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Osteonecrosi dei Mascellari (ONJ): Prevenzione, Diagnosi,Trattamento UPDATE 2009

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23 Giugno 2009

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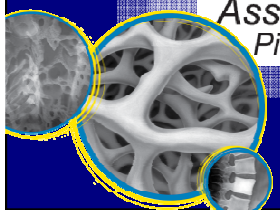

Università degli Studi PALERMO

Facoltà di Medicina e Chirurgia

Dip. Scienze Stomatologiche

A.O.U.P. "P.Giaccone" Palermo

BISFOSFONATI ORALI: UN'ALTRA STORIA?

*Giuseppina Campisi**

*Speaker dichiara: nessun conflitto di interesse

Università degli Studi
OralMed
di Palermo

Settore di Medicina Orale

DOBBIAMO PREOCCUPARCI DI MENO?

225 MILIONI DI PRESCRIZIONI DI BF ORALI SONO STATE EROGATE IN TUTTO IL MONDO -al 2007

I **BIFOSFONATI** (BF) **ORALI** O **ENDOVENOSI** (di recente) RAPPRESENTANO GLI AGENTI FARMACOLOGICI PIÙ PRESCRITTI PER IL **TRATTAMENTO DELL'OSTEOPOROSI PRIMARIA E SECONDARIA**

Il rischio di sviluppare ONJ nei pazienti che assumono BF orali (per osteoporosi) sembra molto basso. TUTTAVIA, NONOSTANTE IL MINOR RISCHIO RELATIVO (legato al farmaco ed alla modalità di assunzione), ATTUALMENTE SONO MILIONI I PAZIENTI CHE ASSUMONO TALI FARMACI.

> IMPATTO SOCIALE

< RISCHIO RELATIVO

Review

Osteonecrosis of the jaw — Who gets it, and why?☆

Ian R. Reid *

Bone 44 (2009) 4–10

When a new clinical entity is described, there is often a period of uncertainty during which some clinicians question whether the condition really exists, and then a further time during which the defining characteristics of the syndrome and its nomenclature are debated. Osteonecrosis of the jaw (ONJ) is progressing through this evolution.

The reality of the condition in oncology patients is beyond doubt, though in **benign bone diseases** the debate continues.

oral bisphosphonates and osteonecrosis - PubMed Results - Windows Internet Explorer

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Search PubMed for bisphosphonates and osteonecrosis and osteoporos Go Clear Advanced Search (beta) Save Search

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All: 207 Review: 70

Items 1 - 20 of 207

Page 1 of 11 Next

1: Nguyen TV, Center JR, Eisman JA.

Related Articles, Links

Pharmacogenetics of osteoporosis and the prospect of individualized prognosis and individualized therapy.

Curr Opin Endocrinol Diabetes Obes. 2008 Dec;15(6):481-8.

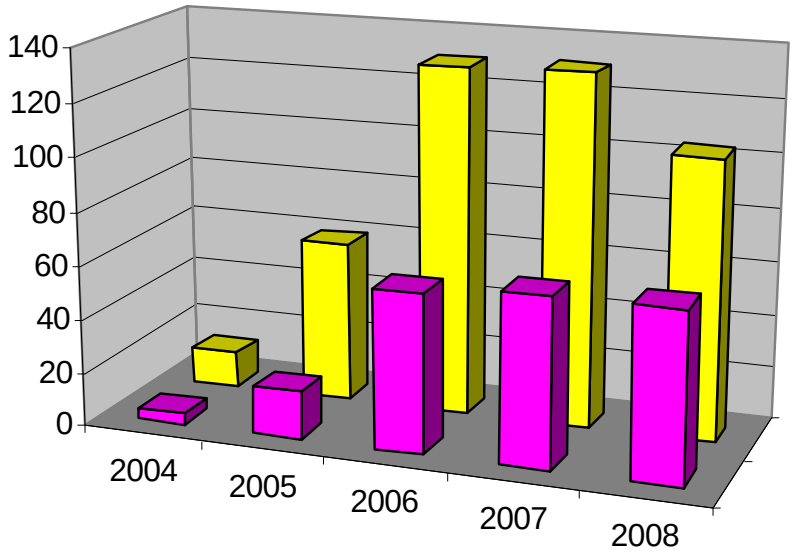
PMID: 18971675 [PubMed - in process]

Bisphosphonates

Osteonecrosis

Osteoporosis

NUMBER OF PUBLICATIONS IN THE YEARS



- Bisphosphonates AND Osteonecrosis AND Osteoporosis
- Bisphosphonates AND Osteonecrosis

KEYWORDS

BP *AND* **ONJ** *AND* **OP**

Vs

BP *AND* **ONJ****

MEDICAL NEWS
& PERSPECTIVES

(Reprinted) JAMA, June 28, 2006—Vol 295, No. 24 2833

Bridget M. Kuehn

Reports of Adverse Events From Bone Drugs Prompt Caution

The FDA has required changes to the labeling of bisphosphonate drugs to reflect the possible risk of osteonecrosis. The labels for alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid posted on the FDA Web site, http://www.fda.gov/, all note reports of osteonecrosis of the jaw.

JAMA, February 18, 2009—Vol 301, No. 7 (Reprinted)

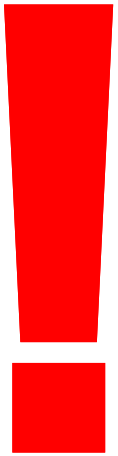
Long-term Risks of Bisphosphonates Probed

A GROWING BODY OF EVIDENCE suggests that long-term use of a popular class of drugs for osteoporosis and other bone disorders may be associated with the development of rare complications in some patients.

P. P. Sedghizadeh and his colleagues analyzed the electronic medical records of 208 dental patients who were also alendronate users and found that 9 of them (4%) had osteonecrosis of the jaw.

JAW PROBLEMS

As early as 2006, dentists began documenting a rare condition in patients taking bisphosphonates, osteonecrosis of the jaw, predominantly those taking high-dose intravenous formulations for cancer-related problems. However, more recent data suggest that a subset of patients taking oral formulations of these drugs may be at greater risk than previously appreciated, according to an analysis of patients at the University of Southern California School of Dentistry in Los Angeles (Sedghizadeh PP et al. *J Am Dent Assoc.* 2009;140[1]:61-66).



J Oral Maxillofac Surg 67:35-43, 2009, Suppl 1

Oral Bisphosphonates as a Cause of Bisphosphonate-Related Osteonecrosis of the Jaws: Clinical Findings, Assessment of Risks, and Preventive Strategies

*Leon A. Assael, DMD**

Oral bisphosphonates are now a ubiquitous medication seen in daily oral and maxillofacial surgery practice. Alendronate (Fosamax; Merck, Whitehouse Station, NJ) emerged during clinical trials in the 1990s, primarily for the purpose of treating osteoporosis in at-risk populations. Alendronate was approved by the Food and Drug Administration for the treatment of postmenopausal osteoporosis, but is also used for osteoporosis in males, Paget's disease, renal osteodystrophy, and other diseases where a reduction of osteoclastic activity is believed desirable. Risendronate

Although the association between bisphosphonate use and osteonecrosis is established, the extent to which osteonecrosis is attributable to the use of oral bisphosphonates is by no means as clear as it is with IV bisphosphonates.

*Professor and Chairman, Department of Oral and Maxillofacial Surgery, and Medical Director, Hospital Dentistry, Oregon Health and Science University, Portland, OR.

Dr Assael is a paid consultant for Novartis and has received honoraria from Novartis and Merck.

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0278-2391/09/6705-0106$36.00/0
doi:10.1016/j.joms.2009.01.003

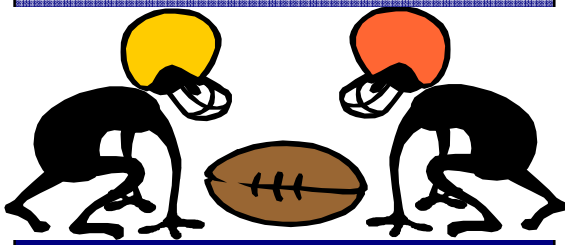
Much evidence is accumulating on the clinical effects of oral bisphosphonates on oral tissues. These questions include:

- What is the risk of osteonecrosis in my patient on oral bisphosphonates?
- Why are so few cases of BRONJ attributable to oral bisphosphonate use?
- What is the importance of cofactors in the development of osteonecrosis?
- How major a clinical problem is BRONJ, typically, in the oral bisphosphonate patient?
- What dental procedures are associated with a risk of BRONJ?
- Are other findings short of BRONJ of importance in the oral bisphosphonate patient?
- Are there proven strategies to prevent BRONJ in the oral bisphosphonate patient?
- Should my patient discontinue the use of oral bisphosphonates temporarily or permanently?

In a survey of American Association of Oral and Maxillofacial Surgeons (AAOMS) members, 1,700 surgeons reported 4,700 cases of BRONJ (Personal communication, Randi Andreasen, AAOMS, Rosemont, IL). This is a reply rate of 30% of all oral and maxillofacial surgeons (OMS) in the United States. A total of 3 to 4 cases per reporting OMS over the course of the previous 3 years, or about 1 case per year/surgeon, was reported. Extrapolated to 5,000 total cases per year (if all practicing surgeons had replied), and about 20% of cases at most attributable to oral bisphosphonates (based on a previous case series showing less than 20% of cases attributable to oral bisphosphonates), there would appear to be about 1,000 new BRONJ cases attributable to oral bisphosphonates per year in the United States. As a factor dependent on the 27 million prescriptions for oral bisphosphonates, this extrapolates to 1 new case of BRONJ per 27,000 prescriptions for oral bisphosphonates. Because this was a postal survey, cases may have been over-reported.

NON-AMMINO BIFOSFONATI

Clodronato
Etidronato
Tiludronato



AMMINO BIFOSFONATI

Alendronato
Ibandronato
Pamidronato
Risedronato
Zoledronato

INDICAZIONI

Lower

- **Osteoporosi ad alto turn-over Primitiva/Secondaria**
- Osteogenesi imperfetta
- Iperparatiroidismo primitivo
- Malattia di Paget
- Chirurgia ortopedica maggiore

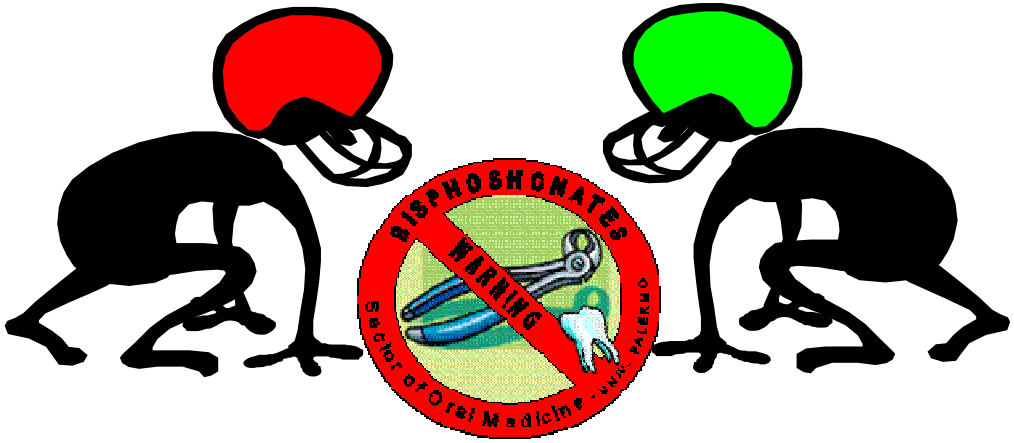
High

- **Mieloma multiplo**
- **Tumori solidi (Ca mammario, Ca prostatico, Ca polmonare)**
- **Prevenzione e terapia di metastasi ossee**

MOLECOLA	*Nome Commerciale*
ACIDO CLODRONICO (EV/cpr)	ACIDO CLODRONICO (SANDOZ-EG-UNION); CLASTEON; CLIMACLOD; CLODEOSTON; CLODRON; CLODRONATO (ABC-TEVA); CLODY; DIFOSFONAL; DISODIO CLODRONATO; MOTICLOD; NIKLOD; OSTEONORM; OSTEOSTAB; OSSITEN; SOCLONAT
ACIDO PAMIDRONICO (EV)	AREDIA; AMIDROX
ACIDO ALENDRONICO sale sodico (cpr) 1°	A. ALENDRONICO FIDIA; ADRONAT; ADROVANCE 70; ALENDRONATO EG; ALENDRONATO M.G;• ALENDRONATO (PLIVA-RANBAXY-RATIO-SANDOZ-TEVA); ALENDROS; ALENIC; DRONAL; DARYX; FOSAMAX; FOSAMAX PLUS;FFOSAVANCE; GENALEN, OSAMAX
ACIDO TILUDRONICO (cpr)	SKELID®
ACIDO IBADRONICO (cpr) 3°	BONDRONAT; BONIVA
ACIDO RISEDRONICO sale sodico (cpr) 2°	ACTONEL; OPTINATE
ACIDO ZOLEDRONICO (EV)	**ZOMETA®** **Aclasta**
ACIDO NERIDRONICO sale sodico (EV)	NERIXIA
ACIDO ETIDRONICO sale sodico (cps)	DIDROCAL; DIDRONEL; ETIDRON

ONJ RISK FACTORS

AT THE BEGINNING (2003)…



INTRAVENOUSLY ADMINISTERED BISPHOSPHONATES

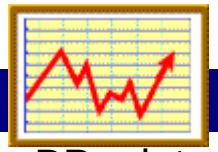
O. N. J

ORALLY ADMINISTERED BISPHOSPHONATES

EPIDEMIOLOGY

BISPHOSPHONATES & ONJ

CANCER PATIENTS ON HIGH POTENCY **INTRAVENOUS BPs**



BP related ONJ could occur in 1-11% (up to **28%) of cancer patients** on high potency intravenous BP (Durie et al, 2005; Bamias et al, 2005; McLeod et al, 2007; Hasmim et al, 2007; Allegra A et al, 2007; Boonyapakorn et al, 2008).

OSTEOPOROTIC AND OTHER THAN CANCER PATIENTS ON **ORAL BPs/**Low potency

The estimated risk of ONJ is **1/10,000 to 1/100,000** patient-years in patients receiving oral BPs in doses registered for osteoporosis.(Khosla et al, 2007)

The prevalence of ONJ related to oral BP accounts for less than 0.3% of individuals (McLeod et al, 2007).

BP-related ONJ in cancer patients (bone metastasis and MM) YES

VS

BP-related ONJ in osteoporotic patients (Y/N)

Intravenously Administered Bisphosphonates

O. N. J

Orally Administered Bisphosphonates

EPIDEMIOLOGY? Frequencies-case series and %

ONJ in OSTEOPOROTIC AND OTHER THAN CANCER PATIENTS ON ORAL BPs/Low potency

Further data:

Oral BP-related ONJ is a relatively rare side effect. The estimated occurrence of ONJ in such patients ranges **between 0,7/100.000 per years of use**, as estimated by Merck, **to one case per a few thousand patients** as reported by Yarom (Yarom et al, 2007) and an Australian group (Mavrokokki et al, 2007).

The study of Parish et al (Parish et al, 2009) reported a minimum and maximum frequency of ONJ in patients receiving oral BPs as one in 2,030 and one in 950, respectively, and a minimum and maximum frequency of patients receiving oral BPs who have undergone extractions as one in 270 and one in 125, respectively. Our data similarly showed a significantly higher frequency of ONJ in people taking alendronate.

Post-marketing surveys to mid-2007 indicated an incidence of 1.2 per 100,000 patient-years for risedronate, and of **0.5–2.5 per 100,000 patient/years for alendronate**.

In a postal survey performed in Australia and New Zealand, Mavrokokki et al reported on cases of ONJ that were solicited in the survey questionnaire. The estimated prevalence rate of BRONJ among osteoporosis patients was 0.01% to 0.04%, (0.25% in case of extraction) or 1 case per 2,260 to 8,470 prescriptions.

Importantly, patients with BRONJ for oral bisphosphonates were taking a mean dose of 9,060 mg of alendronate at time of diagnosis. This is the equivalent of 122 weekly doses of 70 mg.

•McLeod NM et al. Bisphosphonate osteonecrosis of the jaws; an increasing problem for the dental practitioner. Br Dent J. 2007.8;203(11):641-4
•Khosla S et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2007.22(10):1479-91
•Yarom N et al. Osteonecrosis of the jaw induced by orally administered bisphosphonates: incidence, clinical features, predisposing factors and treatment outcome.Osteoporos Int. 2007.18(10):1363-70
•Mavrokokki T et al. Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. J Oral Maxillofac Surg. 2007.65(3):415-23.
•Parish P et al. Oral bisphosphonate use and the prevalence of osteonecrosis of the jaw: An institutional inquiry. J Am Dent Assoc 2009;140:61-66

EPIDEMIOLOGY? Frequencies-case series and %

ONJ in OSTEOPOROTIC AND OTHER THAN CANCER PATIENTS ON ORAL BPs/Low potency

21/03/2009

I punti chiave del documento congiunto SIOMMMS-ANDI sull'ONJ

"..L'incidenza dell'osteonecrosi mandibolare nei pazienti con osteoporosi trattati con bifosfonati non è nota con precisione, come per altro non lo è quella nella popolazione generale. Sembra comunque estremamente inferiore rispetto a quella rilevata in pazienti oncologici che nelle varie casistiche oscilla tra l'1% e 11%.

.

L'incertezza sulla reale prevalenza dell'ONJ è dovuta principalmente alla mancanza di studi longitudinali…"

"..In conclusione il documento di consenso sull'ONJ nei pazienti osteoporotici elaborato congiuntamente dalla SIOMMMS e dall'ANDI, pur non potendo fornire risposte esaurienti a tutti i quesiti posti dall'ONJ, **sgombra il campo da allarmismi ingiustificati e da contrapposizioni artificiose tra le diverse figure professionali contribuendo a scongiurare la conseguenza più temibile della "psicosi ONJ" e cioè l'abbandono o la sottoutilizzazione di una classe di farmaci,** i bisfosfonati, che hanno permesso di cambiare la storia naturale di diverse osteopatie metaboliche e tumorali…"

"..Una recente revisione prodotta da una Task Force della ASMBR ha identificato in totale 57 casi di ONJ in soggetti in trattamento con bifosfonati per osteoporosi di cui 4 maschi. Considerato che l'esposizione mondiale ai bifosfonati per l'osteoporosi è stimata in circa 190 milioni di soggetti, la prevalenza di ONJ in questi pazienti sembra essere estremamente bassa…".

Un dubbio

Publication	Cases Reported	Concomitant Medications Provided
Black et al[10]	Osteoporosis = 1	No
Brooks et al[31]	Osteoporosis = 1	Yes
	Osteopenia = 1	
Carter et al[22]	Paget's disease = 3	Yes
Cheng et al[32]	Osteoporosis = 3	Yes
	Paget's disease = 2	
Clarke et al[33]	Osteoporosis = 1	Yes
Danneman et al[34]	Osteoporosis = 3	No
Dimitrakopoulos et al[35]	Fibrous dysplasia = 1	No
Farrugia et al[36]	Osteoporosis = 4	No
	Paget's disease = 1	
Friedrich and Blake[37]	Diabetes = 1	Yes
Heras-Rincón et al[38]	Osteoporosis = 2	No
Hoefert and Eufinger[30]	Osteoporosis = 1	Yes
Kademani et al[12]	Osteoporosis = 1	Yes
Khamaisi et al[15]	Osteoporosis = 1	No
	Rheumatoid arthritis = 1	
Levin et al[39]	Osteoporosis = 1	Yes
Malden and Pai[40]	Osteoporosis = 1	Yes
	Rheumatoid arthritis = 1	
Marunick et al[41]	Osteoporosis = 1	Yes
Marx[42]	Osteoporosis = 4*	No
Mavrokokki et al[6]	Osteoporosis = 24†	No
	Paget's disease = 4‡	
Merigo et al[43]	Osteoporosis = 3	No
Migliorati et al[24]	Osteopenia = 1	Yes
Milillo et al[44]	Osteoporosis = 9	No
Najm et al[29]	Osteoporosis = 3	No
Nase and Suzuki[45]	Osteoporosis = 1	Partial
Oltolina et al[46]	Microfractures = 1	Yes
Phal et al[47]	Osteoporosis = 4	No
Pozzi et al[48]	Osteoporosis = 1	Yes
Purcell and Boyd[49]	Osteoporosis = 1	No
Ruggiero et al[50]	Osteoporosis = 7	No
Shlomi et al[28]	Osteoporosis = 3	Yes
Wang et al[51]	Osteoporosis = 1	Yes
Yeo et al[52]	Osteoporosis = 1	Yes

*Three osteoporosis cases were previously reported by Marx et al.[23]

†Three additional cases were previously reported in Cheng et al,[32] and were removed from this analysis to avo

‡Two additional cases were previously reported in Cheng et al,[32] and were removed from this analysis to avoi

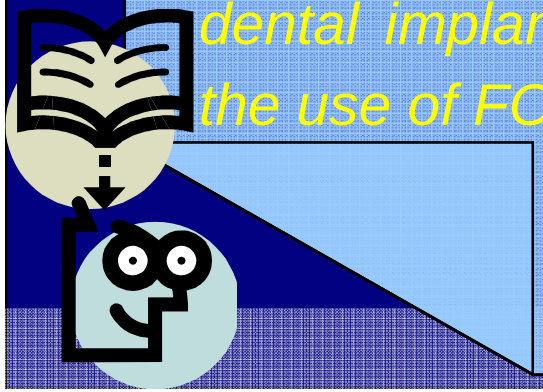
As a result of this search, **99 cases** of osteonecrosis of the jaw among patients receiving bisphosphonates for an indication other than cancer were identified in the published medical literature.

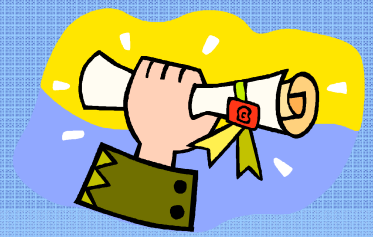
85 osteoporosis patients,
10 patients with Paget's disease,
2 patients with rheumatoid arthritis,
1 patient with diabetes, and
1 patient with maxillary fibrous dysplasia.

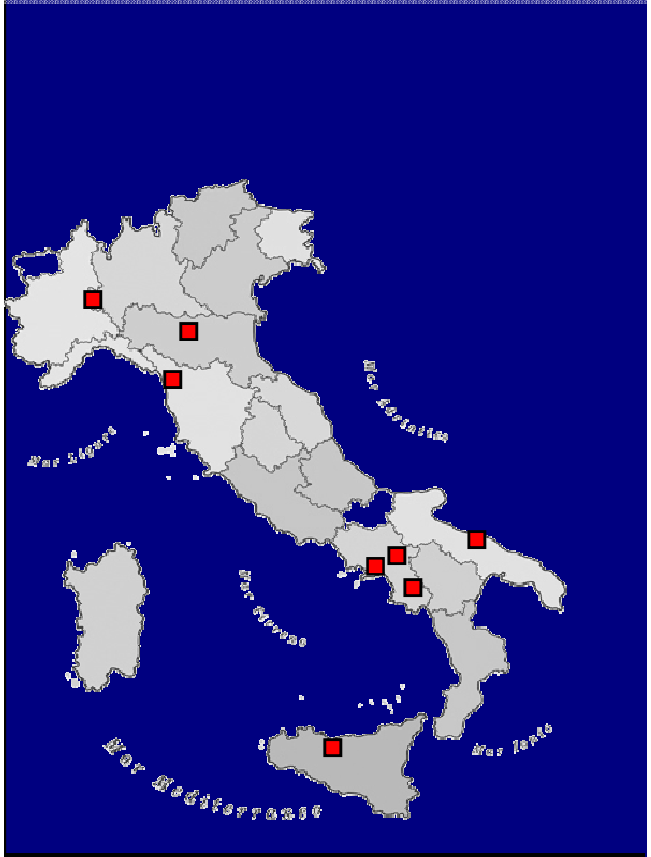
Hess et al. Factors associated with osteonecrosis of the jaw among bisphosphonate users. Am J Med. 2008.121(6):475-483

Merck Reports First-Quarter 2008 Financial Results.
Available at URL:
http://www.merck.com/newsroom/press_releases/financial/2008_0421.html.

''The Company is a defendant in product liability lawsuits in the United States involving FOSAMAX (the "FOSAMAX Litigation"). As of March 31, 2008, approximately 465 cases, which include approximately 940 plaintiff groups, had been filed and were pending against Merck in either federal or state court, including three cases that seek class action certification, as well as damages and medical monitoring. In these actions, plaintiffs allege, among other things, that they have suffered osteonecrosis of the jaw, generally subsequent to invasive dental procedures such as tooth extraction or dental implants, and/or delayed healing, in association with the use of FOSAMAX''







ALESSANDRIA (ReteOnc.)- dr. Fusco;

BARI-Prof.Favia;

CASERTA-Prof.Peluso;

NAPOLI-Prof.Colella;

PALERMO-Prof.Campisi; **PALERMO**-Prof.Solazzo;

PARMA-Prof.Vescovi;

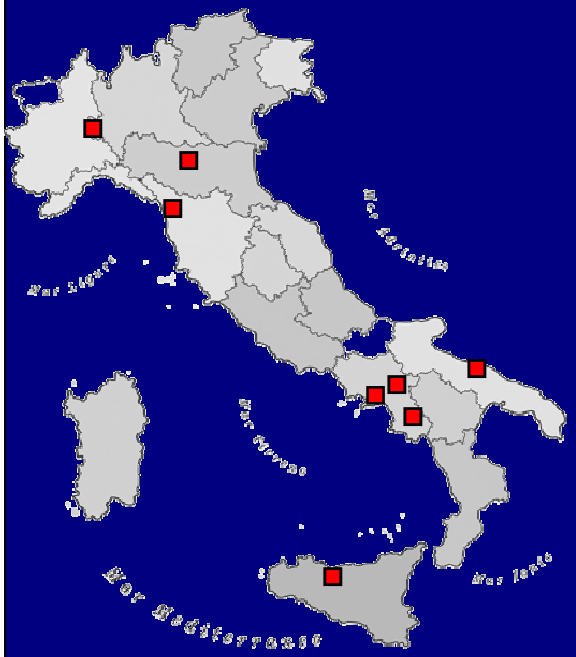
PISA-Prof.Gabriele;

SALERNO-Dr.Gaeta

Data from an ITALIAN MULTICENTRIC STUDY ONJ in Primary Osteoporosis vs Cancer

	Cancer	Osteoporosis	Total
n* ONJ patients *(% overall of ONJ)	**278 (78.5)**	**76 (21.5)**	**354**
Gender, *n (% overall of ONJ)*			
Female	177 (63.7)	76 (100)	253 (72)
Male	101 (36.3)	0 (0)	101 (28)
Median age ±SD (range)	66.9 ± 10.7 (34-92)	69.7±9.8 (53-92)	69 ± 10 (34-92)
Specific Neoplasia *(% overall of cancer ONJ)*	120 MM (43.1) 97 Breast (34.9) 34 Prostate (12.2) 27 Other cancer (9.8)		
Localization ONJ *(% overall of ONJ)*			
Mandible	180 (64.74)	51 (67.1)	231 (65.2)
Maxilla	81 (29.13)	23 (30.3)	104 (29.4)
Mandible AND Maxilla	17 (6.115)	2 (2.6)	19 (5.4)
Duration of administration (month)			
Median value ±SD	23.0 ± 14.8	40.4 ± 29.1	26.7 ± 20.0
(range)	(2-96)	(3-120)	(2-120)
Local Risk factors for ONJ, *n (% overall of ONJ)*			
Tooth extraction	176 (63.3)	50 (65.8)	226 (63.8)
Spontaneous ONJ	77 (27.7)	25 (32.9)	102 (28.8)
Periodontal chronic disease and abscess	11 (3.9)	0 (0)	11 (3.1)
Bone biopsy	1 (0.4)	0 (0)	1(0.3)
Protesic trauma	12 (4.3)	1 (1.3)	13 (3.7)
Implantology	1 (0.4)	0 (0)	1(0.3)
Medications affecting bone turnover, in addition to bisphosphonates use (i.e. corticosteroid therapy) *n (% overall of ONJ)*	109 (39.2) [106 with MM]	3 (3.9)	112 (31.6)
Underlying Medical Conditions			
Diabetes	22 (7.9)	6 (7.9)	28 (7.9)
Hypertension/hyperlipidemia/hypercholesterolemia	60 (21.6)	24 (31.6)	84 (23.7)
HCV-related liver diseases	5 (1.8)	2 (2.6)	7 (2.0)
Other cardiac	23 (8.2)	5 (6.6)	28 (7.9)

Data from an ITALIAN MULTICENTRIC STUDY



	Osteoporosis n=76	Cancer *n*=278	Unadjusted OR OR(CI 95%)
		Univariate analysis	
Gender			
Females	76 (100.0)	177 (63.7)	1.0 (reference)
Males	0(0.0)	101 (36.3)	-
Age			
≤60	19 (25.0)	72 (25.9)	1.0 (reference)
61-75	33 (43.4)	145 (52.2)	0.86 (0.45-1.62)
>76	24 (31.6)	61 (21.9)	1.49 (0.74-2.99)
Specific Neoplasia (% overall of cancer ONJ)		97 Breast (34.9) 34 Prostate (12.2) 27 Other cancer (9.8)	
Localization ONJ, *n (% overall of ONJ)*			
Mandible	51 (67.1)	180 (64.74)	1.0 (reference)
Maxilla	23 (30.3)	81 (29.13)	1.00 (0.57 - 1.75)
Mandible AND Maxilla	2 (2.6)	17 (6.115)	0.42 (0.09 - 1.87)
Staging *(by Ruggiero et al. OOO. Vol. 102 No. 4 October 2006)*			
I (%)	16 (21.1)	73 (26.3)	1.0 (reference)
II (%)	53 (69.7)	174 (62.6)	1.03 (0.38 - 2.76)
III (%)	7 (9.2)	31 (11.2)	1.08 (0.74 - 2.60)
Type of administered BP			
Alendronate	56(73.7)	5 (1.8)	1.0 (reference)
Alendronate AND Risedronate	1 (1.3)	1 (0.4)	0.089 (0.004-1.864)
Pamidronate	2 (2.6)	27 (9.7)	0.007 (0.000-0.141)
Ibadronate	2 (2.6)	2 (0.7)	0.089 (0.009-0.894)
Clodronate	7 (9.2)	4 (1.4)	0.156 (0.031-0.789)
Zoledronate	0 (0.0)	211 (75.9)	-
Zoledronate AND Pamidronate	0 (0.)	25 (9.0)	-
Zoledronate AND Alendronate	0 (0.0)	2 (0.7)	-
Zoledronate AND Ibadronate	0 (0.0)	1 (0.4)	-
Alendronate AND Clodronate	3 (4.0)	0 (0)	-
Clodronate AND Risedronate	1 (1.3)	0 (0)	-
Risedronate	3 (4.0)	0 (0)	-
Neridronate	1 (1.3)	0 (0)	-
Duration of administration (months)			
≤12	17 (22.4)	81 (29.1)	1.0 (reference)
13-36	24 (31.6)	155 (55.8)	0.74 (0.37-1.45)
>36	35 (46.1)	42 (15.1)	3.97 (1.92-8.20)

Data from an ITALIAN MULTICENTRIC STUDY

Geographical area			
North-Center	28 (36.8)	140 (50.4)	1.0 (reference)
South-islands	48 (63.2)	138 (49.6)	**1.74 (1.03-2.94)**
Pain No	11 (14.5)	80 (28.8)	1.0 (reference)
Yes	65 (85.5)	198 (71.2)	**2.39 (1.19-4.79)**
Local Risk factors for ONJ, *n (% overall ONJ)*			
Spontaneous ONJ	25 (32.9)	77 (27.7)	1.0 (reference)
Tooth extraction	50 (65.8)	176 (63.3)	0.88 (0.51 - 1.52)
Other	1 (1.32)	25 (8.9)	0.12 (0.02 - 1.01)
Medications affecting bone turnover, in addition to bisphosphonates use (i.e. **corticosteroid therapy**)			
No	73 (96.1)	169(60.8)	1.0 (reference)
Yes	3 (3.90)	109 (39.2)	**0.06 (0.02-0.22)**
Underlying medical condition			
Diabetes			
No	70 (92.1)	296(92.1)	1.0 (reference)
Yes	6 (7.9)	22(7.9)	0.99 (0.39-2.56)
Hypertension/hyperlipidemia/hypercholesterolemia			
No	52 (68.4)	218 (78.4)	1.0 (reference)
Yes	24 (31.6)	60 (21.6)	1.68 (0.95-2.95)
HCV-related liver diseases			
No	74 (97.4)	273 (98.2)	1.0 (reference)
Yes	2 (2.6)	5 (1.80)	1.48 (0.28-7.78)
Other cardiac			
No	71 (93.4)	255 (91.7)	1.0 (reference)
Yes	5 (6.6)	23 (8.3)	0.78 (0.29-2.13)

	***Multivariate analysis* §**		
	OR'	95%CI	p
Pain			
Yes vs no	5.16	(1.042-25.590)	0.044
Type of administered BP			
Aledronate AND Risedronate vs Aledronate	0.05	(0.002-0.977)	0.048
Clodronate vs Aledronate	0.112	(0.021-0.610)	0.011
Pamidronate vs Aledronate	0.007	(0.001-0.047)	<0.001
Ibadronate vs Aledronate	0.047	(0.005-0.477)	0.010

§ OR' adjusted for the other variables listed in the Table.

Oral bisphosphonate use and the prevalence of osteonecrosis of the jaw

An institutional inquiry

JADA 2009;140(1):61-66.

Parish P. Sedghizadeh, DDS, MS; Kyle Stanley, BS; Matthew Caligiuri, BA; Shawn Hofkes, BS; Brad Lowry, BS; Charles F. Shuler, DMD, PhD

Background. Initial reports of osteonecrosis of the jaw (ONJ) secondary to bisphosphonate (BP) therapy indicated that patients receiving BPs orally were at a negligible risk of developing ONJ compared with patients receiving BPs intravenously. The authors conducted a study to address a preliminary finding that ONJ secondary to oral BP therapy with alendronate sodium in a patient population at the University of Southern California was more common than previously suggested.

Methods. The authors queried an electronic medical record system to determine the number of patients with a history of alendronate use and all patients receiving alendronate who also were receiving treatment for ONJ.

Results. The authors identified 208 patients with a history of alendronate use. They found that nine had active ONJ and were being treated in the school's clinics. These patients represented one in 23 of the patients receiving alendronate, or approximately 4 percent of the population.

Conclusions. This is the first large institutional study in the United States with respect to the epidemiology of ONJ and oral bisphosphonate use. Further studies along this line will help delineate more clearly the relationship between oral BP use and ONJ.

Clinical Implications. The findings from this study indicated that even short-term oral use of alendronate led to ONJ in a subset of patients after certain dental procedures were performed. These findings have important therapeutic and preventive implications.

Tooth extraction patterns in participants receiving alendronate and participants not receiving alendronate.

CRITERION	ALENDRONATE THERAPY (70 MILLIGRAMS PER WEEK) (NO. OF PARTICIPANTS)	NO ALENDROANTE THERAPY (NO. OF PARTICIPANTS)	TOTAL NO. OF PARTICIPANTS
Tooth Extraction	66	4,384	4,450
No Extraction	142	9,138	9,280
TOTAL	208	13,522	13,730

“THE FACT THAT ONJ IS A POSSIBLE RARE COMPLICATION SHOULD NOT TO BE SWEPT UNDER THE CARPET BUT RATHER STATED EXPLICITLY BY THE RESPONSIBLE TREATING PHYSICIAN WHEN PRESCRIBING BP”.

“WE COULD NOT AGREE MORE WITH THE AUTHORS THAT BENEFITS OF ORAL BP APPEAR TO OUTWEIGH THE POTENTIAL RISKS OF DEVELOPING ONJ”.

Yarom N and Elad S. **Comment on Pazianas** et al.: lack of association between oral bisphosphonates and osteonecrosis using jaw surgery as a surrogate marker. Osteoporos Int. 2008.19(6):849-50

ONJ da BPS *per osteoporosi*

≠

ONJ da BPS in paz. neoplastico (metastasi ossee e MM)

POTENTIAL RISK FACTORS
for the development of oral BP related ONJ

- DRUG-RELATED RISK FACTORS
- DEMOGRAPHIC AND SYSTEMIC RISK FACTORS
- LOCAL RISK FACTORS

- GENETICAL RISK FACTORS

DRUG-RELATED RISK FACTORS

AGENT

Potency of the bisphosphonate (**zoledronate** > pamidronate > **alendronate** > clodronate)

DOSE Duration of therapy (?) - threshold of 3/5 years for oral BP

Off-label use *

ROUTE of administration (*intravenous* > *oral*)

Subset of osteoporotic patients

OSTEOPOROSIS

⇩

Long term BPs treatment

⇩

Adverse events

- Excessive Suppression of bone Turnover (**SSBT**)
- Osteonecrosis of the jaws (**ONJ**)

The SSBT leads to fractures for the accumulation microdamages of trabecular bone as a result of long term treatment with BPs.

The suppressive effect of BPs on bone tissue renewal over longer durations (more than 5 years) may weaken the bones through two main mechanisms: inhibition of physiologically occurring microdamage in normal bone and increased mineralization (Lane 2007, Odvina 2005, Armamento-Villareal 2006).

DEMOGRAPHIC AND SYSTEMIC RISK FACTORS

Elderly (>65 years)

Gender: female > male (?)

Caucasian race (?)

Malnutrition

CONCOMITANT MEDICATIONS

Chronic corticosteroid therapy*

Cancer chemotherapy

Estrogenic therapy

Alcohol and cigarettes abuse*

COMORBID CONDITIONS

Haematological diseases* - Anaemia and thalassaemia; coagulopathies; blood dyscrasias and other vascular disorders; hyperlipemia

Not compensated Diabetes Acquired or induced*

Immunodeficiency Acquired or induced by drugs*

***: factors recognised also by SIOMMMS**

ONJ RISK FACTORS

2009

Patients can be stratified into **TWO GROUPS** with different levels of risk for developing BRONJ

HIGH RISK
for developing BP-induced ONJ

Patients with malignant disease receiving intravenous BP therapy (Zoledronate or Pamidronate) and/or with a history of chemotherapy, radiotherapy or also **in osteoporotic patients receiving oral BP** with current exogenous steroid use

LOW RISK
for developing BP-induced ONJ

Patients taking oral BPs without a history of chemotherapy, radiation therapy or current exogenous steroid use (**mainly patients with non-steroid-induced osteoporosis**).

ABU-ID et al. "Bis-phossy jaws" - High and low risk factors for bisphosphonate-induced osteonecrosis of the jaw. Journal of Cranio-Maxillofacial Surgery (2008) 36, 95-103

LOCAL RISK FACTORS

ANY CONDITION OR PROCEDURE THAT INCREASES THE DEMAND FOR BONE TURNOVER/RENEWALL IN THE JAWS

Concurrent dentoalveolar procedures that manipulate bone or periosteum (e.g. extractions, dental implant placement, periodontal surgery involving osseous injury, periapical surgery)*

Inflammatory dental disease (e.g. periodontal abscesses, dental abscesses)

Periodontal disease

Intraoral trauma, including trauma from poorly fitting dentures

Palatal and lingual **tori**, bony exostoses, mylohyoid ridge

Poor oral hygiene

Alcohol and tobacco abuse

History of osteonecrosis/osteomyelitis of the jaws

History of head and neck radiotherapy

*BRONJ rarely occurs “spontaneusly”; the vast majority have been associated as a consequence to oral surgery procedures.

Bilezikian et al. Bisphosphonates and Osteonecrosis of the jaw. March 2009. Wiley-Blackwell. 172 pages.

SYSTEMIC DISEASES IN ELDERLY: RELATIONSHIP WITH HARD AND SOFT ORAL TISSUES

*"..Periodontal disease **is more prevalent in older groups** than in younger groups, though this may be the result of cumulative tissue destruction throughout a lifetime rather than an age-related risk of periodontal susceptibility. In addition, many of the comorbid conditions associated with periodontal disease occur more frequently and with greater severity in people of advanced age.." ***

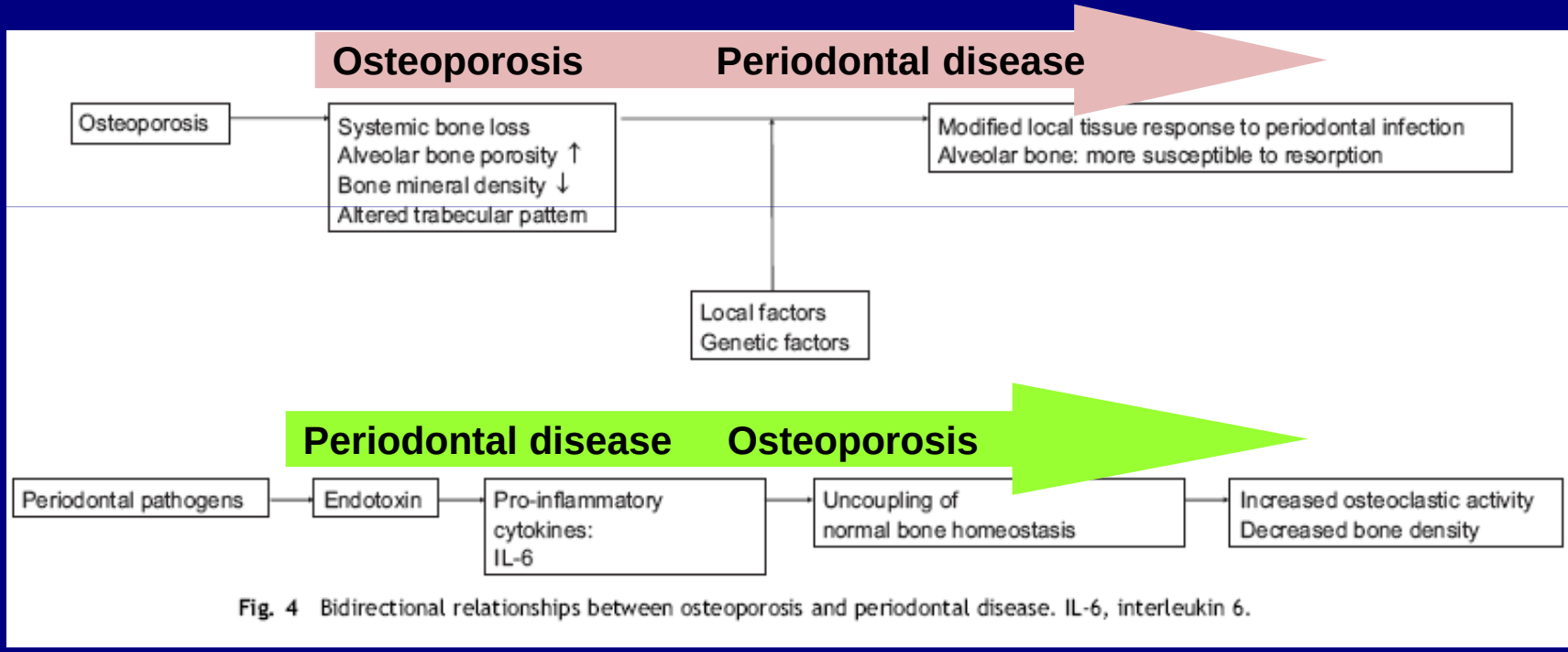
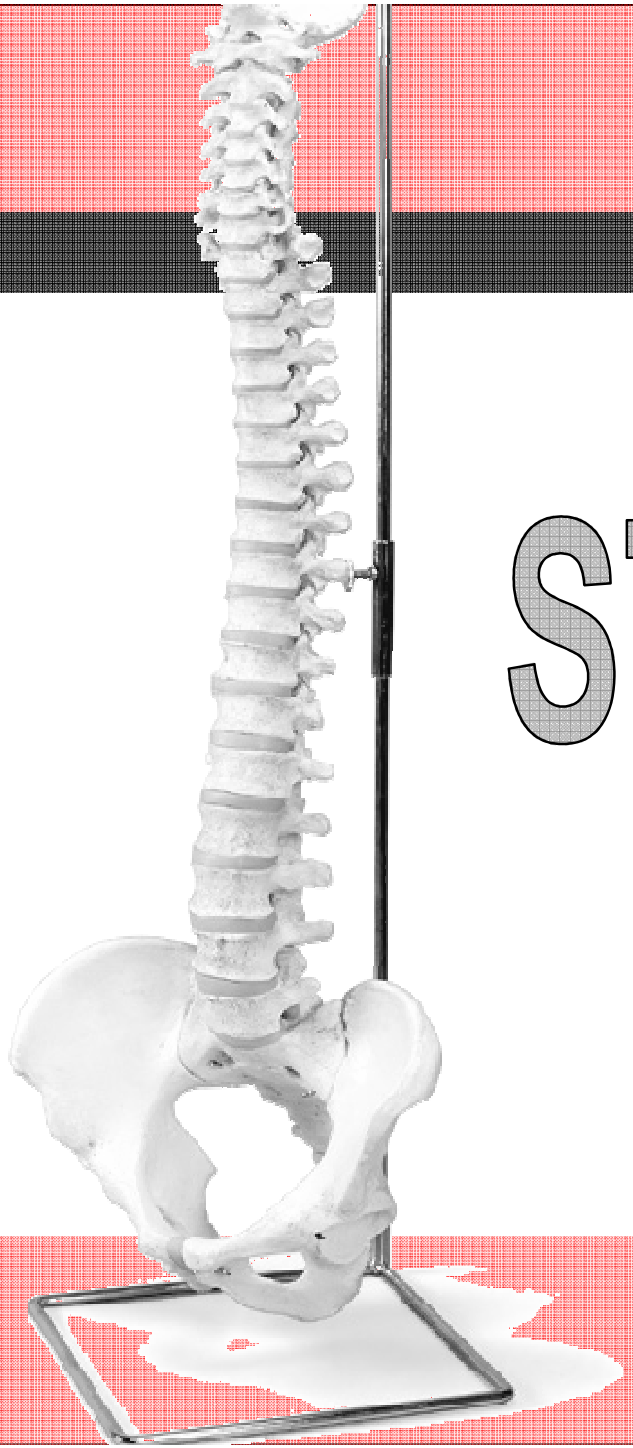


Fig. 4 Bidirectional relationships between osteoporosis and periodontal disease. IL-6, interleukin 6.

Kuo LC, et al Associations between periodontal diseases and systemic diseases: A review of theinter-relationships and interactions with diabetes,respiratory diseases,cardiovascular diseases andosteoporosis Public health 2008;122:417-433

*Douglass CW. Risk assessment and management of pe riodontal disease. J Am Dent Assoc 2006;137: 27S-32S.



STRATEGIES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Main Menu
Site Index
What is Osteoporosis?
Risk Factors and Prevention
Warning Signs and Diagnosis
Treatment and Research
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Osteoporosis
Frequently Asked Questions
1. What is osteoporosis? Click for Answer
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5. What other factors can increase one's chances of developing osteoporosis? Click for Answer
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español
http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a601247.html
MedlinePlus Drug Information: Risedronate
Other drug names: A B C D E F G H I J K L M N O P Q R S T U V W X Y Z 0-9
Alendronate
(a len' droe nate)
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E-mail to a friend
Contents of this page:
Why is this medication prescribed?
How should this medicine be used?
Other uses for this medicine
What special precautions should I follow?
What special dietary instructions should I follow?
What should I do if I forget a dose?
What side effects can this medication cause?
What storage conditions are needed for this medicine?
In case of emergency/overdose
What other information should I know?
Brand names
What special precautions should I follow?
Return to top
Before taking alendronate,
tell your doctor and pharmacist if you are allergic to alendronate, any other medications, or any of the ingredients in alendronate tablets or liquid. Ask your pharmacist for a list of the ingredients.
tell your doctor and pharmacist what prescription and nonprescription medications, vitamins, nutritional supplements, and herbal products you are taking or plan to take. Be sure to mention any of the following: aspirin and other nonsteroidal anti-inflammatory medications (NSAIDs) such as ibuprofen (Advil, Motrin) and naproxen (Naprosyn, Aleve); cancer chemotherapy; or oral steroids such as dexamethasone (Decadron, Dexone), methylprednisolone (Medrol), and prednisone (Deltasone). Your doctor may need to change the doses of your medications or monitor you carefully for side effects.
if you are taking any other medications including supplements, vitamins, or antacids by mouth, take them at least 30 minutes after you take alendronate.
tell your doctor if you are unable to sit upright or stand upright for at least 30 minutes and if you have or have ever had a low level of calcium in your blood or any problems with your esophagus. Your doctor may tell you that you should not take alendronate.
tell your doctor if are undergoing radiation therapy and if you have or have ever had anemia (condition in which the red blood cells do not bring enough oxygen to all the parts of the body);difficulty swallowing; heartburn; ulcers or other stomach problems;cancer; any type of infection, especially in your mouth;problems with your mouth, teeth, or gums; any condition that stops your blood from clotting normally; or dental or kidney disease.
tell your doctor if you are pregnant or are breast-feeding. Also tell your doctor if you plan to become pregnant at any time in the future, because alendronate may remain in your body for many years after you stop taking it. Call your doctor if you become pregnant during or after your treatment.
you should know that alendronate may cause serious problems with your jaw, especially if you have dental surgery or treatment while you are taking the medication. A dentist should examine your teeth and perform any needed treatments before you start to take alendronate. Be sure to brush your teeth and clean your mouth properly while you are taking alendronate. Talk to your doctor before having any dental treatments while you are taking this medication.
you should know that alendronate may cause serious damage to the lining of your mouth, esophagus, or stomach, especially if you do not take it according to the directions listed in the HOW section above. If you experience any of the following symptoms, stop taking alendronate, and call your doctor immediately: new or worsening heartburn, difficulty swallowing, pain on swallowing,

Omissis da un stampato di specialità medicinale BP e.v. per Osteoporosi

“effetti indesiderati in meno di 1 pz su 1000:

...Sono stati riportati **dolore persistente e/o piaghe** che **non guariscono alla bocca** o alla **mandibola** principalmente in pazienti in trattamento con BPS per **altre malattie**’’.

Quali piaghe? ….ONJ?
Quali malattie? ….

Agenzia Italiana del Farmaco
AIFA Servizi Mappa del sito
Via della Sierra Nevada, 60 - 00144 - ROMA - tel. 06 5978401
Gazzetta Ufficiale N. 267 del 16 Novembre 2006

AGENZIA ITALIANA DEL FARMACO

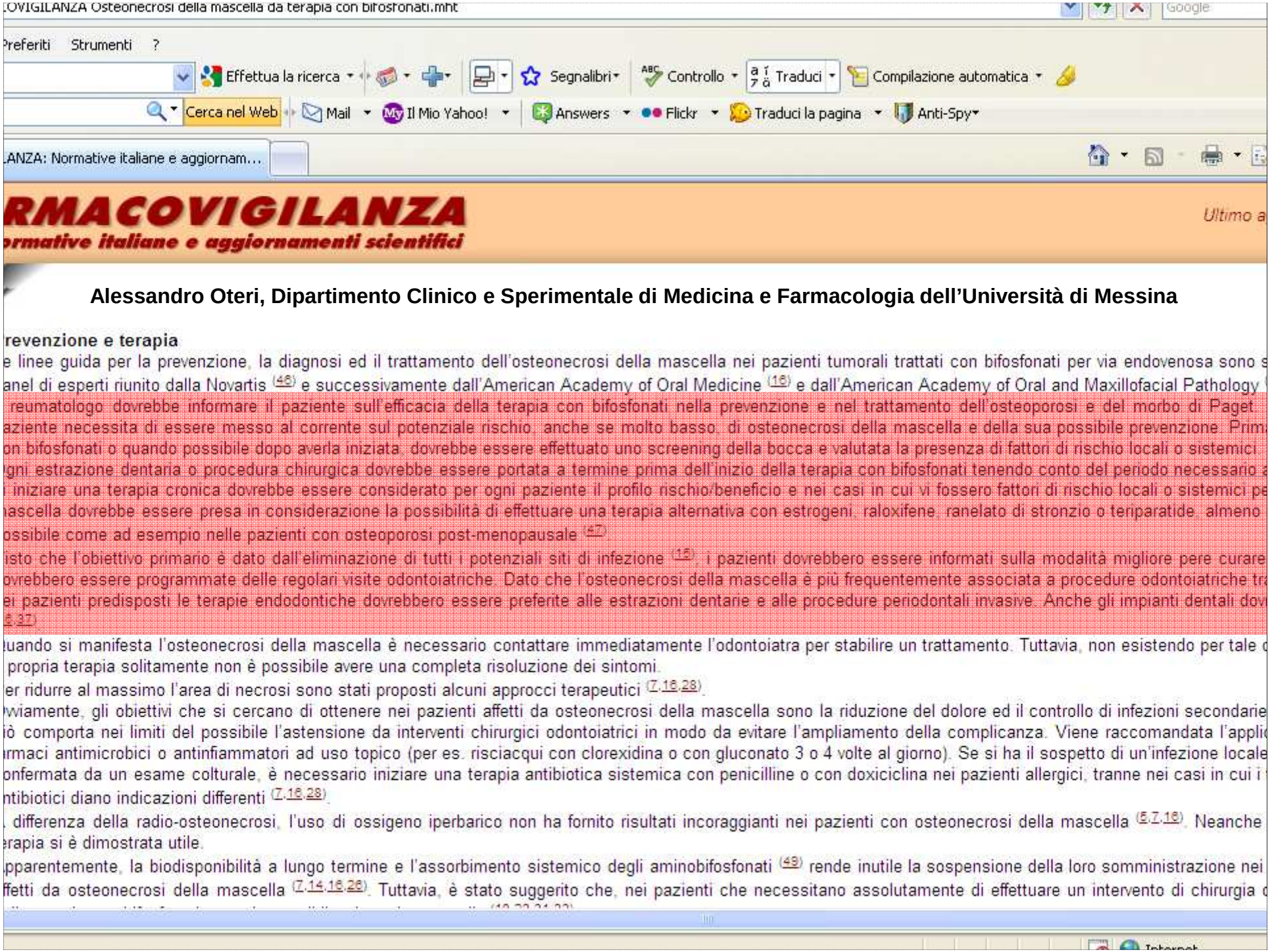
DETERMINAZIONE 9 novembre 2006
Modifica degli stampati di specialita' medicinali contenenti bifosfonati (escluso acido pamidronico e acido zoledronico).

IL DIRIGENTE
dell'Ufficio di farmacovigilanza

Tutte le industrie che producevano BF orali hanno avuto l'obbligo di introdurre **una nota riguardante il rischio di ONJ** sulla scheda tecnica che accompagna la confezione delle singole specialità.

"…prima di iniziare il trattamento con bifosfonati in pazienti con concomitanti fattori di rischio (cancro, radioterapia,chemioterapia, corticosteroidi, **scarsa igiene orale**) deve essere presa in considerazione la necessità di un esame odontoiatrico con le appropriate procedure dentistiche preventive. Durante il trattamento, questi pazienti devono, se possibile, evitare procedure dentistiche invasive.

….Per i pazienti che necessitano di chirurgia dentale, non ci sono dati disponibili per suggerire che l'interruzione del trattamento con BP riduca il rischio di ONJ.



OVIGILANZA Osteonecrosi della mascella da terapia con bifosfonati.mht

Preferiti Strumenti ?

Effettua la ricerca Segnalibri Controllo Traduci Compilazione automatica

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LANZA: Normative italiane e aggiornam...

RMACOVIGILANZA

ormative italiane e aggiornamenti scientifici

Ultimo a

Alessandro Oteri, Dipartimento Clinico e Sperimentale di Medicina e Farmacologia dell'Università di Messina

revenzione e terapia

e linee guida per la prevenzione, la diagnosi ed il trattamento dell'osteonecrosi della mascella nei pazienti tumorali trattati con bifosfonati per via endovenosa sono s
anel di esperti riunito dalla Novartis [46] e successivamente dall'American Academy of Oral Medicine [16] e dall'American Academy of Oral and Maxillofacial Pathology
reumatologo dovrebbe informare il paziente sull'efficacia della terapia con bifosfonati nella prevenzione e nel trattamento dell'osteoporosi e del morbo di Paget.
aziente necessita di essere messo al corrente sul potenziale rischio, anche se molto basso, di osteonecrosi della mascella e della sua possibile prevenzione. Prim
on bifosfonati o quando possibile dopo averla iniziata, dovrebbe essere effettuato uno screening della bocca e valutata la presenza di fattori di rischio locali o sistemici.
gni estrazione dentaria o procedura chirurgica dovrebbe essere portata a termine prima dell'inizio della terapia con bifosfonati tenendo conto del periodo necessario a
iniziare una terapia cronica dovrebbe essere considerato per ogni paziente il profilo rischio/beneficio e nei casi in cui vi fossero fattori di rischio locali o sistemici pe
ascella dovrebbe essere presa in considerazione la possibilità di effettuare una terapia alternativa con estrogeni, raloxifene, ranelato di stronzio o teriparatide, almeno
ossibile come ad esempio nelle pazienti con osteoporosi post-menopausale [47].
isto che l'obiettivo primario è dato dall'eliminazione di tutti i potenziali siti di infezione [16], i pazienti dovrebbero essere informati sulla modalità migliore pere curare
ovrebbero essere programmate delle regolari visite odontoiatriche. Dato che l'osteonecrosi della mascella è più frequentemente associata a procedure odontoiatriche tr
ei pazienti predisposti le terapie endodontiche dovrebbero essere preferite alle estrazioni dentarie e alle procedure periodontali invasive. Anche gli impianti dentali dov
6, 37].
uando si manifesta l'osteonecrosi della mascella è necessario contattare immediatamente l'odontoiatra per stabilire un trattamento. Tuttavia, non esistendo per tale
propria terapia solitamente non è possibile avere una completa risoluzione dei sintomi.
er ridurre al massimo l'area di necrosi sono stati proposti alcuni approcci terapeutici [7,16,28].
vviamente, gli obiettivi che si cercano di ottenere nei pazienti affetti da osteonecrosi della mascella sono la riduzione del dolore ed il controllo di infezioni secondarie
iò comporta nei limiti del possibile l'astensione da interventi chirurgici odontoiatrici in modo da evitare l'ampliamento della complicanza. Viene raccomandata l'appli
rmaci antimicrobici o antinfiammatori ad uso topico (per es. risciacqui con clorexidina o con gluconato 3 o 4 volte al giorno). Se si ha il sospetto di un'infezione locale
onfermata da un esame colturale, è necessario iniziare una terapia antibiotica sistemica con penicilline o con doxiciclina nei pazienti allergici, tranne nei casi in cui i
ntibiotici diano indicazioni differenti [7,16,28].
differenza della radio-osteonecrosi, l'uso di ossigeno iperbarico non ha fornito risultati incoraggianti nei pazienti con osteonecrosi della mascella [5,7,16]. Neanche
erapia si è dimostrata utile.
pparentemente, la biodisponibilità a lungo termine e l'assorbimento sistemico degli aminobifosfonati [49] rende inutile la sospensione della loro somministrazione nei
ffetti da osteonecrosi della mascella [7,14,16,26]. Tuttavia, è stato suggerito che, nei pazienti che necessitano assolutamente di effettuare un intervento di chirurgia

Ostéoporose, bisphosphonates et ostéochimionécrose maxillo-mandibulaire

Osteoporosis, bisphosphonates and jaws osteochemonecrosis

M. Magremanne
Service de Stomatologie et de Chirurgie Maxillo-Faciale, Hôpital Erasme

RESUME

Les bisphosphonates sont régulièrement utilisés dans le traitement de pathologies osseuses bénignes comme l'ostéoporose, la maladie de Paget et dans des pathologies malignes telles que l'hypercalcémie maligne, les métastases osseuses des tumeurs du sein, de la prostate et dans le myélome multiple. Des ostéonécroses maxillo-mandibulaires sont décrites depuis 2003 et sont plus souvent associées à la forme intraveineuse qu'à la forme orale. Après 3 ans de traitement de l'ostéoporose par bisphosphonates oraux, on note de plus en plus de cas d'ostéo-nécrose dont le facteur declenchant est souvent une extraction dentaire ou un geste chirurgical endobuccal.
Le traitement de ces nécroses osseuses est peu satisfaisant. On ne peut qu'insister sur une attitude préventive et une mise en ordre dentaire performante avant d'instaurer ce type de traitement.

ABSTRACT

Bisphosphonates are widely used in the treatment of nonmalignant bone disease like osteoporosis, Paget's disease and malignant disease like malignant hypercalcemia, osteolytic metastasis from breast and prostate cancer and multiple myeloma. Jaws osteonecrosis is described since 2003 and is more often associated with the intraveinous use than oral use. Higher risk of osteonecrosis is noted after 3 years of osteoporosis treatment. The precipitating event is often a tooth extraction or other invasive procedure. There is no effective treatment for this pathology. Careful oral examination is necessary before prescribing bisphosphonates and dental treatment must be achieved before the initiation of treatment.

Rev Med Brux 2008 ; 29 : 262-6

Key words : osteonecrosis, bisphosphonates, osteoporosis

S38-January JOGC JANVIER 2009

Pivotal Fracture Trial (PFT) evaluated the effects of zoledronic acid, given as a single 5-mg intravenous infusion annually, on fracture incidence in men and women 50 years of age or older who had already sustained a low-trauma hip fracture.[42] Compared with placebo, zoledronic acid reduced the 3-year risk of vertebral fracture by 70% (RR, 0.30 [95% CI, 0.24 to 0.38]) and the 3-year risk of hip fracture by 41% (HR, 0.59 [95% CI, 0.42 to 0.83]). Increases in BMD were significantly greater and height loss reduced in the group receiving zoledronic acid.

Bisphosphonate advantages and disadvantages

A major advantage of oral bisphosphonate therapy is ease of administration and excellent tolerability. The most common side effects are abdominal pain and dysphagia. However, in the RCTs conducted to date, the incidence rates of upper gastrointestinal side effects of both alendronate and risedronate have been comparable to those of placebo.[43]

Intravenous administration of bisphosphonates has a number of advantages, including less frequent dosing and less

receiving high-dose intravenous bisphosphonate therapy. Prospective data in oncology and nononcology populations are needed to better understand the underlying pathophysiology of ONJ so that appropriate decisions can be made regarding prevention, diagnosis, and management,[47] as well as to determine the true incidence. At present, evidence indicates that if there is a link between bisphosphonates and ONJ, it is very weak, and the risk of bisphosphonate-associated ONJ may be less than 1 in 100 000.[47] It is important for all Canadians to visit their dentist, as recommended by the Canadian Dental Association, every 6 months to ensure that dental hygiene is maintained, as this is a cornerstone in the prevention and treatment of ONJ.

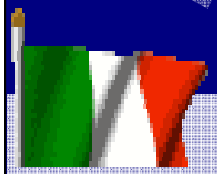
CALCITONIN

Calcitonin, a hormone produced in the thyroid gland, inhibits osteoclastic bone resorption. Its poor oral absorption necessitates either subcutaneous or intranasal administration. Administration of 200 IU by nasal spray is approved

OSTEONECROSI DEI MASCELLARI (ONJ): PREVENZIONE, DIAGNOSI, TRATTAMENTO
UPDATE 2009

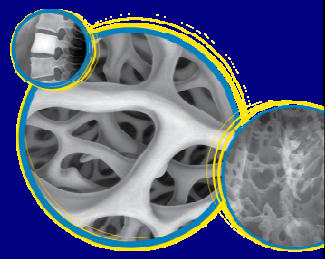
Alessandria, 23 giugno 2009

TAVOLA ROTONDA



ONJ

E' POSSIBILE UNA CONSENSUS ITALIANA?



Moderatori:

G. Campisi (Univ. Palermo), L. Sottosanti (AIFA)

Partecipanti:

O. Alabiso (AIOM), V. Brucoli (CAO), P. Ronchi (SICMF), A. Levis (SIE),

I. Viano (SIF), F. Bertoldo (SIOMMMS), P. Vescovi (SIPMO)

Paziente NON oncologico (BP *per os* oppure E.V.)

Epidemiologia ONJ
Visita odontoiatrica? Si-No? Se sì, quando

Raccomandazioni odontoiatriche pre-terapia
Raccomandazioni odontoiatriche durante la terapia

Implantologia

Cut-off di 3 anni di BP assunzione per rischio ONJ?

Sospensione BP per eseguire manovre odontoiatriche invasive?
Sospensione BP in caso di ONJ? E per quanto tempo?

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Prof.ssa Giuseppina Campisi

Dr.ssa Olga Di Fede
Dr.ssa Vera Panzarella
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Grazie per l'attenzione