RESEARCH ARTICLE

IVIg Use Associated with Ten-Fold Reduction of Serious Infections in Multiple Myeloma Patients Treated with Anti-BCMA Bispecific Antibodies

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ABSTRACT BCMA-targeted bispecific antibodies (BiAb) are efficacious in relapsed/refractory multiple myeloma; however, serious infections have emerged as important toxicities. In this retrospective study, we characterized all infections and their risk factors, and evaluated the impact of infection prophylaxis in patients treated with BCMA-targeted BiAbs. Among 37 patients, 15 (41%) experienced a grade 3–5 infection, with two infection-related deaths during deep remissions. Most (84%) infections occurred during disease remissions. The cumulative probability of grade 3–5 infection increased over time with no plateau. Among responders ($n = 26$), profound hypogammaglobulinemia occurred in 100% and continued throughout the entire duration of treatment. During periods when patients were receiving intravenous immunoglobulin (IVIg), the rate of grade 3–5 infections was 90% lower than during observation (incidence rate ratio, 0.10; 95% confidence interval, 0.01–0.80; $P = 0.0307$). No other risk factors for infection were identified. This study demonstrates that profound hypogammaglobulinemia is universal with BCMA-targeted BiAbs, with intravenous immunoglobulin potentially abrogating most of the infection risk.

SIGNIFICANCE: To the best of our knowledge, this is the first study to comprehensively analyze risk factors and mitigation strategies to prevent infections in myeloma patients receiving anti-BCMA bispecific antibodies. Profound and prolonged hypogammaglobulinemia was universal among responders, while immunoglobulin replacement was associated with 90% lower rates of grade 3–5 infections.

See related commentary by Garfall and Stadtmauer, p. 427.

INTRODUCTION

Multiple myeloma is undergoing a revolution with the development of highly effective immunotherapies, including chimeric antigen receptor T cells (CAR T) and bispecific antibodies (BiAb). There are several BiAbs under development in multiple myeloma, with most of them targeting B-cell maturation antigen (BCMA) including teclistamab, which was the first to obtain FDA approval in 2022 based on the MajesTEC-1 study (1). These BiAbs have demonstrated remarkable overall response rates of 60% to 80% in heavily pretreated, often triple-class–refractory multiple myeloma in both published studies and interim trial reports at national conferences (1–6), and are poised to become an integral component of the multiple myeloma treatment paradigm.

BCMA in particular has emerged as an important target of immunotherapies in multiple myeloma due to its overexpression on malignant plasma cells and limited expression on normal tissue (7, 8). However, BCMA is also expressed on normal plasma cells and mature B cells, and plays an important role in humoral immunity (9). Inhibition of BCMA in a mouse model precluded an antibody response to a highly antigenic protein and to a pneumovax vaccine (10). During the COVID-19 pandemic, multiple groups found that antibody responses to COVID-19 vaccines were blunted in patients with multiple myeloma treated with BCMA-targeted therapy (11–14), although some patients who had received CAR T were able to mount responses (15). Similarly, cellular responses to COVID-19 vaccines were adversely affected by anti-BCMA BiAbs (16). BiAbs are unique among BCMA-targeting modalities due to their frequent and indefinite administration schedule, potentially allowing for continuous suppression of the BCMA system as well as T-cell exhaustion.

Although BCMA-directed BiAbs are generally well tolerated, including manageable low-grade cytokine release syndrome (CRS) and temporary cytopenias, infection has now emerged as an important toxicity. The published phase I/II study of teclistamab reported an overall infection rate of 76.4% and a notable 44.8% rate of grade 3–5 infections at a median follow-up of 14.1 months (1). Among 165 patients, there were 20 (12%) deaths due to infections including 13 (8%) from COVID-19, as well as several nonfatal serious opportunistic infections including 6 cases of *Pneumocystis* pneumonia (PCP), 1 adenoviral pneumonia, and 1 progressive multifocal leukoencephalopathy. Hypogammaglobulinemia (HGG), defined as IgG <500 mg/dL, was reported in 74.5% of patients which is higher than the ORR of 63%, with 65 (39%) patients receiving intravenous immunoglobulin (IVIg). However, no information is available regarding the severity or duration of HGG, its incidence in responders who remained on therapy, disease status at the time of infections, or the impact of IVIg on infection rates. Abstracts presented at national meetings for other BCMA-targeted BiAbs have routinely shown high

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rates of grade 3–5 infections (2, 6), with these rates typically rising with longer duration of follow-up, indicating a class-effect of these therapies.

As the use of these therapies becomes more widespread, especially in earlier lines of therapy where alternative therapies associated with less infections (albeit with potentially less efficacy) are available, a deeper understanding of infections and effective preventive measures is urgently needed. Infection risk in multiple myeloma is multifactorial and includes patient characteristics (age, comorbidities, frailty), disease characteristics (immunoparesis, deficits in T-cell, natural killer (NK) cell, and dendritic cell function), and treatment characteristics (iatrogenic neutropenia, lymphopenia, and HGG). Importantly, to date, no data from randomized controlled trials are available to help elucidate the contribution of each of these components in the attribution of infections to BCMA BiAbs.

In addition, few studies have formally characterized risk factors for infection in multiple myeloma, with results varying widely by therapy and disease setting. For example, one study in newly diagnosed multiple myeloma found International Staging System (ISS) stage, hemoglobin, and CRP to predict for more infections (17), while another analyzed infections in patients with newly diagnosed multiple myeloma treated with daratumumab and found age, LDH, albumin, and ALT as risk factors for infection (18). In the relapsed setting, one study looking at patients receiving lenalidomide–dexamethasone identified albumin, hemoglobin, and prior transplant as risk factors (19), while studies examining infections after BCMA-targeted CAR T found more infections in patients with higher number of prior lines of therapy (20, 21). Previously, we reported on the successful use of IVIg to reduce infection rates in multiple myeloma patients with HGG and nonprogressive disease (22), as well as in multiple myeloma patients receiving daratumumab (23).

In this study, we seek to characterize the timing and nature of infections and HGG, elucidate risk factors for infection, and analyze the effect of immunoglobulin replacement on infection rates in patients with multiple myeloma treated with BCMA-directed BiAbs, with the goal of developing rational mitigation strategies for this serious and common toxicity.

RESULTS

Baseline Characteristics and Treatment

A total of 37 patients were treated with a variety of anti-BCMA BiAbs as monotherapies. The median age was 66 years (range 41–85), 62% were female, and the ethnicities were diverse with 17 (46%) White, 8 (22%) Black, 6 (16%) Hispanic, 3 (8%) Asian, and 3 (8%) other. Most patients had IgG myeloma (59%), while the remainder had light chain only (22%), IgA (16%) and IgD (3%) isotypes. The median time from diagnosis to treatment was 7.4 years, with a median of seven prior lines of therapy (range 2–13). 65% had high-risk cytogenetics, 78% were triple-class refractory, and 24% were penta-drug refractory. Twelve (32%) had previously received a non-BCMA BiAb, 11 (30%) received selinexor, and one (3%) was treated with belantamab mafodotin; no patients had prior CAR T. Full details of staging and prior treatments are listed in Table 1. Patients had a median of two infections (range 0–10) in the year prior to BiAb.

Table 1. Baseline patient characteristics.

Patient characteristics	*N* = 37
Age	66 (range, 41–85)
Female/Male	62%/38%
Ethnicity	
White	46%
Black	22%
Hispanic	16%
Asian	8%
Other	8%
Myeloma isotype	
IgG	59%
IgA	16%
IgD	3%
Light chain only	22%
ISS stage	
1	11%
2	19%
3	22%
Not available	48%
High-risk cytogenetics[a]	65%
Lines of therapy	7 (range, 2–13)
Treatment exposed/ refractory	
Immunomodulatory drugs	100%/92%
Proteasome inhibitors	100%/95%
Anti-CD38	100%/89%
Triple-class[b]	100%/78%
Penta-drug[c]	81%/24%
Bispecific antibody (non-BCMA)	32%/32%
Median time from myeloma diagnosis to bispecific antibody treatment (years)	7.4 (range, 2.1–17.2)
Infections in year prior to bispecific antibody	2 (range, 0–10)
Baseline immunodeficiencies	
IgG mg/dL, median	510 (IQR 418–757)
ANC × 10^3/μL, median	2.8 (IQR 2.1–3.7)
ALC × 10^3/μL, median	0.9 (IQR 0.6–1.5)

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; IQR, interquartile range.

[a]High-risk cytogenetics defined as presence of t(4;14), t(14;16), t(14;20), del17p, gain 1q.

[b]Triple class defined as at least one immunomodulatory drug, proteasome inhibitor, and anti-CD38 antibody.

[c]Penta-drug defined as lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab.

Twenty-one (57%) patients were treated at the recommended phase II dose, while the remainder were treated in dose-escalation cohorts. CRS occurred in 64% and was grade 1/2 except for one patient with grade 3, with tocilizumab used in 50% and corticosteroids in 22% of patients. The overall response rate (ORR) was 70%, including 68% very good partial response (VGPR) or greater, and 41% with an MRD-negative stringent complete response (sCR). Patients were treated for a median of 13 months (range 0.3–33.8+),

with 18 patients still on treatment at the time of data cutoff. Patients received a median of 31 doses of BiAb (range, 4–101), mostly on a weekly or every 2-week schedule. At a median follow-up time of 18.6 months, the median progression-free survival was 17.0 months and the median overall survival was 26.3 months. Fifteen (41%) patients discontinued treatment due to progressive disease, 5 (14%) due to adverse events (3 infections + 2 cytopenias), and 1 due to patient choice. Two patients (5%) died without progressive disease: one had sepsis at 17.6 months from the start of BiAb therapy while in a sCR MRD-negative response, not on antibacterial prophylaxis, with normal absolute neutrophil count (ANC)/absolute lymphocyte count (ALC), IgG level of 397 mg/dL, and most recent IVIg 2.3 months prior, while the other patient died from COVID-19 at 15.1 months from start of therapy, with IgG level of 0 (undetectable), no prior IVIg, and three prior COVID-19 vaccines. Information on ANC/ALC and COVID-19 therapeutics received for this patient is unavailable as the patient was treated at an outside institution.

Hypogammaglobulinemia and Infection Prophylaxis

Although 25 (68%) had HGG prior to the first dose of BiAb, only one (3%) was in the severe range (IgG <200 mg/dL). After BiAb initiation, HGG was universal among responders (26/26, 100%). Censoring for IVIg use ($n = 5$), all responders (21/21, 100%) had severe HGG. The median time to severe HGG was 2.9 months (range, 0.6–5.2). IgA and IgM levels became undetectable by the second month (Fig. 1A). The duration of HGG based on IgG level was difficult to estimate due to frequent IVIg use; however, IgA and IgM levels remained essentially undetectable for the entire duration of therapy. Seven patients had gaps in BiAb treatment of 3 months or greater without disease progression or death (median 4.3 months, range 3.3–13.1 months), and none of these had recovery of IgA or IgM during these gaps. Among nonresponders, there was no change in IgG levels, although IgA and IgM levels did decrease (Fig. 1B).

Among responders, 92% received IVIg at any point for a median of 10 doses (range, 1–25) with patients "On-IVIg" for a total of 56% of the time on study. Only two patients were on IVIg at the start of BiAb treatment or within one month of starting. VZV prophylaxis was universal, however there was no routine antibacterial, antifungal, or PCP prophylaxis.

Infections

There were a total of 118 infections during 424 months of follow-up (3.3 per patient-year), including 26 grade 3–5 infections (0.7 per patient -year) among 15 pts (41%; Table 2). The grade 3–5 infections are detailed in Supplementary Table S1. There were two grade 5 infections, which occurred at 15.1 months (COVID-19) and 17.6 months (sepsis). Infections were mostly in the respiratory tract (58%), followed by urinary tract and skin (15% each), and GI (8%), and were split among viral (46%) and bacterial (43%), with 11% fungal. There were 6 unusual opportunistic infections, including *Eikenella corrodens* empyema, *Neisseria sicca* purulent pericarditis, *Veilonella parvula* bacteremia, PCP, and two cases of cytomegalovirus (CMV) esophagitis. After two cases of CMV esophagitis were observed, monthly CMV PCR monitoring was implemented at our institution. CMV reactivation occurred in 8 patients (22%) including the two cases of esophagitis, with the remainder asymptomatic; two patients were treated with antivirals for asymptomatic titers >1,000 IU/mL in consultation with the infectious diseases team. Although numbers were small, there was no apparent correlation between CMV reactivation and other infections. Two patients had dose delays of 6 weeks and 19 weeks due to CMV. Epstein–Barr Virus (EBV) was not routinely monitored but there were no clinical cases of EBV disease. Of those treated since 2020, 12 (43%) tested positive for SARS-CoV-2, with 3 severe cases including 1 death in a vaccinated patient. In the short period between Evusheld approval and the end of data collection for this study, 3 of 18 (17%) of patients still under observation received Evusheld. Of those who received Evusheld, one experienced a mild COVID-19 infection after having received Evusheld. Among fungal infections, only 1 (PCP) required systemic treatment, while the remainder consisted of topically treated oral candida and fungal skin rashes.

Infection Timing and Risk Factors

Infections occurred in the first month in 10/37 (27%) patients, including 5/37 (14%) with grade 3–5 infections. Six (16%) patients had cooccurrence of infection in the first month and CRS. The estimated median time to first any-grade infection was 3.8 months, and the estimated median time to first grade 3–5 infection was 18.7 months, with no plateau in cumulative infection risk over time (Fig. 2A and B). Infection types and rates varied over time but remained high even after more than one year on therapy (Fig. 3; detailed data available in Supplementary Table S2). Most infections (84%) occurred during periods of disease control (≥PR), with 76% occurring in patients who had achieved a VGPR or greater. HGG was present in 74% of grade 1–2 infections and 88% of grade 3–5 infections, while severe HGG was seen in 16% of grade 1–2 infections but 42% of grade 3–5 infections. High-grade infections had numerically lower median IgG compared to low-grade infections (216 vs. 522) as well as lower mean IgG (294 vs. 529) [Table 2]. ROC analysis of IgG levels and infection severity produced an AUC of 0.734 [95% CI 0.61–0.858]; IgG level of <433 mg/dL was the optimal cut-point to identify high-grade infections, with a sensitivity of 0.83 and specificity of 0.63.

Any grade neutropenia developed in 73% of patients, while grade 3–4 neutropenia developed in 62%; any grade lymphopenia was present in 95% and grade 3–4 in 78%. Cytopenias mostly occurred in early cycles; ANC and ALC trends over time are shown in Supplementary Figures S1 and S2. Neutropenia (ANC $\leq 0.5 \times 10^3/\mu L$) was present in 5% of infections (16% with ANC $\leq 1.0 \times 10^3/\mu L$) and lymphopenia (ALC $\leq 0.5 \times 10^3/\mu L$) in 42% of infections (58% with ALC $\leq 1.0 \times 10^3/\mu L$). There was no association between ANC or ALC and severity of infection.

Univariate regressions did not identify age, sex, myeloma isotype, time since myeloma diagnosis, prior lines of therapy, prior exposure to another BiAb, high-risk cytogenetics, infections in year prior to BiAb, baseline IgG level, receipt of Recommended Phase 2 Dose, presence of CRS, use of tocilizumab, use of steroids, or baseline labs (including hemoglobin, ANC, ALC, albumin, LDH, B2-microglobulin, ALT) as significant risk factors for developing a grade 3–5 infection

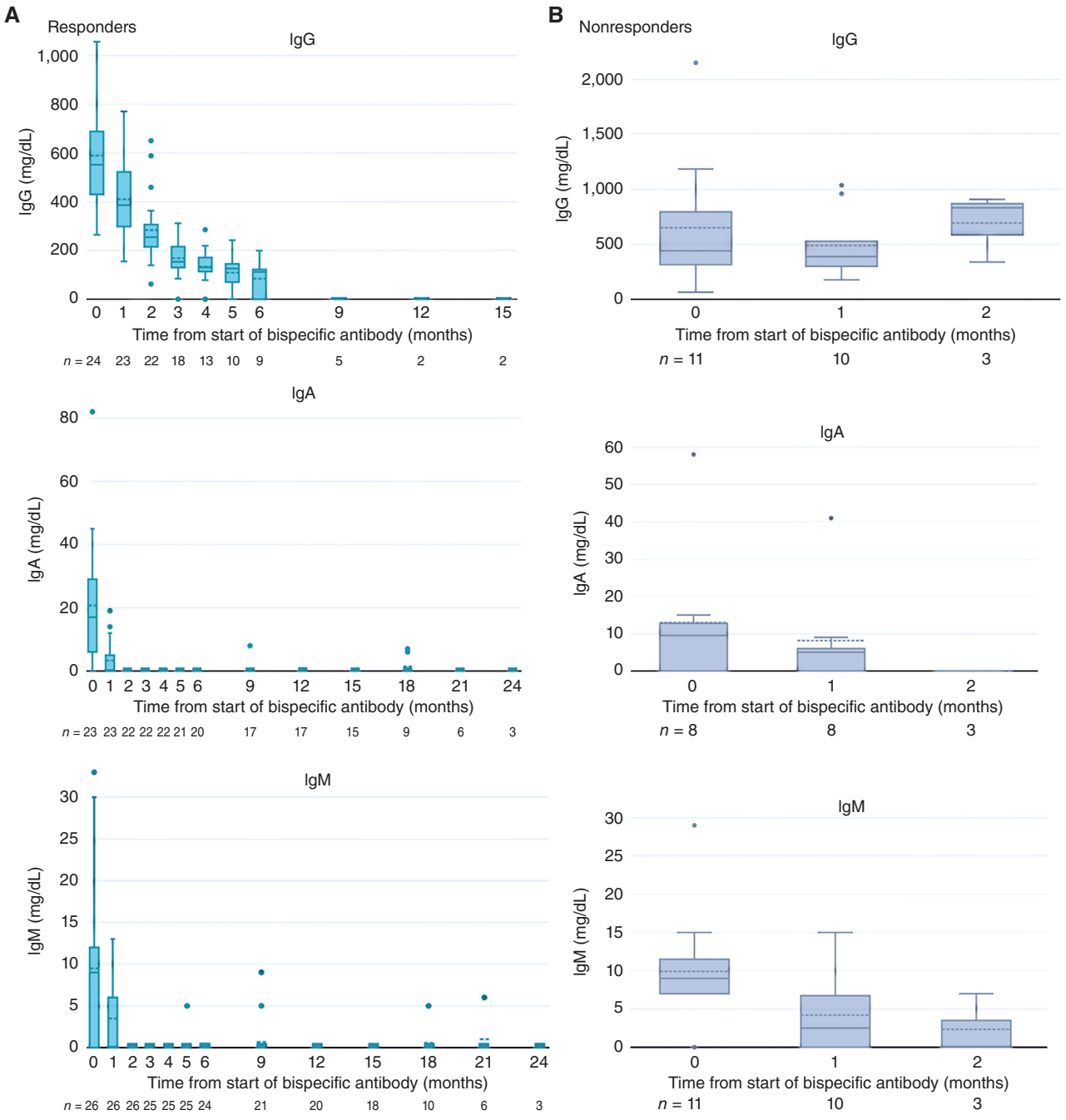

Figure 1. Immunoglobulin levels over time among patients responding to bispecific antibody treatment (**A**) and nonresponders (**B**). In the box-and-whiskers plots, the solid line is the median, the dotted line is the mean, the box is the interquartile range (Q1–Q3), the whiskers represent the minimum (Q1–1.5 IQR) and maximum (Q3 + 1.5 IQR), and individual dots are outliers. IgG levels were censored at the time of IVIg use; for IgG myeloma, the M-spike was subtracted from the total IgG. IgA levels excluded IgA myeloma patients. Reference ranges: IgG 700–1,600 mg/dL; IgA 70–400 mg/dL; IgM 40–230 mg/dL.

(Supplementary Table S3). The only significant factor was the BiAb trial that patients were on, however the number of patients in each trial was very small.

Effect of IVIg On Infections

For the primary endpoint of rate of all grade 3–5 infections, time 'On-IVIg' was associated with 90% fewer infections compared with periods 'Off-IVIg' [incidence rate ratio (IRR) IRR 0.10, 95% CI 0.01–0.80, $P = 0.0307$]. The grade 3–5 infections, as well as IVIg exposure time periods, are shown in a Swimmer's plot in Fig. 4A.

For the secondary endpoints, there were 85% fewer grade 3–5 bacterial infections "On-IVIg," although this did not reach statistical significance (IRR, 0.15; 95% CI, 0.02–1.22, $P = 0.0762$). There were no significant differences between "On-IVIg" and "Off-IVIg" in rates of grade 1–5 infections (all

Table 2. Infection characteristics.

Infection characteristics	All infections ($n = 118$)	Grade 3–5 infections ($n = 26$)
CTCAE grade 1/2/3/4/5	8%/69%/19%/2%/ 2%	
Bacterial/Viral/Fungal	43%/46%/11%	65%/31%/4%
Site (may overlap)		
Upper respiratory tract	33%	8%
Lower respiratory tract	22%	42%
Urinary tract	14%	4%
Skin/soft tissue	14%	0%
Gastrointestinal	9%	12%
Bloodstream	4%	27%
Dental	3%	4%
Catheter-related	3%	12%
Cytomegalovirus	8/37 (22%)	2/37 (5%)
COVID-19	16/37 (43%)	4/37 (11%)
Disease status at time of infection		
PD/SD/MR	16%	23%
PR	9%	19%
VGPR	19%	8%
CR/sCR/sCR MRD negative	57%	50%
Immune deficiencies	Grade 1–2 infections ($n = 92$)	Grade 3–5 infections ($n = 26$)
Hypogammaglobulinemia		
Any (IgG <700 mg/dL)	74%	88%
Moderate (200–399 mg/dL)	17%	33%
Severe (IgG <200 mg/dL)	16%	42%
Median IgG level, mg/dL (interquartile range)	522 (301–701)	216 (92–364)
Mean IgG level, mg/dL (standard deviation)	529 (314)	294 (320)
ANC		
$\leq 0.5 \times 10^3/\mu L$	3%	9%
$\leq 1.0 \times 10^3/\mu L$	13%	27%
ALC		
$\leq 0.5 \times 10^3/\mu L$	48%	24%
$\leq 1.0 \times 10^3/\mu L$	60%	52%

Abbreviations: CR, complete response; MR, minimal response; PD, progressive disease; PR, partial response; sCR, stringent complete response; MRD, minimal residual disease; SD, stable disease.

types or only bacterial). Sensitivity analyses excluding the first 30 days of BiAb therapy did not impact the results of any of these analyses. All results are summarized in a Forest plot in Fig. 4B. Swimmer's plots for the secondary endpoints are included in Supplementary Figures S3–S5.

A summary of our recommendations for infection prevention and management based on our data and clinical experience is outlined in Table 3.

DISCUSSION

Severe and unusual infections have emerged as an important and prevalent adverse event associated with anti-BCMA BiAbs, and a deeper understanding of etiology and preventive measures is urgently needed. This is the first study to thoroughly investigate infections and HGG in patients with multiple myeloma treated with anti-BCMA BiAbs. We found that all patients who respond to treatment experience severe HGG, approximating an agammaglobulinemic state. The 90% lower grade 3–5 infection rates during periods of immunoglobulin replacement is further evidence of the impact of severely impaired humoral immunity. Pending confirmation in other datasets and ideally in randomized prospective studies, these results provide a strong rationale for primary prophylaxis with IVIg or subcutaneous Ig (SCIg) in these patients. However, it is important to note that this is a retrospective study with its inherent limitations including nonrandom use of IVIg, as well as many patients receiving sub-RP2D doses and having received prior non-BCMA–bispecific antibodies. Although univariate analysis did not identify any baseline risk factors for infection, the numbers are relatively small and many of these factors should be investigated as possible contributors to infection risk in larger prospective studies.

Although immunoglobulin replacement has traditionally been recommended for HGG and recurrent infections (24–26), this reactive strategy would appear detrimental in this population given the frequency and severity of infections, with some patients dying from infection even while their myeloma

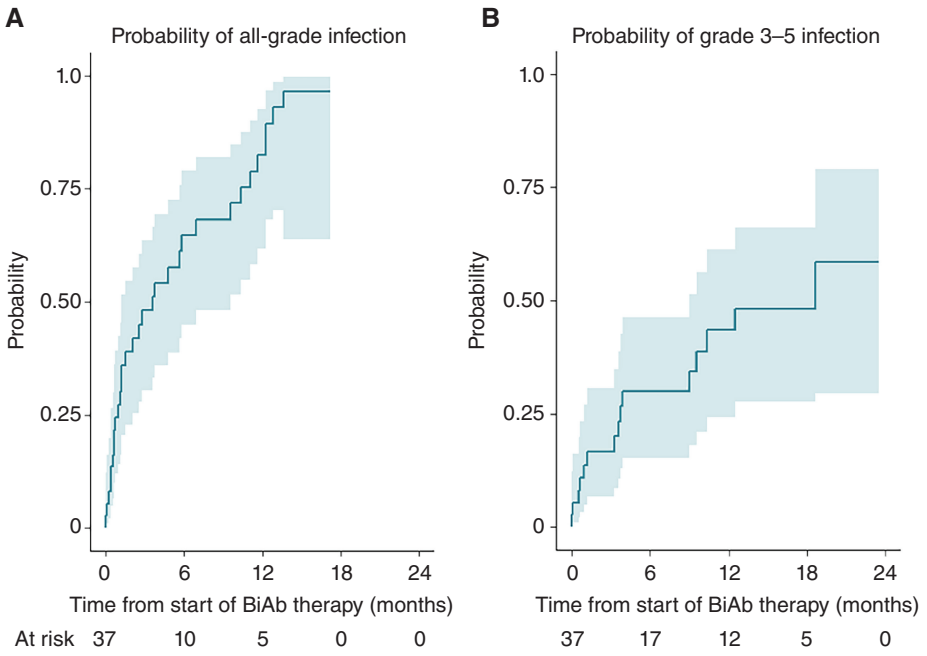

Figure 2. Time-to-event cumulative probability of developing any-grade infection (**A**) and grade 3–5 infection (**B**) from the start of bispecific antibody therapy, as calculated by the Kaplan–Meier method with shaded 95% confidence intervals.

is in a deep remission. Given the long half-life of normal IgG and the recycling of IgG by the neonatal Fc receptor (27), as well as the prevalence of IgG myeloma, waiting for specific IgG cutoffs could lead to several months' delays in identifying true HGG and initiating immunoglobulin replacement; given the approximately 30% risk of grade 3–5 infection in the first 4 months, as well as the inability to mount antibody responses to antigens or vaccines, it may be warranted to start prophylaxis around the time of BiAb initiation. An IgG level <433 mg/dL identified 83% of high-grade infections, although data to guide a specific target for replacement are lacking. In this study, IVIg was given at physicians' discretion at a dose of 400 mg/kg every 4 weeks, regardless of IgG level. Adverse effects due to IVIg were not recorded in this study but are well-described in the literature and include infusion reactions (to be avoided during the CRS period), acute kidney injury in patients with chronic kidney disease (requiring slower infusion/lower osmolarity), thrombosis, false positive serologies (e.g., hepatitis B), as well as infusion time and cost.

There may also be a potential benefit of donor COVID-19 antibodies in the immunoglobulin donor pool, including neutralizing titers (28). This may be particularly relevant given decreased responses to COVID-19 vaccines (11–14, 16) and loss of efficacy of prophylactic monoclonal COVID-19 antibodies with the arrival of new variants. Patients should ideally be vaccinated and boosted against COVID-19 prior to treatment

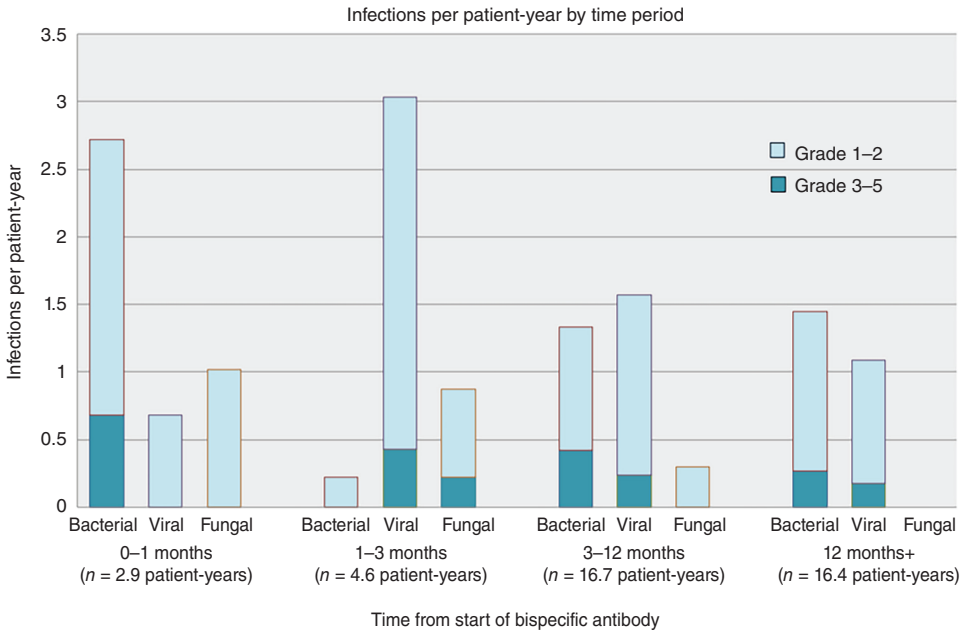

Figure 3. Infection rates (per patient-year) at various time periods from the start of bispecific antibody therapy, divided by microbiology and severity.

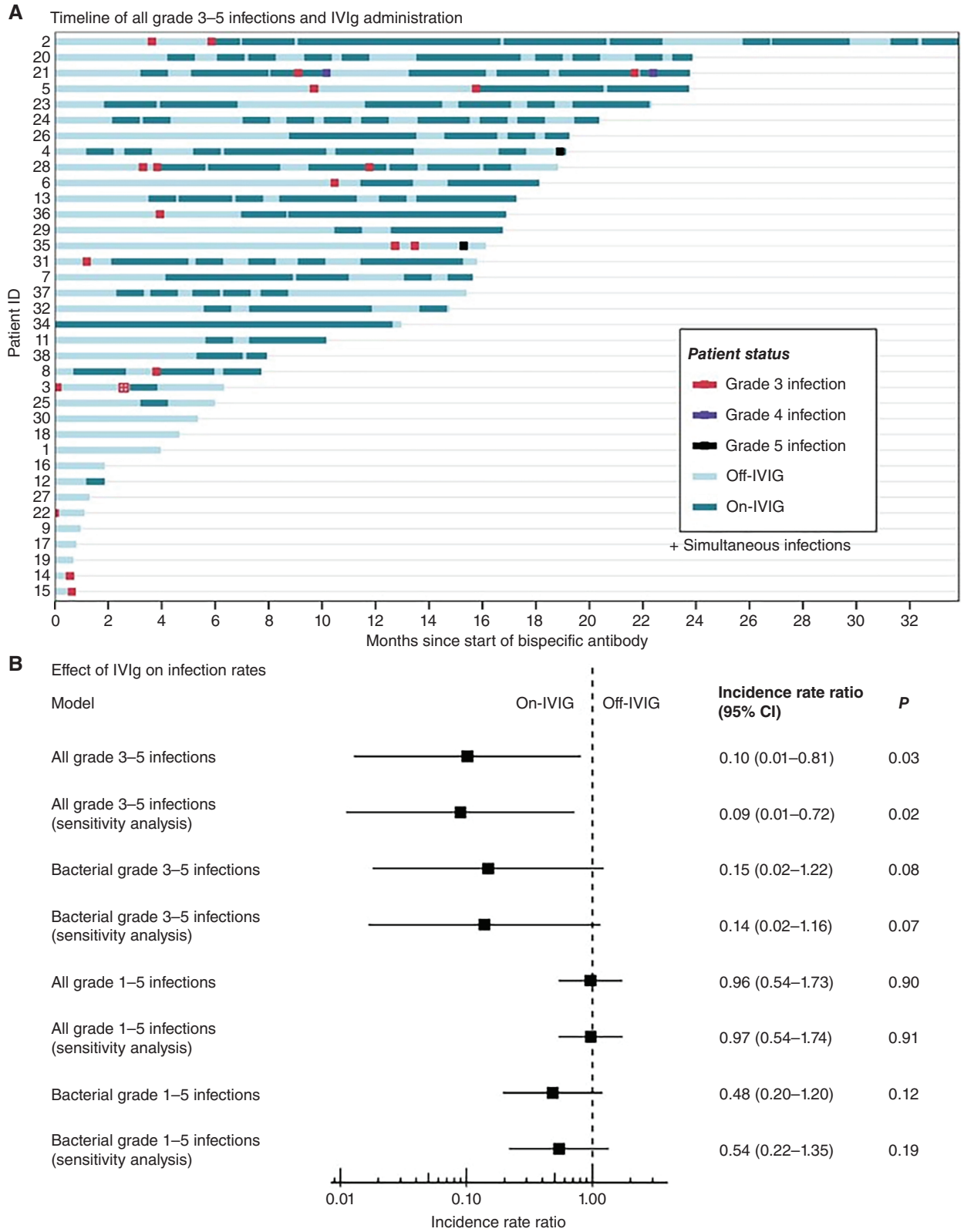

Figure 4. **A,** Swimmer's plot for all grade 3–5 infections during the study period, divided into "on-IVIg" and "off-IVIg" periods. **B,** Forest plot showing the infection incidence rate ratios of "on-IVIg" versus "off-IVIg" periods for various infection categorizations, with *P* values derived from z-test on regression parameters in the self-controlled case series model. Sensitivity analyses excluded the first 30 days of bispecific antibody therapy to attempt to limit confounding risk factors for infection including uncontrolled myeloma, increased health care contact due to mandatory hospitalizations during step-up dosing, and cytokine release syndrome management.

Table 3. Recommendations for prevention and management of infections for patients on BiAbs.

	Infection prevention before BCMA bispecific	Infection prevention during BCMA bispecific	Treatment of infection during BCMA bispecific[a]
Bacterial	Vaccinate if appropriate	IVIg q4 weeks	Based on sensitivities
Viral			
Zoster	Vaccinate if appropriate	VZV prophylaxis	Anti VZV therapeutic dosing
Influenza	Vaccinate if due	Hygiene	Antiviral
Hepatitis	Vaccinate if appropriate	Prophylaxis if evidence of Hep B exposure	Per ID input
CMV	N/A	Monitor CMV PCR q monthly	Treat if rising significantly or symptomatic
RSV	N/A	Hygiene	Consider inhaled ribavirin
COVID-19	Vaccinate/Boost	? Preventative monoclonal antibodies based on viral patterns Hygiene Consider monitoring Ab response and continue boosting	Oral or parenteral agents
Fungal	N/A	N/A	As indicated
PCP	N/A	PCP prophylaxis	Per ID Input

Abbreviations: ID, infectious disease; N/A, not applicable; RSV, respiratory syncytial virus; VZV, varicella zoster virus.

[a]Educate patients/caregivers about monitoring for signs and symptoms of infection. In setting of active infection, hold BCMA bispecific until recovery. Consider cytokine release syndrome, hemophagocytic lymphohistiocytosis, Epstein–Barr virus, *Clostridium difficile*, and unusual organisms in differential diagnosis; collaborate closely with ID team.

initiation, and patients testing positive for COVID-19 should receive prompt antiviral or antibody treatment based on local guidelines and resistance patterns. In addition, with the emergence of neuropathy as a possible toxicity of anti-BCMA BiAbs (2, 29), the impact of IVIg in mitigating this toxicity can be explored further given its use in treating neuropathies associated with plasma cell disorders (30).

Unusually, neutropenia and lymphopenia did not play a significant role in infection severity. Neutropenia, a significant risk factor for severe infections in many other contexts, was present in only a small minority of infections. Lymphopenia was more prevalent but not associated with higher infection severity. No other risk factors, including those identified in prior studies of infection in multiple myeloma in other disease settings (17–21), were found to be significant predictors of severe infections. Further study is needed to understand the impact of continuous BiAb therapy on T-cell subsets and their ability to fight infections while being persistently stimulated and potentially exhausted. There were many infections which are commonly associated with T-cell defects, including CMV reactivation and PCP pneumonia, although these have also been seen rarely in primary agammaglobulinemias (31–35). CMV reactivation occurred in 22%, including two clinically significant cases, and should be monitored routinely. The presence of PCP in this study as well as in 6 patients in MajesTEC-1 warrants primary PCP prophylaxis in all patients receiving BCMA-directed BiAbs. Interestingly the MonumenTAL-1 study of the GPRC5DxCD3 BiAb talquetamab did not show PCP or CMV infections or high rates of COVID-19 complications/deaths despite a similarly intensive administration schedule (36) in a similar population during a similar time period of the COVID-19 pandemic, indicating that the target, rather than the effects of T-cell redirection, may be a more likely explanation for these opportunistic infections. Comparisons with infections in anti-BCMA CAR T studies should be made with the utmost caution. In addition to the usual pitfalls of cross-trial comparisons, patients receiving CAR T-cell therapy often receive extensive supportive care, including antibacterial and antifungal prophylaxis during neutropenia, routine IVIg prophylaxis, and routine PCP prophylaxis. Although IVIg use in CAR T trials is not specified, the very low rates of HGG in responders in two separate trials, 16% (37) and 42% (38), indicate that most patients were likely receiving immunoglobulin replacement. For example, at our institution IVIg was given routinely for at least the first 6 months post-CAR T and often longer. In addition, CAR T tends to have higher infection rates early on due to cytopenias from either lymphodepleting chemotherapy or the CAR T itself (21).

The infection rate in our study, particularly for grade 3–5 infections, closely tracked that of the MajesTEC-1 trial. The cumulative probability of getting a severe infection continuously increased over time with no plateau, with 84% of all infections occurring during periods of disease control. This provides evidence that the treatment, rather than the underlying disease, is responsible for much of the immunosuppression through an on-target off-tumor effect. This has been shown preclinically where BCMA inhibition rendered mice unable to mount an antibody response to antigen or vaccine, implicating BCMA in the physiologic humoral response (10). The duration of this agammaglobulinemic response is still undefined as no fixed duration studies of BCMA BiAbs have been reported. Our study shows definitively that immunoglobulin recovery does not occur during continuous treatment, up to a maximum follow-up of 2.8 years. Seven patients had treatment gaps of at least 3 months (range, 3.3–13.1 months)

without meaningful immunoglobulin recovery, indicating a prolonged pharmacodynamic effect of this therapy.

Future clinical trials of BiAbs in multiple myeloma should report infection and HGG data in more detail, to truly understand the risks and develop appropriate mitigation strategies. For example, teclistamab reported 75% rate of HGG (1) while GPRC5D-targeting talquetamab reported 71%–87% HGG (34), and yet grade 3–5 infections, opportunistic infections, and COVID-19 deaths were substantially lower with talquetamab. Rather than just providing the overall HGG rate, it would be useful to know the prevalence in responders, timing, severity, and duration of HGG. Infections should be reported by remission status to understand if infections are more related to disease or treatment, along with IgG levels and impact of immunoglobulin replacement on infections. Infection deaths in particular, whether on study or off study but prior to the next line of treatment, should be reported with their direct cause (if known), multiple myeloma response status, IgG level, last IVIg dose, and concurrent antimicrobial prophylaxis. As all BiAb studies reported to date are single-arm studies without comparators, randomized studies will be critical to understanding the true infection risk in this population, including the impact of infection deaths. BELLINI, the randomized phase III study of venetoclax–bortezomib–dexamethasone versus bortezomib–dexamethasone in relapsed multiple myeloma, serves as a cautionary tale that even impressive response rates and PFS can be offset by deaths from infection (39).

Our study is limited by its retrospective nature, relatively small size, and nonrandom administration of IVIg (at individual physicians' discretion). However, there are several important conclusions that need to be further explored in larger studies. Patients treated with anti-BCMA BiAbs had high rates of all grade and grade 3–5 infections, including opportunistic infections. Although most grade 3–5 infections occurred in the first 4 months, the risk persists over time, raising the question of optimal duration/dose/frequency of therapy. Severe HGG (IgG <200 mg/dL) was universal among responders. The rate of grade 3–5 infections was 90% lower on IVIg, with only five serious infections occurring on IVIg, suggesting a role for IVIg as primary prophylaxis. IVIg may be additionally useful now given the high prevalence of COVID-19 antibodies in the donor pool. Neutrophil and lymphocyte counts were not significant factors for severe infections, further highlighting the role of impaired humoral immunity in this population. CMV should be monitored routinely given the significant reactivation rate, including symptomatic cases, while PCP prophylaxis should be administered routinely given its prevalence in MajesTEC-1. With a deeper understanding of effective preventive measures for infections, we can maximize the potential of these highly efficacious immunotherapies in multiple myeloma.

METHODS

Patients and Data Collection

We retrospectively reviewed all patients with multiple myeloma treated at Mount Sinai Hospital in New York (New York, NY) with a BMCA-targeting BiAb as monotherapy on four clinical trials (NCT03287908, NCT03761108, NCT04083534, NCT03145181) between January 1, 2019 and June 30, 2022. Patients were included if they received at least one dose of BiAb, and were followed until disease progression, death, or last follow-up if still on study. Data were collected on baseline characteristics, treatment, disease response, HGG, infections, and infection prophylaxis including IVIg.

Definitions

Disease response was assessed by International Myeloma Working Group (IMWG) criteria (40). HGG was defined as IgG <700 mg/dL, moderate HGG as 200–399 mg/dL, and severe HGG as IgG <200 mg/dL, as previously described (41). In cases of IgG myeloma, the M-spike component was subtracted from the total IgG level to approximate the amount of polyclonal and functional IgG. For determination of HGG, patients were censored if they received IVIg given its effect on IgG levels. Infections were captured by comprehensive chart review, which included review of microbiological data, antibiotic prescriptions, and clinical notes for every visit for every patient, and were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Infection prophylaxis was categorized as antibacterial, antiviral, and antifungal, while every administration of IVIg during the study period was recorded. Time periods "On-IVIg" were defined as within 30 days after administration of IVIg, while all other time periods were considered to be "Off-IVIg". IVIg was used at physicians' discretion at a dose of 400 mg/kg, typically at 4-week intervals. CRS was graded on the basis of the consensus system established by the American Society for Transplantation and Cellular Therapy (42).

Statistical Analysis

The Kaplan–Meier method was used for time-to-event calculations, including PFS, OS, and time to first all-grade or grade 3–5 infection. Univariate logistic regressions were used to identify significant baseline risk factors for grade 3–5 infections, including age, sex, myeloma disease characteristics, treatment history, baseline lab values and immunodeficiencies, clinical infection history, and presence of CRS/ICANS. Receiver operating characteristic (ROC) was used to identify IgG levels indicative of severe infections. Incidence rate ratios (IRR) with 95% confidence intervals comparing "on-IVIg" periods with "off-IVIg" were calculated using a self-controlled case series (SCCS) model (43), where IVIg was the exposure and infection rates were compared within patients, with patients serving as their own controls. The primary endpoint was rate of grade 3–5 infections for time periods "on-IVIg" vs. "off-IVIg." A sensitivity analysis was conducted excluding the first 30 days of BiAb therapy to eliminate possible confounding risk factors for infection during this time, including uncontrolled myeloma, increased health care contact due to mandatory admissions for step-up dosing, and CRS management. The SCCS model was used for the secondary endpoints of all grade 1–5 infections, grade 3–5 bacterial infections, and grade 1–5 bacterial infections. $P < 0.05$ was considered statistically significant. R was used for statistical analyses. All patients provided written informed consent, all trials were conducted in accordance with the Declaration of Helsinki, and this study was approved by the Mount Sinai Institutional Review Board.

Data Availability Statement

Anonymized patient-level data are available as a Supplementary File within this article (Supplementary Data: Patient-level Data). Drug names have been deidentified and will be made available upon request once all of the sponsors have published results from these trials.

Authors' Disclosures

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Authors' Contributions

G. Lancman: Conceptualization, data curation, formal analysis, writing–original draft. **K. Parsa:** Data curation, writing–original draft. **K. Kotlarz:** Formal analysis, visualization, writing–review and editing. **L. Avery:** Formal analysis, visualization, writing–review and editing. **A. Lurie:** Data curation, writing–review and editing. **A. Lieberman-Cribbin:** Data curation, writing–review and editing. **H.J. Cho:** Writing–review and editing. **S.S. Parekh:** Writing–review and editing. **S. Richard:** Writing–review and editing. **J. Richter:** Writing–review and editing. **C. Rodriguez:** Writing–review and editing. **A. Rossi:** Writing–review and editing. **L.J. Sanchez:** Writing–review and editing. **S. Thibaud:** Writing-review and editing. **S. Jagannath:** Writing–review and editing. **A. Chari:** Conceptualization, supervision, writing–review and editing.

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Note

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