Making fracture prevention a priority

Amgen symposium at WCO-IOF-ESCEO, Florence, Italy
Saturday 25 March 2017, 12.15–13.45

prolia® denosumab
ACT BEFORE IMPACT

The Amgen-sponsored symposium at the WCO-IOF-ESCEO Congress 2017 provided an engaging and interactive educational opportunity for delegates. The event was led by a panel of specialists in the field of osteoporosis, with Maria Luisa Brandi (Italy) as Meeting Chair, joined by Juliet Compston (UK) and Serge Ferrari (Switzerland), who shared their expert opinions on making fracture prevention a priority.

Finding the patient with increased risk of fracture – a call to action!

Juliet Compston

Over the past two to three decades there have been huge advances in the management of osteoporosis, both in terms of the ability to identify those at high risk of fracture, and in the range of pharmacological interventions available to reduce fracture risk. However, many people at high risk of fracture do not receive appropriate investigation and treatment.[1-4] More concerning is the fact that recent data show a decline in treatment rates.[1-4]

These observations have stimulated a global initiative named the 'Call to Action to Address the Crisis in the Treatment of Osteoporosis', to identify barriers to treatment and develop and implement strategies to close the treatment gap.[5]

Many people at high risk of fracture do not receive appropriate investigation and treatment.[1-4]

Major risk factors for fracture

Several clinical risk factors have been identified for fracture risk, and these include:[6]

- Age
- Previous fragility fracture
- Other risk factors, including initiation of oral corticosteroids.

Current levels of treatment

The use of osteoporosis medications is declining worldwide, even in those patients at very high risk of fracture.[1-4]

The range of pharmacological options available for lowering the risk of fracture result in a 30–70% reduction in vertebral fracture, a 15–20% reduction in non-vertebral fracture, and up to 40% reduction in hip fracture after 3 years of treatment.[7] However, the use of osteoporosis medication is declining worldwide.[1-3] This trend is observed even in those patients at very high risk of fracture, such as those with a recent hip fracture.[4] The Global Longitudinal Study of Osteoporosis in Women showed that treatment rates 1 year after an incident fracture in previously treatment naïve women were below 45%, including in patients with vertebral or multiple fractures.[8]

Poor adherence to therapy is also a significant issue in people with osteoporosis. Non-compliance and non-persistence compound the problem of low treatment rates, and are associated with increased risk of fracture.[9] Less than 45% of post-menopausal women take their prescribed therapy (oral bisphosphonate, raloxifene or strontium ranelate) after 6 months. This rate falls to less than 20% at 3 years.[10]

Less than 45% of post-menopausal women take their prescribed therapy after six months.[10]

There are a number of possible reasons for the treatment gap:

- Low awareness of osteoporosis as a chronic disease
- Poor coordination between different sectors within healthcare systems for fracture patients
- Fear of adverse effects of medication among patients and doctors
- Inadequate access to diagnosis and treatment
- Lack of education about osteoporosis among patients and doctors.

Concerns about side effects of pharmacological treatments coincide with a reduction in treatment rates and patient adherence. It is therefore important to assess the risk/benefit of treatment in all patients, as well as to reassure patients of the efficacy and safety profile of osteoporosis medications.[11]

Reducing the treatment gap

'Call to Action to Address the Crisis in the Treatment of Osteoporosis' is a multi-stakeholder, global initiative by the American Society for Bone and Mineral Research (ASBMR) and Centre for Medical Technology Policy.

The objectives of the initiative are to:

- Identify key barriers to appropriate rates of osteoporosis screening, diagnosis and treatment, to prevent fractures
- Develop strategic options for addressing identified barriers
- Develop a plan for disseminating and implementing the strategy.

Involvement of patients and addressing their concerns is key to this initiative, as is improved interaction with the media. It is crucial that the significant benefits of osteoporosis therapy in people at high risk of fracture are communicated to the public and treating physicians.

"It is crucial that the significant benefits of osteoporosis therapy in people at high risk of fracture are communicated to the public and treating physicians."

Juliet Compston

Patient case study:

Management of osteoporosis in Ms L

Maria Luisa Brandi

As Meeting Chair, Maria Luisa Brandi presented a case study of Ms L, a patient with osteoporosis, and asked the audience for their opinion on treatment decisions at various stages throughout her treatment.

This patient case study was then discussed throughout the symposium, during Serge Ferrari's presentation.

*

Age 63
Left wrist fracture

Treatments:
Calcium and vitamin D

Age 67
Acute back pain for 3 weeks after falling backwards

Treatments:
Calcium and vitamin D

Age 70
New acute back pain from making the bed
2–3 cm heigh loss in past 5 years
DXA: femur neck -3.3, lumbar spine -3.8 T-score
Diagnosed with osteoporosis

Treatments:
Alendronate weekly plus calcium and vitamin D

Age 76
DXA: femur neck -2.8 (+6%), lumbar spine -3.1 (+8%) T-score

Treatments:
Alendronate stopped, calcium and vitamin D maintained

Age 77
Fell and broke left hip

Treatments:
Calcium and vitamin D

Age 79
Fell and broke right hip

Treatments:
Zoledronic acid plus calcium and vitamin D

Age 81
DXA: lumbar spine -3.3, radius -3.7 T-score
BSAP 9.1, PINP 31, CTX 190

Treatments:
Zoledronic acid stopped, plus calcium and vitamin D maintained

*This is not an actual image of the patient

Optimising the management of osteoporosis in the short and long term

Serge Ferrari

Serge Ferrari shared relevant data that could inform management strategies of patients such as Ms L in the future.

Was Ms L started on the most effective medication at her stage of disease?

Prolia® treatment was associated with the greatest reduction in non-vertebral fractures, and reduced the rate of hip fractures by 20% in a large real–life effectiveness study of female patients with osteoporosis.[12]

There is a lack of head-to-head data from clinical trials comparing the effects of osteoporosis treatments on fracture endpoints. However, a large real life effectiveness study has examined the reduction in fracture incidence among female patients with osteoporosis treated in routine clinical practice.[12] All treatments studied except raloxifene (Prolia®, intravenous zoledronic acid, alendronate, risedronate, oral ibandronate and teriparatide) reduced combined hip and vertebral fracture rate within 12 months. Prolia® treatment was associated with the greatest reduction in non-vertebral fractures, and reduced the rate of hip fractures by 20%.[12]

This evidence suggests that initiating treatment with Prolia® at the time of diagnosis of osteoporosis for Ms L – who was at very high risk of fracture, with multiple fractures at diagnosis – may have led to a greater benefit in reducing her fracture risk than starting treatment with an oral bisphosphonate.

Was stopping alendronate therapy after 6 years appropriate for Ms L?

Post hoc analyses of the Fracture Intervention Trial Long-term Extension (FLEX) have shown that patients with a low T-score at the hip (–4.2 to –2.3) after 4–5 years of alendronate therapy are at high risk of any clinical fracture when therapy is discontinued. When compared with patients achieving a higher T-score on therapy (–1.5 to 0.2), their risk of fracture is three-fold higher.[13]

ASBMR recommends continued pharmacological treatment with bisphosphonates in post-menopausal women treated with oral (≥5 years) or intravenous (≥3 years) bisphosphonates with hip BMD T-score ≤–2.5, or those at high risk of fracture.[14]

These data have led to ASBMR recommendations, driven by clinical targets, that advise how long to treat a patient. Bisphosphonate therapy should be continued if hip BMD T score remains ≤–2.5, or the patient is at high risk of fracture (as defined by older age [70–75 years], other strong risk factors for fracture, or FRAX fracture risk score that is above country-specific thresholds). After 5 years of oral bisphosphonate treatment, or 3 years of intravenous bisphosphonate treatment, post-menopausal women should be reassessed, and a bisphosphonate should be continued for up to 10 years, or a switch to an alternative therapy should be considered.[14] The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of the therapy on an individual patient basis, particularly after 5 or more years of use.[15-17]

However, prolonged use of bisphosphonates is associated with no further gains in hip BMD.[18,19] Patients that remain osteoporotic at the femoral neck are at increased risk for hip fracture.[20]

In patients with low hip BMD despite 5 years of bisphosphonate treatment, it is important to consider strategies to increase BMD further, in order to reduce hip fracture risk, for example by switching to another therapy.[14]

The FREEDOM trial and its extension have shown that Prolia® continually increases BMD over 10 years, without therapeutic plateau. Additionally, yearly rates of new vertebral and non-vertebral fractures remained low over 10 years of treatment.[21]

However, it is important to note that Prolia® is a reversible drug, and treatment cessation is associated with hip BMD decreases towards baseline.[22] When Prolia® is discontinued, the incidence of new vertebral fractures is higher than in patients who remain on treatment, but similar to the incidence in patients who receive placebo.[23]

Due to the reversibility of effects after Prolia® discontinuation, in patients who have reached treatment targets, measures should be taken to mitigate these effects. There is evidence to suggest that 1 year of alendronate therapy following Prolia® discontinuation prevents BMD loss, and this could present an effective treatment strategy in these patients.[24]

What could have been done differently in the management of osteoporosis in Ms L?

A recent study has shown that when switching from oral bisphosphonates to an alternate therapy, greater gains in BMD are achieved at all measured sites when patients transitioned to Prolia® as compared to zoledronic acid.[25] BMD change from baseline at month 12 was significantly greater with Prolia® compared with zoledronic acid at the lumbar spine (3.2% vs 1.1%; $p<0.0001$), total hip (1.9% vs 0.6%; $p<0.0001$), femoral neck (1.2% vs –0.1%; $p<0.0001$), and 1/3 radius (0.6% vs 0.0%; $p<0.05$).

However, if a more rapid and sustained fracture reduction with significantly increased BMD is the target, then new treatment paradigms need to be implemented.

> "If rapid and sustained fracture reduction with increased BMD is the target, then new treatment paradigms need to be implemented"
>
> *Serge Ferrari*

References

1. Jha S, Wang Z, Laucis N, et al. Trends in media reports, oral bisphosphonate prescriptions, and hip fractures 1996-2012: an ecological analysis. *J Bone Miner Res.* **2015**;30:2179-87.

2. Hernlund E, Svedbom A, Ivergard M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos*. **2013**;8:136.

3. van der Velde RY, Wyers CE, Teesselink E, et al. Trends in oral anti-osteoporosis drug prescription in the United Kingdom between 1990 and 2012: variation by age, sex, geographic location and ethnicity. *Bone*. **2017**;94:50-5.

4. Solomon DH, Johnston SS, Boytsov NN, et al. Osteoporosis medication use after hip fracture in U.S. patients between 2002 and 2011. *J Bone Miner Res.* **2014**;29:1929-37.

5. ASBMR Initiates Call to Action to Address the Crisis in the Treatment of Osteoporosis. September 2016. https://www.asbmr.org/About/PressReleases/Detail.aspx?cid=7b9b6992-bf2d-44ab-ac89-73515cc591ae.Last accessed: June 2017.

6. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *Lancet*. **2002**;359:1929-36.

7. Compston J. Recent advances in the risk assessment and treatment of osteoporosis. *J Clin Med*. **2012**;12:S2-5.

8. Greenspan SL, Wyman A, Hooven FH, et al. Predictors of treatment with osteoporosis medications after recent fragility fractures in a multinational cohort of postmenopausal women. *J Am Geriatr Soc*. **2012**;60:455-61.

9. Ross S, Samuels E, Gairy K, et al. A meta-analysis of osteoporotic fracture risk with medication nonadherence. *Value Health*. **2011**;14:571-81.

10. Li L, Roddam A, Gitlin M, et al. Persistence with osteoporosis medications among postmenopausal women in the UK General Practice Research Database. *Menopause*. **2012**;19:33-40.

11. Khosla S, Shane E. A crisis in the treatment of osteoporosis. *J Bone Miner Res.* **2016**;31:1485-7.

12. Yusuf A, Guo H, Balasubramanian A, et al. Effectiveness of bone therapies in routine clinical practice: two retrospective database analyses using US Marketscan and Medicare. *Osteoporos Int.* **2016**;27(Suppl. 1):P190.

13. Bauer DC, Schwartz A, Palermo L, et al. Fracture prediction after discontinuation of 4 to 5 years of alendronate therapy: the FLEX study. *JAMA Intern Med.* **2014**;174:1126-34.

14. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* **2016**;31:16-35.

15. Alendronic Acid Summary of Product Characteristics. 2016.

16. Risedronate Sodium Summary of Product Characteristics. 2016.

17. Ibandronic acid Summary of Product Characteristics. 2016.

18. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. **2006**;296:2927-38.

19. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res.* **2012**;27:243-54.

20. Kopperdahl DL, Aspelund T, Hoffmann PF, et al. Assessment of incident spine and hip fractures in women and men using finite element analysis of CT scans. *J Bone Miner Res.* **2014**;29:570-80.

21. Bone H, Brandi M, Brown J, et al. Ten years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM Extension trial. *J Bone Miner Res.* **2015**;30:LB-1157.

22. McClung MR, Wagman RB, Miller PD, et al. Observations following discontinuation of long-term denosumab therapy. *Osteoporos Int.* **2017**:doi 10.1007/s00198-017-3919-1. [Epub ahead of print].

23. Brown JP, Roux C, Torring O, et al. Discontinuation of denosumab and associated fracture incidence: analysis from the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial. *J Bone Miner Res.* **2013**;28:746-52.

24. McClung M, Miller P, Kendler D, et al. Preventing bone loss upon stopping denosumab therapy: findings from two clinical studies. *Osteoporos Int*. **2016**;27(Suppl. 1):OC8.

25. Miller PD, Pannacciulli N, Brown JP, et al. Denosumab or zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates. *J Clin Endocrinol Metab*. **2016**;101:3163-70.

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** Hypoca 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

prolia® denosumab

ACT BEFORE IMPACT

AMGEN®

Amgen (Europe) GmbH,
Dammstrasse 23, CH-6301 Zug, Switzerland.
Date of preparation: June 2017
EUHQ-P-162-0417-048348