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Review Article

A systematic review and meta-analysis of interventional studies of bisphosphonates and denosumab in multiple myeloma and future perspectives

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Abstract

Bisphosphonates (BPs) and denosumab (DENOS), due to their ability to inhibit osteoclast activity, are used to prevent skeletal complications in multiple myeloma (MM) patients. The NCBI PubMed, Web of Science, Scopus and ClinicalTrials.gov databases, were systematically searched for interventional studies, assessing the use of BP and DENOS in MM patients. Overall survival, disease progression, skeletal-related events, bone pain, osteonecrosis of the jaw (ONJ) and renal toxicity were the outcomes of interest. A total of 993 studies were retrieved and 43 were used for qualitative synthesis. Clodronate (CLOD) and zoledronic acid (ZOL) were effective in reducing skeletal complications compared to placebo. Results are mixed regarding the efficacy of pamidronate in reducing skeletal related events. ONJ rates were higher for ZOL, but under 5%, with CLOD having the safest profile. DENOS demonstrated non-inferiority to ZOL, in improving overall survival [pooled Hazard Ratio(HR) 1.02(95% CI 0.72,1.44)], progression free survival [pooled HR 0.92(95% CI 0.76,1.11)] and in reducing skeletal related events [pooled HR 1.03(95% CI 0.92,1.16)], with similar rates of ONJ and better safety profile regarding renal toxicity. Denosumab has comparable efficacy and safety with ZOL and may even replace BPs in the future, in the management of myeloma bone disease.

Keywords: Bisphosphonate, Denosumab, Multiple Myeloma, Skeletal Events, Efficacy

Introduction

Multiple myeloma (MM) is a malignant disease of the haemopoietic system, characterized by plasma cell proliferation contained mainly in the bone marrow, but can also be present in the peripheral circulation, as solitary plasmacytoma. It is a heterogenous condition, that can vary from monoclonal gammopathy of unknown significance to plasma cell leukemia[1,2]. It mainly affects people who are between their sixth and seventh decade of life, although 37% of cases involve younger people. It is rarely encountered in groups younger than 30 years old[1–3]. Skeletal involvement is disease-defining and correlates with disease progression, tumor burden and prognosis[4]. It is estimated that 85% of asymptomatic patients with MM have osteopenia to some extent[3]. MM bone lesions are purely lytic and rarely heal, even in patients in complete remission. They affect predominantly

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areas of bone marrow (vertebral bodies, ribs, skull), but can also occur in any other bone causing significant pain and manifesting from radiographic lytic areas to pathologic fractures or spinal cord compression[5].

MM-induced bone disease interferes with normal bone remodeling, causing excessive differentiation and activation of osteoclasts (OCL), thus turning the balance towards bone resorption[6]. Interaction between MM cells and bone mesenchymal cells (BMSc) leads to expression of receptor activator of nuclear factor Kappa-b ligand (RANKL) from osteoblasts, which stimulates OCL differentiation and activation[7]. Myeloma cells produce cytokines that stimulate stromal and T cells, to form osteoclastogenic activating factors, such as RANKL, MIP-1a, Interleukin-3 (IL-3), IL-6 and tumor necrosis factor-a (TNF-a), which also inhibit the production of osteoprotegerin (OPG), a decoy protein that binds RANKL and deactivates it. The activated OCL further enhance myeloma cell activity, by producing IL-6, osteopontin, annexin II etc.[5,8,9]. The RANKL/OPG ratio demonstrates the metabolic activity in the marrow microenvironment and in myeloma patients it is skewed towards bone resorption, favoring RANKL[9]. It is noteworthy that patients with high RANKL/OPG ratio have inferior survival[10].

Bisphosphonates (BPs) are a diverse group of molecules that inhibit osteoclast activity by binding to hydroxyapatite crystals. After their absorption to bone surface and internalization by OCL, they interfere with their function and cause apoptosis[11,12]. Bisphosphonates are classified according to whether they are nitrogen containing or not, which correlates with their potency. First generation non-nitrogen BPs are etidronate (ETI) and clodronate (CLOD), second generation nitrogen-containing are pamidronate (PAM) and ibandronate (IBA) and third generation nitrogen-containing are zoledronic acid (ZOL). Nitrogen-containing BPs are 10-10,000 times more potent than non-nitrogen, regarding anti-resorption ability[12–14]. They can be administered either intravenously (IV) or orally (PO), but they are poorly absorbed from the gastrointestinal tract and therefore require very careful administration to maximize absorption[15,16]. Based on *in vitro* data ETI is regarded the least potent and ZOL the most potent BP[14,17]. Side effects that have been recorded from their use, include esophageal irritation/ulceration[18], renal function impairment, hypocalcemia and the more rare but severe osteonecrosis of the jaw (ONJ)[19–21]. For their anti-resorptive action they have become important adjuvant agents to the treatment of malignancies that cause bone destruction such as MM, among others.

Denosumab (DENOS) is a human monoclonal antibody that specifically binds with RANKL, thus preventing the last from linking with RANK receptor in OCLs. It mimics the properties of OPG and inhibits OCL activation, contributing to the prevention of bone resorption[22]. It is widely used in fracture prevention in postmenopausal women with high fracture risk and in 2018 its indications were expanded in patients with multiple myeloma, as it proved to be bioequivalent to zoledronic acid in delaying first on study skeletal related event[23].

The aim of the present systematic review is to highlight the use of BPs and DENOS in the treatment of MM, as demonstrated by interventional studies from 1980 up to date, report the benefits and potential harms that arise from their use and demonstrate ongoing research. Furthermore, a meta-analysis of studies comparing denosumab with bisphosphonates is performed, to demonstrate whether the novel denosumab is superior to bisphosphonates in the treatment of multiple myeloma.

Methods

The methods and the results of this review have been carried out in accordance with the principles of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[24]. The study protocol has been published in The International Prospective Register of Systematic Reviews (PROSPERO) under the unique ID CRD42021287267[25]. Amendments to the original protocol include a meta-analysis of the studies that compare DENOS to ZOL.

Search strategy

A systematic search of the literature was conducted in the databases of National Library of Medicine-Pubmed, Scopus, Web of Science and Clinicaltrials.gov for relevant studies. The references from relevant reviews on the subject were also screened. We used keywords through evaluation of Medical Subject Headings (MeSH) which were: bisphosphonates, diphosphonates, zoledronic, pamidronate, alendronate, risedronate, etidronate, denosumab, multiple myeloma, plasma cell myeloma and limited our search criteria to include clinical trials and randomized controlled trials (RCTs) in humans were that was applicable. The search was concluded in September 2021. Detailed search strategy per database is included in the Appendix.

Selection criteria

Inclusion criteria consisted of interventional studies (clinical trials, RCTs) that compared bisphosphonates versus placebo (PLC)/no treatment (NT)/other bisphosphonates/denosumab, in multiple myeloma patients, who were receiving standard chemotherapy treatment or not, according to their disease stage. Eligible studies should include at least one outcome of interest. The outcomes evaluated were overall survival (OS), disease progression (DP) or progression free survival (PFS), skeletal related events (SREs), bone pain, ONJ and renal toxicity (RT). Studies that included patients with MM and other metastatic tumors in the population were also included and when subgroup data were available, only the MM patient subgroup was considered. Regarding large RCTs with multiple publications, all studies reporting different outcomes that came from the same sample were included.

Exclusion criteria consisted of observational studies, case reports, case series, Phase I/II pharmacokinetic and dose-determination studies, *in vitro* studies, animal studies,

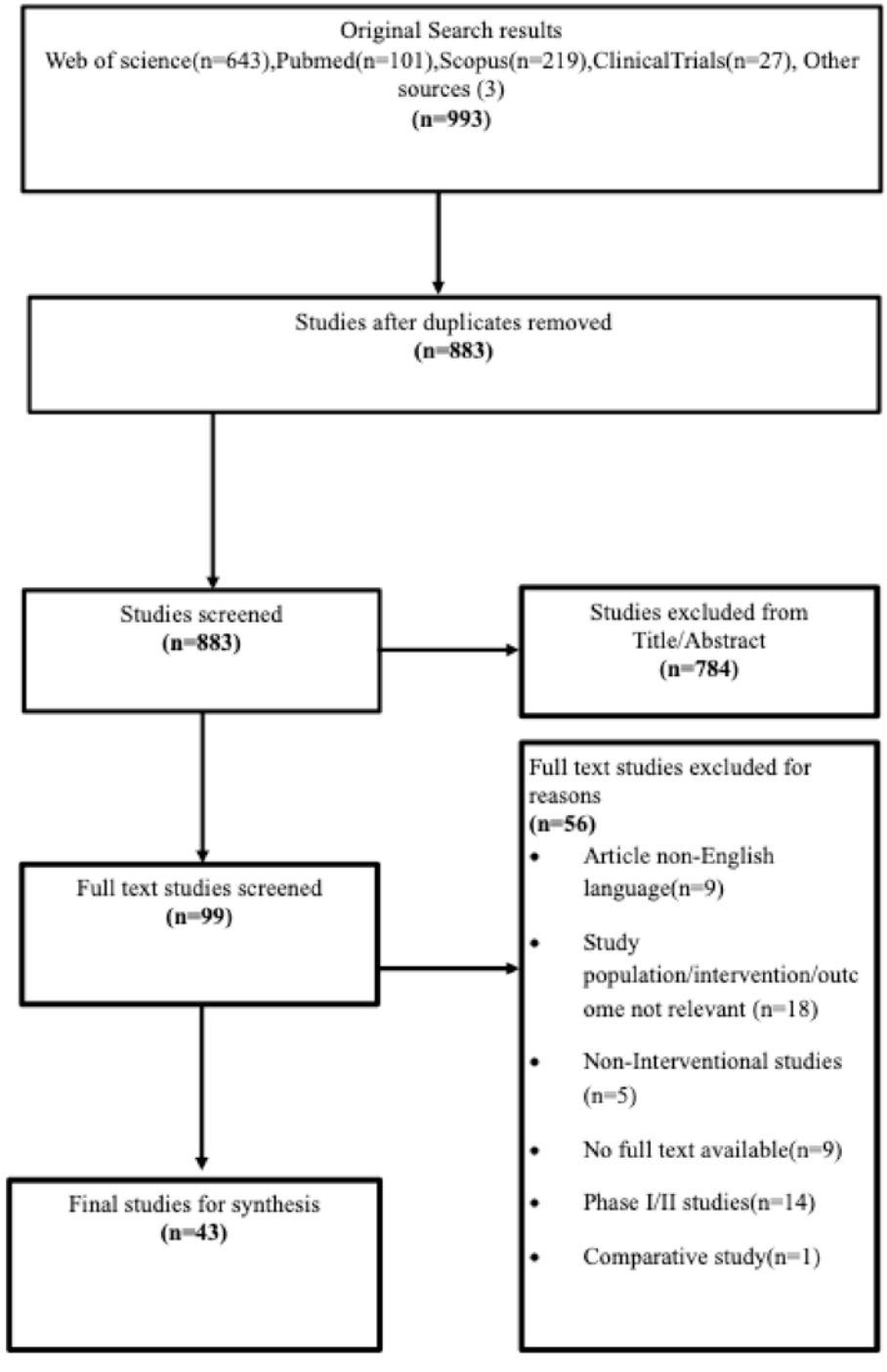

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram.

studies with no full text available or studies where the full text could not be retrieved even after communication with the authors, articles with no full text published in English, studies that were not conducted in the population of interest but in humans with other types of tumors with metastatic bone disease and studies that did not include even one of the outcomes of interest.

Types of participants and interventions

Participants who were diagnosed with MM, as this was defined by researchers in each study. Participants from asymptomatic to advanced MM were included. The intervention group consisted of patients treated with bisphosphonates or denosumab and the control group of patients that received placebo, no treatment or other bisphosphonate type.

Types of Outcomes

Primary outcomes

Disease progression - As it was defined by the authors of each study. There were no uniform criteria in all included studies. Some assessed DP using the International Response criteria[26] and others by clinical, radiographic and/or biochemical evaluation. In some studies DP was reported as progression free survival, as time to disease progression (TTDP) or as time to first skeletal related event (TTSRE).

Overall survival -In terms of mortality

Skeletal related events - As they were defined by the authors of each study. This could include participants experiencing new osteolytic lesions, pathological vertebral or non-vertebral fractures, loss of vertebral height, spinal cord compression or hypercalcemia.

Secondary outcomes

Reduction in bone pain – Multiple scales were used in the assessment of bone pain in the studies included, as reported by the authors. Some authors used the Brief Pain Inventory[27], the 100 mm Visual Analogue Scale[28], questionnaires regarding pain intensity, analgesic use, days of absence from work or hospitalization days, or scales intended to provide scoring on pain frequency, intensity and type of analgesic required.

Number of participants with osteonecrosis of the jaw

Renal toxicity, Grade III/IV (National Cancer Institute common toxicity criteria) events[29].

Study selection

Two reviewers (VC and GK) independently conducted the literature search, according to the pre-specified criteria. Duplicate results were removed manually at the initial stage and the rest of the results were screened for eligibility by Title & Abstract. In the final stage, the full text of the remaining studies was assessed for inclusion. When it was not possible to find full text of a study, the authors were contacted. Studies approved by at least one of the reviewers was considered eligible. Whenever there was dispute a third author, DK, resolved the issue.

Data Extraction

Data extraction was performed by VC and GK and then approved by DK. For all studies we extracted the following data: the name of the first author, year of publication, type/name of study, the population characteristics (disease stage, age), number of participants, intervention drug, comparator drug, dosage, route and frequency of administration of drugs, treatment duration and follow-up duration.

Data analysis

Data were imported in Excel spreadsheet, Microsoft Office 365. Results were reported as hazard ratio (HR), odds ratio (OR), risk ratio (RR) or descriptively with percentages or number of events and the attributed p-value, were that was available. A meta-analysis of studies comparing DENOS versus (vs.) ZOL was conducted, using Review Manager 5.4 software[30]. Level of significance was set at $p<0.05$.

Risk of bias assessment

To assess the risk of bias (methodological quality) of each study included in the review, we used the revised Cochrane risk-of-bias tool for randomized trials (RoB2)[31]. A fixed set of domains of bias (bias arising from randomization process, bias from deviations to the intended interventions, bias from missing data, bias from measurement of the outcome, bias from selection of the reported result) focusing on different aspects of trial design, conduct, and reporting were assessed. Two independent reviewers (VC and GK) evaluated the included articles, and any discrepancies were resolved through discussion.

Results

Search results

Our original search yielded 993 results. Ninety-nine full text studies were screened after duplicates and studies from Title & Abstract were removed. The final number of studies that were eligible for qualitative synthesis after full text assessment were 43. Detailed diagram of the process with reasons for exclusion is illustrated in Figure 1 and the list of excluded studies after full text was sought is included in the Appendix.

Study Characteristics

The total number of included studies were thirty-seven[10,32–64,65], as six[66–71] were multiple publications of large RCTs with subgroup analysis. There were nine studies comparing ZOL with PLC, NT or only chemotherapy(CHEMO)[51,52,56,58,60,62,63,72,73], nine comparing PAM versus(vs) PLC/NT/CHEMO[38,39,41,42,45,46,48,50,54], seven CLOD vs PLC/NT/CHEMO[32,34–37,40,43], one IBA[44] and one ETI vs PLC. Regarding head to head comparisons between bisphosphonates, or denosumab with bisphosphonate, there was one large study, the Medical Research Council Myeloma IX study with its extension phase and another publication regarding adverse events of interest, comparing ZOL with CLOD[53,57,59], one study with the extension phase by Rosen et al. comparing PAM vs ZOL[47] and another comparing different doses of ZOL with PAM[65], one for PAM vs IBA[74] and two large studies regarding DENOS vs ZOL[55,64] and an included third publication[61] for the myeloma subset of patients from the study of Henry et al. 2011. Details of the characteristics of the main studies are presented in Table 1 and studies

Table 1. Study Characteristics.

Author	Year	Study ID	Intervention/ Comparator	Population			No Participants	Route, dose, frequency	Treatment Duration MD (range)	Follow up MD (range)
				Condition	Stage	Age MD(IQR)				
Raje [64]	2018	NCT01345019	DENOS	MM newly diagnosed	ECOG </= 2, 1 dose or no prior BP treatment	59 (54-64)	859	SC, 120mg, Q4W	15.8m	17.3m
			ZOL				859	IV, 4mg, Q4W	14.8m	17.6m
Aviles [62]	2017		ZOL	MM symptomatic	Untreated, ECOG 0-2, DS III, ISS III	57.8 (33-70)	84	IV, 4 mg, Q4W	48m	3.3y (1.9-5.1)
			ZOL				86		24m	
Himelstein	2017	NCT00869206	ZOL	MM, BC or PC	ECOG 0-2, at least 1 osteolytic lesion with or without prior oral BP use	65 (26-94)	139 MM	IV, 4mg , Q12W	24m	1.2y
			ZOL				139MM	IV, 4mg , Q4W		
Raje [61]	2016	NCT00330759 244 STUDY	DENOS	MM SUBSET	ECOG 0-2, at least 1 lytic lesion, biosy confirmed MM	63	87	SC,120mg,Q4W	16.6m	17m
			ZOL				93	IV,4mg,Q4W	16.9m	18.4m
Garcia-Sanz [60]	2015	NCT01087008-AZABACHE	ZOL	MM asymptomatic	Biochemical relapse (IMWG 2006), with or without oseolytic lesions	68(40-87)	51	IV, 4mg, Q4W	12m	3y
			NT				49			
Raje [72]	2015	NCT00622505 Z-MARK STUDY	ZOL	MM	ECOG 0-2, CrCl >/=30ml/ min, previous IV BP treatment, 50% stage I ISS	63.8	117	IV, 4mg , Q12W	24m	2y
			ZOL				4	IV, 4mg , Q4W		
Jackson [59]	2014	ISRCTN68454111 MRC MYELOMA IX	ZOL	MM newly diagnosed	Untreated MM except for BP, ISS I-III	59(intensive path-way) 73(non-intensive pathway)	981	IV, 4mg, Q4W	12m	5.9y
			CLOD				979	PO, 1600mg, daily		
Aviles [58]	2013	NCT01234129	ZOL	MM symptomatic	Untreated,ECOG 0-2, DS IIB-III	56.4	151	IV, 4mg, Q4W	24m	5.8y (3-8)
			NONE			57.8	157			
Morgan [57]	2013	ISRCTN68454111 MRC MYELOMA IX Extended follow up	ZOL	MM newly diagnosed	Untreated MM except for BP, ISS I-III	59 (intensive)/ 73 (non-intensive	981	IV, 4mg, Q4W	12m	5.9y
			CLOD			59 (intense)/ 73 (non-intense	979	PO, 1600mg, daily		
Witzig [56]	2013	NCT00432458	Thal/ZOL	MM asymptomatic	Untreated MM stage I DS, EOG 0-2, No prio BP, No symtomatic lytic lesions	63	35	IV,4mg,Q4W (modified later Q12W and yearly after 1st year)	During study period	5.9y (1.5-8)
			ZOL				33			
Vadhan-Raj [76]	2012	NCT00330759 244 STUDY	DENOS	MM or Solid tumors with bone metastasis exept BC/PC	ECOG 0-2, >/= 1 osteolytic lesion with No prior BP	60	886-180 remained	SC, 120mg, Q4W	675.3p-y	2y
			ZOL				890-178 remained	IV, 4mg, Q4W	651.9p-y	
D'Arena [54]	2011		PAM	MM asymptomatic	ISS Stage I	64.4	89	IV, 60-90mg, monthly	12m	5y
			NT			64.1	88			
Henry [55]	2011	NCT00330759 244 STUDY	DENOS	MM or metastatic solid tumors with bone involvement exept BC/PC	ECOG 0-2, >/= 1 osteolytic lesion with No prior BP	60(18-89)	886(180 at primary analysis at 34m)	SC, 120mg, Q4W	7m	2y
			ZOL			61(22-87)	890(178 at primary analysis at 34m)	IV, 4mg, Q4W	651.9p-y	
Morgan [53]	2010	ISRCTN68454111 MRC MYELOMA IX	ZOL(intensive/ non-intensive pathway	MM newly diagnosed	Untreated MM except for BP, ISS I-III	59(53-63)/ 73(70-77)	981	IV, 4mg, Q4W	12m	3.7y (2.6-4.7)
			CLOD(intensive/ non-intensive pathway)			59(53-63)/ 73(70-77)	979	PO, 1600mg, daily		

Table 1. *(Cont. from previous page).*

Author	Year	Study ID	Intervention/ Comparator	Population			No Participants	Route, dose, frequency	Treatment Duration MD (range)	Follow up MD (range)
				Condition	Stage	Age MD(IQR)				
Musto [52]	2008		ZOL	MM asymptomatic	WHO performance 0-1, no bone lesions (IMWG criteria)	66(41-82)	81	IV, 4mg, Q4W	12m	64.7p-m
			NT			67(42-84)	82			
Aviles [51]	2007		ZOL+CHEMO	MM	ECOG <3, DS Stage III, at least 1 lytic lesion, untreated	67.3 (43-75)	46	IV, 4mg, Q4W	24m	4y (2.8-6)
			CHEMO			65.4 (39-75)	48			
Attal [50]	2006	Inter-Groupe Franco-phone du Myélome	PAM	MM	Without or with one adverse prognostic factor- DS I-III	59(+/-8)	196	IV, 90mg, Q4W (PAM) PO, 400mg, daily (THAL)		2.4y (1.5-4.4)
			PAM+THAL				201			
			NO MAINTENANCE				200			
Kraj [48]	2004		PAM+CHEMO	MM advanced	DS II/III, ECOG 1-4	60	23	IV, 60mg, Q4W	66m	6y-8y
			CHEMO			66	23			
Vogel [49]	2004		ZOL	MM/BC/PC with bone metastasis	DS III, BC or PC with bone metastasis, with or without prior BP treatment, ECOG 0-2	66.4 (+/-11)	638(129MM)	IV, 4mg, Q4W	6m	6m
Musto [46]	2003		PAM	MM untreated	DS IA &IIA	67(47-79)	45	IV, 60mg, Q4W	12m	4.2y (3-6)
			NT			68(45-80)	45			
Rosen [47]	2003	Extension phase after core study Rosen 200194(13m)	ZOL 4mg	MM/BC bone metastasis	DS III for MM or IV for BC with at least 1 bone metast , ECOG 0-2, no prior BP treatment the last 12m	57.5	212	IV,4mg,Q4W	24m	25m
			ZOL 8mg				189	IV,4/ 8mg,Q4W		
			PAM				205	IV, 90mg, Q4W		
Terpos [74]	2003		PAM	MM newly diagnosed	DS II or III, no prior BP treatment the past 2m	66(55-78)	23	IV, 90mg, Q4W	4m	10m
			IBA			65.5 (60-77)	21	IV, 4mg, Q4W		
Martin [45]	2002		PAM	MM	Smouldrenig or indolent MM	57(49-75)	12	IV, 90mg, Q4W	12m	25m
			NT							
Menssen [44]	2002		IBA	MM	DS II-III, at least one osteolytic lesion,no prior BP treatment the past 3m	62.9/63.4	99	IV, 2mg, Q4W	12-24m	4y
			PLC				99			
McCloskey [43]	2001	MRC VI MYELOMA STUDY	CLOD	MM		<75	264	PO, 1600mg, daily		8.6y
			PLC				271			
Berenson [65]	2000		ZOL 0.4mg	MM & metastatic to the bone BC	ECOG 0-2, no prior BP treatment, at least 1 SRE prior to study entry	57.6(12.9)	68 (36% dropout)	IV, 0.4mg, Q4W	10m	10m
			ZOL 2mg			56.5(13.6)	72 (36% dropout)	IV, 2mg, Q4W		
			ZOL 4mg			59.9(11.3)	67 (32% dropout)	IV, 4mg, Q4W		
			PAM			57.7(11.8)	73 (24% dropout)	IV, 90mg, Q4W		
Terpos [42]	2000		PAM+CHEMO	MM newly diagnosed	No prior BP treatment the past 3 months, DS I-IIIB	68(55-78)	32	IV, 90mg, Q4W	14m	14m
			CHEMO			66(46-78)	30			

Table 1. *(Cont. from previous page).*

Author	Year	Study ID	Intervention/ Comparator	Population			No Participants	Route, dose, frequency	Treatment Duration MD (range)	Follow up MD (range)
				Condition	Stage	Age MD(IQR)				
Berenson [41]	1998	MYELOMA AREDIA STUDY GROUP Extended	PAM	MM advanced	DS III and at least one osteolytic lesion, no prior BP treatment the past 2w before study	64.1 (+/-9.1)/	198 original 9 cycles 150 extended 21cycles (41% completed)	IV, 90mg, Q4W	21m	28.2 m
			PLC			62.7 (+/-10.1)	179 original 9 cycles 132 extended 21cycles (41% completed)			28.7m
Brincker [39]	1998	SWEDISH-DANISH PAMIDRONATE STUDY GROUP	PAM	MM newly diagnosed requiring therapy	Perf status 0-4, no prior chemo, most had vertebral collapse at entry	69	152	PO, 150mg	18.3m	4.5y
			PLC				148		18.3m	
McCloskey [40]	1998	MRC VI MYELOMA STUDY	CLOD	MM newly diagnosed	No prior cytotoxic treatment, with or without osteolytic lesions	62(55-67)	264	PO, 1600mg, daily		2.8y (1.3-7.5)
			PLC			63(57-68)	272			
Berenson [38]	1996	MYELOMA AREDIA STUDY GROUP	PAM	MM advanced	Stage III and at least one osteolytic lesion without priop BP treatment for the past 60d before study entry, ECOG 0-4	64(+/-10)	196	IV, 60mg, Q4W	9-12m	9m and 17m for OS
			PLC			63(+/-10)	181			
Heim [37]	1995		CLOD+CHEMO	MM	DS I-III, ECOG 0-2,with bone involvement, no prior BP treatment	62.2(28.6-85.4)	77	PO, 1600mg, daily	12m	1y
			CHEMO			66.7(30.5-87.8)	80			
Riccardi [36]	1994	MM87 PROTOCOL	CLOD	MM	DS I-III	67(43-86)	193	IM, 100-600mg, Q4-6W	THROUGH SURVIVAL	3.5y
			PLC			64(33-87)	148			5.3y
Clemens [35]	1993	INTERIM ANALYSIS OF TUBIGEN	CLOD+CHEMO	MM	ECOG 0-2, no prior BP treatment 1m before study entry, DS II-III, with or without osteolytic lesions	28-76	14	PO, 1600mg, daily	AT LEAST 12m	19.6m
			CHEMO				12			16.5m
Lahtinen [34]	1992	FULL TRIAL FINNISH STUDY GROUP	CLOD	MM newly diagnosed	Untreated, DS I-III, no prior BP treatment, with or without osteolytic lesions	63(+/-1)	168	PO, 2400mg, daily	24m	24m
			PLC			67(+/-1) [p=0.004]	168			
Belch [33]	1991		ETI	MM	No prior cytotoxic treatment, with or without osteolytic lesions		92	PO, 5mg/kg/daily	UNTIL AEs OR DEATH	3.7y
			PLC				74			
Delmas [32]	1982		CLOD	MM	All stages but most in remission		7	PO, 1600mg/daily	6-18m	6-18m
				PLC				6		

MM: Multiple Myeloma; BP: Bisphosphonate; DENOS: denosumab; ZOL: zoledronic acid; CLOD: clodronate; ETI: etidronate; IBA: ibandronate; PAM: pamidronate; PLC: placebo; NT: No Treatment; CHEMO: chemotherapy; m: months; y: years; d: days; w: weeks; AEs: Adverse Events; SC: subcutaneous; IV: intravenous; THAL: thalidomide; SRE: Skeletal Related Events; DP: Disease Progression; OS: Overall Survival; PFS: Progression Free Survival; EFS: Event Free Survival; ONJ: Osteonecrosis of the Jaw; RT: Renal Toxicity; TNT: Time to next Therapy; TTSRE: Time to Skeletal Related Event; TTP: Time to Progression; TTFSRE: Time to First Skeletal Related Event; PO: Per Os; IV: Intravenous; Q4W:Every 4 weeks; Q12W:Every 12 weeks; p-m: person-months; p-y: person-years; DS: Durie-Salmon Staging System; ISS: International Staging System; ECOG: Eastern Cooperative Oncology Group Performance Status; MRC: Medical Research Council; BC: Breast Cancer; PC: Prostate Cancer; WHO: World Health Organization; IMWG: International Myeloma Working Group; MD: Median; IQR: Interquartile Range; p: p-value 5% level of significance

Table 2. Characteristics of Subgroups Studies.

Author	Year	Study ID	Population			No Participants (I/C)	Intervention	Comparator	Route, dose, frequency I/C	I/C Duration MD (range)	I/C Follow up MD (range)
			Condition	Stage	Age MD(IQR)						
Terpos [67]	2021	NCT01345019 Sub-group analysis from study Raje 2018	MM-newly diagnosed ASCT-intent/ASCT-no intent/CrCl>60ml/min/CrCl <60ml/min/ patients > or < 70 yo	ECOG </= 2, 1dose or no prior BP treatment	59(54-64)	1718	DENOS	ZOL	SC, 120mg, Q4W/ IV, 4mg, Q4W	15.8/14.8m	17,3/17,6m
Huang [66]	2020	NCT01345019 Sub-group analysis from study Raje 2018	MM-ASIAN SUBGROUP newly diagnosed	ECOG </= 2, 1dose or no prior BP treatment	61(54-69)	196	DENOS	ZOL	SC, 120mg, Q4W/ IV, 4mg, Q4W	15,9/17,4m	17,3/17,6m
Larocca [68]	2013	ISRCTN68454111-MRC MYELOMA IX Subgroup analysis (ASCT)	MM newly diagnosed	Untreated MM except for BP, ISS I-III	59	1111 (555/556)	ZOL+CHEMO (intensive pathway)	CLOD+CHEMO (intensive pathway)	IV, 4mg, Q21-28D/ PO, 1600mg, daily	12m	5.71y/5.54
Morgan [69]	2012	ISRCTN68454111-MRC MYELOMA IX	MM newly diagnosed-LONG-TERM BIPHOS USE in subgroups of intensive & non-intensive pathway	Untreated MM except for BP, ISS I-III		1970 (981/979)	ZOL+CHEMO (intensive/non-intensive pathway)	CLOD+CHEMO (intensive/non-intensive pathway)	IV, 4mg, Q21-28D/ PO, 1600mg, daily		5.9y
Morgan [70]	2011	ISRCTN68454111-MRC MYELOMA IX Subgroup analysis	MM newly diagnosed	Untreated MM except for BP, ISS I-III	59(intensive both arms)/ 73(non-intensive both arms)	1970 (981/979)	ZOL+CHEMO (intensive/non-intensive pathway)	CLOD+CHEMO (intensive/non-intensive pathway)	IV, 4mg, Q21-28D/ PO, 1600mg, daily	At least 48m	3.7y(2.6-4.7)
Laakso [71]	1994	FINNISH STUDY SUBGROUP ANALYSIS	MM newly diagnosed	Untreated, DS I-III	63(+/-1)/ 67(+/-1) [p=0.004]	336 (168/168)	CLOD	PLC	PO, 2400mg, daily	24m	24m

MM: Multiple Myeloma; BP: Bisphosphonate; DENOS: denosumab; ZOL: zoledronic acid; CLOD: clodronate; ETI: etidronate; IBA: ibandronate; PAM: pamidronate; PLC: placebo; CHEMO: chemotherapy; m: months; y: years; PO: Per Os; SC: subcutaneous; IV: intravenous; SRE :Skeletal Related Events; OS: Overall Survival; PFS: Progression Free Survival; ONJ: Osteonecrosis of the Jaw; RF: Renal Failure; Q21-28D:Every 21-28 Days; DS: Durie-Salmon Staging System; ISS: International Staging System; ECOG: Eastern Cooperative Oncology Group Performance Status; MRC: Medical Research Council; ASCT: Autologous Stem Cell Transplantation; CrCl: Creatinine Clearance; MD: Median; IQR: Interquartile Range; p: p-value 5% level of significance; I/C: Intervention/Comparator

regarding subgroups are presented in Table 2.

As far as population characteristics is concerned, 5 studies included participants with MM and other metastatic solid tumors with bone involvement, namely breast, prostate cancer, and others[47,49,55,63,65]. The rest of the studies had participants with MM only, in various stages. Eleven studies had MM participants in stages II or III, according to the International Staging System (ISS)[4] or Durie Salmon Staging System[75], five with patients with asymptomatic or smoldering myeloma and the rest recruited people in all the stages (Table 1).

Administration of ZOL was 4 mg intravenous (IV)/every 4 weeks in most studies. Two studies[63,72] compared ZOL administration every 4 vs 12 weeks. CLOD was given orally(PO) in most studies, with prevalent dose of 1600 mg/daily. Lastly, the prevalent dose of PAM was 90 mg IV/every 4 weeks (Table 1).

Risk of Bias Assessment

The results from the risk of bias assessment of the included studies are presented in Figure 2. Twenty-nine studies were assessed. There were some concerns arising from the randomization process because detailed information

Figure 2. Traffic Light Presentation of Risk of Bias Assessment of included studies.

about how the randomization was done, was not provided in some studies and some concerns regarding the blinding of personnel. Four studies[53,54,60,63] were open label and in most cases the efficacy and safety analysis included most of the randomized population. Lastly, in most of the studies there was no problem with protocol deviations or selection bias.

Outcome measures

Primary outcomes: Disease progression, overall survival and skeletal related events

CLOD vs PLC/ZOL

Studies regarding the use of CLOD date from 1980 to 2013, with the most recent being a large multicenter RCT, the

Table 3. Overall survival rates of included studies.

Study	Total I	Total C	Rates	p-value	HR/OR(95% CI)
ZOL vs PLC/NO TR/CHEMO ONLY					
Aviles 2017	84	84	68% vs 68%	ns	
Garcia-Sanz 2015	51	49	Overall 73% vs 46%	0.161	HR0.81 (0.39,1.69)
Aviles 2013	151	157	67% vs 48%	<0.001	HR0.57(0.41,0.80)
Aviles 2007	46	48	80% vs 46%	<0.01	HR0.42(0.22,0.81)
PAM vs PLC/NT/CHEMO					
D'Arena 2011	89	88		ns	HR0.98(0.66,1.46)
Attal 2006	196	200		0.7	
Kraj 2004	23	23	21m vs 20m	0.78	HR1.12(0.51,2.46)
Berenson 1998 (21 cycles)	196	181		0.377	HR0.75(0.54,1.04)
Brincker 1998 (9 cycles)	152	148	1183d vs 1063d	0.91	HR0.90(0.14,5.73)
Berenson 1996	196	181	28m vs 23m	0.082	
CLOD vs PLC/CHEMO only					
McCloskey 1997	264	272		0.05 0.37	OR 0.64(pts without vert# at entry) OR1.15 (pts with vert# at entry)
McCloskey 2001	264	271	59m vs 37m (pts without vert # at entry)	0.004	HR0.62(0.43,0.87)
Riccardi 1994	193	148	35.1m vs 31.8m	<0.02	
ETI vs PLC					
Belch 1991	92	74	22% vs 28%	0.08	
IBA vs PLC					
Menssen 2002	99	99	33.1m vs 28.2m	ns	
DENOS vs ZOL					
Raje 2018	850	852			HR0.90(0.70,1.16)
Raje 2016	87(MM only)	93(MM only)			HR1.31 (0.80,2.15)
Henry 2011	886	890			HR2.26(1.13,4.50)
ZOL vs CLOD					
Morgan 2010	981	979	19·5m vs 17·5m	0.07	HR0.84 (0.74,0.96)
Morgan 2013	981	979	52m vs 46m	0.01	HR0.86(0.77, 0.97)

I: Intervention; C: Comparator; CI: Confidence Interval; HR: Hazard ratio; OR: Odds ratio; ZOL: zoledronic acid; CLOD: clodronate; ETI: etidronate; IBA: ibandronic acid; PAM: pamidronate; DENOS: denosumab; PLC: placebo; NT: no treatment; CHEMO: chemotherapy; vs: versus; ns: not significant; m: months; d: days; vert #:vertebral fracture; pts: patients; IQR: interquartile range; MM: multiple myeloma.

Medical Research Council Myeloma IX study, with 1960 total number of participants[53] with follow up ranging from 3.7 years in the original study, to 5.9 years in the extension phase[57]. In this study CLOD was compared to ZOL and patients were further stratified to intensive and non-intensive pathway, according to intensity of induction to chemotherapy, and received two different chemotherapy combinations in each pathway. ZOL was superior to CLOD in increasing overall PFS by 2 months, (HR 0.88;95% CI,0.80–0.98), but when the same outcome was assessed separate for the intensive and non-intensive pathway, it did not reach statistical significance (HR 0.90;95% CI, 0.78–1.05 and HR 0.87;95% CI, 0.74–1.01 respectively). Overall survival was 44.5 months for CLOD and 50 months for ZOL, which was significant (HR 0.84;95% CI, 0.74–0.96). 27% of patients in the ZOL group had a SRE before disease progression, compared to 35% (p=0.0004)[53]. Overall ZOL reduced SREs compared to CLOD, in patients receiving bisphosphonates for more than 2 years (p=0.0102), regardless of other treatment regiments[69]. In the extended follow up, results demonstrated a significant increase in PFS as well as OS (HR 0.89;95% CI, 0.80–0.98 and HR 0.86;95% CI,0.77– 0.97 respectively), increasing OS by 5.5 months. Subgroup analysis of transplant eligible patients in the Myeloma IX study demonstrated that ZOL

Table 4. Skeletal related events rates of included studies

Study	Total I	Total C	Rates	p-value	HR/OR/RR (95% CI)
ZOL vs PLC/NT/CHEMO					
Himelstein 2017	139(Q4W)	139(Q12W)	60% vs 55%	0.14	RD 0.05 (99.9 %CI-0.15, 0.25)
Raje 2015	117	4	5.8% at least one SRE 1st year		
Aviles 2017	84	84	21% vs 43%	0.001	
Garcia-Sanz 2015	51	49	16% vs 41%	0.005	
Aviles 2013	151	157	14% vs 24%	<0.001	
Musto 2008	81	81	55.5% vs 78.3%	0.041	OR 2.90(1.04,8.06)
Aviles 2007	46	48	21% vs 47%		
PAM vs PLC/NT/CHEMO					
D'Arena 2011	89	88	39.2% vs 72.7%	0.009	
Attal 2006	196/ 201(+thal)	200	21% /18% vs 24%	0.4	
Kraj 2004	23	23	52% vs 56%	0.42	
Musto 2003	45	45	40% vs 81.8%	<0.01	
Berenson 1998 (21 cycles)	196	181	38% vs 51%	0.015	
Brincker 1998 (9 cycles)	152	148	0.69(1.02) vs 0.97(1.44) events/y	0.27	
Berenson 1996	196	181	24% vs 41%	<0.001	
CLOD vs PLC/CHEMO ONLY					
McCloskey 1997	264	272	20 vs 36 (pts with non vert#) 80 vs 146 (pts with vert #)	0.025 0.012	
Heim 1995	39	32	59% vs 53% (in favour of PLC)		
Riccardi 1994	193	148	34.8% vs 50.5%	<0.02	
Clemens 1993	14	12	7/6 vs 18/6 (lesions/pt) 12/5 vs 23/5 (#/pt)		
Lahtinen 1992	168	168	12% vs 24% (osteolytic) 30% vs 40% (vert #) 24% vs 23% (non vert#)	0.024	ns ns
Delmas 1982	7	6	0.06 vs 0,44 Vertebral crushes/ pt/6m (favours CLOD)		
ETI vs PLC					
Belch 1991	92	74	22% vs 28%	ns	
IBA vs PLC					
Menssen 2002	99 (50 drop out)	99(57 drop out)	2.13 vs 2.05 per ptn/y	ns	
DENOS vs ZOL					
Raje 2018	859	859	44% vs 45%	0.84	HR1.01(0.89,1.15)
Raje 2016	87(MM only)	93(MM only)		0.3	HR1.21(0.86,1.71)
ZOL vs CLOD					
Morgan 2011	981	979	27% vs 35%	0.0004	HR0.74(0.62,0.87)
ZOL vs PAM					
Rosen 2003	187(MM only)	169(MM only)	50% vs 55%	0.593	RR 0.93(0.7,1.2)
Berenson 2000	68/72/67	73	46%/35%/33% vs 30%	0.05 (0.4ZOL vs PAM)	

I: Intervention; C: Comparator; CI: Confidence Interval; HR: Hazard ratio; OR: Odds ratio; RR: Relative risk; RD: Risk difference; ZOL: zoledronic acid; CLOD: clodronate; ETI: etidronate; IBA: ibandronic acid; PAM: pamidronate; DENOS: denosumab; PLC: placebo; NT: no treatment; CHEMO: chemotherapy; vs: versus; ns: not significant; m: months; d: days; y: years; vert #: vertebral fracture; pt: patient; IQR: interquartile range; Q4W: every 4 weeks; Q12W: every 12 weeks; MM: multiple myeloma; SRE: skeletal related event; thal: thalidomide.

was not superior to CLOD in OS for patients with complete response (CR) to therapy, but significantly improved OS in patients with partial response (PR) (HR 0.53 [95% CI, 0.32-0.86]). ZOL was marginally better than CLOD in reducing SREs only in patients with very good partial response (VGPR) (HR 0.74;95% CI, 0.52-1.05) and not in those with CR[68].

Table 5. Disease progression & Progression free survival of included studies.

Study	Total I	Total C	Rates (DP)	Rates (PFS)	p-value	HR/OR (95% CI)
ZOL vs PLC/NO TR/CHEMO ONLY						
Aviles 2017	84	84		75% vs 72%	ns	
Garcia-Sanz 2015	51	49	67% vs 87%		0.05	
Aviles 2013	151	157		66% vs 52%	<0.001	
Witzig 2013	35	33		86% vs 55%	0.0048	HR1.98 (1.1–3.6)
Musto 2008	81	81				OR1.03(0.55- 1.92)
Aviles 2007	46	48	20% vs 48%		<0.01	
PAM vs CONTROL						
D'Arena 2011	89	88		62.9% vs 62.5%	ns	
Musto 2003	45	45	25% vs 26.8%		ns	
Attal 2006	196	200		39% vs 38%	ns	
Martin 2002	12	-	4 of 12			
CLOD vs PLC/CHEMO only						
Riccardi 1994	193	148	47.1% vs 52.2%		ns	
ETI vs PLC						
Belch 1991	92	74			ns	
PAM vs IBA						
Terpos 2003	23	21	86.9% vs 90.4%			
DENOS vs ZOL						
Raje 2018	859	859				HR0.82(0.68,0.99)
Henry 2011	886	890				HR1.00 (0.89 ,1.12)
ZOL vs CLOD						
Morgan 2010	981	979			ns	HR0.91(0.82,1.01)
Morgan 2013	981	979			0.02	HR0.89(0.80,0.98)

I: Intervention; C: Comparator; CI: Confidence Interval; HR: Hazard ratio; OR: Odds ratio; ZOL: zoledronic acid; CLOD: clodronate; ETI: etidronate; IBA: ibandronic acid; PAM: pamidronate; DENOS: denosumab; PLC: placebo; NT: no treatment; CHEMO: chemotherapy; vs: versus; ns: not significant; DP: disease progression; PFS: progression free survival.

Table 6. Pooled effects of DENOS vs ZOL.

Interventions	Outcomes	Effect sizes	Tests of Association				Tests of Heterogeneity		
			Pooled HR(CI)	P-value	Model	Z-test	X2	P-value	I^2(%)
DENOS vs ZOL	Overall Survival	2	1.02(0.72, 1.44)	0.91	RE	0.11	1.77	0.18	43
	SREs	2	1.03(0.92, 1.16)	0.60	RE	0.53	0.95	0.33	0
	PFS	2	0.92(0.76, 1.11)	0.39	RE	0.87	3.11	0.08	68

HR: Hazard Ratio; CI: confidence interval; RE: random effect; vs: versus; DENOS: denosumab; ZOL: zoledronic acid; SREs: Skeletal Related Events; PFS: Progression Free Survival. p-value< 0.05 is considered significant. I^2 >75% is considered significant heterogeneity

There were two more large RCTs, one from the Finnish Leukemia Group[34] and the VIth MRC Multiple Myeloma Trial[40], recruiting a total number of 871 participants, comparing CLOD with placebo (PLC). In those studies, there was no significant difference in OS, with a follow up, up to 8 years. CLOD was effective in preventing bone progression and reduced osteolytic lesions significantly (p=0.026), but no difference was noted between groups regarding vertebral and non-vertebral fractures. There was low dropout rate after randomization in both studies, but in the study from the Finnish Leukemia Study Group, there was significant difference in age between the CLOD and PLC groups, with the population in the PLC being older. Riccardi et al.[36] and Heim et al.[37] also demonstrated significant improvement in bone progression with CLOD, as well as survival. Finally, the study of Delmas et al. [58] reported less osteolytic lesions compared to PLC at 6 and 12 months but had very few participants. Details are presented in Tables 3, 4, 5.

Table 7. Bone pain, Osteonecrosis of the jaw & Renal toxicity rates of included studies.

Study ID	Intervention/ Comparator	Bone Pain	p-value	Scale	ONJ	p-value	Renal Toxicity
Huang 2020	DENOS	18.6%			6.9%		
	ZOL	22.8%			5.4%		
Raje 2018	DENOS	3%(G3) <1%(G4)			4%	0.147	10% (3% doubled from baseline)
	ZOL	3%(G3) <1%(G4)			3%		17% (7% doubled from baseline)
Himelstein 2017	ZOL Q4W	p=0.96 mean worst pain p=0.38 mean least pain	NS between groups	BPI	2%	0.08	1.2% p=0.1
	ZOL Q12W				1%		0.5%
Aviles 2017	ZOL				0%		0
	ZOL(control)				0%		0
Raje 2015	ZOL Q4W				3.3%		3.3%
	ZOL Q12W						
Raje 2016	DENOS				5%	0.43	
	ZOL				2%		
Garcia-Sanz 2015	ZOL	3pts G I-II bone pain			1pt		0
	None	4 pts G I-II bone pain			0		1pt
Jackson 2014	ZOL				3.7%	<0.0001	5.2%
	CLOD				0.5%		5.8%
Aviles 2013	ZOL				0%		0 pts
	None				0%		
Vadhan-Raj 2012	DENOS	MD time to 2-point increase 5.6m	0.02	BPI			
	ZOL	MD time to 2-point increase 4.7m					
Henry 2011	DENOS				1.1%	1	8.3% (11.3% in patients with CrCl<60ml/min)
	ZOL				1.3%		10.9% (21.6% in patients with CrCl<60ml/min)
D'Arena 2011	PAM				0		10.7% p=NSD
	OBS				0		10.9%
Morgan 2010	ZOL intensive pathway				4-3%	<0.0001	5% p=NS between groups
	ZOL non-intensive						7%
	CLOD intensive pathway				<1%		6%
	CLOD non intensive						6%
Musto 2008	ZOL				1pt		0
	OBS				0		
Attal 2006	NO MAINTENANCE				0	NS	1% p=NS
	PAM				1pt		1%
	PAM+THAL				1pt		2%

Table 7. *(Cont. from previous page).*

Study ID	Intervention/ Comparator	Bone Pain	p-value	Scale	ONJ	p-value	Renal Toxicity
Kraj 2004	PAMID+CHEMO	Reduced first 9m	<0.05 between groups After 9th m NS between groups	Pain frequency and severity 5-point scale(none-intolerable) analgesic drug use 0-4 (none-opiates)			NM
	CHEMO						
Vogel 2004	ZOL	Mean reduction -7.7 +/-27	<0.05	100-mm VAS	0 cases		Increase SCr 7.8%- treat discontinued 17pts
Rosen 2003	ZOL 4mg						0.4% No SD vs PAM
	ZOL 8mg/4mg						2.7% P < 0.001 vs PAM
	PAM						1.9%
Menssen 2002	IBA	Reduction in pts with osteolytic lesions	0.047	Scale 0-4(none-intolerable), Analgesic type scale 0-6(none-opiates >100mg/daily)			No events
	PLC		NS between groups				
Berenson 2000	ZOL 0.4	6.2 mean pain reduction	<0.05 ZOL 4 vs ZOL 0.4	BPI			
	ZOL 2	9 mean pain reduction					
	ZOL 4	9.6 mean pain reduction					
	PAM	9.2 mean pain reduction					
Terpos 2000	PAM+CHEMO	Reduction	<0.01between groups	Questionnaire (analgesia used/days off work/ hospitalization)			
	CHEMO	No change					
Berenson 1996	PAM	Decrease for PAM no increase in analgesic use	<0.05 Between groups p<0.05	Severity & frequency of pain scale 0-3/type & frequency of analgesic use scale 0-3			
	PLC						
Berenson 1998	PAM	Smaller proportion in the PAM group		Severity & frequency of pain scale 0-3/type & frequency of analgesic use scale 0-3			Similar changes in SCr in both groups
	PLC						
McCloskey 1997	CLOD	10.9% had back pain at 24m	<0.05	Semiquantitative 5-point scale (none-incapacitating)			NM
	PLC	19.9% at 24m					
Brincker 1998	PAM	Mean events/year(SD) 0.58(0.97)	0.04	Self -assessment of pain 0-6 scale/analgesic count			No events
	PLC	Mean events/year(SD) 0.80(1.15)	Intensity & analgesic use NS				
Heim 1995	CLOD+CHEMO	80% no pain from 3rd m 13% analgesic consumption from 3rd m	<0.01(for analgesic use)	WHO scoring (scale 0-3) Subjective judgment of pts/analgesic use			No events
	CHEMO	60% no pain from 3rd m 39% analgesic consumption from 3rd m					
Clemens 1993	CLOD+CHEMO	Reduction at 9m	<0.032	WHO scoring (scale 0-3)			No toxicity
	CHEMO only						
Lahtinen 1992	CLOD	23.8% no pain at baseline ->53.6% pain at 24m	<0.01	Scale 0-3 (none-incapacitating)			No events
	PLC	29.3% no pain at baseline->44.1% no pain at 24m	<0.001				
Belch 1991	ETID		NS	Not mentioned			NM
	PLC						
Delmas 1982	CLOD	Decrease at 6m 56% mean pain reduction (at 12m)	0.025 0.05	Pain index according to severity & duration (score 1-9)			NM
	PLC	Increase at 6m					

I: Intervention; C: Comparator; CI: Confidence Interval; HR: Hazard ratio; OR: Odds ratio; RR: Relative risk; ZOL: zoledronic acid; CLOD: clodronate; ETI: etidronate; IBA: ibandronic acid; PAM: pamidronate; DENOS: denosumab; PLC: placebo; NT: no treatment; CHEMO: chemotherapy; vs: versus; ns: not significant; m: months; pt: patient; IQR: interquartile range; Q4W: every 4 weeks; Q12W: every 12 weeks; NM: no mention; ONJ: osteonecrosis of the jaw; BPI: brief pain inventory; VAS: visual analogue scale; WHO: world health organization; G: grade; CrCl: Creatinine Clearance

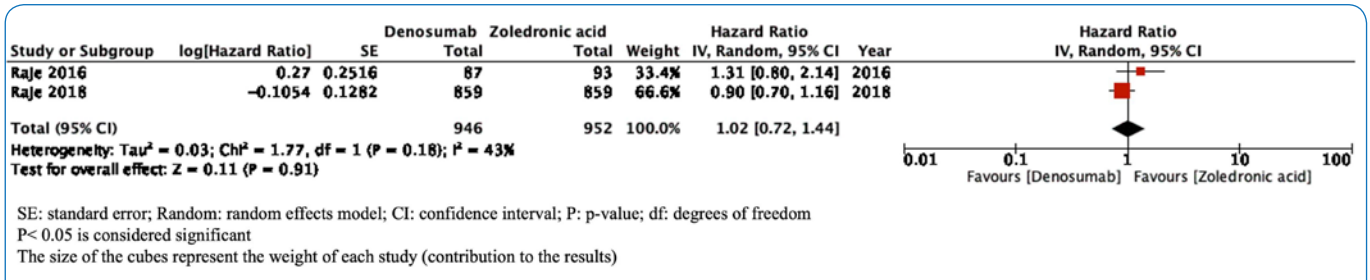

Figure 3. Forest Plot of meta-analysis of denosumab versus zoledronic acid for overall survival.

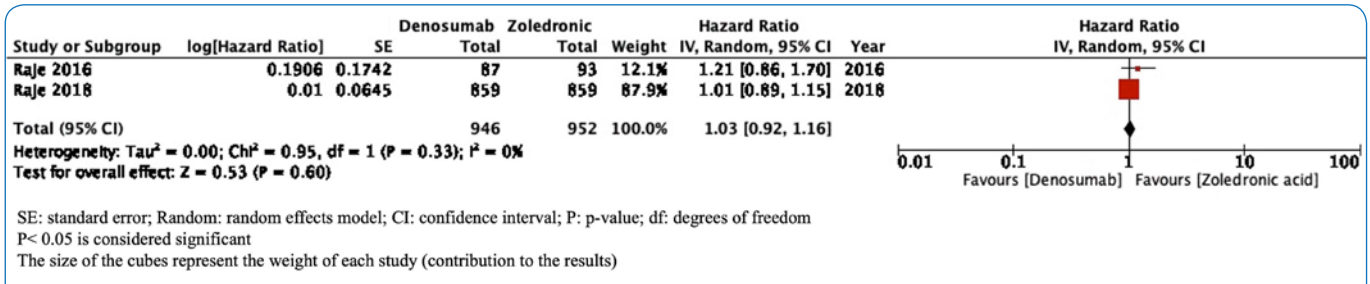

Figure 4. Forest Plot of meta-analysis of denosumab versus zoledronic acid for skeletal related events.

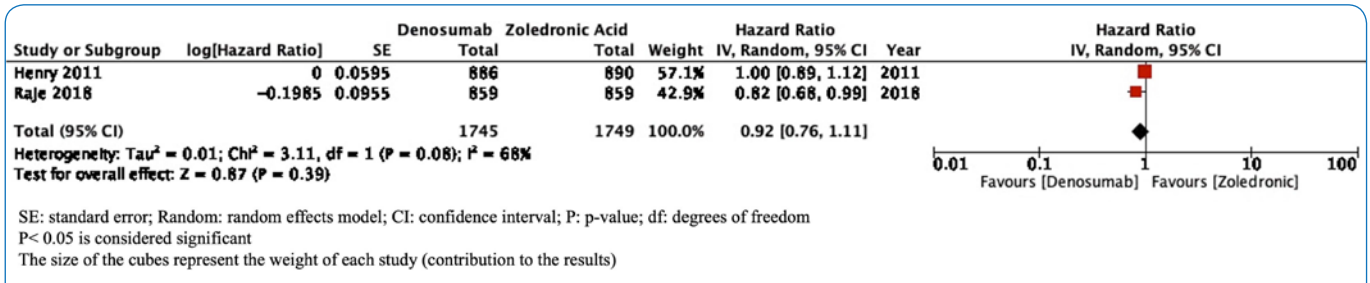

Figure 5. Forest Plot of meta-analysis of denosumab versus zoledronic acid for progression free survival.

PAM vs PLC/NT/CHEMO/ZOL/IBA

PAM versus PLC/NT or only CHEMO demonstrated no significant difference in OS. In four studies SREs were reduced significantly[38,41,46,54] but the same was not evident in the studies of Brincker et al., Attal et al. and Kraj et al.[39,48,50] (Table 3). It is to be noted that of the studies that demonstrated significant reduction in SREs with PAM administration, 2 had patients in early disease stages (DS IA or IIA and ISS I)[46,54] and only the study of Berenson et al. was in patients with advanced myeloma[38,41]. Contrary to that, the studies of Kraj et al. and Attal et al., included patients with advanced disease stage and in Brincker et al., most patients had vertebral collapse at study entry, suggesting a low beneficial effect in the more advanced stages of myeloma (Table 1).

When compared to ZOL, there was no difference in reducing SREs in the study of Rosen et al. for the MM subgroup[47] and the same was demonstrated in DP when compared to IBA[10]. In the study of Berenson et al. 2000, there was no difference in SREs between groups of ZOL 2 mg and 4 mg and PAM, but there was significant difference between 0.4mg ZOL and PAM[65] (Table 4).

ZOL vs PLC/NT/DENOS

The efficacy of ZOL was assessed in studies, from 2000-2018, with comparisons versus PLC, NT, only CHEMO, CLOD, PAM AND DENOS (Table 1). In asymptomatic MM patients, ZOL showed no superiority versus NT in PFS at 5 years. It reduced SREs (OR 2.9;95% CI, 1.04-8.06) but with a wide confidence

interval[52]. When thalidomide (THAL) was added, in the same population type, their combination was significantly better at PFS and time to disease progression (TTDP) than ZOL alone, with a median PFS of 2.4 years compared to 1.2 years in the ZOL group alone[56]. OS and PFS was improved significantly in patients with symptomatic and advanced disease, and SREs were reduced in the ZOL group[51,58]. For patients with biochemical relapses, progressive bone disease occurred in 16% versus 41% (p<0.0005) for ZOL and NT respectively. Survival did not reach statistical significance (73% vs 46%, p=0.161 for ZOL vs NT) in the overall assessment but for patients with lytic lesions at study entry the survival rates were significantly better for the ZOL group (Table 3)[60] Administration of ZOL with longer interval had the same efficacy in reducing SREs[63,72]. Long-term treatment with ZOL, 4 years compared to 2 years, reduced SREs (p<0.001) but not OS or PFS[62] (Table 3, 4, 5).

Lastly, we retrieved 2 trials comparing ZOL with DENOS[55,64], with 3494 participants, of which 1898 were MM patients alone[61,64]. The study of Raje et al. had 2 more publications[66,67] as did the study from Henry et al.,[61,76] one including only the MM subset of patients (Table 2). The meta-analysis demonstrated non-inferiority of DENOS compared to ZOL in all the outcomes of interest (Table 6). There was low heterogeneity of studies regarding OS and SREs (I^2 43% and 0% respectively) but in PFS heterogeneity was higher (I^2 68%) probably due to the study of Henry et al., that included patients mostly with metastatic solid tumors with bone involvement except breast and prostate cancer and high dropout rate. Forest plots of the meta-analysis are presented in Figures 3, 4, 5.

In the large trial of Raje et al.[64], PFS significantly increased for the DENOS group by 10.5 months versus the ZOL group [HR0.82(0.68,0.99)]. In a subgroup analysis of Asian patients that participated in the same study, 38.8% of patients on DENOS had first on study SRE, versus 50.5%, but it did not reach statistical significance[66]. The group that benefited the most from DENOS regarding PFS, were patients <70 years old and those with intent for autologous stem cell transplantation[67]. There was significant participant withdrawal (80%) in the trial of Henry et al., which reduced the sample size from 1776 to 358. There were differences between groups, regarding patient characteristics in the latter study, as demonstrated by Raje et al.[61]. More patients with poor renal function were treated with DENOS and patients taking ZOL, had stem cell therapy and immunomodulation therapy more frequent, which may have affected time to disease progression.

Secondary Outcomes: Bone Pain, Osteonecrosis of the Jaw, Renal Toxicity

Bone Pain

Results from CLOD versus PLC/CHEMO studies, indicated a significant reduction in pain and analgesic use, in patients receiving CLOD from baseline, as well as compared to PLC[32,34,35,37,40]. In the study of Lahtinen et al., no significant difference in pain reduction was evident between groups, but the number of patients with no pain at 2 years was reduced significantly in both groups, with more patients feeling no pain in the CLOD group (53.6% and 44.6% for CLOD and PLC respectively[34]. In the VIth Medical Research Council Myeloma Study[40], which had the largest sample, at 2 years, 10.9% of patients in the CLOD group were having back pain compared to 19.9% in the PLC group, which was significant (Table 7).

In the studies of Berenson et al.[38], Brincker et al.[39] and Terpos et al.[42] PAM was successful in reducing bone pain and analgesic use compared to PLC or CHEMO only. On the other hand, Kraj et al.[48] demonstrated a reduction in pain from PAM administration the first 9 months compared to CHEMO only and no difference after 9 months. Even though the study had only 46 participants the treatment duration was 66 months, with a long follow up period. Administration of ZOL 4 mg/IV, showed greater mean pain reduction than other dose regiments (0.4 mg and 2 mg) and PAM, after 10 months of treatment. Statistically significant levels were reached only between ZOL 4 mg and ZOL 0.4 mg and not among other group comparisons[65]. There were similar pain reduction scores when ZOL was given every 12 weeks compared to every 4 weeks[63]. Patients recruited in a single arm trial for ZOL, experienced significant pain reduction from baseline in at least 4 out of 6 visits[49]. When DENOS was compared to ZOL, one study[76] demonstrated superiority in reducing bone pain (in favor of DENOS), but had 80% participant withdrawal, while in another large trial[64], the same result was not reproduced, with both drugs showing similar effectiveness. Patients with osteolytic lesions receiving IBA had significant pain reduction from baseline, but there was no difference in between group comparisons[44]. ETI did not demonstrate pain reduction effects[33].

Osteonecrosis of the jaw

In patients that were treated with PAM, the rate of ONJ was very small. In the study of Attal et al.[50] only 2 of 397 participants developed ONJ after 26 months of treatment. CLOD when compared to ZOL, in the Medical Research Council Myeloma IX study, had significantly lower incidence of ONJ, in the short and long-term follow up (0.5% versus 3.7% respectively)[53,59]. The incidence of ONJ in patients treated with ZOL was generally less than 4%. There were two studies that reported 0 and 1 patient, but the duration of therapy was short[49,52]. Surprisingly, Aviles et al. 2013[58] reported no patient with ONJ after 2 years of ZOL administration, with a follow up ranging from 3-8 years. In two large studies comparing ZOL with DENOS there was no difference in the incidence of ONJ, which had a range of 1.3-3% and 1.1-4% respectively[55,64] but that percentage was higher in the subgroup analysis of Asian population 66 from the study of Raje et al.[64]. In the latter, there was 6.9% vs 5.4% of ONJ incidence between DENOS and ZOL respectively, which did not have significant difference between groups (Table 7).

Renal Toxicity

In the studies with CLOD versus PLC or CHEMO only, there were no serious events of renal toxicity between groups (Table 7). In the Myeloma IX study, events of acute renal failure were similar for CLOD and ZOL, with no significant difference in the short and long-term follow up (Table 7).

PAM was generally well tolerated and there was no significant toxicity compared to PLC/NT/CHEMO. ZOL, in the 4 mg dose, every 4 weeks, when compared to PAM had similar safety profile but the 8 mg dose had significant difference in renal toxicity vs PAM, therefore causing the investigators to alter ZOL dosing of that group to lower dose[47]. ZOL was generally well tolerated, with low incidence of renal toxicity, but Vogel et al.[49] reported 17 patients with treatment discontinuation due to rise in serum creatinine (Table 7). When compared to DENOS, there was higher percentage of patients with adverse events regarding renal function, and that was more pronounced in participants with baseline lower creatinine clearance (Table 7). Overall ZOL had a good safety profile, when the dosage was adjusted for creatinine clearance[55,64].

Discussion

In MM patients, progression to bone disease is of pivotal importance that affects morbidity. Most patients will eventually develop skeletal lesions (80-90%), due to the imbalance between bone apposition and resorption, that follows when MM tumor burden exceeds 50% in a local area. Histologic studies have demonstrated that there is increased OCL activity adjacent to MM cells[77]. MIP-1a is a chemokine produced by MM cells, which help them adhere to bone marrow BMSc and stimulate production of RANKL, TNF and vascular endothelial growth factor. This in consequence, causes proliferation and differentiation of OCLs, which leads to increased local bone resorption and the creation of lytic lesions[78].

Bisphosphonates' main target is to reduce proliferation of OCLs and induce apoptosis and for that reason they play an important role in the treatment of MM[14].

Results from the study of Lahtinen et al.[34] first demonstrated that there was a beneficial effect of oral CLOD in reducing osteolytic lesions and delaying bone disease progression in MM patients. That result was also evident in the study of Berenson et al.[41], regarding IV PAM. When ZOL became available, clinical trials comparing it to PAM demonstrated similar safety profile and slightly better efficacy in reducing SREs and bone pain[47,65]. In the Myeloma IX study[53], ZOL proved to be superior to CLOD in increasing OS by 5.5 months and reducing SREs. Even though it had higher incidence of ONJ, that percentage was less than 5%. Renal toxicity was slightly higher for ZOL but there was no significant difference. In the future study of Himelstein et al.[63], it was shown that IV 4 mg ZOL administration every 12 weeks had the same efficacy, with reduced incidence of ONJ and renal function impairment, compared to every 4 weeks. Treatment with ZOL has been proven safe and effective for 2 years. The extended follow up of the Myeloma IX study showed low incidence of adverse events and the Z-MARK study, that included patients with 1-2 years of prior bisphosphonate use, extended the safe use of ZOL up to 4 years, in 3-month intervals.

A Mixed Treatment Comparison that compared the efficacy of ZOL, PAM, CLOD and IBA in reducing SREs concluded that ZOL was superior to other BPs. ZOL had 1.43 incidence rate, while PAM had 1.64 and CLOD 1.90. The excess rates of PAM and CLOD versus ZOL in the incidence of SREs were 15% and 33% respectively[79].

In a more recent Cochrane review and meta-analysis[80] bisphosphonates were effective in reducing SREs and pathologic vertebral fractures (moderate quality of evidence). OS was improved with ZOL but not PFS. Regarding ONJ, there was no significant difference in the incidence between BP type and evidence for lesser bone pain was of low quality.

There was no uniform scale used to assess bone pain between studies. The Brief Pain Inventory[27] was applied in three[63,65,76], World Health Organization scoring scale[81] in two[35,37] and the 100-mm Visual Analogue Scale[82] in one[49]. The rest of the studies used questionnaires regarding pain frequency and severity, analgesic type and consumption and descriptive scales to rate pain intensity (Table 7). That diversity in the tools of pain evaluation and in some cases the use of non-validated instruments, is a methodological limitation which contributes to the low quality of evidence on the matter.

Renal function deterioration is the most important complication associated with IV BP infusion. In a retrospective study, McDermott et al. demonstrated that important predictive factors for renal impairment, in patients treated with ZOL, were patient age, myeloma disease, nonsteroidal anti-inflammatory drugs, cumulative doses of BPs and cisplatin therapy[83]. Caution is warranted with PAM as well, but generally doses up to 90 mg every 4 weeks are well tolerated[84]. In a recent retrospective study, there was 8% incidence of acute kidney injury in patients with pre-existing renal impairment compared to others with normal renal function[85]. Oral BPs are not associated with significant nephrotoxicity[84].

All three bisphosphonate types have their contribution in MM treatment, but recommendations differ between various countries. American Society of Clinical Oncology (ASCO) prefers PAM in contrast to the British Committee for Standards in Hematology (BCSH) and International Myeloma Working Group (IMWG), who favor ZOL, due to decreased incidence of ONJ and similar effectiveness. CLOD is preferred in patients that cannot attend hospital visits, but a strict intake protocol should be followed to maximize absorption[86]. All symptomatic MM patients should be started on bisphosphonates regardless of the presence or not of myeloma bone disease, but the same does not apply for smoldering myeloma[46,52,87].

Special precautions are warranted to reduce ONJ incidence, and thorough oral examination is recommended prior to

monthly IV infusion. Dental treatment before initiation of BP therapy has been associated with decreased risk of ONJ[21,88]. BP infusion should be withheld, and dose adjustments are recommended in patients with impaired renal function, and specifically ZOL and PAM are not recommended in patient with creatinine clearance (CrCl)<30 ml/min, while CLOD in CrCl<10 ml/min[86].

The development of DENOS, a human monoclonal IgG antibody that binds to RANKL thus preventing it from activating OCLs, has been tested against ZOL[55,61], in a recent trial including 1718 participants[64]. Results from that study, with 15.8 months median treatment duration, demonstrated longer PFS in favor of DENOS, especially in younger patients and candidates for autologous stem cell transplantation, and increased TTFSRE[64,67]. Furthermore, it showed non-inferiority in OS, in preventing SREs and similar safety. The incidence of hypocalcemia was more pronounced compared to ZOL, but there is no need for dose adjustments according to renal function[89]. Overall, these results have led to DENOS being approved by the FDA for use in prevention of SREs secondary to MM[23].

To test the safety of longer use of DENOS, an open label extension phase of the NCT01345019 trial was conducted[90], offering patients to the choice to continue or switch to DENOS. A total of 844 patients participated (426 DENOS/DENOS & 418 ZOL/DENOS) with a cumulative exposure of 29.2 months (original and extension phase) and mean exposure during the extension phase of 17.5 months. 23.2 % compared to 19.4% of patients in the DENOS/DENOS and ZOL/DENOS groups respectively, discontinued the medication due to serious adverse events. Hypocalcemia events had similar frequency in both groups (7% vs 7.2%) and ONJ incidence was higher in the DENOS/DENOS group (7.7% vs 6.2%) but notably more patients in the DENOS/DENOS group recovered (42%) compared to ZOL/DENOS group (23%). Sabatelli et al.[91] used statistical models on data from the primary study (NCT01345019) to try and extrapolate long-term trends on PFS and quantify potential health benefits from DENOS in MM patients. According to their analysis, the effect of DENOS in disease progression could translate in lifetime health benefit between 1.5 and 2.3 extra months in perfect health, 1.9 and 2.8 extra months in the same condition as pre-progression and between 2.3 and 3.5 extra months with the same state (quality of life) as post-progression[91].

Currently there are two ongoing, single arm, open label studies recruiting. The first will assess the potential value of DENOS in preventing myeloma disease in patients with smouldering myeloma (NTC03839459/www.clinicaltrials.gov) and the other will estimate the therapeutic and safety potential of DENOS in patients with MM and renal insufficiency (ClinicalTrials.gov Identifier: NTC02833610). The DEFENCE trial (ClinicalTrials.gov Identifier: NCT03792763), a randomized, 2-arm phase II, placebo-controlled trial, which is active but not recruiting, is designed to test whether DENOS may prove beneficial in delaying SREs and reduce the risk of DP in patients with high and ultra-high risk smouldering multiple myeloma patients. Unfortunately, recruiting was slow and only 8 participants were enrolled, when the original estimation was 164.

Regarding ZOL, there is an ongoing randomized, open label study (ClinicalTrials.gov Identifier: NCT02286830) that will investigate time to progressive bone disease in patients with newly diagnosed MM continuing ZOL treatment for a total of 4 years. All patients will receive ZOL for the first 2 years and they will be further randomized between ZOL and PLC for the following 2 years.

Conclusion

Bisphosphonates are established drugs in the treatment of MM, with a good safety profile for long-term administration. They are effective in reducing bone disease but their ability to improve overall survival and progression free survival is not clearly established. Their use is not without adverse events and limitations, especially in patients with renal impairment. The use of newer drugs like DENOS, is gaining ground and if long term administration is proved safe and efficacious, it may even replace BP use in the treatment of MM.

Limitations & strengths

Our study has certain limitations. First, we did not conduct a meta-analysis of the studies with bisphosphonates but rather provide a comprehensive evaluation of the included studies. The reason was that no new studies have been identified since the published meta-analysis from the Cochrane Collaboration[80] and we did not have access to all the raw data. Some publications provided adequate information, while others did not, to be able to extrapolate uniform measures to proceed with a meta-analysis. Another limitation is that we could not gain access to the full publication of the study by Daragon et al.[92], Kraj et al.[93] and Rosen et al.[94]. We extracted data from the publications on the extension phase of the original studies by Kraj et al. and Rosen et al., where the full text was available. Moreover, only articles published in English were included, which did not allow us to consider more studies (see Appendix). Nevertheless, regarding the strengths of this study, it is a comprehensive analysis of the research conducted from 1980 up to date, regarding the effectiveness of bisphosphonates in myeloma patients. We also included trials that compared the more recent pharmaceutical agent, denosumab and its potential value to the management of bone disease in MM patients, as well as ongoing research on the field. In this way we summarized, in a structured way older research and novel perspectives regarding the use of antiresorptive agents in the prevention of bone disease in patients suffering from MM.

Authors' contributions

VC contributed to the conceptualization, investigation, methodology, data curation and drafting the manuscript. GK contributed to investigation, methodology and data curation of the manuscript. DK contributed to methodology, data curation and editing of the manuscript. CD contributed to editing and reviewing the

manuscript. IS contributed in reviewing and approving final version of the manuscript and EZ in validation of methodology, reviewing and approving the manuscript.

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Supplementary Table 1. Search strategy per database.

Database	Search string
Pubmed https://pubmed.ncbi.nlm.nih.gov	Search: (multiple myeloma[Title/Abstract] OR plasma cell myeloma[Title/Abstract]) AND (bisphosphonates[Title/Abstract] OR denosumab OR zoledronic[Title/Abstract] OR pamidronate[Title/Abstract] OR clodronate[Title/Abstract] OR etidronate[Title/Abstract] OR ibandronic[Title/Abstract] OR risendronate[Title/Abstract] OR alendronate[Title/Abstract])Filters: Clinical Trial, Randomized Controlled Trial
Scopus https://www.scopus.com/search/form.uri?display=advanced	(TITLE-ABS-KEY (multiple AND myeloma OR plasma AND cell AND myeloma) AND TITLE-ABS-KEY (bisphosphonates OR diphosphonates)) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (EXACTKEYWORD, "Human")) AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (EXACTKEYWORD, "Diphosphonates") OR LIMIT-TO (EXACTKEYWORD, "Humans") OR LIMIT-TO (EXACTKEYWORD, "Multiple Myeloma") OR LIMIT-TO (EXACTKEYWORD, "Bisphosphonic Acid Derivative") OR LIMIT-TO (EXACTKEYWORD , "Zoledronic Acid"))
Web of Science https://www.webofscience.com/wos/woscc/advanced-search	(ALL=(multiple myeloma OR plasma cell myeloma)) AND ALL=(bisphosphonates OR zoledronic OR pamidronate OR aledronate OR risedronate OR etidronate OR zoledronic acid OR risedronic acid) Refined By:NOT Document Types: Review Articles or Editorial Materials or Letters or Book Chapters Web of Science Categories: Oncology or Hematology or Orthopedics or Immunology
ClinicalTrials.gov https://clinicaltrials.gov	Status: All studies Condition or disease: multiple myeloma Other terms: bisphosphonates OR denosumab

Supplementary Table 2. Studies excluded after full-text screening.

Study reference	Reason for exclusion
Canfield RE, Siris ES, Jacobs TP. Dichloromethylene diphosphonate action in hematologic and other malignancies. Bone 1987;8 Suppl 1:S57-62. PMID: 2961356	No full text available
Thürlimann B, Morant R, Jungi WF, Radziwill A. Pamidronate for pain control in patients with malignant osteolytic bone disease: a prospective dose-effect study. Support Care Cancer 1994;2(1):61-5. doi: 10.1007/BF00355241. PMID: 8156259	Phase II study
Slabý J, Spicka I, Hulejová H, Spacek P, Cieslar P, Klener P. Ucinek klodronátu u pacientů s mnohocetným myelomem. Hodnocení specifickými markery osteoresorpce [Effect of clodronate in patients with multiple myeloma. Evaluation of specific markers of bone resorption]. Cas Lek Cesk 1997;136(2):57-60. Czech. PMID: 9147856	Article in Czeck
Vinholes JJ, Purohit OP, Abbey ME, Eastell R, Coleman RE. Relationships between biochemical and symptomatic response in a double-blind randomised trial of pamidronate for metastatic bone disease. Ann Oncol 1997;8(12):1243-50. doi: 10.1023/a:1008238422151. PMID: 9496390	Not relevant population
Koeberle D, Bacchus L, Thuerlimann B, Senn HJ. Pamidronate treatment in patients with malignant osteolytic bone disease and pain: a prospective randomized double-blind trial. Support Care Cancer 1999;7(1):21-7. doi: 10.1007/s005200050218. PMID: 9926970.	Not relevant population
Serkies K, Jereczek-Fossa B, Badzio A, Jassem J. Clodronate in the management of bone metastases: a clinical study of 91 patients. Neoplasma 1999;46(5):317-22. PMID: 10665850.	Not relevant population
Martin Wilhelm, Volker Kunzmann, Susanne Eckstein, Peter Reimer, Florian Weissinger, Thomas Ruediger, Hans-Peter Tony; γδ T cells for immune therapy of patients with lymphoid malignancies. Blood 2003; 102(1):200–206. doi: https://doi.org/10.1182/blood-2002-12-3665	Phase I/II trial
Berenson JR, Vescio R, Henick K, Nishikubo C, Rettig M, Swift RA, Conde F, Von Teichert JM. A Phase I, open label, dose ranging trial of intravenous bolus zoledronic acid, a novel bisphosphonate, in cancer patients with metastatic bone disease. Cancer 2001;91(1):144-54. doi: 10.1002/1097-	Phase I
Morris TC, Ranaghan L, Morrison J; Northern Ireland Regional Haematology Group. Phase II trial of clarithromycin and pamidronate therapy in myeloma. Med Oncol 2001;18(1):79-84. doi: 10.1385/MO:18:1:79. PMID: 11778973.	Phase II
Jagdev SP, Purohit P, Heatley S, Herling C, Coleman RE. Comparison of the effects of intravenous pamidronate and oral clodronate on symptoms and bone resorption in patients with metastatic bone disease. Ann Oncol 2001;12(10):1433-8. doi: 10.1023/a:1012506426440. PMID: 11762816.	Not relevant population

Supplementary Table 2. *(Cont. from previous page).*

Study reference	Reason for exclusion
Leng Y, Chen SL, Shi HZ. [Effects of pamidronate disodium (Bonin) combined with chemotherapy on bone pain in multiple myeloma]. Space Med Med Eng (Beijing) 2002;15(5):377-8. Chinese. PMID: 12449148.	Article in Chinese
Ciepłuch H, Baran W, Hellmann A. Combination of pamidronate and thalidomide in the therapy of treatment-resistant multiple myeloma. Med Sci Monit 2002;8(4):PI31-6. PMID: 11951079.	Observational study
Wang T, Song ST, Jiang ZF, Bian SG, Wang YJ, Li LQ, Zhu J. [Clinical trial on ibandronate in patients with tumor-associated hypercalcemia]. Zhonghua Zhong Liu Za Zhi 2004;26(12):739-41. Chinese. PMID: 15733393.	Article in Chinese
Ma M. [Clinical observation on effect of combined therapy of pamidronati sodium and shenfu injection in treating multiple myeloma caused ostealgia]. Zhongguo Zhong Xi Yi Jie He Za Zhi 2004;24(1):67-8. Chinese. PMID: 14976895.	Article in Chinese
James R. Berenson, Ori Yellin, John Crowley, Herbert Duvivier, Youram Nassir, Regina A. Swift; Factors That Determine Overall Survival among Patients (Pts) with Multiple Myeloma (MM) Treated with Zoledronic Acid (ZOL): Lack of Skeletal-Related Events (SREs) and Occurrence of Osteonecrosis of the Jaw (ONJ) Predict Improved Survival. Blood 2007;110 (11):4842. doi: https://doi.org/10.1182/blood.V110.11.4842.4842	
Observational study	
Dong M, Feng FY, Zhang Y, Xie GR, Wang YJ, Liu JW, Song ST, Zhou QH, Ren J, Jiao SC, Li J, Wang XW, Chen Q, Wang ZH, Xu N, Feng JF. [Phase III clinical study of zoledronic acid in the treatment of pain induced by bone metastasis from solid tumor or multiple myeloma]. Zhonghua Zhong Liu Za Zhi 2008;30(3):215-20. Chinese. PMID: 18756940.	Article in Chinese
Abe Y, Muto M, Nieda M, Nakagawa Y, Nicol A, Kaneko T, Goto S, Yokokawa K, Suzuki K. Clinical and immunological evaluation of zoledronate-activated Vgamma9gammadelta T-cell-based immunotherapy for patients with multiple myeloma. Exp Hematol 2009;37(8):956-68. doi: 10.1016/j.exphem.2009.04.008. Epub 2009 May 4. PMID: 19409955.	Observational study
Zhang X, Chang CK, Wu LY, Zhang Z, Zhou LY, Xiao C, Li X. [The affection of bisphosphonates combined with chemotherapy on bone metabolism index in multiple myeloma]. Zhonghua Xue Ye Xue Za Zhi 2011;32(10):660-3. Chinese. PMID: 22339822.	Article in Chinese
Zhang X, Chang CK, Zhang Z, Zhao YS, Xiao C, Li X. [Influence of bisphosphonate combined with chemotherapy on bone mineral density of patients with multiple myeloma]. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2012;20(5):1135-8. Chinese. PMID: 23114134.	Article in Chinese
Teoh G, Chen Y, Kim K, Srivastava A, Pai VR, Yoon SS, Suh C, Kim YK. Lower dose dexamethasone/thalidomide and zoledronic acid every 3 weeks in previously untreated multiple myeloma. Clin Lymphoma Myeloma Leuk 2012;12(2):118-26. doi: 10.1016/j.clml.2011.11.002. Epub 2011 Dec 28. PMID: 22206804.	Phase II study
Qu S, Liao LS, Wei TN, Lin Y, Chen BY, Chen WM. [Effect of bortezomib combined with bisphosphonates on bone metabolism index in multiple myeloma]. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2013;21(6):1482-5. Chinese. doi: 10.7534/j.issn.1009-2137.2013.06.021. PMID: 24370033.	Article in Chinese
Liang B, Yin JJ, Wang ZL, Zhan XR. [Clinical Comparative Study of Two Kind Doses of Bortezomib Combinated with Bisphosphonates for Treating Patients with Multiple Myeloma Ostespathy]. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2016;24(3):769-72. Chinese. doi: 10.7534/j.issn.1009-2137.2016.03.025. PMID: 27342507.	Article in Chinese
Pyridinium cross-links in multiple myeloma: correlation with clinical parameters and use for monitoring of intravenous clodronate therapy--a pilot study of the German Myeloma Treatment Group (GMTG). Eur J Cancer 1996;32A(12):2053-7. doi: 10.1016/s0959-8049(96)00228-6. PMID: 9014744.	No outcome of interest
Smith AG, Soutar RL, Schey S, Andrews CD, Baister ER, Bilbrough C, Connelly M, Joyce A, Child JA. Home care versus hospital care in patients with multiple myeloma treated with pamidronate. Int J Palliat Nurs 2004;10(3):144-9. doi: 10.12968/ijpn.2004.10.3.12602. PMID: 15126959.	No outcome of interest
Tosi P, Zamagni E, Cellini C, Parente R, Cangini D, Tacchetti P, Perrone G, Ceccolini M, Boni P, Tura S, Baccarani M, Cavo M. First-line therapy with thalidomide, dexamethasone and zoledronic acid decreases bone resorption markers in patients with multiple myeloma. Eur J Haematol 2006;76(5):399-404. doi: 10.1111/j.0902-4441.2005.t01-1-EJH2520.x. Epub 2006 Feb 15. PMID: 16480429.	No outcome of interest
Spencer A, Roberts A, Kennedy N, Ravera C, Cremers S, Bilic S, Neeman T, Copeman M, Schran H, Lynch K. Renal safety of zoledronic acid with thalidomide in patients with myeloma: a pharmacokinetic and safety sub-study. BMC Clin Pharmacol 2008;8:2. doi: 10.1186/1472-6904-8-2. PMID: 18377658; PMCID: PMC2330021.	Phase II trial
Gimsing P, Carlson K, Turesson I, Fayers P, Waage A, Vangsted A, Mylin A, Gluud C, Juliusson G, Gregersen H, Hjorth-Hansen H, Nesthus I, Dahl IM, Westin J, Nielsen JL, Knudsen LM, Ahlberg L, Hjorth M, Abildgaard N, Andersen NF, Linder O, Wisløff F. Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial. Lancet Oncol 2010;11(10):973-82. doi: 10.1016/S1470-2045(10)70198-4. PMID: 20863761.	Phase II

Supplementary Table 2. *(Cont. from previous page).*

Study reference	Reason for exclusion
Royle KL, Gregory WM, Cairns DA, Bell SE, Cook G, Owen RG, Drayson MT, Davies FE, Jackson GH, Morgan GJ, Child JA. Quality of life during and following sequential treatment of previously untreated patients with multiple myeloma: findings of the Medical Research Council Myeloma IX randomised study. Br J Haematol 2018;182(6):816-829. doi: 10.1111/bjh.15459. Epub 2018 Jul 9. PMID: 29984830; PMCID: PMC6175065.	No outcome of interest
Jung A, Chantraine A, Donath A, van Ouwenaller C, Turnill D, Mermillod B, Kitler ME. Use of dichloromethylene diphosphonate in metastatic bone disease. N Engl J Med 1983;308(25):1499-501. doi: 10.1056/NEJM198306233082503. PMID: 6222257.	Not relevant outcome
Thiébaud D, Leyvraz S, von Fliedner V, Perey L, Cornu P, Thiébaud S, Burckhardt P. Treatment of bone metastases from breast cancer and myeloma with pamidronate. Eur J Cancer 1991;27(1):37-41. doi: 10.1016/0277-5379(91)90056-j. PMID: 1826438.	Not relevant population
Fazzi R, Petrini I, Giuliani N, Morganti R, Carulli G, Dalla Palma B, Notarfranchi L, Galimberti S, Buda G. Phase II Trial of Maintenance Treatment With IL2 and Zoledronate in Multiple Myeloma After Bone Marrow Transplantation: Biological and Clinical Results. Front Immunol 2021;11:573156. doi: 10.3389/fimmu.2020.573156. PMID: 33613510; PMCID: PMC7890401.	Phase II study
Søe K, Delaissé JM, Jakobsen EH, Hansen CT, Plesner T. Dosing related effects of zoledronic acid on bone markers and creatinine clearance in patients with multiple myeloma and metastatic breast cancer. Acta Oncol 2014;53(4):547-56. doi: 10.3109/0284186X.2013.844358. Epub 2013 Oct 28. PMID: 24164102.	Phase II study
Coleman RE, Purohit OP, Black C, Vinholes JJ, Schlosser K, Huss H, Quinn KJ, Kanis J. Double-blind, randomised, placebo-controlled, dose-finding study of oral ibandronate in patients with metastatic bone disease. Ann Oncol 1999;10(3):311-6. doi: 10.1023/a:1008386501738. PMID: 10355575.	Phase II study
Daragon A, Humez C, Michot C, Le Loet X, Grosbois B, Pouyol F, Euller-Ziegler L, Azais I, Bernard JF, Menard JF, et al.. Treatment of multiple myeloma with etidronate: results of a multicentre double-blind study. Groupe d'Etudes et de Recherches sur le Myélome (GERM). Eur J Med 1993;2(8):449-52. PMID: 8258043.	No full text available
Khalafallah AA, Slancar M, Cosolo W, Abdi E, Chern B, Woodfield RJ, Copeman MC. Long-term safety of monthly zoledronic acid therapy beyond 1 year in patients with advanced cancer involving bone (LoTESS): A multicentre prospective phase 4 study. Eur J Cancer Care (Engl) 2018;27(2):e12638. doi: 10.1111/ecc.12638. Epub 2017 Jan 30. PMID: 28134499; PMCID: PMC5901400.	Prospective cohort study
Iyer SP, Beck JT, Stewart AK, Shah J, Kelly KR, Isaacs R, Bilic S, Sen S, Munshi NC. A Phase IB multicentre dose-determination study of BHQ880 in combination with anti-myeloma therapy and zoledronic acid in patients with relapsed or refractory multiple myeloma and prior skeletal-related events. Br J Haematol 2014;167(3):366-75. doi: 10.1111/bjh.13056. Epub 2014 Aug 19. PMID: 25139740.	Phase I study
Chiang PH, Wang HC, Lai YL, Chen SC, Yen-Hwa W, Kok CK, Ou YC, Huang JS, Huang TC, Chao TY. Zoledronic acid treatment for cancerous bone metastases: a phase IV study in Taiwan. J Cancer Res Ther 2013;9(4):653-9. doi: 10.4103/0973-1482.126471. PMID: 24518712.	Observational study
Scagliotti GV, Hirsh V, Siena S, Henry DH, Woll PJ, Manegold C, Solal-Celigny P, Rodriguez G, Krzakowski M, Mehta ND, Lipton L, García-Sáenz JA, Pereira JR, Prabhash K, Ciuleanu TE, Kanarev V, Wang H, Balakumaran A, Jacobs I. Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab versus zoledronic acid: subgroup analysis from a randomized phase 3 study. J Thorac Oncol 2012;7(12):1823-1829. doi: 10.1097/JTO.0b013e31826aec2b. PMID: 23154554.	Not relevant population
Zoledronic acid therapy versus control in patients with multiple myeloma in stage I (Durie & Salmon): results of a phase III study of the DSMM and OSHO. O Sezer, C Jakob, A Aldaoud, K Schmidt, A Schwarzer, C Maintz, M Kropff, K Blumenstengel, J Mittermueller, W Aulitzky, H Wolf, H Duerk, H Cordes, C Beck, H Einsele, U Haus, U Friedrichs, M Freund. 15th congress of the european hematology association abstr 0361, 2010 | added to CENTRAL: 30 September 2017 | 2017 Issue 9	Congress publication-Not found
Barlogie B, van Rhee F, Shaughnessy JD Jr, Epstein J, Yaccoby S, Pineda-Roman M, Hollmig K, Alsayed Y, Hoering A, Szymonifka J, Anaissie E, Petty N, Kumar NS, Srivastava G, Jenkins B, Crowley J, Zeldis JB. Seven-year median time to progression with thalidomide for smoldering myeloma: partial response identifies subset requiring earlier salvage therapy for symptomatic disease. Blood 2008;112(8):3122-5. doi: 10.1182/blood-2008-06-164228. Epub 2008 Jul 31. PMID: 18669874; PMCID: PMC2569167.	Phase II study
Johansson E, Langius-Eklöf A, Engervall P, Wredling R. Patients' experience of ambulatory self-administration of pamidronate in multiple myeloma. Cancer Nurs 2005r;28(2):158-65. doi: 10.1097/00002820-200503000-00011. PMID: 15815186.	No outcome of interest
Allan Lipton, Robert E. Coleman, Pierre Major, Janet E. Brown, Ker-Ai Lee, Matthew Smith, Fred Saad, YinMiao Chen, Yong Jiang, Richard Cook,Baseline N-Telopeptide Levels Correlate with Risk of Skeletal Morbidity in Patients with Multiple Myeloma during Zoledronic Acid Therapy. Blood, Volume 106, Issue 11, 2005, Page 3456, ISSN 0006-4971,https://doi.org/10.1182/blood.V106.11.3456.3456.	No full text

Supplementary Table 2. *(Cont. from previous page).*

Study reference	Reason for exclusion
Mancini I, Dumon JC, Body JJ. Efficacy and safety of ibandronate in the treatment of opioid-resistant bone pain associated with metastatic bone disease: a pilot study. J Clin Oncol 2004;22(17):3587-92. doi: 10.1200/JCO.2004.07.054. PMID: 15337809.	Not relevant population
Conte, P; Rosen, LS; Gordon, D; Zheng, M; Hei, YJ, Zoledronic acid is superior to pamidronate in patients with breast cancer and multiple myeloma: analysis of patients at high risk for skeletal complications, Annals of Oncology 2004, ISSN:0923-7534	Not found
Wilhelm M, Kunzmann V, Eckstein S, Reimer P, Weissinger F, Ruediger T, Tony HP. Gammadelta T cells for immune therapy of patients with lymphoid malignancies. Blood 2003;102(1):200-6. doi: 10.1182/blood-2002-12-3665. Epub 2003 Mar 6. PMID: 12623838.	No outcome of interest
Kraj M, Pogłód R, Maj S, Pawlikowski J, Sokołowska U, Szczepanik J. Comparative evaluation of safety and efficacy of pamidronate and zoledronic acid in multiple myeloma patients (single center experience). Acta Pol Pharm 2002;59(6):478-82. PMID: 12669777.	Comparative study of single center (9 patients – part of a larger study by Rosen 2003)
Berenson J, Lichtenstein A, Porter L, Bordoni R, George S, Lipton A, Keller A, Simeone J, Heffernan M, Seaman J, Knight R. Pamidronate Disodium Reduces The Occurrence of Skeletal Related Events (SRE) in Advanced Multiple-Myeloma (MM), Blood, Nov 1994, A386	Not found
Terpos E, Palermos J, Viniou N, Vaiopoulos G, Meletis J, Yataganas X. Pamidronate increases markers of bone formation in patients with multiple myeloma in plateau phase under interferon-alpha treatment. Calcif Tissue Int 2001;68(5):285-90. doi: 10.1007/BF02390835. PMID: 11683535.	No outcome of interest
Berenson JR, Rosen LS, Howell A, Porter L, Coleman RE, Morley W, Dreicer R, Kuross SA, Lipton A, Seaman JJ. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. Cancer. 2001 Apr 1;91(7):1191-200. doi: 10.1002/1097-0142(20010401)91:7<1191::aid-cncr1119>3.0.co;2-0. Erratum in: Cancer 2001;91(10):1956. PMID: 11283917.	Phase II – dose determination study
Abildgaard N, Rungby J, Glerup H, Brixen K, Kassem M, Brincker H, Heickendorff L, Eriksen EF, Nielsen JL. Long-term oral pamidronate treatment inhibits osteoclastic bone resorption and bone turnover without affecting osteoblastic function in multiple myeloma. Eur J Haematol 1998;61(2):128-34. doi: 10.1111/j.1600-0609.1998.tb01073.x. PMID: 9714526.	No outcome of interest
Monitoring the action of clodronate with type I collagen metabolites in multiple myeloma Elomaa, I. et al. European Journal of Cancer, Volume 32, Issue 7, 1166 - 1170.	No outcome of interest
Siris ES, Sherman WH, Baquiran DC, Schlatterer JP, Osserman EF, Canfield RE. Effects of dichloromethylene diphosphonate on skeletal mobilization of calcium in multiple myeloma. N Engl J Med 1980;302(6):310-5. doi: 10.1056/NEJM198002073020602. PMID: 6444241.	No outcome of interest
Berenson JR, Boccia R, Lopez T, Warsi GM, Argonza-Aviles E, Lake S, Ericson SG, Collins R. Results of a multicenter open-label randomized trial evaluating infusion duration of zoledronic acid in multiple myeloma patients (the ZMAX trial). J Support Oncol 2011;9(1):32-40. doi: 10.1016/j.suponc.2010.12.002. PMID: 21465735.	Bioequivalence study
Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, Apffelstaedt J, Hussein M, Coleman RE, Reitsma DJ, Seaman JJ, Chen BL, Ambros Y. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. Cancer J 2001;7(5):377-87. PMID: 11693896.	No full text available
Kraj M, Pogłód R, Pawlikowski J, Maj S, Nasiłowska B. Effect of pamidronate on skeletal morbidity in myelomatosis. Part 1. The results of the first 12 months of pamidronate therapy. Acta Pol Pharm 2000;57 Suppl:113-6. PMID: 11293237.	No full text available
Daragon A, Humez C, Michot C, Le Loet X, Grosbois B, Pouyol F, Euller-Ziegler L, Azais I, Bernard JF, Menard JF, et al.. Treatment of multiple myeloma with etidronate: results of a multicentre double-blind study. Groupe d'Etudes et de Recherches sur le Myélome (GERM). Eur J Med 1993;2(8):449-52. PMID: 8258043.	No full text available