Infection risk in 158 patients with relapsed/refractory multiple myeloma treated with bispecific antibodies: a single-center experience

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Abstract

Four bispecific antibodies (BsAb) are approved for the treatment of relapsed refractory multiple myeloma (RRMM), but their use is associated with infection risks, requiring mitigation strategies. This single-center retrospective study evaluated the incidence, etiology, and risk factors for infections in 158 RRMM patients treated with BsAb. A total of 101 patients received BCMAxCD3 BsAb (teclistamab and elranatamab), and 57 GPRC5DxCD3 BsAb (talquetamab). Prophylactic measures included herpes zoster and *Pneumocystis jirovecii* coverage, along with monthly intravenous immunoglobulin (IVIG) as primary prophylaxis. Tocilizumab was used for the prevention of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, and BsAb frequency was reduced in responding patients. Cytomegalovirus (CMV) viral load was assessed monthly. Median follow-up was 6.1 *versus* 4.5 months for anti-BCMA *versus* anti-GPRC5D group. The cumulative incidence of the first any-grade infection at 5 and 10 months was 38.6% and 47.9% in the anti-BCMA group, and 28.1% and 30.3% in the anti-GPRC5D group (P=0.06). IVIG administration significantly reduced the risk of grade ≥3 infections in multivariate analysis (hazard ratio =0.38; P<0.01). Most infections were viral (60%), mainly upper respiratory (38%). The cumulative incidence of CMV infections at 5 and 10 months was 45.1% and 48% in the anti-BCMA group, *versus* 27.3% at both time points in the anti-GPRC5D group (P=0.03). With the limitation of a short follow-up, our results showed a higher incidence of any-grade infections in patients receiving anti-BCMA BsAb. Primary IVIG prophylaxis reduced severe infections. CMV infections were more frequent in patients treated with anti-BCMA agents.

Introduction

The outcome for patients with relapsed refractory multiple myeloma (RRMM) has dramatically improved in recent years. The treatment landscape has been revolutionized by the introduction of T-cell re-directing therapies, including bispecific antibodies (BsAb).[1] Four BsAb are approved for RRMM patients who have previously received a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 monoclonal antibody (mAb). These BsAb are the B-cell maturation antigen (BCMA) targeting agents teclistamab, elranatamab and linvoseltamab, and the G-protein-coupled receptor family C group 5 member D (GPRC5D) targeting agent, talquetamab.[2-5]

Despite their efficacy, these treatments are associated with an increased risk of infections, making it crucial to improve prophylactic measures, evaluating the impact of treatment frequency on infection susceptibility, and identifying other factors that may contribute to increased vulnerability to infections.[6] Data from pooled analysis, clinical trials and real-world studies showed that anti-BCMA BsAb are associated with higher rates of all-grade and grade ≥3 infections compared to anti-GPRC5D BsAb.[7-9] This difference may be attributed to several mechanisms, including the elimination of normal BCMA-expressing plasma cells which leads to hypogammaglobulinemia, cytokine-mediated suppression of hematopoiesis resulting in neutropenia, and impaired plasma cell survival and proliferation.[10,11] The spectrum of toxicity associated with BsAb, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), along with their management, can also contribute to an increased risk of infections, while

the exhaustion of T-cell and B-cell immunity may increase the risk of opportunistic infections, such as Cytomegalovirus (CMV) and *Pneumocystis jirovecii* pneumonia (PJP).[11] However, the way infections are analyzed, especially in clinical trials, might introduce bias. The rate of infections varies widely, due to the heterogeneous observation periods and the cumulative incidence of infections in patients treated with BsAb. Furthermore, adverse events are typically counted only once, which likely leads to an underestimation of infectious events and an approximate representation of their incidence over time.[12]

In this study, we analyzed our institutional cohort of RRMM patients treated with BsAb in clinical practice, with the aim of characterizing the incidence, timing, and risk factors associated with infections.

Methods

Patients and disease variables

We conducted a retrospective analysis of 158 RRMM patients at Winship Cancer Institute of Emory University. This study was approved by the Emory University Institutional Review Board (IRB). Demographic and clinical data were obtained from our IRB-approved myeloma database and manual abstraction. All patients with RRMM who received commercial BsAb (teclistamab, elranatamab, and talquetamab) between December 21, 2022, and June 30, 2024, were included. Patients were followed-up for 6 months post last BsAb dose, until next treatment line or death, with a data cutoff of October 30, 2024.

Patients with MM refractory to IMiD, PI, and anti-CD38 mAb were classified as triple-class refractory. CRS and ICANS were graded based on the American Society for Transplantation and Cellular Therapy Criteria and managed according to institutional guidelines.[13] A hypogammaglobulinemia was defined by an IgG level <400 mg/dL.

Infection prevention and monitoring

The institutional prophylaxis guidelines included antiviral therapy for varicella zoster virus (VZV), as well as prophylaxis for PJP (trimethoprim-sulfamethoxazole as standard agent). Monthly intravenous immunoglobulin (IVIG) administration was recommended for all patients, regardless of their IgG serum levels. CMV viral load was monitored on day 1 of each cycle. By institutional guideline, prophylactic tocilizumab was administered 4 hours prior to second step-up dose, and by January 1, 2024 it was administered prior to first step-up dose. In addition, patients changed to every-other-week BsAb administration from cycle 3 upon achieving partial response or better, and to every 4 weeks from cycle 7 if response was sustained.

Infection characterization

We assessed the rates of clinically relevant infections, as well as CMV infections, hypogammaglobulinemia rates, and neutropenia rates and grades. Infections were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, and were diagnosed based on clinical evaluation, with microbiological tests performed according to the patient's presenting symptoms. Radiological imaging was conducted when deemed appropriate by the treating physicians.

CMV infections were defined according to standard definition.[14] CMV DNA detection was defined as the detection of CMV DNA in peripheral blood using quantitative polymerase chain reaction. Clinically significant CMV infection was defined as CMV DNAemia leading to initiation of anti-CMV therapy or meeting criteria for CMV disease. CMV disease required compatible clinical symptoms along with virological and/or histopathological evidence of organ involvement. Initiation of anti-CMV therapy was based on the judgment of the treating physician, considering either kinetics of viral load increase or the presence of related symptoms.

CMV DNA detections were excluded from the overall infection count as they did not receive therapy and were not clinically significant. No baseline CMV serology was performed before starting BsAb.

Statistical analysis

χ^2 test and Fisher's exact tests were used for comparing differences between categorical variables, while the non-parametric Mann-Whitney test was used for continuous variables. Rates of first infections and CMV infections were estimated using cumulative incidence curves with initiation of new therapy or death as competing risk events and were compared using Gray's test. Univariate and multivariate analyses were conducted to identify variables associated with severe (grade ≥3) infectious events, treating infections as time-dependent variables. The Fine and Gray model was applied, with the initiation of new therapy or death considered as competing risks. Only selected variables reaching statistical significance of *P* value <0.05 on univariate analysis were included in the multivariate analysis adjusted for hazard ratio (HR) and 95% confidence interval (CI). A complete-case approach was used, including only patients with available data for all variables in the model. R version 4.4.1 was used for statistical analysis.

Results

Patient characteristics

Patient characteristics are listed in Table 1. We identified 158 RRMM patients treated with BsAb. One-hundred and one (64%) patients received anti-BCMA BsAb (teclistamab [N=77] or elranatamab [N=24]) and 57 (36%) received anti-GPRC5D BsAb (talquetamab). The median follow-up was 6.1 months (interquartile range [IQR], 2-12) for the anti-BCMA and 4.5 months (IQR, 2-7) for the anti-GPRC5D group. The median age for the anti-BCMA and the anti-GPRC5D group

was 66 years (range, 43-87) and 65 years (range, 38-89). Median number of prior lines of therapy was 5 (range, 2-14) in the anti-BCMA and 6 (range, 3-16) in the anti-GPRC5D group. Compared to patients who received anti-BCMA BsAb, a higher proportion of patients treated with anti-GPRC5D BsAb had prior treatment with anti-BCMA therapy (22% *vs.* 75%; *P*<0.001). Prophylactic tocilizumab was administered in 96% of patients in the anti-BCMA and in 100% of patients in the anti-GPRC5D group. Consequently, the rates of CRS were 28% and 21%, respectively, while the incidence of ICANS was 11% in both groups.

Hypogammaglobulinemia was observed more frequently

Table 1. Characteristics of the 158 patients receiving therapy.

Characteristic	Total N=158	BCMA-targeting BsAb N=101	GRPC5D-targeting BsAb N=57	*P*
Age, years, median (range) >75, N (%)	66 (38-89) 33 (21)	66 (43-87) 24 (24)	65 (38-89) 9 (16)	0.33[1]
Median prior lines of therapy (range)	5 (2-16)	5 (2-14)	6 (3-16)	<0.01[1]
Myeloma type, N (%) IgG IgA Light chain Missing	 74 (51) 35 (24) 35 (24) 14	 42 (42) 24 (24) 21 (21) 14	 32 (56) 11 (19) 14 (25) 0	0.50[2]
Triple class refractory myeloma, N (%)	131 (83)	80 (79)	51 (89)	0.15[2]
Prior BCMA therapy, N (%) ADC CAR-T BsAb	65 (41) 20 (13) 38 (24) 30 (19)	22 (22) 11 (11) 15 (15) 4 (4)	43 (75) 9 (16) 23 (40) 26 (46)	<0.001[2]
Prior ASCT, N (%)	128 (81)	74 (73)	54 (95)	0.0021[2]
R-ISS, N (%) I II III Missing	 7 (18) 17 (43) 15 (38) 118	 6 (20) 13 (43) 11 (37) 71	 1 (10) 4 (40) 4 (40) 47	1.0[3]
All-grade CRS, N (%)	40 (25)	28 (28)	12 (21)	0.46[2]
All-grade ICANS, N (%)	17 (11)	11 (11)	6 (11)	1.0[2]
Herpes zoster prophylaxis, N (%) Missing	155 (99) 1	98 (98) 1	57 (100) 0	0.53[3]
PJP prophylaxis, N (%) Missing	132 (85) 2	79 (80) 2	53 (93) 0	0.04[3]
Prophylactic tocilizumab, N (%)	154 (97)	97 (96)	57 (100)	0.30[3]
Steroid for CRS/ICANS, N (%)	22 (14)	13 (13)	9 (16)	0.79[2]
Hypogammaglobulinemia <400 mg/dL during therapy, N (%) Missing	83 (54) 3	61 (62) 3	22 (39) 0	0.006[2]
IVIG replacement, N (%) Missing	108 (70) 3	67 (68) 3	41 (72) 0	0.78[2]
Switch to Q2W, N (%) Missing	81 (52) 2	50 (51) 2	31 (54) 0	0.76[2]
Switch to Q4W, N (%) Missing	54 (35) 2	42 (42) 2	12 (21) 0	0.01[2]
ANC <1,000 cells/mm^3 during therapy, N (%) Missing	93 (61) 5	60 (63) 5	33 (58) 0	0.70[2]

[1]Wilcoxon rank sum test; [2]χ^2 test; [3]Fisher exact test. BsAb: bispecific antibodies; MM: multiple myeloma; N: number; ADC: antibody drug conjugated; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; ASCT: autologous stem cell transplantation; IVIG: intravenous immunoglobulin; Q2W: every other week; Q4W: every 4 weeks; R-ISS: revised international staging system; BCMA: B-cell maturation antigen; GPRC5D: G-protein-coupled receptor family C group 5 member D; ANC: absolute neutrophil count; PJP: *pneumocisti jirovecii* pneumonia; CAR T: chimeric antigen receptor T.

in patients treated with anti-BCMA BsAb (62% *vs*. 39%; *P*=0.006). IVIG replacement was administered in 68% of the patients in the anti-BCMA group and in 72% patients in the anti-GPRC5D group. Grade ≥3 neutropenia occurred in 63% of patients treated with anti-BCMA BsAb and 58% of those treated with anti-GPRC5D BsAb, with a median time to onset of 0.89 months and 0.53 months, respectively.

Characteristics of infections

Among the 158 patients analyzed, 72 (46%) experienced at least one clinically relevant infection during treatment. Cumulative incidence of the first any-grade infection at 5, 10, 15 and 20 months in anti-BCMA group was 38.6% (95% CI: 0.29-48.2), 47.9% (95% CI: 0.38-0.58), 52.8% (95% CI: 0.43-0.63), and 56.9% (95% CI: 0.46-0.68), respectively, while in the anti-GPRC5D group it was 28.1% (95% CI: 0.16-0.40) and 30.3% (95% CI: 0.18-0.43) at 5 and 10 months, respectively. The difference between the two groups approached statistical significance (Gray's test; *P*=0.062), Figure 1.

Thirty-nine (25%) patients experienced at least one grade ≥3 infection. Cumulative incidence of the first grade ≥3 infection at 5, 10, 15 and 20 months in anti-BCMA group was 21.1% (95% CI: 0.13-0.29), 26% (95% CI: 0.17-0.34), 27% (95% CI: 0.18-0.36) and 32% (95% CI: 0.21-0.43), while in the anti-GPRC5D group it was 19% (95% CI: 0.09-0.29) at 5 and 10 months (Gray's test; *P*=0.46), *Online Supplementary Figure 1S*.

Focusing on risk factors for developing a first grade ≥3 infection, administration of IVIG (HR=0.28; 95% CI: 0.15-0.50; *P*<0.0001) and increased BsAb dosing interval to once every-other-week (HR=0.37; 95% CI: 0.20-0.69; *P*<0.01) were associated with a lower risk in the univariate analysis. In contrast, receiving steroid for treatment of CRS/ICANS (HR=2.93; 95% CI: 1.35-6.33; *P*<0.01) was associated with a higher risk. In a multivariate model adjusted on administration of IVIG, switch administration to once every-other-week and on use of steroids for CRS/ICANS, only receipt of IVIG (HR=0.38; 95% CI: 0.19-0.79; *P*<0.01) remained significantly correlated with a lower risk of developing at least a grade ≥3 infection (Table 2).

Accounting recurrent infections, we observed 116 clinically relevant any-grade infections and 53 grade ≥3 infections. Median of number of infections per patient was 1 (range, 1-5). The total number of any-grade and grade ≥3 infections, including recurrent ones, over time in anti-BCMA *versus* anti-GPRC5D groups are summarized in Figure 2, expressed in months per 100 patients.

Four patients (3%) reduced the frequency of BsAb administration due to infectious complications, while 11 patients (7%) discontinued BsAb treatment because of infections. Hospital admission was required for 48 infectious events (41%), while five infections (4%) were fatal. The causes of death included three cases of pneumonia, one due to *Pseudomonas aeruginosa*, one related to COVID-19, and one undocumented. Additionally, there were two cases of fatal sepsis, one caused by *Pseudomonas aeruginosa* and the other by *Klebsiella pneumoniae*.

The most common sites of infection were the upper respiratory tract (N=44, 38%), followed by disseminated infections (N=25, 22%), and the lower respiratory tract (N=25, 22%). Among the documented infections (N=70, 60%), 42 (60%) were viral, 26 (37%) were bacterial and two (3%) were fungal. Two fungal infections were reported: one case of esophageal candidiasis, successfully treated with fluconazole and a temporary teclistamab hold, which was later resumed without complications; and one case of dematiaceous fungal infection, which required prolonged antifungal treatment and led to permanent discontinuation of teclistamab. Most frequently isolated pathogens were respiratory viruses (43%) within the viral group and *Enterobacteriaceae* (17%) in the bacterial group.

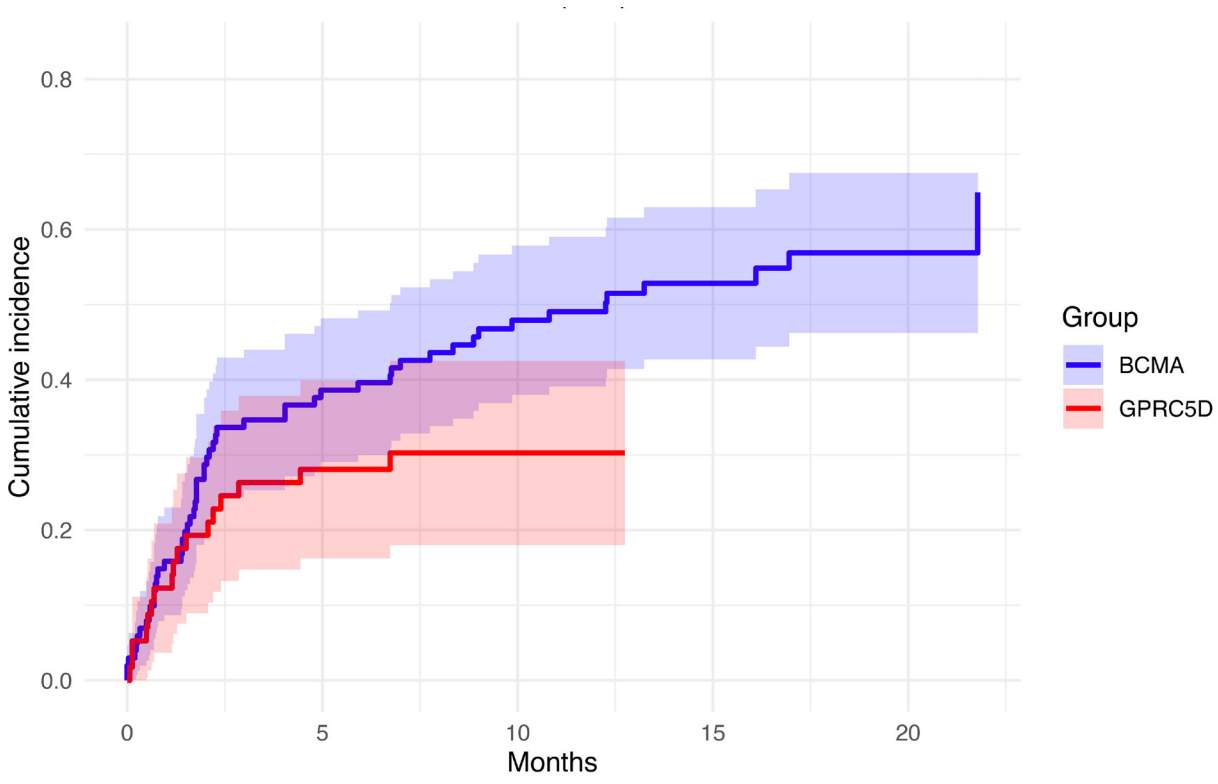

Figure 1. Cumulative incidence of first any-grade infection among patients treated with BCMA- and GPRC5D-directed bispecific antibodies. BCMA: B-cell maturation antigen; GPRC5D: G-protein-coupled receptor family C group 5 member D.

VZV infections were 3%, while no PJP occurred (Table 3). During monthly routine surveillance, 59 (47%) patients experienced a CMV infection. Among them, 51 (40%) patients had a CMV DNAemia detection, while eight (6%) patients developed a clinically significant CMV infection.

The estimated cumulative incidence of CMV infection in the anti-BCMA group was 45.1% (95% CI: 0.33-0.57) at 5 months and 48% (95% CI: 0.36-0.48) at 10 months, remaining stable at 15 and 20 months. In contrast, the cumulative incidence in the anti-GPRC5D group was 27.3% (95% CI: 0.15-0.39) at 5 months and remained unchanged at 10 months. The difference between the two groups was statistically significant (P=0.03), Figure 3.

Among the eight patients who developed clinically significant CMV infections, seven (6%) were in the anti-BCMA group and one (2%) in the anti-GPRC5D group. All eight patients were treated with preemptive antiviral therapy, and none progressed to CMV disease with organ involvement. Three of the eight patients had a documented episode of CMV DNAemia within 6 months prior to initiating BsAb therapy. More details on CMV infections are summarized in the Table 4.

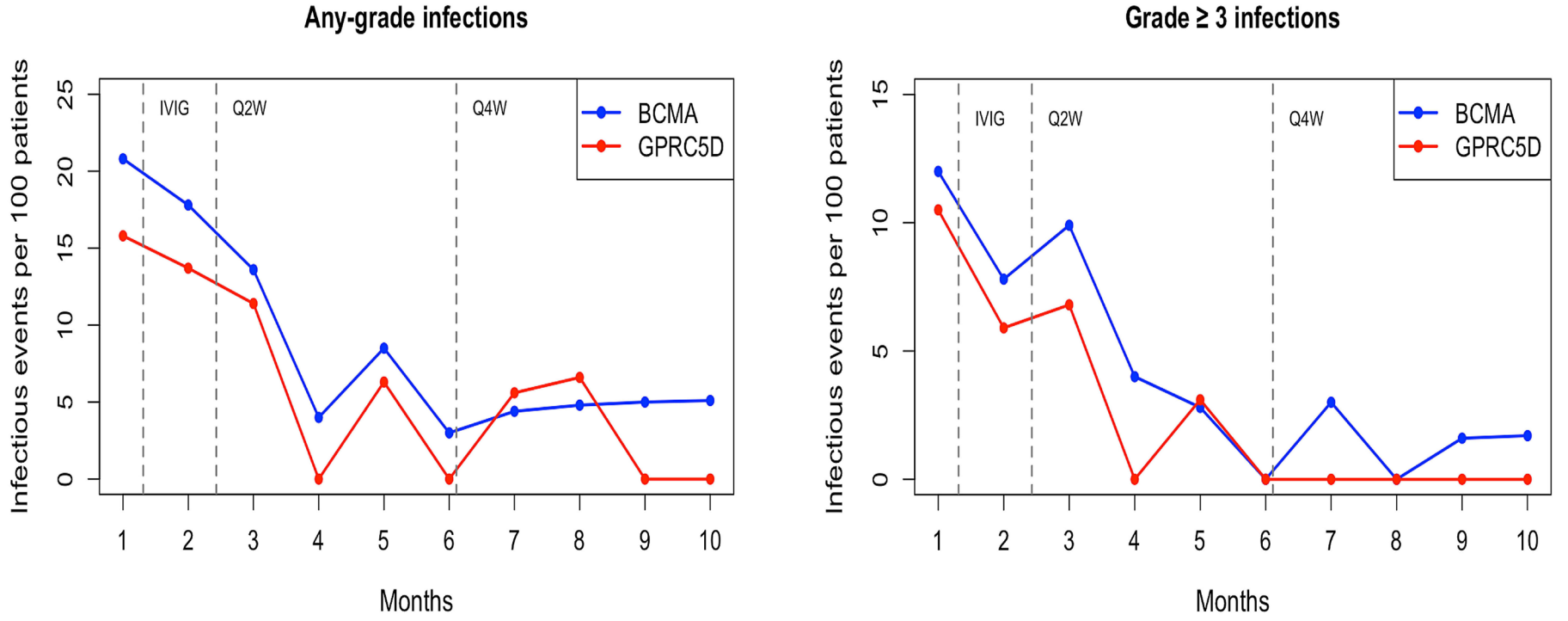

Figure 2. Incidence of each infectious event per month per 100 patients in BCMA *versus* GPRC5D-directed bispecific groups over the first 10 months. The graphs are generated accounting the decreasing number of patients still on study in every period of time. The dotted lines indicate the median times for initiating intravenous immunoglobulin (IVIG, 1.3 months), switching to every-other-week administration (Q2W, 2.4 months), and switching to every-4th-week administration (Q4W, 6.1 months) for the entire population. BCMA: B-cell maturation antigen; GPRC5D: G-protein-coupled receptor family C group 5 member D.

Table 2. Fine and Gray univariate and multivariate analysis of risk factors for developing a first grade ≥3 infection.

Risk factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
IVIG: yes *vs.* no	0.28 (0.15-0.52)	<0.0001	0.38 (0.19-0.79)	<0.01
Steroids for CRS/ICANS: yes *vs.* no	2.93 (1.35-6.33)	<0.01	2.20 (0.98-4.94)	0.06
Switch to Q2W: yes *vs.* no	0.37 (0.20-0.69)	<0.01	0.65 (0.31-1.36)	0.25
BCMA *vs.* GPRC5D	1.19 (0.59-2.40)	0.62	-	-
N of prior lines of therapy >5: yes *vs.* no	0.96 (0.51-1.78)	0.89	-	-
Prior BCMA therapy: yes *vs.* no	1.06 (0.56-1.99)	0.86	-	-
Hypogammaglobulinemia < 400 mg/dL during therapy: yes *vs.* no	1.28 (0.66-2.46)	0.47	-	-
ANC < 1,000 during therapy: yes *vs.* no	1.42 (0.73-2.79)	0.30	-	-

CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; IVIG: intravenous immunoglobulin; BCMA: B-cell maturation antigen; GPRC5D: G-protein-coupled receptor family C group 5 member D; Q2W: every other week; ANC: absolute neutrophil count; HR: hazard ratio; CI: confidence interval.

Discussion

In this real-world, single-center study, we characterized infections in a cohort of 158 patients with RRMM treated with BsAb. The incidence of all-grade infections was higher in patients receiving anti-BCMA BsAb compared to those treated with anti-GPRC5D agents, with a trend toward statistical significance (P=0.06), in line with prior studies.[12] However, no significant difference was found for grade ≥3 infections, possibly due to the relatively short follow-up.

Other factors may contribute to altering the risk of developing a severe infection. In our univariate analysis, steroids use for managing CRS and ICANS emerged as a risk factor. Conversely, the use of IVIG and the switch to every-other-week BsAb administration were associated with a lower risk. Nevertheless, the multivariate analysis confirmed only IVIG administration as an independent protective factor, reducing severe infection risk by 62%.

Hypogammaglobulinemia is a frequent adverse event, especially with anti-BCMA BsAbs compared to anti-GPRC5D,[15] as highlighted by our study (62% *vs*. 39%). Indeed, current guidelines recommend immunoglobulin replacement therapy for patients with IgG levels <400 mg/dL or recurrent severe infections, and monthly IgG monitoring. The role of IVIG in preventing severe infections, in patients treated with BsAb is increasingly well-established,[16,17] though optimal timing remains undefined. At our institution, due to the high incidence of hypogammaglobulinemia observed in patients receiving BsAb, often with IgG levels falling <400 mg/dL, or effectively under this threshold when correcting for the monoclonal component on serum protein electrophoresis, we implemented a primary prophylactic strategy, starting after cycle 1 (median time, 1.31 months). However, 30% of patients did not receive it due to due to an initial different protocol, insurance denials, or patient refusal, enabling a comparative analysis.

Furthermore, a recent study demonstrated that administering IVIG within 60 days of starting teclistamab significantly reduced the risk of severe infections compared to no IVIG administration.[18] Together, these findings support the early initiation of IVIG, although additional studies are needed to confirm these benefits.

Reducing BsAb administration frequency is another approach to mitigate infections. Sub-analyses from the MajesTEC-1 and the MagnetisMM-3 trials demonstrated lower infection rates with every-other-week dosing in responder patients without compromising efficacy.[19,20] In our cohort, this strategy reduced severe infections, though significance was lost in multivariate analysis, possibly due to limited follow-up, highlighting the need for longer-term data.

Steroid use for CRS/ICANS management was linked to an increased risk of severe infections, although it approached statistical significance in multivariate analysis (P=0.06). Given the known immunosuppressive effects of steroids,[7] their use should be limited to essential cases.

To minimize steroid use and toxicity, targeted prophylactic strategies to mitigate the cytokine storm are increasingly being considered. Prophylactic tocilizumab use has shown promise in reducing CRS incidence and steroids reliance in teclistamab-treated patients.[21] However, the impact of prophylactic tocilizumab on infection rates remains unex-

Table 3. Characteristics, grades and documented pathogens of the clinically relevant infections.

Variables	Total N=116
Site of infection, N (%)	
Upper respiratory tract	44 (38)
Disseminated	25 (22)
Lower respiratory tract	25 (22)
Urinary tract	10 (9)
Gastrointestinal tract	5 (4)
Skin and soft tissue	4 (3)
Otitis	2 (2)
Osteomyelitis	1 (1)
Pathogens isolated, N (%)	70 (60)
Bacteria	26/70 (37)
Enterobacteriaceae	12/70 (17)
E.coli	6/70 (9)
Enterobacter cloacae	2/70 (3)
Salmonella	2/70 (3)
Klebsiella pòneumoniae	2/70 (3)
Pseudomonadaceae	4/70 (6)
Pseudomonas aeruginosa	3/70 (4)
Stenotrophomonas	1/70 (1)
Streptococci	4/70 (6)
Streptococcus pneumoniae	3/70 (4)
Streptococci sanguinis	1/70 (1)
Anaerobic bacteria	3/70 (4)
Clostridium difficile	2/70 (3)
Parvimonas micra	1/70 (1)
Atypical and mycobacteria	2/70 (3)
Bordetella bronchiseptica	1/70 (1)
Mycobacterium avium	1/70 (1)
Enterococci	1/70 (1)
Enterococcus faecalis	1/70 (1)
Viral pathogens, N (%)	42/70 (60)
Respiratory viruses[a]	32/70 (46)
CMV	8/70 (17)
VZV	2/70 (3)
BK virus	1/70 (1)
Fungal pathogens, N (%)	2/70 (3)
Candida	1/70 (1)
Dematiaceous	1/70 (1)
Undocumented, N (%)	46 (40)
Grade of infection, N (%)	
1	17 (15)
2	46 (40)
3	33 (28)
4	15 (13)
5	5 (5)

[a]Including Sars-Cov-2 (N=12), influenza/parainfluenza (N=6), rhinovirus (N=7), rhinovirus/enterovirus (N=5), respiratory syncytial virus (RSV, N=1), metapneumovirus (N=1). VZV: varicella zoster virus; CMV: Cytomegalovirus; BK: polyomavirus.

amined. Although our study did not allow for a comparison with patients who did not receive prophylactic tocilizumab, infection rates were comparable to or lower than those reported in pivotal BsAb trials. Despite the inherent limitations of comparing clinical trials with retrospective studies, these findings suggest that prophylactic tocilizumab may be a safe strategy in terms of infection risk.

A thorough understanding of infection rate is crucial for optimizing therapy dosing and instituting optimal preventive measures. Yet, differences in follow-up duration and the frequent omission of recurrent infections can bias comparisons across studies. To address this and evaluate whether the incidence of each recorded infections (including recurrent ones) varies over time, we analyzed data from the first 12 months of therapy, focusing on monthly infection rates (any-grade and grade ≥3) per 100 patients in the anti-BCMA and anti-GPRC5D group, as suggested in a recent study by Ludwig *et al.*[12] The curves showed a clear decrease in infection rates, especially after the third month. Notably, both the median time for starting IVIG and switching the BsAb to every-other-week administration occurred before the third month, suggesting a possible temporal association.

We also investigated CMV infections, which occurred more frequently in patients treated with BCMA-directed BsAb (P=0.04), aligning with previous reports of greater impact of BCMA-targeting agents on T-cell function.[22] Most CMV infections occurred early during treatment, highlighting the need for close monitoring, especially in the anti-BCMA group. A total of eight CMV infections were clinically signif-

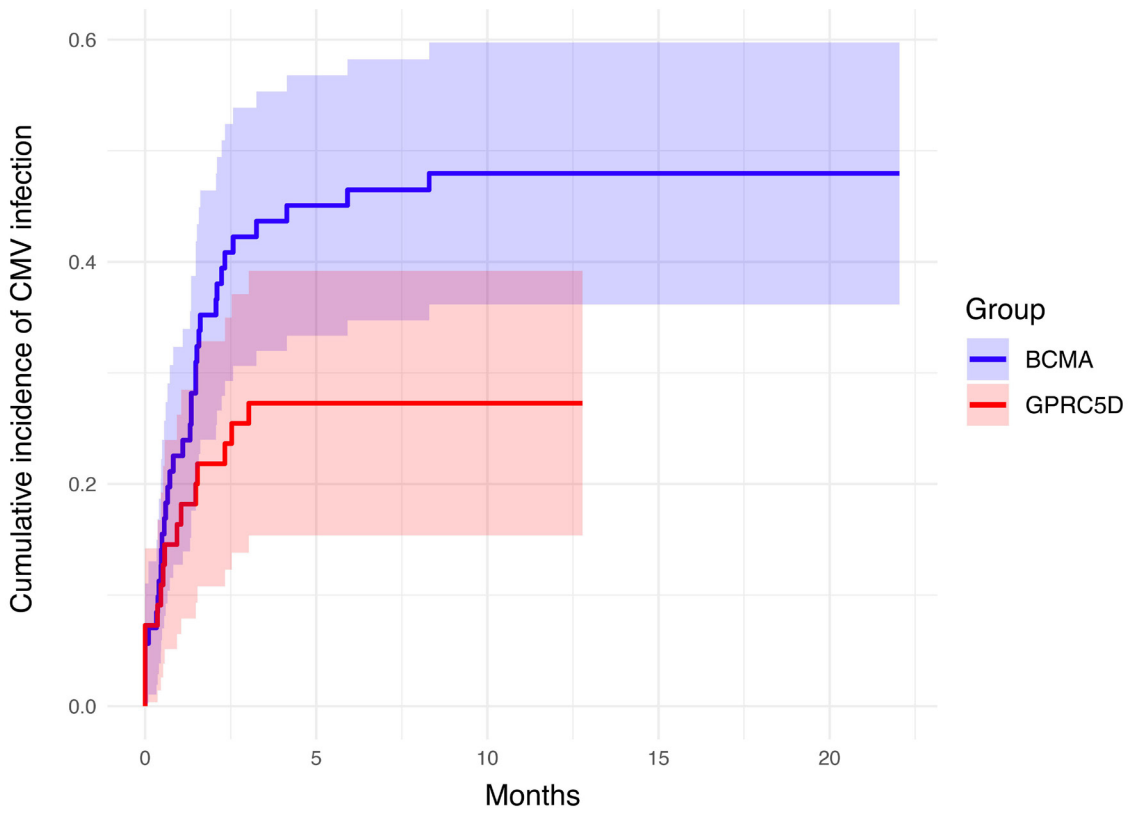

Figure 3. Cumulative incidence of Cytomegalovirus infections among patients treated with BCMA- and GPRC5D-directed bispecific. BCMA: B-cell maturation antigen; GPRC5D: G-protein-coupled receptor family C group 5 member D; CMV: Cytomegalovirus.

Table 4. Characterization of Cytomegalovirus infections.

	Total N=126^	Anti-BCMA BsAb N=71	Anti-GPR5CD BsAb N=55
CMV DNAemia detection, N (%)	43 (34)	36 (51)	15 (27)
CMV clinically significative, N (%)	8 (6)	7 (10)	1 (2)
CMV disease, N (%)	-	-	-
CMV DNAemia peak viral load, UI/mL, median (range)	48 (35-134,000)	50 (35-34,700)	47 (35-134,000)
Threshold at time of treatment, UI/mL, median (range)	7520 (452-134,000)	5630 (452-29,900)	134,000
Duration of viremia, days, median (range)	42 (14-489)	42 (14-489)	56 (28-87)
Time to first CMV DNAemia detection, days, median (range)	20 (0-159)	21 (0-159)	17 (0-91)
Time from CMV DNA detection to peak in pts treated for CMV, days, median (range)	53 (5-143)	58 (5-143)	32

^Cytomegalovirus (CMV) data were available for 71 and 55 patients in the anti-BCMA and anti-GPRC5D group, respectively. BCMA: B-cell maturation antigen; GPRC5D: G-protein-coupled receptor family C group 5 member D; BsAb: bispecific antibodies; pts: patients.

icant; all were managed with preemptive antiviral therapy, preventing progression to CMV disease, hospitalization, and CMV-related mortality. Treatment was initiated at viral loads ranging from 452 to 134,000 IU/mL, in the absence of a standardized threshold. Notably, three of the eight patients who received preemptive therapy had detectable CMV DNAemia within 6 months prior to BsAb initiation, suggesting that prior CMV history may inform risk assessment. The most common infection site was the respiratory tract, followed by disseminated infections. Viral infections were numerically higher than bacterial ones among documented cases. Among opportunistic infections, CMV was the most frequent. No PJP were observed, and only two VZV cases were reported. Of the VZV reported, two of two patients were receiving prophylaxis at the time of infection, indicating that other factors could affect infections risk. Taken together, this data support the efficacy and the recommendations of prophylaxis for these pathogens. SARS-CoV-2 caused one fatal infection and was identified as etiological agent in 12 other infection events. The high incidence of SARS-CoV-2 highlights the importance of keeping patients undergoing cellular therapies updated on immunizations. In addition to SARS-CoV-2 vaccines, annual influenza, pneumococcal, and recombinant varicella zoster vaccinations are essential, alongside the recently available respiratory syncytial virus vaccine.[23]

Our study has several limitations. Its retrospective design and short follow-up period may have impacted the robustness of the analysis and contributed to an underestimation of infection incidence. Infections diagnosed outside our center, particularly those of mild severity, may also have not been consistently captured, potentially contributing to incomplete recording. Moreover, the absence of CMV serology data prior to the initiation of therapy prevents us from distinguishing between reactivations and CMV *de novo* occurrences.

In conclusion, despite a short follow-up, BsAb are associated with frequent any-grade infections, with a trend of higher incidence in patients treated with BCMA-directed therapies. The use of IVIG has proven crucial in reducing severe infections, and primary administration may be a promising strategy for further exploration. In contrast, reducing BsAb dose frequency requires extended follow-up to better assess its impact. Steroids use for CRS/ICANS management should be restricted to necessary cases. CMV infections are more frequent with anti-BCMA agents, and regular monitoring should be prioritized in these patients. Including recurrent infection events and reporting them as rates per 100 patient-months could improve the characterization of infection risk associated with BsAb therapy.

Disclosures

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Contributions

Writing of the original draft by LC. Conception and design by LC, JLK, AKN, SAS and SL. Provision of study materials/patients by SAS, DR, CCH, VAG, MVD, JLK, SL and AKN. Collection and assembly of data by SAS, DR and LC. Data analysis and interpretation by all authors. Final approval of manuscript by all authors. All authors are also accountable for all aspects of the work.

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Data-sharing statement

After the publication of this article, data collected for this analysis will be made available to others upon reasonably justified request, which needs to be written and addressed to the attention of the corresponding author.

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