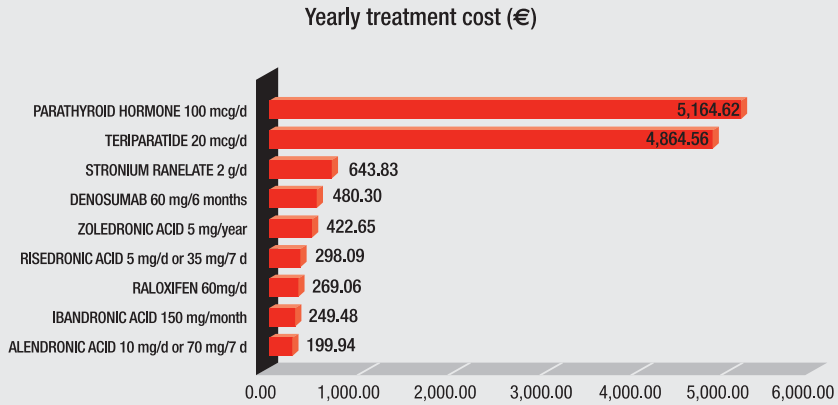
www.dtb.navarra.es

02/2012

Denosumab (▲Prolia®) for osteoporosis

New mechanism but questionable efficacy



There are no efficacy data comparing denosumab to biphosphonates

- Denosumab is the first monoclonal antibody that binds to RANKL inhibiting its action and activating the RANK receptor on the surface of osteoclasts and other cells of the immune system.
- Studies on the efficacy of denosumab compared to alendronate have only been carried out with surrogate measurements like the increase in bone density, which has limited value in predicting the risk of fracture.
- The main uncertainty concerns long-term safety given its effects on the immune system.
- Its price is higher than alendronate and risedronate.

Indications[1]

Treatment of osteoporosis in postmenopausal women at increased risk of fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

Mechanism of action and pharmacokinetics[1]

This monoclonal antibody impedes the interaction between RANKL/RANK inhibiting the formation of osteoclasts, and reducing bone resorption. Subcutaneous bioavailability reaches 78% and the elimination half-life is 26 days.

Posology and method of administration[1]

A 6 mg dose is administered in a single subcutaneous injection once every 6 months in the thigh, abdomen or posterior side of the arm. Administration should be carried out by a trained person in this technique. Calcium and/or vitamin D supplements should be added to the diet if daily uptake and sun exposure are not sufficient.

Clínical efficacy

Osteoporosis in postmenopause women

The FREEDOM[3] study compared denosumab 60 mg every 6 months for 3 years in 7,807 postmenopausal women with or without any previous fracture, between 60 and 90 years and with basal lumbar or hip T-scores between -2.5 and -4.0. The estimated absolute average probability of fracture after 10 years was 18.6% for major osteoporotic fractures and 7.33% for hip fracture[1]. However, after the 3 years of follow-up, the placebo group experienced an incidence of 1.2% of hip fractures which meant that the risk of hip fracture was overestimated considerably. After 3 years of treatment denosumab significantly reduced the incidence of new radiological vertebral fractures with respect to placebo (2.3% vs 7.2% RR=0.32 [CI95% 0.26-0.41, NNT=21). There was also a significant reduction in the incidence of non-vertebral frac-

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

tures compared to placebo (6.5% vs 8.0%, HR=0.80 [CI 95% 0.67-0.95], ARR=1.5%, NNT=67), and hip fractures (0.7% vs 1.2%; HR 0.60 [CI 95% 0.37-0.97], ARR=0.5%, NNT=200) and clinical vertebral fractures (0.8% vs 2.6%; HR 0.31 [CI 95% 0.2-0.47], ARR=1.8%, NNT=56).

Another 3 studies evaluated the effect of denosumab on bone mineral density (BMD) and bone markers: the DEFEND[4] trial employed placebo as a comparator and the DECIDE[5] and STAND[6] trials compared denosumab with alendronate.

Treatment of bone loss associated with hormone suppression in men with prostate cancer

In this study[7] the effect of denosumab 60 mg once every 6 months was evaluated in comparison to placebo during a period of 3 years in 1,468 patients with an increased risk of fracture defined as patients ≥70 years or <70 years with BMD lumbar, hip or femoral neck T-scores of < -1.0 or previous history of an osteoporosis related fracture. The primary endpoint was the percentual change in BMD with respect to the baseline values in the lumbar region after 2 years, which was higher in the case of denosumab.

Safety

Adverse reactions[1]

Frequent (≥1/100 to <1/10): urinary and upper respiratory tract infections, schiatica, cataracts, (mainly in patients who receive treatment for prostate cancer), constipation, skin eruptions, and pain in extremities. **Less frequent (≥1/1.000 to <1/100):** diverticulitis, cellulitis that in some occasions required hospital admission, ear infections and eczema. **Rare (<1/10.000):** hypocalcemia. Some cases of neoplasms and pancreatitis have been reported in published studies although no confirmation of a causal relationship with denosumab has been established[8,9].

Contraindications[1]

Hypocalcemia and hypersensitivity to the main substance or any of its excipients.

Warnings and precautions[1]

Patients under treatment with denosumab require an adequate intake of calcium and vitamin D to avoid hypocalcemia. In addition, calcium levels should be monitored in cases of severe renal impairment (creatinin clearance <30 mL/min) or dialysis. The risk of skin infections (mainly cellulitis). It is recommended to carry out dental checkups before initiating and during treatment, and if possible, to avoid any invasive dental procedures given the risk of osteonecrosis of the jaw (ONJ) especially in cancer patients. The cover of the needle contains natural rubber which can cause allergic reactions. This treatment should not be given to patients with hereditary problems of fructose intolerance.

Use in special situations[1]

Pregnancy: not recommended. **Lactation:** it is unknown whether it is excreted in breast milk. **Severe renal impairment:** monitor calcium levels. **Liver impairment:** no data is available currently. **Elderly:** no dose adjustments are necessary. **Children:** there is no data available.

Interactions[1]

No studies on drug interactions have been carried out.

Risk plan of the European Medicines Agency (EMA)[1]

The EMA has not established any risk plan for this drug. However the FDA has considered risk in the cases of hypocalcemia, severe infections, skin alterations and osteonecrosis[14].

Place in therapeutics

Postmenopausal women with osteoporosis

Osteoporosis is a risk factor for bone fractures. The BMD decreases naturally over time after reaching a peak value of bone mass at approximately 30 years of age. This decrease is more accentuated in women after menopause.

Pharmacological management of osteoporosis has shown to be effective in reducing the loss of bone mass. However, this improvement in BMD with respect to placebo does not mean that in the majority of cases there is a reduction in terms of clinically relevant fractures. Calcitonins were employed for many years with no real demonstration of their efficacy in reducing bone fractures. The use of hormonal replacement therapy has been discontinued because of the excess cardiovascular risk associated with its use which does not justify the benefits. Raloxifen, strontium ranelate, teriparatide and parathyroid hormone have not demonstrated their efficacy in preventing hip fractures and the efficacy of biphosphonates still remains quite uncertain. Moreover data on the efficacy of these drugs with regard to vertebral fractures were obtained from studies where the fractures were diagnosed by morphometric radiological methods (determined with uncertain diagnostic precision). The clinical trascendence of this evidence is therefore uncertain.

Today the use of drugs in the reduction of fractures is questionable. The most adequate approach is the prevention of osteoporosis through diet and the prevention of falls, especially in the elderly.

There are no direct comparative data between denosumab and biphosphonates. Nor are there any studies on the efficacy in women who do not respond to bisphosphonates. With respect to denosumab s safety profile, besides the inabilty to rule out typical adverse reactions related to biphosphonate, such as osteonecrosis and atypical fractures, there have been reported cases of neoplasm and severe infection. Long term safety and efficacy is yet to be determined.

Treatment of bone loss associated with hormonal suppression in patients with prostate cancer

Androgen deprivation is the initial treament in the majority of patients with localized advanced prostate cancer[11]. This treatment can cause a reduction in BMD in the long term, which in turn can increase the risk of pathological fractures.

Bisphosphonates are the most studied drugs employed in this group of patients and although the effect produced is an increase in BMD, there is no evidence of a reduction in the incidence of fractures. Therefore routine use of these drugs is not recommended[11].

Currently, risedronic acid, zoledronic acid and teriparatide are indicated for the treatment of osteoporosis in men with a high risk of fracture. There is no approved drug for the specific indication of treating bone loss associated with hormonal suppression in men with prostate cancer. The FDA has not approved denosumab for this indication due to lack of evidence[19].

Denosumab has shown to increase BMD. In terms of fracture, there is no clear translation of a low BMD in the absence of other risk factors. The effect of denosumab in preventing fractures or increasing survival rates in this group of patients has not been shown. The risk-benefit relationship in the long term is still to be determined.

Presentations

Prolia® (Amgen Europe B.V.) 60 mg prefilled syringe 1 mL injectable solution (240.15 €).

References

A complete report on denosumab is available at: http://www.dtb.navarra.es

Servicio Navarro de Salud
Osasunbidea

INFORMATION:
Servicio de Prestaciones Farmacéuticas Plaza de la Paz s/n, 4ª planta - 31002 Pamplona **T** 848429047 **F** 848429010

NEW DRUGS ASSESSMENT COMMITTEE:
Iñaki Abad, Mª José Ariz, Ana Azparren, Mª Concepción Celaya, Juan Erviti, Javier Garjón, Javier Gorricho, Antonio López, Rodolfo Montoya, Mikel Moreno, Lourdes Muruzábal