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RENAL SAFETY AND EFFICACY OF DENOSUMAB COMPARED WITH ZOLEDRONIC ACID IN CANCER-RELATED BONE DISEASE AND OSTEOPOROSIS: A NARRATIVE REVIEW

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ABSTARCT

Denosumab (DMAb), a monoclonal antibody against RANK ligand, and zoledronic acid (ZA), an intravenous bisphosphonate, are widely used to prevent skeletal-related events (SREs) in patients with bone metastases and osteoporosis. This narrative review compares the efficacy and safety of DMAb and ZA, with a particular focus on renal outcomes across malignancy- and osteoporosis-related indications. In patients switched from ZA to DMAb, bone mineral density (BMD) gains were greater; however, discontinuation of DMAb was reported rapid BMD loss and an increased risk of multiple vertebral fractures in some studies**.** Acute phase reactions were higher with ZA therapy. Several studies reported higher rates of hypocalcaemia with DMAb than ZA, while data on hypercalcaemia are heterogeneous, with some suggesting increased rates under DMAb and others favouring ZA. Hypercalcaemia can be treated with ZA. Hypocalcaemia occurred frequently in patients who are not onsupplements. Renal function deterioration was more frequently reported with ZA than with DMAb. In contrast, in long-term DMAb extension studies, fewer than 3% of participants with baseline CKD stages 2–3 progressed to stage 4 CKD. High adherence to DMAb had high eGFR levels. Renal failure, Acute kidney injury and other adverse renal events are frequent with ZA. A higher percentage of patients experienced grade3 or 4 elevations in serum creatinine with ZA than with DMAb. When comparing denosumab and zoledronic acid, the available data indicate that

denosumab provides greater benefits, particularly in terms of renal safety. As a potent anti-resorptive agent, denosumab shows fewer renal adverse events and is generally safer for patients with compromised kidney function compared to zoledronic acid.

KEYWORDS: Zoledronic Acid, Denosumab, Sres, Adverse Renal Events, Sr.Cr, Hypercalcaemia, Hypocalcaemia, Onj, Bmd Gain, Ckd, Cancers, Osteoporosis.

INTRODUCTION

Bone metastases are common in patients with advanced solid tumours. Bone loss and bone degradation are more frequently observed in them, which may be due to the side effects of treatment for cancer or directly due to bone metastasis, which leads to hypercalcemia by various mechanisms like tumor and surrounding cells, such as macrophages and endothelial cells that releases cytokines which act similarly to Parathyroid hormone (PTH) and Parathyroid hormone-related protein (PTHrP), this leads to increased secretion of RANKL by osteoblasts, which results in increased osteoclast activity and ultimately leading to resorption of bone and hypercalcemia. Other reasons of hypercalcemia includes excessive production of calcitriol, which is associated with lymphomas like Hodgkin lymphoma, increased secretion of calcium binding immunoglobulins also contributes to hypercalcemia in patients with multiple myeloma.[1] and breast cancer cause early menopause and estrogen levels to decline, leading to an increase in levels of RANK-ligand, which binds to osteoclast and results in bone resorption, Which causes a decrease in bone strength and density, eventually leading to fractures.[2] So blocking osteoclast activity and inhibiting rank ligands by bisphosphonates and rank ligand inhibitors, respectively, helps to prevent bone resorption.

Denosumab is a type of rank ligand inhibitor used in the treatment of secondary bone cancer of various cancers, like lungs and prostate, in the prevention of skeletal-related events, which helps to prevent fractures of the bones, strengthen them, and increase gain in bone mineral density. It has also shown better potential as a new treatment option for managing bone metastases in breast cancer patients.[3]

Zoledronic acid, the first bisphosphonate, has a significant and durable clinical benefit in reducing skeletal complications through anti-resorptive activity for patients with malignant bone involvement from multiple myeloma and a various of solid tumours, including breast cancer, prostate cancer and lung cancer. It is also used in the prevention of Post menopausal osteoporosis (PMO), hip fractures, male osteoporosis and paediatric osteoporosis, geriatric

osteoporosis, glucocorticoid induced osteoporosis, thalassemia-induced osteoporosis, localized transient osteoporosis and Paget's disease.[4]

Zoledronic acid is a nitrogen containing compound that has an effect on osteoclasts by direct inhibition of farnesyl diphosphate synthase, an enzyme present in the mevalonate pathway that occurs in osteoclasts, followed by decreased levels of prenylated proteins and later leads to cytotoxicity, leading to alterations in integrin signalling, endosomal trafficking, membrane ruffling, and ultimately results in the induction of apoptosis. Zoledronic acid also impairs cellular energy and disrupts cytoskeleton assembly within osteoclasts. The same effects are exerted by zoledronic acid in tubular and visceral epithelial cells, thereby producing toxic acute tubular necrosis(ATN) and collapse of the Focal segmental glomerulosclerosis (FSGS). Podocytes, much like osteoclasts, have a highly complex cytoskeleton, and disruption of this cytoskeleton plays a role in the development of collapsing FSGS which results in renal injury.[5]

METHODOLOGY

This is a narrative review. We searched PubMed/MEDLINE, Cochrane Library, and Google Scholar for English-language human studies published between 2000 and 2024 using combinations of the following terms: "denosumab", "zoledronic acid", "bisphosphonate", "bone metastases", "renal safety", "chronic kidney disease", and "skeletal-related events". We included randomized controlled trials, prospective and retrospective cohort studies, and extension analyses comparing DMAb and ZA with explicit reporting of renal outcomes. Case reports and small case series were used selectively to illustrate rare adverse events such as osteonecrosis of the jaw. Reference lists of relevant articles and guidelines were screened to identify additional studies.

COMPARE AND CONTRAST

NAME OF THE STUDY	CONDITION	RECOMMENDED WITH RESPECT TO DENOSUMAB AND ZOLEDRONIC ACID	
Broadwell et al.,[6]	With and without renal impairment in osteoporosis	Denosumab 60 mg SC Q6 months	Denosumab was effective in gaining bone mineral density (BMD) and reducing risk of fracture in women with both normal renal function and mild to moderate renal insufficiency.
Wang et al.,[7]	Breast cancer	ZA 6-24 month	2 Renal impairment, 9 ONJ(Osteonecrosis of jaw) was observed.
		ZA >24 month	4 renal impairment, 6 ONJ, 1 hearing impairment was observed. More SREs was seen in advanced breast cancer than 6-24 group.
Stopeck et al.,[8]	Breast cancer with bone metastasis	Denosumab	Bone turnover is effectively suppressed and greater gain in BMD, Prevention of SRE, hypocalcaemia were more common with denosumab.
		Zoledronic acid	Acute phase reactions(flu-like syndrome including pyrexia, chills, flushing, bone pain, arthralgias, and myalgias) are 3 times more and increased serum Creatinine and more renal toxicity with extended use was observed with ZA.
Naruto et al.,[9]	HCC with bone metastases	Denosumab 120 mg infused for 15 min Q4 weeks (Switch from ZA)	Switching of zoledronic acid to denosumab did not show a significant difference in change of pain and activity of daily living, but Urinary NTx clearance normalized in all patients but serum NTx levels decreased slightly.
Raje et al.,[10]	Multiple myeloma	Denosumab	Denosumab was superior to Zoledronic acid in delaying SRE and renal adverse events especially in patients with renal insufficiency (creatinine clearance ≤ 60 mL/min). Denosumab has shown bone related benefits and prolongation of progression free survival and a higher renal safety profile.
		Zoledronic acid	Renal related adverse events were two-fold increase higher with ZA. And experienced high level of creatinine than denosumab.
Terpos et al.,[11]	Multiple myeloma	Sc Denosumab 120 mg plus IV placebo vs IV zoledronic acid 4 mg plus SC placebo Q4 weeks.	Largest PFS benefit was reported denosumab compared with zoledronic acid who received ASCT and triple therapy or bortezomib based induction regimen. It was observed only in patients with CrCl >60 mL/min and not in patients with impaired renal function (CrCl ≤60 mL/min). Better PFS was observed only in <70 year old Patients while it was not observed in ≥70 patients.
Yamasaki et al.,[12]	Bone metastases from prostate, renal cell, and urothelial cancers	Denosumab vs Zoledronic acid	Patients who experienced renal function deterioration with zoledronic acid showed improvements after switching to denosumab.
Adhoubi et	CKD vs Normal	Denosumab	High infection rate among CKD patients specifically

al.,[13]	renal function		with stage 4 and 5 who are on steroid medications or immunosuppressive medications compared to the patients who were not taking steroids. There were no renal function deterioration. But hypocalcaemia was the potential side effect observed in patients with advanced stages of CKD.
			Patients with normal renal function developed musculoskeletal effects and mild upper respiratory tract infection who were on steroids and immunosuppressive agents. Patients who were on biologics also showed moderate infection.
Boonen et al.,[14]	Osteoporotic postmenopausal women	Zoledronic acid vs Placebo	In mild to moderate renal impairment there was no correlation between % change in creatinine clearance and baseline creatinine clearance. AKI was diagnosed in both groups. Short term renal impairment occurred only with CrCl 30-35ml/min. 3 annual ZA showed no long term renal adverse events in patients with CrCl >30ml/min than those with placebo. Annual administration of ZA found to be safe and well tolerated, lowering the risk of new vertebral and hip fractures.
Black et al.,[15]	Postmenopausal women with osteoporosis	Zoledronic acid vs placebo	Zoledronic acid showed greater improvement in BMD and bone metabolism markers and decreased the risk of vertebral fracture during 3 year period of therapy. Change in renal function was observed in both groups. serious atrial fibrillation observed more often in the ZA group
Reid et al.,[16]	Postmenopausal osteoporosis	Zoledronic acid vs Placebo	Up to 1 year of ZA infusion administration gained higher bone density and bone turnover as observed with daily oral dosing with bisphosphonates. More BMD was seen in spine, femoral neck than placebo. Biochemical markers of bone resorption were greatly suppressed in all ZA groups. Adverse effects like Myalgia and pyrexia were common with ZA.
Jamal et al.,[17]	CKD	Denosumab	Denosumab found to be safe and statistically significant in reducing fracture risk and BMD gain in women with post menopausal osteoporosis and CKD stage1-3, but was not significant with CKD stage4.
Costa et al.,[18]	GU cancers (like prostate, renal, bladder) and bone metastasis	Denosumab vs Zoledronic acid	Disease progression time and over all survival were similar between both the groups. Denosumab significantly prolonged the time to first and subsequent SRE. Osteonecrosis of jaw was similar between 2 groups where as Hypocalcaemia was found to be higher with denosumab compared to

			ZA. Renal adverse events were more with zoledronic acid than denosumab.
Miller et al.,[19]	Postmenopausal women with osteoporosis	Denosumab 60 mg Q6M plus iv placebo	Eczema, Serious Infections and cardiac AEs were similar in both groups. Denosumab showed greater gains in BMD and higher inhibition of bone remodeling and turnover.
		Zoledronic acid 5 mg iv once plus SC placebo Q6M	Musculoskeletal pain was greater with ZA than Denosumab.
Nasser et al.,[20]	Cancers	Denosumab vs zoledronic acid	Hyper and hypocalcaemia both were associated with denosumab therapy. Incidence of hypocalcaemia was higher and hypercalcaemia was approximately 3 times more with denosumab when compared with zoledronic acid. Hypocalcaemia was Commonly observed in patients with breast cancer followed by ovarian cancer and multiple myeloma and some other cancers like lung, rectal and gastric cancers. Incidence of hypocalcaemia was 1.3 times higher in patients who did not receive supplements compared to who did.
Fizazi et al.,[21]	Men with bone Metastases from castration-resistant prostate cancer	120mg Sc Denosumab Q4 weeks	Denosumab was found to be better than zoledronic acid for prevention of SRE. Hypocalcaemia was found to be higher within 6months of therapy of denosumab than zoledronic acid. Denosumab had higher number of ONJ than Zoledronic acid. At week 13, Patients on denosumab showed uNTx and serum bone-specific alkaline phosphatase were significantly higher than Zoledronic acid.
		4mg iv zoledronic acid Q4 weeks	Acute phase reactions, renal impairment were higher with Zoledronic acid during first 3days of treatment. Concentrations of PSA were similar between 2 groups. The adverse and serious adverse events were similar between both groups which includes anaemia, back pain, decreased appetite, nausea, fatigue, constipation, and bone pain.
Henry et al.,[22]	Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma.	Denosumab	Denosumab was superior to ZA in preventing first on-study SRE. No difference was observed in Overall survival and disease progression. Hypocalcaemia was more associated with denosumab. Higher suppression of bone turnover markers(uNTx/Cr) were observed with denosumab. Decreased bone specific alkaline phosphatase was with denosumab when compared to ZA.
		Zoledronic acid	Acute phase reactions including pyrexia, fatigue, arthralgia within first 3 days of 1st dose was more frequently observed with ZA after the first

			dose. Abnormal levels of serum creatinine was observed with ZA. Low rates of ONJ with both groups. Infectious adverse events and serious adverse events were almost similar.
Vogel et al.,[23]	Cancer-related bone lesion either Durie-Salmon stage III multiple myeloma or breast or prostate cancer	4 mg Zoledronic Acid i.v. over 15 minutes every 3–4 weeks for six doses	AEs like Fatigue was most frequent with prostate cancer and multiple myeloma. Grade ½ nausea was observed with breast cancer and it was more frequent in patients with no previous bisphosphonate therapy. Dyspnea and vomiting were frequent with breast cancer than prostate cancer /MM. Osteonecrosis were not reported. Sr. Cr was a little higher in patients who previously received bisphosphonate therapy for >6months compared with the patients who received ≤ 6months of bisphosphonate treatment. Only one case of grade 2 renal failure was suspected to ZA in patient with prostate cancer. Significant reduction in pain scores from base line scores in at least 4/6 visits observed in MM and breast cancer. Only in 2 visits in prostate cancer.
Fizazi et al.,[24]	Bone metastasis and elevated uNTx levels despite iv BP therapy	180mg Denosumab Q12week	Denosumab normalized elevated levels of uNTx than the continuation of iv bisphosphonates. and at the first visit, reductions in sCTx, P1NP, TRAP-5b, BSAP and Osteocalcin were found and it continued till week 25. Denosumab did not show apparent increase in SAEs like infections. Grade 3,4,5 AEs were less common in denosumab group than iv BP. Similar SAEs was observed between both groups. No ONJ and change in Sr. Cr was seen in both the groups. Despite patients who are on Ca and Vit D supplements, hypocalcaemia was observed after 8 days of start of denosumab therapy this was in a context of rapid cancer progression, more weight loss and because of hyperparathyroidism with hypophosphatemia. SAE like Temporary decrease in Sr. Ca was observed with denosumab.
Imai et al.,[25]	Bone metastases from gastrointestinal cancer like esophageal cancer, gastric cancer, and	Denosumab 120mg/body weight vs zoledronic acid 4mg/body weight vs no	Denosumab was more effective in delaying SREs than zoledronic acid. Percentage of patients with no SRE was more in DMAb group than ZA and no treatment group. ZA and no treatment group showed same proportion of patients without SREs.
	colorectal cancer, pancreas-biliary system cancer, and rare	bone-modifying agent group	Percentage of patients with elevated serum creatinine of grade 3 or 4 observed with ZA>DMAb and zero in no-treatment group. And Percentage of

	cancers like sarcoma, neuroendocrine carcinoma, cancer of unknown primary, melanoma, anal cancer, and adrenal cancer.		patients with grade 3 or 4 hypocalcaemia was found with DMAb>ZA and zero in no-treatment group. Hypocalcaemia was seen more with denosumab than ZA. Where as hypercalcaemia was more with ZA than denosumab. There was no case of ONJ.
Smith et al.,[26]	castration-resistant prostate cancer and bone metastases	Zoledronic acid vs placebo	Zoledronic acid showed no significant improvement in SRE in zoledronic acid group and adverse events were reported such as elevation of Sr.Cr levels, Hypocalcaemia, Hypophosphatemia, Pain, Osteo necrosis were more in zoledronic acid group than placebo group Renal injury was seen in zoledronic acid group.
Hirsh et al.,[27]	NSCLC	Zoledronic acid vs placebo	Zoledronic acid group showed significant improvement in SRE and survival rates compared with placebo in patients with high NTx levels
Lipton et al.,[28]	Patients with RCC	Zoledronic acid vs placebo	SRE, skeletal complications, or skeletal morbidity rate was significantly reduced in zoledronic acid group , zoledronic acid has a measurable impact on reducing the severity of bone lesions. nausea, fatigue, emesis, and pyrexia more in zoledronic acid group than placebo group. Malignant neoplasm, bone pain, dehydration, dyspnea, and pneumonia. More in placebo group than zoledronic acid group. Adverse renal events were reported in both the groups emphasizing on zoledronic acid showed adverse renal effect when administered iv.
Major et al.,[29]	Lung cancer	Zoledronic acid	Zoledronic acid was more effective in treatment of hypercalcemia . corrected serum calcium fever, hypophosphatemia, and asymptomatic hypocalcaemia , Renal adverse events reported in zoledronic group
Rosen et al.,[30]	Lung cancer	Zoledronic acid vs placebo	Zoledronic acid showed significant improvement in reducing annual incidence of SRE and skeletal complications. ECOG (Eastern Cooperative Oncology Group Performance Status)slightly increased from base line in both the groups. Ntx levels slightly decreased in zoledronic acid than placebo. Alkaline phosphatase remained steady or slightly below baseline levels in patients treated with 4 mg of zoledronic acid over a period of time. No significant improvement in survival. Nausea, emesis, dyspnea, and headache reported when administered iv. Bone pain, acute-phase reactions of nausea,

			anaemia, and emesis, decrease in renal function, increases in serum creatinine occured in zoledronic acid group.
Saad et al.,[31]	Hormone-Refractory Metastatic Prostate Carcinoma	zoledronic acid-at-4-mg vs zoledronic acid 8/4-mg vs placebo	zoledronic acid at 8/4 mg and 4 mg : experienced one SRE, Bone metastases was more stable ,bone resorption was significantly decreased. zoledronic acid at 4 mg : experienced fracture ,The N-telopeptide-to-creatinine ratio. placebo : alkaline phosphatase increased at the end of the study than other groups. Renal function deterioration occurred with the 15-minute infusion regimen and Serum creatinine increases : zoledronic acid at 4 mg > zoledronic acid at 8/4 >placebo.
Berenson et al.,[32]	NSCLC, prostate carcinoma, multiple myeloma, small cell lung carcinoma, or lymphoma	Zoledronic acid 1 mg, 2 mg, 4 mg, 8 mg, 16 mg	Adverse event in this study :pain and fever influenza-like symptoms , and rigors nausea, leg edema, emesis, anorexia, diarrhoea, and constipation. NAG, levels : < 4 U/L in the 2-mg, 4-mg, 8-mg, and 16-mg zoledronic acid dose groups and 16 U/L in the 1-mg dose group 1 mg group : Haemoptysis 2-mg group : Hypophosphatemia, hospitalized with enterococcal bacteraemia, altered mental status, pneumonia, and disease progression 8-mg group : Hypophosphatemia, chest catheter infection 16 mg group: hypoxia and progressive disease , tinnitus and vertigo , and acute renal failure secondary to dehydration hypocalcaemia was not observed. 1 mg group ; NTX and DPD decreased maximally and subsequently increased incrementally indicating renewed bone resorption. doses ≥ 2 mg bone markers data indicate that zoledronic acid is highly effective in suppression of bone resorption.
De Castro et al.,[33]	Lung Cancer:	Denosumab vs zoledronic acid	Denosumab was superior to zoledronic acid in delaying SRE. Denosumab > zoledronic acid: hypocalcaemia zoledronic acid > Denosumab :Renal AEs , ONJ , Acute phase reactions:
Hatoum et al.,[34]	Breast (women), prostate, or lung cancer	Zoledronic acid vs untreated groups	Zoledronic acid associated with delayed SRE and reduced skeletal complications. The study revealed that patients who remained on zoledronic acid (ZA) for a longer period had a

			longer follow-up duration and experienced a lower monthly rate of skeletal complications compared to those who received no treatment.
Lipton et al.,[35]	Breast cancer, prostate cancer, other solid tumours or multiple myeloma	Denosumab vs zoledronic acid	Denosumab was superior to zoledronic acid in reducing the risk of multiple SRE and effective in delaying all four types of SRE relative to zoledronic acid. Hypercalcaemia : zoledronic acid > denosumab Hypophosphatemia : denosumab > zoledronic acid Denosumab and zoledronic acid ; Osteonecrosis of the jaw , cardiac adverse events and the incidence of new malignancies during the study were reported. Denosumab : hypocalcaemia was reported. zoledronic acid : incidences of renal adverse events and acute-phase reactions were higher than denosumab.
Henry et al.,[36]	Solid tumors (except breast or prostate) or multiple myeloma	Denosumab vs zoledronic acid	Multiple SRE risk reduction was seen in denosumab group. Both groups similarly reported Anaemia and hypocalcaemia. zoledronic acid> denosumab : showed renal toxicity, Acute phase reactions. zoledronic acid showed renal toxicity on iv administration and no dose adjustment was required for subcutaneously as adjusted in iv administration.
Stopeck et al.,[37]	Castration-resistant prostate cancer, breast cancer, non-small-cell lung cancer and bone metastases	Denosumab vs zoledronic acid	Denosumab was reported a significant reduction in the number of SREs compared and an improvement in patients' quality-of-life compared with zoledronic acid
Scagliotti et al.,[38]	Lung cancer	Denosumab vs zoledronic acid	Denosumab showed significant improvement and survival advantage over Zoledronic acid. zoledronic acid > denosumab : showed respiratory failure , metastases to the central nervous system, pneumonia ,deterioration of physical health. Denosumab > zoledronic acid : showed tumour progression ,Hypocalcaemia both the groups had dyspnea.
Wu et al.,[39]	Chronic Kidney Disease	Denosumab high adherence vs denosumab low adherence	Denosumab High adherence (HA) group users had higher eGFR levels initially compared with the Low Adherence (LA) group but in terms of one-year average eGFR or adherence to a 2 years treatment plan with denosumab there was no significant decline in renal function and also showed better survival in the HA group than the LA group

			The HA group had lower no cardiovascular mortality than the LA group.
Cummings et al.,[40]	Vertebral Fractures	Denosumab vs placebo	Higher risk of multiple vertebral fracture seen in patients soon after stopping denosumab treatment and has higher rate of BMD loss than those who developed a single vertebral fracture, but no nonvertebral fractures after discontinuing denosumab
Fraser et al.,[41]	BMD	Denosumab vs zoledronic acid	A significant increase in BMD was seen in the group switched to denosumab and no significant difference in change in BMD between patients previously on iv zoledronic acid .
Purvey et al.,[42]	Kidney function	Denosumab vs zoledronic acid	There was a decline in GFR on ZA and an improvement of GFR on denosumab. Patients who switched from zoledronic acid to denosumab, there was a significant reduction in serum calcium, no events of hypocalcaemia. Switching from Zoledronic acid to denosumab is a safe strategy for kidney recovery in renal impairment patients who are on ZA
Gabr et al.,[43]	Breast cancer	Denosumab vs zoledronic acid	After 6 months of treatment denosumab more commonly caused hypocalcaemia , osteoporosis than zoledronic acid , Zoledronic acid more commonly caused renal toxicity allergy than denosumab. The median time to bone disease progression in both the groups showed no significant difference.

DISCUSSION

EFFICACY

In cancers with bone metastasis, The effectiveness of DMAb in delaying SREs was higher than ZA. Percentage of patients with no SRE was more in DMB group than ZA and no treatment group. ZA and no treatment group showed same proportion of patients without SREs.[25]

In Lung cancer and bone metastasis, The majority of bone metastases arise from primary tumors such as breast, prostate, thyroid, lung, and kidney carcinomas and among all of them, patients with lung carcinoma have evidence of skeletal metastasis.[30] Zoledronic acid group showed significant improvement in reducing annual incidence of SRE and skeletal complications and also significantly extended the time to first pathologic fracture than placebo with their Ntx levels slightly decreased in ZA than placebo and ALP remained steady or slightly below baseline levels in patients treated with 4 mg of ZA over a period of time and ECOG

performance status slightly increased from base line in both the groups. After a period of time placebo group showed more than zoledronic acid group with No significant improvement in survival.[30] In contrast to this when the study was conducted with NSCLC patients Zoledronic acid treated patients who already had high ntx levels showed significant improvement in survival and reduce risk of SRE and reduced mortality rate compared to a placebo. In contrast, survival was similar between the treatment and placebo groups in patients with low NTX levels with nonsignificant increased risk of SRE. Possible explanation of high survival rates in high ntx levels zoledronic acid group could be due to high NTX levels might indicate a higher risk of skeletal- related events (SREs), which could be life-limiting. Early intervention with zoledronic acid could mitigate these risks, improving survival.[27] when ZA was compared with DMAb, DMAb was superior to ZA in delaying SRE and also prolonged overall survival in lung cancer patients.[33][38] and suggest that denosumab may have an additional effect on this disease other than the previously demonstrated bone-protective effects, the increased survival may be due to indirect or direct mechanism by inhibiting RANKL in RANKL expressing tumor cells which reduced osteoclast activity which could reduce the prognosis of disease.[38]

In most of the GI cancers and few rare cancers, Denosumab normalized elevated levels of uNTx in patients who had increased uNTx levels despite continuous iv bisphosphonates therapy. Time to reduce uNTx levels took 9 days and maintained upto 160 days for DMB when compared with BP therapy which took 65 days and maintained upto 24 days. At the first visit, reductions in sCTx, P1NP, TRAP-5b, BSAP and Osteocalcin were found and it continued till week 25[24] and in GU cancers (like prostate/renal/bladder) DMB significantly delayed first and subsequent on-study SRE.[18]

In prostate and Breast cancer with bone metastasis, ZA delayed time to first time SRE[34] only in patients with history of bisphosphonate therapy in their life time, but it showed no significant improvement in SRE when compared to placebo.[26] In contrast to this ZA reduced skeletal complications and also revealed that patients who remained on ZA for a longer period had a longer follow-up duration and experienced a lower monthly rate of skeletal complications compared to those who received no treatment.[34] and placebo group had slightly higher survival rates than ZA group with no statistical significance.[26] when compared to ZA, DMAb demonstrated to be well tolerated and non-inferior in delaying first and subsequent development of multiple on-study SRE[35][8], and effective in reducing risk of multiple SRE[35]

greater suppression of bone turnover markers also greater reduction in the levels of bone specific ALP[35] uNTx to Cr ratio and BSAP levels[8], but in contrast to this in advanced cancers excluding (breast and prostate) and multiple myeloma, DMAb was not statis-tically superior to ZA in delaying time to first on-study SRE or time to first-and-subsequent SRE.[36][22] But multiple SRE reductions[36] and greater suppression of bone turnover markers uNTx/Cr, ALP were high with DMAb than with zoledronic acid.[22] It also delayed worsening of pain but showed no difference in time to disease progression between denosumab and zoledronic acid group.[36]

Bone metastases from castration-resistant prostate cancer, breast, non-small-cell lung cancer, In ZA therapy of 4mg and 8/4mg vs placebo, patients with prostate cancer experienced one SRE and Bone metastasis was more stable and bone resorption was decreased significantly and also experienced fractures but the placebo group showed increased ALP at the end of the study than ZA groups.[31] but few studies of prostate and breast cancer showed desired effect in reducing SRE. But when compared to DMAb, denosumab showed greater efficacy[37] in significantly delaying the time to first on-study skeletal-related event, significant reduction in the number of SREs[37] and showed higher Suppression of uNTx and Sr. BSAP than ZA group.[21] and improved quality of life with DMAb[37] therefore, DMAb was found to be a better potential treatment option than ZA in breast cancer patients.[43]

Multiple myeloma, DMAb was superior to ZA in delaying time to first on-study SRE.[10] In HCC with bone metastasis, switching of ZA to DMAb normalized urinary NTx clearance but Sr. NTx levels decreased slightly.[9]

Renal cell carcinoma, In Zoledronic acid study, ZA was more significant in reducing SRE, Skeletal complications and Skeletal morbidity rate. zoledronic acid has a measurable impact on reducing the severity of bone lesions.[28]

In postmenopausal osteoporotic patients, when effectiveness of denosumab was compared according to the eGFR, found to be safe and was significant in higher BMD gain in lumbar spine >femoral neck >total hip and reducing the fracture risk was similar in normal renal function, CKD stage 1, 2, 3a, and 3b subgroups, but was not significant with CKD stage-4[6].[17] and the incidence of nonvertebral fractures were reduced in patients with DMAb when compared with placebo but was not statistically significant for stages 3 and 4 CKD.[17] also the Annual administration of ZA found to be safe and well tolerated, lowered the risk of

new vertebral and hip fractures.[14] Zoledronic acid showed greater improvement in BMD in total hip>lumbar spine>femoral neck and decreased the risk of vertebral fracture by 70% during 3 year period of therapy. CTx, bone- specific ALP, and P1NP were decreased significantly but after 3 infusions no progressive reduction in marker values were seen.[15] Up to 1 year of ZA infusion administration, higher gain in bone mineral density and bone turnover was observed with daily oral dosing with bisphosphonates. ZA showed 4.3- 5.1% higher BMD gain in lumbar-spine than placebo. Higher gain in BMD was seen in Femoral neck but it reduced by 0.4% in placebo arm. No vertebral fractures were seen, but non vertebral fractures were observed with 0.25mg and 1mg of ZA treated groups. Biochemical markers of bone resorption like Sr. CTx and uNTx: Cr were greatly suppressed in ZA than placebo group.[16] where as when DMAb was compared to ZA, DMAb showed greater gains in BMD at Lumbar spine >total hip >femoral neck and higher inhibition of bone remodeling and turnover. But Absolute Sr. CTx and P1NP Concentrations reduced in both DMAb and ZA groups. The median percentage reduction of Sr. CTx and Sr.P1NP was significantly higher with DMB at all the points after day 10 and month 3 than ZA.[19] Significant increase in BMD was seen in group switched to denosumab and no significant difference in change in BMD between patients previously on intravenous zoledronic acid.[41] But higher risk of multiple vertebral fracture was seen in patients soon after stopping denosumab treatment and has higher rate of BMD loss than those who developed a single vertebral fracture, But no non-vertebral fractures precipitated after its discontinuation.[40]

CKD vs Normal renal function, among patients who were given DMAb 70% of them showed BMD gain in lumbar and hip region where as 30% of them showed worsening in their BMD.[13]

SAFETY

Serious side effects observed more often in ZA than DMAb group. Few days After initiation of ZA therapy acute phase reactions like pyrexia, influenza like symptoms, myalgia, toothache, headache, arthralgia, back pain, anaemia, anorexia , nausea, vomiting , fatigue, constipation, haemoptysis, altered mental status were Occurred. During start of 15 days after infusion of ZA, inflammatory ocular adverse events i.e., conjunctivitis was observed.[30][33][15][16][21][32][8][28]

Zoledronic acid also showed respiratory failure, pneumonia but Dyspnea observed in both ZA and DMAb groups.[38][28] Musculoskeletal pain was greater with ZA than DMAB. whereas Events involving Eczema, dermatitis, and allergic dermatitis, Serious Infections[19] Cardiac

AEs were similar in both groups.[19] and serious atrial fibrillation observed more often in the ZA group.[15]

ONJ was seen in patients receiving both ZA and DMAb[8][22][35] but DMAb receiving patients had higher incidence with no statistical significance.[8] In contrast to this, ONJ was highly significant with DMAb than ZA.[21] There are also studies where no incidence of ONJ was seen in the both groups[18][24][25][23][13] Because of poor dental hygiene and dental extraction, patients developed ONJ, but recovered the jaw completely after surgery.[7]

HYPERCALCAEMIA /HYPOCALCAEMIA

Hypercalcemia was more seen with ZA than DMAb.[8][25][35] In contrast to this, in other study showed Hypercalcemia was approximately 3 times higher and more associated with DMAb therapy than ZA.[20] and Significant improvement in treating hypercalcemia was seen with ZA[29] whereas grade 3 or more hypocalcemia was seen more with DMAb than ZA.[33][8][21][18][25][22][35][43] but there is one study which found out that incidence of grade-1 Hypocalcemia was found to be higher and was commonly observed in patients with breast cancer followed by ovarian cancer and multiple myeloma and some other cancers like lung, rectal and gastric cancers. There was no new incidence of Hypocalcemia in long-term therapy of denosumab but shift in hypocalcemia was observed from grade 0 to 1 more was in stage 3b of CKD, whereas in cross over arm patients developed hypocalcemia.[6] It is the potential side effect observed in patients with stage 5 of CKD. Higher % of patients with CKD shown Side effects while taking DMAb than the side effects observed in patients with normal renal function.[13] Incidence of hypocalcemia was 1.3 times higher in patients who did not received supplements compared to who received.[20]

Hypophosphatemia was seen in DMAb group[9][35]and also few studies of zoledronic acid also showed hypophosphatemia.[26][29][32] In patients with HCC, Grade 3 or 4 Adverse events like high levels of hepatic enzymes ALP, AST, ALT were observed. The patients recovered immediately and was not due to drug use but which was due to cancer progression, biliary infections or temporary dehydration.[9]

RENAL SAFETY

Osteoporotic postmenopausal women, AKI was diagnosed in both placebo and ZA groups. In mild to moderate renal impairment there was no correlation between % change in creatinine clearance and baseline creatinine clearance. Short term renal impairment occurred

only with CrCl 30-35ml/min. 3 annual ZA showed no long term renal adverse events was observed with CrCl >30ml/min than those with placebo. In this 3 year study, at 36th month patients where both group had Cr.Cl <30ml/min, Sr.Cr more increased from baseline in ZA compared to placebo.[14] Difference in renal function was observed in both PLACEBO and ZA groups.[15] In DMAb studies, Only<3% patients progressed to stage4 CKD, from baseline CKD stages 2 & 3.[6] There was no statistically significant difference in change in Cr.Cl among DMAb and placebo arms.[17]

CKD vs Normal renal function, There were no renal function deterioration with DMAb.[13] Switching from Zoledronic acid to denosumab is a safe strategy for kidney recovery in renal impairment patients who are on ZA.[42] In DMAb therapy, High adherence (HA) group users had higher eGFR levels initially compared with the Low Adherence (LA) group but in terms of one- year average eGFR or adherence to a 2 years treatment plan with DMAb there was no significant renal function decline, also showed better survival in the HA group than the LA group.[39]

Lung cancer, In ZA studies, Increase in the Sr.Cr and decline in the renal function was observed.[30][29] when it was compared with DMAb renal AEs were greater with ZA therapy.[33]

Durie-Salmon stage III multiple myeloma or breast or prostate cancer, Durie-Salmon stage III multiple myeloma or breast or prostate cancer, Sr.Cr was slightly greater in patients who had previously received bisphosphonate therapy for >6 months compared to patients who received ≤6 months of bisphosphonate treatment. Only one case of grade 2 renal failure was suspected to ZA in patient with prostate cancer.[23]

Breast cancer with bone metastasis, Greater renal events[35], where reduction in baseline CrCl from ≥60 mL/min to <60 mL/min and acute phase reactions were 2.7 times more frequently occurred within 3 days of ZA therapy than DMAb and found out that with extended use of ZA increased Sr.Cr and more renal toxicity was observed.[8]

Bone metastases from prostate, renal cell, and urothelial cancers, Patients who experienced renal function deterioration with zoledronic acid showed improvements after switching to denosumab. Renal function was assessed in patients with DMAb therapy as the first line BMA showed no significant change in renal function levels. And in those patients before ZA therapy showed higher Ccr when compared to the patients after ZA therapy. The Ccr levels after DMAb

administration tend to increase.[12]

In castration resistant prostate cancer, Renal failure[26] and Renal function deterioration occurred Within 15-minutes infusion regimen and Elevation of Sr. Cr was observed more in ZA 4mg than 8/4mg than in placebo group.[31] even when it was compared with ZA, DMAb showed less renal side-effects.[37]

Bone lesions in advanced cancers(excluding breast and prostate)and multiple myeloma, Increased Sr.Cr and renal toxicity were common with ZA than DMAb on iv administration.[36][22]

Multiple myeloma, Renal events were more common with ZA than DMB, although patients with CrCl<30mL/min were excluded where as with CrCl≤60mL/min renal toxicity was 2 folds lower.[10]

Bone metastasis from GI cancers, Percentage of patients with Elevated Sr.Cr of grade 3 or 4 observed with ZA than the DMB and nil in no treatment group.[25] In contrast to these studies there was no change in Sr.Cr in both groups.[24]

In RCC, adverse renal events were reported in both the groups emphasizing on zoledronic acid showed adverse renal effect when administered iv.[28]

CONCLUSION

Most of the studies support DMAb for significantly delaying the time to cause skeletal-related events, evidence of greater gain in BMD, suppression of bone turnover markers was high when compared to ZA. But upon discontinuation of DMAb, there is a rise in the vertebral fractures and BMD loss. Adverse and serious adverse events were comparatively more frequent with ZA than DMAb. Also Respiratory events, cardiovascular complications, musculoskeletal pain, ocular and dermatological events were less common with DMAb. Though there are only a few supporting studies where ONJ and hypercalcemia are seen more with DMAb therapy, still many studies support that hypocalcemia is more common with DMAb than ZA. Annual administration of ZA didn't show long-term adverse renal events, but at the 3rd annual study, Sr.Cr levels increased. Many studies support that adverse renal events were more associated with ZA when it was compared with DMAb. And with the extended use of ZA, increased Sr.Cr and more renal toxicity like deterioration of renal function, acute kidney injury, and renal failure were observed. The 8-mg dose was reported an increase in serum creatinine in some

patients therefore, protocol amendments increased the infusion time from 5 minutes to 15 minutes and increased the infusate volume from 50 mL to 100 mL. Because of continued concern regarding safety, the 8-mg dose was reduced to 4 mg.[30] Even after an appropriate adjusting dose, there are still renal adverse events with ZA. On the other hand, DMAb is safe to use compared to ZA and found efficient in all stages of CKD. As Denosumab is a monoclonal antibody and is eliminated by intracellular catabolism in phagocytes, similar to the clearance mechanism of other therapeutic monoclonal antibodies, and is not metabolized or excreted by the kidneys, there is no requirement of renal function monitoring on subcutaneous injection.[8][22] In ASCT intent subgroup, the largest PFS benefit was reported denosumab compared with zoledronic acid for those who received ASCT and triple therapy or a bortezomib-based induction regimen. This PFS benefit is due to the synergistic effect between bortezomib and denosumab, but this effect is suppressed in patients receiving IMiD. In ASCT- no-intent subgroup, the median PFS was lower with DMAb compared to ZA, who received triple therapy. With baseline renal function with CrCl ≤60 mL/min, PFS was the same for denosumab and ZA. And with mild renal impairment or good baseline renal function with CrCl >60 mL/min, a PFS benefit was seen in patients for DMAb when compared to ZA. Impaired renal function was reported worst outcomes in terms of PFS compared with baseline renal impairment in the DMAb and ZA groups.[11]

ABBREVATIONS

Abbreviation	Full Form
DMAb	Denosumab
RANK	receptor activator of nuclear factor kappa
ZA	Zoledronic Acid
CKD	Chronic Kidney Disease
NSCLC	Non-Small Cell Lung Cancer
LC	Lung Cancer
RCC	Renal Cell Carcinoma
HCC	Hepatocellular Carcinoma
GU	Genitourinary Oncology
SREs	Skeletal-Related Events
ONJ	Osteonecrosis of the Jaw
BMD	Bone Mineral Density
NAG	N-Acetylglucosamine
AKI	Acute Kidney Injury
PTH	Parathyroid Hormone
PTHrP	Parathyroid Hormone-Related Protein
CrCl	Creatinine Clearance
PFS	Progression-Free Survival
ASCT	Autologous Stem Cell Transplant

MM	Multiple Myeloma
BSAP	Bone-Specific Alkaline Phosphatase
AEs	Adverse Events
ECOG	Eastern Cooperative Oncology Group Performance Status
NTX	N-Terminal Telopeptide
ALP	Alkaline Phosphatase
TRAP-5b	Tartrate-Resistant Acid Phosphatase-5b
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
eGFR	Estimated Glomerular Filtration Rate
HA	High Adherence
LA	Low Adherence
IMiDs	Immunomodulatory Drugs
Sr.Cr	Serum creatinine

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