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REVIEW

De-escalation of bone-modifying agents in patients with bone metastases from breast cancer: a systematic review and meta-analysis

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Abstract

Purpose Bone-modifying agents (BMAs) such as bisphosphonates and denosumab are usually administered every 4 weeks (standard) in patients with bone metastases from breast cancer to prevent skeletal-related events (SREs). Recent randomized controlled trials suggest every 12-week (de-escalated) dosing interval may be non-inferior. The objective of this systematic review and meta-analysis was to compare the efficacy and harms of standard with de-escalated administration of BMA's in patients with bone metastases from breast cancer.

Methods We searched Medline, PubMed, and the Cochrane Register of Controlled Trials from 1947 to March 14, 2018 and conference abstracts from (2014–March 14, 2018) for randomized clinical trials comparing every 4-week and every 12-week dosing interval of bone-modifying agents. Using PRISMA guidelines, meta-analyses were performed using random-effects models, with findings reported as risk ratios with 95% confidence intervals (CI).

Results From a total of 1311 citations, we identified 8 full-text articles and 1 abstract comprising data from 5 completed randomized clinical trials ($n = 1807$). Zoledronate administration every 12 weeks compared to every 4 weeks produced a summary risk ratio of 1.05 (95% CI 0.88–1.25) for patients with ≥ 1 on-study SRE indicating similar efficacy. These results did not differ whether patients had received prior intravenous bisphosphonate. De-escalation was associated with a non-statistically significant lower risk of increased creatinine (summary risk ratio 0.41 [95% CI 0.15–1.16]). Currently, there are insufficient data for pamidronate and denosumab de-escalation.

Conclusions These data are supportive of de-escalation of zoledronate from onset for patients with bone metastases from breast cancer.

Keywords Bisphosphonates · Denosumab · Breast cancer · Bone metastasis · Skeletal-related event · De-escalated treatment

Introduction

Bone remains the most frequent site of metastatic disease in patients with breast cancer [1–4]. Bone metastases are incurable and associated with worsened survival, significant morbidity, and health care costs [5, 6]. The bisphosphonates

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and denosumab are bone-modifying agents (BMA) that suppress osteoclast-mediated bone resorption and reduce the incidence of first and subsequent skeletal-related events (SREs) including pathological fractures, radiation and/or surgical interventions to bone, spinal cord compression, and hypercalcemia of malignancy [4, 7–9]. BMAs are endorsed by evidence-based practice guidelines [10–12] and are typically prescribed from the time of diagnosis of bone metastasis until the end-of-life [13–15].

The product monograph for pamidronate, zoledronic acid, and denosumab indicates the dosing interval to be every 3–4 weeks. There has been increasing interest in de-escalation of BMA and from the results of three randomized controlled studies, it appears that dosing of zoledronate every 12 weeks is non-inferior to every 3–4-weekly dosing for patients with ≥ 1 SRE [16–18]. As a result, de-escalation of zoledronate from 3- to 4-weekly to 12-weekly dosing was endorsed in the most recent—American Society of Clinical Oncology—Cancer Care Ontario guideline, while the schedules for pamidronate and denosumab remain unchanged [10]. However, the National Comprehensive Cancer Network (NCCN) guideline recommends dosing of zoledronate monthly for 12 months then quarterly [12].

While the existing guidelines summarize the current treatment strategies, there remains uncertainty regarding efficacy of de-escalation of different BMAs and the effects of de-escalation on adverse events [19]. To address these issues, we performed a systematic review and meta-analysis of randomized trials comparing the efficacy and harms of standard 3–4-weekly BMAs with de-escalated dosing (every 12 weeks) in breast cancer patients with bone metastases.

Methods

The protocol was drafted in consultation of PRISMA-P guidance [20] and registered with the PROSPERO International prospective register of systemic reviews (CRD42017076661) (Electronic Supplement Material 1). This systematic review had no formal funding source.

Study objective

The research question of interest was specified according to the elements of the PICOS (Population-Intervention-Comparators-Outcomes-Study design) framework. The research question was: What are the comparative efficacy and harms of standard 3–4-weekly versus 12-weekly dosing of BMAs in breast cancer patients with bone metastases? As exploratory outcomes, we assessed prior intravenous (IV) bisphosphonate use on efficacy and discontinuation due to adverse events.

Electronic search of the literature

Using a literature search strategy designed by an information specialist (RS), we searched Medline, PubMed, and the Cochrane Register of Controlled Trials without date restrictions indicating starting year of 1946; the search was last updated on March 14, 2018. We also searched for relevant abstracts from ASCO, ESMO, and SABCS conferences from 2014 to March 14, 2018. The search strategies for Ovid Medline ®, the Cochrane Register of Controlled Trials, and abstract databases are provided in Electronic Supplement Material 2.

Study eligibility criteria

Eligible studies had to be randomized controlled trials enrolling breast cancer patients with bone metastases that compared q3–4-weekly versus q12-weekly dosing of systemically administered pamidronate, zoledronate, ibandronate, or denosumab. Orally administered agents were not included. There were no restrictions regarding duration of treatment or prior BMA use. We excluded studies that compared different doses of BMAs, non-randomized studies, abstracts later published as full text, letters, commentaries, guidelines, review articles, case reports, editorials, and studies not reported in English.

Process of study selection

All titles and abstracts were screened by two authors (AA, BB, MC, LV). Full-text articles of potentially relevant citations were subsequently screened in full text. When multiple articles reported findings from the same clinical trial, we compiled the most accurate information from all sources. Any discrepancies in study selection were resolved with consultation from a third party (MC). The process of study selection was documented using a flow diagram as recommended by PRISMA (Fig. 1) [20].

Data collection

Data collection was performed and verified by two authors (AA, BB) using a standardized data collection form in Microsoft Excel®. The form gathered data including publication information, study design, eligibility criteria, demographics, calcium/Vitamin D supplementation, efficacy (SRE, Skeletal Morbidity Rate (SMR), time to first SRE, bone pain), and safety data (osteonecrosis of jaw,

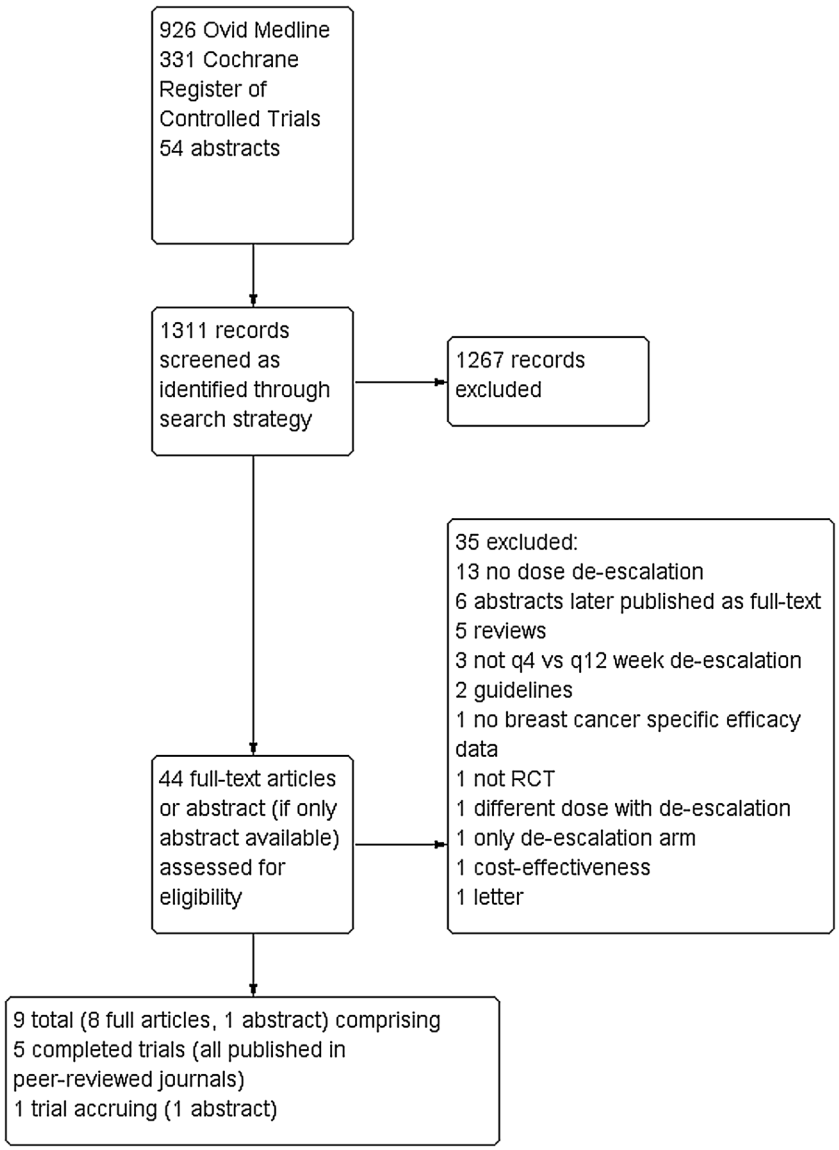


Fig. 1 Study review profile

renal toxicity, hypocalcemia, pain syndromes, acute phase reaction, atrial fibrillation, atypical femur fractures). For pre-specified exploratory analyses, we recorded prior use of BMA and discontinuation due to adverse events. Study authors/sponsors were contacted to provide detailed individual primary data on the CALGB 70604 and OPTIMIZE-2 studies [17, 18]. For the CALGB 70604, which stratified randomization by tumor types (breast cancer, prostate cancer, and multiple myeloma), we used efficacy data reported separately for breast cancer patients, but the demographics and safety data include prostate and multiple myeloma patients.

Risk of bias assessment of individual studies and confidence in cumulative evidence

Studies were independently assessed for risk of bias by two reviewers (AA, BB) using the Cochrane Collaboration's risk of bias tool for randomized trials at the study level [21]. Any discrepancy was resolved by discussion with a third party (BH). Studies were assigned as low, unclear, or high risk of bias for the domains of selection, performance, detection, attrition, and reporting biases. For the outcomes of patients with ≥ 1 SRE, osteonecrosis of the jaw , and increased creatinine, we assigned the Grading of Recommendations Assessment, Development and Evaluation (GRADE) using the GradePRO GDT® software [22–24].

Approach to meta-analysis

If studies were sufficiently homogenous in terms of patient characteristics, design, and outcome definitions/measurement, random-effects meta-analyses using inverse variance approach were conducted. Binary outcomes were synthesized using risk ratios (RR) as the summary measure and

reported with corresponding 95% confidence intervals (CI). Statistical heterogeneity for each meta-analysis was assessed using the Cochrane Q statistic and I^2 statistic, with values > 50% considered to be indicative of potentially important heterogeneity [25]. We used Review Manager Software (Version 5.3, Cochrane Collaboration, UK) for all analyses and generation of forest plots [26]. The standard treatment arm (q3–4 week) was used as the reference treatment for all meta-analyses. A result was considered statistically significant if the 95% confidence interval of the summary statistic did not include 1. Reporting of this review was guided by the PRISMA Statement [20, 27].

Results

Study selection

The search identified 926 citations from Medline, 331 trials from Cochrane library, and 54 abstracts from the ASCO, ESMO, and SABCS conferences for a total of 1311 citations (Fig. 1). We identified 44 potentially relevant studies for which the full texts were reviewed. Our final selection identified 8 full-text articles and 1 abstract comprising 5 completed clinical trials that enrolled 1807 patients and 1 trial currently undergoing accrual [16–18, 28–33]. All completed trials were published in peer-reviewed journals. There were 3 publications of REFORM [28, 29, 31] and two publications of the Lipton trial [32, 33]. The selected abstract belongs to SAKK96/12, REDUSE, a phase III trial assessing de-escalation of denosumab undergoing accrual with no available results and therefore it was excluded from further analysis [34]. Included and excluded abstracts are available in Electronic Supplement Material 3.

Notable exclusions are BISMARK trial, which was a biomarker-directed trial using zoledronate; however, it closed early due to slow accrual with analysis of inadequate number of patients for statistical analysis (289 out of 1500 projected participants) and used dosing intervals of q8–9 and q15–16 weeks [30]. Another trial assessed denosumab de-escalation but did not provide efficacy data separately for the breast cancer patients and was excluded [35].

Study and intervention characteristics

An overview of study characteristics is provided in Table 1. Trials included intravenous zoledronate (3 trials), intravenous pamidronate (1 trial), or subcutaneous (SC) denosumab (1 trial). There were no trials with intravenous ibandronate de-escalation. Two trials (OPTIMIZE-2 [18] and CALGB 70604 [17]) with zoledronate de-escalation were published in 2017, while ZOOM (zoledronate) [16] and REFORM (pamidronate) [29] were published/presented in 2012–2013. The Lipton trial (denosumab) was published in 2007 and 2009 [32, 33]. Of note, the dose of denosumab used in the clinical trials was 180 mg SC and not the standard dose of 120 mg SC. All studies, with the exceptions of the CALGB 70604 [17] and REFORM [29] trials, were industry-funded. CALGB 70604 [17] and Lipton trial [32, 33] did not allow prior intravenous bisphosphonate, whereas all other trials mandated at least 3–12 months of prior intravenous bisphosphonate. All trials mandated calcium and vitamin D administration. The percentage of patients who had a prior SRE, a risk factor for subsequent SRE, was reported in all trials except OPTIMIZE-2 and REFORM [18, 29]. The clinical trial with denosumab was multi-national, whereas all the clinical trials with bisphosphonates were performed in a single country (2 US [17, 18], 1 Italy [16], 1 Canada [29]). The follow-up period ranged from 40 to 60 weeks. The accrual period ranged from 1 to 7 years, and studies were published 1–3 years after completion.

Patient characteristics

We compiled data on baseline age, ECOG performance status, ethnicity, and prior SRE and used weighed average for both groups. The mean and median patient age was 59 years for both the standard and de-escalated groups (Electronic Supplement Material 4, Table 1). The ECOG performance status was reported in all trials except REFORM and was 0–1 in 91% of patients in both groups [29]. Ethnicity was provided in all trials except REFORM, with majority of women, 87% and 86% of Caucasian origin in the standard and de-escalated groups, respectively [29]. The proportions of patients with a prior SRE were 37% (26–63% across studies) and 35% (26–64% across studies) in the standard and de-escalated groups, respectively. The rate of prior SRE between groups was balanced except for Lipton trail [32, 33] where 20/43 (47%) had an SRE in the denosumab every 4 weeks compared to 8/43 (19%) in the denosumab every 12-week arm.

Risk of bias assessment

The risk of selection bias was considered low to unclear in all studies (Fig. 2). When details of the randomization and concealment were not provided, we deemed the studies to be of unclear risk. OPTIMIZE-2 [18] and Lipton trial [32, 33] were deemed to be at low risk for performance bias given their inclusion of blinding with placebo injections in the de-escalated arm, whereas all other studies were open-label (and judged to be at high risk). REFORM [29] was deemed to be at low risk of attrition bias as outcome data were available for all patients. Reporting bias was considered high risk in ZOOM [16] as there was a difference in number of visits in the standard and de-escalated arms. As the complete

Table 1 Main features of included studies

BMA	First author last name	Published peer-reviewed journal	Industry funding	Trial features q3-4 vs q12 weeks	sample size q12; q3-4 weeks	Median Prior IV BMA duration q12; q3–4 weeks (months)	Patient inclusion criteria	Duration of BMA on study	Mean/ median follow-up	Selected Outcomes	Patients with ≥ 1 SRE q12w n (%)	Patients with ≥ 1 SRE q3–4w n (%)
Denosumab	Lipton et al. [32, 33]	Yes	Yes	Phase II, blinding to patients, denosumab 180 mg SC	43; 43	No	MBC (bone mets)	24 weeks	24 week treatment and 32 weeks after treatment	Bone biomarkers, SRE, safety	4 (9)	6 (14)
Pamidronate	Amir et al. (REFORM) [28, 29, 31]	Yes	No	Pilot, open-label, non-inferiority, pamidronate 90 mg IV	19; 19	9; 8	women, MBC, sCTx levels < 600 ng/L	48 weeks	35/38 patients followed for 48 weeks	Feasibility, bone biomarkers, pain, symptomatic SRE, adverse effects	4 (21)	3 (19)
Zoledronic acid	Amadori et al. (ZOOM) [16]	Yes	Yes	Phase III, open-label, non-inferiority, zoledronic acid 4 mg IV	209; 216	12–15 months each arm	Women, MBC (bone mets)	1 year	0.91 year	SMR, proportion of patients with SRE, time to first SRE, bone pain, safety	31 (15)	33 (15)
	Himelstein et al. (CALGB 70604) [17]	Yes	No	Phase III, open-label, non-inferiority, zoledronic acid 4 mg IV	breast/total: 428/911; 427/911	No	Breast cancer, prostate cancer or multiple myeloma.	2 years	1.2 years	Proportion of patients with ≥ 1 SRE 2 years from randomization and within 2 years; safety	122 (29)	114 (27)

Table 1 (continued)

BMA	First author last name	Published peer-reviewed journal	Industry funding	Trial features q3-4 vs q12 weeks	sample size q12; q3-4 weeks	Median Prior IV BMA duration q12; q3–4 weeks (months)	Patient inclusion criteria	Duration of BMA on study	Mean/ median follow-up	Selected Outcomes	Patients with ≥ 1 SRE q12w n (%)	Patients with ≥ 1 SRE q3–4w n (%)
	Hortobagyi et al. (OPTIMIZE-2) [18]	Yes	Yes	Phase III, double blind, non-inferiority, zoledronic acid 4 mg IV q4 vs q12 weeks	203;200	Z 15, P 11 but not reported per arm	women, MBC (bone mets)	1 year	1 year	Proportion of patients with ≥ 1 SRE during study, time to first SRE; skeletal morbidity rate (SMR); safety	47 (23)	44 (22)

BMA bone-modifying agent, *MBC* metastatic breast cancer; *IV* intravenous, *SC* subcutaneous, *SRE* skeletal-related event, *SMR* skeletal morbidity rate, *Ca* calcium, *Z* zoledronate, *P* pamidronate

clinical trial protocols were only available for the CALGB 70604 and OPTIMIZE-2 studies, these were deemed at low risk of other bias. A detailed narrative summary of findings from these assessments is provided in Electronic Supplement Material 5.

Confidence in cumulative evidence (GRADE)

For the primary efficacy outcome of patients with ≥ 1 SRE, we restricted the GRADE assessment to randomized trials with zoledronate with ZOOM, OPTIMIZE-2, and CALGB 70604 as data for pamidronate and denosumab de-escalation were sparse [16–18]. We deemed these trials to have no serious risk of bias. For the outcome of patients with ≥ 1 SRE, we deemed the certainty to be high (Electronic Supplement Material 4, Table 2). For the outcomes of osteonecrosis of the jaw and increased creatinine, the certainty was deemed to be moderate (Electronic Supplement Material 4, Table 2).

Findings, efficacy outcomes

Patients with ≥ 1 skeletal-related event during treatment or follow-up SREs were defined in all studies to be a composite outcome measure consisting of fracture, surgery or radiation to bone, or spinal cord compression; the ZOOM [16] and REFORM [29] studies also included hypercalcemia. A forest plot presenting meta-analyses of patients with ≥ 1 SREs while on treatment and only in the case of Lipton trial [32, 33] during the pre-specified follow-up period with different BMAs is presented in Fig. 3. While summary findings related to comparisons between standard and de-escalated treatment with pamidronate and denosumab found no differences between approaches, available data, however, are sparse. For zoledronate de-escalation, the risk ratio of 1.05 (95% CI 0.88–1.25) indicates no significant difference.

Skeletal morbidity rate Skeletal Morbidity Rate (SMR) was defined as SREs per patient-year. It was reported only in trials of zoledronate: ZOOM [16], OPTIMIZE-2 [18], and CALGB 70604 [17]. However, different statistical representations of variance between studies were reported. These trials reported mean SMR values with no statistically significant difference between standard vs de-escalated arms as follows: ZOOM [29]: 0.22 (95% CI 0.14–0.29) vs 0.26 (95% CI 0.15–0.37) [16]; OPTIMIZE-2 [18]: 0.46 (SD 1.06) vs 0.5 (SD 1.50) [18]; CALGB 70604: 0.4 (IQR 0–0.5) versus 0.4 (IQR 0–0.5) [17]. Given the heterogeneity in reporting of SMR, we did not perform a quantitative analysis.

Time to first on-study SRE Time to first on-study SRE analysis was planned for the ZOOM [16], OPTIMIZE-2 [18], and CALGB 70604 [17]. However, it could not be calculated

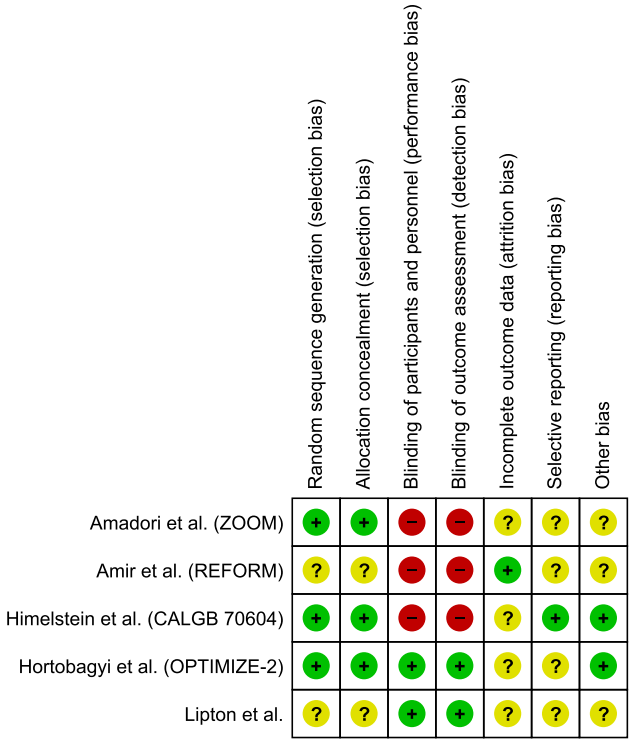


Fig. 2 Risk of bias assessment; (+) = low risk, (?) = unclear risk, (−) = high risk

in ZOOM due to low event rate [16]. OPTIMIZE-2 [18], where prior bisphosphate use was required, reported a non-statistically significant hazard ratio for time to first SRE of 1.06 (95% CI 0.70–1.60). CALGB 70604 [17], where no prior IV bisphosphate use was required, reported time to first on-study SRE or death was 15.7 months with standard dosing and 16.8 months with de-escalated dosing, respectively; of note, however, this includes data from patients with multiple myeloma and prostate cancer in addition to those with breast cancer.

Findings, harm outcomes

Osteonecrosis of the jaw All 5 trials reported data regarding osteonecrosis of the jaw; however, the method of evaluation differed between them. In OPTIMIZE-2 [18], oral examinations were mandated at 1 and 6 months after randomization and at the end of the study, whereas CALGB 70604 [17] included a monthly oral questionnaire. In ZOOM [16], patients were simply advised to have dental evaluations before starting treatment. REFORM [28, 29] and Lipton trial [32, 33] did not report their method of monitoring for osteonecrosis of the jaw and reported zero occurrence events of this complication. Across studies, the aggregate incidence was 0.9% (13/1421) in the de-escalated arm compared to 1.6% (23/1427) in the standard arm, resulting in a summary estimate from meta-analysis of RR 0.59 (95% CI 0.30–1.17) favoring the de-escalated group, though this difference did not reach statistical significance (Fig. 4a).

Renal function

The dosing, definition, monitoring, and reporting of renal function deterioration differed among studies. OPTIMIZE-2 [18] and ZOOM [16] used "usual" zoledronate product monograph instructions limiting use to patients with baseline serum creatinine ≤ 3.0 mg/dL (or creatinine clearance of ≥ 30 mL/min) and used baseline Cockroft–Gault creatinine clearance to determine zoledronate dosing. Serum creatinine was checked within 72 h of zoledronate dosing, and if a patient's serum creatinine level rose by ≥ 0.5 mg/dL (baseline < 1.4 mg/dL) or ≥ 1 mg/dL (baseline ≥ 1.4 mg/dL), then zoledronate was delayed until serum creatinine reduced to 10% of baseline value. OPTIMIZE-2 [18] defined increased serum creatinine as ≥ 0.5 mg/dL (baseline < 1.4 mg/dL) and ≥ 1 mg/dL (baseline ≥ 1.4 mg/dL) and used Common Terminology Criteria for Adverse Events version 3 [36]. However, CALGB 70604 [17] used Cockroft–Gault creatinine clearance within 7 days prior to zoledronate administration to determine dosage instead of baseline creatinine clearance as per product monograph. Furthermore, renal adverse event data from CALGB 70604 [17] were not available separately for breast cancer patients and include patients with multiple myeloma where renal involvement may occur due to underlying disease. Therefore, CALGB 70604 data were excluded from analysis. REFORM [29] excluded patients with serum creatinine above normal limit for the institution. The aggregate incidence of increased creatinine/renal adverse event was 1.2% (5/430) in the de-escalated arm compared to 2.8% (12/433) in the standard arm, resulting in a summary estimate from meta-analysis of RR 0.41 (95% CI 0.15–1.16) favoring the de-escalated group, though this difference did not reach statistical significance (Fig. 4b). Lipton reported no renal adverse events with denosumab.

Other assessments of harms including hypocalcemia, pain syndromes, acute phase reaction, atrial fibrillation, local skin reaction, and atypical femur fracture indicating either little data to draw conclusions or no statistically significant difference between standard or de-escalated dosing of BMA is reported in Electronic Supplement Material 6.

Exploratory analysis

Prior use of IV bisphosphonate We assessed whether use of IV bisphosphonate as in ZOOM for 12–15 months, OPTIMIZE-2 for 11–15 months, and REFORM for 8–9 months prior to de-escalation compared to upfront de-escalation as

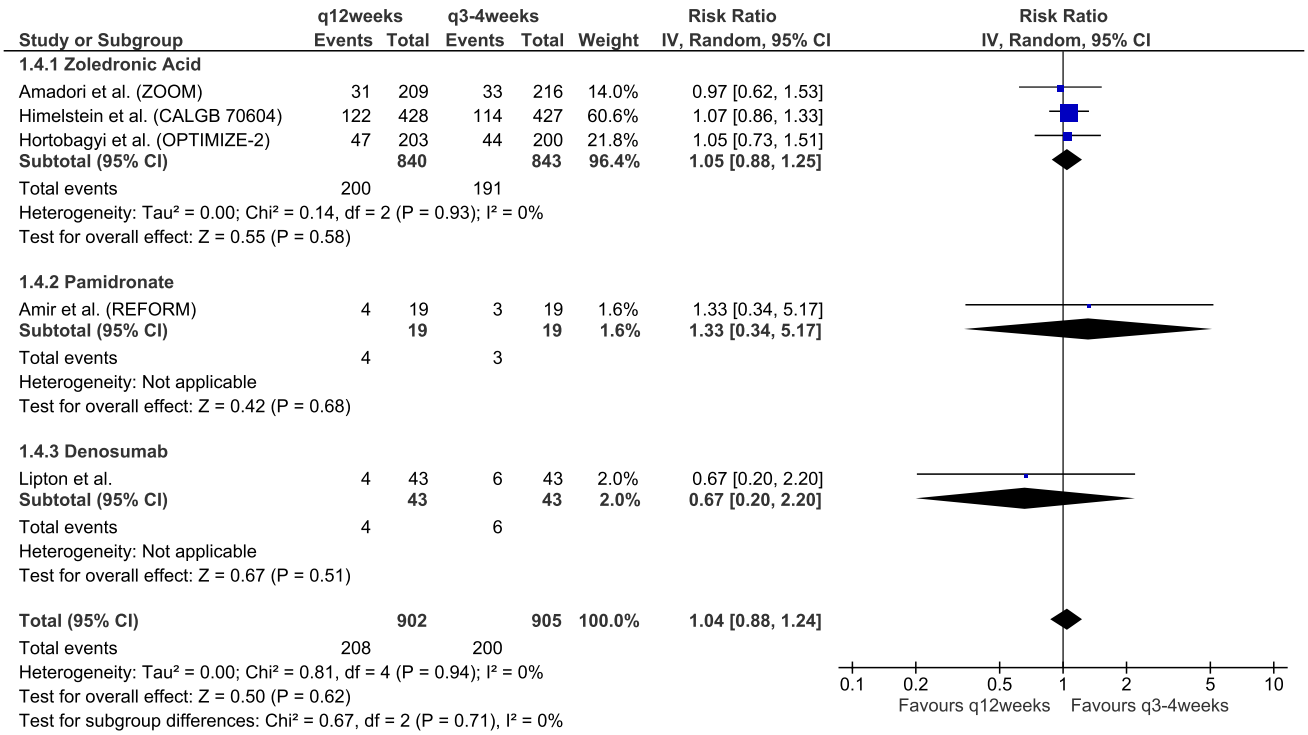
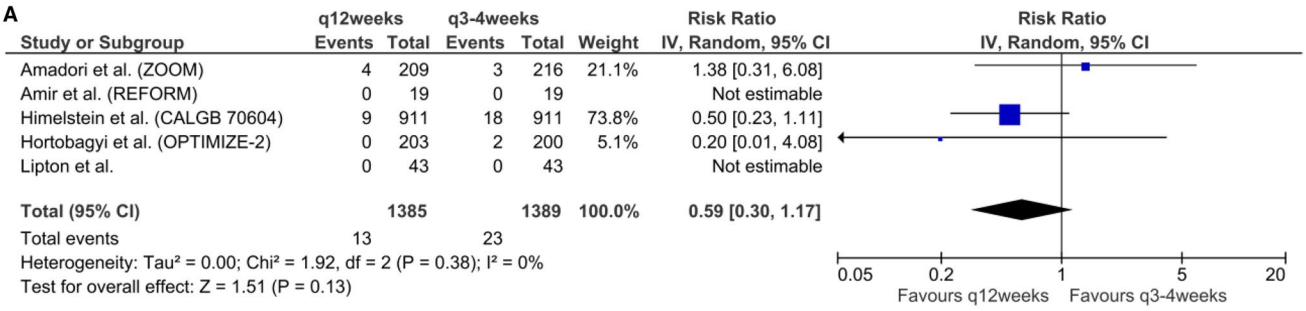


Fig. 3 Patients with ≥ 1 SRE during treatment and follow-up with different bone-modifying agents



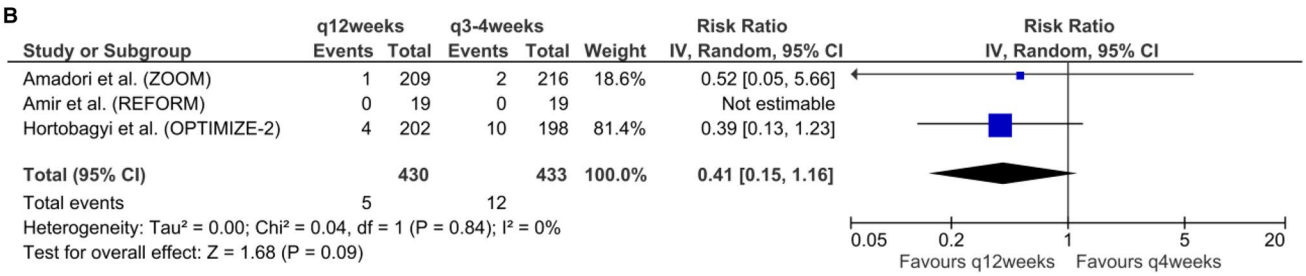


Fig. 4 Harms associated with bone-modifying agents: **a** Osteonecrosis of the jaw and **b** increased serum creatinine with bisphosphates defined as ≥ 0.5 mg/dL with a baseline creatinine level < 1.4 mg/dL and ≥ 1 mg/dL or greater with baseline creatinine level of ≥ 1.4 mg/dL

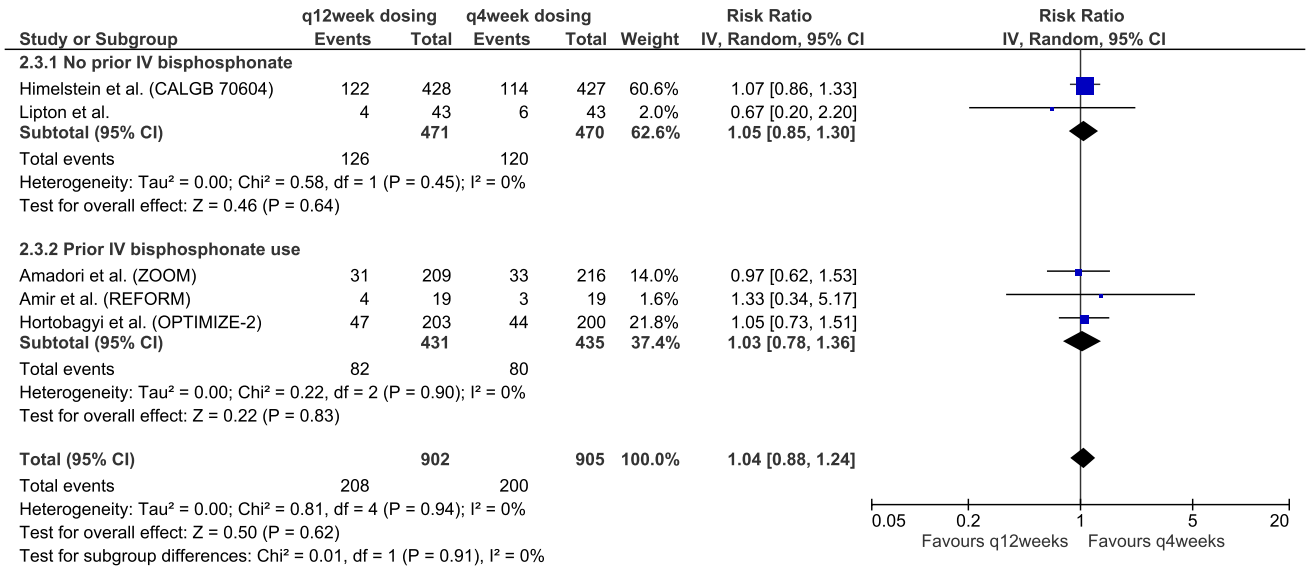


Fig. 5 Patients with ≥ 1 SRE for patients with and without prior IV bisphosphonate

in CALGB 70604 and Lipton trial was as effective [16–18, 29, 32, 33]. We found similar risk ratio of patients with ≥ 1 on-study or during follow-up SRE in patients with no prior IV bisphosphate RR 1.05 (95% CI 0.85–1.30) compared to RR 1.03 (95% CI 0.78–1.36) with prior IV bisphosphonate (Fig. 5).

Discontinuation due to adverse events

The ZOOM, REFORM, CALGB 70604, and OPTIMIZE-2 trials reported patients who discontinued their treatment due to adverse events [16–18, 29]. A meta-analysis showed 2.8% (38/1342) of patients in the de-escalated arm compared to 5.5% (74/1346) in the standard arm discontinued treatment due to an adverse event with RR 0.51 (95% CI 0.30–0.89) (Electronic Supplement Material 4, Fig. 1).

The assessment of pain as an efficacy outcome showed no difference between standard and de-escalated dosing of BMA (Electronic Supplement Material 6).

Discussion

This meta-analysis and systematic review demonstrates that de-escalation of zoledronate to every 12 weeks instead of every 4 weeks provides equal efficacy in terms of patients with ≥ 1 SRE on study, skeletal morbidity rate, and time to first SRE regardless of whether patients have had previous standard dosing of intravenous bisphosphonate. Furthermore, zoledronate de-escalation is possibly associated with non-statistically significant reduced risk of increase creatinine and osteonecrosis of the jaw. Patients were twice as likely to discontinue treatment due to an adverse effect in standard compared to de-escalated arm. No conclusions regarding the efficacy or safety of pamidronate or denosumab de-escalation can be made until results are available from the REaCT-BTA (available in 2019, NCT02721433) and SAKK96/12, REDUSE trials (available around 2022, NCT02051218).

There are limitations to this meta-analysis. We had data for SRE for breast cancer patients from CALGB 70604, but safety data included in this meta-analysis include patients with prostate cancer and multiple myeloma [17]. However, given randomization stratified by cancer type, we do not think this has significant impact on the findings. This meta-analysis did not use individual patient data as it was unavailable in a timely fashion despite requests. Furthermore, the five trials included had varying study designs with mostly open-label trials, different methods for recording efficacy and safety outcomes, and REFORM mandated a cutoff for marker of bone turnover in their inclusion criteria [29]. However, despite these limitations, the overall conclusions of these multiple trials were similar.

All trials except REFORM trial used skeletal-related event (SRE) instead of Symptomatic Skeletal Event (SSE) which excludes asymptomatic radiographically detected fractures or spinal cord compression [29]. SSE is being increasingly used as an endpoint of interest in trials with bone metastases. However, a recent trial showed similar results whether SRE or SSE is used as outcomes [37].

There is one prior systematic review assessing de-escalation of BMA in breast cancer patients with bone metastases but this was done prior to publication of the large

OPTIMIZE-2 and CALGB 70604 trials [17, 18, 38]. There is another review assessing de-escalation of only zoledronate without limitation to tumor type with significant deficiencies with incomplete adherence to the PRISMA statement (no review protocol registered or provided, errors in risk of bias assessment) [39]. They reported efficacy outcome as occurrence of SRE, data which are not provided in any of the trials included in their analysis [39]. However, both these reviews provide similar findings to our analysis but without commentary on prior bisphosphonate use or assess efficacy or harm outcomes in detail.

In an era personified by personalized therapy, optimization of bone-targeted therapy use has the potential to have great impact on patient care. However, there remains a significant need to select patients who would benefit from standard or de-escalated therapy. Factors such as bone-only disease, presence of visceral metastases, burden and location of bone metastases, and selective use of markers of bone turnover remain to be evaluated [40]. Furthermore, no trials have assessed de-escalation of BMA after 2 years of use in breast cancer, which may be a population that has lesser benefit and greater harm. Therefore, there remain many ongoing questions that researchers will need to address around the role of de-escalation of these agents.

Conclusion

The results from 3 phase III trials and guidelines such as ASCO-CCO and NCCN® suggest evidence of zoledronate de-escalation [10, 12]. This meta-analysis confirms that de-escalation of zoledronate is reasonable for patients with bone metastases from breast cancer. Furthermore, contrary to NCCN® guidelines which recommend standard zoledronate for 12 months and then de-escalation, our meta-analysis reveals similar efficacy in patients without prior IV bisphosphonate use. Patients will benefit from fewer clinic visits, potentially reduced toxicity, and reduced costs to the patient and the health care system as demonstrated in recent cost effectiveness analysis from the CALGB 70604 data [41]. There are ongoing studies that will give data for other BMAs such as pamidronate (NCT02721433) and denosumab (NCT02051218) [34, 42].

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Compliance with ethical standards

Conflict of interest Dr. Awan reports participating in the Novartis Canada Advisory Board on the use of Ribociclib. Dr. Hutton reports personal fees from Cornerstone Research, outside the submitted work. Dr. van Poznak reports personal fees from UpToDate and institutional research funds from Bayer, outside the submitted work. The remaining authors declare that they have no conflicts of interest (Hilton, Mazzarello, Vandermeer, Bota, Stober, Sienkiewicz, Fergusson, Shorr, and Clemons).

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Not applicable as this is a systematic review.

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