CASE REPORT

DENOSUMAB ASSOCIATED WITH BONE DENSITY INCREASE AND CLINICAL IMPROVEMENT IN A LONG-TERM HEMODIALYSIS PATIENT. CASE REPORT AND REVIEW OF THE LITERATURE

Sylvie Dusilová Sulková1,2, Jiří Horáček1, Roman Šafránek1,4, Petr Gorun4, Ondřej Viklický6, Vladimír Palička7

Hemodialysis Centre, University Hospital Hradec Králové, Czech Republic1, Department of Internal Medicine II, Charles University, Faculty of Medicine and University Hospital, Hradec Králové, Czech Republic2, Department of Internal Medicine IV, Charles University, Faculty of Medicine and University Hospital, Hradec Králové, Czech Republic3, Department of Internal Medicine III, Charles University, Faculty of Medicine and University Hospital, Hradec Králové, Czech Republic4, Hemodialysis centre BBraun Avitum, Ustí nad Orlicí, Czech Republic5, Department of Nephrology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic4, Department of Clinical Biochemistry, Charles University, Faculty of Medicine and University Hospital, Hradec Králové, Czech Republic6, Department of Internal Medicine III, Charles University, Faculty of Medicine and University Hospital, Hradec Králové, Czech Republic7

Summary: Denosumab is a human monoclonal antibody representing a novel therapy of osteoporosis. Contrary to always other antosteoporotic drugs, it is not contraindicated in advanced chronic kidney disease, as its pharmacokinetic does not differ from patients with normal kidney function. However, published case reports in chronic kidney disease (CKD) patients stopped the therapy after single dose because of hypocalcemia. We present a case of successful treatment of osteoporosis in a young hemodialysis patient with repeated denosumab doses.

Key words: Denosumab; Bone density; Hemodialysis; Hypocalcemia; Parathormone

Introduction

Denosumab is a full length human monoclonal antibody binding to the receptor activator of nuclear factor kappa-B ligand (RANKL), mimicking the action of osteoprotegerin (OPG, natural decoy receptor of RANKL) and representing a novel therapy of osteoporosis, approved by FDA in 2010 (1). By its action on RANKL, denosumab reduces the signal that is essential for osteoclasts formation, maturation, function and survival. RANKL inhibition has no effect on osteoblasts.

Denosumab is not cleared by the kidneys. In chronic kidney disease (CKD) dose adjustment of denosumab is not required but calcium and vitamin D supplementation is strongly recommended (2).

So far, only few case reports or very limited case series describing the experience with denosumab in CKD have been published. They all stopped the therapy after single dose because of hypocalcemia (3, 4, 5, 6, 7, 8) (Table 1).

We present a case of successful treatment of osteoporosis in a young hemodialysis patient with repeated denosumab doses.

Case report

A 30-year-old woman with end-stage renal disease (ESRD) has been hemodialyzed since 2002. In 2004, she underwent unsuccessful kidney transplantation. Genetic form of atypical hemolytic-uremic syndrome (HUS) was confirmed in 2006 and she has been treated with low-dose methylprednisolone and fresh-frozen plasma replacement since.

She suffered from severe back pain. Her concomitant secondary hyperparathyroidism (SHPT) has been well controlled using calcitriol (2005–2008) or paricalcitol (5–15 ug per week starting in 2008) respectively. In 2008, her T-score was −3.9 (DXA, lumbar spine) and −3.6 (total hip). Off-label alendronate between 2008 and 2011 was without any clinical effect.

After careful examination, in-label denosumab (60 mg s.c.) was first given in August 2011. Oral calcium together with nutritional vitamin D was supplemented accordingly. At six-month intervals, four further doses of denosumab were administered.

The bone turnover markers decreased considerably (Table 2). The decrease was sharp shortly after the start of therapy, but in the later period, bone turnover markers normalized. Of interest is namely a profound decrease of serum osteocalcin from 154.1 μg/l to 1.9 μg/l within two months after the first dose, but with further slight increase (these serum samples for bone markers assessment were taken always before denosumab administration). Vitamin D status was well presented with vitamin D supplementation (300,000 IU in regular three months intervals).
Tab. 1: Published case-reports with denosumab use in advanced CKD stages (only 1 dose in all cases).

<table>
<thead>
<tr>
<th>Author</th>
<th>No of patients</th>
<th>CKD stage; RRT</th>
<th>Age (years)</th>
<th>Lowest serum Ca (mmol/l)</th>
<th>Symptoms</th>
<th>Time point of low Ca (post dose)</th>
<th>Serum PTH before denosumab administration</th>
<th>Serum PTH after denosumab</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCormick (2012)</td>
<td>1 (3)</td>
<td>HD</td>
<td>61</td>
<td>1.34</td>
<td>fatigue</td>
<td>1 month</td>
<td>186 pg/ml</td>
<td>1044 pg/ml</td>
<td></td>
</tr>
<tr>
<td>Torregrosa (2013)</td>
<td>1</td>
<td>CKD 3-4T</td>
<td>64</td>
<td>1.91</td>
<td>not reported</td>
<td>6 months</td>
<td>442 pg/ml</td>
<td>1745 pg/ml</td>
<td></td>
</tr>
<tr>
<td>Ivanov (2013)</td>
<td>2</td>
<td>CKD 4–5T; HD</td>
<td>64; 64</td>
<td>1.96; 1.97 mmol/l</td>
<td>not reported</td>
<td>&gt;190 pmol/l; 54.8 pmol/l</td>
<td>&gt;100 pmol/l; 108 pmol/l</td>
<td>cinacalcet not discontinued</td>
<td></td>
</tr>
<tr>
<td>Ungprasert (2013)</td>
<td>1</td>
<td>CKD3</td>
<td>61</td>
<td>ionized 2.3 mg/dl</td>
<td>carpopedal spasm; QTc 520 ms</td>
<td>520 pg/ml</td>
<td>778 pg/ml</td>
<td>intravenous Ca</td>
<td></td>
</tr>
<tr>
<td>Talreja (2012)</td>
<td>1</td>
<td>CKD</td>
<td>68</td>
<td>6.7 mg/dl</td>
<td>generalized pain, tenderness</td>
<td>11 days</td>
<td>not done</td>
<td>409 pg/ml</td>
<td>intravenous Ca</td>
</tr>
<tr>
<td>Agarwal (2013)</td>
<td>1</td>
<td>PD</td>
<td>58</td>
<td>6.3 mg/dl</td>
<td>tetany</td>
<td>7 weeks</td>
<td>315 pg/ml</td>
<td>647 pg/ml</td>
<td>intravenous Ca</td>
</tr>
</tbody>
</table>

Abbreviations: CKD = chronic kidney disease; RRT = renal replacement therapy; HD = maintenance hemodialysis, PD = peritoneal dialysis, Ca = calcium; PTH = parathyroid hormone. Units are presented in accordance with the relevant reference.

Tab. 2: Bone metabolism markers in the course of denosumab treatment.

<table>
<thead>
<tr>
<th>Reference range</th>
<th>Ca (mmol/l)</th>
<th>PTH (pmol/l)</th>
<th>25(OH)D (nmol/l)</th>
<th>Osteocalcin (μg/l)</th>
<th>CTX (μg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before the 1st dose</td>
<td>2.15–2.51</td>
<td>1.6–6.9</td>
<td>&gt;75 (recommended)</td>
<td>11–43</td>
<td>0.162–0.436</td>
</tr>
<tr>
<td>Two months after 1st dose</td>
<td>2.26</td>
<td>30.5</td>
<td>not available</td>
<td>1.9</td>
<td>0.256</td>
</tr>
<tr>
<td>Before the 2nd dose</td>
<td>2.45</td>
<td>13.6</td>
<td>30.7</td>
<td>10.5</td>
<td>0.179</td>
</tr>
<tr>
<td>Before the 3rd dose</td>
<td>2.68</td>
<td>5.0</td>
<td>113.0</td>
<td>26.3</td>
<td>0.297</td>
</tr>
<tr>
<td>Before the 4th dose</td>
<td>2.63</td>
<td>7.0</td>
<td>60.8</td>
<td>33.9</td>
<td>0.724</td>
</tr>
</tbody>
</table>

Note: Serum samples taken in interdialysis period (during out-patient visit in tertiary centre).

Predialysis serum calcium, phosphate and PTH concentrations were monitored on at least monthly basis. Phosphate concentration did not exceed 1.8 mmol/l. Several episodes of asymptomatic hypocalcemia with concomitant increase in PTH levels were observed (Figure 1). They always responded to the adjustment of calcium supplementation and/or paricalcitol administration and nutritional vitamin D supplementation was not interrupted.

No soft tissue calcifications were detected either on hands or on lumbar and thoracic spine lateral x-rays. Very mild wedge-shaped deformity of 11th thoracic vertebral body remained stable, with no change on x-ray in October 2013. In 2010, ultrasonography revealed a small mass (0.07 ml) behind the left thyroid lobe. In 2013, the same observer (J.H.) described a smaller mass (0.03 ml) in the same location. In 2013, her lumbar spine and total hip T-score improved to −2.8 and −2.9, respectively. Importantly, her back pain disappeared shortly after the first denosumab dose and did not occur again, which resulted in marked improvement of subjective feeling and quality of life.

Discussion

In CKD, the DXA interpretation is not straightforward. However, low bone density in our patient indicated osteoporosis, with likely contribution of long-term methylprednisolone and secondary amenorrhea. Moreover, it was symptomatic, and neither years on hemodialysis nor awaited future kidney transplantation (following eculizumab administration in her case) would improve it. Previous treatment with bisphosphonate therapy did not improve her status. That is why we indicated denosumab shortly after its approval as novel antosteoporotic drug.

What is our experience? The administration of the drug was clinically well tolerated. There was a permanent clinical improvement, an increase in bone density, a sustained decrease of bone resorption markers and, in accord with the published case reports, also episodes of hypocalcemia associated with PTH increase (Table 2, Figure 1).

However, these episodes were asymptomatic, and we were always able to return her calcium and PTH levels to
normal within short time. Her secondary hyperparathyroidism remained responsive to conservative treatment with vitamin D receptor activators and her parathyroid glands did not enlarge.

Various explanations for denosumab-induced hypocalcemia in CKD patients have been presented. Westenfeld suggested hungry bone syndrome with prevailing activity of osteoblasts (9). In our case, however, the osteoblast activity actually decreased, as it is shown by decreasing osteocalcin concentrations (Table 2), which may be due to preserved association of osteoclasts and osteoblasts activity known in renal failure. Vitamin D deficiency would bring another explanation but in our case its levels were well controlled (Table 2). Cinacalcet, mentioned in another case report (4), was not used in our patient. Thus, the exact mechanism remains to be elucidated.

We consider the PTH increase to be a secondary response to hypocalcemia. We offer two parallel explanations why this response, i.e. PTH increase, is so sharp in end-stage renal disease (ESRD): skeletal resistance to PTH (10) and the imbalance between RANKL and OPG. RANKL is eliminated during hemodialysis and its serum concentration in ESRD usually remains normal (11). Conversely, serum OPG concentration is increased (12, 13). The RANKL/OPG ratio thus becomes abnormally low in ESRD. This low ratio is actually further diminished by denosumab. This may lead to over-suppression of the osteoclasts activity and to very low bone resorption. Indeed, in our case there was an 85% decrease in CTX within two months. Due to skeletal resistance to PTH and low RANKL/OPG ratio associated with ESRD, mobility of calcium from bone is abnormally low. Much higher PTH-mediated stimulus for calcium release from bone is therefore needed.

The parallel decreases both in CTX as well as in osteocalcin level may tentatively be explained by a preserved coupling between osteoblasts and osteoclasts in ESRD.

The published case reports are summarized in Table 1. Nadir of serum calcium decrease was observed at variable time points (from 11 days to 6 months) (3, 4, 5, 6, 7, 8). This means that the risk for calcium decrease is continuous. Two authors did not report clinical significance, but remaining four authors observed clinical manifestation of hypocalcemia. In three of them, it was severe (tetany, generalized pain, carpopedal spasm, prolongation of QTc) (see Table 2). Concomitant administration of cinacalcet is definitely not recommended due to augmented risk of serum calcium decrease. Serum parathyroid hormone sharply increased in all but one patient. However, no further course of PTH is given in any of these reports, as all authors stopped denosumab administration after the first dose. McCormick concluded with the definite warning against denosumab administration in hemodialysis patients. Various aspects for the differences between our and published experience may be found, including unsupervised administration and insufficient laboratory and clinical monitoring.

Contrary to their opinion and warning, our experience with denosumab in CKD is positive. Though we also observed a fall in calcium associated with sharp rise in PTH levels, neither was critical, also because we anticipated them from the published reports, and adjusted the concomitant treatment accordingly. Especially, we fully normalized serum vitamin D concentration. We therefore strongly believe that the fear of hypocalcemia in hemodialyzed patients is not a contraindication of denosumab and the benefit of the drug is prevailing.
Supported by Research Project NT/11355-4/2010 Ministry of Health of the Czech Republic.

References


Received: 12/01/2014
Accepted in revised form: 26/02/2014

Corresponding author:

Sylvie Dusilova Sulkova, M.D., Ph.D., prof., Hemodialysis centre; University Hospital Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech Republic; e-mail: sylvie.dusilova@fnhk.cz