywords mRNA-1273 · COVID-19 · Adverse events · Risk perception · Allogeneic stem cell transplantation

Introduction

Allogeneic hematopoietic stem cell transplant (HCT) recipients are at increased risk of severe COVID-19 and complications, including psychologic distress [1–4]. There is limited data on specific side effects. We examined the safety of the SARS-CoV-2 Spikevax vaccine and COVID-19 risk perception in recently transplanted HCT recipients.

Methods

This single-center, prospective and observational study (IIBSP-COV-2021–43) included adult allogeneic HCT recipients between 3 and 26 months after their stem cell infusion date ("recently transplanted"). All patients received

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the mRNA-1273 vaccine (Spikevax) and were fluent in Spanish. Those receiving chemotherapy were excluded.

Patients completed a standardized phone survey 72 h to 7 days after each vaccine dose. Vaccine adverse events (AEs) were classified according to Baden et al. (graded 0–4) [5]. Disease risk perception was examined with the Brief Illness Perception Questionnaire (BIP-Q5), which consists of five items with a maximum total score of 50. The BIP-Q5 was validated in Spaniards during the COVID-19 pandemic [6].

Statistical analysis was performed using SPSS v. 25. Alpha = 0.05 was set for all statistics. Wilcoxon's test was used for time-paired comparisons. A one-half-standard deviation was used to indicate clinically significant differences [7]. Correlations were performed with Pearson and Spearman tests; significant variables ($p < 0.05$) were entered in the multivariable models. Multivariable stepwise logistic and linear regression were performed to examine variables associated with AE degree and COVID-19 risk perception.

Results

From March to August 2021, 54 patients were evaluated. The median age was 53.5 years (range 25–73) and 48.1% were women. The median time from HCT to the first vaccine dose was 13 months (range 3–26). Forty patients (74%) were on active immunosuppression and 19 (35.2%) and 10 (18.5%) had prior acute and chronic graft-versus-host disease (GVHD), respectively. Five patients (9.3%) had suffered COVID-19 and 15 (27.8%) had a first-degree relative with COVID-19.

Vaccine safety data

Figure 1 shows AE incidences. Nearly all patients developed at least one AE: 94.4% with the first and 85.2% with the second dose. Pain at the site of injection was the most common AE (92.6% and 85.2% of patients after first and second doses). Systemic AEs were more frequent and severe after the second dose ($p = 0.007$) (Fig. 1).

Only three (5.6%) patients had grade 3 fatigue and/or chills, which occurred after the second dose. No serious AEs requiring hospitalization (i.e., grade 4) occurred. No new-onset GVHD, GVHD flares, graft dysfunction, or immune-mediated cytopenias were documented.

Female sex was significantly associated with a higher rate of overall AEs after the first dose (OR 3.94, 95% CI 1.14–13.58, $p = 0.03$). Time from HCT was associated with a higher rate of systemic AEs after the second dose (OR 1.09, 95% CI 1.01–1.18, $p = 0.04$), especially due to higher rates of chills (OR 1.15, 95% CI 1.01–1.31, $p = 0.04$). Systemic AEs were more common as the time interval since HCT increased. Having had prior COVID-19 correlated with the development of fever after the second dose (OR 10.22, 95% CI 1.21–86.59, $p = 0.03$).

Age, graft source, donor type, donor age, number of $CD34^+$ cells infused, conditioning type, GVHD prophylaxis, disease type and status, GVHD, immunosuppression, T-cell chimerism, and total lymphocyte, $CD4^+$, $CD8^+$, and

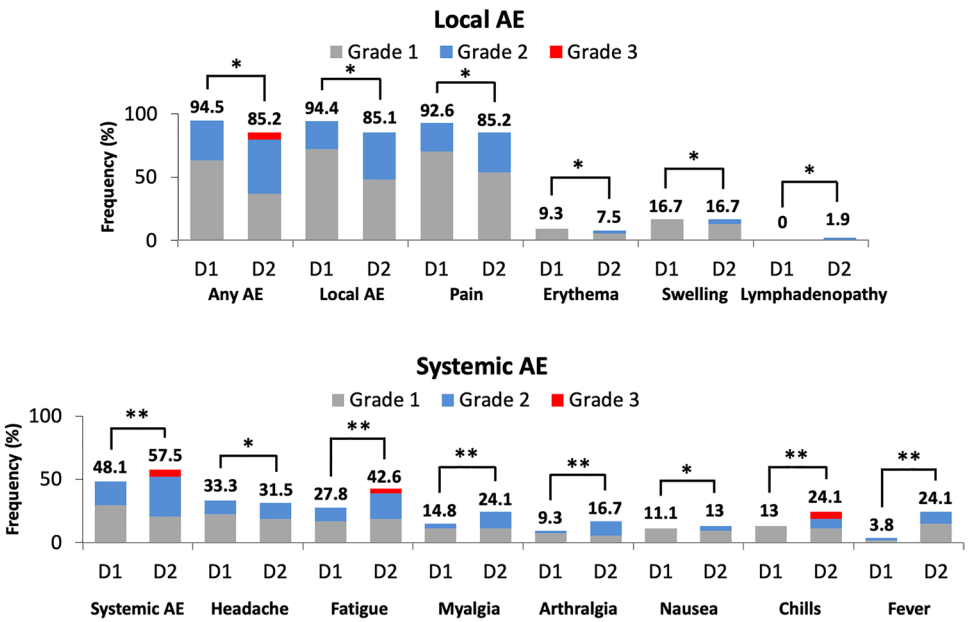

Fig. 1 Adverse event (AE) incidence and severity for doses 1 (D1) and 2 (D2). *Non-significant. **Significant differences between the distribution of medians ($p < 0.05$ in Wilcoxon's test)

$CD19^+$ lymphocyte counts and level of IgG had no apparent impact on the occurrence or severity of any AE.

Risk perception

COVID-19 risk perception tended to decrease over time (first dose: mean = 29.43, SD = 9.35; second dose: mean = 28.05, SD = 10.07) ($p = 0.077$). A post hoc exploratory analysis of the BIP-Q5 items revealed that, at the time of the second dose, patients perceived that the end of the pandemic was closer (first dose: mean = 7.07, SD = 2.06; second dose: mean = 6.11, SD = 2.67) ($p < 0.0001$) and reported being less concerned about COVID-19 than before vaccination (first dose: mean = 7.91, SD = 2.16; second dose: mean = 7.11, SD = 2.69) ($p = 0.012$). Both differences were also clinically significant ($p < 0.05$). Females ($r = 0.42$, $p < 0.001$), patients receiving myeloablative conditioning ($r = -0.300$, $p = 0.027$), post-transplant cyclophosphamide-based GVHD prophylaxis ($r = -0.371$, $p = 0.006$), having lower absolute neutrophil counts ($r = -0.288$, $p = 0.034$), prior acute GVHD ($r = -0.355$, $p = 0.008$), and having a relative with COVID-19 ($r = 0.285$, $p = 0.036$) were significantly associated with greater COVID-19 risk perception. None of these variables retained their significance in multivariable analysis (data not shown).

Discussion

The observed side effects of the mRNA-1273 SARS-CoV-2 vaccine in recent HCT recipients appear similar to those in the general population. Prior studies in HCT recipients with somewhat different characteristics, such as age, time from HCT, immunosuppression, or vaccine type, have reported variable incidence and severity of AE following SARS-CoV-2 mRNA vaccination [8–10]. In our series, systemic AEs were more frequent and severe after the second dose, which was also in line with that observed in the general population [5]. We found no new-onset cytopenias nor GVHD flares after vaccination. Contrarily, other groups have reported these complications in around 10% of patients [9].

A recent publication examined another mRNA vaccine (BNT163b2) in "long-term" HCT recipients and showed lower-than-expected AE incidence and severity [11]. Thus, time since HCT may have a strong impact on the occurrence of AEs. Prior COVID-19 and female sex were two other variables that led to higher rates of AE in our study and which have also been reported in large studies in the general population [12].

Our study is the first to report COVID-19 risk perception in HCT recipients. Patients reported lower disease risk perception over time, which may be due to a myriad of factors, including SARS-CoV-2 vaccination and changes in COVID-19 incidence rates in our city. Appropriate reductions in disease risk perception have been associated with precautionary behaviors [13], all of which may have contributed to managing the COVID-19 hazard and related restrictions [14, 15]. Despite some patient characteristics being associated with increased COVID-19 risk perception, none predicted risk perception in multivariable analysis. Future studies should evaluate longer periods of follow-up with more determinations of risk perception, and include a control group as well as additional variables, such as patients' psychological symptoms, to further comprehend the role of vaccines and to identify risk factors associated with increased disease risk perception in this population.

Conclusion

Our study suggests a similar incidence and severity of AE in recent HCT recipients compared to the general population with no vaccine-associated cytopenias or GVHD flares. In addition, certain COVID-19 risk perception items decreased over time. Since HCT recipients reported increased distress during the ongoing COVID-19 pandemic [15], further understanding of the factors that predict emotional distress is needed to provide timely manner interventions.

Author contribution NA was responsible for designing and writing the study protocol, writing the main draft, designing and filling the main database, gathering variable data and analyzing them, interpreting results, creating tables and figures, and manufacturing reference lists. OA was responsible for obtaining data and organizing patients' schedules, as well as obtaining written consents. LG-P filled a substantial amount of the database with the gathered data. MT, NR, and EL equally obtained patient and variable data. AE, JS, and RM reviewed and corrected the final form of the manuscript. IG provided infrastructural coordination and freed nurses' schedules to work on the study. JL-C provided vaccination timelines and infrastructure, organized patients' appointments for vaccination, and coordinated the Infectious Diseases Department with ours. RM also gave feedback on the study design and methods and contributed to the interpretation of the results. IG-C was responsible for designing and writing the study protocol, contributing to structuration, designing and writing the main draft as well as correcting the final form, obtaining ethics committee approval, obtaining financial support, gathering the research team, identifying the population of the study, obtaining patients' data, interpreting results, and eventually coordinating the study overall.

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Data availability We declare that the analyzed data is original and available on request.

Declarations

Ethics approval The study was performed in accordance with the Declaration of Helsinki and was approved by the IIB Sant Pau ethics committee.

Consent to participate All participants signed the informed consent.

Conflict of interest AB: Stocks in Grifols, Almirall. Other authors declare no competing financial interests.

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