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Review

Treatment of myeloma bone disease: When, how often, and for how long?☆

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HIGHLIGHTS

- ZOL treatment beyond 24 months reduces SRE, with few side effects.
- Prolonged intervals between each ZOL infusion seems safe in MM.
- Denosumab treatment is non-inferior to ZOL treatment.

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ABSTRACT

The landscape of MM has changed dramatically in recent years. Several new and more effective treatments have been introduced that not only makes patients live longer but also brings them into a deeper remission. This makes the potential total exposure of bone protective treatment much higher but perhaps also less needed. New and more precise imagining techniques have been introduced making detection of bone disease more sensitive, and the introduction of SLiM-CRAB criteria have changed the parameters used in old clinical trials investigating treatment of MM bone disease. New data have also emerged investigating the effect of the RANKL inhibitor denosumab compared to zoledronic acid (ZOL). Randomized trials have investigated longer treatment durations, which becomes more relevant as patients now live longer.

In addition in this review, data regarding interval between individual treatment, impact of remission status, new data in relation to rebound after discontinuation and of denosumab, as well as the rational for drug holidays before dental procedures will also be discussed.

1. Introduction

1.1. Multiple myeloma

Multiple myeloma (MM) is a plasma cell dyscrasia defined by clonal bone marrow plasma cells ≥10 % or biopsy-proven bony or extramedullary plasmacytoma and presence of one myeloma-defining disorder [1]. According to recent American cancer statistics, MM accounts for 17 % of all hematological malignant disorders [2]. MM has a number of complications including anemia, hypercalcemia, kidney damage, and immunoparesis [3]. The most notable complication to MM however is bone disease with 79 % of new MM patients presenting with pathological imaging, and with 60 % experiencing bone pain at diagnosis [3].

1.2. Myeloma treatment and survival

Randomized studies of the bone protective bisphosphonates clodronate and pamidronate were published 20 years ago. Since then a number of more effective anti-myeloma treatments have become standard MM treatment including immunomodulatory drugs [4], proteasome inhibitors [5] and CD38 antibodies [6], with bispecific antibodies [7] and CAR-T recently becoming standard of care in many countries The results have been increasing survival, with studies demonstrating 5-year survival increase from 27.4 % (1994–2001) to 47.4 % (2010–2016) and median OS from 2.8 years (2000–2004) to 4.4 years (2017–2021), and even 9.2 years for patients who received autologous stem cell transplant [8]. Data from the Norwegian cancer registry shows even further

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improvement with overall 5-year survival of 78 % for patient 70 or younger and 55 % for older patients [9]. With longer survival, supportive treatment to prevent morbidity becomes increasingly important.

1.3. Morbidity in multiple myeloma patients

MM bone disease severely affects morbidity in MM patients. A Danish registry study found MM patients had 44 % risk of ending on disability pension compared to 5 % in controls. Even compared to more aggressive hematological cancers like Diffuse Large B cell Lymphoma and Acute Myeloid Leukemia the risk of disability pension was still increased 3-fold in MM [10]. The high morbidity of MM is considerably increased due to bone disease. In a quality-of-life study 50 % of MM patients complained of pain, of which half considered it of severe degree [11]. Other common complaints in MM patients were trouble with role functioning, physical role functioning and fatigue, which was found in 80 %, 54 % and 67 % of patients respectively [11]. In addition, effects of MM bone disease include vertebral collapse, which can lead to paresis or paralysis due to nerve- or spinal-cord compression [3].

1.4. Myeloma bone disease

In healthy people bone remodeling includes resorption of old bone followed by replacement with new bone matrix in the form of osteoid. The involved cells in this process are osteoblasts, which are specialized bone anabolic cells [12,13], and osteoclasts that resorb bone by attaching to the bone surface and secreting hydrogen ions and enzymes [14]. Both osteoclasts and osteoblasts are essential for bone remodeling and for upholding calcium homeostasis [15]. Additionally, osteocytes initiate bone remodeling through endocrine and mechanic sensors [16,17], and bone lining cells cover the bone surface [18].

MM disrupts normal bone homeostasis in several ways (see Fig. 1). An important mechanism is disruption of the balance between receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG) by increasing the RANKL/OPG ratio. RANKL is pivotal as osteoclast differentiation is supported by RANK/RANKL interaction, [19] and RANKL is inhibited by OPG. Co-cultures of MM and stromal cells have been found to decrease OPG production and increase RANKL [20,21].

MM cells can interact with the microenvironment, which may increase risk of MM relapse as well as drug resistance [22]. MM interaction with stromal cells have further been shown to increase IL-6, which can interrupt the Wingless type (Wnt) pathway increasing MM cell survival and activating osteoclast formation [23,24]. Another antagonist of the Wnt pathway is the secreted Frizzled-related protein, which has been found to be highly secreted in patients with advanced bone disease [25]. MM cells can produce a number of molecules reducing osteoblasts function e.g. dickkopff-1 as well as sclerostin [26,27] Finally, Runt-related transcription factor 2 (Runx2), which leads mesenchymal stems cell in the direction of differentiation to osteoblast, is possibly inhibited by MM cells [28,29].

Overall, MM severely affects bone health and increase risk of skeletal related events (SRE) (spinal cord compression, pathologic fracture, radiation to bone, or surgery to bone) as well as osteolytic lesions and hypercalcemia [3]. These symptoms can by itself indicate need for initiation of myeloma treatment (CRAB criteria) [30].

1.5. Imaging/monitoring

CT imaging (whole body low dose CT, WBLDCT) is the gold standard for myeloma bone imaging, as it has shown superiority both retrospectively and prospectively to conventional radiography for detecting osteolytic lesions [31–34]. Conventional radiography was previously used for staging [35], but is no longer recommended today [36–38]. Conventional radiography have limited sensitivity, and large amounts of bone can be destroyed without lesions being visible on images [39]. Several of the studies we will discuss are based on conventional radiology, and may underestimate the extent of skeletal related events in patients compared to the studies based on WBLDCT.

MRI and PET can supplement WBLDCT and can be relevant for prognosis. MRI examines the tissues polarity in a magnetic field taking advantage of water being a polarized molecule, unlike fat. It can thus estimate the cellular infiltration of a normally fatty bone marrow. Unlike other modalities MRI investigation can be done without exposure to radiation [40] which can be relevant especially in younger patients.

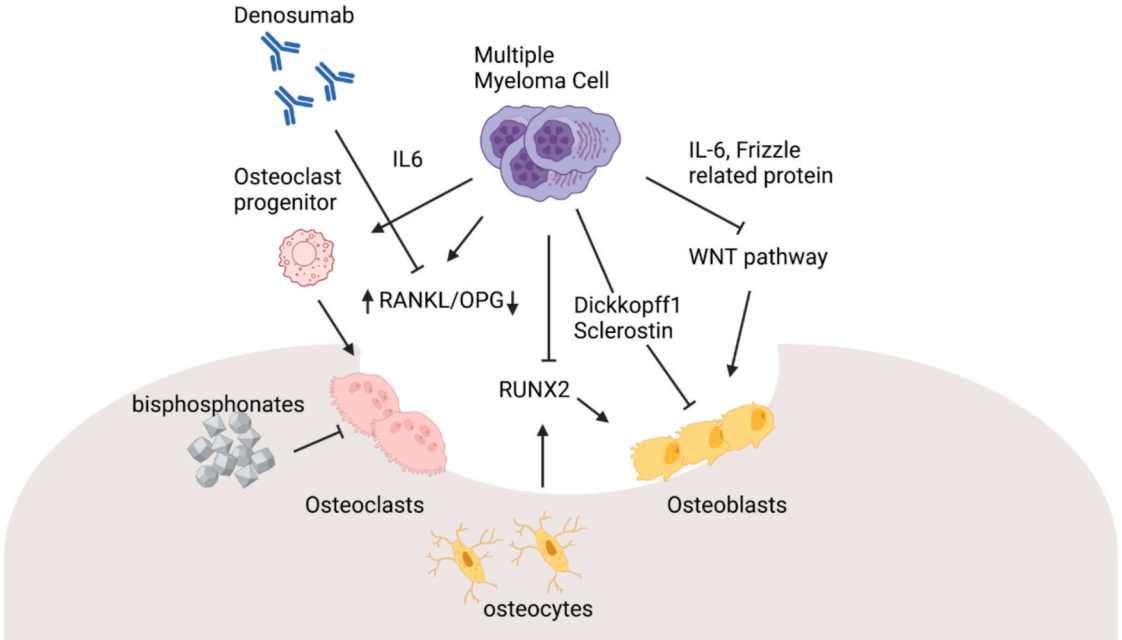

Fig. 1. Multiple Myeloma can increase bone degradation through a number of pathways including increasing RANK/OPG ratio and IL6 which increases osteoclast recruitment and maturation as well as inhibiting osteoblast directly (dickkopff1, sclerostin) or through inhibition of pathways essential for osteoblast function and maturation (WNT pathway, RUNX2). Denosumab Inhibit RANKL hereby suppressing osteoclast formation. Bisphosphonates are embedded into the bone and released to osteoclasts during bone absorption.

PET-CT combines CT investigation with a radioactive tracer (usually 18F-fluorodeoxyglucose) and is especially useful to show extramedullary disease. Additionally focal lesion found by PET-CT have been shown to have predictive value with more than 3 PET-positive focal lesions predicting inferior OS and PFS, and normalization on PET after treatment indicating better PFS and OS [40,41].

MRI can also define treatment demanding myeloma according to current guidelines with >1 focal lesions [42] Still the WBLDCT is primarily used for its availability and high accuracy and specificity [40].

For newly diagnosed MM patients the presence of abnormal MRI patterns or SRE have been found to predict shorter OS compared to patients who do not have these findings [43].

2. Topics for discussion

An overview of discussed studies can be seen in Table 1. An overview of recommendations from International Myeloma Working group (IMWG), European Society for Medical Oncology-European Hematology Association (ESMO-EHA) and National Comprehensive Cancer Network (NCCN) related to SMM, MM, relapse of MM and treatment period can be seen in Table 2.

2.1. Smouldering MM

Bisphosphonates for smouldering MM (SMM) have been investigated with both pamidronate [44,45] and ZOL [46], but not with denosumab. The two pamidronate studies included 177 and 90 patients with untreated SMM. In these studies, patients with pamidronate treatment had significantly less SRE at progression to active myeloma (22/56 vs. 40/55P = 0.009), (4/10 vs. 9/11, p < 0.01), however no difference in time to progression was observed. Regarding ZOL, a 2008 study by Musto *et. al.* [46] prospectively investigated 163 SMM patients who were randomized to receive either monthly ZOL for one year (n = 81) or no ZOL (n = 82). Patients were followed for a median of 65 months. Imaging was performed with conventional X-rays every year or if deemed clinically indicated. While ZOL did not delay progression to symptomatic myeloma, patients who had received ZOL had significantly lower incidence of SRE at progression (55.5 % vs 78.3 % p = 0.041). While this was found to be significant, the difference was small (29 vs. 20 patients) and the overall number and nature of lesions was not described. The 2008 Musto *et.al.* study was ended early for safety concerns as reports of MRONJ in MM treated with ZOL began to emerge at the time [46]. Furthermore, these studies were performed before the introduction of the 2014 SLiM CRAB criteria [42] and likely a number of patients designated SMM would have been treatment demanding by these current criteria and would hence receive treatment.

The overall consensus has so far been that SMM should not be treated with bone protective treatment unless there are concomitant osteoporosis in which case osteoporosis guidelines with treatment every six months are recommended [30]. Patients with SMM who are being treated with regimens containing dexamethasone, should be evaluated for osteoporosis before and during treatment.

2.2. Active MM

The myeloma IX study investigated different MM treatment regimens, as well as monthly ZOL and clodronate, on 1960 newly diagnosed treatment demanding MM patients.

The induction regimens were: cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD) versus cyclophosphamide, thalidomide, and dexamethasone (CTD; intensive) or melphalan and prednisolone versus attenuated oral CTD (CTDa; nonintensive) In the intensive arms patients were planned for ASCT which 747 received. Patients were further randomized to either receive thalidomide or no anti-myeloma maintenance [47]. While relevant at the time, the induction and maintenance were suboptimal compared to the current SOC which often include combinations of bortezomib, lenalidomide, daratumumab and lenalidomide [48,49].

The study randomized all patients between ZOL and clodronate, and found that monthly ZOL reduced risk of death (HR = 0.84, P = 0.012) In the Intention to treat group the difference in overall survival was 5.5 months and difference in progression free survival 2 months. ZOL further decreased risk of SRE compared to clodronate, regardless of whether bone disease was found at baseline radiological examination of the skeleton. The hazard ratio for risk of SRE with or without bone disease at baseline was HR = 0.77, P = 0.0038) and HR = 0.53; P = 0.0068, respectively [50]. Given that clodronate is known to have bone protective effects in MM [51], the effects of ZOL is likely to be larger compared to no bone protective treatment, overall underlining effects of ZOL even in MM patients with no bone disease at diagnosis. However, radiological evaluation in this study was performed on X-rays, not CT. As CT is a more sensitive modality it is uncertain whether these findings can be extrapolated to MM patients with no bone disease at baseline on CT. Though acknowledging this weakness, it is still recommended to treat all symptomatic myeloma patients from diagnosis regardless of bone status [30]. However, it remains unclear if the intensity of bisphosphonate treatment in patients with no bone disease on CT should be reduced.

The importance of early ZOL initiation was investigated in a retrospective study by Wu *et. al.* This study compared 126 MM patients who had ZOL treatment initiated within 60 days of diagnosing symptomatic MM compared to 186 patients who had not [52].The follow up period was two years, and the endpoint was time to first SRE, number of SRE, and pathological fractures. MM patients with initiation of ZOL within 60 days were found to have both longer time to first SRE (SRE free rate 74.6 % vs. 56.5 % after 2 years, p = 0.005), fewer overall SRE, and fewer pathological fractures (mean SRE 0.39 vs. 0.72p = 0.002). It must be noted that this was a non-randomized retrospective study. The patients who received early ZOL had higher age (62.1 vs. 60.1P = 0.02), higher average myeloma stage, and higher average number of osteolytic lesions at diagnosis (7.1 vs. 4.8P = 0.0006) compared to the patients without early ZOL treatment. On the other hand, osteopenia was more common in the group with ZOL treatment later than 60 days after diagnosis (11.9 % vs. 15.6 % P = 0.03) [52].

2.3. Type of treatment: Bisphosphonates/denosumab

Bisphosphonates function by attaching to the hydroxyapatite binding sites in the skeleton. Osteoclasts are exposed to bisphosphonates as they absorb bone. Bisphosponates can inhibit osteoclast absorption through an number of mechanisms [53]. In MM, pamidronate [54], clodronate [55], and zoledronate (ZOL) [47,56,57] have been investigated [58]. Bisphosphonates have been found to decrease bone pain and pathological fractures, vertebral collapse as well as other skeletal related events [58], and the bisphosphonates clodronate and pamidronate have shown efficacy in randomized trials compared to placebo [54,55]. Randomized studies on ZOL have shown superior efficacy compared to other bisphosphonates and has even demonstrated increased progression free survival and overall survival [47,56,57]. ZOL is furthermore superior to pamidronate for decreasing malignant hypercalcemia [59]. ZOL have been found to have a long half-life in bones with bisphosphonate still being present in bones 10 years after treatment [60]. Yearly administrations have been found sufficient in some nonmalignant diseases [61].

RANK/RANKL interaction is essential for function and development of osteoclasts. Denosumab is a humanized RANKL antibody inhibiting this process [62]). In a large landmark study by Raje *et. al.* in 2018 [63] long term treatment with ZOL was compared to denosumab. The phase 3 study was double blinded, randomized and included 1718 newly diagnosed MM patients with at least 1 lytic or focal lesion [63]. Included patients were stratified by first-line myeloma treatment novel-based (IMiDs, proteasome inhibitors) yes/no, intent to undergo autologous stem cell transplant, and ISS disease stage, as well as whether they had

Table 1
Overview of the studies discussed in the paper in the order they are discussed with title, authors study type, year of publication, number of participants as well treatment, strategy for monitoring, follow up period and major findings.

Title:	Author	Year	Participants	Study type	Groups (n)	Treatment	Follow up	Monitoring strategy	Major findings
Pamidronate versus observation in asymptomatic myeloma: final results with long-term follow-up of a randomized study. Leuk Lymphoma. 2011;52(5) :771–5.	D'Arena *et. al.*	2011	Asymptomatic MM (n = 177)	Prospective, randomized	Pamidronate (n = 89), observation (n = 88)	Pamidronate 60–90 mg/ month for one year	minimum 5 years	Conventional radiography 1/year or if clinically indicated.	SRE 72.7 % in observation group at time of progession vs. 39.2 % in pamidronate group (P = 0.009). No significant change in OS, rate of progressions, and no difference in side effects.
A multicenter, randomized clinical trial comparing zoledronic acid versus observation in patients with asymptomatic myeloma.Cancer. 2008;113(7) :1588–95.	Musto *et. al.*	2008	Asymptomatic MM (n = 163)	Prospective, randomized	ZOL 81, observation 82	Zoledronic acid 4 mg/month for one year	Median 64.7 months	Conventional radiography 1/year or if clinically indicated. Blood samples monthly	SRE 78.3 % in observations group at time of progression vs. 55.5 % in the zoledronic acid group (P = 0.041). . No significant changes in TTP or in side effects.
Comparison of skeletal complications and treatment patterns associated with early vs. delayed zoledronic acid therapy in multiple myeloma. Clinical lymphoma, myeloma & leukemia. 2011;11 (4):326–35.	Wu *et. al.*	2011	Symptomatic MM (n = 312)	Retrospective	Initiation of ZOL within of 60 days of diagnosis n = 126 vs later than 60 days after diagnosis n = 186	Zolodronic acid	2 years	Decided by clinicians	Pt initiated with ZOL within 60 days had less SRE (0.39 vs 0.72P = 0.002), lower rate of first-line radiation therapy (4.0 % vs. 10.2 %; P = 0.0422 and less pathologiocal fractures (0.15 vs 0.27, P = 0.03).
Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. The New England journal of medicine. 1996;334 (8):488–93.	Berenson *et. al.*	1998	Durie-Salmon grade III MM (n = 392) with osteolysis	Prospective, randomized	Pamidronate (n = 198), placebo (n = 179)	Pamidrnate 90 mg monthly	21 months	Monthly visits, conventional radiography at baseline + after 6,9,12,15 and 21 cycles	Pamidronate decreased SRE/ year (1.3 vs 2.2, P = 0.008), decreased time to first SRE (P = 0.001), time to first pathological fracture (P = 0.006), and significantly decreased pain. No significant changes in side effects or OS.
Randomised, placebo-controlled multicentre trial of clodronate in multiple myeloma. Finnish Leukaemia Group. Lancet. 1992;340 (8827):1049–52.	Lahtinen *et. al.*	1992	Treatment demanding MM (n = 350)	Prospective, randomized	Clodronate (n = 168), placebo (n = 168)	Clodronate 2.4 g/day or placebo	24 months	–	Decreased progression of osteolytic bone disease in treatment group (24 % vs 12 % p = 0.026), increased freedom from pain 54 % vs. 44 % (P < 0.01).

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Table 1 (*continued*)

Title:	Author	Year	Participants	Study type	Groups (n)	Treatment	Follow up	Monitoring strategy	Major findings
									No significant difference in side effects in both groups.
VTD consolidation, without bisphosphonates, reduces bone resorption and is associated with a very low incidence of skeletal-related events in myeloma patients post ASCT. Leukemia. 2014;28 (4):928–34.	Terpos *et. al.*	2014	MM patients in remission after first ASCT (n = 42)	Prospective single group	Single group	Bortezomib + thalidomide 4 + 4 cycles No bisphosphonate treatment in period.	12 months	Conventional radiography baseline and 12 months	Only one new case of SRE in study period, despite no bisphosphonate treatment. Side effects with periferal neuropathy in 25/42 patients 15/42 grade II/III.
Consolidation therapy with the combination of bortezomib and lenalidomide (VR) without dexamethasone in multiple myeloma patients after transplant: Effects on survival and bone outcomes in the absence of bisphosphonates. American journal of hematology. 2019;94(4):400–7.	Terpos *et. al.*	2019	MM patients in PR or better after first ASCT (n = 59)	Prospective single group	Single group	Bortezomib + lenalidomide 4 cycles No bisphosphonate treatment in period.	Median 62 months	Conventional radiography baseline and end of treatment and if clinically indicated	Only one SRE observed after 62 median months of observation without bisphosphonate.
Effects of induction and maintenance plus long-term bisphosphonates on bone disease in patients with multiple myeloma: the Medical Research Council Myeloma IX Trial. BLOOD. 2012;119:5374–83. /First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX) : a randomised controlled trial. Lancet 2010; 376: 1989–99	Morgan *et. al.*	2012 / 2010	Newly diagnosed MM patients (n = 1960	Prospective, randomized	Clodronate vs ZOL in MP/CTDa/CVAD/CTD myeloma treated patients	Monthly Clodronate vs ZOL at least until disease progression	–	SRE data collected every 3 month, conventional radiology	For treatment for at least 2 years ZOL improved OS and time to disease progression and incidence of SRE (p = 0.01) compared to clodronate. After first disease progression OS remained significantly improved in the ZOL group HR = 0.58 (P = 0.03). HR for OS remained in favor of ZOL 1, 2, 3, and 4 years after initial randomization. More cases of MRONJ in ZOL group (4.1 % vs 0 %).
Prospective observational study of treatment pattern, effectiveness and safety of zoledronic acid therapy beyond 24 months in patients with multiple myeloma or bone metastases from solid tumors. Supportive care in	Wyngaert *et. al.*	2013	Patients with MM (n = 93) or other cancer with solid bone metastases (n = 205) who had recived ZOL at least 2 years	Prospective, observational	Continued vs. discontinued zoledronic acid treatment	Zoledronic acid 3–4 mg/month	18 months	Pain (VAS) every 3 months, conventional radiography as clinicaly indicated, creatinine before each treatment	Overall persistent treatment with ZOL after two years showed lower rate of SRE (HR 0.42P = 0.01) but not in MM (HR 1.02P = 0.9). Overall MRONJ incidence at 6 %.

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Table 1 (*continued*)

Title:	Author	Year	Participants	Study type	Groups (n)	Treatment	Follow up	Monitoring strategy	Major findings
cancer: official journal of the Multinational Association of Supportive Care in Cancer. 2013;21 (12):3483–90.									
Prolonged Use of Zoledronic Acid (4 Years) Did Not Improve Outcome in Multiple Myeloma Patients. Clinical Lymphoma, Myeloma & Leukemia,. 2017;17 (4):207–10.	Aviles *et. al.*	2017	Symptomatic MM (newly diagnosed), candidates for ASCT, ISS III	Prospective, randomized	ZOL for two years (n = 86) vs. ZOL for four years (n = 84).	4 mg/month	Up to 4 years (median 40.4 months)	Oral examination and conventional radiography every 6 months	Patients treated with ZOL up to 4 years had significantly fewer SRE 21 % vs 41 % P = 0.01. No significant changes in PFS and OS between the two groups.No cases of MRONJ was observed.
In multiple myeloma, monthly treatment with zoledronic acid beyond two years offers sustained protection against progressive bone disease. Blood Cancer Journal. 2024;14(1):65.	Lund *et. al.*	2024	Symptomatic MM patients treated with ZOL for 2 years	Prospective, randomized	Observation after ZOL two (n = 89) years or continued ZOL up to four years (n = 94)	4 mg/month	Up to 4 years	WBLDCT and oral examinations every 6 months, QoL questionnaire every 3 months, monthly blood samples	Patients treated with ZOL up to 4 years had significantly fewer SRE HR 0.40, P = 0.021). No significant diffence in OS, or side effects were observed
Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. Lancet Oncol. 2018;19(3):370–81.	Raje *et. al.*	2018	Newly diagnosed MM with osteolytic lesions (n = 1718)	Prospective, randomized	Denosumab (n = 859) vs. ZOL (n = 859)	Denosumab 120 mg or ZOL 4 mg every 4 weeks	Median 17.3 (ZOL), 17.8 (denosumab) months	Conventional radiography every 12 weeks, Oral examination every 12 months	Denosumab was non-inferior to ZOL for preventing SRE (HR 0.98, 95 % CI 0.85–1.14). MRONJ not significantly different (4 % denosumab vs 3 % ZOL P = 0.147). Denosumab was surperior to ZOL for time to fist SRE after 15 months (HR 0.66, P = 0.039) (POSTHOC analysis).
Zoledronic acid as compared with observation in multiple myeloma patients at biochemical relapse: results of the randomized AZABACHE Spanish trial. Haematologica. 2015;100 (9):1207–13.	Garcia-Sanz *et. al.*	2015	MM patients with asymptomatic biochemical relapse	Prospective, randomized	ZOL (n = 51) observation (n = 49)	ZOL 4 mg/4 weeks, up to 12 doses	Median 38 months	Every 4 weeks for disease response, adverse events and CRAB criteria. Imaging strategy not described	Fewer SRE in treatment group (2 vs 14P < 0.001). No significant difference in time to next treatment or OS.
A different schedule of zoledronic acid can reduce the risk of the osteonecrosis of the jaw in patients with multiple myeloma. Leukemia. 2007;21 (7):1545–8.	Corso *et. al.*	2007	MM patientens treated with ZOL or pamidronate for 1 year	Retrospective	Monthly (n = 51) vs. monthly the first year followed by treatment every 3 months (n = 55)	Pamidronate 90 mg, ZOL 4 mg	Mean 26 months	CT of the jaw if suspicion of MRONJ	No difference in risk of SRE between groups. Lower HR of MRONJ of 0.12 (6vs1cases) for 12 week interval (P = 0.049)

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Table 1 (*continued*)

Title:	Author	Year	Participants	Study type	Groups (n)	Treatment	Follow up	Monitoring strategy	Major findings
Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases. JAMA. 2017;03 48–58.	Himelstein *et. al.*	2017	Patients with breast (n = 855), prostate (n = 689) or MM (n = 278) with at least one site of bone involvement (1822)	Prospective randomized	ZOL every 4 (n = 991) vs. every 12 (n = 911) weeks	ZOL 4 mg	2 years	CTX baseline + 12 week intervals, Skeletal event form collected every 4 weeks. No type of imaging specified.	Percentage of cases with at least 1 SRE within two years were non-inferior in treatment every 12 weeks. No significant different in mean pain score. CTX bone turnover marker was higher in 12 week group
Bone Marker-Directed Dosing of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Multiple Myeloma: Results of the Z-MARK Study. Clinical cancer research: an official journal of the American Association for Cancer Research. 2016;22 [6]:1378–84.	Raje *et. al.*	2016	MM patients with 1–2 years ZOL-treatment (n = 121)	Prospective non-randomized	ZOL every 4 or 12 weeks depending on uNTX and disease status	ZOL 4 mg	2 years	SRE asseses at baseline and every 12 week (bone survey), uNTX every 12 weeks	Overall MRONJ incidence rate 3.3 % 12/121 patients experienced SRE within two years with a 4 or 12 week regimen based on uNTX and disease status

previous skeletal-related events [63]. In this study denosumab was found non-inferior to ZOL relating to time to first SRE. They also found a higher PFS in patients treated with denosumab (HR 0·82 (95 % CI 0·68–0·99, P = 0.036) for a median increased PFS of 10.7 months although OS showed no difference [63]. A secondary analysis they compared findings of new SRE in ZOL and denosumab group using patients treated for 15 months as a new baseline and following patients up until 42 months. In this sub-analysis they found lower rate of SRE (HR 0.66 95 % CI 0.44–0.98, P = 0.039) for denosumab, [63]. A later analysis of this phase 3 study was performed by Terpos *et. al.* in a 2021 paper to identify which factors contributed to the longer PFS of denosumab and whether the benefit was larger in specific subgroups [64]. The analysis was performed by age (<70 years vs older), treatment, intent to have ASCT, and kidney function (<60 mL/min). The study found better PFS of denosumab in patients intended for ASCT with a hazard rate of 0.65 [0.47–0.90]. The study also found increases in PFS in patients younger than 70 and with better kidney function of at least 60 mL/min while no PFS was found in patients not intended for ASCT, older than 70 or with kidney function (<60 mL/min). This study demonstrates the viability of denosumab for long term treatment and suggest that denosumab might be favorable to ZOL especially in fitter subgroups of MM patients.

A *meta*-analysis later found denosumab non-inferior for preventing spinal cord compression [65]. Non-inferiority of denosumab to ZOL has also been seen in earlier small studies including other cancers. These studies had similar side effect profile to ZOL apart from not being nephrotoxic [65,66]. Overall, denosumab has been less studied than ZOL, and it has overall been found non-inferior for time to first SRE and with similar side effects to ZOL except for renal insufficiency. While PFS may be increased by denosumab compared to ZOL, no increase in OS has so far been shown [63]. Denosumab is currently recommended for MM over ZOL in case of renal dysfunction [30].

2.4. Side effects to bone protective treatments

Bisphosphonates have several significant side effects. The most notable is treatment-related osteonecrosis of the jaw (MRONJ), a side effect which can cause part of the jaw to dissolve, leading to significant pain and disability [67]. Studies demonstrate that MRONJ is observed in 2.6–4 % of MM patients treated with bisphosphonates [56,57]. Increased risk of MRONJ is seen with prolonged treatment duration, increasing potency of bisphosphonates, as well as in patients with poor dental health status before initiation of treatment, and in patients undergoing tooth extractions after initiation of bisphosphonate treatment [68,69]. Denosumab may also cause MRONJ and does so at a level comparable to ZOL [63].

A number of precautions have been identified to decrease risk of MRONJ in bisphosphonate treated patients. Baseline dental inspections and necessary dental procedures being done before ZOL initiation, waiting 6–8 weeks after procedures to initiate ZOL as well as practicing less invasive techniques when possible was investigated in MM patients. The study compared occurrence of MRONJ before or after preventive measures were implemented. An almost fourfold reduction was seen (26.3 % vs 6.7 % P = 0.002) [70]). A related study in solid cancers (mostly breast) with early dental inspections showed a smaller but similar effect [71]. A 2008 retrospective study compared patients who received prophylactic antibiotics before oral surgeries to patients that did not, and found that antibiotics had significantly protective effect [72]. Pausing Zoledronic acid for oral surgery (drug holiday) has later been investigated in a review and a randomized study, but this was not found to decrease risk of MRONJ [73,74],

As most of the studies are made with bisphosphonates (mostly ZOL),

Table 2
Recommendations from International Myeloma Working group (IMWG), European Hematology Association/European Society for Medical Oncology (EHA/ESMO) and National Comprehensive Cancer Network (NCCN) for bone protective treatment for smoldering myeloma, treatment demanding myeloma, relapse of myeloma and length of treatment. The recommendation are generally similar.

	IMWG 2021	ESMO-EHA 2021	NCCN 2025
Smouldering Myeloma	For patients with smouldering multiple myeloma, monoclonal gammopathy of undetermined significance, or solitary plasmacytoma, bisphosphonates are recommended only if there is coexistence of osteoporosis; patients with monoclonal gammopathy of undetermined significance and smouldering multiple myeloma should be monitored and treated according to osteoporosis guidelines	In smouldering MM (SMM), bisphosphonates or denosumab are not recommended; in case of osteoporosis in monoclonal gammopathy of undetermined significance (MGUS) or SMM, antiresorptive agents have to be used according to osteoporosis guidelines.	Observe at 3- to 6-mo intervals
Treatment demanding Myeloma	Bisphosphonates (namely, zoledronic acid or pamidronic acid) should be administered to all patients with active multiple myeloma, regardless of the presence (grade A recommendation) or absence (grade B recommendation, for zoledronic acid only) of multiple myeloma-related bone disease on imaging studies. Denosumab is recommended for the treatment of newly diagnosed multiple myeloma	All myeloma patients with osteolytic disease at diagnosis should be treated with antiresorptive agents, i.e. zoledronic acid [I, A] or denosumab [I, A], in addition to specific anti-myeloma therapy Patients without bone disease, assessed by conventional radiography, should also receive bone-targeted agents, but their advantage is not clear for patients with no bone involvement on whole-body low-dose computed tomography (WBLD-CT) or positron emission tomography-computed tomography (PET-CT) ..	All patients receiving primary myeloma therapy should be given bone-targeting treatment (bisphosphonates or denosumab)
Relapsed Multiple Myeloma	If discontinued, zoledronic acid or pamidronic acid should be reinitiated at the time of biochemical relapse to reduce the risk of a new bone event at clinical relapse (grade B recommendation).	At relapse, zoledronic acid has to be reinitiated	
Treatment period of bone protective treatment	Zoledronic acid should be administered monthly for at least 12 months (grade B recommendation). If, after 12 months, a very good partial response or better is achieved, the treating physician can consider decreasing the dosing frequency to every 3 months or, on the basis of osteoporosis recommendations, to every 6 months or yearly, or even zoledronic acid discontinuation.	Zoledronic acid should be given for more than two years only in patients who have not achieved a partial response (PR) after initial therapy. For patients who have achieved CR or very good partial response (VGPR), 12–24 months of therapy with zoledronic acid is adequate	Continue bone-targeting treatment (bisphosphonates or denosumabc) for up to 2 years. The frequency of dosing (monthly vs. every 3 months) would depend on the individual patient criteria, response to therapy, and agent used. Continuing beyond 2 years should be based on clinical judgment.

(1) IMWG.
(2) EHA-ESMO.
(3) NCCN.
1. Evangelos Terpos Prof EZM, Suzanne Lentzsch Prof, Matthew T Drake MD, Ramón García-Sanz MD, Niels Abildgaard Prof, et al. Treatment of multiple myeloma-related bone disease: recommendations from the Bone Working Group of the International Myeloma Working Group. Lancet Oncol. 2021;Volume 22 (3):e119-e30.
2. Dimopoulos MA, Moreau P, Terpos E, Mateos MV, Zweegman S, Cook G, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.
3. NCCN Guidelines Version 1 2025 https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1445.

it is uncertain whether the effect of these precautions is similar in patients treated with denosumab. Patients treated with denosumab have been found at risk of accelerated bone degradation and fractures upon pausing or ending treatment [75]. This has been seen in metastatic breast cancer, osteoarthritis, osteoporosis, as well as in patients who received glucocorticoids and denosumab due to kidney transplant, but the effect has not yet been investigated specifically for MM [75,76]. As RANKL is found on immune cells and is produced by activated T-cells, it has been suggested that denosumab could affect the immune system [77]. However, this has not been seen in the non-inferiority study, which found similar rates of infections and neutropenia between ZOL and denosumab groups [63].

An important side effect to bisphosphonates is nephrotoxicity. A common complication of MM is decreased kidney function, and bisphosphonates should be avoided in MM patients with considerably decreased kidney function (eGFR < 30). Additionally, ZOL can negatively affect kidney function in MM patients leading to the need for dose reduction, pause in treatment or termination of treatment. In these cases, denosumab is often recommended [62,63].

Special care must be taken when deciding whether to end denosumab treatment, as it has been shown to have a rebound phenomenon with increased risk of SRE upon discontinuation, especially vertebral fractures and increases in catabolic bone markers [76]. While some studies suggest that this risk can be somewhat mitigated by bisphosphonate treatment at the end of denosumab treatment, the evidence is not strong and is generated from other diseases than MM [78–80], thus more data is needed regarding this question.

2.5. Length of treatment

Currently, the 2021 recommendations from the International Myeloma Working Group, suggest that for patient achieving at least very good partial regression (VGPR) frequency of ZOL doses could be reduced or even terminated after one year of treatment [30]. Logically, sufficient suppression of MM should stop development of MM bone disease, and with development in effectiveness of MM treatment the importance of ZOL may be lowered over time. It has also been reported that most cases of SRE occur early in MM disease, which could indicate less value of long-term treatment [63,81].

The original studies showing effects of bisphosphonates (clodronate, pamidronate) had intervals of four weeks and a follow up 21 and 24 months, respectively [51,54,55]. As described earlier, the risk of side effects has been found to increase with treatment length and potency [70].

Two studies have shown low rates of SRE without any bisphosphonates or bone protective treatment at all. [82,83]. In these studies patients with at least partial regression (PR) after autologous stem cell transplant (ASCT) were followed by consolidation with either bortezomib and lenalidomide (n = 59) or VTD (n = 42), [82,83]. These studies had high response rates including 36 % and 51 % achieving stringent complete response (sCR). The treatments further resulted in suppression of circulating CTX possibly indicating reduced bone catabolism. For these two studies, it must however be noted that the number of patients were of limited size (59and42patients), the studies were non-randomized and SRE evaluations were done with traditional radiology with limited sensitivity.

The Myeloma IX trial was the first randomized trial that investigated long term treatment with ZOL for MM. In addition to analysis of the whole patient group of 1960 patients described earlier, a sub analysis on the 582 MM patients who received at least two years of bisphosphonate treatment was performed [50]. [50,84]. This study showed increased overall survival (OS) (median not reached HR 0.60, P = 0.02) from randomization and significant reduction in incidence of SRE in ZOL compared to clodronate (P = 0.01) as well as OS benefit after first disease progression (median 34 vs 27 months HR 0.58, P = 0.03) [50] That bisphosphonates can increase PFS and/or overall survival in phase 3 studies may not be solely due to the bone protective properties as increased apoptosis of myeloma cells lines has been demonstrated in vitro [85,86].

A prospective observational study by Wyngaert *et. al*. was published in 2013 [87]. This study followed 298 patients with either MM (n = 93) or solid tumor bone metastases (n = 205) who had received 24 months of ZOL treatment, and patients were observed for an additional 18 months for whether ZOL treatment was continued and whether patients had new SRE. The study was observational, and imaging was conducted as conventional x-ray when clinically indicated. It showed that patients who continued ZOL in the observation period had lower risk of SRE (Hazard ratio 0.42, P = 0.01), but could not show this specifically for the smaller MM subgroup (Hazard ratio 1.08, p = 0.9). Due to the observational nature, strict conclusions cannot be drawn. The study does not describe baseline characteristics of the different groups.

Avilés *et. al.* (2017) [88] investigated if ZOL treatment for four years compared to two years increased progression free survival (PFS) or OS, as well as safety of prolonged ZOL treatment. A secondary endpoint was the difference in SRE rate. The population consisted of 170 previously untreated, but symptomatic, ISS grade III MM patients randomized to two (n = 86) or four (n = 84) years of monthly ZOL treatment. Patients underwent x-ray examination and oral examination at inclusion and every 6 months of study. OS after 5 years was compared between the two groups and found to not be significantly different with 72 % (95 % CI: 62–78 %) in the four-year group vs 68 % (95 % CI:60–75 %) in the two-year group. The study observed significantly fewer cases of SRE in the group treated for up to four years, with a considerable reduction in SRE by 20 percentage points (41 % vs. 21 %, p < 0.01). Side effects were described as modest with no cases of renal impairment, and surprisingly no cases of MRONJ at all.

The Magnolia study [89] followed a total of 193 of symptomatic MM patients (any ISS) who were randomized to either stop ZOL after two years of initial treatment or continue for an additional two years. Both groups were followed by WBLDCT imaging every 6 months. The study showed a significantly reduced rate of progression in bone disease by 22 percentage points from 43 % till 21 % in the treatment group (HR 0.40, p = 0.021). A non-significantly higher number of MRONJ cases was seen in the treatment group (6 vs. 1, P = 0.12), but only two cases of symptomatic MRONJ grade 2 were seen. There was no significant difference in the number of patients with creatinine increase (p = 0.08) or change in OS. This study also included QoL data, in which pain was found to be significantly increased in the months before SRE, and pain was found near-significantly increased in the observation group overall [89].

Overall, studies including myeloma IX [50] data and the landmark denosumab study [63] and the studies randomizing ZOL to two or four years treatment, demonstrated limited side effects of long term treatment. In the randomized studies significant reductions in occurrence of SRE were observed with continued treatment with ZOL beyond two years [88,89].

2.6. Re-initiation of treatment at relapse

Reinitiating bone protective treatment in cases of relapse makes intuitive sense, especially in the case of progressive bone disease, however the studies in this area are limited. In the Spanish AZABACHE trial [90] 100 MM patients were randomized to either initiate ZOL or observation at biochemical relapse. In both groups no anti myeloma therapy was initiated; the median follow up was 38 months. The group randomized to initiating treatment at biochemical relapse had significantly fewer SREs (2 vs. 14, P < 0.001), while the overall time to next therapy was not increased. Of the 100 patients in study, one patient in the treatment group experienced MRONJ. There were no significant differences in other adverse events in the study. This study suggests that treatment with ZOL should be re-initiated at biochemical relapse. It must however be noted that in the AZABACHE trial anti-myeloma treatment was not initiated at biochemical relapse but at symptomatic progression. This may affect the results compared to current standard of care as anti-myeloma treatment at relapse could lessen risk of SRE and thus lessen importance of initiating ZOL. It should also be mentioned that patients with frequent relapses would thus be on bisphosphonate treatment continuously if ZOL is initiated at each relapse. Considering this, a case-by-case judgement should be performed, aiming to balance long-term toxicity with the need for bone protective treatment, and the extent of the patients' bone disease should be an important part of this decision.

It is worth noting that most patients in the AZABACHE study (exact proportions are not described) probably had received long term treatment with ZOL before inclusion, and 24 months bisphosphonate treatment for new MM patients was the recommended treatment in Spain at the time [90]. This indicates that the benefit is not likely to be limited to patients without previous long-term bisphosphonates.

The length of treatment in relapse is not well studied. The AZABACHE trial [90] used at total of 12 ZOL doses with one dose given every 4 weeks, which could be a suggestion. With time to progression often decreasing with each line of treatment, initiation at every relapse does risk some patients receiving ZOL for the rest of their lives which would result in large overall exposure with additional risk of side effects. The value of treatment with ZOL beyond first relapse is currently not known, and the value in relapsing patients specifically without increasing bone disease is not known.

2.7. Treatment interval

As the risk of side effects increase with higher cumulative doses, an

important question is whether longer spaced regimens could retain bone protective effect with diminished side effects. In breast as well as lung cancer patients with bone metastases, administration of ZOL with 12-week intervals have been found non-inferior to 4-week intervals, [91–93].

In 2007 Corso *et. al.* retrospectively followed 106 MM patients who were treated with ZOL or pamidronate [94]. The treatment schedule was monthly the first year and then either continued monthly treatment as long as tolerated (n = 51) or treatment every three months (n = 55). The baseline characteristics were comparable. Mean observation time after the first year was 25.8 months. Baseline characteristics were not significantly different regarding gender, bone disease, bisphosphonate type, thalidomide treatment, bone status or disease status at baseline. No difference was observed in the incidence of SRE between the groups (incidence 100 person years 95 % CI 8.4–27.3 vs. 11.0–28.4). In the group with lengthened interval treatments, cox regression demonstrated a lower hazard rate of MRONJ of 0.12 (p = 0.049) [94]. However, it must be noted that this is a retrospective study, and the lower hazard rate was based on only 7 cases of MRONJ of which 1 was in the regimen with treatment every three months. While interesting, one should be careful not to overestimate the value of marginally significant findings in retrospective studies based on a small number of cases.

In a study published in 2017, Himelstein *et. al.* prospectively investigated treatment intervals in 1822 patients suffering from either MM (n = 278), bone metastatic breast cancer (n = 855) or bone metastatic prostate cancer (n = 689), who were randomized to receive ZOL every four (n = 911) or 12 (n = 911) weeks for two years [95]. The baseline or treatment status of MM patients was not described distinctly from the other cancers, but overall the groups were not significantly different. No significant differences were found for the primary endpoint of incidence of at least one SRE within two years at 29.5 % (4 weeks) vs. 28.6 % (12 weeks). This finding was non-inferior within the planned 7 % non-inferior margin. Further, this proportion did not significantly differ between treatment regimens for any specific cancer (including MM). The study further found no significant difference in reported pain, and a near significant higher risk of MRONJ in the 4-week group (2 % vs 1 % p = 0.08). The study also investigated the rate of grade 3/4 kidney dysfunction, which was not significantly different (1.2 % vs. 0.5 % P = 0.1). Although no clinical difference was found between groups, the study also used C-terminal telopeptide (CTX) as a marker of bone turnover, which was found to be higher in the longer interval treatment group, suggesting that the shorter interval treatment might have achieved stronger suppression of bone catabolism.

Another study treating MM patients with ZOL either every four or 12 weeks is the Z-MARK study published in 2016 by Raje *et. al.* The study used urinary measurements of the bone degradation marker N-telopeptide of type 1-collagen (uNTX) to determine intervals of continued ZOL treatment [96]. The patient group consisted of 121 MM patients with 52–104 weeks (1to2years) previous ZOL treatment, with patients with uNTX < 50 mmol/mmol creatine receiving ZOL every 12 weeks and patients with higher uNTX receiving treatments every four weeks. 117 MM patients started on the 12-week regimen and four patients on the 4-week regimen. During the study 38 patients were changed to 4-week regimen due to either MM progression (n = 20), increased uNTX (n = 14) or SRE (n = 4). The value of the uNTX measurements for guiding ZOL treatments is not clear, and most patients in the study received ZOL every 12 weeks. 5.8 % of patients experienced SRE within the first year [89]. The rate of MRONJ was within what we currently expect at 3.3 % [96].

Considering these studies overall, treatment regimens with ZOL every 12 weeks seems to be well tolerated and efficacious. Data from breast-, prostate-, and lung cancer [95,91–93] finds the 12-week regimen non-inferior, and the data we do have from myeloma patients support this. The studies seem to trend towards fewer side effects with a longer interval regimen, but the data are far from clear. If a 12-week regimen becomes generally accepted, then the question is when to increase treatment intervals from four to 12 weeks. In both the study by Corso *et. al.* [94] and the Z-MARK study by Raje *et. al.* [96] patients received at least one year of ZOL before lengthening intervals, while the Himelstein *et. al.* study [95] started randomization at inclusion. From a cautionary point of view the value of ZOL treatment in MM patients is well established, and until stronger data is available one might be wary of lengthening interval before the first year of treatments have been completed. A possible solution to this question may be bone markers. However, it is uncertain whether bone turnover is an indication for initiating more intensive treatment and the predictive value of bone markers in this area have yet to be shown. Treatment regimen may pose a specific problem in patients treated with denosumab. The studies comparing denosumab to ZOL compared treatment every 4 weeks. As seen earlier, 4 vs. 12-week non-inferiority studies of ZOL in MM have been conducted [95,96], but it is far from certain that this can be transferred to denosumab. In the FREEDOM studies of long term denosumab for osteoporosis, treatment every 6 months however is safely used [80] although this might not transfer directly to MM.

2.8. Changes in ZOL treatment depending on treatment response

As MM cause bone disease, one would logically assume that patients with less MM disease due to better treatment responses are at lower risk.

Data from a subgroup analysis the Myeloma IX study showed ZOL superior to clodronate for SRE in patients having achieved VGPR or less by day 100 post-transplant. For OS, ZOL was superior only in patients achieving PR or less [97]. For patients with better responses this superiority was not seen. When considering this, it is important to note that ZOL was not compared to no treatment, but to another bisphosphonate that (while inferior to ZOL) does have bone protective properties one should therefore be careful not interpret no difference in better responses as evidence that no bone protective treatment is needed in these patients. The sub-analysis was also conducted on transplant eligible MM patients only, who represent around one third of MM patients. On a contrary point of view both induction and maintenance in the study was subpar compared to current regimens with better responses and maintenance likely to reduce overall risk of SRE. The SRE investigations were made by conventional radiography, which have a lower sensitivity than WBLDCT [31–34], and as such some cases of SRE could have been missed in the study possibly affecting results.

The long term ZOL vs observation study by Aviles *et. al.* did not present treatment response data, and can therefore not answer this question [88]. In the Magnolia study by Lund *et. al.* comparing two additional years of ZOL vs. observation after two years of ZOL for newly diagnosed MM, it was reported that a number of SRE findings were seen on patients who had achieved VGPR. 16 of cases with SRE had achieved VGPR at latest treatment and 9 had achieved CR or better [89]. A subgroup analysis of patients in the study who had achieved VGPR or better during latest treatment before randomization at two years was later performed. It was found that there were still significantly higher risk of SRE in the ZOL non-treatment group (HR 0.37 with 95 % CI (0.15–0.89) P = 0.027) indicating that ZOL treatment may be warranted even in patients with deep responses to anti-myeloma treatment [98]. The Magnolia study did not have a size that allowed further sub-analyses for patients receiving autologous stem cell transplantation. It is unclear at what treatment response, if any, that ZOL can safely be withdrawn, and if there is a difference between patients undergoing autologous stem cell transplantation or not. As suggested previously, a compromise is a reduction in frequency in patients with a deep hematological response.

3. Treatment modification by monitoring

Monitoring MM patients with imaging without symptoms is currently not recommended [38].

An early study tested serial imaging with conventional x-ray over a time period of 60 weeks in 15 MM patients without significant findings,

and as such did not find serial X-rays suitable for monitoring MM [39]. A sub-study of the Magnolia study by Gundesen *et. al.* followed 267 symptomatic MM patients with preplanned WBLDCT every 3–6 months for up to four years. The study found a number (n = 21) of incidences with SRE in patients without biochemical progression, symptoms or other CRAB criteria. These findings suggest that monitoring of bone disease with WBLDCT at regular intervals could reveal early bone disease possibly allowing for early treatment [99].

An important way forward for bone protective treatment for MM would be if a marker or measurement could indicate if a patient had a need for bone protective treatment, allowing for an individualized approach. In the Z-MARK study, a strategy measuring urinary NTX was used with low rates of SREs [96]. However, it is unknown if this shows value of uNTX as a marker for treatment strategy, or if the lower treatment regimen of ZOL every 12 weeks is simply sufficient.

Other markers have been suggested including mRNA strands [100]. However, while correlation to bone disease have been seen in a number of markers, a predictive finding on individual patient level sufficient to guide treatment have yet to be shown [101].

3.1. Anti myeloma treatment effect on bone in MM

Selected anti-myeloma treatment have shown bone protective or even possible anabolic effects; especially proteasome inhibitors including bortezomib but also carfilzomib [102,103] and later the CD38 antibody daratumumab [104]. For proteasome inhibitors an increase in alkaline phosphatase has been seen and in the Vista trial, radiological signs of bone healing was seen in more than half of patients treated with bortezomib plus melphalan and prednisone [105]. However, side effects of bortezomib, especially neuropathy, can limit the possibility of long term treatment. For ixazomib, a nonrandomized study showed significantly decreased catabolic bone marker and significantly increased trabecular bone in bone biopsies after 3 months of treatment [106]. Daratumumab has been investigated in a bone marker study (REBUILD) and showed decrease of catabolic markers (CTX, TRACP 5B) and increases of the anabolic markers osteocalcin, bone-specific alkaline phosphatase and procollagen type-I N-pro-peptide though the suggesting improved bone formation with reduced osteoblast inhibition [104].

4. Conclusions

Determining the optimal initiation, length, and treatment intervals of ZOL or denosumab is no simple matter, and existing bone disease, side effects, treatments status, and bone markers must be considered.

For active MM, regardless of bone status, bone protective treatment should be initiated early after diagnosis. ZOL is superior among bisphosphonates, and denosumab, while less examined, has been found to be non-inferior to ZOL. Most cases of SRE happen within the first year and monthly treatment with ZOL is recommended, except for patients with considerably decreased kidney function (eGFR < 30) where denosumab is the preferred choice.

After the first year of treatment with monthly ZOL, prolonging interval of treatment to every 12 weeks have been tried in a number of myeloma and non-myeloma studies and have generally been found non-inferior to monthly treatment. Increasing intervals of denosumab in MM is experimental but have been tested in other cancers and osteoporosis with good results. If stopping denosumab treatment, extra care should be taken as risk of especially vertebral SRE may increase, and additional bisphosphonate treatment may be warranted. It is uncertain whether treatment safely can be stopped after one year for patients with deep remissions. Data from the Magnolia trial suggests that a response of at least VGPR is not sufficient to omit ZOL treatment without risking an increased SRE rate.

While most SREs in myeloma happen within the first year, two separate randomized studies indicate that longer term treatment may significantly reduce the risk of SRE at least up to four years with few side effects. Data beyond four years of treatment is very limited.

To minimize risk of MRONJ Dental evaluation should be performed before initiating bone protective treatment and prophylactic antibiotics should be used for oral surgeries.

A suggestion that is based on the totality of data discussed here, is to reduce ZOL treatment to every 12 weeks after at least 12 doses, and when reaching 24 months of treatment or at least VGPR, whichever comes first. Treatment can then be continued to 4 years with a frequency of 12 weeks.

In patients who are not actively receiving bone protective treatment, it should be re-initiated at disease progression, or at new SREs unless there are contraindications. Treatment of relapsing patients without bone disease can be based on individual judgement. The only relapse trial with bisphosphonates used ZOL every 4 weeks for 12 months.

While individualized bone protective treatment in MM patients based on bone markers may be tempting, the clinical value is still unproven.

CRediT authorship contribution statement

Michael Tveden Gundesen: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Fredrik Schjesvold:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Thomas Lund:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Thomas Lund reports financial support was provided by Nordic Cancer Union. Thomas Lund reports financial support was provided by Danish Cancer Society. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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