DISCONTINUATION OF DENOSUMAB THERAPY Is the rebound effect a catastrophe?

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I recommend watching the 40-minute lecture on the VuMedi platform.

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DISCONTINUATION OF DENOSUMAB THERAPY

Is the rebound effect a catastrophe?

TOPICS

- Antiresorptive drugs in the long-term treatment of osteoporosis

- Denosumab discontinuation – rebound effect: pathogenesis
- Use of bisphosphonates in preventing the rebound effect
- Fracture risk after denosumab discontinuation
- Complications of long-term osteoporosis treatment
- Current recommendations of international organizations

Summary

The main cause of the rebound effect is activation of persistent pre-osteoclast forms. There is also dysregulation of the OPG–RANK–TRAP system and other mechanisms regulating bone metabolism. After Dmab discontinuation, there is a rapid increase in bone resorption, a decrease in BMD, and an increased risk of vertebral and non-vertebral fractures.

In the FREEDOM study, after denosumab discontinuation, spinal BMD decreased within one year by 50%, and total hip BMD by 100%. The risk of vertebral fracture returned to the pretreatment level, and in patients with previous vertebral fracture, multiple vertebral fractures occurred. The longer the Dmab treatment, the greater the BMD decrease. Bisphosphonate administration reduces this effect, but does not eliminate it completely. In real-world studies, after a mean treatment duration of 7.5 years, from the 16% BMD gain achieved, 11.0% remained.

In Burckhardt's study of 797 women, the risk of fracture after Dmab discontinuation and ZOL administration was: 10% for vertebral fractures and 2.0% for non-vertebral fractures. Seventy-five percent of vertebral fractures after Dmab discontinuation occur between 6 and 12 months. The median is

12 months. 61-73.

The strongest risk factors for multiple vertebral fractures were: non-vertebral fracture, OR 6.15, and BTMs, OR 2.31. The lowest risk was observed in patients who received BP. The current standard at DD is administration of zoledronate or another BP. A second dose is given in patients with persistently high CTX ≥280 ng/L or P1NP ≥35 µg/L, or in case of fracture. Early administration of romosozumab may reduce the rebound effect. Gradual Dmab dose reduction is controversial; raloxifene administration does not produce good results. Earlier ZOL administration has been described only in experimental animals.

According to ASBMR 2024, a treatment break should be considered when there is no imminent fracture risk and the T-score is between −2.5 and −1.5. In the FREEDOM study, the risk of osteonecrosis of the jaw after 10 years was low – 0.27%. In real-world publications, after 3 years it was 0.32–0.95%. The risk of MRONJ increases with treatment duration. After tooth extraction in patients treated with Dmab, the risk is 2.3%. The rebound effect may be catastrophic if BP is not used preventively. Otherwise, BMD decreases and fracture risk increases, including the risk of multiple vertebral fractures.