Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours

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Scientific summary

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Scientific summary

Background

Bone metastases are associated with a poor prognosis, reduced quality of life and increased risk of complications. The term 'skeletal-related event' (SRE) is used to group the following complications together: pathological fracture, spinal cord compression (SCC) and radiotherapy or surgery to bone. Bisphosphonates (BPs) can be used to prevent SREs or to treat bone pain in cases where conventional analgesics have failed. Patients who are not treated with BPs receive best supportive care (BSC), which can vary depending on the type of primary cancer but may include chemotherapy, palliative radiotherapy, antibiotics, steroids, analgesics or surgery. The specific place of BPs in the care pathway varies. Denosumab (Xgeva®, Amgen Inc.), administered by subcutaneous injection every 4 weeks, offers an alternative therapy to BPs and/or BSC for the prevention of SREs in patients with bone metastases from solid tumours.

Objectives

The aim of this review was to assess the clinical effectiveness and cost-effectiveness of denosumab, within its licensed indication, for the treatment of bone metastases from breast cancer, prostate cancer, non-small cell lung cancer (NSCLC) or other solid tumours (OSTs).

Methods

Electronic searches were undertaken to identify published and unpublished reports. The databases searched included MEDLINE, EMBASE, The Cochrane Library and Web of Science with Conference Proceedings. Other sources including the 2010 and 2011 meeting abstracts of the American Society of Clinical Oncology (ASCO), American Urological Association and San Antonio Breast Cancer symposium were also searched. The date of the last searches was July 2011. The types of studies considered were systematic reviews or randomised controlled trials (RCTs); observational studies were also considered for data on safety. Participants had breast cancer, prostate cancer, lung cancer or OSTs and at least one bone metastasis. Outcome measures included time to first on-study SRE, risk of first and subsequent SREs, incidence of SREs, hypercalcaemia, overall survival, pain, health-related quality of life (HRQoL) and adverse events related to treatment.

Two reviewers screened the titles and abstracts of all reports identified by the search strategy. Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer. The quality of the RCTs was assessed using the Cochrane risk-of-bias tool. As scoping searches had indicated that there were no direct comparisons of denosumab with BPs (other than zoledronic acid) or BSC we planned to undertake a network meta-analysis (NMA), pooling direct and indirect evidence in a single analysis to obtain an indirect estimate of the relative effectiveness of denosumab against these comparators.

The economic modelling approach adopted was to amend the inputs to the manufacturer's model to revise the base-case estimates, coupled with some additional sensitivity analyses around clinical inputs and costs. The impact of the results from the assessment group (AG)'s NMA were then applied and contrasted with those of the manufacturer. The AG then rebuilt the manufacturer's model as a cross check and to enable the introduction of the structural model elements of (1) SCC having a sustained impact on quality of life beyond 5 months from diagnosis, and (2) a decay in quality of life in the final year. This was coupled with additional sensitivity analyses.

Results

Description of studies

Thirty-nine studies met the inclusion criteria for the review of clinical effectiveness. Of these, 31 did not contribute data to the NMA and none reported denosumab. Eight studies were included in the NMA, of which four studies, involving more than 3700 patients, reported breast cancer; two studies, involving more than 2300 patients, reported prostate cancer; and two studies, involving more than 2100 patients, reported OSTs, both of which included subgroups of (1) NSCLC ($n = 946$) and (2) OSTs excluding NSCLC ($n = 1164$).

Quality of studies

All studies were generally of good quality. Three of the breast cancer studies were multicentre and international, while the fourth was multicentre and set in Japan.

Summary of risk/benefits

In terms of the direct evidence, for breast cancer, there was a statistically significant difference in favour of denosumab compared with zoledronic acid for the time to first on-study SRE for all patients [hazard ratio (HR) 0.82; 95% confidence interval (CI) 0.71 to 0.95; not reached vs median 26.4 months (academic-in-confidence information has been removed)].

For prostate cancer, there was a statistically significant difference in favour of denosumab compared with zoledronic acid for the time to first on-study SRE for all patients (HR 0.82; 95% CI 0.71 to 0.95; median 20.7 vs 17.1 months) and for those with no previous SRE (HR 0.80; 95% CI 0.67 to 0.95). (Academic-in-confidence information has been removed.) There was also a statistically significant difference in favour of denosumab for reducing the risk of developing first and subsequent SREs for all patients [relative risk (RR) 0.82; 95% CI 0.71 to 0.94] (academic-in-confidence information has been removed).

For the subgroup of patients with NSCLC, the time to first on-study SRE for all patients favoured denosumab without being statistically significant (HR 0.84; 95% CI 0.64 to 1.10; academic-in-confidence information has been removed). For the subgroup of patients with OSTs excluding NSCLC, there was a statistically significant difference in favour of denosumab for median time to first on-study SRE for all patients (HR 0.79; 95% CI 0.62 to 0.99; academic-in-confidence information has been removed).

For OSTs including NSCLC, there was a statistically significant difference in favour of denosumab for time to first on-study SRE for all patients (HR 0.81; 95% CI 0.68 to 0.96; 21.4 vs 15.4 months). (Academic-in-confidence information has been removed.) For risk of developing first and subsequent SREs, for all patients, the difference was borderline significant in favour of denosumab (RR 0.8; 95% CI 0.72 to 1.00), (academic-in-confidence information has been removed).

In the denosumab studies the vast majority of SREs consisted of pathological fracture and radiation to bone, whereas there were few occurrences of SCC or surgery to bone. Overall survival was similar between the treatment groups in the three studies apart from an ad hoc analysis of the subgroup with NSCLC, which reported a statistically significant difference in favour of denosumab (HR 0.79; 95% CI 0.65 to 0.95). However, this was a subgroup of a study that was not powered to detect differences in overall survival and until further evidence becomes available this result should be interpreted with caution.

Denosumab delayed the time to development of moderate or severe worst pain (worst pain score of >4 points) compared with zoledronic acid (breast cancer: median 9.7 vs 5.8 months, $p = 0.0024$; prostate cancer: HR 0.89; 95% CI 0.77 to 1.04; median 5.8 vs 4.9 months; OSTs including NSCLC: HR 0.81; 95% CI 0.66 to 0.99; median 3.7 vs 2.8 months; $p = 0.038$). In all three studies, in terms of quality of life, overall mean Functional Assessment of Cancer Therapy (FACT) scores remained similar between the groups. (Academic-in-confidence information has been removed.)

In terms of adverse events, for breast cancer, prostate cancer and OSTs respectively, there were more occurrences of hypocalcaemia in the denosumab group compared with the zoledronic acid group (5.5% vs 3.4%; 12.8% vs 5.8%; 10.8% vs 5.8%), rates of osteonecrosis of the jaw were slightly higher (2.0% vs 1.4%; 2.3% vs 1.3%; 1.3% vs 1.1%), while there were lower rates of events associated with renal impairment (4.9% vs 8.5%; 14.7% vs 16.2%; 8.3% vs 10.9%) and acute-phase reactions (10.4% vs 27.3%; 8.4% vs 17.8%; 6.9% vs 14.5%).

In terms of the NMAs, for breast cancer, prostate cancer and OSTs including NSCLC, the AG's NMA reported a statistically significant difference in favour of denosumab compared with placebo for both time to first on-study SRE (HR 0.46; 95% CI 0.29 to 0.72; HR 0.56; 95% CI 0.40 to 0.77; and HR 0.49; 95% CI 0.30 to 0.78, respectively) and risk of first and subsequent SREs (RR 0.45; 95% CI 0.28 to 0.72; RR 0.53; 95% CI 0.39 to 0.72; and RR 0.62; 95% CI 0.46 to 0.85, respectively). (Academic-in-confidence information has been removed.) For NSCLC, the AG's NMA comparison of denosumab with placebo favoured denosumab without being statistically significant for time to first on-study SRE (HR 0.68; 95% CI 0.45 to 1.03), whereas there was a statistically significant difference in favour of denosumab for risk of first and subsequent SREs (RR 0.63; 95% CI 0.42 to 0.97). For OSTs excluding NSCLC, the AG's NMA reported a statistically significant difference in favour of denosumab compared with placebo for both time to first on-study SRE (HR 0.30; 95% CI 0.11 to 0.82) and risk of first and subsequent SREs (RR 0.61; 95% CI 0.39 to 0.97). The manufacturer's NMA did not report these last two outcomes.

Summary of costs

The manufacturer's estimates through a survey of oncology nurses and pharmacists are that denosumab will result in staff time savings compared with zoledronic acid of around (academic-in-confidence information has been removed) minutes per administration.

This time saving coupled with consumables and fixed costs estimated within the micro-costing study yields the following total annual direct drug and administration costs as per the manufacturer: denosumab £4466.80 without a patient access scheme (PAS), (commercial-in-confidence information has been removed); zoledronic acid £3364.66 [*British National Formulary* (BNF) 62 states £3245.97]; disodium pamidronate £4117.23 (BNF62 states £4081.74); ibandronic acid (intravenous) £3369.73; and ibandronic acid (oral) £2464.80. These costs do not include withheld doses due to poor renal function, or any patient management costs due to poor renal function. Without the PAS the annual denosumab cost is around £1102 more expensive than zoledronic acid.

The PAS proposed by the manufacturer has recently been approved. (Commercial-in-confidence information has been removed.)

Among those receiving 3-weekly intravenous chemotherapy the likelihood is that any intravenous BPs would also be administered 3-weekly. Whether or not denosumab would be administered on a 3-weekly basis in this situation is a moot point. Four-weekly dosing would seem a possibility and be likely to result in denosumab being cost saving.

Summary of cost-effectiveness

The manufacturer's case is broadly that while the average patient benefits from the reduced number of SREs is not large. (Commercial-in-confidence information has been removed.)

(Commercial-in-confidence information has been removed.) The manufacturer's cost-effectiveness estimates for denosumab compared with BSC are typically in excess of £100,000 per quality-adjusted life-year (QALY), and even with the PAS are closer to £100,000 per QALY than £50,000 per QALY.

Assessment group within-trial analyses suggest that for breast cancer patients denosumab results in a slightly lower average number of SREs compared with zoledronic acid, and that this will translate into a small average annual gain of perhaps 0.003 to 0.006 QALYs. Without the PAS the additional cost of

denosumab does not justify these relatively minor gains but with it denosumab is estimated to be broadly cost neutral to slightly cost saving compared with zoledronic acid, but this is sensitive to the price of zoledronic acid.

The within-trial analyses for prostate cancer again suggest a lower average number of SREs from denosumab compared with zoledronic acid and a slightly larger additional average annual gain of perhaps 0.008 to 0.016 QALYs owing to the greater proportion of SCCs within the overall number of SREs in prostate cancer. But there may be slightly fewer zoledronic acid administrations than denosumab administrations, and this triangulates with the higher proportion of zoledronic acid patients having doses withheld for creatinine clearance. This aspect is not considered in either the manufacturer's model or the AG's economic model.

Without the PAS, the additional cost of denosumab does not justify the small estimated gains. With the PAS (commercial-in-confidence information has been removed) annual costs are estimated to increase by around £100, which translates into cost-effectiveness estimates of between £6545 per QALY and £15,272 per QALY. Again, this result is sensitive to the price of zoledronic acid.

For the cost–utility modelling within breast cancer, the lifetime gains across all patients are estimated to be around 0.007 QALYs compared with zoledronic acid, which does not justify the additional cost of £1707 per patient. With the PAS (commercial-in-confidence information has been removed) denosumab is estimated to dominate zoledronic acid. But for those contraindicated to BPs the cost-effectiveness is poor: even with the PAS the cost-effectiveness is £157,829 per QALY.

For the cost–utility modelling within prostate cancer, across all patients the gain from denosumab over zoledronic acid is around 0.009 QALYs whereas compared with BSC it is 0.035 QALYs, at net costs without the PAS of £1059 and £3951, respectively.

With the PAS, denosumab is estimated to be cost saving compared with zoledronic acid and so dominate it. For those contraindicated to BPs, denosumab is again not estimated to be cost-effective compared with BSC.

Applying the SRE-naive and -experienced subgroup-specific clinical effectiveness has a reasonably large impact on the results. The impact of this on the modelling is not symmetric because more patients fall into the SRE-experienced group over time. As a consequence the estimated cost-effectiveness of denosumab worsens. But the PAS is still sufficient for (commercial-in-confidence information has been removed) denosumab to be estimated to remain dominant over zoledronic acid.

Within the cost–utility modelling of OSTs including lung, the gains from denosumab over zoledronic acid are estimated to be less than 0.01 QALYs. Without the PAS denosumab is not cost-effective, but with it the small additional overall costs of around £50 result in cost-effectiveness estimates of between £5400 per QALY and £15,300 per QALY. The impact of applying the SRE subgroup-specific estimates within this group is quite large; even with the PAS it is not sufficient to render it cost-effective. Owing to the lower SRE-experienced RR for SREs (academic-in-confidence information has been removed) compared with zoledronic acid, the cost-effectiveness estimate for denosumab worsens dramatically to £155,285 per QALY compared with zoledronic acid among these patients.

For lung cancer, possibly because of the short life expectancy, the patient gains from denosumab over zoledronic acid among SRE-experienced patients are estimated to be small: 0.003 QALYs. With the PAS, the additional cost of £43 results in a cost-effectiveness of £12,743 per QALY.

Sensitivity analysis

A concern within the modelling is BSC being assumed to have a zero incidence of the modelled serious adverse events (SAEs). Sensitivity analyses that exclude SAEs from the analysis improve the

cost-effectiveness of denosumab compared with BSC, but are not sufficient to render denosumab cost-effective. Even with the PAS, all but one of the cost-effectiveness estimates remain above £50,000 per QALY with most being above £100,000 per QALY.

A range of additional univariate sensitivity analyses explored the effects of applying the manufacturer's clinical estimates and cost estimates within the model; the rates of discontinuations assumed for active treatments; the assumed step change in utility for a SRE-naive patient experiencing a SRE; applying utility multipliers for those nearing death; limiting or excluding the effects of SAEs; altering the time horizon to 5 years and to 2 years; excluding general mortality; and extending the effect of SCC to beyond 5 months from diagnosis.

Excluding the step change in utility estimated between SRE-naive patients and SRE-experienced patients has quite a large impact on the results for SRE-naive patients. This is not to say that there is no effect, only that aspects of the cancers other than just SREs may be contributing to this, particularly if SRE-naive patients tend to be earlier in the disease pathway than SRE-experienced patients.

Another aspect that may have an impact is the treatment of SCCs. Extending the average quality-of-life decrement measured during the trial through to death improves the estimated cost-effectiveness. Applying the average (maximum) decrement through to death improves the cost-effectiveness of denosumab among SRE-naive prostate cancer patients from £72,269 per QALY to £56,420 (£49,032) per QALY compared with BSC.

Cost estimates from averaging reference costs for SCC may be too low. Clinical guideline (CG) 75 suggests an average therapy cost of £14,173 (£13,705). Adding this to the average rehabilitation costs and applying the maximum decrement through to death results in a cost-effectiveness estimate for SRE-naive prostate patients of (commercial-in-confidence information has been removed) of £38,553 per QALY compared with BSC.

Probabilistic modelling suggests central estimates that are in line with deterministic estimates.

Discussion

Strengths, limitations of the analyses and uncertainties

In terms of strengths, our review focused on RCTs, resulting in a high level of evidence. We undertook a NMA to provide an indirect estimate of the effectiveness of denosumab against relevant comparators. In terms of limitations, non-English-language studies were excluded. Only subgroup data were available for denosumab for NSCLC, and for OSTs excluding NSCLC. The NMAs are not randomised comparisons but rather observational findings across studies and therefore subject to considerable uncertainty and should be interpreted with caution.

In terms of uncertainties:

- SREs are composite end points. Therefore, higher event rates and larger treatment effects that are associated with the less important components of a composite end point could result in a misleading impression of the treatment's effectiveness in relation to components that are clinically more important but occur less frequently.
- Pathological fractures vary from unnoticeable, asymptomatic fractures to vertebral fractures associated with SCC that result in paraplegia.
- The AG's economic analysis is in part framed by the manufacturer's analysis in terms of outlook and approach. The cost–utility modelling relies on it for the greater part of its input, because of the paucity of other data sources for elements such as quality-of-life values. But the broad conclusions of

the assessment appear relatively insensitive to the approach adopted, as shown by the much simpler within-trial analyses.

Several questions remain concerning the underlying assumptions:

- The base-case cost-effectiveness results apply the clinical effectiveness estimates pooled across all patients for denosumab versus zoledronic acid. SRE-naive and -experienced clinical effectiveness estimates are available. Applying these considerably worsens the estimated number of SREs avoided and the QALY gain for denosumab compared with zoledronic acid among SRE-experienced patients for prostate cancer and OSTs. Should the base case apply to the SRE subgroup-specific clinical effectiveness estimates?
- To what extent do the available data on SRE-naive patients and SRE-experienced patients reflect the likely patient groups for whom zoledronic acid is used? Is the manufacturer's case review sufficient to conclude that most SRE-experienced patients within the cancers reviewed are typically receiving BPs, leading to zoledronic acid being the appropriate comparator?
- To what extent should zoledronic acid coming off patent in 2013 be considered? The anticipated patient benefits from denosumab over zoledronic acid are small. Only a relatively small drop in the price of zoledronic acid would be sufficient to make denosumab not cost-effective when judged by conventional thresholds.

Generalisability of the findings

The three RCTs comparing denosumab with zoledronic acid were large, international, multicentre trials. The participants all had advanced cancer (breast, prostate, lung or OSTs) with one or more bone metastases, European Cooperative Oncology Group status ≤ 2 and a life expectancy of ≥ 6 months. Therefore, it is reasonable to expect that the results of the trials would be generalisable to patients meeting the above criteria, although not to patients with a life expectancy of < 6 months. (Academic-in-confidence information has been removed.) Patients with poor renal function (creatinine clearance < 30 ml/minute) were excluded from the trials on the basis that they could not be randomised to zoledronic acid, as the drug would be contraindicated. Therefore, the effects of denosumab on patients with advanced cancer with bone metastases and poor renal function are unknown. The RCT for OSTs (excluding breast or prostate cancer) included a number of different types of solid tumour. This makes it difficult to assess whether denosumab is more effective in one type of tumour than another.

Conclusions

Implications for service provision

Compared with zoledronic acid and BSC, denosumab is effective in delaying time to first on-study SRE and reducing the risk of multiple SREs. These results are mostly statistically significant and met the minimal clinically significant change described by clinical experts (HR reduction of more than 20%). However, the importance of the composite SRE outcome, and the spectrum of corresponding possible health states, to an individual patient is not clear. Evidence for the effectiveness of denosumab compared with zoledronic acid in reducing pain and improving relative quality of life is less evident. The NMA results indirectly comparing denosumab with BSC are subject to considerable uncertainty and should be interpreted with caution.

The impact on service provision of denosumab depends on whether the patient would alternatively have received an intravenous or oral BP, or BSC. Compared with intravenous delivery, subcutaneous injections would require a shorter time to administer and could potentially be given to some patients in an outpatient setting, general practitioner surgery or even at home. However, such a shift may require additional resources and training in the community. For patients who would have previously been treated with BSC alone, the addition of denosumab would usually mean additional health-care appointments.

The manufacturer's model, the AG's within-trials analyses and the AG's cost–utility model all estimate denosumab to result in patient benefits from reduced SREs compared with zoledronic acid, and larger benefits compared with BSC. But the estimates of the numbers of SREs avoided per patient are small: when compared with zoledronic acid typically less than 0.3 SREs over the patient lifetime and often a lot less than this. SCC is relatively rare. The QALY gains from the number of SREs avoided compared with zoledronic acid are small: typically less than 0.02 QALYs over the patient lifetime and again often quite a lot less than this.

(Commercial-in-confidence information has been removed.) Given this and the small QALY gains, denosumab is in the main estimated to dominate or be cost-effective compared with zoledronic acid. But zoledronic acid comes off patent soon. Only a relatively minor price reduction (commercial-in-confidence has been removed) for zoledronic acid is required to result in the additional net costs from denosumab rendering it not cost-effective at current thresholds.

For those patients for whom BPs are not currently recommended or are not used, possibly owing to contraindications, both the manufacturer and the AG conclude that denosumab is not cost-effective compared with BSC.

Suggested research priorities

Further research would be helpful in the following areas:

- The effectiveness of denosumab compared with zoledronic acid in delaying time to first SRE and reducing the risk of first and subsequent SREs in patients with hormone-refractory prostate cancer and painful bone metastases for whom other treatments have failed.
- Whether or not there is an identifiable subgroup of patients at higher risk of SCC for whom denosumab might result in larger QALY gains.
- The safety and efficacy of denosumab in (1) patients with severe renal impairment and advanced cancer (breast, prostate, NSCLC and OSTs) and (2) patients with advanced cancer who have previously been exposed to a BP.
- The role of bone markers in identifying subgroups of patients with advanced cancer and bone metastases who may be likely to benefit from bone-targeting therapies.
- Given the NSCLC subgroup result, further exploration of the effectiveness of denosumab compared with zoledronic acid for overall survival in patients with NSCLC and bone metastases.

Trial registration

The systematic review is registered as PROSPERO CRD42011001418.

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