The efficacy and safety of bisphosphonates in patients with bone marrow edema syndrome/transient osteoporosis: A systematic literature review

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ABSTRACT

Background: The purpose of our systematic literature review study was to critically analyze all current data including time to achieve pain relief and resolution of bone marrow edema (BME) on magnetic resonance imaging (MRI) in patients with bone marrow edema syndrome (BMES) when using bisphosphonates.

Methods: A systematic review was performed to address studies which concerned the efficacy and safety of bisphosphonates in patients with BMES. A systematic search was conducted by two investigators using databases including Pubmed and Scopus.

Results: Nine studies were included between July 2002 and June 2019 with a total of 187 patients out of whom 150 had been treated with bisphosphonates. Mean age of patients was 44.14 (mean ranges 34.9–54.0), 113 males and 54 females (excluding one study which did not mention ages). Five studies described the outcomes from MRI on follow-up (42 out of 78 patients achieved resolution with time ranging from 3 to 12 months with a mean of 3.85 months) and eight studies described the outcomes regarding pain resolution (128 out of 140 achieved resolution with mean time 4.20 months, ranging from 0.7 months to 12 months). Adverse events related to the administration of bisphosphonates included flu-like symptoms in 6 patients, musculoskeletal pain in 1 patient, arthralgias and fever in 9 patients.

Conclusions: The outcome of this systematic review indicated that the effect of bisphosphonates on pain relief and on regression of BME on MRI is controversial, but due to the low level of evidence of the included studies, no definite conclusions can be acquired and no evidence based recommendation could be given.

1. Introduction

Bone marrow edema (BME) is a radiological term that is found on MRI and is used to describe a region of increased signal intensity on T2, fat suppressed, short tau inversion recovery sequences and decreased signal intensity on T1 sequences on MRI.¹ This term is associated with a variety of conditions characterized by BME pattern with common symptomatology of pain but of miscellaneous etiologies, histological pictures and prognosis.² Bone marrow edema syndrome (BMES) or transient osteoporosis (TO) is a self-limited condition which is characterized by the presence of BME on MRI and is mainly of unknown etiology. It affects most commonly the hip joint, while other joints include

the knee, foot, ankle joint and the upper extremities (most commonly the shoulder).^{3,4} The syndrome is manifested with acute onset of pain, reduced joint motion, and is characterized by the absence of trauma, normal radiographs or osteopenia, increased uptake of tracer on bone scintigraphy and normal laboratory panel.³ The first who described this clinical entity was Curtiss in 1958 in 3 women in the third trimester of pregnancy who presented with hip pain and plain radiographs characterized by transient osteopenia which subsequently resolved.⁵

BMES should be differentiated from avascular necrosis (AVN), especially in the early stages of AVN when both diseases are similar. The hallmark of diagnosis is MRI. Common findings of AVN include the presence of subchondral anomaly such as single line sign on T1

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sequences, double line sign on T2 sequences and crescent sign.⁶ Treatment options initially include restriction of weight bearing, immobilization, anti-inflammatory drugs, analgesics, and additional regimens are extracorporeal shock wave therapy (ESWT), bisphosphonates, iloprost, and whether all the above fail then core decompression maybe an alternative solution.⁷ To our knowledge there are not currently any high quality systematic literature review articles published regarding the administration of bisphosphonates in patients with BMES.

The purpose of our systematic literature review study was to critically analyze all current data including time to achieve pain relief and resolution of bone marrow edema (BME) on magnetic resonance imaging (MRI) in patients with bone marrow edema syndrome (BMES) when using bisphosphonates.

2. Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.⁸ Two reviewers (P. K. and V. A.) independently carried out the literature search, eligibility evaluation and data extraction. Any discrepancies were solved by consensus.

2.1. Inclusion and exclusion criteria

This systematic review included articles regarding the utilization of bisphosphonates for the management of painful BMES. The studies were eligible to be included if the following inclusion criteria were presented: 1) English language, 2) diagnosis established through clinical and MRI findings suggestive of BMES, 3) studies that included outcomes as time to BME or/and pain resolution, function, quality of life and safety, 4) human trials.

Studies were excluded if they met the following exclusion criteria: 1) patients having BME secondary to trauma, tumor, AVN, osteoarthritis, infection, fractures, 2) review articles, case reports, case based reviews, letters to the editor, commentaries, editorials, study protocols, experimental trials, and books, 3) studies we could not find full texts, 4) co-administration of bisphosphonates with prostacyclin analogues or ESWT or hyperbaric oxygen therapy (HBOT).

2.2. Data sources and search strategy

A systematic search was done in databases including Pubmed (on April 23, 2020) and Scopus (on April 23, 2020). Our search was conducted with the following algorithm: “bisphosphonates” OR “alendronate” OR “ibandronate” OR “zoledronic acid” AND “bone marrow edema syndrome” OR “bone marrow edema syndrome” OR “transient osteoporosis” OR “regional migratory osteoporosis” OR “bone marrow edema” OR “bone marrow edema”. We did not use any filters upon the search. We used Endnote to remove potential duplicates. The articles that were identified were screened by two reviewers (P. K. and V. A.). Firstly, screening of the titles and abstracts was made and any articles that described BMES/TO treated with utilization of bisphosphonates were analyzed further. Secondly, screening of the full-texts of the articles was conducted independently by both reviewers and therefore the necessary articles which met the aforementioned inclusion-exclusion criteria were included in this systematic review.

2.3. Data extraction

Relevant data were extracted as follows: characteristics of the included studies (study design, year and country of publication), population and demographics of the patients, type of intervention and the doses, localization of BMES, length of follow-up, clinical outcome measures, adverse events associated with medication, and the required times until resolution of BME and/or resolution of symptoms.

2.4. Quality assessment

The quality assessment of the studies included in the systematic review was conducted by two reviewers (K. A. and T. K.) and any discrepancies between them were managed by consensus. Level of evidence rating was matched to each study by the utilization of the criteria by Wright et al.⁹ For the quality appraisal of case series, the checklist developed by Moga et al. using a modified Delphi technique was used.¹⁰ The checklist consists of 18 items, score of 13 or greater indicates high quality, a score of 7–12 moderate, and a score of 0–6 low quality. On the other hand, quality assessment for comparative and non-comparative studies except case series was made by using the 12-point Methodological Index for Non-randomised Studies (MINORS) criteria.¹¹

3. Results

3.1. Results of the search

A total of 2062 articles were identified through electronic databases. After duplicates removal, 1964 articles remained for screening. Screening of title and abstract was conducted on those studies, excluding 1935. The remaining 29 studies were assessed by full-text and eventually 9 studies were included in the systematic analysis (Fig. 1).

3.2. Study characteristics

Of the 9 included studies,^{12–20} 4 were case series,^{13–16} 2 were prospective observational trials,^{17,18} 2 were retrospective comparative trials^{12,19} and 1 was retrospective observational trial.²⁰ Dates of publication ranged between July 2002 and June 2019. Countries of publication included 3 in Germany,^{12,17,18} 2 in Italy,^{15,20} 2 in India,^{13,16} 1 in Spain,¹⁴ and 1 in Switzerland.¹⁹ A total of 187 patients included in those studies, out of whom 150 had been treated with bisphosphonates. Mean age of patients was 44,14 (mean ranges 34.9–54.0),^{12–20} 113 males and 54 females^{13–20} (excluding one study which did not mention ages).¹¹ BME was located in different parts of the body, 79 in the foot and ankle region, 74 in the hip joint, 43 in the knee joint, and 3 are not mentioned^{12–20} (Table 1). Throughout the studies a variety of clinical outcome measures have been utilized to assess the results including MRI, VAS score, WOMAC score, SF-36, BMD, Larson score, Mazur score, gait and range of motion, EVS. Summary of the characteristics are presented in (Table 2).

3.3. Quality assessment

According to the level of evidence criteria by Wright et al., our systematic review included 4 level IV,^{13–16} 3 level III,^{12,19,20} and 2 level II studies.^{17,18} 3 of the 4 case series were deemed to be of high quality according to modified Delphi technique by Moga et al.,^{13–15} and the remaining 1 was of moderate quality.¹⁶ According to MINORS checklist, comparative studies had a mean of 17,66 (range 15–22) out of 24 points,^{12,18,19} and non-comparative observational studies had mean of 9 (range 6–12) out of 16 points.^{17,20}

3.4. Effects of bisphosphonates on pain

We used 8/9 studies^{13–20} in which we identified the number of population who achieved pain resolution with a total follow-up of 140 patients, out of whom 128 achieved complete pain resolution with mean time of 4.20 months (range from 0.7 months to 12 months). Specifically, 19 patients in 0.7 months,¹³ 7 patients in 1 month,¹⁵ 7 patients in 2 months,¹⁵ 36 patients in 3 months,^{15,18,19} 12 patients in 4.27 months,¹⁶ 23 patients in 4.3 months,²⁰ 7 patients in 6 months¹⁷ and 17 patients in 12 months.^{14,18}

Fig. 1. Flow diagram of study selection process.

3.5. Effects of bisphosphonates on BME on MRI

MRI results are described in 5/9 studies included in our review.^{12–15,18} A total of 78 patients had available MRI results on follow-up out of whom 42 had complete resolution,^{12–15} 30 had near complete resolution after treatment with bisphosphonates.¹⁸ Of the 42 patients that achieved regression of BME on MRI, mean time was 3.85 months with ranges from 3 to 12 months.^{12–15} 36 patients had complete resolution of BME after 3 months,^{13–15} 3 patients after 6 months,¹³ 3 had complete resolution after 12 months,¹² 30 patients had near complete resolution in 6 months,¹⁸ while the remaining 5 patients had less response^{12,14} and 1 was non-responder.¹²

3.6. Scores regarding the pain, function and quality of life across studies

VAS scores were available in 5/9 studies.^{12,13,15,17,18} Across these studies, a total of 87 patients who were administered with bisphosphonates had available VAS scores. Baseline VAS scores ranged from 5.6 to 8.5 with a mean of 7.56 across the studies.^{12,13,15,17,18} VAS scores from final follow up in these studies varied from 1 month to 12 months with scores ranging from 0.00 to 1.5 with a mean of 0.67.^{12,13,15,17,18}

A variety of different clinical scores have been utilized including

WOMAC, SF-36, BMD, Larson and Mazur score (Table 2). 4/9 studies had described the aforementioned scores.^{12,15,17,18} Due to the fact that 2 out of 4 studies had WOMAC score,^{12,15} 2 out of 4 studies had BMD scores,^{15,17} 1 out of 4 studies had SF-36 score¹² and 1 out of 4 studies had the Mazur and Larson scores,¹⁸ it prevented us from direct quantitative comparison across those studies.

3.7. Adverse events related to bisphosphonates

Adverse events related to the administration of bisphosphonates was observed in 3/9 studies^{12,15,18} including flue-like symptoms in 6 patients, musculoskeletal pain in 1 patient, arthralgias and fever in 9 patients.

4. Discussion

To our knowledge this is the first review regarding the use of bisphosphonates in BMES/TO. In our study, we aimed to systematically review the literature and to address studies which described the use of bisphosphonates in patients with BMES. We attempted to pool data from each study regarding the time to resolution of pain and of BME on MRI. For this purpose we identified 9 studies out of which 5 studies described

Table 1
Study design, treatment protocols and Patient's demographics.

Study (Year)	Study design (level) [9]	Treatment protocol (n)	Total population	Mean age	Gender	Joint (n)
Singh et al. (2015) ¹⁹	Therapeutic; Retrospective comparative trial (III)	Single IV infusion of 5 mg zoledronic acid (n = 9) Weekly oral dose of alendronate (n = 2) Pneumatic walker alone (n = 7)	18 11 (BiG)	54	M/F = 6/12	Multiple joints (n = 8) Talus (n = 10) Cuboid (n = 3) Cuneiforms (n = 5) Metatarsals (n = 6) Os calcis (n = 2) Distal tibia (n = 1) Navicular (n = 1)
Baier et al. (2012) ¹²	Therapeutic; Retrospective comparative study (III)	Daily IV iloprost for 5–6 h on 5 consecutive days. 20 lg on first day, 30 lg on second day and 40 lg for the remaining 3 days.(n = 10) IV Ibandronate once monthly in a dosage of 6 mg for 3 consecutive m. (n = 10) All patients were mobilized with WB + analgesics on demand	20 10 (BiG)	34.9	N/A	Knee (n = 11) Talus (n = 5) Navicular (n = 4)
Ringe et al. (2005) ¹⁷	Therapeutic; Prospective observational trial (II)	Single IV ibandronate of 4 mg. Second IV of 2 mg -optional after 3 m + daily calcium 1 g + vitamin D 800 IU supplements (n = 12)	12	44	M/F = 5/7	Hip (n = 7) Calcaneus (n = 2) Other (n = 3)
Agarwala et al. (2019) ¹³	Therapeutic; Case series (IV)	Single IV zoledronic acid of 5 mg, daily calcium 500 mg, daily vitamin D 400 UI, analgesics as required + WB as tolerated (n = 19)	19	42.1	M/F = 17/2	Hip (n = 19)
Flores-Robles et al. (2017) ¹⁴	Therapeutic; Case series (IV)	Single dose of 5 mg of IV zoledronic acid (n = 17)	17	53.9	M/F = 8/9	Hip (n = 5) Ankle (n = 9) Foot (n = 2) Knee (n = 1)
Bartl et al. (2012) ¹⁸	Therapeutic; Prospective observational trial (II)	IV Ibandronate 6 mg in 100 mL sodium chloride over 30 min, once monthly-total 3 m (n = 30) Diclofenac sodium 2 × 75 mg per day for 3 w + crutches for 3 w + another 3 w PWB (n = 20)	50 30 (BiG)	42.5	M/F = 38/12	<i>Ibandronate group</i> Ankle (n = 15) Knee (n = 15) <i>Control group</i> Knee (n = 10) Talus (n = 10) (Control)
Varenna et al. (2002) ¹⁵	Therapeutic; Case series (IV)	3 IV infusions, one every 3 d, over 4 h of 45 mg of pamidronate in 500 mL of isotonic saline solution (n = 16)	16	38.3	M/F = 13/3	Hip (n = 16)
Trevisan et al. (2016) ²⁰	Therapeutic; Retrospective observational trial (III)	PWB + Bisphosphonates (n = 23)	23	48.4	M/F = 15/8	Hip (n = 13) Knee (n = 6) Ankle (n = 2) Feet (n = 2)
Vaishya et al. (2017) ¹⁶	Therapeutic; Case series (IV)	Bisphosphonates + NSAIDs + calcium + vitamin D	12	41	M/F = 11/1	Hip (n = 14)

n: number of patients, M/F: male/female, BiG: bisphosphonate group, IV: intravenous, WB: weight bearing, PWB: partial weight bearing, m: months, w: weeks, d: days, N/A: not available.

the outcomes from MRI on follow-up (42 out of 78 patients achieved resolution with mean time of 3.85 months ranging from 3 to 12 months) and 8 studies described outcomes regarding pain resolution (128 out of 140 achieved resolution with mean time 4.20 months, ranging from 0.7 months to 12 months). Most patients had complete resolution of BME on MRI (n = 32) after 3 months of follow-up, and complete resolution of pain (n = 36) after 3 months of follow-up. BMES is a self-limited condition which subsides with an estimated mean time in the literature in 3–18 months with only standard care.¹² The main aim for the management of BMES is to reduce the clinical course of the disease by reducing the pain and BME associated with it.⁷ In our review the mean time to achieve pain relief was 4.20 months (range 0.7–12 months) and mean time for regression of BME on MRI was 3.85 months (range 3–12 months), therefore involved in the interval of 3–18 months that is required with standard care.

Regarding the time from onset of symptomatology to diagnosis of BMES, a variety of periods ranging from mean of 4 weeks–7.1 months have been noticed.^{13–16,19,20} Thus, clinicians should be aware of BMES in order to establish early diagnoses and if possible avoid early surgical intervention.

The adverse events that were associated with the use of bisphosphonates were of minor significance and in one study was managed with paracetamol,¹⁵ in another with non-steroid anti-inflammatory drugs,¹⁸ and in the third it was resolved without therapy.¹²

4.1. Limitations

Our systematic review has limitations. The included studies were of low level of evidence. Significant heterogeneity including patient's population, doses/mode of administration/length of therapy of bisphosphonates and measures of clinical outcomes were presented in the studies which prevented direct quantitative comparison across studies. Only 3 comparative studies are included with varied control groups, thus preventing us from direct comparison but we rather pooled data regarding the mean times of pain relief and MRI from the bisphosphonates groups and summarized them.

5. Conclusion

The effect of bisphosphonates on pain relief and on regression of

Table 2

Follow-up, results on clinical outcomes and adverse events.

Study (Year)	Follow-up	Clinical outcome data	Onset to diagnosis	Pain resolution time	Adverse events
Singh et al. (2015) ¹⁹	Mean 5.75y (range 2–11y)	N/A	Mean 22w (2–42w)	Mean 12w or 3 m = 11/11 of BiG	Recurrence of pain (n = 4)
Baier et al. (2012) ¹²	Mean 12 m (range 10–17)	<p>VAS in BiG (n = 10)</p> <p>> Baseline = 5.6</p> <p>> 3 m = 2.6</p> <p>> 12 m = 1.5 (p < 0.001)</p> <p>WOMAC in BiG (n = 10)</p> <p>> Baseline = 50.5</p> <p>> 3 m = 27.5</p> <p>> 12 m = 20.8 (p < 0.001)</p> <p>SF-36 physical in BiG (n = 10)</p> <p>> Baseline = 24.3</p> <p>> 3 m = 66.1</p> <p>> 12 m = 80.8 (p = 0.002)</p> <p>SF-36 mental in BiG (n = 10)</p> <p>> Baseline = 56.5</p> <p>> 3 m = 79.2</p> <p>> 12 m = 84.0 (p < 0.001)</p> <p>MRI (n = 6)</p>	N/A	N/A	Flue-like symptoms (n = 3)
Ringe et al. (2005) ¹⁷	Final 6 m	<p>> 1y = 3/6 R, 2/6 marked reduction, 1/6 non responder</p> <p>VAS (n = 12)</p> <p>> Baseline = 8.4</p> <p>> 6 m = 0.5 (p < 0.0001)</p> <p>BMD (n = 12)</p>	N/A	6 m = 7/12	None
Agarwala et al. (2019) ¹³	Mean 35 m (range 6–54 m)	<p>> 6 m = 4% increase</p> <p>VAS (n = 19)</p> <p>> Baseline = 7.16</p> <p>> 2w = 2.11 (p < 0.0001)</p> <p>> 4w = 0.74 (p < 0.0001)</p> <p>> 6w = 0.00 (p < 0.0001)</p> <p>MRI (n = 19)</p> <p>> 12w or 3 m = 16/19 R</p> <p>> 6 m = 19/19 R</p> <p>Limp (n = 15)</p> <p>> 12w = 15/15 R</p> <p>Painful range of motion (n = 17)</p>	Mean 4w (2–8w)	Mean 2.8w or 0.7 m: 19/19	None
Flores-Robles et al. (2017) ¹⁴	Final 12 m	<p>> 12w = 17/17 R</p> <p>MRI (n = 8)</p> <p>> ≥3 m = 5/8 R, 3/8 50% reduction</p> <p>Pain (n = 17)</p>	Mean 4.4 ± 3.6 m	1y or 12 m = 13/17	None
Bartl et al. (2012) ¹⁸	Final 12 m	<p>> Baseline = 16/17 moderate to severe</p> <p>> 3 m = 15/16 pain reduction or even complete resolution</p> <p>VAS of knee in BiG (n = 15)</p> <p>> Baseline = 8.5</p> <p>> 6 m = 1.6 (p < 0.0001)</p> <p>> 12 m = 1.2 (p < 0.0001)</p> <p>VAS of ankle in BiG (n = 15)</p> <p>> Baseline = 8.2</p> <p>> 6 m = 1.9 (p < 0.0001)</p> <p>> 12 m = 0.9 (p < 0.0001)</p> <p>Mazur score in BiG (n = 15)</p> <p>> Baseline = 51</p> <p>> 6 m = 88 (p < 0.001)</p> <p>> 12 m = 91 (p < 0.001)</p> <p>Larson score in BiG (n = 15)</p> <p>> Baseline = 54</p>	N/A	3 m:23/30 12 m:27/30	<p>Flue-like symptoms (n = 3)</p> <p>Musculoskeletal pain (n = 1)</p>

(continued on next page)

Table 2 (continued)

Study (Year)	Follow-up	Clinical outcome data	Onset to diagnosis	Pain resolution time	Adverse events
Varenni et al. (2002) ¹⁵	Mean 39.5 ± 17.7 m	<p>> 6 m = 86 (p < 0.001)</p> <p>> 12 m = 89 (p < 0.001)</p> <p>MRI (n = 30)</p> <p>> Baseline = stage 2.9</p> <p>> 6 m = stage 0.8 (p < 0.001)</p> <p>MRI (n = 15)</p> <p>> 3 m = 15/15 R</p> <p>VAS (n = 16)</p> <p>> Baseline = 7.15</p> <p>> 1 m = 0.4 (p < 0.00001)</p> <p>WOMAC (n = 16)</p> <p>> Baseline = 64.5</p> <p>> 1 m = 7 (p < 0.00001)</p> <p>EVS (n = 16)</p> <p>> 1 m = 4 significant improvement, 5 excellent, 7 asymptomatic</p> <p>BMD (n = 16)</p> <p>> 2 m = total hip increased by 10.9% (p < 0.00001), femoral neck increased by 12.3% (p < 0.00001)</p> <p>> 4 m = total hip increased 1.8% (p = 0.009), femoral neck increased 2.0% (p = 0.0009)</p>	8 ± 3.8w	<p>1 m = 7/16</p> <p>2 m = 14/16</p> <p>3 m = 16/16</p>	Arthralgias and fever (n = 9)
Trevisan et al. (2016) ²⁰	N/A	N/A	Mean 7.1 m (3–14 m)	Mean 4.3 m = 23/23	N/A
Vaishya et al. (2017) ¹⁶	Mean 1.3 y (1–2.6y)	N/A	Mean 3.2 m (1–6 m)	Mean 17.1w or 4.27 m = 12/12	N/A

m: months, w: weeks, y: years, N/A: not available, n: number of patients, BiG: bisphosphonates group, R: resolved, BMD: bone mineral density, VAS: Visual Analogue Scale, WOMAC: The Western Ontario and McMaster Universities Osteoarthritis Index, SF-36: 36-Item Short form survey, EVS: efficacy verbal score.

BME on MRI is controversial according to our results. Mean time for pain relief and resolution of BME on MRI was 4.20 (0.7–12 months) and 3.85 months (3–12 months) respectively. Due to the low number and level of evidence of the included studies, no definite conclusions can be acquired and no evidence based recommendation could be given. This systematic review shows lack of standardized guidelines with respect to the pharmacological treatment of BMES with the administration of bisphosphonates. We suggest future researchers to conduct large multicenter randomized control trials that concern the utilization of bisphosphonates compared with standard care (restriction of weight bearing and analgesics) and other potential treatment regimens such as iloprost, ESWT and HBOT in order to acquire high evidence based recommendations.

Declaration of competing interest

No potential conflict of interest relevant to this article was reported.

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