Systematic Review Of The Effects Of Bisphosphonates On Bone Density And Fracture Incidence In Childhood Acute Lymphoblastic Leukaemia

AM Harris [1], AR Lee [1], SC Wong [1]

[1] Developmental Endocrinology Research Group, University of Glasgow, Royal Hospital for Children, Glasgow, UK

Corresponding Author and requests for reprints

Dr Sze Choong Wong

Senior Clinical Lecturer Paediatric Endocrinology,

Developmental Endocrinology Research

Royal Hospital for Children

1345 Govan Road, Glasgow G51 4TF, UK.

Email.: Jarod.Wong@glasgow.ac.uk

Tel.: +44 141 4515841

Fax: 0044 141 201 2215

Abstract Word Count: 236 words

Manuscript Word Count: 2673 words

Tables: 3

Figures: 1

Short title: Bisphosphonate in paediatric acute lymphoblastic leukaemia

Keywords: Bone health, Dual energy absorptiometry, Leukaemia, Pamidronate, Vertebral fracture, Zoledronate

ABSTRACT (236 words)

Purpose: Skeletal fragility is a common complication of childhood acute lymphoblastic leukaemia (ALL) but the impact of bisphosphonate therapy on bone mass and fracture is unclear. We aim to conduct a systematic review to evaluate the effects of bisphosphonates on bone mineral density (BMD) and fracture incidence in children with ALL.

Methods: EMBASE, Medline and the Cochrane Library were thoroughly searched by two researchers. Inclusion criteria was any child under the age of 18 years with a diagnosis of ALL who had received any bisphosphonate treatment and had serial measurements of bone density performed thereafter. All primary research studies of any study design, excluding case reports, were included.

Results: Ten full text papers were identified with 2 exclusively meeting the inclusion criteria. Both studies administered bisphosphonates to children receiving maintenance chemotherapy for varying durations. Bone density was assessed at regular intervals by dual x-ray absorptiometry (DXA). The majority of participants had an improvement in bone density at the end of each study. However, no size adjustment of DXA data was performed. Limited information on fracture occurrence was provided by one study but did not include routine screening for vertebral fractures.

Conclusions: This systematic review identified that there is insufficient evidence to support routine use of prophylactic bisphosphonate therapy in childhood ALL for prevention of fracture and improvement of bone mass. Future well-designed clinical trials in those at highest risk of fractures in ALL are now needed.

Introduction

Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer accounting for almost one third of paediatric malignancies. Skeletal fragility is a significant complication of ALL, with fracture incidence of up to 28% in the 5 year period post ALL diagnosis, based on clinical presentation of fracture [1-3]. The STeroid-associated Osteoporosis in the Paediatric Population (STOPP) studies highlighted the significant issue of vertebral fractures, the current accepted definition of osteoporosis in the young [4], when systematic screening with spine x-rays were performed in children with ALL [5-7]. Over a quarter of children were diagnosed with vertebral fractures in the four year period following diagnosis of ALL [7]. The highest incidence of vertebral fracture is in the first year post diagnosis when there is greatest glucocorticoid exposure, almost half were asymptomatic [7].

The concept of reshaping of vertebral body in those with vertebral fracture is a phenomenon unique to growing children, dependent on removal of the skeletal insult and opportunity for catch-up growth. This phenomenon can be observed in some children with ALL and vertebral fracture [8, 9]. Some studies suggest that bone mineral density (BMD) is significantly reduced in survivors even many years after cessation of treatment [10-12], although others do not identify any deficits [13, 14].

Bisphosphonates are a family of drugs which decrease bone turnover by inhibiting osteoclastic bone resorption [15]. They have been used for several years in the management of paediatric primary osteoporosis in children with osteogenesis imperfecta [16, 17] . Despite limited evidence in paediatric secondary osteoporosis due to an underlying chronic condition, its use has been largely limited to those with fragility fractures, especially when the skeletal insult is likely to be persistent and where there is limited opportunity for linear growth [18]. Therefore, at least in a sub-set of children with ALL [9], there may be a need to consider bone protective therapy to prevent fragility fractures and permanent vertebral deformities. This systematic review has been conducted to evaluate the effects of bisphosphonates on BMD and fracture incidence in childhood ALL.

Methods

We performed a systematic review of the literature in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.

Inclusion and exclusion criteria

To be eligible, papers had to fulfil the following criteria as per PICO principle, determined at the start of the project:

Population: Children and adolescents aged 0-17 years with acute lymphoblastic leukaemia

Intervention: Bisphosphonate therapy

Comparison: Children and adolescents aged 0-17 years with acute lymphoblastic leukaemia not exposed to bisphosphonate therapy

Outcome: Densitometry measurement of bone mass and/or fracture

Studies involving children with ALL and other malignancies or chronic conditions were excluded. Furthermore, studies investigating multiple treatment options for reduced BMD were also excluded. There was an open time frame with no limit to the year of publication. Only English language articles were considered. All primary research studies of any study design (excluding case reports with less than 3 subjects) investigating the outcome of bisphosphonate therapy on BMD and/or fracture incidence in paediatric ALL patients were included.

Search strategy

A systematic computerised literature search of EMBASE, MEDLINE and the Cochrane Library by two independent reviewers (AMH, ARL) were performed to source relevant articles in April 2019. A combination of title headings and free text were used. The following key terms were searched for: "bisphosphonates" or "alendronate" or "pamidronate" or "risedronate" or "zoledronate" AND "acute lymphoblastic leukaemia" AND "children" or "toddler" or "adolescent" AND "bone density" or "osteopenia" or "fractures". Bibliographic

references from all included studies were manually searched for potentially relevant studies based on the inclusion and exclusion criteria. Authors were not contacted and grey literature was not reviewed.

Study selection

Both reviewers reviewed all titles and abstracts to filter out duplicates and irrelevant articles. The researchers then sought full articles of potentially suitable abstracts and read these thoroughly to determine eligibility for the review. The following data were then extracted from the studies suitable for inclusion: study design, study population size, age range, bisphosphonate used, administration route, dose of drug, treatment duration, baseline dual energy absorptiometry (DXA) BMD and/or bone mineral content (BMC), mean change in DXA BMD and/or BMC and fractures.

Assessment of bias and quality

Assessment of bias using the "A Cochrane Risk Of Bias Assessment Tool: For Non-Randomised Studies of Interventions" (ACROBAT-NSRI) of the eligible studies were performed independently by two reviewers (AMH, ARL). Disagreements were resolved by discussion by two of the authors and a consensus reached (AMH, SCW).

Results

The PRISMA flow diagram with the numbers of included and excluded papers at each step of the review is shown in Figure 1. The literature search identified 117 articles of which 28 were duplicate articles and immediately removed (Figure 1). The title and abstract of the remaining 89 articles were read and papers screened for eligibility. The majority of these, 79, were not relevant and therefore excluded. 10 full text papers were assessed for inclusion. The 8 excluded studies were excluded for the following reasons: case report in 2 children with ALL and vertebral fractures treated with IV pamidronate (n,1) [19]; retrospective review of children with symptomatic chemotherapy related osteonecrosis treated with IV zoledronate (n,1) [20]; open label prospective studies of oral alendronate and IV pamidronate in children with ALL and other haematological malignancies (n, 2) [21, 22]; review articles (n, 4) [8, 23-25]. These 8 papers were excluded from full review and the 2 papers that met the inclusion criteria were included in this review (Table 1) [26, 27]. Given the small number of studies, both studies are described in detailed.

Barr et al. (2002) was a prospective open label study reviewing the use of six months of intravenous pamidronate in children receiving maintenance chemotherapy for ALL (Table 1) [26]. Outcome measure was DXA total body BMC and lumbar spine BMD. No fracture outcome was included. Ten children were recruited: 8 had standard disease and 2 with high risk disease. Intravenous pamidronate was administered (1mg/kg) over 4 hours for 3 consecutive days with the first dose being on the first day of a chemotherapy cycle. Children had a repeat course of pamidronate 3 months and 6 months later with the same regimen. DXA was measured at baseline prior to pamidronate administration, after the third infusion at 3 months and 6 months. Only six children completed the study: 3 withdrew as a result of hyperpyrexia (>40C) in combination with bilateral conjunctivitis and 1 withdrew secondary to scheduling conflicts. Serum osteocalcin, a marker of bone formation and c-telopeptide, a marker of bone resorption, were reduced in subjects receiving pamidronate which returned to near baseline three months after discontinuation of pamidronate. Baseline deficits in DXA BMD especially at lumbar spine were noted. Six months of IV pamidronate treatment led to

an increase of +0.96 SD at total body and +1.11 SD at lumbar spine. Nine subjects experienced asymptomatic hypocalcaemia during the first pamidronate course. There was no information on glucocorticoid therapy, growth and puberty before and after pamidronate therapy.

Lethaby et al. (2007) was a prospective open label study reviewing the use of oral alendronate in children receiving maintenance chemotherapy for ALL (Table 1) [27]. Outcome measure was DXA lumbar spine BMD. Fracture was briefly discussed in this study. Fifteen children undergoing treatment for ALL were enrolled in this prospective open label study. Eight subjects had standard disease and 7 had high risk ALL. Oral alendronate was given once weekly during maintenance chemotherapy. Doses were based on body weight (ranging from 20-70mg). Duration of alendronate varied from 6 to 24 months. Seven remained on alendronate even after completion of ALL treatment. DXA was performed to assess bone density at lumbar spine and were repeated 6 monthly. Fourteen of the 15 children had an improvement in BMD Z score at the end of the study with a median gain of +0.64 (30). Two subjects experienced several fractures whilst taking alendronate which the authors attributed to possible non-compliance with medication. Similarly, no information on glucocorticoid, growth or puberty were reported.

Table 2 shows the results of the assessment of bias of the two studies included in this systematic review. Assessment of bias revealed serious and moderate risk of bias in the two included studies (Table 2).

Excluded Studies

There were 4 further studies identified in the literature which were formally excluded from this review as they included patients with non-hodgkin's Lymphoma (NHL) as well as ALL treated with bisphosphonate [21, 22]. The results of these studies (Table 3) were comparable with the included studies showing a reduced baseline DXA z-score which improved after bisphosphonates therapy. One study which evaluated the use of IV zoledronate for symptomatic chemotherapy related osteonecrosis reported improvement in

unadjusted LS BMD and TB BMC but when TBC BMC was adjusted for lean mass, no significant improvement was observed.

Goldbloom et al was a retrospective report of 2 children with ALL with symptomatic VF treated with IV pamidronate [19]. Wiernikowski et al was a prospective pilot study reviewing the effect of six months of oral alendronate in ten children: 8 with ALL and 2 with NHL, during maintenance chemotherapy [22]. Lee at al was a prospective study reviewing the use of intravenous pamidronate for a mean duration of 12 months in 24 children: 16 with ALL, 4 with NHL and 4 with acute biphenotypic leukaemia [21]. These subjects were selected from a total of 105 who underwent DXA and pamidronate was administered in those with DXA BMD Z-score < -2.0 or bone pain with DXA BMD Z-score < 0. Ten others who did not satisfy the criteria for pamidronate therapy acted as the control group: 8 with ALL and 2 with NHL [21]. Padhye et al was a retrospective study reviewing the use of intravenous zoledronate for median duration of 13 months in 20 children with symptomatic chemotherapy osteonecrosis: 12 with ALL, 2 with NHL, 3 with Hodgkin's lymphoma, 1 with acute myeloid leukaemia and 2 with benign haematological disorders. Of note, 8 have also had stem cell transplant [20].

Discussion

This systematic review highlights that there has been a very limited number of studies investigating the effects of bisphosphonates on bone health and fracture incidence in children with ALL. Both studies were of low quality and had moderate to serious overall risk of bias.

Bisphosphonates in both studies were administered during the maintenance phase of chemotherapy. However, glucocorticoid exposure is generally highest in the initial phases of chemotherapy and therefore in these uncontrolled studies, improvement in bone could be due to reduction or discontinuation of glucocorticoid therapy with good catch-up linear growth. The STOPP studies highlighted that fracture frequency was highest in the first year after diagnosis [7]. Ideally, bone protective agents should be given as early as possible during chemotherapy to minimise bone morbidity and fracture incidence, as the insult to the skeleton is present from early on. There are undoubtedly significant challenges of conducting a clinical trial in the initial phases of chemotherapy. It is possible that acute phase reaction adverse effects to bisphosphonate and hypophosphotaemia may be more pronounced during periods where glucocorticoid load is higher [28]. Clinical trials recruiting older children with ALL and/or those with more severe vertebral collapse in the first year of chemotherapy seems logical given that these are factors associated with lack of recovery from osteoporosis in childhood ALL [9].

Duration of bisphosphonate therapy varied in both studies. One study administered bisphosphonates for 6 months [26] whilst the other treated patients for a mean of 12 months [27] with no long term follow up from either study. Both studies used DXA z scores to quantify bone mineral capacity or bone mineral density as outcome measures. Both did not employ method of size adjustment for interpretation of results, which is recommended by the International Society for Clinical Densitometry [29]. Barr et al reported both whole body BMC, BMD and lumbar spine BMD [26] while Lethaby et al only evaluated lumbar spine BMD [27]. The European Medicines Agency (EMA) advised that treatment in paediatric osteoporosis trials should be for a minimum of one year with at least one year follow-up

thereafter to evaluate outcome, and that fracture should be the primary outcome measure and not DXA based bone density. Given the frequency of asymptomatic VFs in chronic conditions like ALL, outcome measures in future trials should include systematic routine screening with lateral thoracolumbar imaging to detect VFs. Both studies included in this systematic review did not include the use of routine spine imaging to identify VFs [21, 22].

There are a number of confounding factors which may contribute to improvement in osteoporosis in ALL including discontinuation of glucocorticoids, ALL in remission which results in increased physical activity, improved nutrition, reduced infection and less cytokine activation, improvement in linear growth and progression through puberty in older adolescents [18]. For these reasons, ideally a randomised trial is needed to ascertain the true impact on a bone protective therapy in this population.

There are a number of challenges in designing a paediatric randomized controlled trial in this area. Investigators in Melbourne report their attempt at a randomized controlled trial of intravenous bisphosphonate (pamidronate) in children with glucocorticoid associated osteoporosis (but not including haematological malignancies like ALL) in 2005 [30]. The investigators could only enrol 12 subjects over a period of 4 year (out of the projected 60). Despite being one of the most common childhood cancers worldwide, there are only 400 new ALL cases annually in the United Kingdom. Consequently, international collaboration maybe required to achieve an adequate sample size for a randomized controlled trial. Incorporating bisphosphonates or other bone protective agents as investigative therapies into an existing haematology-oncology trial may also facilitate recruitment.

Current studies suggest that chronic condition and GC osteoporosis maybe associated with a low bone turnover state. Serum markers of bone formation are reduced at ALL diagnosis with bone resorption markers being low or normal in the majority of studies [31, 32]. Bisphosphonates decrease bone turnover by inhibiting osteoclastic bone resorption [15]. Whilst bisphosphonates have been the main focus of this present review, a more logical alternative as a bone protective agent may be emerging anabolic bone therapies like anti-

sclerostin antibody [33]. Currently, no published clinical data in children are available but trials are underway.

Recommendation

This review has shown that there are only a very small number of non-randomised studies of low quality of bisphosphonates in childhood ALL on bone morbidity. Whilst BMD appears to improve after bisphosphonate treatment in these studies [26, 27], the lack of size adjustment makes it almost impossible to interpret the true benefit of bisphosphonates on BMD. There is insufficient evidence to support prophylactic bisphosphonates to improve bone mass and reduce fracture occurrence in children with ALL. Future large-scale well-designed randomized controlled trials are needed. In our opinion, these should be

(a) Primary prevention randomised trials (ie fracture free at recruitment). In our opinion, there may be a case to target recruitment in older children as they have been shown to show persistence of osteoporosis even following completion of chemotherapy [9]. On the other hand, a larger proportion of children with ALL are younger at presentation, and such issues will need to be considered carefully when developing future trials;

(b) Secondary prevention randomised trials of those with vertebral fractures, those with long bone fractures and /or those with low BMD. Ideally, this should include subjects with symptomatic and asymptomatic vertebral fractures but recruitment of those who already have symptoms may be extremely challenging.

In our opinion, efficacy outcomes in planned clinical trials should include fractures which are centrally reported including routine screening of the spine for VF, size adjusted DXA based densitometry, measure of back pain and quality of life. In addition, measures of safety should be assessed including acute phase reactions like fever, musculo-skeletal pain, gastrointestinal intolerance and disease progression including relapse if the follow-up period is sufficiently lengthy enough.

1

2

Conclusion

This systematic review has highlighted that at present there is insufficient evidence to support the use of prophylactic bisphosphonate treatment routinely in ALL. Given the high fracture occurrence, well designed trials of bone protective therapies are needed. Recommendations laid out by the EMA on paediatric osteoporosis clinical trials should be used by investigators in their design of such trials.

Disclosure

SCW has received consultancy fees from Novartis.

The rest of the authors have no conflict of interest to declare.

References

1. Hogler W, Wehl G, van Staa T, Meister B, Klein-Franke A, Kropshofer G (2007) Incidence of skeletal complications during treatment of childhood acute lymphoblastic leukemia: comparison of fracture risk with the General Practice Research Database. Pediatr Blood Cancer 48:21-27
2. te Winkel ML, Pieters R, Hop WC, et al. (2014) Bone mineral density at diagnosis determines fracture rate in children with acute lymphoblastic leukemia treated according to the DCOG-ALL9 protocol. Bone 59:223-228
3. Strauss AJ, Su JT, Dalton VM, Gelber RD, Sallan SE, Silverman LB (2001) Bony morbidity in children treated for acute lymphoblastic leukemia. J Clin Oncol 19:3066-3072
4. Gordon CM, Leonard MB, Zemel BS, International Society for Clinical D (2014) 2013 Pediatric Position Development Conference: executive summary and reflections. J Clin Densitom 17:219-224
5. Halton J, Gaboury I, Grant R, et al. (2009) Advanced vertebral fracture among newly diagnosed children with acute lymphoblastic leukemia: results of the Canadian Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) research program. J Bone Miner Res 24:1326-1334
6. Alos N, Grant RM, Ramsay T, et al. (2012) High incidence of vertebral fractures in children with acute lymphoblastic leukemia 12 months after the initiation of therapy. J Clin Oncol 30:2760-2767
7. Cummings EA, Ma J, Fernandez CV, et al. (2015) Incident Vertebral Fractures in Children With Leukemia During the Four Years Following Diagnosis. J Clin Endocrinol Metab 100:3408-3417
8. Dal Osto LC, Konji VN, Halton J, Matzinger MA, Bassal M, Rauch F, Ward LM (2016) The Spectrum of Recovery From Fracture-Induced Vertebral Deformity in Pediatric Leukemia. Pediatr Blood Cancer 63:1107-1110
9. Ward LM, Ma J, Lang B, et al. (2018) Bone Morbidity and Recovery in Children With Acute Lymphoblastic Leukemia: Results of a Six-Year Prospective Cohort Study. J Bone Miner Res 33:1435-1443
10. Warner JT, Evans WD, Webb DK, Bell W, Gregory JW (1999) Relative osteopenia after treatment for acute lymphoblastic leukemia. Pediatr Res 45:544-551
11. Arikoski P, Komulainen J, Voutilainen R, Riikonen P, Parviainen M, Tapanainen P, Knip M, Kroger H (1998) Reduced bone mineral density in long-term survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol 20:234-240
12. Tillmann V, Darlington AS, Eiser C, Bishop NJ, Davies HA (2002) Male sex and low physical activity are associated with reduced spine bone mineral density in survivors of childhood acute lymphoblastic leukemia. J Bone Miner Res 17:1073-1080
13. Kadan-Lottick N, Marshall JA, Baron AE, Krebs NF, Hambidge KM, Albano E (2001) Normal bone mineral density after treatment for childhood acute lymphoblastic leukemia diagnosed between 1991 and 1998. J Pediatr 138:898-904
14. van der Sluis IM, van den Heuvel-Eibrink MM, Hahlen K, Krenning EP, de Muinck Keizer-Schrama SM (2000) Bone mineral density, body composition, and height in long-term survivors of acute lymphoblastic leukemia in childhood. Med Pediatr Oncol 35:415-420
15. Rodan GA, Reszka AA (2002) Bisphosphonate mechanism of action. Curr Mol Med 2:571-577
16. Ward LM, Konji VN, Ma J (2016) The management of osteoporosis in children. Osteoporos Int 27:2147-2179
17. Simm PJ, Biggin A, Zacharin MR, et al. (2018) Consensus guidelines on the use of bisphosphonate therapy in children and adolescents. J Paediatr Child Health 54:223-233
18. Joseph S, McCarrison S, Wong SC (2016) Skeletal Fragility in Children with Chronic Disease. Horm Res Paediatr 86:71-82
19. Goldbloom EB, Cummings EA, Yhap M (2005) Osteoporosis at presentation of childhood ALL: management with pamidronate. Pediatr Hematol Oncol 22:543-550

20. Padhye B, Dalla-Pozza L, Little DG, Munns CF (2013) Use of zoledronic acid for treatment of chemotherapy related osteonecrosis in children and adolescents: a retrospective analysis. Pediatr Blood Cancer 60:1539-1545
21. Lee JM, Kim JE, Bae SH, Hah JO (2013) Efficacy of pamidronate in children with low bone mineral density during and after chemotherapy for acute lymphoblastic leukemia and non-Hodgkin lymphoma. Blood Res 48:99-106
22. Wiernikowski JT, Barr RD, Webber C, Guo CY, Wright M, Atkinson SA (2005) Alendronate for steroid-induced osteopenia in children with acute lymphoblastic leukaemia or non-Hodgkin's lymphoma: results of a pilot study. J Oncol Pharm Pract 11:51-56
23. Wasilewski-Masker K, Kaste SC, Hudson MM, Esiashvili N, Mattano LA, Meacham LR (2008) Bone mineral density deficits in survivors of childhood cancer: long-term follow-up guidelines and review of the literature. Pediatrics 121:e705-713
24. Sala A, Barr RD (2007) Osteopenia and cancer in children and adolescents: the fragility of success. Cancer 109:1420-1431
25. Sala A, Mattano LA, Jr., Barr RD (2007) Osteonecrosis in children and adolescents with cancer - an adverse effect of systemic therapy. Eur J Cancer 43:683-689
26. Barr RD, Guo CY, Wiernikowski J, Webber C, Wright M, Atkinson S (2002) Osteopenia in children with acute lymphoblastic leukemia: a pilot study of amelioration with Pamidronate. Med Pediatr Oncol 39:44-46
27. Lethaby C, Wiernikowski J, Sala A, Naronha M, Webber C, Barr RD (2007) Bisphosphonate therapy for reduced bone mineral density during treatment of acute lymphoblastic leukemia in childhood and adolescence: a report of preliminary experience. J Pediatr Hematol Oncol 29:613-616
28. Nasomyont N, Hornung LN, Gordon CM, Wasserman H (2019) Outcomes following intravenous bisphosphonate infusion in pediatric patients: A 7-year retrospective chart review. Bone 121:60-67
29. Crabtree NJ, Arabi A, Bachrach LK, Fewtrell M, El-Hajj Fuleihan G, Kecskemethy HH, Jaworski M, Gordon CM, International Society for Clinical D (2014) Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD Pediatric Official Positions. J Clin Densitom 17:225-242
30. Brown JJ, Zacharin MR (2005) Attempted randomized controlled trial of pamidronate versus calcium and calcitriol supplements for management of steroid-induced osteoporosis in children and adolescents. J Paediatr Child Health 41:580-582
31. Crofton PM, Ahmed SF, Wade JC, Stephen R, Elmlinger MW, Ranke MB, Kelnar CJ, Wallace WH (1998) Effects of intensive chemotherapy on bone and collagen turnover and the growth hormone axis in children with acute lymphoblastic leukemia. J Clin Endocrinol Metab 83:3121-3129
32. Arikoski P, Komulainen J, Riikonen P, Voutilainen R, Knip M, Kroger H (1999) Alterations in bone turnover and impaired development of bone mineral density in newly diagnosed children with cancer: a 1-year prospective study. J Clin Endocrinol Metab 84:3174-3181
33. Ward LM, Rauch F (2018) Anabolic Therapy for the Treatment of Osteoporosis in Childhood. Curr Osteoporos Rep 16:269-276

Legend to figures

Figure 1 Study flow diagram showing the study selection process

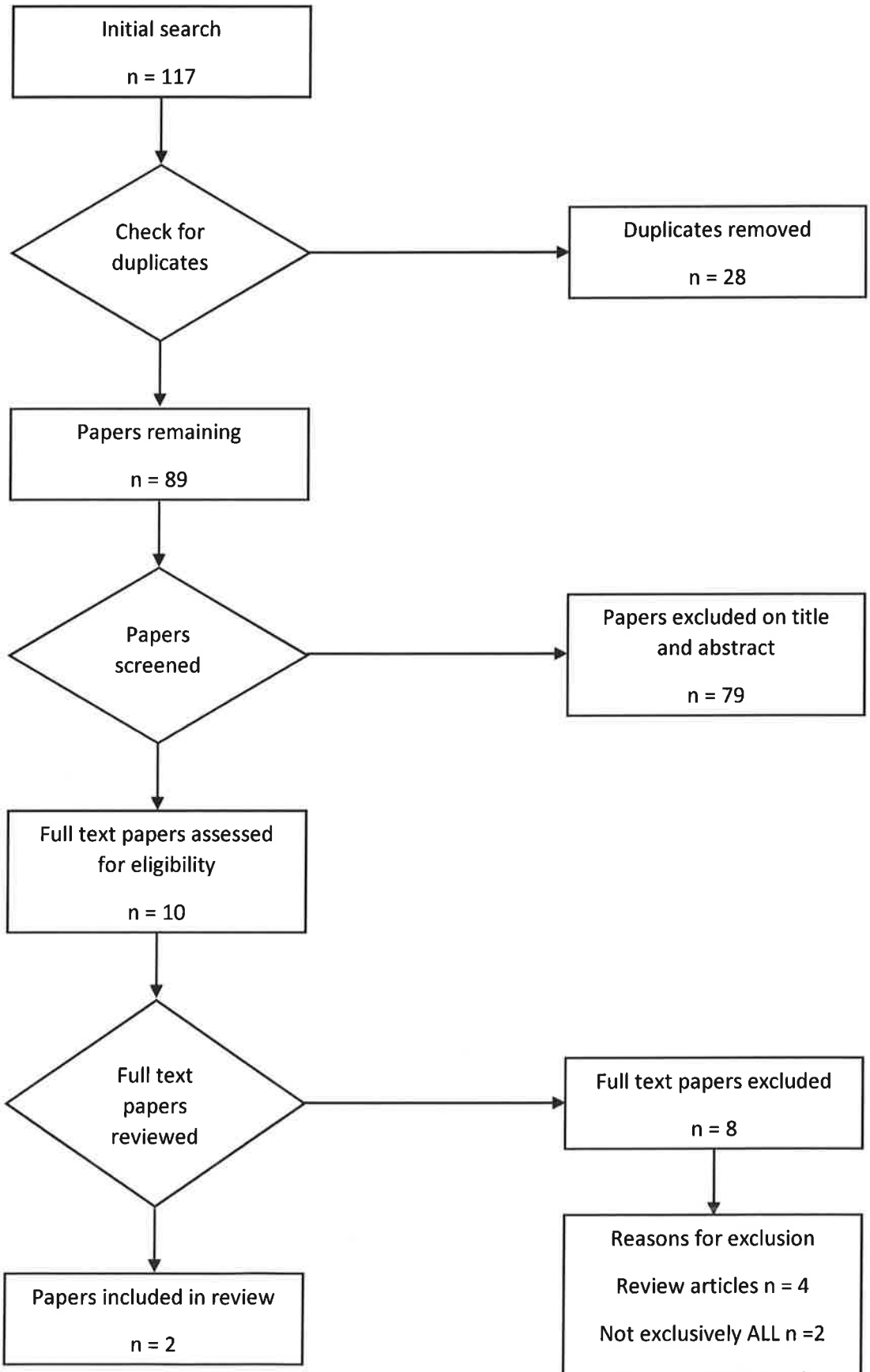
Initial search
n = 117
Check for duplicates
Duplicates removed
n = 28
Papers remaining
n = 89
Papers screened
Papers excluded on title and abstract
n = 79
Full text papers assessed for eligibility
n = 10
Full text papers reviewed
Full text papers excluded
n = 8
Reasons for exclusion
Review articles n = 4
Not exclusively ALL n =2
Not exclusively ALL & therapy for osteonecrosis n=1
Case Report n = 1
Papers included in review
n = 2

Figure 1

Author, (year)	Study design	Number of subjects	Age range (years)	Bisphosphonate and administration route	Dose range	Duration of treatment (months)	Change in DXA z score after BP	Size adjustment method employed	Fracture incidence
Barr et al. (2002) [26]	Prospective non-randomised study	10	3.5 to 16.1	IV pamidronate	1mg/kg/day for 3 days every 3 months	6	TB BMD +0.96 LS BMD +1.11	No	Not reported
Lethaby et al. (2007) [27]	Prospective non-randomised study	15	2.5 to 18.2	Oral alendronate	20-70mg once weekly (weight dependent dosing)	Median 6 to 24	LS BMD +0.64	No	2/15 had multiple fractures during the period of study but no data on fracture prior to the study and treatment with alendronate

Table 1: Description of included studies of bisphosphonates in childhood ALL

IV: intravenous; mg: milligram; kg: kilogram; DXA: dual energy absorptiometry; BP bisphosphonate; TB: total body; BMD: bone mineral density; LS: lumbar spine

Author, year	Bias due to confounding	Bias of selection of participants into the study	Bias in measurement of intervention	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results	Overall bias
Barr et al. (2002) [26]	Moderate	Moderate	Low	Serious	Moderate	Moderate	Low	Serious
Lethaby et al. (2002) [27]	Moderate	Moderate	Low	Moderate	Low	Moderate	Low	Moderate

Table 2: Assessment of bias of included studies

Author, year	Study design	Study population (n)	Age range (years)	Bisphosphonate and administration route	Dose range	Duration of treatment (months)	Mean change in DXA z score after BP	Size adjustment method employed	Fracture incidence
Goldbloom EB et al. (2005) [19]	Retrospective study	2	3.9 year boy	IV pamidronate	IV pamidronate for 28 days then followed by treatment every 2 months	20	TB BMD +0.7 (at 20 months)	No	No new fractures
			8.0 year girl	IV pamidronate	IV pamidronate baseline, 3 weeks followed by treatment every 2 months	Not reported	TB BMD +1.02 (at 20 months)	No	Further vertebral collapse at 5 months
Wiernikowski et al. (2005) [22]	Prospective, non-randomised study	10 (8 with ALL)	3.6 to 14.6	Oral alendronate	30 – 70mg once weekly: age dependant dosing	6	TB BMC +0.49 LS BMD +0.21	No	Not reported
Lee et al. (2013) [21]	Prospective, non-randomised study	24 (16 with ALL)	3.7 to 20.0	IV pamidronate	1mg/kg/day for 3 days every 1 – 4 months	Median 12 (6 to 30)	LS BMD +2.06	No	Not reported
Padhye et al (2013) [20]	Retrospective study	20 (12 with ALL)	7.8 to 14.5	IV zoledronate	0.025 mg/kg/dose every 3 months	Median 13 (5 to 25)	TB BMC adjusted for lean mass -0.37	Yes	Not reported

Table 3: Description of excluded studies of bisphosphonate including childhood ALL

ALL: acute lymphoblastic leukaemia; IV: intravenous; mg: milligram; kg: kilogram; DXA: dual energy absorptiometry; BP: bisphosphonate; TB: total body; LS: lumbar spine; BMC: bone mineral content; BMD: bone mineral density