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REVIEW

Denosumab Use in Chronic Kidney Disease Associated Osteoporosis: A Narrative Review

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Abstract: Chronic kidney disease (CKD) and hemodialysis (HD) patients have a high incidence of bone disease and increased fracture risk, making effective management of their bone health a clinical challenge. Denosumab, a human monoclonal antibody, has been investigated as a therapeutic option in this patient population. In this review, we summarize the current evidence on the efficacy and safety of denosumab in CKD and HD patients. A comprehensive search of the relevant literature was conducted, including randomized controlled trials, observational studies, and meta-analyses. The findings suggest that denosumab reduces the risk of fractures and improves bone mineral density in all stages of CKD. The results of this review support the use of denosumab as a promising option for managing bone disease in CKD and HD patients.

Keywords: denosumab, chronic kidney disease, hemodialysis, bone disease, fracture risk reduction

Introduction

Both osteoporosis and Chronic Kidney Disease (CKD) have a significant impact on bone health.[1] Bone and mineral turnover disturbances are common complications in patients with impaired kidney function, advanced CKD, or on maintenance dialysis.[2,3] Because of low bone mineral density (BMD) and poor bone quality, patients with chronic kidney disease-mineral and bone disorders (CKD-MBD) are at a higher risk of bone fractures and associated morbidity and mortality.[1,4,5] The term CKD-MBD was coined by the Kidney Disease Improving Global Outcomes Foundation (KDIGO) in replacement of the term renal osteodystrophy. It includes broader abnormalities (mineral metabolism disorders, skeletal health, and soft tissue calcifications).[6] CKD-MBD develops in conjunction with secondary hyperparathyroidism due to phosphorus accumulation in circulating plasma, increasing the risk of cardiovascular disease and bone fracture.[7] Studies have shown that measuring BMD with dual-energy x-ray absorptiometry (DXA) predicts incident fracture, allowing nephrologists for the first time to risk classify patients for skeletal fragility and develop targeted anti-fracture strategies.[6,8]

Diagnosis and pharmacological treatment of osteoporosis in patients with advanced kidney disease (CKD stages 4–5/5D) are difficult, and prevention of related fragility fractures is complicated due to the highly variable pathophysiology of bone disease, as well as the limitations and unique side effects of current therapeutic options.[9–11] The levels of bone turnover markers present in osteodystrophy patients range from severely suppressed to markedly elevated, which may influence osteoporosis treatment options.[9] Endocrinology scientific societies have established therapy guidelines for patients with osteoporosis based solely on glomerular filtration rate and have recommended avoiding the use of certain drugs in advanced stages of CKD. Therefore, there is no clear treatment strategy for patients with advanced CKD and bone abnormalities.[12]

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Over the last few decades, the therapeutic options for osteoporosis have greatly expanded. The introduction of nitrogen-containing bisphosphonates, which work by inhibiting bone resorption, was a significant step forward.[13–16] However, fear of nephrotoxicity and lack of clear recommendation in the nephrology guidelines have limited their widespread use. Teriparatide, which is another option, also helps to prevent fractures but its high cost and the need for daily injections limit its use.[17] Denosumab, a human monoclonal antibody directed against the receptor activator of nuclear factor kappa B ligand (RANKL), has been shown to reduce the formation, function, and survival of osteoclasts.[18] It was first approved by the US Food and Drug Administration (FDA) in 2010 for use in osteoporosis and in CKD-associated osteoporosis in 2018.[19] In this review, we aim to summarize the therapeutic effects of denosumab in CKD and HD patients and review the associated complications.

Methodology

The present review employed a systematic approach to identify and critically evaluate relevant studies concerning the use of denosumab in patients with CKD and those undergoing HD. The search was conducted in several electronic databases including PubMed, Embase, and the Cochrane Library. The search encompassed all available literature without language restrictions, from the earliest date of publication to the present. The search terms used included "denosumab", "chronic kidney disease", "hemodialysis", "bone disease", and "fracture risk reduction".

The inclusion criteria for selecting the relevant studies comprised original investigations of denosumab's use in CKD and HD patients, written in English, reporting on denosumab's efficacy or safety outcomes, and published as full-text articles. A qualitative synthesis was performed to analyze the data, and a narrative synthesis was conducted to provide an overview of the results. The selected studies were meticulously evaluated to offer a comprehensive perspective on the current evidence surrounding the use of denosumab in CKD and HD patients.

The study's findings were thoroughly scrutinized and discussed, considering the quality of the evidence, the studies' strengths and limitations, and their implications for clinical practice. The final synthesis was used to develop evidence-based conclusions and recommendations for future research.

Discussion

Denosumab is a monoclonal antibody that binds to and inhibits the receptor activator of nuclear factor-kappa B ligand (RANKL), a protein essential for osteoclast formation, function, and survival.[9,18,20,21] Denosumab is a novel treatment which showed strong beneficial effects (clinically meaningful increase in BMD and reduction in fracture risk) as well as an excellent profile even in CKD patients.[11,18,22,23] Block et al in his single-dose study of 60 mg denosumab given to patients with varying degrees of kidney function (stage 1 to 5) found that renal function did not have a significant effect on denosumab pharmacokinetics or pharmacodynamics which suggested that dose modification of denosumab was not necessary.[24] The same recommendation is given by others who showed that denosumab was neither metabolized nor excreted by the kidney. It was also found not to be dialyzable.[9,24–26] Consequently, the use of denosumab in CKD patients was found to be safe. Jamal et al used denosumab every 6 months for a total of 36 months in patients with CKD stage 1–4.[25] Adverse events or serious infections were similar in all stages of CKD reinforcing the concept of safety. On the other hand, kidney function remained stable over the treatment period and no clinically significant changes were observed. Similar results were also seen by Bonani et al.[27]

Efficacy of Denosumab

The use of denosumab and other osteoporosis treatments in CKD and HD patients was the subject of a recent systematic review and meta-analysis by Chen et al, 2022.[28] It included 17 studies and a total of 10,412 CKD patients who were at stage 2–5, receiving hemodialysis or had kidney transplantation. It concluded the superiority of denosumab in improving femoral BMD. Denosumab was also the second best in improving vertebral BMD and in reducing fracture risk. In this meta-analysis, we have noticed a recent and crucial Randomized Controlled Trial (RCT) comparing the effects of two anti-osteoporotic therapies (denosumab and alendronate) on bone health in 46 hemodialysis patients. Denosumab induced a significant and maintained reduction in bone resorption markers after three months of treatment. Denosumab also increased lumbar spine BMD significantly.[29] The benefit of denosumab in dialysis patients was clearly demonstrated in

a Japanese case–control study. At one year, BMD significantly increased in patients on denosumab (n = 17) versus those not on denosumab (n = 20).[30] Another RCT which involving 90 kidney transplant patients found that denosumab improved BMD at the lumbar spine and total hip after 12 months of treatment.[27] In patients with CKD stage 1–4, denosumab reduced the incidence of vertebral and non-vertebral fractures over 36 treatment and also increased BMD at all sites, lumbar spine, femoral neck, and total hip.[25]

Denosumab-Induced Hypocalcemia

In a meta-analysis of six observational studies including 84 end stage renal disease (ESRD) patients, the incidence of denosumab-induced hypocalcemia was found to be reaching 42%. It occurred at 7 to 20 days after initiation of treatment and reached a nadir of low calcium in the first 2 weeks up to two months.[26] Similarly, Festuccia et al observed in their retrospective study, the occurrence of hypocalcemia approximately 20 days after the first dose of denosumab.[31] However, the incidence was lower (25%), and no hospitalization for hypocalcemia was required.[31]

Block et al showed that the incidence and severity of hypocalcemia was higher in patients with advanced kidney failure compared to patients with moderate CKD.[24] Males were also found to be more associated with denosumab-induced hypocalcemia.[32] In their series involving 55 patients with varying degree of kidney impairment, none of the patients with mild-to-moderate impaired kidney function had any episode of severe hypocalcemia. Moderate hypocalcemia was noticed in a few of them. It was asymptomatic and easily managed with calcium and vitamin D supplementation.[24] In the patients with severe chronic kidney disease, two patients experienced severe hypocalcemia and required hospitalization and intravenous calcium gluconate. These two patients had shown high level of intact Parathyroid Hormone (iPTH). This latter aspect was also highlighted in the work of Iseri et al, who noticed that only patients with secondary hyperparathyroidism were more susceptible to developing hypocalcemia.[29] Denosumab use in hemodialysis patients was, however, found to be safe and hypocalcemia episodes could be effectively prevented with a 2-week course of calcium supplementation.[29] However, others found significantly higher risk of experiencing hypocalcemia as a result of denosumab treatment even in dialysis patients who are receiving active vitamin D and/or CaCO3.[33] Interestingly, the ability of denosumab to induce hypocalcemia was used by to correct hypercalcemia and BMDs in kidney transplant patients.[34] On the other hands, severe hypocalcemia was also reported in patients receiving denosumab in combination with intravenous iron.[35] This latter was postulated to increase fibroblast growth factor-23 (FGF-23) levels with consequently a decrease in serum phosphorus levels and therefore a weakened parathyroid hormone (PTH) response to denosumab induced hypocalcemia.[36]

Denosumab-Induced Changes of Intact Parathyroid Hormone (iPTH)

Several case reports and clinical trials have reported a critical side effect of denosumab in CKD patients, namely an increased level of iPTH.[24,29] Hiramatsu et al reported asymptomatic hypocalcemia and compensatory iPTH increase in 11 Japanese hemodialysis patients who received a single dose of denosumab.[37] This increase is thought to be a compensatory mechanism for the low levels of calcium.[38] It is observed as early as one week after the first dose of denosumab and may last for up to six months post-treatment.[37–40] In order to avoid hypocalcemia and the compensatory increase in iPTH, some authors advise calcium and calcitriol replenishment before starting denosumab. This approach was adopted by Chen et al in their 24-week open-label study in Taiwan. Hypocalcemia observed in one-third of the cohort was rapidly corrected with calcium and calcitriol supplements. On the other hand, the co-administration of calcitriol and denosumab resulted in a significant decrease in iPTH and the authors found that denosumab use may allow supra-physiologic doses of calcitriol in order to reduce parathyroid secretion.[40] Similarly in kidney transplant patients on denosumab, the addition of calcitriol to cholecalciferol was necessary to control hypocalcemia and persistently high PTH levels.[41] Overall, the potential impact of denosumab on iPTH levels in CKD patients warrants close monitoring and further investigation.

Conclusion

In light of the high prevalence of osteoporosis and chronic kidney disease (CKD) among elderly individuals, it is imperative to understand the safety and effectiveness of osteoporosis treatments in patients with renal insufficiency, as

well as their impact on intrinsic renal function. Treatment decisions should consider the severity and reversibility of biochemical abnormalities and CKD progression. While evidence for the anti-fracture efficacy of antiresorptive and osteoanabolic therapies has only been established for osteoporosis patients, their use in patients with impaired renal function warrants large-scale, randomized clinical trials. The occurrence of denosumab-associated hypocalcemia remains a concern for CKD patients, especially those with severely impaired renal function. To gain a comprehensive understanding of the long-term effects of denosumab in hemodialysis patients, further research is required.

Ethical Approval

Ethical approval was not required for this review article as it did not involve any human subjects, data collection, or experimentation.

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