RESEARCH LETTER

blood advances

TO THE EDITOR:

Even after SARS-CoV-2 booster, there is increased COVID-19 breakthrough infection in patients with plasma cell disorders

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Patients with multiple myeloma (MM) face elevated risk of experiencing serious complications from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) because of immune deficiencies from myeloma and immunosuppressive treatments.[1] Despite SARS-CoV-2 vaccination being an effective approach in the general population, we previously found that patients with MM experience significantly higher rates of breakthrough infection and severe coronavirus disease 2019 (COVID-19) after vaccination compared with matched controls without plasma cell neoplasms.[2] With the wide availability of vaccine booster shots, we set out to evaluate the risk of breakthrough infections after vaccine boosting in patients with MM and monoclonal gammopathy of undetermined significance (MGUS) compared with matched patients without plasma cell disorders.

We designed a retrospective matched cohort study using data from the national Veterans Affairs (VA) health care system. Patients with MM or MGUS who were fully boosted were matched 1:1 with fully boosted control individuals without MM or MGUS. Patients were matched on factors potentially associated with SARS-CoV-2 exposure or severity: age, race, VA facility, rurality of home address, and date of full boosting.[2] Each matched pair was followed from the time of full boosting until SARS-CoV-2 infection, death, or end of the study. We used the Fine-Gray subdistribution hazard model to account for the competing risk of death. SARS-CoV-2 infection was laboratory confirmed, and severe COVID-19 was defined as SARS-CoV-2 infection within −1 to 14 days of a documented oxygen saturation of <94% or supplemental oxygen use.[3] Full boosting was defined to start 7 days after receipt of the third dose of a messenger RNA (mRNA)-based vaccine (BNT162b2 or mRNA-1273). Patients who were fully boosted between 1 August 2021 and 22 June 2022 were included. We did not evaluate second or subsequent booster doses, and patients vaccinated with Janssen Ad26.COV2.S or with prior SARS-CoV-2 infection were excluded. Patients with MM were required to have at least 3 MM International Classification of Disease (ICD)–coded visits and have received at least 1 systemic anti-MM treatment before 15 December 2020.[4] Patients with MGUS were required to have at least 3 MGUS ICD-coded visits and to never have had any MM treatment before 15 December 2020. Controls were required to have no ICD codes for MM or MGUS. Information on SARS-CoV-2 vaccination and infection status was obtained from the VA COVID-19 shared data resource. All other data were obtained from the VA Corporate Data Warehouse, which collates electronic health record information from VA facilities nationwide. We filtered for regular users of the VA system, which is defined as those who had at least 1 billable outpatient or inpatient visit every year for 3 years before the study start date, to exclude patients whose data may have been incomplete. This study was approved by the VA Boston Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

We identified 1822 patients with MM and 6971 patients with MGUS who were fully boosted with an mRNA-based vaccine during the study period. Of these, 1706 patients with MM and 6503 patients with MGUS could be fully matched 1:1 with control patients who did not have MM or MGUS. The median

Submitted 28 June 2023; accepted 24 August 2023; prepublished online on *Blood Advances* First Edition 30 August 2023; final version published online 3 November 2023. https://doi.org/10.1182/bloodadvances.2023011063.

age was 73.5 years among patients with MM and 74.9 years among patients with MGUS. Non-Hispanic White individuals comprised the largest percentage of both MM and MGUS cohorts (59.5% and 56.1%, respectively), followed by non-Hispanic Black (30.0% and 33.8%), Hispanic (5.3% and 4.2%), and other/unknown (5.3% and 5.9%) patients. The median follow-up time was 260 days for patients with MM and 225 days for patients with MGUS, and the median date of boosting was 23 September 2021 and 5 November 2021, respectively.

Patients with MM had an increased risk of breakthrough infection after boosting compared with matched controls who were boosted but did not have MM or MGUS (hazard ratio [HR], 2.60; 95% confidence interval [CI], 1.96-3.45; $P < .001$; Figure 1), as did patients with MGUS (HR, 1.90; 95% CI, 1.60-2.25; $P < .001$). Patients with MM also had an increased risk of severe COVID-19 after boosting compared with boosted controls without MM or MGUS (HR, 2.39; 95% CI, 1.33-4.29; $P = .003$); however, patients with MGUS did not (HR, 1.06; 95% CI, 0.75-1.51; $P = .74$). The incidence of breakthrough infections increased in all groups ~3.5 months after the booster, with the highest increase observed among patients with MM, possibly because of waning immunity, the increased prevalence of vaccine-resistant SARS-CoV-2 variants, or a combination thereof (Figure 1).

We also examined the impact of disease control on breakthrough infection. We stratified by complete response or better vs very good partial response or less at the time of boosting and found that there was not a statistically significant increase in breakthrough infection among patients with MM with complete response or better compared with matched controls without MM or MGUS (HR, 1.85; 95% CI, 0.62-5.53; $P = .27$). In contrast, among patients with very good partial response or worse, there is a strong and statistically significant increase in risk (HR, 2.66; 95% CI, 1.98-3.56; $P < .001$). Similarly, we found that patients with MM on single-agent lenalidomide at the time of boosting did not have a statistically significant increased risk of breakthrough infection compared with matched controls without MM or MGUS (HR, 1.28; 95% CI, 0.66-2.47; $P = .46$). We stratified by patient age, aged >65 years and ≤65 years at the time of boosting, and found that patients with MM aged >65 and those aged ≤65 years had similarly increased risk of breakthrough infection compared with matched controls without MM or MGUS, although the increase was slightly higher in those aged >65 years (>65: HR, 2.44;

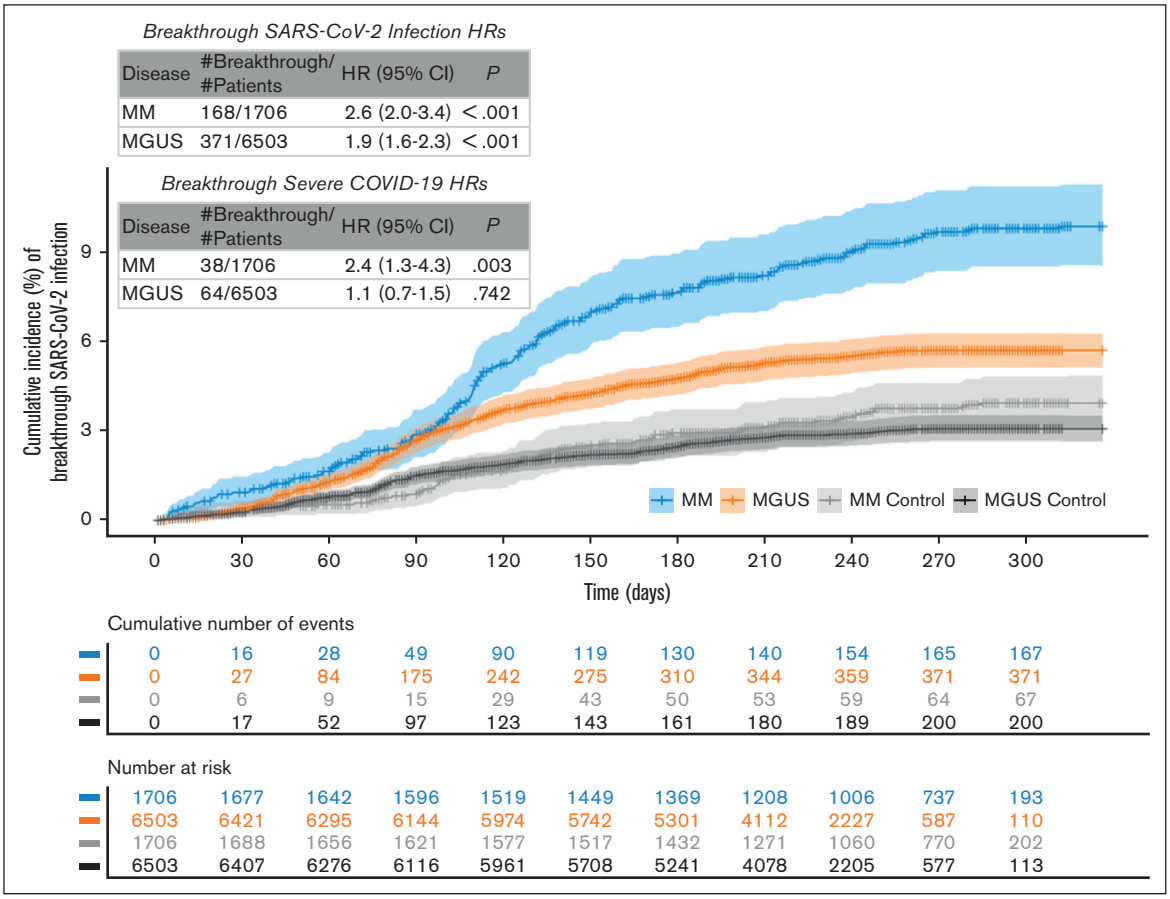

Figure 1. Cumulative incidence of SARS-CoV-2 infection in fully boosted patients with MM or MGUS, and controls. Cumulative incidence curves of breakthrough SARS-COV-2 infection by disease state (MM, MGUS, and their matched controls) are shown, with time 0 set as 14 days after the day of third dose of vaccination. Confidence intervals were calculated by bootstrapping. The number at risk are also shown. The inset tables show HRs for SARS-CoV-2 breakthrough infection and severe COVID-19 in MM and MGUS relative to matched controls.

95% CI, 1.79-3.34; $P < .001$; ≤65: HR, 2.32; 95% CI, 1.14-4.72; $P = .02$).

Given that anti-MM treatment can negatively affect the immune system, we also evaluated the breakthrough risk in patients who had undergone recent treatment (Table 1). Whereas a total of 180 patients with MM (9.9%) experienced a breakthrough infection, patients who had received systemic anti-MM treatment <90 days before receiving a booster experienced more than twice the rate of breakthrough infections (11.3%, $P < .001$) compared with those who received their last treatment between 90 and 180 days before boosting (5.0%) or >180 days before boosting (5.2%). Receiving anti-CD38 therapy <90 days before boosting was strongly associated with breakthrough infection, with 16.3% of patients experiencing breakthrough infection ($P < .001$), as were the receipts of proteasome inhibitors (12.5%, $P < .001$) and immunomodulatory imide drugs (11.0%, $P = .007$).

Our results suggest that patients with MM continue to be at increased risk of SARS-CoV-2 breakthrough infection and severe COVID-19 relative to the general population, even after a third mRNA vaccine dose. However, patients with MGUS appear to be protected against severe COVID-19 after receiving a third dose. This contrasts with our previous findings in the same population that found patients with MGUS at continued risk of severe COVID-19 after 2 mRNA vaccine doses.[2] These data complement data on surrogate markers of vaccine response, such as serologic studies showing reduced antibody response to SARS-CoV-2 vaccination among patients with MM, especially among those receiving anti-CD38 therapy.[5-7] In contrast, the immune response among patients with MGUS is typically closer to normal.[8,9] For patients with myeloma on anti-CD38 therapy, seroconversion is still possible after repeated SARS-CoV-2 vaccine doses.[10] Our finding that patients with MM were at the highest risk 3.5 months after the booster, compared with controls and patients with MGUS, is consistent with data showing that patients with MM have a more rapid decline in antibody levels after SARS-CoV-2 vaccination compared with healthy controls.[11] It also indicates potential need for repeat booster vaccination.

Table 1. Treatment characteristics of fully vaccinated patients with MM by breakthrough infection status

		Breakthrough infection		
	Overall	Yes	No	*P* value
Full cohort	1822	180 (9.9)	1642 (90.1)	
Treatment timing*				
Within 90 d	1413	159 (11.3)	1254 (88.7)	<.001
90 to 180 d	159	8 (5.0)	151 (95.0)	.045
>180 d	250	13 (5.2)	237 (94.8)	.011
Treatment type†				
IMiD	1352	149 (11.0)	1203 (89.0)	.007
Proteasome inhibitor	1035	129 (12.5)	906 (87.5)	<.001
Chemotherapy	566	66 (11.7)	500 (88.3)	.104
Anti-CD38	399	65 (16.3)	334 (83.7)	<.001
Other	49	9 (18.4)	40 (81.6)	.076

IMiD, immunodulatory imide drugs.

*Defined on the basis of the date of last dose of systemic antimyeloma therapy received before the third vaccine dose.

†Defined on the basis of all systemic antimyeloma therapies received within 90 days before the third vaccine dose. Patients who received multiple treatment types in this time period are included in multiple treatment type categories.

The study was conducted among veterans, which is a predominantly male population. It covered periods with varying levels of community COVID-19 incidence, which was addressed by matching on date of booster receipt and setting the index date for each matched pair to this date. Because this is a retrospective study based on electronic health record data, certain variables such as antibody titers and COVID variant were not available. In addition, the risk from individual antimyeloma drugs cannot be fully distinguished because these are often used in combination. Despite these limitations, our study represents, to our knowledge, the largest cohort of boosted patients with MM or MGUS to date. It directly reports on real-world risk of infection and severe COVID-19 instead of only immune response and, thus, is likely to translate to external settings with high clinical validity.

In conclusion, MM is associated with elevated risk of breakthrough SARS-CoV-2 infection and severe COVID-19, even after boosting, especially in those on anti-CD38 therapy compared with matched controls. In contrast, MGUS was associated with elevated risk of infection but not severe COVID-19 disease. These vulnerable populations may benefit from additional preventive strategies, such as ongoing targeted boosting campaigns and strategies to increase uptake of oral antivirals during early COVID-19 infection.[12]

Acknowledgements: This work was supported by the VA Office of Research and Development, Cooperative Studies Program (N.R.F, J.L., M.T.B., N.V.D.); VA Merit Review Award 1I01BX001584 (N.C.M.), National Institutes of Health grants P01-155258-07 and P50100707 (N.C.M.); American Heart Association 857078 (N.R.F.). The views expressed are those of the authors and do not necessarily represent the views of VA or the US Government.

Contribution: N.R.F., J.L., J.T.-Y.W., and N.C.M. designed the research; N.R.F., J.L., and J.K.C. collected and analyzed data; N.R.F. and N.C.M. wrote the manuscript; and all authors interpreted the data and critically edited the manuscript.

Conflict-of-interest disclosure: W.B.-E. reports receiving research grants (site principle investigator for multicenter study) from Gilead Sciences; and has received funds to institution and grants from VA Health Services Research and Development Service outside the submitted work. N.C.M. reports receiving personal fees from Bristol Myers Squibb, Janssen, Amgen, Takeda, OncoPep, AbbVie, Karyopharm, Novartis, Legend, Raqia, Adaptive Biotechnology, and Pfizer outside the submitted work; has intellectual property licensed to OncoPep; and held stocks in C4 Therapeutics. The remaining authors declare no competing financial interests.

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