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LETTER TO THE EDITOR

# Antibody responses to SARS-CoV-2 vaccination in patients with acute myeloid leukaemia and high risk MDS on active anti-cancer therapies

To the editor,

Encouraging seroconversion rates to SARS-CoV-2 vaccination in acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) patients have been reported in large cohort studies[1–4]; however, the majority of these patients were not receiving active systemic anti-cancer therapy (SACT) and its impact on vaccine responses remains to be fully elucidated. Mori et al.[5] report seroconversion rates of 94.7 and 100% respectively in Japanese patients with AML and MDS after two doses of mRNA SARS-CoV-2 vaccine, of which 39% received SACT. We report SARS-CoV-2 antibody responses following vaccination in a UK cohort of AML and HR-MDS patients all receiving, or having recently completed SACT, and stratified by prior SARS-CoV-2 infection. Demographics, SACT history and laboratory parameters were collected from the electronic health records of patients following two doses of SARS-CoV-2 vaccine (BNT162b2 or ChAdOx1nCoV-19) between December 2020 and July 2021. Serological testing was performed using Roche Elecsys anti-SARS-CoV-2 enzyme immunoassays. A total of 39 patients (85% AML, 15% HR-MDS, median age 63 [21–76]), underwent serological testing after receiving two doses of vaccine (Table 1). All were tested for anti-S antibodies after two doses (median 40 days post-dose) and 59% after the first dose (median 39 days). Thirty-three patients (85%) underwent testing for anti-N antibodies, and seven (21% of those tested) had previous SARS-CoV-2 infection. Eleven patients (28%) received intensive chemotherapy, 51% venetoclax-combination therapy (with azacitidine, low-dose cytarabine or gilteritinib) and 21% non-intensive azacitidine. Seropositivity rates and antibody titres increased with consecutive vaccine doses, from 74% in all patients (75% AML, 67% MDS) to 95% (94% AML, 100% MDS), with a median anti-S titre of 5.90 U/ml (IQR 0.58–56.7) after dose one, rising to 333 U/ml (IQR 86.8–1971) post dose two. Significantly higher titres were detected after dose two in AML patients, but not in MDS, though numbers are small (Figure 1B). We report similar seroconversion rates following two doses as seen by Mori et al. (Figure 1A, Table 1), despite all our patients receiving SACT compared to 39% of their cohort; however, we found no difference in anti-S titres between AML and HR-MDS patients receiving SACT after two vaccine doses (333 iu/ml [IQR 105.9–1896] vs. 495.9 iu/ml [IQR 82.15–2320], $p = 0.99$). These patterns persisted in patients with no prior SARS-CoV-2 infection and negative anti-N serology (Figures 1C,D and S1, Table 1), although seroconversion rates and median anti-S titres were somewhat reduced. Previous SARS-CoV-2 infection was associated with higher titres after two vaccinations (median 2500 U/ml [IQR 141–2500]), consistent with higher post-vaccination antibody titres in healthy individuals with prior natural infection.[6,7] This highlights the importance of measuring antibody titres, as opposed to seropositivity alone, and considering prior SARS-CoV-2 infection to delineate vaccine responses. Mori et al. reported lower antibody titres after two doses in those AML/MDS patients receiving active SACT as treatment or maintenance therapy (the majority received HMA) compared to those receiving non-chemotherapeutic treatments or completed treatment.[5] We observed that no significant difference in seropositivity or anti-S titres was seen in AML patients receiving intensive (28%) compared to non-intensive chemotherapy (21%); however, anti-S titres were significantly reduced in venetoclax-based regimens (55% AML patients, 33% HR-MDS, median 158.5 U/ml [IQR 34.85–873], $p = 0.04$), independent of previous SARS-CoV-2 infection (Figure 1E,F). Reduced serological responses in patients receiving venetoclax have been previously reported in mature B cell neoplasms and myeloma, but not in AML or MDS.[3,8,9] Further studies to define the impact of SACT regimens on the magnitude/duration of humoral and T cell responses to SARS-CoV-2 vaccination will have clear implications for this vulnerable group and should be priority questions for larger studies.

## AUTHOR CONTRIBUTIONS

Jenny O'Nions conceived of the study, performed data collection, data analysis, literature search, and manuscript writing and revision; Wei Yee Chan data collection, data analysis, manuscript writing, and revision; Catherine Zhu performed data collection, manuscript review and revision; Elspeth M. Payne conceived of study, manuscript review and revision; Emilie Sanchez data collection, manuscript review and revision; Adele K. Fielding, Asim Khwaja, Rajeev Gupta, manuscript review and revision.

**TABLE 1** Patient demographics, disease and treatment characteristics

| Characteristics | All patients *n* = 39 | AML *n* = 33 | HR-MDS *n* = 6 | Negative baseline *n* = 26 | Positive baseline *n* = 7 |
|---|---|---|---|---|---|
| Gender (% male) | 21 (54) | 17 (52) | 4 (67) | 13 (50) | 3 (43) |
| Median age [range] | 63 [21–76] | 58 [21–76] | 70 [50–76] | 60 [21–76] | 47 [22–73] |
| Diagnosis (%) | | | | | |
| AML | 33 (85) | 33 (100) | – | 22 (85) | 6 (86) |
| HR MDS | 6 (15) | – | 6 (100) | 4 (15) | 1 (14) |
| SARS-CoV-2 infection[a] (%) | 7/33 (21) | 6/28 (21) | 1/5 (20) | – | – |
| Treatment (%) | | | | | |
| Intensive AML chemotherapy | 11 (28) | 11 (33) | 0 (0) | 8 (31) | 3 (27) |
| Venetoclax based regimens | 20 (51) | 18 (55) | 2 (33) | 12 (34) | 3 (27) |
| Ven and Aza | 16 | 14 | 2 | 10 | 2 |
| Ven and LDAC | 2 | 2 | – | 1 | 0 |
| Ven and Gilt | 1 | 1 | – | 1 | 0 |
| Ven, Gilt and Aza | 1 | 1 | – | 0 | 1 |
| Azacitidine therapy | 8 (21) | 4 (12) | 4 (67) | 6 (23) | 1 (10) |
| Seropositive[b], 1 dose (%) | 17/23 (74) | 15/20 (75) | 2/3 (67) | 10/13 (77) | 6/7 (86) |
| Seropositive[b], 2 doses (%) | 37/39 (95) | 31/33 (94) | 6/6 (100) | 25/26 (96) | 6/7 (86) |
| Seroconversion[c] post 2 doses (%) | 25/26 (96) | 21/22 (95) | 4/4 (100) | 25/26 (96) | – |
| Vaccine type (%) | | | | | |
| BNT162b2 | 26 (67) | 21 (64) | 5 (83) | 16 (62) | 7 (100) |
| ChAdOx1 nCoV-19 | 8 (21) | 7 (21) | 1 (17) | 6 (23) | 0 (0) |
| Unknown | 5 (13) | 5 (15) | 0 (0) | 4 (15) | 0 (0) |
| Median time (days) from first dose to serology [range] | 39 [24–79] | 35 [24–79] | 42 [31–68] | 31 [24–79] | 44 [29–68] |
| Median time (days) from second dose to serology [range] | 40 [13–133] | 40 [13–133] | 51.5 [29–78] | 40 [13–133] | 41 [15–72] |
| Median titres post first dose in all patients U/ml (IQR) | 5.90 U/ml (0.58–56.70) | 5.395 U/ml (0.64–49.85) | 220 U/ml (0.4–2500) | 5.90 U/ml (0.62–38.35) | 1412 U/ml (2.2–2500) |
| Median titres post first dose in patients with negative baseline U/ml (IQR) | 5.90 U/ml (0.62–38.35) | 4.43 U/ml (0.51–19.50) | 130.1 U/ml (40.2–220) | – | – |
| Median titres post second dose in all patients U/ml (IQR) | 333 U/ml (86.80–1971) | 333 U/ml (105.9–1896) | 495.9 U/ml (82.15–2320) | 235 U/ml (82.15–1670) | 2500 U/ml (141–2500) |
| Median titres post second dose in patients with negative baseline U/ml (IQR) | 235 U/ml (82.15–1670) | 235 U/ml (81.65–1670) | 494.6 U/ml (78.25–1921) | – | – |

*Note*: Patients received two doses of SARS-CoV-2 vaccine, with 8–12 weeks between doses as per UK vaccination programme. All patients consented for excess serum to be stored and used as part of the "UCL Biobank for Studying Health and Disease – Haematology Project", reference no. NC10.13.

Abbreviations: AML, acute myeloid leukaemia; Aza, azacitidine; Gilt, gilteritinib; HR-MDS, high risk MDS; LDAC, low dose cytarabine; Ven, venetoclax.

[a]SARS-CoV-2 infection defined by presence of anti-N (nucleocapsid) antibodies.

[b]SARS-CoV-2 seropositive defined by presence of anti-S (Spike) antibodies.

[c]Seroconversion defined by the detection of anti-S antibodies in patients who had previously undetectable anti-S antibodies.

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## CONFLICT OF INTEREST

All authors declare no conflicts of interest.

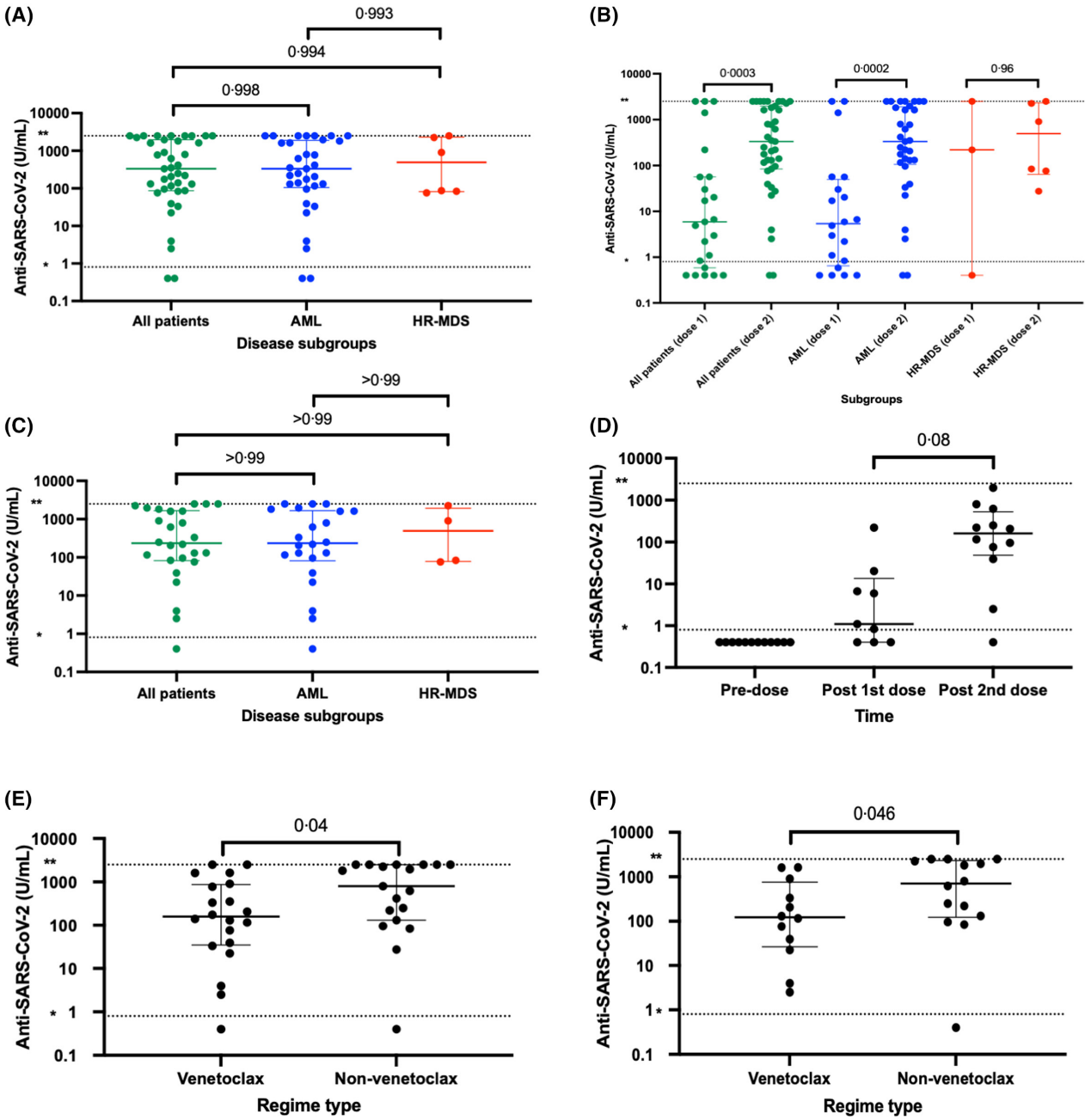


**FIGURE 1** Serological responses in patients with AML and HR-MDS after SARS-CoV-2 vaccination. All figures are presented with a Log10 scale on the y-axis. *lower limit of assay, **upper limit of assay, HR-MDS high risk MDS. (A) Seropositivity for anti-S antibodies in all patients following two doses of SARS-CoV-2 vaccine, categorized by disease subtype. (B) Anti-S antibody titres following the first and second vaccine doses by disease category. (C) Serological response to two vaccination doses in patients with no previous SARS-CoV-2 infection. (D) Seroconversion rates in patients with no previous SARS-CoV-2 infection, after one and two doses of vaccine (paired predose, post first dose and second dose) in all patients. (E) Serological response following two doses of vaccine in all patients treated with venetoclax-based regimens. (F) Serological response following two doses of vaccine in AML/HR-MDS treated with venetoclax-based regimens and no evidence of previous SARS-CoV-2 infection. [Colour figure can be viewed at wileyonlinelibrary.com]

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