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Systematic Meta Analysis

Interval Comparison of Zoledronic Acid Treatment in Patients with Metastatic Bone Disease, Is 4-Weekly or 12-Weekly More Effective?: A Systematic Review and Meta-analysis

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Abstract

Objectives: The aim of bisphosphonate treatment in patients with metastatic bone disease is to prevent metastatic skeletal morbidity and prevent cancer treatment-induced skeletal damage. The classical recommendation of Zoledronic acid treatment is to be given indefinitely as intravenous infusion every 3 to 4 weeks until patients' health deteriorates. Data on zoledronic acid's long-term effectiveness and safety are insufficient, and some recent literatures start to consider 12-weekly administration as a reasonable alternative in order to minimize the adverse effects.

Methods: A systematic search was conducted based on PRISMA guideline to identify relevant studies through PubMed, Google Scholar, and Cochrane database. A total of 5 studies (2867 patients) were included, divided into outcome analysis, processed using Review Manager 5.3.

Results: The search of electronic databases yielded a total of 299 entries. Five studies were included in the qualitative and quantitative synthesis following the steps of identifying, screening, determining eligibility, eliminating duplicates, and excluding studies. Out of a total of 2.867 patients, 1.427 received ZA for 12 weeks and 1.440 received ZA for 4 weeks, making up the total number of patients included in this meta-analysis. Each trial had a comparable one-year follow-up duration after ZA was given. We discovered that the incidence of adverse effects varied significantly between the two groups. In contrast, there is no statistically significant difference in the rates of SRE, ONJ, renal dysfunction, or death between the two groups.

Conclusion: Our systematic review and meta-analysis reveals that 12-week intervals of zoledronic acid is as effective as the standard 4-week interval in terms of skeletal related event, jaw osteonecrosis, renal dysfunction, and mortality rate. However, the standard 4-week intervals led to higher rate of adverse effects.

Keywords: Extended regimen, meta-analysis, standard regimen, zoledronic acid

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Cancer and its treatment can have profound effects on bone health.[1] Clinicians treating cancer patients need to be aware of the multidisciplinary treatments available to reduce skeletal morbidity from metastatic disease and minimize cancer treatment-induced damage to the normal skeleton.[2]

Zoledronic acid is a potent bisphosphonate that inhibits osteoclast-mediated bone resorption.[3] It has been approved for treatment of patients with bone metastases from solid tumors or multiple myeloma and for the management of tumor induced hypercalcemia. Because Skeletal-Related Events (SREs) can occur repeatedly during metastatic disease

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that involves the bone, American Society of Clinical Oncology clinical guidelines recommend zoledronic acid be taken indefinitely as intravenous infusion every 3 to 4 weeks until there is deterioration of the general health of the patients.[4]

Data regarding efficacy and safety of zoledronic acid beyond 1 year of treatment are limited.[5,6] This lack of data is particularly significant in patients with breast cancer in whom survival with bone metastases usually exceeds 1 year. Additional concern regarding long-term administration of zoledronic acid pertains to its preferential binding and accumulation in bone, thus prolonging its pharmacologic activity after discontinuation of long-term treatment.[5,6]

Until recently, there has not been any consensus thoroughly describing the efficacy or benefits between standard and extended regiment of zoledronic acid as the treatment for metastatic bone disease. Through this meta-analysis, we aim to objectively describe the efficacy of zoledronic acid in its use as a 4-weekly standard regimen and extended 12-weekly regimen.

Methods

The study design was a systematic review and meta-analysis of relevant comparative studies. A systematic search was conducted from January 2012 to January 2022 to identify relevant studies through PubMed, Google Scholar, Cochrane, Medline, and EMBASE Database based on PRISMA guidelines (Fig. 1). The keywords used were: "Zoledronic Acid" AND "4-weekly" AND "12-weekly" AND "Metastatic".

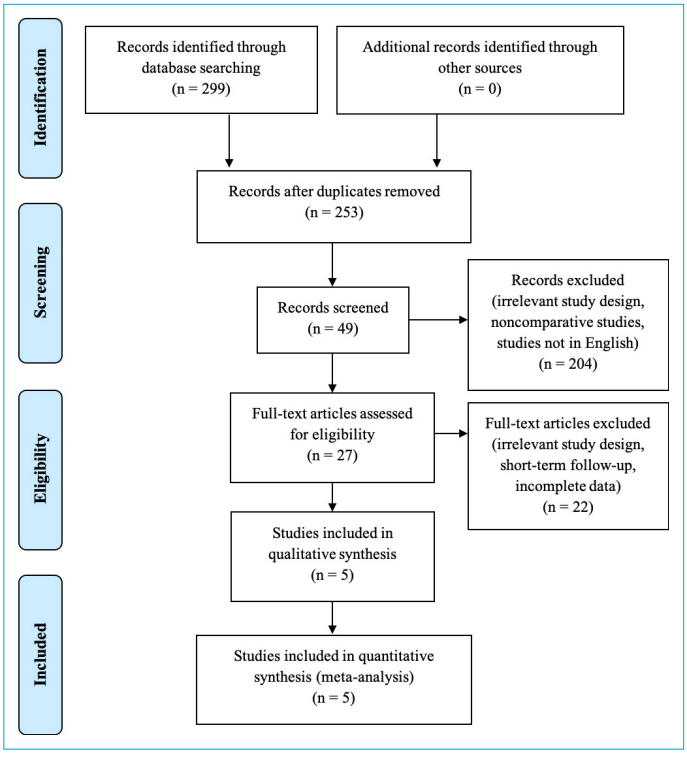

Figure 1. Flowchart showing article selection based on PRISMA guidelines.

Those studies were then manually scanned and reviewed by all authors according to the following inclusion criteria: (1) metastatic cancer patient administered with zoledronic acid; (2) the population included patients with metastatic cancer diagnosed through clinical, radiological, and/or laboratory studies; (3) at least one of the following outcomes was reported: adverse event, skeletal related event, kidney dysfunction, osteonecrosis of the jaw, mortality rate (4) the study was published in English, and (5) applied a randomized controlled trial (RCT) or cohort study design. The exclusion criteria were: (1) less than 1 year of follow up, (2) trauma and degenerative pathology, (3) animal studies, (4) case reports or series, review articles, and noncomparative studies are also excluded. Table 1 presents the inclusion and exclusion criteria according to the PICO method (Population, Intervention, Comparison, and Outcome).

Of all potential studies, critical appraisal was performed to assess the eligibility of those studies using a scoring system adapted from Joanna Briggs Institute (JBI), comprising 10 aspects from the view of population, exposures, confounding factors, outcome, follow-up, and statistical analysis. From each included study, data related to patient and study characteristics (e.g. age, sex, primary tumor) and outcomes were extracted and aggregated. Dichotomous variables — skeletal related event, osteonecrosis of the jaw, adverse event, kidney dysfunction and mortality rate — were assessed in terms of odds ratio (OR) and 95% confidence intervals (CI). Calculations were performed using Review Manager (RevMan) software (Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). A fixed-effect model was used when heterogeneity (I2) was <50%, whereas a random-effect model was used when it was >50%.

Results

Literature Search, Study Selection and Study Characteristics

The electronic research resulted in 299 records from various databases. After the process of identification, screening, eligibility, duplication elimination, and exclusion, the remaining 5 studies were included in qualitative and quantitative synthesis (Table 2). Critical appraisal of all studies based on the Joanna Briggs Institute Scoring System showed that none failed to meet more than two validity criteria (Fig. 2).

Table 1. PICO Table Describing Inclusion and Exclusion Criteria

Study Component	Inclusion	Exclusion
Population	• Metastatic bone disease diagnosed through clinical, radiological, and/or laboratory studies	• Less than 1 year of follow up • Trauma and degenerative pathology
	• Age 18 years or older	• Animal studies
Intervention and Comparison	• Zoledronic Acid given 4-weekly	• All other treatments
	• Zoledronic Acid given 12-weekly	• Other kinds of bisphosphonate
Outcome	• Skeletal Related Event	• No outcome mentioned or different outcomes
	• Osteonecrosis of the Jaw	
	• Adverse Event	
	• Kidney Dysfunction	
	• Mortality Rate	
Publication	• Primary research published in English in a peer-reviewed journal	• Abstracts, editorials, letters • Duplicate publications of the same study/ cohort that do not report on different outcomes
		• Conference presentations or proceedings
Design	• Randomized controlled trials	• Case reports or series
	• Cohort studies	• Review articles

PICO; Population; Intervention; Comparison, and Outcome.

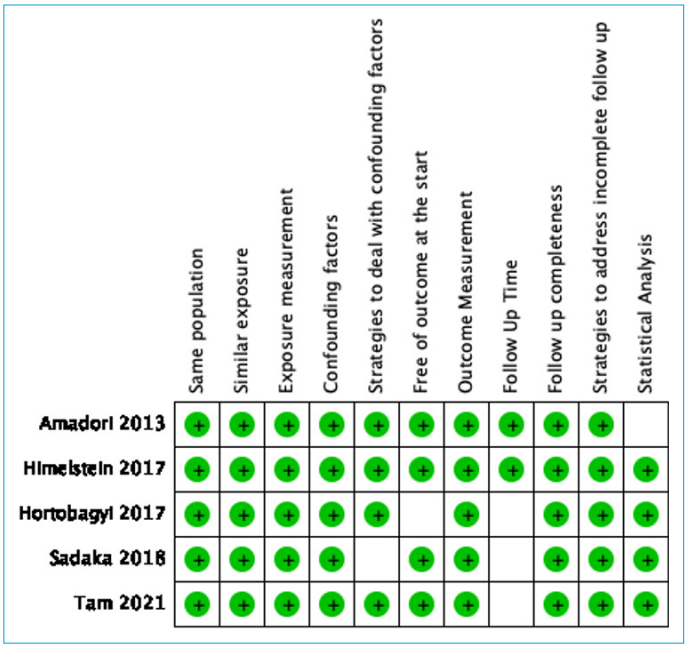

Figure 2. Eligibility Assessment based on Joanna Briggs Institute Criteria.

Statistical Analysis

We utilized the Review Manager version 5.4 software (RevMan; The Cochrane collaboration Oxford, England) to perform all statistical analyses. Based on heterogeneity of the current study, we performed a sensitivity analysis to further assess the overall results. The heterogeneity across studies was examined through the I^2 statistic, where we applied the fixed-effect models when the Heterogeneity was <50% and random-effect models when the Heterogeneity was >50%. Studies with a P values less than 0.05 were thought to have statistical significance. Forest plots showed the findings of our meta-analysis.

Outcome Analysis

This meta-analysis included a total number of 2.867 patients with 1.427 patients undergoing 12 weeks of ZA administrations and 1.440 patients undergoing 4 weeks ZA administrations. The characteristic of included studies are described in Table 3 and 4.

Table 2. Studies included in the analysis

No	Reference	Journal	Study Design	Level of Evidence
1	Amadori et al., 2013	The Lancet Oncology	Randomized Controlled Trial	I
2	Himelstein et al., 2017	Journal of the American Medical Association	Randomized Controlled Trial	I
3	Hortobagyi et al., 2017	Journal of the American Medical Association Oncology	Randomized Controlled Trial	I
4	Sadaka et al., 2018	Cancer Biology	Randomized Controlled Trial	I
5	Tam et al., 2021	Annals of Pharmacotherapy	Retrospective Cohort	III

Table 3. Studies general characteristics included in the analysis

No	References	Sample Size	Age (years)		Sex		Primary Tumor		Patients		Follow Up	
			4 Wks ZA	12 Wks ZA	4 Wks ZA	12 Wks ZA	4 Wks ZA	12 Wks ZA	4 Wks ZA	12 Wks ZA	4 Wks ZA	12 Wks ZA
1	Amadori et al., 2013	425	59.8±11.8	60.4±11.9	F=100%	F=100%	Breast Cancer (100%)		216	209	337 (205-346 days)	
2	Himelstein et al., 2017	1822	65 (26-93)	65 (33-94)	M=45.4% F=54.6%	M=47.0% F=53.0%	• Breast: 46.9% • Prostate: 37.9% • MM: 15.3%	• Breast: 47% • Prostate: 37.8% • MM:15.3%	911	911	15.7 (6.4-24.1 months)	6.8 (6.4-24.0 months)
3	Hortobagyi et al., 2017	403	59.2±11.1	58.6±11.2	F=100%	F=100%	Breast Cancer (100%)		200	203	430±334 weeks	369±307 weeks
4	Sadaka et al., 2018	140	65 (26-93)	65 (33-94)	NA	NA	Breast Cancer (100%)		69	71		1 year
5	Tam et al., 2021	80	62.2±11.0	64.2±9.5	M=39.1%	M=44.1%	Lung Cancer		46	34		1 year

Table 4. Characteristic of Outcome of studies

No.	References	Outcome Measures									
		SRE n (%)		ONJ n (%)		Adverse effect, n (%)		Kidney Dysfunction n (%)		Mortality Rate n (%)	
		4 Wks ZA	12 Wks ZA	4 Wks ZA	12 Wks ZA	4 Wks ZA	12 Wks ZA	4 Wks ZA	12 Wks ZA	4 Wks ZA	12 Wks ZA
1	Amadori et al., 2013	33 (15)	31 (15)	3 (1)	4 (2)	29 (13)	21 (10)	2 (1)	1 (<1)	0 (0)	0 (0)
2	Himelstein et al., 2017	616 (68)	619 (68)	18 (2)	9 (1)	42 (4.61)	18 (1.98)	10 (1.2)	4 (0.5)	122 (13.39)	118 (12.95)
3	Hortobagyi et al., 2017	44 (22)	47 (23.3)	2 (1)	0 (0)	189 (95.5)	189 (93.6)	19 (9.6)	16 (7.9)	10 (5)	7 (3.4)
4	Sadaka et al., 2018	15 (21.7)	16 (22.5)	0 (0)	0 (0)	NA	NA	2 (0.029)	1 (0.014)	NA	NA
5	Tam et al., 2021	11 (23.9)	8 (23.5)	0 (0)	0 (0)	1 (2.2)	0 (0)	2 (4.3)	2 (5.9)	26 (56.5)	NA

SRE Outcome

We performed a subgroup analysis to evaluate SRE outcome between 12 weeks ZA administrations versus 4 weeks ZA administrations in Metastatic Bone Disease patient. We found that there is no significant difference statistically between these two groups (MD 0.98; 0.83 to 1.16; I=0%; 95% CI; p = 0.84) (Fig. 3).

ONJ Outcome

We performed a subgroup analysis to evaluate ONJ outcome between 12 weeks ZA administrations versus 4 weeks ZA administrations in Metastatic Bone Disease patient. We found that there is no significant difference statistically between these two groups (MD 1.74; 0.89 to 3.42; I=0%; 95% CI; p=0.11) (Fig. 4).

Adverse Effect Outcome

We performed a subgroup analysis to evaluate adverse effect between 12 weeks ZA administrations versus 4 weeks ZA administrations in Metastatic Bone Disease patient. We found that there is significant difference statistically between these two groups with less adverse effect in favours of 12 weeks ZA administrations (MD 1.73; 1.20 to 2.48; I=0%; 95% CI; p=0.003). Some adverse effects mentioned are fatigue, arthralgia, nausea, musculoskeletal pain, constipation, diarrhea, headache, dyspnea, anemia, cough, peripheral neuropathy (Fig. 5).

Kidney Dysfunction Outcome

We performed a subgroup analysis to evaluate kidney dysfunction outcome between 12 weeks ZA administrations versus 4 weeks ZA administrations in Metastatic Bone Disease patient. We found that there is no significant difference statistically between these two groups (MD 1.47; 0.86 to 2.52; I=0%; 95% CI; p=0.16) (Fig. 6).

Mortality Rate Outcome

We performed a subgroup analysis to evaluate mortality rate outcome between 12 weeks ZA administrations versus 4 weeks ZA administrations in Metastatic Bone Disease patient. We found that there is no significant difference statistically between these two groups (Mean difference 0.79; 95% CI 0.61 to 1.01; p>0.05) (Fig. 7).

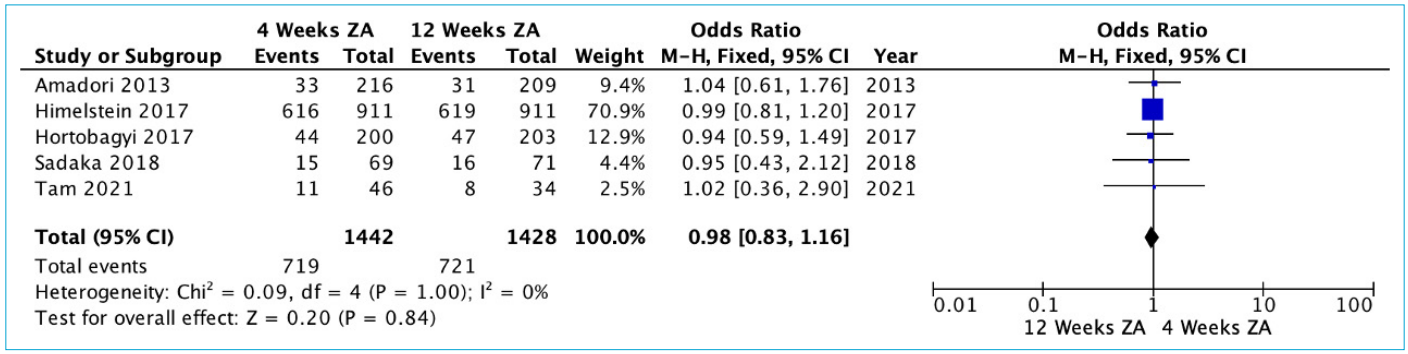

Figure 3. Pooled analysis of SRE outcome.

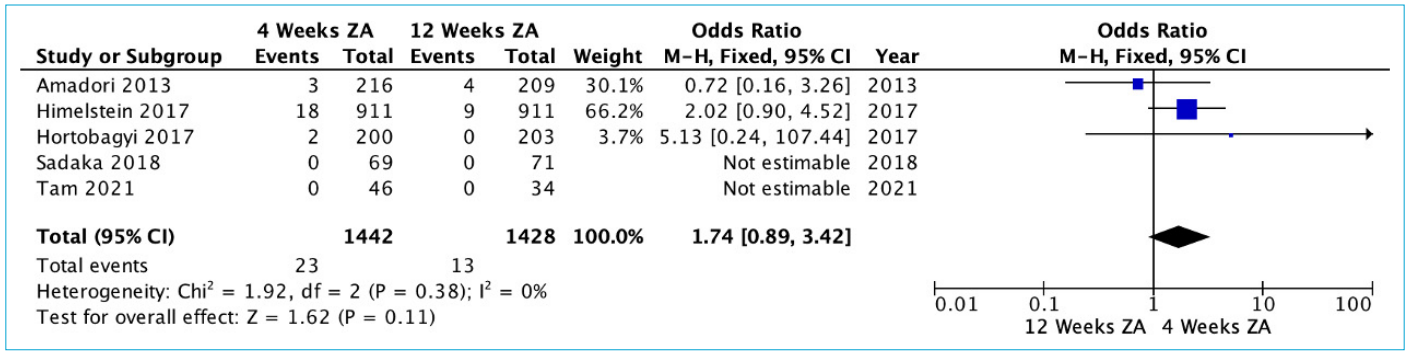

Figure 4. Pooled analysis of ONJ outcome.

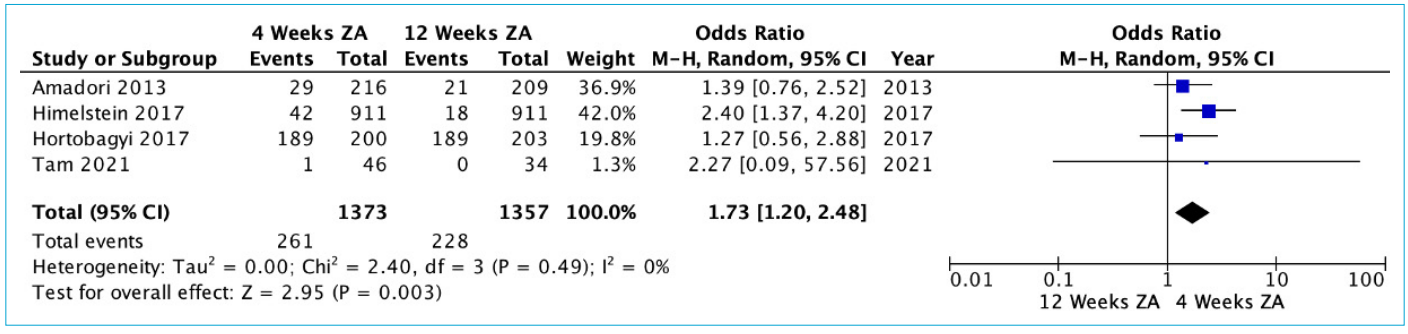

Figure 5. Pooled analysis of Adverse Effect outcome.

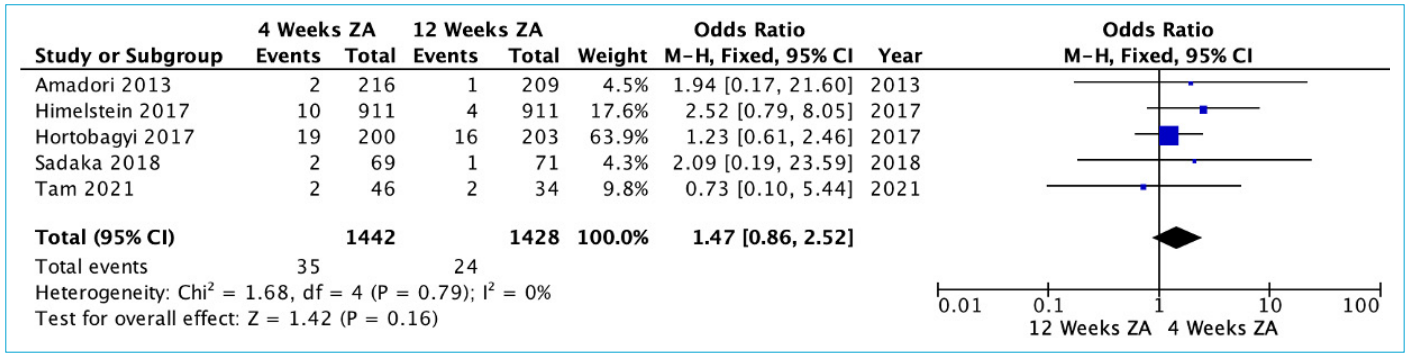

Figure 6. Pooled analysis of Kidney Disfunction outcome.

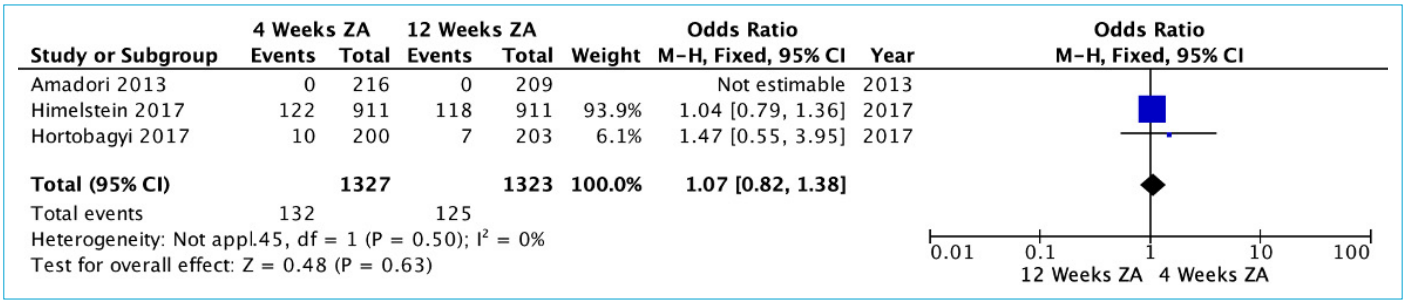

Figure 7. Pooled analysis of Mortality Rate outcome.

Discussion

From the moment of diagnosis of bone metastases until the patient passes away, zoledronic acid is typically provided once every three to four weeks. This dose regimen was developed from investigations of individuals with hypocalcemia who received anticancer medicines. However, these regimens did not take into account the toxicity that is associated with the usage of zoledronic acid over a prolonged period of time. Oncologists are becoming more interested in identifying the best dose interval for zoledronic acid, which not only assures the success of the treatment but also lowers the toxicity that it causes.[7,8]

In this meta-analysis of individuals with bone metastases, the 12-week dose intervals of zoledronic acid were shown to be non-inferior to the conventional 4-week dosing intervals in lowering the incidence of SREs. The standard dosing intervals were found to be inferior. Because this finding is in line with those of the five clinical studies that were eligible for analysis, it demonstrates that the effectiveness of the 12-week regimen may be relied upon. Radiation to the bone was the sort of serious adverse effects that was reported the most commonly by patients in both treatment groups, followed by pathologic fractures and spinal cord compression. When the safety profiles of several dosage schedules were compared, the one with the 12-weeks ZA regimen had a reduced incidence of side events of grade 3 or 4. These results were inline with our hypothesis which extended interval of ZA administration favouring less adverse effects from the drugs itself. Kumar et al. also exhibit the same outcome with patients which treated by 12-weeks ZA regimen would increase the compliance, therefore decreased the side effects and utilization costs.[9] Other features, such as osteonecrosis of the jaw, renal failure and mortality rate, were comparable across the two regimens, despite the fact that there are no statistically significant differences were identified between the two.

A meta-analysis was performed on this subject in 2015, and the results were published. However, the focus of that research was on bone-targeting medicines, such as pamidronate, zoledronate, and denosumab; the data about zoledronic acid were not discussed. Because of this, those data were insufficient to evaluate whether or not the time periods between administrations of zoledronic acid may be extended. To the best of our knowledge, this is the first meta-analysis that has been conducted to determine whether or not the administration of zoledronic acid at intervals of 12 weeks is appropriate. Even though just five RCTs were included in our research, the quality of those studies was quite good. In addition to this, there was very little variation in the data; as a consequence, the findings are believable.[10]

The bone turnover biomarker concentrations (C-telopeptides and N-telopeptides) were greater in patients who received the 12-week regimen of zoledronic acid, despite the fact that there were no statistically significant differences between the two regimens in terms of effectiveness and safety. In a number of investigations, biomarkers of bone turnover have been used as an alternative indication of mortality and, therefore, SRE risk. Only one year was spent on follow-up procedures in the RCTs that were considered appropriate for our research. It is still not apparent if the follow-up intervals were long enough to uncover differences in the two groups' effectiveness and safety. Because of this, lengthier follow-up studies are required in order to determine whether or not the number of SREs in the 12-week group rises over time.[11–13]

This study has several limitations. Firstly, the primary tumor of the metastases in our studies are only of limited types of cancer. Therefore, further study is needed to evaluate the efficacy of zoledronic acid in other types of metastatic bone disease. Secondly, due to the scarcity of qualified studies, only five studies were included into the analysis. However, most of the studies included were of level I evidence with low heterogeneity (I<50%) indicating low possibility of analysis bias. Furthermore, this study is hoped to give insights to surgeons in treating metastatic bone disease as a guideline in choosing the appropriate regimen of zoledronic acid, and further inspire other researchers to conduct well-designed trials with a bigger number of samples and perform subgroup analysis.

Conclusion

Our systematic review and meta-analysis reveals that 12-week intervals of zoledronic acid is as effective as the standard 4-week interval in terms of skeletal related event, jaw osteonecrosis, renal dysfunction, and mortality rate. However, the standard 4-week intervals led to higher rate of adverse effects.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – I.G.E.W.; Design – S.D.S.; Supervision – P.A.; Data collection and processing – S.D.S., A.S.P., I.G.A.W.A., I.M.A.D.Y; Analysis – P.A.D.; Literature search – I.M.A.D.Y., P.A.D., S.D.S.; Writing – A.S.P.; Critical Review – I.G.E.W., P.A.

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