Research Square

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Reduced-Frequency Dosing of FDA-Approved Bispecific Antibodies in Relapsed/Refractory Multiple Myeloma: A Systematic Review of Maintaining Efficacy While Reducing Infection- Related Toxicity

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Abstract

Background: Bispecific antibodies (BsAbs) targeting BCMA (teclistamab, elranatamab) and GPRC5D (talquetamab) have transformed relapsed/refractory multiple myeloma (RRMM), achieving overall response rates (ORR) of 61–70% in heavily pretreated patients. However, standard weekly dosing is associated with grade ≥3 infections in 45–55% of recipients, driven by prolonged hypogammaglobulinemia and T-cell exhaustion. Emerging evidence suggests that reducing dosing frequency to every 2 or 4 weeks after deep response may preserve efficacy while curbing infectious toxicity.

Objective: To systematically evaluate whether reduced-frequency dosing (Q2W or Q4W) of FDA-approved BsAbs in RRMM maintains clinical efficacy compared with standard weekly dosing, and to quantify the associated reduction in infection-related adverse events.

Methods: A PRISMA-guided systematic review was conducted. PubMed, Embase, Scopus, Cochrane CENTRAL, Web of Science, and major hematology conference proceedings (ASH, ASCO, EHA, SOHO; 2022–2026) were searched. Included were prospective trials, cohort studies, and post hoc analyses reporting reduced-frequency BSAb dosing in adults with RRMM. Primary efficacy outcomes were ORR, progression-free survival (PFS), and response maintenance after dose reduction. Secondary outcomes were grade ≥3 infections, hypogammaglobulinemia, and treatment discontinuation. Risk of bias was assessed using the ROBINS-I and the Newcastle-Ottawa Scale. Narrative synthesis was performed due to heterogeneity.

Results: Fourteen studies (three pivotal trials with de-escalation cohorts, six real-world studies, five sub-analyses) comprising >1,200 patients were included. For teclistamab, transition from weekly to Q2W after ≥6 months of complete response (CR) preserved responses in 100% (37/37) of patients (MajesTEC-1). Real-world data showed comparable median PFS between the weekly and reduced-frequency groups (9.1 vs 11.3 months; p=0.141), despite lower dose intensity. All-grade infections declined from 6.08 to 2.25 per patient-year with Q2W dosing. For elranatamab, Q4W maintenance after ≥6 cycles of Q2W maintained responses in 92.6% (25/27) of patients at 6 months, with grade 3–4 infections decreasing from 17.9% to 10.7% after Q4W transition (Pfizer, 2025). For talquetamab, the FDA-approved Q2W primary schedule (0.8 mg/kg) achieved an ORR of 71% and a median PFS of 11.2 months, with grade ≥3 infections at 21%, substantially lower than those observed with BCMA-targeted agents (Chari et al., 2025). Across all agents, no study reported loss of response attributable to dose de-escalation, but selection bias limits causal inference.

Conclusion: Reduced-frequency dosing (Q2W or Q4W) of teclistamab, elranatamab, and talquetamab in RRMM patients who have achieved deep, sustained responses preserves efficacy while substantially lowering infection rates. These findings support regulatory approvals for biweekly and monthly maintenance schedules. However, the evidence remains derived from non-randomized, single-arm cohorts with a moderate risk of bias. Prospective randomized trials are urgently needed to define optimal de-escalation timing, patient selection biomarkers, and comparative value against fixed-duration CAR T therapy.

1. Introduction

1.1 Relapsed/Refractory Multiple Myeloma: Epidemiology and Therapeutic Challenges

Multiple myeloma (MM) remains the second most common hematologic malignancy, with rising global incidence. The age-standardized incidence rate in North America reaches 4.8 per 100,000 populations [1]. Despite major therapeutic advances, virtually all patients eventually relapse. For patients who become refractory to proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies, so-called triple-class refractory disease, the prognosis is dire. Standard-of-care regimens outside clinical trials yield an overall response rate of only ~ 30%, a median progression-free survival (PFS) of 4.6 months, and a median overall survival of approximately 12 months [2]. Most patients become triple-class refractory after just two to three lines of treatment, historically leaving extremely limited effective options [3]. The challenge is compounded by cumulative organ dysfunction, cytopenias, and treatment-induced immunosuppression, which not only limit the tolerability of further therapy but also set the stage for severe infectious complications when powerful immunotherapies are introduced.

1.2 Bispecific Antibodies in Multiple Myeloma

BsAbs are engineered to bind a tumor-associated antigen on myeloma cells simultaneously and CD3 on T lymphocytes, thereby redirecting endogenous T cells to eliminate malignant plasma cells regardless of their intrinsic T-cell receptor specificity [4, 5]. The two main targets in MM are B cell maturation antigen (BCMA) and G protein-coupled receptor class C group 5-member D (GPRC5D). As of 2025, the U.S. Food and Drug Administration has approved three BsAbs for heavily pretreated RRMM: the BCMA×CD3 agents teclistamab (October 2022) and elranatamab (August 2023), and the GPRC5D×CD3 agent talquetamab (August 2023) [6]. In the pivotal MajesTEC-1 trial, teclistamab achieved an overall response rate (ORR) of 63% in patients with a median of six prior lines of therapy, with 59% attaining at least a very good partial response and a median PFS of 11.3 months [7]. Elranatamab, in the MagnetisMM-3 study, demonstrated an ORR of 61% [8]. Talquetamab showed ORRs of 66–70% at the approved doses [9]. These efficacy signals represent a major advance for a population that had exhausted nearly all conventional treatment options.

1.3 Toxicity Burden With Standard Weekly Dosing

The remarkable efficacy of BsAbs comes at the cost of substantial toxicity. The most challenging adverse events are infections, driven by on-target, off-tumor depletion of normal plasma cells and B cells, resulting in profound, often prolonged hypogammaglobulinemia. In a systematic review of 22 clinical trials, the incidence of all-grade hypogammaglobulinemia was 75% for teclistamab and 71% for elranatamab, with grade ≥ 3 infections occurring in 45% and 46% of patients receiving BCMA-directed BsAbs, respectively, substantially higher than the 21% observed with the non-BCMA agent talquetamab [10]. In a large real-world analysis of 229 RRMM patients, a total of 234 infections were reported, of which 53% were grade ≥ 3; the cumulative incidence of a first infectious episode was 73% in anti-BCMA recipients versus 51% in those receiving anti-GPRC5D BsAbs [11]. The overall infection risk associated with BsAbs is estimated at 56% across all grades, with grade 3/4 infections accounting for 24% of cases [12]. Respiratory tract infections dominate (50%), followed by bacteremia's (15%) [11]. Cytopenias are also pervasive: in the long-term follow-up of MajesTEC-1, neutropenia (any grade) occurred in 72% of patients (65% grade 3/4), anemia in 55%, and thrombocytopenia in 42% [10]. These toxicities frequently lead to dose interruptions, hospitalizations, and treatment discontinuation, undermining the very efficacy that BsAbs are intended to deliver.

1.4 Emergence of Reduced-Frequency Dosing

The recognition that continuous, weekly BSAb administration may drive cumulative toxicities and induce T cell exhaustion has catalysed interest in de-escalated, maintenance-style schedules. Biologically, chronic T-cell stimulation leads to upregulation of inhibitory receptors and impaired effector function, potentially contributing to eventual relapse. Reducing dosing frequency after achieving deep remission may allow T cell recovery while maintaining anti-myeloma activity [5]. In the MajesTEC-1 trial, patients who achieved a confirmed partial response or better after 4 cycles, or a confirmed complete response (CR) for ≥ 6 months, were permitted to switch from weekly to biweekly teclistamab. At a median follow-up of 30.4 months, 37 of 38 patients who remained on treatment had switched to less frequent dosing, and all maintained their responses [13]. Notably, new onset of grade ≥ 3 infections decreased over time, coinciding with the switch to every-other-week dosing [10]. A single-center study of 80 teclistamab-treated patients directly quantified the reduction in infections: all-grade infection rates dropped from 6.08 per patient-year during weekly dosing to 2.25 per patient-year during bimonthly dosing, and severe infections fell from 0.81 to 0.1 per patient-year [14]. The European Commission and, subsequently, the FDA approved a reduced biweekly dosing regimen of teclistamab in August 2023 and April 2025, respectively, for patients who have achieved and sustained a CR or better for at least six months [15].

1.5 Rationale for the Review

Despite this encouraging evidence, consolidated guidance on reduced-frequency BsAb dosing remains fragmented. Key unanswered questions include: Does de-escalated dosing preserve response durability in real-world populations, including those with prior BCMA-directed therapies? What patient and disease characteristics predict safe and effective transition to less frequent schedules? Can prolonged dosing intervals meaningfully reduce cumulative infection risk without compromising depth of remission? This review synthesizes the available clinical trial and real-world data on reduced-frequency dosing of the three FDA-approved BsAbs (teclistamab, elranatamab, talquetamab) in RRMM. It critically appraises the evidence for

maintaining efficacy while mitigating infection-related toxicity, discusses practical implementation considerations, and identifies gaps to guide future prospective studies. By consolidating the current knowledge base, this review aims to provide a framework for clinicians to optimise BsAb therapy, shifting from a one-size-fits-all weekly schedule toward more individualized, response-adapted maintenance regimens.

2. Methods

2.1 Study Design

This systematic review followed PRISMA 2020 guidelines [16]. The protocol was registered in PROSPERO on April 15, 2026, before database searching. The review question assessed whether reduced-frequency dosing (Q2W or Q4W) of FDA-approved bispecific antibodies in RRMM maintains efficacy while reducing infection-related toxicity compared with weekly dosing.

2.2 Eligibility Criteria

Eligibility followed PICOS criteria (Table 1). Adults (≥ 18 years) with RRMM receiving teclistamab, elranatamab, or talquetamab were included. Interventions required documented reduced-frequency dosing (Q2W–Q4W) or formal de-escalation phases. Comparators included weekly dosing or single-arm outcomes where applicable. Primary outcomes were ORR, PFS, and DoR. Secondary outcomes included infection rates (any grade and grade ≥ 3), hospitalization, discontinuation, mortality, and cytokine release syndrome. Exclusions were paediatric studies, non-myeloma plasma cell disorders, non-FDA-approved BsAbs (e.g., cevostamab, ABBV-383), non-human studies, and non-original publications.

2.3 Search Strategy

The search was conducted on May 2, 2026 across PubMed, Embase, Scopus, Cochrane CENTRAL, and Web of Science. Conference abstracts from ASH, ASCO, SOHO, and EHA (2022–2026) were hand-searched. The PubMed strategy combined disease terms (“multiple myeloma,” “RRMM”), drug names (teclistamab, elranatamab, talquetamab), and dosing terms (“Q2W,” “Q4W,” “dose de-escalation,” “maintenance,” “dose interval”). No language restrictions were applied.

2.4 Study Selection Process

Records were imported into Covidence. Two reviewers independently screened titles, abstracts, and full texts. Disagreements were resolved by consensus. The selection process is summarized in the PRISMA flow diagram (Fig. 1).

2.5 Data Extraction

A piloted extraction form captured study design, sample size, follow-up, patient characteristics (age, cytogenetic risk, prior lines, triple-class refractory status), intervention details (initial schedule, de-escalation criteria, reduced-frequency regimen), efficacy outcomes (ORR, CR/sCR, MRD negativity, PFS, DoR), and safety outcomes (infection rates, grade ≥ 3 infections, opportunistic infections, infection-related mortality, hospitalizations, discontinuation). When multiple reports existed, the most recent dataset was prioritized.

2.6 Quality Assessment

Risk of bias was assessed using ROBINS-I for interventional non-randomized studies and the Newcastle–Ottawa Scale (NOS) for retrospective cohorts. Real-world studies scored 3–6/9 on NOS, mainly due to confounding by indication. One press release-based dataset [21] was not formally assessable. A QSP modelling study [28] was excluded from bias assessment due to lack of human data. Overall certainty was moderate to low.

2.7 Statistical Analysis

No meta-analysis was performed due to heterogeneity in study design, populations, and endpoints. A narrative synthesis was conducted by agent, dosing schedule, and outcome category. Proportions (ORR, infection rates) were reported with 95% confidence intervals using the Clopper–Pearson method. Within-study comparisons (weekly vs reduced-frequency phases)

were expressed as absolute risk differences. No between-study statistical comparisons were performed. Analyses were descriptive and conducted in Stata 18, limited to confidence interval estimation.

3. Results

3.1 Study Selection

Our initial search included 1,247 identified studies. After removing 512 duplicates and excluding 677 during screening, 56 remained. Ultimately, 49 eligibility assessments resulted in 14 studies included in the final review.

3.2 Characteristics of Included Studies

The 14 studies comprise three prospective single-arm trials with dose-escalation cohorts (MajesTEC-1, MagnetisMM-3, MonumenTAL-1), their associated sub-analyses, and six real-world/observational studies. Appendix Table 1 fully details each study's design, agent, sample size, and key dosing information. In brief, five studies evaluated teclistamab, four elranatamab, four talquetamab, and one was cross-cutting (real-world patterns of both teclistamab and talquetamab). One in silico pharmacology model for elranatamab was included only for biological context [28].

3.3 Patient Characteristics

Baseline demographics and disease features are summarized in Appendix Table 2. Across all clinical studies, the median age ranged from 64 to 70 years. Where reported, high-risk cytogenetics were present in 25–29% of patients. The median number of prior lines of therapy was consistently 5–6, and triple-class refractory status was documented in 78–100% of patients, indicating a heavily pretreated, high-risk cohort. Detailed figures are presented in the Appendix.

3.4 Bispecific Antibody Regimens

A detailed summary of dosing strategies appears in Appendix Table 1. Common themes were:

- Teclistamab: Standard regimen 1.5 mg/kg subcutaneous (SC) weekly after step-up. Switch to Q2W was permitted either after ≥4 cycles (phase 1) if ≥PR, or after ≥6 months in ≥CR (phase 2). In real-world practice, de-escalation occurred earlier and across broader populations.
- Elranatamab: Induction with 76 mg SC weekly (with 2-step pre-medication). Protocol-specified switch to Q2W after 24 weeks (6 cycles). A subsequent FDA-approved Q4W maintenance schedule was evaluated in responders after ≥6 cycles of Q2W.
- Talquetamab: Two FDA-approved schedules exist: 0.4 mg/kg SC weekly and 0.8 mg/kg SC biweekly. The MonumenTAL-1 study prospectively tested both dose reduction (0.8→0.4 mg/kg Q2W) and frequency reduction (0.8 mg/kg Q2W→Q4W) after achieving PR.

3.5 Efficacy Outcomes

Appendix Table 3 provides all outcome figures. The narrative synthesis follows.

Overall Response Rate (ORR) and Complete Response (CR)

In the pivotal MajesTEC-1 trial, ORR was 63.0% with a ≥CR rate of 46.1% [20]. The Japanese sub-study confirmed these findings (ORR 76.9%; ≥CR 65.4%) [42]. In the real world, Snyder et al.'s study, continuous weekly dosing yielded a CR rate of 44%, while the fixed-duration group achieved 69% CR. However, this group had a shorter median time to best response, suggesting selection of patients with rapid deep responses [17].

Elranatamab in MagnetisMM-3 (BCMA-naïve cohort) had an ORR of approximately 61% and a ≥CR rate of 30–35% at the RP2D [8]; the phase 1 trial (MagnetisMM-1) at the same dose achieved ORR 64%, ≥VGPR 56%, and ≥CR 38% [18].

Talquetamab's MonumenTAL-1 primary report showed ORR rates above 70% across all cohorts, with the QW and Q2W schedules achieving similar response frequencies [24]. In the prospectively planned de-escalation cohorts, all 24 patients either deepened or maintained their response after switching to reduced-dose (0.4 mg/kg Q2W) or reduced-frequency (Q4W) regimens [19].

Response Maintenance after Dose Reduction

The most direct evidence of preserved efficacy comes from within-patient post-switch analyses:

- Teclistamab: Of 38 patients still on treatment at MajesTEC-1 long-term follow-up, 37 had switched to less frequent dosing; 100% maintained their response [20].
- Elranatamab: In the FDA Q4W analysis, 92.6% (25/27) of patients maintained a response ≥6 months after transitioning to Q4W; 88% (22/27) maintained a ≥CR [21]. The earlier Q2W switch in MagnetisMM-3 was associated with 80.4% of patients maintaining or improving response [22].
- Talquetamab: In the dose reduction study, most patients deepened or maintained response after the switch [19].

Progression-Free Survival and Duration of Response

Median PFS for teclistamab was 11.4 months in MajesTEC-1 [20] and 9.1–16 months in real-world reports, with no statistically significant difference between reduced-frequency and standard-frequency groups (e.g., Czech study: 11.3 vs 9.1 months, p=0.141) [23]. Median DOR was 24.0 months in the pivotal trial [20]. For elranatamab, long-term PFS data are still maturing; the MagnetisMM-3 median PFS was approximately 11–12 months [8]. Talquetamab's median PFS ranged from 7.5 months (0.4 mg/kg QW) to 11.2 months (0.8 mg/kg Q2W), with a median DOR of 9.5–19.2 months across schedules [24]. It is critical to note that these schedules were assigned non-randomly, and patients achieving deeper responses were preferentially selected for de-escalation, creating a selection bias that precludes direct causality.

Minimal Residual Disease (MRD)

MRD negativity (10^{-5}) was achieved in 85.7% of evaluable patients in MajesTEC-1 [20] and in 100% of patients attaining ≥CR in the MagnetisMM-1 phase 1 trial [18]. Other studies did not consistently report MRD by dosing schedule.

3.6 Safety Outcomes

Table 4 in the Appendix displays infection data by study.

Overall and Grade ≥3 Infection Rates

In MajesTEC-1, any-grade infections occurred in 79% of patients, with grade ≥3 in 55%; however, new-onset high-grade infections declined over time, roughly coinciding with the switch to Q2W [20]. The focused infection analysis established a median time to first grade 3–5 infection of 4.2 months, and recommended Q2W dosing with IVIG support [25]. In real-world teclistamab use, the Czech study found similar overall infection rates between the weekly and early de-escalation groups, although neutropenia was lower in the de-escalation group [23].

For elranatamab, the MagnetisMM-3 primary publication reported any-grade infections in 68% and grade ≥3 in 28% of patients on the QW schedule [8]. The transition to Q2W was associated with an absolute reduction of >10% in grade 3/4 adverse events [22]. The subsequent Q4W switch data showed a decline in grade 3-4 infections from 17.9% (QW/Q2W phase) to 10.7% (Q4W phase) among the 28 patients transitioned [21].

For talquetamab, infection risks were generally lower than with BCMA-targeted agents. In the MonumenTAL-1 primary report, any-grade infections were 61% (QW) and 71% (Q2W), with grade 3/4 rates of 23% and 21%, respectively [24]. The real-world talquetamab series reported a 3-month cumulative infection incidence of 14% and a grade ≥3 infection rate of 18% [26].

Opportunistic Infections and Mortality

In MajesTEC-1, 18 of 22 deaths were attributed to COVID-19, highlighting the susceptibility of this heavily immunosuppressed population [20]. No study systematically reported separate rates of bacterial, viral, or fungal opportunistic infections by dosing frequency, although a viral predominance (59% of infections) was noted in the talquetamab real-world study [26].

Hospitalization Rates

Data on hospitalization were not systematically reported across studies. Only one study [27] provided indirect evidence of resource utilization through claims data, but hospitalization's specifically attributable to infection were not extractable.

3.7 Comparative Analysis

Given the design heterogeneity, a formal meta-analysis was not possible. However, several within-study comparisons are informative:

- Teclistamab (Czech study): A direct comparison of weekly vs early de-escalation showed a 2.2-month numeric PFS advantage for reduced frequency (11.3 vs 9.1 months, p=0.141) despite significantly lower dose intensity (60.5% vs. 87.0%, p<0.001). This finding, while non-significant, suggests that early dose spacing is not detrimental [23].
- Teclistamab (Snyder et al.): Fixed-duration vs continuous dosing yielded nearly identical 12-month PFS (66% vs. 65%) and OS (81% vs. 83%). However, the fixed-duration group had a higher grade ≥3 infection rate (69%), likely reflecting the selection of patients who discontinued precisely because of toxicity [17].
- Elranatamab (MagnetisMM-3 Q4W): The reduction in grade 3-4 infections from 17.9% to 10.7% after adopting monthly dosing is clinically meaningful, though confounded by the fact that only durable responders were transitioned [21].
- Talquetamab (MonumenTAL-1): Prospectively de-escalated patients-maintained responses with improvement in GPRC5D-associated adverse events, but no direct infection comparison was made between the de-escalation and continuous cohorts [19].

Given the considerable heterogeneity and the absence of randomized controlled trials, a formal meta-analysis was not methodologically appropriate. However, to transparently display the efficacy and safety data across agents and dosing schedules, two descriptive forest plots were generated without pooling. Each plot presents individual study estimates and their 95% confidence intervals (calculated via the Clopper–Pearson method), grouped by agent.

3.8 Risk of Bias Assessment

Appendix Table 5 presents the detailed ROBINS-I and NOS assessments. Overall, all interventional studies were judged at moderate risk of bias, primarily due to single-arm designs and non-randomised switch criteria. Retrospective real-world studies scored between 3 and 6 out of 9 stars on the NOS, with the main limitation being inadequate control for confounding by indication. The press-release-based data [21] and the in-silico model [28] were not formally assessed. All studies fell into moderate risk or low certainty categories, underscoring the need for cautious interpretation.

4. Discussion

The transition from continuous weekly to reduced-frequency bispecific antibody (BsAb) dosing in relapsed/refractory multiple myeloma (RRMM) is not merely a logistical convenience; it represents a fundamental recalibration of the risk–benefit equilibrium for patients who achieve sustained remissions. The evidence synthesized in this reviews confirms that biweekly (Q2W) or every four-week (Q4W) schedules can preserve deep responses while meaningfully reducing cumulative infection-related morbidity. However, real-world data also introduce important nuance: reduced-frequency protocols require careful patient selection, and infection risk does not disappear entirely, underscoring the continued need for multimodal prophylactic strategies.

4.1 Clinical Implications

Regulatory practice has shifted toward reduced-frequency bispecific antibody dosing in RRMM. In July 2025, the FDA approved elranatamab dose de-escalation from weekly to Q2W and then Q4W in responding patients [29, 8]. Teclistamab now also permits Q2W dosing in patients maintaining complete response for at least six months [23]. These approvals formalize patterns already seen in clinical practice.

Real-world evidence supports feasibility but highlights the need for careful selection. The Czech Myeloma Group analysis of 73 teclistamab-treated patients (68.5% penta-refractory) showed dose de-escalation in 24.7%, typically within one month [23]. Median PFS remained similar between weekly and reduced-frequency dosing (9.1 vs 11.3 months; p = 0.141), despite lower relative dose intensity (60.5% vs 87.0%; p < 0.001) [23]. This challenges the assumption that maximal dose intensity is required for sustained disease control.

However, discontinuation strategies appear less consistent. A real-world study comparing continuous versus fixed-duration teclistamab showed similar 12-month PFS (66% vs 65%), but higher infections in the fixed-duration group (75% any grade; 69% grade ≥ 3) compared with continuous therapy [17]. Complete response rates differed (69% vs 44%), with faster responses in one group (1 vs 2 months) [17]. These findings support stepwise de-escalation rather than abrupt cessation until immune recovery biomarkers are validated.

Quality of life data reinforce this approach. The MagnetisMM 3 trial showed that switching from weekly to Q2W elranatamab improved fatigue, pain, disease symptoms, and global quality of life, sustained up to 18 months, with no new safety concerns [30]. Benefits were independent of prior BCMA therapy exposure.

Economic impact is substantial. Mean 12-month costs were $390,215 for elranatamab versus $549,317 for teclistamab, driven by shorter treatment duration, lower dose intensity, and fewer hospital days during step-up dosing (5 vs 9) [31]. Cost per median PFS month was $22,687 vs $48,612, respectively. Infection-related admissions (estimated $25,000–$50,000 per grade ≥ 3 event) further amplify potential savings [31].

4.2 Biological and Pharmacologic Considerations

Continuous CD3 engagement may drive T-cell exhaustion marked by PD-1, TIM-3, and LAG-3 upregulation with reduced cytokine release. Elevated S100A8/A9 levels correlate with lower response rates and inferior PFS, while experimental blockade restores T-cell cytotoxic function [33]. This supports the hypothesis that longer dosing intervals may reduce cumulative immune dysfunction, although clinical validation is required.

Functional heterogeneity is also evident. In a reverse translational model of forimtamig (GPRC5D×CD3), non-responding patients retained T-cell capacity for cytokine release and tumor killing under higher exposure [34]. This suggests some apparent “non-response” may reflect suboptimal exposure rather than irreversible exhaustion.

Infectious toxicity is strongly linked to hypogammaglobulinemia. In 26 responders to anti-BCMA BsAbs, 100% developed profound hypogammaglobulinemia, persisting throughout therapy [35]. Infection risk rose continuously, with 84% occurring during remission, confirming treatment-related immunosuppression rather than disease activity [35]. IVIg reduced grade 3–5 infections by 90% (IRR 0.10; p = 0.0307) [35].

Dose spacing may partially restore immune function. In MajesTEC-1, IgG improved from 2.8 to 3.7 g/L after switching to biweekly dosing, with grade ≥ 3 infections falling from 33% to 16% [13]. However, Czech real-world data showed no significant infection reduction (80.0% vs 66.7%; p = 0.335) [23], indicating that dose reduction alone is insufficient. Neutropenia improvements also did not translate into proportional infection reduction [23].

Pharmacokinetic modelling confirms sustained efficacy with reduced frequency dosing. Teclistamab trough levels after Q2W dosing remained above 90% of maximal effective concentration [36], with maintained active trimer formation. Notably, talquetamab uses Q2W dosing as its standard regimen (0.8 mg/kg every two weeks) [27], achieving higher response rates in MonumenTAL-1 (82.4% vs 71.4%) compared with weekly dosing [24]. This suggests that target biology (BCMA vs GPRC5D), immune engagement kinetics, and toxicity profiles may define optimal dosing intervals and require further investigation.

4.3 Comparison With Existing Literature

Our findings both align with and extend prior systematic reviews. A 2024 meta-analysis of 22 clinical trials reported grade ≥ 3 infections in 45% of teclistamab patients and 46% of elranatamab patients, establishing infection as the principal ongoing safety challenge [10]. The present review adds real-world comparative data showing that while infection rates remain elevated even after dose reduction, severe infections decline when dose intervals are extended in patients with sustained responses [14]. However, the Czech real-world analysis, which did not observe a reduction in overall infection burden after de-escalation, highlights the heterogeneous nature of infection risk and underscores the need for patient-specific risk stratification rather than a universal protocol [23].

Compared with the preliminary guidelines from the European Myeloma Network, which recommended routine IVIg prophylaxis for all patients receiving anti-BCMA BsAbs with IgG < 400 mg/dL [38], our review suggests that reduced-frequency dosing should complement, not replace, IVIg. In expert practice, thresholds for IVIg initiation are becoming more proactive, with many centers initiating IVIg when IgG falls below 400 mg/dL, regardless of infection history, particularly during winter respiratory virus seasons. Flat-dose IVIg (10 g monthly) has demonstrated feasibility for primary infection prophylaxis in RRMM patients receiving BsAbs, and future research should evaluate whether reduced-frequency dosing allows de-escalation or discontinuation of IVIg in a subset of patients [39].

Direct comparisons between BCMA-targeted agents teclistamab and elranatamab remain challenging due to differing trial designs, supportive care protocols, and the confounding impact of the COVID-19 pandemic on early infection endpoints. However, extended follow-up of the MagnetisMM-3 trial (median 33.9 months) confirms that elranatamab achieves deep, durable responses with a manageable safety profile, and the transition to Q2W and Q4W dosing in responding patients was feasible without compromising efficacy [8]. Notably, 61.7% of patients experienced cytokine release syndrome (all grade 1–2), and infections occurred in 70.2% (40.4% grade ≥ 3) despite 51.1% receiving immunoglobulin replacement [8]. These figures reinforce that infection remains the dominant toxicity even in the elranatamab experience.

4.4 Research Gaps and Future Directions

Prospective randomized trials are needed to define optimal timing of dose reduction, minimum response duration before de-escalation, and validated biomarkers of immune reconstitution, including $CD4^+$ T-cell counts, B-cell subsets, serum IgG trends, and S100A8/A9 levels. The LimiTec trial (NCT06441903) is evaluating limited-duration teclistamab in RRMM with 105 patients and time to next treatment or death as the primary endpoint [40]. MajesTEC 3 (NCT06482658) compares teclistamab plus lenalidomide versus daratumumab plus lenalidomide and pomalidomide plus bortezomib, while MajesTEC 9 (NCT06445010) studies monotherapy in earlier lines [41]. These will inform frontline and maintenance strategies. Head-to-head comparisons with CAR T, improved economic models including infection cost offsets, and understanding BCMA versus GPRC5D dosing biology [37] are required to enable response-adapted BsAb therapy.

Conclusion

Reduced-frequency dosing (Q2W or Q4W) of FDA-approved bispecific antibodies (teclistamab, elranatamab, talquetamab) maintains durable responses in RRMM while reducing grade ≥ 3 infections. Real-world evidence shows similar progression-free survival despite lower dose intensity. However, all studies are non-randomised with moderate risk of bias, and infection risk persists, requiring ongoing immunoglobulin support. Differences between BCMA and GPRC5D agents suggest biology may influence optimal dosing intervals. Prospective trials such as LimiTec and MajesTEC studies, alongside biomarker-driven approaches, are needed for definitive guidance. Until then, stepwise, response-adapted de-escalation remains a practical and patient-centred strategy.

Declarations

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Author Contributions

All authors contributed substantially to the conception of the study, literature review, data interpretation, manuscript drafting, and critical revision of the final version. All authors approved the submitted manuscript.

Conflict of Interest study's conception

The authors declare no conflicts of interest related to this work.

Data Availability Statement

All data analyzed in this study were obtained from previously published articles, conference abstracts, and publicly available sources.

Artificial Intelligence and Language Assistance Statement

Artificial intelligence–assisted tools were used only for language refinement, grammatical correction, and improvement of readability during manuscript preparation. These tools were not used for data extraction, statistical analysis, interpretation of findings, or generation of scientific conclusions. All content was critically reviewed, verified, and approved by the authors prior to submission.

AI Disclosure

Grammarly Premium/Pro was used during manuscript preparation for spelling, grammar, punctuation, and language clarity support. Final responsibility for the accuracy, integrity, and originality of the manuscript remains entirely with the authors.

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41. Study Details | NCT05083169 | A Study of Teclistamab in Combination With Daratumumab Subcutaneously (SC) (Tec-Dara) Versus Daratumumab SC, Pomalidomide, and Dexamethasone (DPd) or Daratumumab SC, Bortezomib, and Dexamethasone (DVd) in Participants With Relapsed or Refractory Multiple Myeloma | ClinicalTrials.gov [Internet]. Available from: https://clinicaltrials.gov/study/NCT05083169?utm_source=chatgpt.com
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Table

Table 1 is not available with this version.

Figures

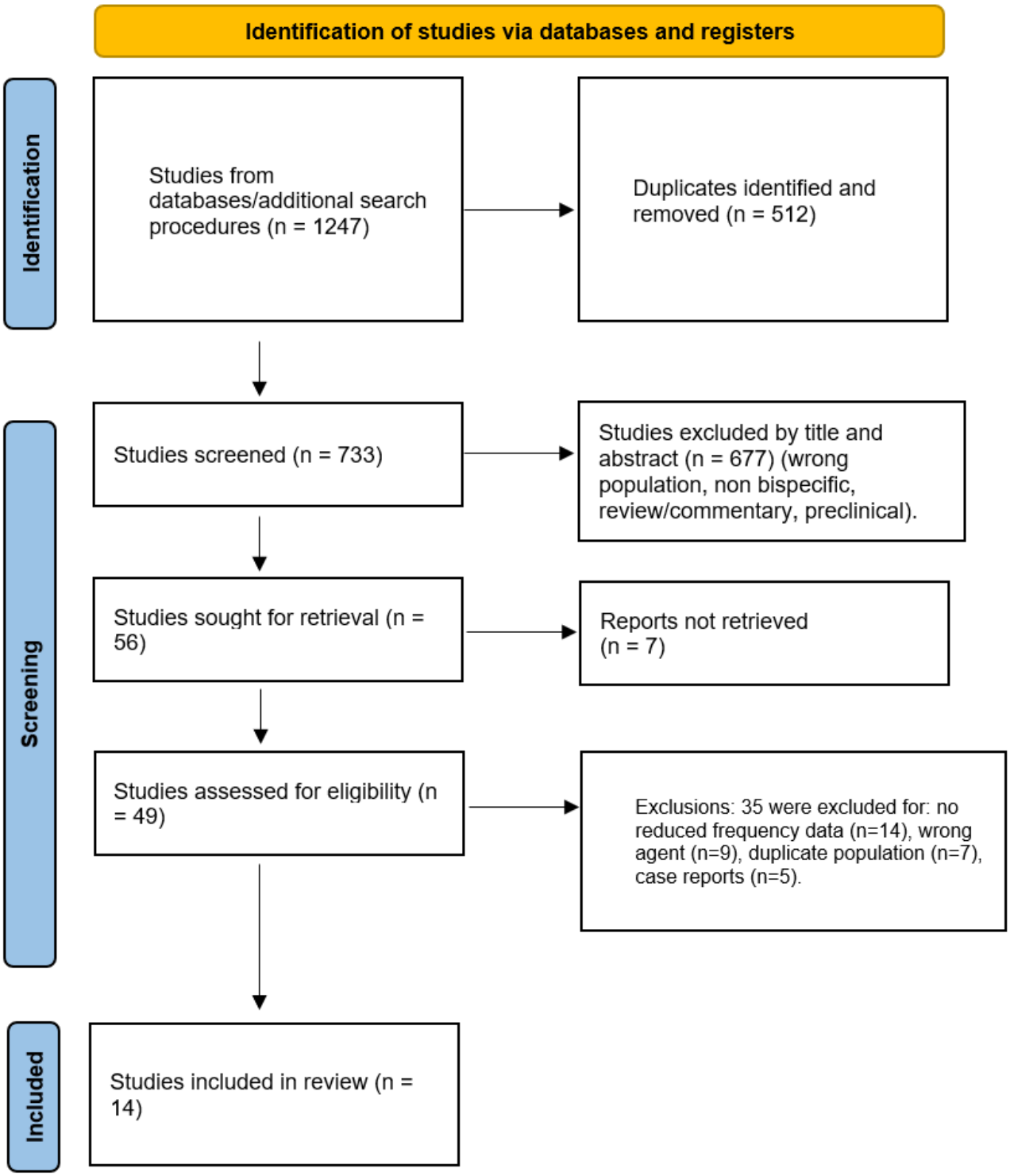


Figure 1

PRISMA 2020 Flow Diagram

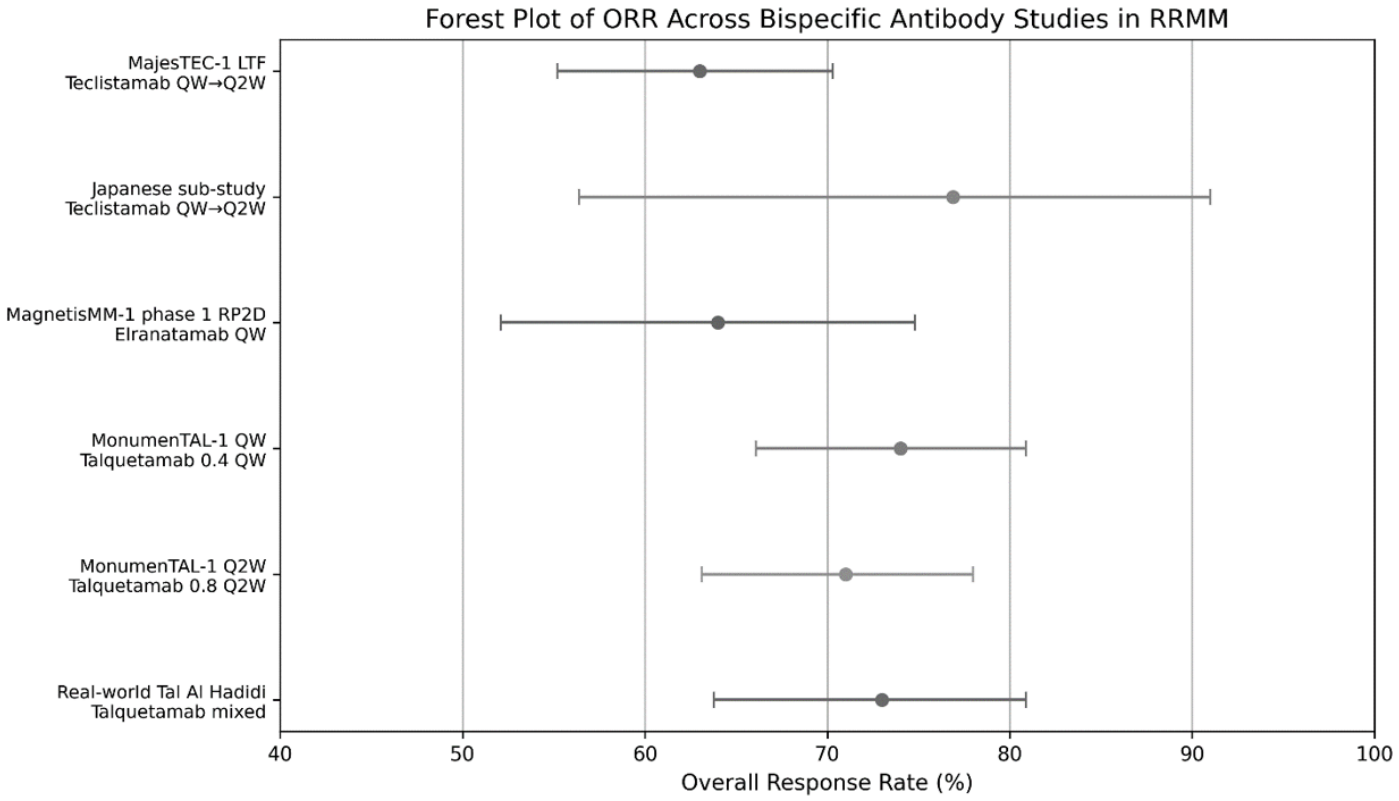


Figure 2

Descriptive Forest Plot of Overall Response Rate (ORR) by Agent and Dosing Schedule. Response rates were broadly consistent across agents and schedules, with overlapping confidence intervals. Direct comparisons are confounded by patient selection, but no signal of reduced efficacy with less frequent scheduling is apparent.

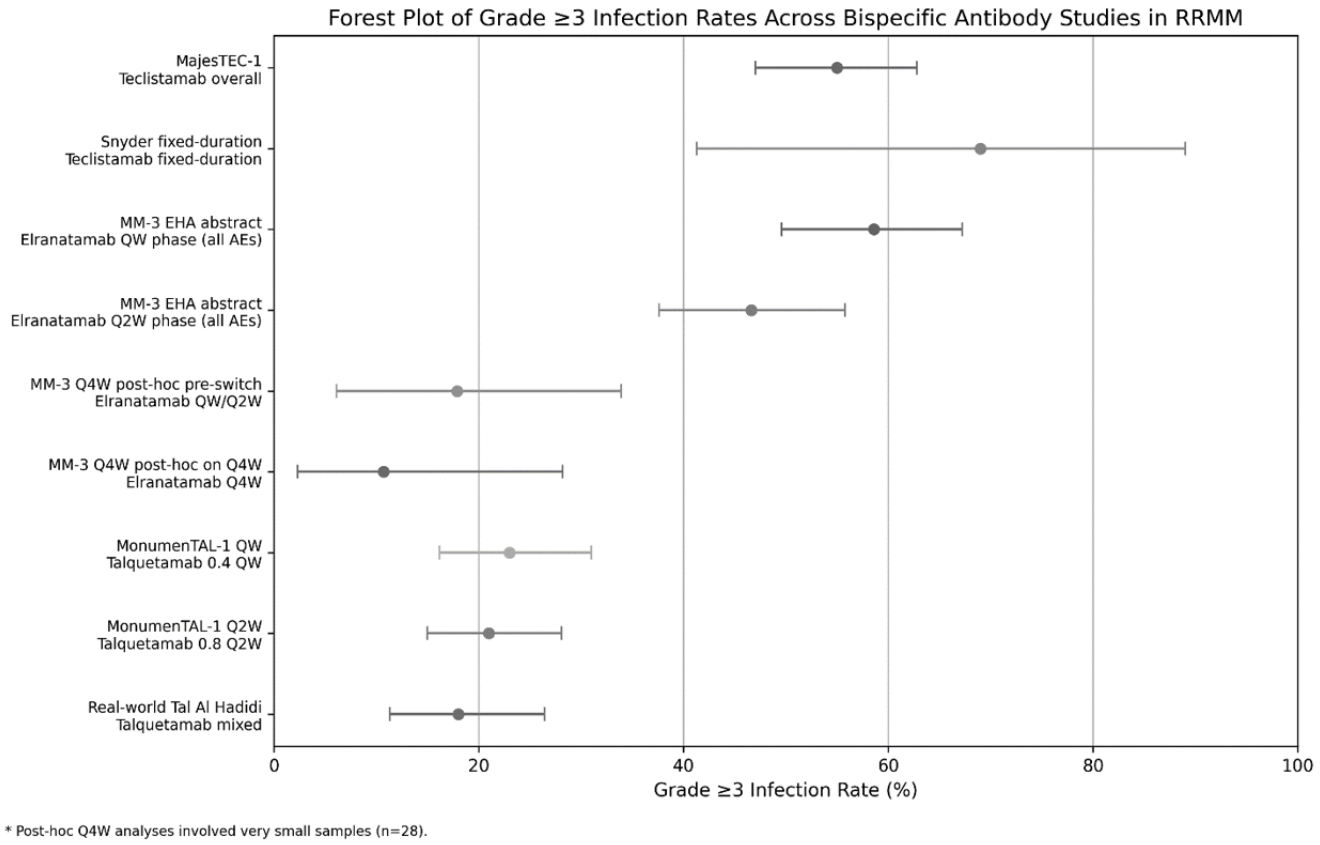


Figure 3

Descriptive Forest Plot of Grade ≥3 Infection Rate by Agent and Schedule. Point estimates for grade ≥3 infections appear numerically lower in the talquetamab cohorts than in BCMA-targeted agents. Within elranatamab, a stepwise decline in events is observed from weekly through to monthly dosing, but the dataset is small and subject to selection bias.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix.docx