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Denosumab-Induced Central Nervous System Events in Postmenopausal Women without Hypocalcemia

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Abstract

Denosumab is an effective human monoclonal antibody used for postmenopausal women with osteoporosis at high risk for fracture. There are serious adverse effects associated with the use of denosumab, such as hypocalcemia, hypophosphatemia, hypomagnesemia, and increased blood alkaline phosphatase. Hypocalcemia associated with the use of denosumab can lead to central nervous system complications (seizure) in chronic kidney disease patients (CKD 4-5D). The patient, in this case, had osteoporosis and started a denosumab regimen (60 mg subcutaneous injection every 6 months for 2 years) with normal renal function and magnesium and calcium levels but developed reversible convulsion, amnesia, irritability hallucination, marked elevation Gamma-Glutamyl Transferase (GGT), and slight elevations in alkaline phosphatase and Aspartate Aminotransferase (AST). In all previously documented cases, CNS events after the administration of denosumab were associated with hypocalcemia or renal impairment. We hereby report a case of reversible convulsion following denosumab administration for the treatment of osteoporosis in postmenopausal women with normal renal functions, endocrine, and metabolic profiles. The findings of this study suggest careful monitoring of serum levels of calcium, phosphorus, and magnesium and symptoms of CNS events before initiation and during denosumab therapy.

Keywords: Denosumab • Hypocalcemia • Osteoporosis • Seizure

Introduction

The Centers for Disease Control and Prevention defines osteoporosis as a health condition where bones become weak and fragile and easily break. The percentage of females 65 years of age and older with osteoporosis of the femur neck or lumbar spine is 24.5% [1]. Many antiresorptive drugs are available for the treatment of osteoporosis, including bisphosphonates and a human monoclonal antibody such as denosumab [2]. Denosumab is an entirely human monoclonal antibody that binds to receptor activator of nuclear factor kappa-B ligand (RANKL) to inhibit osteoclast receptor activation, which results in reduced bone resorption and improved bone density [3]. Denosumab demonstrates nonlinear pharmacokinetics and is dose dependent. For example, after a single Subcutaneous (SQ) administration of 60 mg of denosumab, the maximum serum concentration (C_{max}) is reached in a median of 10 days (range, 3-21 days). In addition, the concentration of denosumab in the serum after reaching C_{max} declines over a period of 3-5 months and is undetectable in over half of patients (53%) at 6 months postdose. The drug has an elimination half-life of 26 days following C_{max} [4]. Denosumab causes many adverse effects, including hypercholesterolemia (7.2%) and dizziness. There are other serious adverse effects associated with the use of denosumab, such as endocarditis (0.08%), cellulitis (2.5% to 5.1%), hypocalcemia (bone loss, bone metastases, giant cell tumor of bone or multiple myeloma, 1.7% to 18%), hypophosphatemia (bone metastases, 32%), hypercalcemia of malignancy, 76%), bone metastases, giant cell tumor of bone, multiple myeloma (severe), 9.5% to 21%), pancreatitis (0.2% to 0.8%) and serious infections (3.9% to 6%) [3]. A retrospective study carried out in chronic kidney disease patients (CKD 4-5D) found a high risk of severe hypocalcemia and CNS complications (seizure) in those patients [5]. Another study reported severe hypocalcemia in patients with metastatic prostate cancer [6]. This case report seeks to investigate the cause of CNS events following denosumab administration for the treatment of osteoporosis in postmenopausal women with normal renal functions, endocrine, and metabolic profiles.

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Case Report

A 70-year-old woman visited the orthopedic clinic with complaints of severe bone pain and osteoporosis one month after a fall and fracture. Her laboratory assessment (Table 1) showed a normal Complete Blood Count (CBC) and normal calcium, chloride, magnesium, albumin, and liver enzyme levels, with blood glucose elevation. Dual-energy X-ray Absorptiometry (DXA) measurements confirmed osteoporosis with a T score of -5.6 at the lumbar spine and –2.6 at the total hip. The patient did not have any chronic diseases or neurological disorders; viral hepatitis A, B and C and human herpes viruses 6-7 were negative by serology. The treating physician prescribed 60 mg denosumab subcutaneous injection every 6 months for 2 years. However, five days after initiating denosumab administration, the patient experienced recurrent convulsion episodes, amnesia, irritability hallucination, disturbance in attention, and change in mental status, with slight elevations in alkaline phosphatase and Aspartate Aminotransferase (AST) and marked elevation Gamma-Glutamyl Transferase (GGT) increasing to more than 5 x the upper limit of the normal reference range (ULN) (Table 2). Magnetic Resonance Imaging (MRI) findings included brain involutional changes and bilateral frontoparietal periventricular arteriosclerotic leukoencephalopathy. Currently, the patient is taking phenytoin 100 mg three times daily, levetiracetam 500 mg twice daily and calcium carbonate 600 mg twice daily for six months. After two months, the patient stopped treatment with a normal MRI and a free convulsion attack.

Discussion

Denosumab is a human monoclonal antibody indicated for postmenopausal women with osteoporosis at a high risk for fracture. A meta-analysis conducted to compare the efficacy and safety profile between denosumab at a dose of

Table 1. Laboratory and endocrine profile before starting denosumab.

Test Name	SI Units	Reference Range
Calcium	2.18 mmol/L	2.15-2.55 mmol/L
Chloride	103.9 mmol/L	98-107 mmol/L
Magnesium	0.89 mmol/L	0.66-1.07 mmol/L
Potassium	3.15 mmol/L	3.5-5.1 mmol/L
Sodium	139 mmol/L	135-145 mmol/L
Glucose-Random	9.77 mmol/L	4.11-6.05 mmol/L
BUN	3.5 mmol/L	2.14-7.14 mmol/L
Albumin	39.9 g/L	35-52 g/L
ALT	10.1 U/L	0-33 U/L
AST	20.4 U/L	0-32 U/L
ALP	62 U/L	35-104 U/L
GGT	31 U/L	0-40 U/L

Table 2. Laboratory and endocrine profile after starting denosumab.

Test Name	SI Units	Reference Range
ALT	33.4 U/L	0-33 U/L
ALP	173 U/L	35-104 U/L
GGT	213 U/L	0-40 U/L
AST	55.3 U/L	0-32 U/L
Potassium	4.41 mmol/L	3.5-5.1 mmol/L
Chloride	96.2 mmol/L	98-107 mmol/L
Sodium	134 mmol/L	135-145 mmol/L
Glucose-Random	6.51 mmol/L	4.11-6.05 mmol/L
BUN	4 mmol/L	2.14-7.14 mmol/L
Serum Amylase	56 U/L	28-100 U/L
Serum creatinine	56 µmol/L	44-80 µmol/L
Direct Bilirubin	0.7 µmol/L	0-3.4 µmol/L
Total Bilirubin	2.7 µmol/L	0-21 µmol/L
WBC count	8.61 × 10^3/ µL	4.5-11× 10^3/µL
RBC	4.61 × 10^6 /UL	4-5.2 × 10^6/µL
HGB	11.7 g/dL	12-16 g/dl
HCT	39.4%	33-51%
MCV	85.5 Fl	80-100 Fl
MCH	25.4 pg	25-35 pg
MCHC	29.7 g/dl	32-36 g/dl
Platelet count	369 × 10^3/UL	150-450× 10^3/UL
RDW-CV	14.4%	11.5-13.1%
MPV	9.8 Fl	6.5-10 Fl

60 mg subcutaneously per 6 months and alendronate at a dose of 70 mg orally per week for the treatment of postmenopausal osteoporosis found that denosumab was associated with a greater increase in Bone Mineral Density (BMD) [7]. Another study reported that denosumab was associated with a reduced risk of hip, vertebral, and nonvertebral fractures [8]. According to the Uppsala Monitoring Center, adverse drug reactions reported with denosumab use include hypocalcemia (9.4%), increased blood alkaline phosphatase (0.8%), hypomagnesemia (0.7%), hyperglycemia (1.3%), hypophosphatemia (1.2%), amnesia (1.1%) and seizure (1.7%) [9]. our case also had a high level of alkaline phosphatase (ALP 173 U/L). This finding may be explained by the fact that osteoblastic activity increases in disorders of the bone or as an adverse reaction associated with denosumab use [10]. The patient started a denosumab regimen with normal renal function and magnesium and calcium levels but developed reversible seizure. It may be hypothesized that long-term complications associated with denosumab can be prevented if the drug is initiated in a patient with normal calcium levels. Despite the long elimination half-life of this drug (4 to 5 months), she recovered from the convulsion episode, and antiepileptic drugs were stopped within 1 month from the initiation of phenytoin and levetiracetam [3].

In all previously reported cases, symptoms affecting the nervous system after the administration of denosumab were associated with hypocalcemia or renal impairment [11]. One case report involved a 61-year-old female on maintenance hemodialysis who developed severe hypocalcemia with a total serum calcium level of 1.34 mmol/following administration of a single subcutaneous 60 mg dose of denosumab [12]. On the other hand, another study reported hypocalcemia in a patient with good renal function [13]. Regardless, the patient in the present case developed reversible convulsion and a recurrent episode of amnesia and hallucination with no past medical history of hypocalcemia, hypomagnesemia, underlying malignancy, or renal impairment. The Naranjo algorithm is the most commonly used tool to assess adverse drug events causality. This tool has 10 simple questions that cover the following areas: temporal relationship, pattern of response, dechallenge or administration of an antagonist, rechallenge, alternative causes, placebo response, drug level in body fluids or tissue, dose-response relationship, previous patient experience with the drug, and confirmation by any other objective evidence. The answer to each question is then collected as a score. A score of zero or less means that an ADR is unlikely, a score of 1 to 4 suggest an ADR a possible event, a score of 5 to 8 indicates that an ADR is a probable event and a score of 9 or greater denotes that an Adverse Drug Reaction (ADR) is highly probable. In our case, the Naranjo score of 5-8 is considered probable adverse drug reactions for denosumab, and amnesia, convulsion, and elevations in blood glucose, alkaline phosphatase and gamma-glutamyl transferase are considered probable adverse drug reactions for denosumab (Table 3) [14]. We also used the updated Roussel Uclaf Causality Assessment Method for hepatocellular injury in Drug Induced Liver Injury (DILI) and Herb Induced Liver Injury (HILI). The items specifically refer to hepatocellular injury rather than cholestatic or mixed liver injury, with a total score and resulting causality grading as follows: ≤ 0, excluded; 1-2, unlikely; 3-5, possible; 6-8, probable; and ≥ 9, highly probable [15]. In our case, the grading was considered highly probable (Table 4). To the best of our knowledge, reversible seizures associated with denosumab administration in patients with no medical history of hypocalcemia, hypomagnesemia, underlying malignancy, and renal impairment have not been evaluated in previously documented cases. Further studies that take these variables into account will need to be undertaken.

Table 3. The Naranjo adverse drug reaction probability scale.

The Naranjo adverse drug reaction probability scale	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	0
Did the adverse event occur after the suspected drug was administered?	+2	-1	0	2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	0
Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0	2
Did the reaction reappear when a placebo was given?	-1	+1	0	1
Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	1
Total				7

Table 4. Updated RUCAM for cholestatic or mixed liver injury of DILI and HILI.

Items for Cholestatic or Mixed Liver Injury	Score	Results
1. **Time to onset from the beginning of the drug/herb**		
· 5–90 days (re-challenge: 1–90 days)	+2	+2
· <5 or >90 days (re-challenge: >90 days)	+1	
· **Alternative:** Time to onset from cessation of the drug/herb (except for slowly metabolized chemicals: ≤30 days)	+1	
2. Course of ALP after cessation of the drug/herb Percentage difference between ALP peak and N		
· Decrease ≥ 50% within 180 days	+2	+2
· Decrease < 50% within 180 days	+1	
· No information, persistence, increase, or continued drug/herbuse	0	
3. Risk factors		
Alcohol use current drinks/d: >2 for women, >3 for men	+1	+1
Alcohol use (current drinks/d: d'2 for women, d'3 for men)	0	
Pregnancy	+1	
Age ≥ 55years	+1	
Age < 55 years	0	
4. Concomitant use of drug(s)/herb(s)		
· None or no information	0	0
· Concomitant drug/herb with incompatible time to onset	0	
· Concomitant drug/herb known as hepatotoxin and with	-1	
· Compatible or suggestive time to onset	-2	
· Concomitant drug/herb with evidence for its role in this case (positive rechallenge or validated test)	-3	
5. **Search for alternative causes**	**Tick if negative**	**Tick if not done**
vGroup I (7 causes)		
· **HAV:** Anti-HAV-IgM		
· **HBV:** HBsAg, anti-HBc-IgM, HBV-DNA		
· **HCV:** Anti-HCV, HCV-RNA		
· **HEV:** Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA		
· Hepatobiliary sonography/color Doppler sonography of liver vessels/endosonography/CT/MRC		
· Alcoholism (AST/ALT ≥2)		
· Acute recent hypotension history (particularly if underlying heart disease)		
v Group II (3 causes)		
• Complications of underlying disease(s) such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver diseases		
• **Infection suggested by PCR and titer change for:**		
• CMV (Anti-CMV-IgM, anti-CMV-IgG)		
• EBV (Anti-EBV-IgM, anti-EBV-IgG)		
• HSV (Anti-HSV-IgM, anti-HSV-IgG)		
• VZV (Anti-VZV-IgM, Anti-VZV-IgG) Evaluation of Group I and II		
• **All causes—Groups I and II—Reasonably ruled out**	+2	+2
• The 7 causes of group I ruled out	+1	
• 6 or 5 causes of group I ruled out	0	
• Less than 5 causes of group I ruled out	-2	
• Alternative cause highly probable	-3	
6. **Previous hepatotoxicity of the drug/herb**		
• Reaction labeled in the product characteristics	+2	+2
• Reaction published but unlabeled	+1	
• Reaction unknown	0	

Conclusion

The efficacy of denosumab has been established as an antiresorptive drug for the treatment of osteoporosis. We report reversible central nervous system events and elevations of liver enzymes associated with the use of denosumab in a patient with normal levels of calcium and magnesium. Finally, we recommend careful monitoring of serum levels of calcium, phosphorus, and magnesium and symptoms of CNS events before initiation and during denosumab therapy, especially in the geriatric patient.

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