Denosumab

Denosumab (trade names **Prolia** and **Xgeva**) is a human monoclonal antibody[1] for the treatment of osteoporosis,[1] treatment-induced bone loss, metastases to bone,[1] and giant cell tumor of bone.[2]

The most common side effects are joint and muscle pain in the arms or legs.[3] Denosumab is contraindicated in people with low blood calcium levels. Denosumab is a RANKL inhibitor,[1] which works by preventing the development of osteoclasts which are cells that break down bone. It was developed by the biotechnology company Amgen.[4]

1 Medical uses

Denosumab is used for those with osteoporosis at high risk for fractures, bone loss due to certain medications, and in those with bone metastases.[5]

1.1 Cancer

A 2012 meta-analysis found that denosumab was better than placebo, zoledronic acid and pamidronate in reducing the risk of fractures in those with cancer.[6]

1.2 Post-menopausal osteoporosis

In those with postmenopausal osteoporosis it decreases the risk of fractures but increases the risk of infection.[7] A 2013 review concluded that it is a reasonable treatment for this condition.[8]

2 Adverse effects

The most common side effects are joint and muscle pain in the arms or legs.[3] There is an increased risk of infections such as cellulitis, hypocalcemia (low blood calcium), hypersensitivity allergy reactions, and osteonecrosis of the jaw and atypical hip fractures.[3] Another trial showed significantly increased rates of eczema and hospitalization due to infections of the skin.[9] It has been proposed that the increase in infections under denosumab treatment might be connected to the role of RANKL in the immune system.[10] RANKL is expressed by T helper cells, and is thought to be involved in dendritic cell maturation.[11]

3 Contraindications and interactions

It is contraindicated in people with hypocalcemia, and sufficient calcium and vitamin D levels must be reached before starting on denosumab therapy.[12] Data regarding interactions with other drugs are missing. It is unlikely that denosumab exhibits any clinically relevant interactions.[12]

Denosumab works by lowering the hormonal message that leads to excessive osteoclast-driven bone removal and is active in the body for only six months. Similarly to bisphosphonates, denosumab appears to be implicated in increasing the risk of osteonecrosis of the jaw (ONJ) following extraction of teeth or oral surgical procedures but, unlike bisphosphonate, the risk declines to zero approximately 6 months after injection.[13]

4 Mechanism of action

Bone remodeling is the process by which the body continuously removes old bone tissue and replaces it with new bone. It is driven by various types of cells, most notably osteoblasts (which secrete new bone) and osteoclasts (which break down bone); osteocytes are also present in bone, but their role is still not well understood.

Precursors to osteoclasts, called pre-osteoclasts, express surface receptors called RANK (receptor activator of nuclear factor-kappa B). RANK is a member of the tumor necrosis factor receptor (TNFR) superfamily. RANK is activated by RANKL (the RANK-Ligand), which exists as cell surface molecules on osteoblasts. Activation of RANK by RANKL promotes the maturation of pre-osteoclasts into osteoclasts. Denosumab inhibits this maturation of osteoclasts by binding to and inhibiting RANKL. This mimics the natural action of osteoprotegerin, an endogenous RANKL inhibitor, that presents with decreasing concentrations (and perhaps decreased avidity) in patients who are suffering from osteoporosis. This protects bone from degradation, and helps to counter the progression of the disease.[2]

5 Regulatory approval

5.1 United States

In June 2010, denosumab was approved by the U.S. Food and Drug Administration (FDA) for use in postmenopausal women with risk of osteoporosis under the trade name *Prolia*,[14] and in November 2010, as *Xgeva*, for the prevention of skeleton-related events in patients with bone metastases from solid tumors.[15] Denosumab is the first RANKL inhibitor to be approved by the FDA.[16]

On 13 August 2009, a meeting was held between Amgen and the Advisory Committee for Reproductive Health Drugs (ACRHD) of the (FDA) to review the potential uses of denosumab. A press release summarizing this meeting said:

> "After reviewing safety and efficacy data from 30 clinical studies involving more than 12,000 patients, the Committee recommended approval of Prolia for the treatment of postmenopausal osteoporosis, and for the treatment of bone loss in patients undergoing hormone ablation for prostate cancer.[17]

In October 2009, the U.S. Food and Drug Administration (FDA) delayed approval of denosumab, stating that they needed more information.[18]

On 2 June 2010, denosumab was approved for postmenopausal osteoporosis by the US FDA.[16]

In November 2010, the US FDA approved denosumab (to be marketed as *Xgeva*) for the prevention of skeletal-related events in patients with bone metastasis from solid tumors.[15]

On 13 June 2013, the US FDA approved denosumab for treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where resection would result in significant morbidity.[19]

5.2 Europe

On 17 December 2009, the Committee for Medicinal Products for Human Use (CHMP) issued a Positive Opinion for denosumab for the treatment of postmenopausal osteoporosis in women and for the treatment of bone loss in men with hormone ablation therapy for prostate cancer.[3] Denosumab was approved for marketing by the European Commission on 28 May 2010.

6 References

[1] Pageau, Steven C. (2009). "Denosumab". *MAbs*. **1** (3): 210–215. doi:10.4161/mabs.1.3.8592. PMC 2726593. PMID 20065634.

[2] McClung, Michael R.; Lewiecki, E. Michael; Cohen, Stanley B.; Bolognese, Michael A.; Woodson, Grattan C.; Moffett, Alfred H.; Peacock, Munro; Miller, Paul D.; et al. (2006). "Denosumab in Postmenopausal Women with Low Bone Mineral Density". *New England Journal of Medicine*. **354** (8): 821–31. doi:10.1056/NEJMoa044459. PMID 16495394.

[3] European Medicines Agency. European Public Assessment Report (EPAR) for Prolia. Updated October 16, 2014.

[4] "Prolia (denosumab)". *Products*. Amgen. Retrieved 6 May 2012.

[5] "Denosumab". The American Society of Health-System Pharmacists. Retrieved Mar 16, 2015.

[6] Lipton, A; Fizazi, K; Stopeck, AT; Henry, DH; Brown, JE; Yardley, DA; Richardson, GE; Siena, S; Maroto, P; Clemens, M; Bilynskyy, B; Charu, V; Beuzeboc, P; Rader, M; Viniegra, M; Saad, F; Ke, C; Braun, A; Jun, S (November 2012). "Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials.". *European journal of cancer (Oxford, England : 1990)*. **48** (16): 3082–92. doi:10.1016/j.ejca.2012.08.002. PMID 22975218.

[7] Zhou, Z; Chen, C; Zhang, J; Ji, X; Liu, L; Zhang, G; Cao, X; Wang, P (2014). "Safety of denosumab in postmenopausal women with osteoporosis or low bone mineral density: a meta-analysis.". *International journal of clinical and experimental pathology*. **7** (5): 2113–22. PMID 24966919.

[8] Josse, R; Khan, A; Ngui, D; Shapiro, M (March 2013). "Denosumab, a new pharmacotherapy option for postmenopausal osteoporosis.". *Current medical research and opinion*. **29** (3): 205–16. doi:10.1185/03007995.2013.763779. PMID 23297819.

[9] Cummings, Steven R.; Martin, Javier San; McClung, Michael R.; Siris, Ethel S.; Eastell, Richard; Reid, Ian R.; Delmas, Pierre; Zoog, Holly B.; et al. (2009). "Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis". *New England Journal of Medicine*. **361** (8): 756–65. doi:10.1056/NEJMoa0809493. PMID 19671655.

[10] Khosla, S (2009). "Increasing options for the treatment of osteoporosis". *New England Journal of Medicine*. **361** (8): 818–820. doi:10.1056/NEJMe0905480. PMID 19671654.

[11] EntrezGene 8600 TNFSF11 tumor necrosis factor (ligand) superfamily, member 11; Homo sapiens

> also known as *RANKL* .. This protein was shown to be a dentritic cell survival factor and is involved in the regulation of T cell-dependent immune response.

[12] Haberfeld, H, ed. (2009). *Austria-Codex* (in German) (2009/2010 ed.). Vienna: Österreichischer Apothekerverlag. ISBN 3-85200-196-X.

[13] "Injectable Prolia — Osteoporosis Update".

[14] Matthew Perrone (June 2, 2010). "FDA clears Amgen's bone-strengthening drug Prolia". BioScience Technology.

[15] "Amgen's Denosumab Cleared by FDA for Second Indication". 19 Nov 2010.

[16] "FDA Approves Denosumab for Osteoporosis". 2 June 2010.

[17] "Amgen Issues Statement on Outcomes of Advisory Committee for Reproductive Health Drugs (ACRHD) Meeting". PRNewswire/FirstCall. August 13, 2009.

[18] Pollack, Andrew (19 October 2009). "F.D.A. Says No to an Amgen Bone Drug". *The New York Times*.

[19] "FDA Approval for Denosumab".

7 Further reading

- Lacey, D. L.; Boyle, W. J.; Simonet, W. S.; Kostenuik, P. J.; Dougall, W. C.; Sullivan, J. K.; San Martin, J. S.; Dansey, R. (2012). "Bench to bedside: Elucidation of the OPG–RANK–RANKL pathway and the development of denosumab". *Nature Reviews Drug Discovery*. **11** (5): 401–419. doi:10.1038/nrd3705. PMID 22543469.
- Walker, Emily P. (February 7, 2012). "Benefit of Bone Drug in Prostate Cancer in Doubt". *MedPage Today*.

8 External links

- "Prolia — Official website".
- "Xgeva — Official website".
- Prolia full prescribing information
- Xgeva full prescribing information

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9.1 Text

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