Making fracture prevention a priority

Amgen symposium at the Fragility Fracture Network (FFN) Congress, Malmö, Sweden
Friday 25 August 2017, 12:30–13:20

prolia® denosumab
ACT BEFORE IMPACT

The Amgen-sponsored symposium at the FFN 2017 Congress provided an interactive educational opportunity for delegates, and was led by Mattias Lorentzon (Sweden) as meeting chair. He was joined by Bente Langdahl (Denmark) who presented on the treatment options and optimal timing for post-fracture care.

What are the treatment options and optimal timing for post-fracture care?

Bente Langdahl

As fractures in elderly patients are associated with life-changing events, there is a need to prevent fractures in this population. Evidence demonstrates that patients who have recently experienced a fracture are at risk of experiencing a subsequent fracture. Professor Langdahl highlighted imminent fracture risk in specific populations including the elderly, and summarized the effects and optimal timing of two therapeutic options for the management and treatment of fractures.

Many post-menopausal women falsely perceive their risk of fracture as low.[1] Fractures are perceived as random events linked to environmental hazards, accidental falls and unsafe behavior, rather than to an underlying condition such as osteoporosis.[2,3]

Risk factors for first and subsequent fractures

There are many known risk factors for first and subsequent fractures; in addition to risk of falling, these are most commonly associated with poor bone quality and include reduced bone mass, increased bone turnover, and compromised bone architecture. Risk factors for future fracture include demographic factors (such as age, previous fractures, family history of osteoporosis, smoking, alcohol consumption), and diseases and drugs affecting bone quality.[4]

Imminent fracture risk

Several studies provide evidence of an increased risk of fracture following a previous fracture.[5-7] A prospective cohort study conducted in Australia assessed the annual risk of developing a first and subsequent fracture, and showed that the risk of a subsequent fracture was almost 2-fold higher in women and approximately 3.5-fold higher in men, than the risk of experiencing a first fracture.[5] The study showed that 41% and 52% of subsequent fractures in women and men, respectively, occurred within 2 years of the initial fracture.[5] Further evidence from two cohort studies similarly demonstrated that the imminent fracture risk remains highest in the initial years following a first fracture, but even after many years post-fracture, the fracture risk remains higher than that in patients with no previous fracture.[6,7]

41% AND 52% OF SUBSEQUENT FRACTURES IN WOMEN AND MEN, RESPECTIVELY, OCCURRED WITHIN 2 YEARS OF THE INITIAL FRACTURE[5]

More research is needed to determine exact risk factors for imminent fracture risk, but current factors include:[4]

- The presence of the underlying condition that led to the first fracture
  - Diseases, pharmacological treatments, etc.
- Fracture treatment and post-fracture care
  - Walking aids, plastering and impaired coordination
  - Surgery may cause cognitive impairment
- Immobilization
  - Bone loss

The location of the first fracture can also provide predictive information about the location of subsequent fractures, and should be considered when assessing a patient's risk of subsequent fractures. For example, vertebral fractures are known to predict subsequent vertebral fractures,[8,9] and non-vertebral fractures are known to predict subsequent non-vertebral fractures.[10] Increased risk of hip fracture, however, is associated with any type of prior fracture, including previous humeral and wrist fractures.[11,12]

Strategies for the prevention of subsequent fractures

There are various strategies in place to help reduce patients' risk of subsequent fractures, particularly in patient populations identified as high-risk. The inclusion of patients in the Fracture Liaison Services (FLS) programme is associated with reduced risk of subsequent fractures and mortality, notably in patients who have already experienced hip fractures.[13]

THE INCLUSION OF PATIENTS IN THE FRACTURE LIAISON SERVICES (FLS) PROGRAMME IS ASSOCIATED WITH REDUCED RISK OF SUBSEQUENT FRACTURES AND MORTALITY

A number of antiresorptive therapy options exist for prevention of osteoporotic fragility fractures, and Professor Langdahl reviewed data on the bisphosphonate zoledronic acid, and Prolia® (denosumab), a fully human monoclonal antibody. These two treatment options work differently. Prolia® targets RANK ligand, and prevents it from binding to its receptor, RANK, thereby inhibiting the formation, function and survival of osteoclasts.[14,15] By contrast, bisphosphonates bind to bone mineral and likely inhibit osteoclast function by being taken up by osteoclasts at sites of bone resorption.[14] There is evidence that both of these treatment options reduce the risk of first and subsequent fractures.

A large, randomized, double-blind trial, The Health Outcome and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial, studied the effects of zoledronic acid in post-menopausal women with osteoporosis (≥65 years old), and showed that an annual 5 mg dose of intravenous zoledronic acid during a 3-year period significantly reduced the risk of vertebral, hip and non-vertebral fractures.[16] The HORIZON Recurrent Fracture Trial also showed that zoledronic acid significantly reduced the risk of all clinical fractures in men and women (≥50 years old) when administered within 90 days of surgical repair of a hip fracture.[17] Data suggest that drug efficacy is reduced in patients dosed within 2 weeks of their fracture repair.[18]

The long-term efficacy and safety of Prolia® has been established in the FREEDOM trial and its extension.[19] Treatment with Prolia® significantly reduced the risk of new vertebral, non-vertebral and hip fractures in post-menopausal women with osteoporosis

in the 3-year FREEDOM trial.[20] The FREEDOM extension data show that treatment with Prolia® is associated with increases in BMD over 10 years without therapeutic plateau, and sustained low incidence of vertebral and non-vertebral fractures.[19, 21] A post hoc analysis of the FREEDOM data provided evidence that Prolia® effectively prevented subsequent fractures in patients with a previous fracture.[22] To evaluate if Prolia® treatment impacts fracture healing, a further post hoc analysis of the FREEDOM trial was performed.[23] This analysis showed that in patients experiencing a non vertebral fracture, there were no delays in fracture healing within 6 weeks of Prolia® administration, indicating that Prolia® can be administered at any time post-fracture.[23] In patients who had recently received a knee implant, Prolia® was found to reduce the migration of the implant when administered within 24 hours of surgery.[24]

PROLIA® CAN BE ADMINISTERED AT ANY TIME POST-FRACTURE[23]

Professor Langdahl concluded her presentation by summarizing that an initial fragility fracture is a clear warning of subsequent fractures, and the risk of subsequent fractures should be assessed as soon as possible. This can be done by evaluating the patient's risk factors, bone mass, and risk of falling. Measures to help prevent secondary fracture must be put in place (e.g. FLS) and anti-osteoporosis treatment should be initiated. In addition, it is hugely important to educate patients and their relatives on the serious consequences and chronicity of osteoporosis.

AN INITIAL FRAGILITY FRACTURE IS A CLEAR WARNING OF SUBSEQUENT FRACTURES, AND THE RISK OF SUBSEQUENT FRACTURES SHOULD BE ASSESSED AS SOON AS POSSIBLE

IT IS HUGELY IMPORTANT TO EDUCATE PATIENTS AND THEIR RELATIVES ON THE SERIOUS CONSEQUENCES AND CHRONICITY OF OSTEOPOROSIS

References

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Prolia® (denosumab) Abbreviated Prescribing Information

Please refer to the Summary of Product Characteristics (SmPC) before prescribing Prolia. **Pharmaceutical Form:** Pre-filled syringe with automatic needle guard containing 60mg of denosumab in 1ml solution for injection for single use only. Contains sorbitol (E420). **Indication:** Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. **Dosage and Administration:** 60mg Prolia administered as a subcutaneous injection once every 6 months. Patients must be supplemented with calcium and vitamin D. No dosage adjustment required in patients with renal impairment. Not recommended in paediatric patients under 18 years of age. Give Prolia patients the package leaflet and patient reminder card. **Contraindications:** Hypocalcaemia or hypersensitivity to the active substance or to any of the product excipients. **Special Warnings and Precautions:** ***Hypoca*** **esirable** Hypocal ed: Very vitamin mmon (≥ levels is fection, to hypo sh, and calcium ellulitis, ***Impairr*** s of the clearan caemia) develop setting, in these patients is especially important. ***Skin infections:*** Patients receiving Prolia may develop skin infections (predominantly cellulitis) requiring hospitalisation and if symptoms develop then they should contact a health care professional immediately. ***Osteonecrosis of the jaw (ONJ):*** ONJ has been reported rarely with Prolia 60mg every 6 months. Delay treatment in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventative dentistry and an individual benefit:risk assessment is recommended prior to treatment with Prolia in patients with concomitant risk factors. Refer to the SmPC for risk factors for ONJ. Patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups and immediately report oral symptoms during treatment with Prolia. While on treatment, invasive dental procedures should be performed only after careful consideration and avoided in close proximity to Prolia administration. The management plan of patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. ***Atypical femoral fracture (AFF):*** AFF has been reported in patients receiving Prolia. Discontinuation of Prolia therapy in patients suspected to have AFF should be considered pending evaluation of the patient based on an individual benefit risk assessment. ***Concomitant medication:*** Patients with rare hereditary problems of fructose intolerance should not use Prolia. ***Dry natural rubber:*** The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex) which may cause allergic reactions. **Interactions:** Prolia did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 3A4 (CYP3A4). There are no clinical data on the co-administration of denosumab and hormone replacement therapy (HRT), however the potential for pharmacodynamic interactions would be considered low. Pharmacokinetics and pharmacodynamics of Prolia were not altered by previous alendronate therapy. **Fertility, pregnancy and lactation:** There are no adequate data on the use of Prolia in pregnant women and it is not recommended for use in these patients. It is unknown whether denosumab is excreted in human milk. A risk/benefit decision should be made in patients who are breast feeding. Animal studies have indicated that the absence of RANKL during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum. No data musculoskeletal pain (including severe cases) rare cases of severe symptomatic hypocalcaemia, and rare events of hypersensitivity (including rash, urticaria, facial swelling, erythema and anaphylactic reactions) have been reported. Please consult the Summary of Product Characteristics for a full description of undesirable effects. **Pharmaceutical Precautions:** Prolia must not be mixed with other medicinal products. Store at 2°C to 8°C (in a refrigerator). Prolia may be exposed to room temperature (up to 25°C) for a maximum single period of up to 30 days in its original container. Once removed from the refrigerator Prolia must be used within this 30 day period. Do not freeze. Keep in outer carton to protect from light. **Legal Category:** POM. **Marketing Authorisation Number:** EU/1/10/618/003. **Marketing Authorisation Holder:** Amgen Europe B.V., Minervum 7061, NL-4817 ZK Breda, The Netherlands. Further information is available from Amgen Limited, 240 Cambridge Science Park, Milton Road, Cambridge, CB4 0WD. Prolia is a registered trademark of Amgen Inc. **Date of PI preparation:** June 2015 (Ref: UKIE-P-162-0515-106061)

Local countries to insert approved PI

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.

Adverse events should also be reported to Amgen Limited on +44 (0) 1223 436712

Adverse events should be reported to the appropriate health authority in your country

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