

# A case of Denosumab induced severe hypocalcemia causing Seizure in a patient with advanced chronic kidney disease

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## **Abstract-** Background:

Denosumab, a RANKL inhibitor, inhibiting osteoclast formation, can cause severe symptomatic hypocalcemia especially in cases with renal impairment stage 4 and 5 (1). MHRA safety alert warns that the patients with severe renal impairment with Creatinine clearance of  $\leq 30$ ml/min or those who are receiving dialysis, are at the highest risk of hypocalcemia (1). In individuals with CKD stages 4-5, anti-resorptive bone protection therapy might cause harm with increase the risk of fracture and vascular calcifications in low bone turnover conditions by further inhibiting osteoclasts while high bone turnover diseases are more susceptible to hypocalcemia (3). The incidence of hypocalcemia in CKD is reported to be 14-15% (4).

**Index Terms-** Denosumab, CKD, hypocalcemia

**Abbreviation:** RANKL receptor activator of nuclear factor kappa B ligand; CKD chronic kidney disease; MBD mineral and bone disease; CT computerized tomography; eGFR estimated glomerular filtration rate; P1NP N- terminal propeptide of type 1 collagen; FGF fibroblast growth factor

## I. CASE PRESENTATION

A 70 years old lady was admitted to the emergency department after the first episode of generalized tonic-clonic seizures for 10 minutes during her sleep. Her general and neurological examination were normal. Her blood glucose level was normal.

Her past medical history included chronic kidney disease stage IV, recent left fractured neck of femur requiring hemiarthroplasty, osteoporosis, hysterectomy, asthma, hypertension, chronic back pain and spondylosis.

On admission, her blood tests with Full Blood Count and renal function were at the baseline. Her Calcium level on venous blood gas was 0.62 mmol/l. She had significantly low adjusted serum calcium level of 1.43 mmol/L and a serum magnesium level of 0.5 mmol/l. Her CXR and CT head were reported normal. Her ECG showed prolonged corrected QT of 526ms. Her provoked seizure was secondary to severe hypocalcemia.

Endocrinology advice was sought and she received 2x10ml of 10% IV calcium gluconate injection followed by infusion with the target adjusted serum calcium of 1.8mmol/L and above. After the first dose, her corrected QT was improved to 490ms and

adjusted calcium level improved to 1.52 mmol/l. Her low magnesium was corrected by IV magnesium. Subsequently, her hospital stay was complicated with the development of AKI on CKD and pneumonia during requiring intravenous fluid and antibiotics. She gradually recovered from her illness and was discharged after 18 days.

On reviewing her medical notes, we found, 12 days before admission, she had received the first dose of Denosumab injection 60mg SC, for bone protection in the osteoporosis clinic. On the day of the injection, her routine blood test showed vitamin D 25(OH) level of 59.1 mmol/l, adjusted calcium 2.42 mmol/L and eGFR 11 ml/min/1.72m<sup>2</sup> (CKD stage 5). Her GP was advised to commence her on ADCAL D3 1-tab BD following Denosumab injection, however, she did not receive this due to delay in the communication.

A clear discussion was made with the patient regarding the cause of the seizure with an apology and following a detail discussion, she decided not for any further Denosumab injection.

## II. DISCUSSION & CONCLUSION

In people with chronic kidney disease, especially stage 4 and 5, osteocytes increased FGF23 which suppressed parathyroid hormone secretion and reduced 1 $\alpha$  hydroxylase production, affecting less absorption of calcium from the gut in addition to phosphate retention, leading to reduced free calcium. All these mechanisms cause hypocalcemia in CKD (4).

Denosumab inhibits osteoclastic activity, reducing calcium resorption from the bone which ends up in hypocalcemia.

The FREEDOM trial including 7808 postmenopausal women with vertebral, non-vertebral and femur fracture with osteoporosis reported that Denosumab significantly lowers the risk of fracture after 36 months. It increased BMD by 9.2% (95% CI: 8.2, 10.1) at the lumbar spine and 6.0% (95% CI: 5.2, 6.7) at the total hip compared with placebo. However, the trial excluded severe CKD patients and on dialysis. (5)

Usually, Denosumab was not excreted by kidneys, thus could be used in patients with renal failure with no need for dose adjustment. It is relatively well tolerated.

Subset analysis of FREEDOM trial showed Denosumab 60mg every 6 months was not associated with increase adverse events among patients with severe renal failure (n=73, Cr Cl 15-29 ml/min) or impaired renal function (n=2817 Cr Cl 30-59

ml/min) compared to those with normal renal function (n= 4911 Cr Cl>60 ml/min). Thus, Denosumab does not require monitoring renal function or dose adjustment before administration (2).

Serum adjusted calcium must be >2.2 mmol/L and vitamin D levels adequate (50-100 nmol/L) before each injection. Patients must be adequately supplemented with Calcium (at least 700 mg daily) and vitamin D (at least 800 units daily) (1).

Although hypocalcemia most commonly occurs within the first 6 months of treatment, it may occur at any time following Denosumab injection. It is reported to happen in the first 2 weeks of the first dose (1). The overall incidence of hypocalcemia with Denosumab is between 5.5-15% as compared to Zoledronate 3.4-6%. Incidence of severe hypocalcemia is also higher in patients treated with Denosumab as compared to Zoledronic acid (3.1% vs 1.3%) (6).

Risk of developing hypocalcemia depends on renal failure (Cr Cl <30) or patients on dialysis, advanced metastatic cancer prostate or non-small cell cancer, Vitamin D deficiency, Lack of calcium or calcitriol supplement, concomitant treatment with loop diuretics and history of parathyroidectomy (3).

### III. TAKE-HOME MESSAGE

We wanted to highlight this case to increase the awareness of severe hypocalcaemia in Denosumab treatment causing potentially life-threatening complications even after a single dose. We also emphasized the patient education of such complication and clear communication with GP regarding post-injection advice on calcium supplement and monitoring calcium level to avoid such preventable condition. Also, we emphasized careful

consideration and risk assessment of Denosumab in patients with severe renal impairment.

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