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Clinical and Healthcare Resource Utilization (HRU) Impact in Spain from the use of Denosumab for the Prevention of Skeletal-Related Events (SRE) in Patients with Bone Metastases Secondary to Breast Cancer (BC), Prostate Cancer (PC) and Other Solid Tumors (OST)

Ignasi Campos Tapias[1], Joaquim Cristino[2], Montserrat Pérez[3], Robert Ikenberg[4]

[1]Amgen Spain, Barcelona, Spain; [2]Amgen (Europe) GmbH, Zug, Switzerland; [3]Hospital Universitario Fundación Alcorcón, Madrid, Spain; [4]Amgen GmbH, Muenchen, Germany

INTRODUCTION

- Bone is the most common site for metastasis in cancer and is of particular clinical importance in breast and prostate cancers because of the prevalence of these diseases *(Coleman et al 2006)*.
- Bone metastasis (BM) is the cause of considerable morbidity in patients with advanced cancer. Skeletal-related events (SRE) include pathological fracture (PF), radiation to bone (RB), spinal cord compression (SCC) or surgery to bone (SB) *(Coleman et al 2006)*.
- SREs are associated with a significant consumption of healthcare resources that generate a substantial economic burden for the Spanish healthcare system *(Duran 2014)*.
- Management costs per SRE (€, 2013) in Spain are 5.113,27€ for PF, 2.579,0€ for RB, 8.574,34€ and 4.625,00€ for SB *(Segui 2014; Duran 2014)*
- Denosumab and zoledronic acid (ZA) are approved and reimbursed in Spain for the prevention of SREs in adults with bone metastases from solid tumors (XGEVA® SmPC, zoledronic acid SmPC).
- Denosumab was superior to ZA in preventing SREs with favorable safety and convenience in patients with bone metastases from advanced cancer (Lipton 2012). Results of exploratory analyses amongst patients with solid tumors showed denosumab was also better than ZA in reducing the risk of first on-study SRE and multiple on-study SREs (Lipton 2012).

OBJECTIVES

- To estimate clinical and HRU impact in Spain when a novel therapy such as denosumab is used in substitution of an existing alternative (ZA) to prevent SREs in patients with bone metastases secondary to Breast Cancer (BC), Prostate Cancer (PC) and Other Solid Tumors (OST).

MATERIAL AND METHODS

- An Excel-based model was developed to estimate the number of SREs avoided, the reduction in number and duration of hospitalizations, the delay of severe pain, the reduction of acute phase reactions and drug administration time in patients with bone metastases secondary to BC, PC and OST in Spain.
- Analyses for denosumab and ZA were conducted separately in order to attribute the effect of each of the treatment option to an equal patient population.
- Analyses was perfomed from the data retrieved from January 2013 Until October 2014.

Inputs

- The number of patients who received denosumab for SRE prevention was estimated from internal sales data and distributed by tumor type based on market research (estimated figures were applied to both treatments).
- Clinical data (annual rate of any SRE and acute phase reactions) were taken from the rates seen in phase 3 clinical trials with denosumab and ZA (Lothgren 2013, Stopeck 2011, Fizazi 2011 and Henry 2014), time to worsening pain, and health-resource utilization (HRU) data (i.e. hospitalizations rate per SRE) was derived from Spanish observational studies when available (Cleeland 2013; Brown 2011; Vadhan-Raj 2012).

Table 1. Annual Rate of SREs, Time to Worsening Pain and Acute Phase Reactions by Active Agent and Tumor Type

Tumor Type	Active Agent	Annual Rate of Any SRE	*Median time to worsening pain (days)	Acute phase reactions in the first 3 days (% of patients)
BC				
	DMAB	0,486	295	10,4%
	ZA	0,631	176	27,3%
PC				
	DMAB	0,777	177	8,3%
	ZA	0,947	148	17,7%
OST				
	DMAB	0,796	143	7,1%
	ZA	0,936	103	14,8%

*Time to worst pain score>4 points among patients with no or mild pain (0-4) at baseline

- Inpatient hospitalizations rate and the length of stay associated with each type of SREs were derived from a multinational retrospective chart review and were dependent on the different SREs across tumor types (Duran 2014). Distributions of SREs in BC, PC and OST patients with bone metastases were those reported in the pivotal trials (Lothgren 2013, Stopeck 2011, Fizazi 2011 and Henry 2014).

Table 2. Inpatient hospitalization and duration of hospital stays by SRE and tumor type

Tumor Type	SRE Type	Pooled Distribution of SREs	Inpatient Hospitalizations per SRE	Duration of hospitalization (days)
BC				
	PF	58,2%	0,48	20,6
	RB	35,4%	0,17	20,8
	SB	4,7%	1,00	9
	SCC	1,7%	0,73	21,6
PC				
	PF	26,8%	0,48	20,6
	RB	66,1%	0,17	20,8
	SB	1,5%	1,00	9
	SCC	5,6%	0,73	21,6
OST				
	PF	31,4%	0,48	20,6
	RB	57,5%	0,17	20,8
	SB	6,2%	1,00	9
	SCC	5,0%	0,73	21,6

MATERIAL AND METHODS (cont.)

- Percentage of synchronization (sync) of bone-targeted therapy with chemotherapy (CT) was obtained by prescription patterns study in a reference hospital in Spain (Anglada 2012)
- *Table 3. Percentage of synchronization with CT by tumor type*

Sync with CT	YES	NO
BC	64,2%	35,8%
PC	68,4%	31,6%
OST	52,6%	47,4%

- Based on the posology described in the SmPC (XGEVA® SmPC), the number of administrations per year for denosumab was assumed to be 13. For ZA (zoledronic acid SmPC) 13 administrations were also assumed when there is no sync with CT, nevertheless a mean number of 14,47 administrations per year was observed in clinical practice (Segui 2014).
- Administration duration depends on sync with CT for ZA (Oglesby 2009). No data has been identified for denosumab, although it has been reported for other subcutaneous antibody drugs (Rubio-Terrés 2007) -assumed same time for dmab-.
- *Table 4. Number and length of drug administrations by drug and synchronization with CT*

	ZA		DMAB
Administrations per year (#)	NO sync with CT 13	YES sync with CT 14,47	13
Time per administration (min)	NO sync with CT 69,4	YES sync with CT 29,4	3,6

- The outcomes of the model included total number of SREs, number of hospitalizations and length of in-patient stays, delay of severe pain, reduction of acute phase reactions, drug administration time associated with patients treated with either denosumab or ZA
- The total number of SREs was estimated from the number of patients with bone metastasis multiplied by the SRE annual rates for each active agent, by tumor type (Table 1).
- The number of inpatient stays is obtained from multiplying the total number of SREs predicted, by type, by the probability of hospitalization, per SRE type (Table 2)
- Inpatient hospital days were calculated from the previous estimation multiplied by the duration of hospitalization by SRE (Table 2).
- Time to worsening pain was obtained by multiplying the median reported time to severe pain, by treatment, by the total number o patients, per treatment, per tumor type (Table 1).
- Acute phase reactions were calculated by multiplying the estimated number of patients by tumor type by the reported frequency of acute phase reactions (Table 1).
- To calculate the administration time, it was necessary to estimate the number of patients with or without synchronized CT, as administration time for ZA is different for these two treatment patterns. Therefore for ZA, the estimated number of patients was multiplied by the respective % of synchronized and non synchronized CT and again multiplied by the corresponding time of administration and the number of administrations per patient. For denosumab, the estimated number of patients was multiplied by the time per administration and the total number of administrations (Table 3 and Table 4).

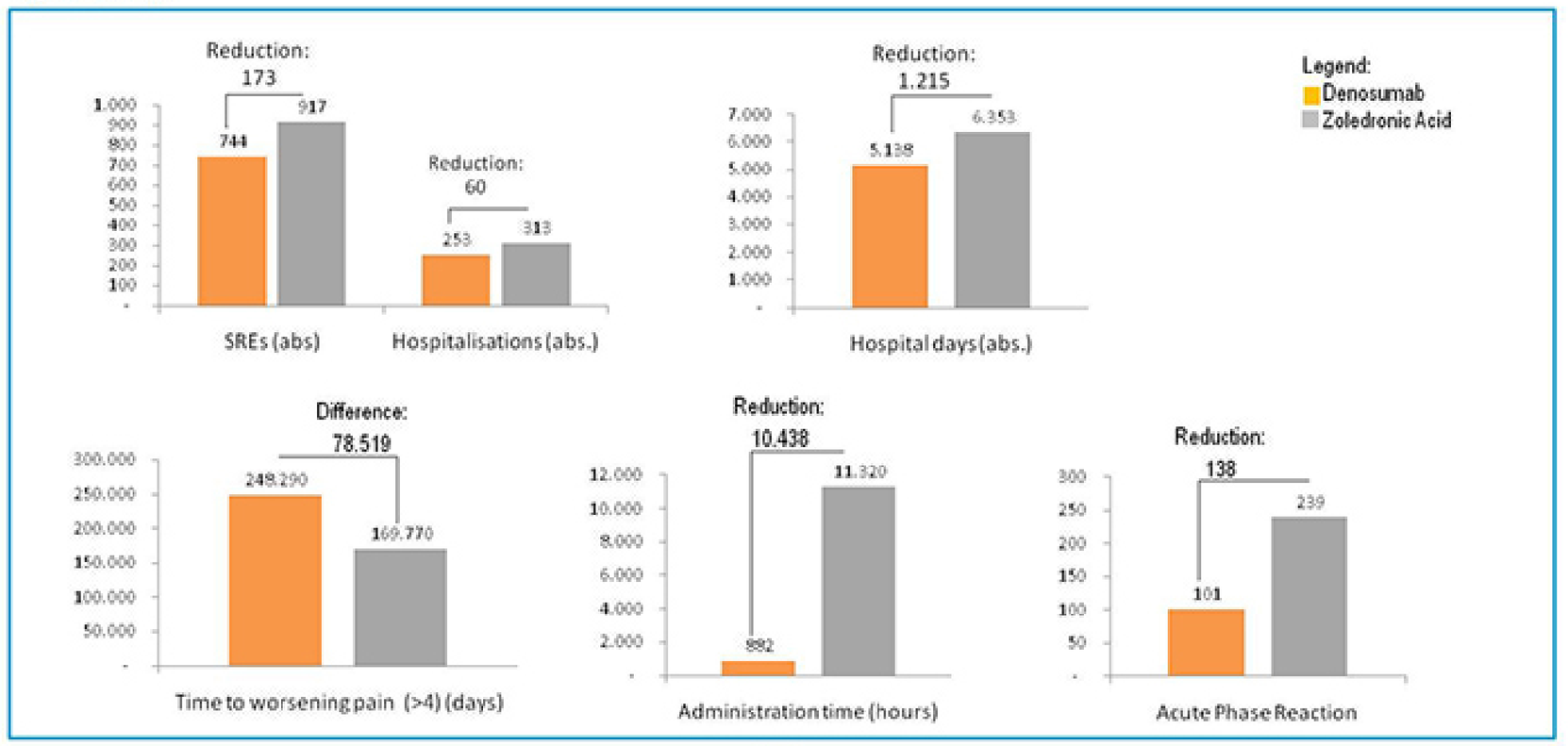
RESULTS

- From January 2013 until October 2014, 1131 patients were estimated to have been treated with denosumab in the NHS in Spain, corresponding to 478 patients with BC, 409 with PC and 243 with OST.
- All results are presented in Table 5 and Figure 1, respectively.
- Assuming that patients would otherwise have been treated with ZA, the use of denosumab instead of ZA would result in:
  - 173 SREs prevented (18,9% reduction)
  - 60 less hospitalizations (19,2% reduction)
  - 1.215 days per inpatient stay avoided (19,1% reduction)
  - A delay of severe pain of 78.519 days (46,3% increase)
  - A reduction of 138 acute phase reactions (57,7% reduction)
  - A reduction of the administration time of 10.438 hours (reduction of 92,2%)

Table 5. Results

Active Agent	Patients treated	SREs (abs)	Inpatient hospital stays	Hospital days (abs.)	Median time to worsening pain (days)	Acute phase reactions in the first 3 days (# of patients)	Patients with sync CT	Patients with NO sync CT	Administration time (hours)
Dmab	1.131	744	253	5.138	248.290	101	*NA*	*NA*	882
ZA	1.131	917	313	6.353	169.770	239	715	416	11.320
Difference	*Absolute*	*-173*	*-60*	*-1.215*	*78.519*	*-138*	*NA*	*NA*	*-10.438*
	%	*-18,9%*	*-19,2%*	*-19,1%*	*46,3%*	*-57,7%*	*NA*	*NA*	*-92,2%*

Figure 1. Results



LIMITATIONS

- No Spanish data has been identified assessing the different outcomes: different published sources had to be combined to estimate the different parameters.

CONCLUSIONS

- Superior efficacy of denosumab versus ZA reduces the clinical and HRU impact by decreasing the number of SREs, associated hospitalizations, duration of inpatient stays, while delaying time to worsening pain. In addition, the use of denosumab implies less administration time and acute phase reactions when compared to ZA.

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