EVENITY (Romosozumab) for Severe Osteoporosis

On December 12th 2019, the European Commission approved EVENITY for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture, after having been approved by the FDA on April 9th 2019

What is EVENITY? It is a bone-forming monoclonal antibody which inhibits the activity of sclerostin and results in a dual effect. It is indicated for the treatment of osteoporosis in postmenopausal women at high risk for fracture (history of osteoporotic fracture, multiple risk factors for fracture, or failed or are intolerant to other available osteoporosis therapy)

**Label Warning**
Potential risk of myocardial infarction, stroke and cardiovascular death

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Medical Management of Patients after Atypical Femur Fractures: ECTS Recommendations (2019)

- Atypical femoral fracture (AFF) is a spontaneous or low-trauma, sub-trochanteric or femoral shaft fracture frequently complicated by delayed healing or non-union
- Estimated incidence rate of AFF is 1.8 per 100,000 person years in patients on bisphosphonates (BP) for <2 years and increases to 113 per 100,000 person years in those treated for >8 years
- When diagnosis is made during the use of BP or denosumab, **this treatment should be stopped**
- Extensive monitoring with imaging of both upper legs is advised during the first 1-2 years after the diagnosis of AFF

- **Assess the risk of fragility fracture after AFF:**
  **HIGH RISK:**
  - Teriparatide or abaloperatide for 2 years (first line)
  - Romosozumab or selective estrogen receptor modulators (SERMs) or hormone replacement therapy (HRT) or tibolone ,or calcitonin (second line)
  - Post teriparatide treatment monitor bone turnover markers and BMD:
    — If very low bone turnover markers consider no follow up therapy
    — Re-administer BP or denosumab if bilateral intramedullary pins, or use any of the following : SERMS, Romosozumab, HRT , tibolone or Calcitonin

  **LOW RISK:**
  - Weak data supporting faster healing with Teriparatide: consider for 3-6 months in patients who underwent surgery
  - Currently no evidence for faster AFF healing with teriparatide in non-surgical cases

**ECTS: European Calcified Tissue Society, 2019**

Photo from Canadian Medical Association journal: A) an atypical femoral fracture (B) an incomplete atypical femoral fracture with cortical thicken
Adult Cancers and Bone Loss

ASCO RECOMMENDATIONS: MANAGEMENT OF OSTEOPOROSIS IN SURVIVORS OF ADULT CANCERS WITH NON-METASTATIC DISEASE

Who is at Risk?
Patients with non metastatic cancer who meet any of the following criteria:
- Advanced age (>65 in women and >70 in men)
- Current cigarette smoking
- Excessive alcohol consumption (>10 servings per week)
- History of prior non-traumatic fracture in adulthood
- Hypogonadism or postmenopausal status
- Impaired mobility
- Increased risks for falls
- Long-term exposure to glucocorticoids (prednisone >2.5 mg/d for ≥3 months)
- Low body weight
- Parental history of hip fracture
- Specific anticancer therapy (aromatase inhibitors, antiandrogens, or gonadotropin-releasing hormone (GnRH) agonists or chemotherapy-induced ovarian failure (CIOF))

How to screen at risk patients?
- Bone mineral density (BMD) testing at baseline and every two years
- Use a risk assessment tool such as FRAX

Whom to Treat?
- T scores of ≤-2.5 (Clinicians could consider treatment at higher bone density or T score)
- US-adapted FRAX 10-year probability of >20% for major osteoporotic fractures or >3% for hip fractures

Consider bone-modifying agents if:
- Premenopausal women receiving GnRH therapies causing ovarian suppression or with CIOF or who have undergone oophorectomy
- Postmenopausal women on aromatase inhibitors
- Men who have received or are receiving androgen deprivation therapy
- Patients undergoing or with a history of bone marrow transplantation
- Patients with chronic glucocorticoid use

What Treatment Agents to Use?
- Non-pharmacologic intervention:
  - Diet with adequate calcium (1,000 to 1,200 mg/d) and vitamin D (at least 800 to 1,000 IU/d)
  - Exercise: balance training, flexibility or stretching, endurance, and resistance and/or progressive strengthening, to reduce the risk of fractures caused by falls
  - Smoking cessation and limiting alcohol intake
- Bone Modifying Agents:
  - Oral bisphosphonates, intravenous bisphosphonates or subcutaneous denosumab

FDA will CONTINUE its RECALL for NATPARA®
A recombinant human PTH (1-84) used for treatment of hypoparathyroidism, due to rubber particle in the solution!!

ASBMR– Endocrine Society Guidance on Transitioning Hypoparathyroidism Patients from NATPARA®
A-12 hours after NATPARA injection, double or triple calcitriol dose & keep calcium dose same. Check serum Calcium several times for 1 to 2 weeks and adjust replacement accordingly.
B-Transition to teriparatide, recombinant human PTH (1-34), is not FDA-approved for hypoparathyroidism, with an effect to raise calcium concentration that is shorter-lived than NATPARA’s. If used to replace NATPARA, 2-3 times daily injections are typically necessary.
Calcium intake from dietary sources DOES NOT increase the risk of Cardiovascular Disease while calcium supplementation >1,000 mg/d might increase the risk of Coronary Heart Disease, specifically Myocardial Infarction. A systematic review and meta-analysis of 26 cohort studies (N=1,221,041) and 16 randomized controlled trials (N=138,188) from PubMed, Cochrane Central, Scopus, and Web of Science (search period till Mar 2019) explored the associations between calcium (Ca) from dietary and supplemental intakes and cardiovascular disease (CVD) risk. Cohort studies showed that dietary Ca (200-1,500mg/day) did not affect CVD risk. RCTs showed that Ca supplementation did not affect CVD risk except at 1,000-1,400 mg/d where it increased the risk of Coronary Heart Disease by 8% (with or without vitamin D) and by 20% (alone). Yang et al 2019, Journal of the American College of Nutrition.

Supplementing pregnant women with more than the recommended vitamin D dose (200-600 IU/d) may reduce the risk of gestational diabetes mellitus. Vitamin D deficiency during pregnancy is associated with pre-eclampsia, gestational diabetes, preterm birth, and low birth-weight. An updated Cochrane review (search period till JUL 2018) assessed the effects and safety of different regimens of vitamin D supplementation (>600 vs ≤ 600 IU/d; and ≥4,000 IU/d vs <4,000 IU/d) alone or in combination with calcium or other vitamins, minerals or nutrients supplementation during pregnancy. Compared to pregnant women receiving ≤ 600 IU of vitamin D supplementation with > 600 IU/d has no effect on the risk of pre-eclampsia, preterm and low birth-weight, but reduces the risk of gestational diabetes by 46%. However, comparing supplementation with higher doses of vitamin D, ≥4,000 IU/d vs <4,000 IU/d showed no effect on any outcome. Palacios et al 2019, Cochrane Database of Systematic Reviews.

Supplementation with vitamin D and calcium seems to be a more promising strategy in fracture prevention compared to D alone. A systematic review and meta-analysis assessed the risks of fracture associated with differences in concentrations of 25-hydroxyvitamin D [25(OH)D] in observational studies and the risks of fracture associated with supplementation with vitamin D alone or in combination with calcium in RCTs. The search was performed using PubMed, EMBASE, Cochrane Library, and other RCT databases (search period until Dec 2018).

a- 11 observational studies (N=39,141), baseline 25(OH)D (10.6 to 26.3ng/mL) showed that each 10 ng/mL increase in 25(OH)D concentration was associated with 7% lower risk of any fracture and 20% lower risk of hip fracture.

b- 11 randomized controlled trials (RCTs) of Vitamin D supplementation alone (400-30,000 IU/d) (N=34,243) did not show a significant reduction in risk of any fracture or hip fracture.

c- 6 RCTs of combined supplementation with vitamin D (400-800 IU/ day) and calcium (1,000-1,200mg/day) (N=49,282) showed a 6% reduced risk of any fracture and a 16% reduced risk of hip fracture. Yao et al 2019, JAMA Network Open.

In the general healthy population not selected for Vitamin D insufficiency, vitamin D supplementation did not improve bone mineral density. This is an ancillary study of VITamin D and OmegA-3 TriaL (VITAL); a double-blind, placebo-controlled RCT of supplemental vitamin D3 (2,000 IU/day) versus placebo (N=771). It aimed at assessing whether vitamin D3 supplementation in the general population improves spine, hip and whole body areal BMD or volumetric BMD at the radius and tibia. There was no significant difference between the two groups in any of the parameters of interest. However, in participants with low baseline free vitamin D (FVD) (<14.2 pmol/L) compared to higher levels, there was a slight improvement in spine aBMD and less bone loss at total hip aBMD with vitamin D3 supplementation at the end of the study. Further studies are needed to confirm whether patients with low FVD are ideal candidates for vitamin D supplementation. LeBoff et al 2020, Journal of Bone and Mineral Research.

High dose vitamin D supplementation in critically ill deficient patients has no benefit. A randomized, double-blind, placebo-controlled, phase 3 trial in vitamin D- deficient critically ill patients recruited 1,360 patient who were randomized after 12 hours of admission to ICU to receive either a single enteral does of 540,000 IU of vitamin D or matched placebo. Early administration of high-dose enteral vitamin D in this population did not offer any benefit over placebo on 90-day mortality or other, nonfatal outcomes. Ginde et al 2019 , New England Journal of Medicine.
Denosumab has a safe cardiovascular profile while Romosozumab may increase the risk of major cardiovascular outcomes

The aim of this systematic review and meta-analysis of RCTs is to examine the effect of denosumab (Dmab) or romosozumab therapy on cardiovascular (CV) outcomes in patients with primary osteoporosis. Four databases were systematically searched and 17 RCTs (Dmab: N=1,113,615/ Romosozumab: N= 612,219) were included. There was no association between Dmab therapy and risk of CV outcomes. Romosozumab therapy increased the risk of 4 P MACE (CV death or death, MI, stroke and heart failure) by 39% among elderly men and postmenopausal woman with osteoporosis over a period of 1 to 3 years. Lv et al, 2019, Bone

A single intravenous infusion of Zoledronate given 6 months after the last Denosumab injection prevents bone loss for at least 2 years

The study aimed to assess the efficacy of single infusion of zoledronate (ZOL) to prevent bone loss in women with postmenopausal osteoporosis who were treated with denosumab (Dmab) for a mean of 2.2 years and discontinued treatment after achieving osteopenia. Women were randomized to receive either ZOL 5mg within 3 weeks of the expected date of Dmab injection or continued Dmab every 6 month for 2 additional injections. At 24 months lumbar spine bone mineral density was maintained in ZOL group but decreased significantly in the Dmab. Bone turnover markers were higher in the Dmab group compared to ZOL and remained elevated at 24 months in the majority of women. Anastasilakis et al 2019, JBMR

YOGA IN PATIENTS WITH OSTEOPOROSIS

- Some yoga postures may increase the risk for vertebral fracture
- Seek a class that is designed for higher risk older adults and is led by an instructor

Postures to Avoid:
- Postures that place inappropriate and excessive forces on the vertebrae
- Postures that place the hip in forced, end-range external rotation
- Advanced spinal extension postures
- Seated postures

Encouraged Postures:
- Supine postures or standing (on both fee with a stable base of support)
- Postures emphasizing spinal alignment or extension should be the foundation


Recent 2020 Publications

SAVE THE DATE!

Mar 14, 2020: OSTEOS Annual Meeting, Lebanon
Mar 28-31, 2020: Endocrine Society Annual Meeting, San Francisco, CA, USA
Jun 26-28, 2020: Lebanese Society of Endocrinology Diabetes and Lipids (LSEDL), Lebanon

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