Effectiveness and safety of bisphosphonates in inflammatory bone disorders: a systematic review

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Abstract

Objective

We aimed to evaluate the available evidence on the use of bisphosphonates, with a focus on pamidronate, in the treatment of inflammatory bone disorders (IBDs).

Methods

A comprehensive literature search was conducted using PubMed, Google Scholar, Scopus, the Cochrane Library, and the Directory of Open Access Journals (DOAJ) for articles published between January 2000 and July 2024. Following PRISMA 2020 guidelines, this review focused on studies of childhood IBDs treated with bisphosphonates, assessing clinical and radiological remission and safety based on predefined criteria. Study quality was evaluated using the National Institutes of Health's quality assessment tools for observational studies.

Results

The review included 26 articles comprising 895 patients (603 females and 292 males) with a mean age of 10.1 years. Pamidronate was the primary treatment for 393 patients (43.9%), demonstrating significant improvements in remission rates, symptom reduction, and radiological outcomes. Bisphosphonates were well tolerated and provided substantial clinical benefits.

Conclusion

Bisphosphonate therapy, particularly pamidronate, is effective and well tolerated in children with IBDs, particularly when combined with other treatments. Further research is needed to establish standardised treatment protocols and long-term safety profiles.

Key words

inflammatory bone disorders, non-bacterial osteomyelitis, chronic recurrent multifocal osteomyelitis, pamidronate, bisphosphonates

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Introduction

Inflammatory bone disorders (IBDs) are classified as autoinflammatory disorders – a group of rare and diverse diseases characterised by chronic sterile osteomyelitis. These include chronic nonbacterial osteomyelitis (CNO), which presents with lesions in single or adjacent bones, most commonly in the metaphyses of long bones, and chronic recurrent multifocal osteomyelitis (CRMO), which involves recurrent episodes of bone inflammation at multiple sites either simultaneously or sequentially. These terms are often used interchangeably. During disease exacerbations, patients report bone pain, fever, localised tenderness, swelling, and a limited range of movement in the affected sites (1-3). SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) is not restricted to adults, as it can also manifest in paediatric patients. However, clinical differences distinguish between these two conditions. In children, the extremities and clavicles are often affected, whereas SAPHO mainly affects the axial skeleton and sternoclavicular joints. Palmoplantar pustulosis and acne are the predominant cutaneous manifestations of SAPHO, whereas CRMO rarely presents with dermatological features (4, 5). While the metaphyseal plates of long bones, vertebral bodies, and clavicles are most commonly affected, any bone can potentially be involved (6, 7).

IBDs cause significant morbidity, with approximately 25% of patients experiencing persistent symptoms. Patients with vertebral involvement and bone loss typically have a worse prognosis, often due to inadequate treatment (6-9). Currently, non-steroidal anti-inflammatory drugs (NSAIDs) are the first line of treatment. However, many patients require additional therapies. Unfortunately, treatment remains empirical and lacks specific therapies for IBDs. However, different treatment options are being considered, including the use of biological agents such as tumor necrosis factor inhibitors (TNFi) (10-15). Recent consensus treatment plans have been developed to provide standardised treatment regimens for managing refractory IBDs cases (16). The use of bisphosphonates, specifically pamidronate, for treating IBDs has increased; however, studies investigating their safety and effectiveness are inadequate. This systematic review evaluated the available evidence on the use of bisphosphonates, with a focus on pamidronate, in the treatment of IBDs.

Materials and methods

Search strategy and sources

A comprehensive literature review was conducted using the following MeSH terms: "chronic recurrent multifocal osteomyelitis", "CRMO", OR "chronic nonbacterial osteomyelitis", OR "CNO", "osteomyelitis", OR "inflammatory bone disease", AND "children", OR "pediatric," AND "treatment", OR "pamidronate", AND "bisphosphonate", AND "bone scan", AND "magnetic resonance imaging", AND "safety", and "response". A search was conducted in PubMed, Google Scholar, Scopus, the Cochrane Library, and the Directory of Open Access Journals (DOAJ) for articles published between January 2000 and July 2024. The eligible studies investigated the use of bisphosphonates in childhood IBDs, included a safety assessment, and reported the outcomes after six months of follow-up. Our inclusion criteria included case-control studies, case series with at least five patients, cohort studies, pilot studies, and clinical trials. The exclusion criteria were studies involving adult patients, systematic reviews, literature reviews, non-English articles, meta-analyses, case reports, opinions, commentaries, editorials or case series with fewer than five patients, conference abstracts, articles without full-text availability, and studies without sufficient treatment assessment.

References from selected publications were reviewed and cross-referenced with electronic search results. Additional articles were identified through manual searches and reference list reviews. After removing duplicates, each included article was assigned a unique identifier in a spreadsheet (including year of publication, country, author, and journal) for review. Publications were assessed using the PICO approach: population/patients (IBDs patients), inter-

vention (bisphosphonates), comparison (no direct comparator was included), and outcome (response to treatment response evaluated clinically and radiologically and side effects) (17).

Criteria of screening

Two researchers (A.A and R.A) independently reviewed the titles and abstracts of the studies identified in the searches. Another pair of reviewers (L.F. and F.A.) independently examined the titles and abstracts of the articles, which generally met the inclusion criteria. Subsequently, four researchers (S.A, Y.K, L.F and R.A) evaluated the full text of the selected articles to determine their eligibility for the study. Any discrepancies between the researchers were resolved by the lead researcher (S.M.). The review process followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 checklist to minimise bias and ensure an organised approach (17).

Data extractionand management

A data collection spreadsheet was created using Microsoft Excel 2013 to record variables and extract information in the following domains: basic study components (study design, year of publication, study title, study sample, first author, and country of publication), participant characteristics (age, age at onset, and sex), clinical and laboratory manifestations (bone pain, swelling, arthritis, site involvement, skin involvement, inflammatory markers, blood cell count, autoantibodies, renal function, liver function, relevant immunological tests, genetic tests, x-rays, magnetic resonance imaging (MRI), bone scintigraphy, bone biopsy, and interventions (bisphosphonates, other treatments including corticosteroids, methotrexate and biological agents). Evaluations and treatment outcomes were based on these variables, with a specific focus on clinical and radiological remission, absence of complications, and drug side effects.

Quality assessment

Two reviewers (S.A and Y.K) independently assessed the quality of the included studies using the National Institutes of Health's quality assessment tools for observational studies (18). After reaching a consensus among all authors, the quality of each study was classified as poor, fair, or good.

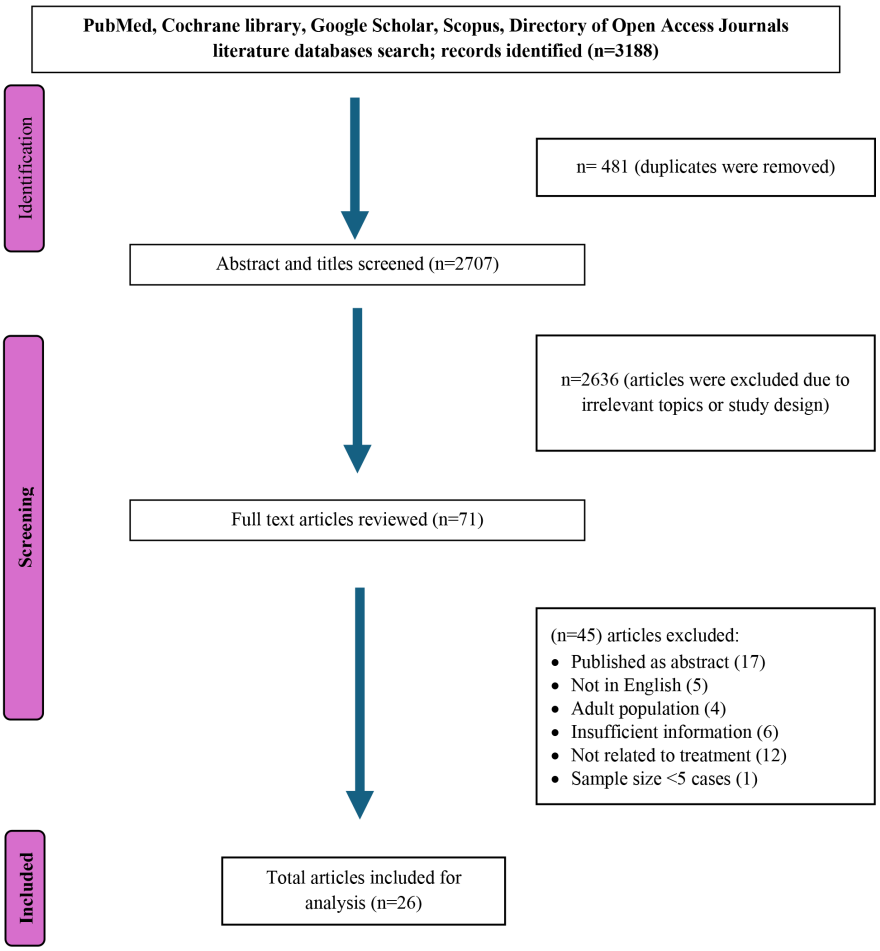

Fig. 1. Flowchart search strategy summary for bisphosphates in inflammatory bone disorders.

Data synthesis

A meta-analysis was not feasible due to the descriptive and exploratory nature of most of the included articles, thereby making quantitative synthesis inadequate. Consequently, this systematic review uses a narrative synthesis, allowing the incorporation of various study designs without requiring data homogeneity for statistical aggregation.

Ethics approval

Ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

The ethics committee of the Research Affairs Council of King Faisal Specialist Hospital & Research Center approved the study protocol. Ethical approval was obtained from the ethics committee of the participating centres.

Results

Results of the included articles and studies

The initial search yielded 3,188 articles, of which 481 were duplicates and were removed. After a thorough review of the abstracts and titles of the remaining 2,707 articles, 71 articles that met the inclusion criteria were identified. The full texts of these articles were subjected to a detailed eligibility assessment, which resulted in the exclusion of 45 articles for various reasons. Consequently, 26 articles were included in this review (7-8, 19-42) (Fig. 1). The studies included 25 retrospective and one prospective study and involved 895 patients. Among the included patients, 603 (67.4%) were female, with an average age of 10.1 years. Regard-

ing the quality of evidence, 10 studies (38.5%) were classified as good quality, 13 studies (50%) as fair quality, and three studies (11.5%) as poor quality (Table I).

Pamidronate therapy

All patients were prescribed bisphosphonates, specifically pamidronate. While 393 patients (43.9%) received pamidronate monotherapy (7-8, 19-23, 25, 26, 28-34, 38-42), most patients received pamidronate in combination with other drugs. These combination therapies included antibiotics, NSAIDs, corticosteroids, methotrexate, TNFi and interleukin-1 inhibitors (IL1i).

NSAIDs were administered as initial therapy in most of the studies. In 16 articles, pamidronate was combined with disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (7-8, 20, 23-30, 32-36, 39). Sulfasalazine use was reported in four articles (24, 36, 38, 41). In addition, corticosteroids were used together with pamidronate in nine articles (22-25, 29, 34, 39-40, 42).

In 12 articles, TNFi was administered with pamidronate (8, 20, 22, 23, 26, 29, 30, 32-35, 40). Other drugs, such as azathioprine and mesalazine, were administered in two studies (20, 38). In some cases, pamidronate has been administered after the initial treatments have failed; pamidronate has been administered to patients who have relapsed during TNFi treatment or who did not respond to DMARDs (20). Additionally, pamidronate was administered to patients who did not respond to NSAIDs and corticosteroids (7). Some patients achieved complete remission after treatment with pamidronate, NSAIDs, methotrexate, and corticosteroids (7).

Clinical disease activity following pamidronate therapy

Table II summarises the results of evaluating the effectiveness of pamidronate in IBDs. Most studies evaluated the clinical activity of the disease after initiating pamidronate therapy. Schnabel *et al*. (2017) compared treatment outcomes between TNFi and pamidronate, finding that pamidronate led to faster clinical improvement in CNO patients (8). Specifically, 32% of patients achieved complete clinical remission after three months, with rates increasing to 54% and 69% at six and 12 months, respectively (8). In contrast, patients treated with TNFi had lower rates of complete remission (21%, 51%, and 65% at three, six and 12 months, respectively) (24). Gaal *et al*. (2020) used Kaplan-Meier curves and log-rank tests to compare the time to complete treatment response between TNFi and pamidronate. The results showed that pamidronate led to a significantly shorter time to complete response compared to TNFi (26). Andreasen *et al*. (2019) reported that 38% of children with extended CNO achieved clinical inactivity while taking medication during their first year. The proportion of children with clinical and radiological activity was 67% after one year and 71% after two years (29).

For patients with persistent radiological activity, reducing medication typically led to clinical relapse (30). Among patients with limited CNO, 53% achieved clinical inactivity during the first year of treatment, and 63% maintained this inactivity without medication in the second year. However, in the fifth year of treatment, second-line drugs were still being used in 57% of children with extended and 38% of children with limited CNO.

Kerrison *et al*. (2004) presented the first case series of the use of pamidronate for childhood-onset SAPHO syndrome and reported marked clinical improvement with no obvious adverse effects (7). Patients reported pain relief after the first course of pamidronate, confirming its effectiveness and safety profile for the treatment of SAPHO syndrome symptoms (22). Miettunen *et al*. (2009) found that all patients who received pamidronate experienced significant pain relief and a reduction in bone inflammation, with pain relief occurring within 48 hours of initial pamidronate administration, regardless of the location of the CRMO lesions (41).

Surendran *et al*. (2018) reported that all six patients treated with pamidronate showed a favourable response to treatment; notably, three of these patients had not previously responded to DMARDs (32). Furthermore, Gleeson *et al*. (2008) found that after six months of pamidronate treatment, 86% of participants reported a reduction in bone pain. Even after stopping pamidronate for an average of 27 months, 67% of patients continued to show improvement (40). Patients reported improvement within a week after receiving the infusion, with a single infusion providing pain relief for 10–12 weeks. However, that study found that pamidronate therapy was less effective in providing significant pain relief in patients with synovial joint inflammation, particularly in the elbow and small joints of the foot (42).

Schnabel *et al*. (2017) evaluated the effectiveness of NSAIDs, pamidronate, corticosteroids, and TNFi in the treatment of paediatric patients with CNO and found that pamidronate consistently achieved the best response and the fastest remission, even in patients with challenging traits, such as multifocal bone lesions, resistance to other drugs, and long-term disease activity (8). All patients who received pamidronate therapy remained stable for two years after achieving clinical remission in less than six months (12). According to Hoffman *et al*. (2016), 88% of patients achieved complete clinical remission within six months of using pamidronate therapy, whereas the remaining 12% showed partial clinical remission (10). One patient could resume regular activities without the use of a wheelchair, demonstrating restored functionality as part of the overall rehabilitation process (10).

X-ray and MRI imaging assessment

Several studies have evaluated disease activity using radiological images, mainly MRI (4, 7, 24, 27, 31, 35-37). Schnabel *et al*. (2016) reported that 75% of children underwent MRI, with most findings indicating involvement of the lower extremities (12). Of the patients, 26% achieved complete radiological remission using NSAIDs, whereas the bisphosphonate group had the best results after four cycles of bisphosphonate, with none developing new lesions. In contrast, 47% of patients in the corticosteroid group with CNO relapsed within one year (12). Kaut *et al*. (2022) found that 90% of patients

Table I. Studies included in the review and their characteristics.

Author last name, year	Country	Study design	Quality of evidence	Study sample	M/F	Age at onset/ diagnosis [c]	no. of cases on Pamidronate monotherapy	Previous/ Concomitant Treatment	HLA-B27 (%)	ESR (mm/h [c]	ESR % of elevated
Mohamedbhai *et al*., 2024 [17]	UK	Retrospective single centre	Fair	10	2 / 8	9.8	3	NSAIDs	89	20	20%
Kaut *et al*., 2022 [18]	Belgium	Retrospective multicentre	Fair	30	8 / 22	10.3	4	NSAIDs, TNFi, MTX, azathioprine	29	12–101	87%
Andreasen *et al*., 2022 [19]	Denmark	Retrospective single centre	Fair	18	7 / 11	9.8	18	NSAIDs	11	20	NR
Schnabel *et al*., 2022 [20]	UK, Germany	Retrospective multicentre	Good	47 [a]	21 / 26	9.7	69	NSAIDs, TNFi, antibiotic, GCs	20	33	NR
Panwar *et al*., 2021 [21]	Canada	Retrospective single centre	Fair	32	11 / 21	11.5	32	NSAIDs, GCs, DMARDs, TNFi	3	NR	NR
Açarı *et al*., 2021 [22]	Turkey	Retrospective multicentre	Fair	28	10 / 18	10.2	N/A	NSAIDs, TNFi, MTX, colchicine, SSZ, GCs	25	42	85.7%
Bustamante *et al*., 2021 [23]	Spain	Retrospective multicentre	Good	25	5 / 20	8.8	15	NSAIDs, TNFi, GCs, MTX, antibiotic	0	47.6	84.2%
Gaal *et al*., 2020 [24]	USA	Retrospective single centre	Poor	22	14 / 8	11	6	NSAIDs, TNFi, Antibiotic, GCs, DMARDs	7	NR	NR
Concha *et al*., 2020 [25]	Chile	Retrospective multicentre	Good	19	9 / 10	10	N/A	NSAIDs, MTX, SSZ, GCS, TNFi	16	22	53%
Bhat *et al*., 2019 [26]	UK	Retrospective single centre	Poor	46	11 / 35	11.6	31	NSAIDs, MTX	NR	NR	NR
Andreasen *et al*., 2019 [27]	Denmark	Retrospective single centre	Fair	51	19 / 32	10.7	18	NSAIDs, TNFi, antibiotic, DMARDs, GCs	5	11	NR
Sağ *et al*., 2019 [28]	Turkey	Retrospective single centre	Fair	15	8 / 7	9	3	NSAIDs, MTX, TNFi	12.5	29	66.6%
Sułko *et al*., 2019 [29]	Poland	Retrospective single centre	Good	41	7 / 34	10	41	NSAIDs	NR	18.3	NR
Surendran *et al*., 2018 [30]	India	Retrospective single centre	Good	20	15 / 5	10.3	6	NSAIDs, TNFi, Antibiotic, GGCs, DMARDs	NR	43	NR
Jiménez *et al*., 2018 [31]	Spain	Retrospective single centre	Poor	12	37 / 94	11	3	NSAIDs, TNFi, Antibiotic, GCs, DMARDs	NR	53.4	NR
Bhat *et al*., 2018 [32]	UK	Retrospective multicentre	Good	131	25 / 27	9.5	89	NSAIDs, MTX, GCs, TNFi	7	1-148	39.7%
Kostik *et al*., 2018 [33]	Germany	Retrospective single centre	Fair	52	3 / 5	8.4	n/a	NSAIDs, DMARDs, TNFi	NR	NR	0%
Schnabel *et al*., 2017 [8]	Germany	Retrospective single centre	Good	8 [b]	55 / 123	11.1	8	NSAID, TNFi, DMARDs, GGCs	21	31.7	52%
Wipff *et al*., 2015 [34]	America	Retrospective multicentre	Fair	178	10 / 31	9.8	N/A	NSAIDs,MTX, SSZ, TNFi, IL1i	48	37.7	86%
Kaiser *et al*., 2015 [35]	Switzerland	Retrospective multicentre	Fair	41	1 / 7	9.5	N/A	GCs, Alendronat, TNFi	21	34	82%
Hofmann *et al*., 2014 [36]	Germany	Retrospective single centre	Fair	8	0 / 11	10.5	8	NSAIDs, GCs, SSZ, mesalazine	NR	NR	NR
Roderick *et al*., 2014 [37]	UK	Retrospective single centre	Good	11	7 / 20	14 [d]	11	NSAIDs, MTX, antibiotic, GCs	NR	NR	NR
Hospach *et al*., 2010 [38]	Germany	Retrospective single center	Fair	27	4 / 5	10.3	7	NSAIDs, GCs, TNFi	n/a	NR	71.4%
Miettunen *et al*., 2009 [39]	Canada	Prospective observational single centre	Good	9	1 / 6	12.9 [d]	9	NSAIDs, SSZ, GCs, Amitriptyline, Ketorolac, morphine, Fentanyl, Codeine	33.3	23.7	NR
Gleeson *et al*., 2008 [40]	Australia	Retrospective single centre	Good	7	0 / 7	8	7	Antibiotic, NSAIDs, GCs	NR	NR	43%
Kerrison *et al*., 2004 [7]	UK	Retrospective single centre	Fair	7	0 / 7	11	5	Analgesic, NSAIDs, MTX	NR	NR	NR

NSAIDs: non-steroidal anti-inflammatory drugs; TNFi: (TNF)-alpha inhibitors; GGCs: glucocorticoids; MTX: methotrexate; SSZ: SSZ; DMARDs: disease-modifying anti-rheumatic drugs; NR: not reported; HLA-B27: human leukocyte antigen B27; ESR: erythrocyte sedimentation rate.

[a] This study sample size was 91 patients, but only 47 patients received pamidronate.

[b] This study sample size was 56 patients, but only 8 patients received pamidronate.

[c] Reported as mean or median or range.

[d] The age was documented in these two studies at treatment start only.

Table II. Summary of results assessing the effectiveness of pamidronate in inflammatory bone disorders.

Author last name, year	Pamidronate dose	Radiological improvement	Renal profile	Hepatic profile	Clinical improvement
Mohamedbhai *et al*., 2024 [17]	NR	100%	normal	normal	100%
Kaut*et al*., 2022 [18]	NR	87%	biochemical remission	biochemical remission in 90%	87%
Andreasen *et al*., 2022 [19]	NR	61% radioactive lesions resolved, 17% achieved radiological remission	NR	NR	44%
Schnabel *et al*., 2022 [20]	1 mg/kg/day (max 60 mg) for 3 days ever 3 months, first dose 0.5 mg/kg/day	69%	Subnormal	Subnormal	63%
Panwar *et al*., 2021 [21]	1 mg/kg (max 60 mg) once per month. Repeated every 3 months	34% lesions resolved after first cycle, 34% required a 2nd cycle, resulting in 76% resolved lesions	NR	NR	NR
Açarı *et al*., 2021 [22]	NR	NR	NR	NR	100%
Bustamante *et al*., 2021 [23]	1 mg/kg once a month initially	4/19 patients had local deformity involving clavicle and medial malleolus.	n/a	n/a	20%
Gaal *et al*., 2020 [24]	NR	75%	NR	NR	67%
Concha *et al*., 2020 [25]	NR	NR	NR	NR	40% 1–5 years of follow-up :37% in a median follow-up of 18 months
Bhat *et al*., 2019 [26]	1 mg/kg/day (max 60 mg) for 3 days. Repeated every 3 months	67% had good to moderate radiological response, 10% had mild response, 22% had no response	NR	NR	36%
Andreasen *et al*., 2019 [27]	1 mg/kg/day (max 60 mg/day) for 3 consecutive days every 3 months, first dose in the first series 0.5 mg/kg/day	32%	NR	NR	71% in extended CNO, 63% in limited CNO
Sağ *et al*., 2019 [28]	NR	100%	NR	NR	33%
Sułko *et al*., 2019 [29]	1 mg/kg/day for 3 consecutive days. Such sequence was repeated every 12 weeks until remission was achieved	NR	NR	NR	78%
Surendran *et al*., 2018 [30]	NR	67%	biochemical remission	biochemical improvement	5%
Jiménez *et al*., 2018 [31]	Day 1: 0.5 mg/kg, days 2 and 3: 1 mg/kg, repeat after one dose monthly/ 3 days every 3 months	NR	NR	NR	83%
Bhat *et al*., 2018 [32]	NR	61%	NR	NR	68%
Kostik *et al*., 2018 [33]	NR	NR	NR	NR	88%
Schnabel *et al*., 2017 [8]	Day 1: 0.5 mg/kg, days 2-3: 1 mg/kg, repeat at 3 and 6 months with 1 mg/kg for 3 days	50%	Normal	Subnormal	62%
Wipff *et al*., 2015 [34]	NR	NR	NR	NR	43%
Kaiser *et al*., 2015 [35]	NR	NR	NR	NR	30%
Hofmann *et al*., 2014 [36]	1 mg/kg every 4 weeks for 6 months (max 60 mg per cycle)	10% complete radiological remission, 90% partial remission	NR	NR	88%
Roderick *et al*., 2014 [37]	1 mg/kg/day for 3 consecutive days	60% of lesions fully resolved, 13% moderately resolved, 27% unchanged	NR	NR	60%
Hospach *et al*., 2010 [38]	Initial dose of 0.5 mg/kg/day followed by 1 mg/kg/day on three consecutive days.	NR	NR	NR	90%
Miettunen *et al*., 2009 [39]	Day 1: 0.5 mg/kg then 1mg/monthly, or every 3 months	100% reached >90% remission post-therapy, 44% relapsed with 50% achieving >90% remission after retreatment	Decrease in uNTX/uCr from 738 to 522 nmol/ mmol/creatinine upon pamidronate discontinuation with a median follow up of 31 months	NR	NR
Gleeson *et al*., 2008 [40]	Monthly at a dose of 30 mg/m2 or second monthly 1.5 mg/kg	3 cases had significant improvement in vertebral lesions, but all had persistent or new non spinal lesions	urinary creatinine decreased by 19% post pamidronate	17% decrease after pamidronate	86%
Kerrison *et al*., 2004 [7]	1 mg/kg/day (max 30 mg)for 3 days. Repeated every 3 months	NR	NR	NR	57%

CNO: chronic non-bacterial osteomyelitis; NR: not reported

undergoing targeted MRI and 60% of those undergoing whole-body MRI had multifocal lesions, most commonly in the pelvis (20). NSAIDs monotherapy was sufficient to achieve remission in almost half of the patients, whereas the remaining patients required second-line therapy, including bisphosphonate therapy. Remarkably, 87% of patients achieved remission in an average of 37.6 months (20).

A retrospective study reported appendicular involvement, particularly in the femur, and decreased bone mass (42). After starting pamidronate treatment, radiological improvements were observed in approximately 90% of the patients, with a median time to improvement of 26 months (33). Gaal *et al*. (2020) demonstrated radiological remission after therapy, with all patients showing bone marrow hyperintensity and 71% showing bone expansion and soft tissue oedema. Pamidronate and TNFi achieved better results than NSAIDs, with response rates of 67%, 60%, and 11%, respectively, with pamidronate showing a higher response rate than TNFi (26).

Surendran *et al*. (2018) found that MRI findings showed hypointense lesions and bone marrow oedema in all patients, whereas x-ray images revealed lytic and sclerotic lesions (32). Pamidronate therapy was associated with radiological improvement in 66% of patients (32). A prospective study showed that more than 90% of MRI signal irregularities were eliminated within an average of six months following pamidronate therapy. Among the patients with CRMO recurrence verified by MRI, 44% received bisphosphonate treatment as a retreatment measure and achieved remission within two months (41).

Panwar *et al*. (2021) reported that the lower limbs were the most commonly affected regions with lesions and demonstrated a significant difference in effectiveness between one and several cycles of pamidronate therapy (23). A single cycle of pamidronate resulted in 34% resolution of the lesions, while a subset of patients who received two or more cycles showed a 76% resolution rate after the second cycle. The first cycle revealed a greater number of newly detected and existing lesions than the second cycle, as detected by MRI.

Andreasen *et al*. (2022) observed a reduction in the total number of spinal lesions in 62% of patients who received extended CNO therapy for two years following pamidronate treatment (21). Among these patients, 38% achieved complete remission and 67% relapsed. However, of the 38% of patients who did not experience a reduction in the total number of spinal lesions, 53% achieved remission after one year of pamidronate treatment, with no relapse (21). Another study found that 61% of patients achieved resolution of radiologically active lesions after one year of pamidronate treatment (29). A retrospective study by Rodrick *et al*. (2014) showed that bone lesions improved after pamidronate therapy, with 60% of the lesions showing complete resolution after one year of treatment (39). Additionally, 13.3% of the lesions showed partial improvement and 26.7% remained stable; only 19% of the patients developed new lesions (39). A previous study comparing pamidronate and TNFi in the treatment of CNO found that the TNFi group had a greater number of lesions than the pamidronate group, with these differences observed six and 12 months after the start of treatment (31). In the TNFi group, 30% of patients achieved radiologic remission at six months, which increased to 52% at 12 months, while the pamidronate group had remission rates of 29% and 43% at the same intervals. Despite persistent active lesions during follow-up, all patients eventually achieved remission.

Bhat *et al*. (2019) demonstrated a 30% reduction in the number of lesions after pamidronate therapy, with vertebral disease responding more effectively, achieving 82% complete resolution (28). Approximately 43% of patients achieved complete resolution of all lesions, whereas 22.5% experienced worsening during or after treatment with pamidronate (28). Kerrison *et al*. (2004) found that at least two rounds of pamidronate therapy resulted in significant symptom improvement and subsequent remission (7). MRI revealed hyperintense, inflammatory lesions. Jiminez *et al*. (2018) and Kerrison *et al*. (2004) documented lytic lesions and medullary oedema in almost half of the patients, with the lower limbs being the most frequently affected areas. None of the studies reported any radiological improvement (7, 33).

Relapse

Relapse has been documented in several studies, with an average of 42% of patients relapsing and requiring additional therapy across all the studies (7-8, 22, 29, 38-39, 41). Three studies reported that retreatment with pamidronate improved symptoms after recurrence (7, 39, 41). According to Schanbl *et al*. (2022), 31% of patients continued to show persistent disease activity despite pamidronate therapy and were subsequently treated with TNFi (22). Another study reported that NSAIDs effectively controlled symptom recurrence in some patients (7). Hofmann *et al*. (2014) found that 38% of patients experienced relapse and received additional pamidronate therapy (38). Of these, 60% achieved sustained clinical remission. The remaining 40% were treated with etanercept, resulting in only partial clinical and radiological remission. Furthermore, one study indicated that 67% of individuals who received pamidronate relapsed (38).

Safety of pamidronate

In general, pamidronate was well tolerated, with only minor adverse effects observed. No serious adverse effects, such as mandibular osteonecrosis, have been reported (19, 23-24, 26, 30-32, 34-36, 39, 40). Mild adverse effects, including flu-like symptoms, nausea, fever, and headaches, have been reported in nine studies (7, 22, 26, 28, 40, 41). Two studies reported arthralgia and two studies observed mild asymptomatic hypocalcaemia (29, 38). Additionally, two retrospective studies have documented cases of phlebitis at the injection site (26, 38). A retrospective study found that 14% of patients experienced redness, swelling, and pain at the injection site after infusion, whereas 57% reported generalised diffuse aches and pains (42). In one retrospective study, 4% of patients discontinued treatment

because of infusion-related side effects, whereas in another study, 38% required a dose reduction (28, 38).

Several studies have evaluated the impact of pamidronate on bone profile and markers (20, 22, 32, 41, 42). One study observed a reduction in urinary creatinine, while another reported a decrease in urinary N-telopeptide/urinary creatinine (uNTX/uCr), a marker of bone resorption (41, 42). Gleeson *et al*. (2008) reported a 19% reduction in urinary creatinine after pamidronate, while Miettunen *et al*. (2009) found a significant reduction in uNTX/uCr from a mean baseline of 738 nmol/mmol/creatinine to 522 nmol/mmol/creatinine after pamidronate discontinuation, with a median follow-up of 31 months (41). Kaut *et al*. (2022) and Surendran *et al*. (2018) reported biochemical remission in most patients with unstable biochemistry profiles. In contrast, Schnabel *et al*. (2016) found minimal changes in liver and kidney profiles (12, 20, 32).

Discussion

The primary goals in treating IBDs are achieving remission, preventing disease progression, and improving patients' quality of life. Currently, there are no specific therapies or treatment guidelines for IBDs. However, various treatment options have been explored, including NSAIDs, systemic corticosteroids, and conventional and biological DMARDs (10-13, 34). This variation highlights the differences in treatment regimens and patient responses reported in the literature. There has been a growing trend toward the use of bisphosphonates, especially pamidronate, for treating IBDs. However, limited data on the safety and effectiveness of treatments for IBDs hinders optimal patient care and treatment outcomes. Treatment strategies for IBDs have been adapted from experience with pamidronate use in CRMO. We conducted a comprehensive literature review to evaluate the available evidence on the use of bisphosphonates, with a focus on pamidronate, in the treatment of IBDs.

Our search yielded 26 articles, including 25 retrospective and one prospective study, with a total of 895 patients with an average age of 10.1 years. The lack of consensus on nomenclature creates confusion. Several studies have used "CNO", whereas others use "CRMO", and the terms are used interchangeably. All patients received bisphosphonates, particularly pamidronate.

The frequent use of pamidronate in combination with other drugs makes it challenging to assess its therapeutic effectiveness as a standalone treatment. Interestingly, 393 patients were treated exclusively with this drug. In general, bisphosphonate therapy was well tolerated, with minimal adverse events. Despite the lack of standardised outcome measures, including monitoring of disease progression and organ damage, the overall results indicate that pamidronate is well tolerated and provides clinical benefits. The effectiveness of bisphosphonates has been evaluated on the basis of pain reduction and radiological improvement, with most studies revealing significant benefits, such as disease remission, alleviation of symptoms, and improved radiological findings.

A key consideration is whether bisphosphonates should be regarded as a first-line therapy for CNO/CRMO, particularly in cases without extraosseous involvement such as joint, skin, or intestinal comorbidities. Although NSAIDs, corticosteroids, and TNFi are frequently employed prior to bisphosphonates, the reviewed studies suggest that bisphosphonates provide notable benefits even in patients unresponsive to these first-line treatments. Mechanistically, bisphosphonates exhibit a high affinity for bone, accumulating at sites of active remodelling, which enables targeted action while minimising systemic adverse effects. At higher doses, these agents can induce apoptosis in osteoclasts and inflammatory cells, exerting a rapid and selective anti-inflammatory effect. However, their efficacy in treating extraosseous symptoms remains limited.

This review had limitations due to discrepancies in the data included in the studies. Statistical analysis was hindered by disparities in measurement outcomes and follow-up intervals. Furthermore, our study was limited because it was not registered in the International Prospective Register of Systematic Reviews.

Conclusion

In summary, bisphosphonates, such as pamidronate, are effective and well tolerated in paediatric patients diagnosed with CRMO or CNO, especially when used in combination with other drugs. This combined approach yields favourable outcomes, including symptom relief, disease remission, and improved radiological findings, contributing to better management of these conditions in children.

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