Denosumab for glucocorticoid-induced osteoporosis

SUMMARY

Denosumab is intended to be used for the treatment of glucocorticoid-induced osteoporosis. If licenced, it would offer an additional treatment option for this patient group, and may be of particular benefit to patients who are unable to use bisphosphonates due to contraindication, intolerance or non-compliance. Denosumab is a monoclonal antibody that inhibits osteoclast activity which is critical in the pathogenesis of osteoporosis. Denosumab is currently licenced for the treatment of osteoporosis in post-menopausal women, bone loss in men with prostate cancer, and the prevention of skeletal-related events in adults with bone metastases from solid tumours.

The most common secondary cause of osteoporosis is glucocorticoid use. It has been estimated that the prevalence of oral glucocorticoid use in the UK is 0.9% of the total adult population. Twenty percent of those treated with oral glucocorticoids have an osteoporotic fracture within the first year of treatment. Osteoporotic fractures occurring at the spine, forearm and humerus are associated with significant morbidity, while fracture occurring at the hip is also associated with a significant increase in mortality.

Patients treated with glucocorticoids should be encouraged to partake in physical activity and consume adequate amounts of calcium and vitamin D. Bone-protective therapies such as bisphosphonates, alendronate, etidronate, risedronate, and zoledronic acid are currently used in the treatment and prevention of glucocorticoid-induced osteoporosis in high-risk individuals. Denosumab is currently in phase III clinical trials comparing its effect on bone mineral density against risedronate. This trial is expected to complete in June 2015.
TARGET GROUP

- Glucocorticoid-induced osteoporosis.

TECHNOLOGY

DESCRIPTION

Denosumab (Prolia; Xgeva; AMG 162) is a fully human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL. It prevents RANKL from binding to its receptor, RANK, on the surface of osteoclast precursors and osteoclasts, thereby inhibiting osteoclast differentiation, activation, and survival. Increased osteoclast activity is critical in the pathogenesis of diseases that result from excessive bone resorption such as osteoporosis. In a phase III clinical trial of denosumab for glucocorticoid-induced osteoporosis, denosumab is administered by subcutaneous injection (SC) at 60mg every six months.

Denosumab currently has Marketing Authorisation in the EU as Prolia and Xgeva. Prolia (60mg) is indicated for the treatment of: osteoporosis in post-menopausal women, and bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. Xgeva (120mg) is indicated for the prevention of skeletal-related events in adults with bone metastases from solid tumours. Very common (>10%) adverse effects of denosumab when used for its licenced indications include: pain in extremities (in patients treated for post-menopausal osteoporosis), and dyspnoea and diarrhoea (in adults treated for bone metastases from solid tumours). Denosumab (60mg) is currently in clinical trials for the treatment of osteoporosis in men and rheumatoid arthritis. Denosumab (120mg) is currently in clinical trials for the prevention of cancer-related bone damage or malignant hypercalcaemia, and bone cancer.

INNOVATION and/or ADVANTAGES

If licensed, denosumab will offer an additional treatment option for individuals at risk of glucocorticoid-induced osteoporosis; it may be of particular benefit to patients for whom oral bisphosphonates cannot be prescribed due to contraindication, intolerance or non-compliance.

DEVELOPER

Amgen; Astrazeneca; Daiichi Sankyo; Glaxosmithkline (EU licence holder).

AVAILABILITY, LAUNCH OR MARKETING

Denosumab is currently in phase III clinical trials for glucocorticoid-induced osteoporosis.

PATIENT GROUP

BACKGROUND

Osteoporosis is a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue with a subsequent increase in bone fragility and
susceptibility to fracture\(^2\). Bone mineral density (BMD) is defined as the mass of bone mineralisation per unit volume (g/cm\(^2\)) and can be measured using dual energy x-ray absorptiometry (DEXA)\(^3\). Osteoporosis is defined by a T-score of −2.5 standard deviations (SD) or below the age and sex corrected mean BMD as measured by DEXA scanning\(^4\).

The clinical consequences of osteoporosis are fractures that arise from low BMD. Common sites include: vertebral compression fractures, fractures of the distal radius and the proximal femur, and fractures of the proximal humerus\(^2\). Glucocorticoid-induced osteoporosis has distinct characteristics, in particular, rapid bone loss and increased fracture risk occur early after therapy is initiated. Additionally, fracture risk is increased even with relatively low daily doses of glucocorticoids and rises further with increasing daily dose\(^5\). Glucocorticoids contribute to the increase in fracture risk over and above the effect of low BMD; for a given BMD, the risks of fracture are higher in glucocorticoid-induced osteoporosis than in post-menopausal osteoporosis\(^6\).

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:
- An outcomes strategy for COPD and Asthma (2011).

**CLINICAL NEED and BURDEN OF DISEASE**

In England, it is estimated that 2.3 million people suffer from osteoporosis\(^7\). The risk of osteoporosis increases with age and women are more likely to develop osteoporosis than men; one in three women and one in twelve men over the age of 50 will suffer an osteoporotic fracture\(^7,8\). In 2012, there were 24,424 admissions for osteoporosis (M80, M81) in England, resulting in 61,005 bed-days and 27,342 finished consultant episodes\(^9\). Osteoporotic fractures occurring at the spine, forearm and humerus are associated with significant morbidity, but hip fracture is also associated with a significant increase in mortality, particularly in the elderly\(^2\). In the first year following hip fracture in women, the relative mortality risk varies in women from 2 to greater than 10, depending on age\(^2\).

The most common secondary cause of osteoporosis is the long-term use of oral glucocorticoids\(^2\). Glucocorticoids are the most widely and frequently used class of anti-inflammatory drugs, often prescribed for the treatment of respiratory disease, musculoskeletal disease, and cutaneous disease\(^2,10\). The prevalence of oral glucocorticoid use in the UK is estimated to be 0.9% of the total adult population, but the prevalence increases with age, rising to 2.5% between the ages of 70 and 79 years\(^6\). One in five patients treated with oral glucocorticoids has an osteoporotic fracture within the first 12 months of treatment. This proportion increases to 50% after 5-10 years\(^6\). The population likely to be eligible to receive denosumab could not be estimated from available published sources.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (TA160). 2011\(^4\).
- NICE technology appraisal. Denosumab for the prevention of osteoporotic fractures in postmenopausal women (TA204). October 2010\(^11\).
- NICE technology appraisal. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (TA161). October 2008\(^12\).
- NICE clinical guideline. Osteoporosis: assessing the risk of fragility fracture (CG146). August 2012\(^13\).

Other Guidance

- National Osteoporosis Guideline Group. Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. 2010\(^14\).
- National Osteoporosis Foundation. Clinician’s guide to prevention and treatment of osteoporosis. 2010\(^15\).
- Scottish Intercollegiate Guidelines Network. Management of osteoporosis (Guideline 71). 2003\(^8\).
- Royal College of Physicians. Glucocorticoid-induced osteoporosis: A concise guide to prevention and treatment. 2002\(^6\).

CURRENT TREATMENT OPTIONS

For individuals prescribed glucocorticoids, good nutrition (especially an adequate intake of calcium and vitamin D), in addition to appropriate physical activity should be encouraged. Individuals prescribed glucocorticoids should also be advised against the use of tobacco, and to avoid abusing alcohol. Individuals at high risk (those aged 65 years or over, and those with a prior fragility fracture) should be advised to commence bone-protective therapy at the time of starting glucocorticoids. Oral and intravenous bisphosphonates are the main bone-protective therapy used in the treatment and prevention of glucocorticoid-induced osteoporosis\(^10\). Alendronate, etidronate, risedronate, and zoledronic acid have been shown to prevent bone loss or increase BMD at the spine and hip in patients receiving glucocorticoids\(^10\). Measurement of bone density is not required before starting treatment in high risk individuals\(^6\). In other individuals, measurement of BMD using DEXA is recommended for the assessment of fracture risk\(^6\).

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01465568; denosumab vs bisphosphonates; phase IV.</th>
<th>NCT01575873; denosumab vs risedronate; phase III.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Tuen Mun hospital.</td>
<td>Amgen.</td>
</tr>
<tr>
<td>Status</td>
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<td>Ongoing.</td>
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### Source of information
- Trial registry[^16].
- Trial registry[^1].

### Location
- China.
- EU (not UK), USA, Canada and Argentina, Korea, Mexico and Russia.

### Design
- Randomised, active-controlled.
- Randomised, active-controlled.

### Participants
- n=40 (planned); aged 18 years and older; participants must have been treated with a daily dose of prednisolone (or equivalent) >2.5mg/day within 3 months of study entry, received oral bisphosphonate treatment for at least 2 years, and reported suboptimal response to bisphosphonate treatment, i.e. failure of lumbar spine, femoral neck or total hip BMD values to increase and/or remain osteoporotic, and/or development of new fragility vertebral or non-vertebral fractures despite at least 2 years' treatment with good compliance.
- n=776 (planned); aged 18 years and older; glucocorticoid treatment; those <50 years must have had a fracture as an adult to be eligible; those ≥50 must have BMD value equivalent to a T-score ≤-2.0 at lumbar spine, total hip or femoral neck; or BMD value equivalent to a T-score ≤-1.0 at lumbar spine, total hip or femoral neck and a prior osteoporotic fracture.

### Schedule
- Randomised to 60mg denosumab SC, 6 monthly for 2 doses; or continuation of bisphosphonates at their recommended schedule.
- Randomised to 60mg denosumab SC, 6 monthly with oral placebo daily; or 5mg risedronate orally, daily with placebo SC, 6 monthly.

### Follow-up
- Active treatment for 2 cycles (12 months).
- Active treatment for 2 years.

### Primary outcome/s
- BMD change at the lumbar spine.
- BMD in the lumbar spine after one year of treatment.

### Secondary outcome/s
- BMD changes in the total hip and femoral neck, bone turnover markers, new vertebral fractures, and adverse events. No quality of life measurement included in trial outcomes.
- BMD at the lumbar spine and total hip after one and two years of treatment, adverse effects and patient preferences[^a]. No quality of life measurement included in trial outcomes.

### Expected reporting date
- Primary completion date reported as Dec 2013.
- Primary completion date reported as June 2015.

### ESTIMATED COST and IMPACT

#### COST
Denosumab is already marketed in the UK for the treatment of osteoporosis in post-menopausal women; a 1mL prefilled syringe (60mg/mL) costs £183.00[^17].

#### IMPACT - SPECULATIVE

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: reduced impact on carers of patients with fragility fractures.
- No impact identified

[^a]: Measured by the Preference and Satisfaction Questionnaire (PSQ)
Impact on Health and Social Care Services

- Increased use of existing services
- Re-organisation of existing services: day case facilities are not likely to be required for administration of denosumab as is currently required with some treatment options\(^b\).
- Decreased use of existing services
- Need for new services
- Other
- None identified

Impact on Costs and Other Resource Use

- Increased drug treatment costs: as compared to bisphosphonate therapy.
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs:
- Other:
- None identified

Other Issues

- Clinical uncertainty or other research question identified: clinical trials evaluating the use of denosumab for this indication have not listed fracture rates as a primary or secondary outcome measure\(^c\).
- None identified

REFERENCES

1 ClinicalTrials.gov. A study to show that treatment with denosumab is as good as treatment with risedronate in subjects who are starting to take or currently taking glucocorticoids. http://www.clinicaltrials.gov/ct2/show/NCT01575873?term=amg+162&rank=43 Accessed 6 February 2014.

\(^b\) Expert personal opinion.