Cost-effectiveness of Denosumab versus Zoledronic Acid in patients with bone metastases from solid tumours in Spain

P033

Ignacio Durán[1], Miguel Ángel Seguí[2], Dolores Isla[3], Itziar Oyagüez[4], Celia Roldán[4], Miguel Ángel Casado[4], Mickael Lothgren[5], Guy Hechmati[5], Laura Gutiérrez[6], José Antonio Gasquet[7]

[1]Hospital Universitario Virgen del Rocio, Seville, Spain; [2]Corporació Sanitària Parc Taulí, Sabadell, Spain; [3]Clinico Universitario Lozano Blesa Hospital, Zaragoza, Spain; [4]Pharmacoeconomics and Outcomes Research Iberia, Madrid, Spain; [5]Global Health Economics, Amgen (Europe) GmbH, Zug, Switzerland; [6]Pharmacoeconomics department, Amgen, Barcelona, Spain, [7]Medical department, Amgen, Barcelona, Spain

BACKGROUND

- Bone metastases often lead to the development of pathologic fractures, spinal cord compression and the need for surgery or radiation to bone, commonly referred to as bone complications or skeletal-related events (SREs).[1]
- SREs can greatly impact upon a patient's quality of life[1] and represent a significant economic burden to European healthcare systems.[2]
- Until recently, bisphosphonates have been the mainstay of treatment for the prevention of SREs. Among them, zoledronic acid (generic formulation now available in Spain) has been by far the most widely used in Spain (approximately 93% of patients).[3]
- The recently approved fully human monoclonal antibody, denosumab[4] (subcutaneous injection), was proven to be superior to intravenous zoledronic acid in the prevention of SREs in patients with bone metastases from solid tumours in an integrated analysis of three large phase 3 clinical trials.[5]

OBJECTIVE

- To assess the cost-effectiveness of subcutaneous denosumab versus intravenous generic zoledronic acid in patients with bone metastases from breast cancer, prostate cancer and other solid tumours in Spain.

METHODS

- A Markov model (4-week-cycle duration) was used to estimate the lifetime costs, SRE incidence (pathologic fracture, spinal cord compression, radiation to bone and surgery to bone) and quality adjusted life years (QALYs) from the perspective of the Spanish Healthcare System.
- Three health states were considered: "on treatment"; "off treatment"; and "death".
- A constant rate of SREs and the QALY impairment attributable to the SREs was applied in each cycle.

Clinical parameters

- Transition probabilities (discontinuation and death rates), adverse event rates and rate ratio of SREs (denosumab versus zoledronic acid) and distribution by SRE type were obtained from the clinical trials[5,6] (Table 1 and 2).

Table 1. SRE rate and distribution by type[6]

	Breast cancer	Prostate cancer	Other solid tumours
SRE rate (per year)			
Denosumab	0.486	0.777	0.796
Zoledronic acid	0.631	0.947	0.936
SRE Rate Ratio (denosumab vs zoledronic acid)	0.77	0.82	0.85
Pathologic fractures	58.2%	26.8%	31.4%
Radiation to bone	35.4%	66.1%	57.5%
Surgery to bone	4.7%	1.5%	6.2%
Spinal cord compression	1.7%	5.6%	5.0%

SRE, skeletal related event

Table 2. Discontinuation rate

	Breast cancer	Prostate cancer	Other solid tumours
Denosumab	0.409	0.284	0.619
Zoledronic acid	0.476	0.228	0.628

- Adverse events rates (0.057 [denosumab] and 0.052 [zoledronic acid]) and distribution by type were estimated based on the integrated safety results across the three clinical trials.
- Adverse events included in the model were those considered clinically and economically relevant: hypocalcaemia, osteonecrosis of the jaw and renal toxicity.[7]
- Mean overall survival (3.73 years [breast cancer], 2.24 years [prostate cancer] and 1.73 years [other solid tumours]) was estimated using pooled data from both treatment groups in the clinical trials as no significant differences were observed overall between the two treatment arms.[5]

Quality of Life

- Baseline utilities (0.66 [breast cancer], 0.68 [prostate cancer] and 0.58 [other solid tumours])[8] were assessed through self-reported EQ-5D (generic standardised questionnaire for the measurement of quality of life) from patients that did not experience any on-study SRE.
- Utility decrements associated with SREs (-0.07 [pathologic fracture], -0.10 [radiation to bone], -0.14 [surgery to bone], -0.56 [spinal cord compression]) and adverse events were obtained from a time trade-off study.[9]

Table 3. Unit costs

	(€, 2013)
Drug cost	
Denosumab (ex-factory price)[10]	€293.00
Zoledronic acid (generic ex-factory price)[10]	€153.82
Drug administration costs	
Denosumab subcutaneous administration[11]	€14.58
Zoledronic acid intravenous infusion < 2 hours[11]	€135.03
Monitoring costs	
Calcium test[11]	€7.17
Creatinine test[11]	€6.43
SRE costs	
Pathologic fracture[2,12]	€5,113.27
Radiation to bone[2,12]	€2,579.90
Spinal cord compression[2,12]	€8,574.34
Surgery to bone[2,12]	€4,625.00
Drug-related adverse event management costs	
Renal toxicity[11]	€6,647.70
Hypocalcaemia[11]	€3,922.46
Osteonecrosis of the jaw*[11]	€3,272.71

SRE, skeletal-related event; *Resources were identified by an expert panel

Costs

- Analysis included drug, administration, monitoring and SRE costs. These costs were based on annual administrations: 13 for denosumab[4] and 14.47 for zoledronic acid, obtained by considering the different administration schedules observed in clinical practice in Spain: 60.2% of patients receive zoledronic acid every 4 weeks, 36.4% every 3 weeks and 3.4% every 6 weeks.[3]
- Conservatively, it was assumed that denosumab and zoledronic acid administration and monitoring costs would apply only to doses not administered concomitantly with intravenous chemotherapy. The percentages of zoledronic acid doses not administered concomitantly with intravenous chemotherapy were obtained from a Spanish observational study: 64.2% (breast cancer); 68.4% (prostate cancer); 52.6% (other solid tumours).[13]
- Unit costs (2013, €), were procured from the literature[2,12] and local databases[10,11] (Table 3).
- Published public ex-manufacturer prices were used for both denosumab and generic zoledronic acid.[10]

Base case and sensitivity analysis

- The base case did not consider discontinuation other than death or adverse events as in the integrated analysis of the clinical trials, the overall incidence was similar between the two treatment arms.[5]
- Sensitivity analyses were performed: for SRE management costs (±20%); considering administration and monitoring costs (±50%); using SRE rates from clinical practice in patients with breast and prostate cancer[7]; and including discontinuation and adverse event rates. Thus, a total of 9 scenarios were assessed for breast and prostate cancer patients and 8 scenarios for other tumours.
- A 3% annual discount was used in costs and outcomes.[14]

RESULTS

- Denosumab yielded 0.044, 0.041 and 0.026 additional QALYs and avoided 0.48, 0.35 and 0.22 SREs in patients with breast cancer, prostate cancer and other solid tumours, respectively (Table 4).
- In patients with breast cancer and prostate cancer, denosumab was also associated with savings of €704 and €606 per patient (Table 4).

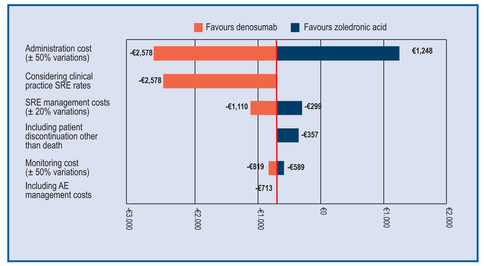
Table 4. Base case results: cost-effectiveness of denosumab vs generic zoledronic acid in patients with solid tumours

Results		Breast cancer		Prostate cancer		Other solid tumours	
		Dmab	ZA	Dmab	ZA	Dmab	ZA
Effectiveness	QALY	2.124	2.080	1.271	1.229	0.809	0.784
	QALY gained	0.044		0.041		0.025	
	SREs	1.645	2.122	1.614	1.962	1.270	1.490
	SREs avoided	0.477		0.348		0.220	
Costs	Total Cost	€20754	€21458	€14449	€15056	€11356	€11200
	Cost difference	-€704		-€606		€156	
	Drug costs	€13132	€7674	€8185	€4783	€6284	€3672
	Adminstration costs	€420	€4325	€279	€2872	€164	€1695
	Monitoring costs	€206	€436	€137	€289	€81	€171
	SRE cost	€6996	€9024	€5848	€7111	€4827	€5662
Cost-effectiveness	Cost per QALY gained	Dominant		Dominant		€6140.14	
	Cost per SRE avoided	Dominant		Dominant		€665.42	

Dmab, denosumab; SRE, skeletal-related event; ZA, zoledronic acid

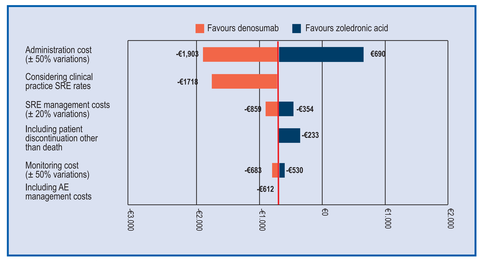
- Sensitivity analyses showed SRE rates and administration costs to be the inputs with the greatest impact on model results (Figures 1–3).
- Denosumab was dominant (more effective and less costly) in 69% of scenarios and remained cost-effective in 97% (using €30,000/QALY threshold).
- Denosumab was cost-effective in 100% of the breast cancer and prostate cancer scenarios.

Figure 1. Cost difference (denosumab vs generic zoledronic acid) in patients with breast cancer



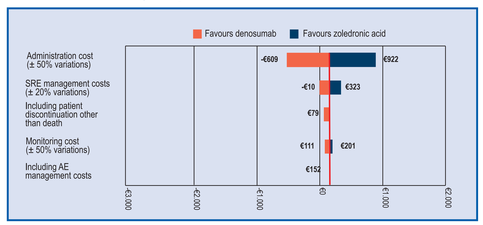
AE, adverse events; SRE, skeletal-related event

Figure 2. Cost difference (denosumab vs generic zoledronic acid) in patients with prostate cancer



AE, adverse events; SRE, skeletal-related event

Figure 3. Cost difference (denosumab vs generic zoledronic acid) in patients with other solid tumours



AE, adverse events; SRE, skeletal-related event

LIMITATIONS

- Cost savings outside the healthcare system were not taken into account nor were other requirements for healthcare resource use such as pain management or time spent by hospital staff in the administration of denosumab and zoledronic acid. Therefore, these results might be considered conservative and to be underestimating denosumab's economic advantages.
  - It has been observed that treatment with denosumab delays the onset of pain, pain worsening and reduces the requirement for progression to strong opioid analgesics, versus zoledronic acid.[15,16]
  - Time needed for administration of zoledronic acid greatly exceeds that for denosumab, it could therefore be assumed that there may be additional costs associated with zoledronic acid.[4,17,18]
- Adherence and persistance to treatments were considered to be 100% until patients' death, although this is likely not the case in the real-world setting.
- The analysis did not consider patient preference related to the mode of administration,[19] duration of treatment relating to patients health, or the quality of life gains associated with denosumab's prolonged time to severe pain onset,[14] suggesting QALYs gained might be underestimated for denosumab.
- All analyses were performed with the official drug prices. However, drug acquisition costs might be lower in hospitals and might change the results and conclusion of the analysis.

CONCLUSIONS

- Denosumab is cost-effective versus generic zoledronic acid in the prevention of SREs in patients with bone metastases from solid tumours and is considered dominant (more effective and less costly) in most scenarios assessed.

REFERENCES

1. Coleman RE. *Cancer Treat Rev* 2001;27:165-76.
2. Hechmati G, *et al. J Med Econ.* 2013;16(5):691-700.
3. Rodríguez-Penin, *et al.* ASCO 2010; (abs 19667). http://www.asco.org.
4. XGEVA® (denosumab). SmPC. www.ema.europa.eu.
5. Lipton A, *et al. Eur J Cancer.* 2012 Nov;48(16):3082-92.
6. Lothgren M, *et al. Eur J Hosp Pharm.* 2013;0:1-5.
7. Stopeck A, *et al. J Med Econ.* 2012;15(4):712-23
8. Lothgren M, *et al. Value in Health* 2011;14:455 (PCN 116)
9. Matza LS, *et al. Eur J Health Econ.* 2013. PubMed PMID: 23355121.
10. BOT Plus. www.portalfarma.com.
11. e-Salud. Oblikue Consulting. www.oblikue.com.
12. Durán I, *et al. Clin Trans Oncology.* 2013 [Epub ahead of print]
13. Anglada-Martínez H, *et al. Int J Clin Pharm* 2012;34:832-6
14. López Bastida J, *et al. Gac Sanit.* 2010;24:154–70.
15. Cleeland C, *et al.* ESMO 35. 2010. (Poster 1248P). www.esmo.poster-submission.com.
16. Martin M, *et al. Clin Cancer Res.* 2012;1;18(17):4841-9.
17. Zoledronic acid. SmPC. www.ema.europa.eu.
18. Oglesby A, *et al. Commun Oncol* 2009;6:494–502.
19. Matza L, *et al. Patient Preference and Adherence* 2013;7:855-865

ACKNOWLEDGEMENTS

This study was funded by Amgen S.A. Medical writing and editorial support were provided by Emma Thomas and Sarah Petrig of Amgen (Europe) GmbH.

AMGEN® © 2013 Amgen Inc.