Hypercalcemia after discontinuation of long-term denosumab treatment

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INTRODUCTION

- Denosumab (Dmb) is an anti-resorptive agent used to treat osteoporosis
- After discontinuation of Dmb bone resorption increases, and the bone mass gained during therapy declines
- Treatment with Dmb is considered to be reversible

AIMS

- We present a case report of hypoparathyroid hypercalcemia with renal impairment in a patient who discontinued 10 years treatment with Dmb.

CASE DESCRIPTION AND DISCUSSION

- A 67-year-old woman with osteoporosis participated in the FREEDOM-trial from October 2004 to May 2014
- She was treated with Dmb 60mg subcutaneously every 6 months
- In November 2014 biochemistry showed an increased p-ionized calcium (I-Ca) 1.64 mmol/l (1.18-1.32 mmol/l), suppressed p-parathyroid hormone (PTH) 1.6 pmol/l (1.6-6.9 pmol/l), and a decreased estimated glomerular filtration rate (eGFR) of 58ml/min (>60ml/min) (table 1).
- Additional investigations including a CT scan of the thorax, abdomen and pelvis, a bone scintigraphy, an MRI scan of both ankles and blood tests showed no evidence of malignancy, humoral hypercalcemia of malignancy, granulomatous disease, vitamin A intoxication or multiple myeloma.
- The hypercalcemia was unlikely to be attributed to her medication.
- The patient initiated treatment with Alendronat 70mg once weekly in January 2015.

骨转换标记（BTMs）未被调查直到2015年4月。然而，2004年到2014年，Dmb的使用是造成由骨吸收抑制剂引起的骨吸收增加的可能原因，这可能影响到骨转换。

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- During treatment with Dmb the patient had been normocalcemic most of the time for the first five years. Thereafter, total p-calcium was with one exception above the reference range and increasing.
- We speculate that the marked increase in BTMs after discontinuation of long-term Dmb is caused by a counter regulatory increased production of RANKL.
- The increased production of RANKL and potentially accumulation of RANKL will lead to a rebound activation of bone turnover, when the effect of the last denosumab administration wears off. This may cause hypercalcemia.
- If Dmb is administered again after 6 months bone resorption will effectively be inhibited again but in a situation like our case, where Dmb is not administered after 6 months, high bone turnover and hypercalcemia may persist for months.

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CONCLUSION

- We report the first association between discontinuation of long-term Dmb therapy for the treatment of osteoporosis and hypercalcemia with renal impairment and marked increase in BTMs.
- Our findings emphasize the need to develop evidence-based guidelines on discontinuation of treatment with Dmb in order to both avoid side-effects of long-term therapy and side effects of discontinuation as well as to preserve BMD.

DISCLOSURE

Anne Sophie Koldkjær Sølling and Andreas Kaal have nothing to declare. Torben Harsløf received lecture fees from Amgen. Bente Langdahl is a consultant for MSD, Amgen, Eli Lilly, and UCB and has received lecture fees from MSD, Eli Lilly, and Amgen. Lars Rejnmark has received lecture fees from Amgen and Eli Lilly and has consulted for NPS Pharma.