RESEARCH LETTER

blood advances

TO THE EDITOR:

Infections in patients with lymphoma treated with bispecific antibodies: a systematic review and meta-analysis

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Bispecific antibodies (BsAbs) have demonstrated efficacy in newly diagnosed and relapsed/refractory (R/R) lymphomas. BsAbs form immune synapses between effector cells (T cells) and target cell surface markers; typically, CD19 and CD20 in B-cell lymphomas. BsAb use in myeloma has raised concerns about increased infection risk[1]; less is known about infection rates after BsAb treatment for lymphoma. Three CD20-directed BsAbs are now available for lymphoma as standard of care, and approvals across jurisdictions such as the United States, Canada, and Europe are evolving rapidly.[2] US Food and Drug Administration (FDA) approvals were largely based on small phase 1b/2 studies in heterogenous populations with different dosing schedules, treatment durations, and supportive care protocols. Despite regulatory approvals, there are no guidelines for anti-infective prophylaxis and an incomplete understanding of the rates, timing, and types of infections experienced. Therefore, a systematic review and meta-analysis were undertaken to better characterize infection risks associated with BsAb therapy.

We conducted a PRISMA systematic review and meta-analysis (PROSPERO: CRD42023433207).[3] The search strategy is detailed in the supplemental appendix. Studies reporting infection outcomes after CD20–directed BsAb therapy for the treatment of B-cell lymphoma in adult patients were included. Study identification, data extraction, and bias assessment[4] were performed independently by 2 authors (G.K.R. and M.M.).

The primary outcome was the proportion of patients with lymphoma receiving BsAb treatment in a clinical trial who experienced ≥1 infection of any grade. Secondary outcomes included the rate of severe (grade ≥3) and fatal (grade 5) infections. Subgroup analyses of severe infections were performed according to aggressive vs indolent lymphomas (defined by the World Health Organization diagnostic criteria),[5] monotherapy vs combination therapy, newly diagnosed vs R/R disease, and bispecific agent. Observational studies were described separately.

Meta-analysis of proportions estimated the pooled infection incidence. Cochran Q test examined heterogeneity (I^2). Secondary outcomes and subgroup analyses were performed using random effects models (Mantel-Haenszel). Institutional review board approval was not sought because this study did not constitute human participant research.

Submitted 12 February 2024; accepted 1 April 2024; prepublished online on *Blood Advances* First Edition 16 April 2024. https://doi.org/10.1182/bloodadvances.2024012916.

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PRISMA systematic review protocol is available through PROSPERO (PROSPERO: CRD42023433207).

Extracted data (COVIDENCE) are available on request from the corresponding author, Gemma K. Reynolds (gemma.reynolds@petermac.org)

The full-text version of this article contains a data supplement.

Table 1. Summary of included clinical trials by malignant target and bispecific product

Malignant target	BsAb	No. of trials	Lymphoma subtype (no. of trials)	No. of patients	All-grade infection, % (95% CI)	Median length of follow-up, mo (IQR)
CD20	Epcoritamab	7	Aggressive (5), indolent (1), and B-cell NHL NOS (1)	470	39 (29-47)	11.4 (6.1-17.1)
	Glofitamab	7	Aggressive (6) and B-cell NHL NOS (1)	618	42 (30-53)	10.6 (6-15)
	Mosunetuzumab	6	Aggressive (3), indolent (2), and B-cell NHL NOS (1)	599	43 (47-50)	12.5 (8-28.5)
	Odronextamab	3	Aggressive (1), indolent (1), and B-cell NHL NOS (1)	414	59 (48-69)	21 (NR)

NR, not reported; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

Of the 1133 studies screened, 27 studies (2228 patients; 58% male) were included (supplemental Figure 1). Twenty-three clinical trials (2100 patients) and 4 observational studies (128 patients) reported infection outcomes after the receipt of 1 of 4 CD20-targeting BsAbs (Table 1).

The median cohort age was 65 years (interquartile range [IQR], 61.2-67). Patients received a median of 3 prior therapies (IQR, 1-3) and had infrequently undergone autologous stem cell transplantation (16%) or prior chimeric antigen receptor T-cell therapy (17%). The pooled prevalence of grade ≥3 cytokine release syndrome, immune-effector cell–associated neurotoxicity syndrome (ICANS), and grade ≥3 neutropenia was 1% (95% confidence interval [CI], 0-2), 1% (95% CI, 0–2), and 22% (95% CI, 6-27), respectively. Grade ≥3 leukopenia was 17% (rate reported in 6 studies; 490 patients). Treatment-emergent hypogammaglobulinemia was not routinely reported. Median follow-up was 12 months (IQR, 6-15). Additional extracted variables are presented in supplemental Table 1.

Our primary outcome of any-grade infections occurred in 44% patients treated with a CD20-BsAb (21 studies; 1961 patients; 95% CI, 37-50; $I^2 = 88\%$). Twenty percent of patients experienced a grade ≥3 infection (19 studies; 1791 patients; 95% CI, 15-21). The causes of severe infections were incompletely reported (12/19 studies; supplemental Table 2); just 4 studies reported the cause of all-grade 3 or 4 infections,[6-9] 2 studies reported only the proportion of severe infections attributable to COVID-19,[10,11] and 6 studies reported the etiology of at least 1 severe infection in addition to COVID-19.[12-16] Aggregated across studies, just 133 of 319 grade ≥3 infections (42%) had an etiology reported. Among these 133, the commonly reported causes of severe infection were COVID-19 (32%), clinically diagnosed pneumonia (26%), and sepsis (12%). Severe opportunistic infections were reported specifically in 6 studies (included in supplemental Table 2), including herpes simplex virus/varicella-zoster virus reactivations (9 patients), cytomegalovirus, Epstein-Barr virus and severe influenza (2 patients each), toxoplasmosis (1 patient), *Pneumocystis pneumonia* (1 patient), and fungal pneumonia (fungus not specified, 1 patient)

Fatal infections occurred in 79 of 1774 patients (3%; 95% CI, 2-5). The cause of fatal infection was reported in 54 of 79 (67%; Table 2). Of reported infections, microbiologically confirmed fatal infections (53%) were more common than clinically defined fatal infections (15%). Viral infections were the most common microbiological cause of fatal infections (32/79 [41%]), largely reflecting COVID-19 mortality (91% of viral infections), followed by fungal infections (6% of total fatal infections, predominately *Pneumocystis*, and 1 case of systemic mycosis) and bacterial infections (5% of total fatal infections). One case of fatal toxoplasmosis was reported.[16] In the included observational studies, viral infections were also the most common cause of fatal (73%) and severe infections (100%), which detailed 75 infections (11 fatal; supplemental Table 3).

Several planned subanalyzes were then performed. The rate of all-grade (47% vs 48%), grade ≥3 (20% vs 21%), and fatal infections (4% vs 3%) did not differ significantly between patients with diffuse large B-cell lymphoma (DLBCL) vs follicular lymphoma (FL)(supplemental Table 4).

Additionally, in DLBCL, the rates of all-grade (41% vs 49%; $P = .17$) and severe infections (19% vs 20%; $P = .91$) did not differ between patients with DLBCL who received BsAb for first-line therapy (4 studies; 164 patients) or for R/R disease (8 studies; 715 patients; $P = .17$). In follicular lymphoma, the pooled rates of all-grade infections (59% vs 26%) and grade ≥3 infections (25%

Table 2. Etiology of fatal infections

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Fatal infections	79
Microbiologically confirmed	**42 (53% of fatal infections)**
Viral	32 (41% of fatal infections)
SARS-CoV-2	>29*
EBV	1
CMV	1†
PML	1
Bacterial	4 (5% of fatal infections)
Gram-negative bacteremia	4
Fungal	5 (6% of fatal infections)
Candidemia	1
Pneumocystis jirovecii pneumonia	3
Systemic mycoses	1
Protozoan	
Toxoplasmosis	1
Clinically diagnosed	**12 (15% of fatal infections)**
Sepsis	4
Pneumonia	8
Etiology not reported	25 (32% of total infections)

CMV, cytomegalovirus; EBV, Epstein-Barr virus; PML, Progressive Multifocal Leukoencephalopathy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
*Some studies reported at least the proportion or total number of SARS-CoV-2 associated deaths, thus the acutal number may be higher.
†After first-line therapy.

vs 5%; $P < .01$; supplemental Figure 1) were significantly higher in patients receiving BsAb for R/R follicular lymphoma (4 studies; 372 patients) than that of the single published study examining first-line FL treatment with epcoritamab (39 patients).

When considering monotherapy with BsAb, there were no differences in all-grade (49% vs 50%) or grade ≥3 infections (18% vs 27%) in patients with R/R DLBCL receiving a BsAb as monotherapy compared with as part of combination therapy (supplemental Figure 2). The impact of combination therapy could not be analyzed in patients receiving upfront treatment because all BsAb were administered in combination with chemotherapy.

In agent-specific analyses, in patients with DLBCL receiving BsAb as first-line therapy, there were no significant differences in severe infection rates between BsAb products (supplemental Figure 3A). In R/R DLBCL, the significant differences observed between products was driven by single studies of mosunetuzumab (9%; 95% CI, 4-17) and odronextamab (37%; 95% CI, 29-45; supplemental Figure 3B). In follicular lymphoma, rates of grade ≥3 infections did not differ significantly between patients treated with mosunetuzumab (2 studies; 133 patients [25%]; 95% CI, 7-42) and epcoritamab (1 study; 111 patients [13%]; 95% CI, 7-20; $P > .05$).

Our systematic review of infections in patients with lymphoma receiving BsAbs reveals a notable rate of all-grade (44%) and grade ≥3 infections (20%), with highly variable reporting of infection type. The etiologies of severe (grade ≥3) and fatal infections were underreported. Yet, infection remains a prominent cause of treatment interruption, nondisease-related treatment discontinuation, and nonrelapse mortality.[7,17] Preventive strategies including antimicrobials, infection screening, and vaccination require a detailed understanding of the types of infections they aim to prevent; similarly for diagnostic investigation. Infection reporting is crucial to the safe implementation of these approaches.

A significant proportion of serious and fatal infections were viral, in contrast to other treatments for R/R lymphoma such as chimeric antigen receptor T-cell therapy, in which fatal bacterial infections predominate, although this may relate to study timing.[18] Fatal viral infections were frequently due to COVID-19, which highlights the importance of understanding both antibody and T-cell–specific responses to COVID-19 vaccines in the context of B-cell depletion, as well as optimal vaccine timing in this patient cohort.[19] Additionally, reporting of center-specific prophylaxis regimens could help elucidate whether the severe viral reactivations observed (eg, cytomegalovirus, varicella-zoster virus, and herpes simplex virus), not frequently seen in patients with lymphoma, would benefit from more intensive preventative or monitoring approaches. For clinicians, our results highlight the importance of investigating for reactivated or disseminated viral infection in the context of clinically compatible syndromes in a patient who has received or is receiving a BsAb.

Analysis of infection rates by advanced disease, aggressive disease, and combination therapy did not identify any specific BsAb cohorts at higher infection risk. These results contrast some observational studies highlighting advanced disease and extensive pretreatment as risk factors for infection in patients with lymphoma, which reflect the cohorts of patients who are typically treated on clinical trials.[20] Based on currently available information, some risk factors for infection cannot be separated by subgroup meta-analysis, which is a limitation of our study. For example, first-line BsAb regimens were administered in combination with CHOP chemotherapy, likely confounding the effect of disease stage and combination therapy on infection outcomes. Agent-specific effects were likely also confounded by variable follow-up duration; for example, odronextamab demonstrated the highest any-grade infection rate in the context of the longest median follow-up.[21,22] Comprehensive registries and accelerated public access to individual patient data will help reduce interstudy heterogeneity and rapidly identify cohorts at higher infection risk.[23,24]

Additionally, evaluation of host- and treatment-related risk factors for opportunistic infections may be critical to understanding infection in BsAb-treated patients, given the small but notable occurrence of these infections in a hematological patient population in which these infections are typically relatively uncommon. The duration of neutropenia, lymphopenia, and hypogammaglobulinemia were infrequently reported; insufficient data precluded regression analysis. Cumulative steroid exposure was also underreported, differed notably between treatment regimens and correlated with BsAb therapy duration. Recent studies suggesting that continuous T-cell reduction with BsAbs may induce functional T-cell exhaustion may provide a further mechanistic explanation for the occurrence of opportunistic infections in BsAb-treated patients.[25] Future studies should report more detail around the timing of infections to help compare the relative contribution of early cytokine release syndrome (and its treatment), steroids, and drug ramp up with the effects of long-term exposure to BsAb. Prospectively collected minimum data set of validated risks for opportunistic infection, such as depth and duration of cytopenia, steroid burden, and infection prophylaxis may help better define these periods of infection risk.[23] It also provides impetus for the consideration and investigation of time limited and/or response-adapted BsAb therapy, especially in curative contexts such as DLBCL.[14]

The analysis presented is limited by incomplete reporting of infections across different grades and incomplete reporting of infection etiologies. Similarly, information specific to COVID-19 risk, such as vaccination status, predominant viral strain, and timing of COVID-19 infection was not available to provide further comment on the high proportion of COVID-19 deaths observed. Significant heterogeneity across products, lymphoma subtypes, and combination therapies was observed and although addressed by planned subgroup analyses, resulted in small groups available for pooled analysis.

As BsAbs are increasingly integrated into a broader range of treatment paradigms for lymphoma, the risk of infection needs to be fully and proactively characterized, monitored, and managed. The fatal and severe viral and fungal infections in this cohort contrast to the higher rates of bacterial infections after other antilymphoma therapies and highlights the potential for rapid induction of B- and T-cell dysfunction as a CD20-BsAb class effect. Comprehensive registries and enhanced reporting as part of clinical trials are required to design and implement careful strategies to minimize morbidity and mortality associated with increased utilization of BsAbs.

Acknowledgments: The authors acknowledge the patients who were treated with bispecific antibodies and their families.

G.K.R. is supported by NHRMC PhD scholarship #2013970.

Contribution: G.K.R. designed the study, performed the research, data extraction, meta-analysis, and drafted and edited the manuscript; M.M. performed data extraction and manuscript editing; E.R.S.C. performed data extraction and manuscript preparation; B.W.T., K.A.T., and M.A.S. performed manuscript editing; M.A.A. and E.A.H. performed study design, manuscript preparation and editing.

Conflict-of-interest disclosure: G.K.R. reports research funding from the National Health and Medical Research Council. E.R.S.C reports research funding from Arnold Ventures. B.W.T. reports membership on an entity's board of directors or advisory committees for CSL Behring, Takeda, and Moderna; honoraria from Alexion, Pfizer, and Gilead; and research funding from Merck Sharpe & Dohme (MSD), CSL Seqirus, and Sanofi. M.A.S. reports honoraria from Pfizer and F2G; research funding from the National Health and Medical Research Council, Merck, and F2G; consultancy fees from Pfizer, Takeda, Gilead, and Merck; a leadership or fiduciary role in other board, society, committee, or advocacy group in the Australasian Society of Infectious Diseases-Immunocompromised Host Special Interest Group; and membership on an entity's board of directors or advisory committees in Roche and Pfizer. M.A.A. reports patents and royalties with and being an employee of the Walter and Eliza Hall Institute of Medical Research, which receives milestone and royalty payments related to venetoclax; is a recipient of share in royalty payments; and receives honoraria from Roche, Novartis, Takeda, Kite, AbbVie, Janssen, BeiGene, AstraZeneca, Gilead, and CSL. E.A.H. reports membership on an entity's board of directors or advisory committees in Antengene; other interests with BeiGene; honoraria from and membership on an entity's board of directors or advisory committees in Specialised Therapeutics; speakers bureau fees from Regeneron; membership on an entity's board of directors or advisory committees and other interests in Novartis; membership on an entity's board of directors or advisory committees in and speakers bureau fee from Janssen; membership on an entity's board of directors or advisory committees in MSD and Gilead; membership on an entity's board of directors or advisory committees in and other interests including travel expenses, research funding, and speakers bureau fees from AstraZeneca; research funding from Merck KGaA; and membership on an entity's board of directors or advisory committees in and research funding from Roche and Bristol Myers Squibb. The remaining authors declare no competing financial interests.

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