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

23 Giugno 2009

Associazione Cultura e Sviluppo
Piazza F. De Andre' 76 - Alessandria

Università Degli Studi Di Torino

Azienda Ospedaliera
San Giovanni Battista di Torino
Direttore di Dipartimento Prof Carossa
S. S.S.C.V.D. Chirurgia Stomatologica
Responsabile Dr. Marco Mozzati

Sospendere o non sospendere i BF: questo è il dilemma..

Matteo Scoletta

Sospensione dai BF

SI

NO

- Migliore guarigione tessuti molli
  (Landesberg R et al. JOMS 2008)
- Migliore guarigione ossea
- Riduzione dolore e progressione
- Drug holiday: non è un rischio (?)

- Rischio ripresa o avanzamento patologia primaria:

CONDIZIONI SISTEMICHE

SI

AAOMS position paper

Journal of Oral and Maxillofacial Surgery
Volume 65, Issue 3, March 2007, Pages 369-376

American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws—2009 Update

J Oral Maxillofac Surg
67:2-12, 2009, Suppl 1

*Salvatore L. Ruggiero, DMD, MD,**

ticosteroid use. *If systemic conditions permit*, the clinician might consider discontinuation of oral bisphosphonates for a 3-month period before and 3-month period after elective invasive dental surgery to lower the risk of

→ 3 mesi prima
3 mesi dopo

‡Discontinuation of IV bisphosphonates has shown no short-term benefit. However, *if systemic conditions permit*, long-term discontinuation might be beneficial in stabilizing established sites of BRONJ, reducing risk of new site development, and reducing clinical symptoms. Risks and benefits of continuing bisphosphonate therapy should be made only by treating oncologist in consultation with oral and maxillofacial surgeon and patient.

§Discontinuation of oral bisphosphonate therapy in patients with BRONJ has been associated with gradual improvement in clinical disease. Discontinuation of oral bisphosphonates for 6-12 months may result in either spontaneous sequestration or resolution after debridement surgery. *If systemic conditions permit*, modification or cessation of oral bisphosphonate therapy should be done in consultation with treating physician and patient.

→ Condizioni sistemiche
In accordo col curante

oral

bisphosphonate for fewer than 3 years and have also taken corticosteroids concomitantly,

→ 3 mesi prima

bisphosphonate for more than 3 years with or without any concomitant prednisone or other steroid

→ Fino alla guarigione ossea

IV Bisphosphonates

if systemic conditions permit,

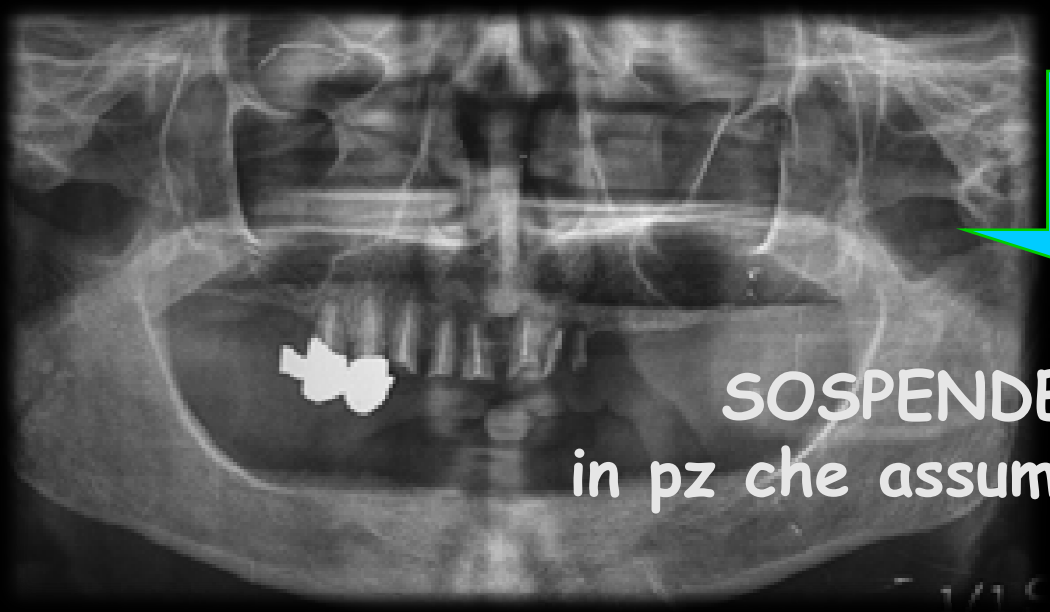
→ Potrebbe aiutare a risolvere il dolore e la progressione

SI

Bisphosphonate-Related Osteonecrosis of the Jaw: Diagnosis, Prevention, and Management

Annu. Rev. Med.
2009. 60:85–96

Salvatore L. Ruggiero and Bhoomi Mehrotra



SOSPENDERE 3 MESI PRIMA
in pz che assumono BF da almeno 3 anni

In accordo con le direttive AAOMS

SI

Annals of Oncology Advance Access published May 22, 2009

E. Terpos[1,2*], O. Sezer[3], P. I. Croucher[4], R. García-Sanz[5], M. Boccadoro[6], J. San Miguel[5], J. Ashcroft[7], J. Bladé[8,9], M. Cavo[10], M. Delforge[11], M.-A. Dimopoulos[1], T. Facon[12], M. Macro[13], A. Waage[14] & P. Sonneveld[15]

The use of bisphosphonates in multiple myeloma: recommendations of an expert panel on behalf of the European Myeloma Network

review

Authors and year	Type of BP	Dosage	No. of MM patients	Reduction of pain	Reduction of SREs[a]	Survival benefit
Placebo controlled						
Belch et al. (1991) [55]	Etidronate	5 mg/kg/day, p.o.	173	No	No	No
Daragon et al. (1993) [56]	Etidronate	10 mg/kg/day, p.o., for 4 months	94	No	No	No
Lahtinen et al. (1992) [57] and Laakso et al. (1994) [58]	CLO	2.4 g/day, p.o., for 2 years	350	Yes	Yes	NE
McCloskey et al. (1998) [17] and (2001) [59]	CLO	1.6 g/day, p.o.	530	Yes	Yes	+/−[b]
Brincker et al. (1998) [60]	PAM	300 mg/day, p.o.	300	Yes	No	No
Berenson et al. (1996) [61] and (1998) [62]	PAM	90 mg, i.v., every 4 weeks for 21 cycles	392	Yes	Yes	+/−[c]
Menssen et al. (2002) [63]	Ibandronate	2 mg, i.v., monthly	198	No	No	No
PAM controlled						
Berenson et al. (2001) [64][d]	ZOL	2 or 4 mg, i.v., monthly	108	Yes	Yes	NE
Rosen et al. (2001) [65] and (2003) [66][d]	ZOL	4 or 8 mg, i.v., monthly	513	Yes	Yes	[e]

should be considered. There is a paucity of data to propose a recommendation, so any decision to suspend BP treatment should be considered on a case-by-case basis. Recent data

Temporary suspension of BP treatment should be considered if invasive dental procedures are necessary (grade D). Initial therapy of ONJ should include discontinuation of BP until healing occurs (grade C). The decision to restart BP should be individualized, until prospective long-term studies are available

SOSPENDERE FINO A GUARIGIONE AVVENUTA

SI

Ten Years' Experience with Alendronate for Osteoporosis in Postmenopausal Women

Henry G. Bone, M.D., David Hosking, M.D., Jean-Pierre Devogelaer, M.D., Joseph R. Tucci, M.D., Ronald D. Emkey, M.D., Richard P. Tonino, M.D., Jose Adolfo Rodriguez-Portales, M.D., Robert W. Downs, M.D., Jayanti Gupta, Ph.D., Arthur C. Santora, M.D., Ph.D., and Uri A. Liberman, M.D., Ph.D

The New England Journal *of* Medicine

350:1189-1199 2008

- Alendronato x os
- ctr: 10 anni
- 247 donne
- 2 gruppi : assunzione continua/discontinua del farmaco

Misurazione effettuate tramite:

- Ntx urine
- Fosfatasi alcalina
- Rx x calcificazione ossea:
  - spina lombare
  - femore

LA SOSPENSIONE DAL BF (Alendronato)
Porta ad una graduale riduzione dei suoi effetti

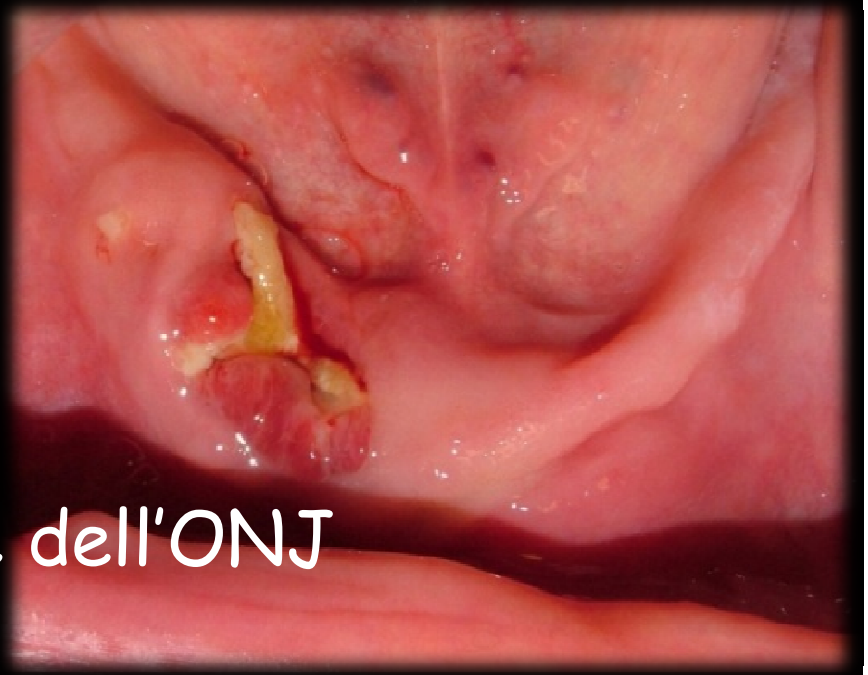
SI

Osteonecrosis of the Jaw in Patients Receiving Intravenous or Oral Bisphosphonates

Amber E.King, Pharm D., and Elena M, Umland, Pharm D.

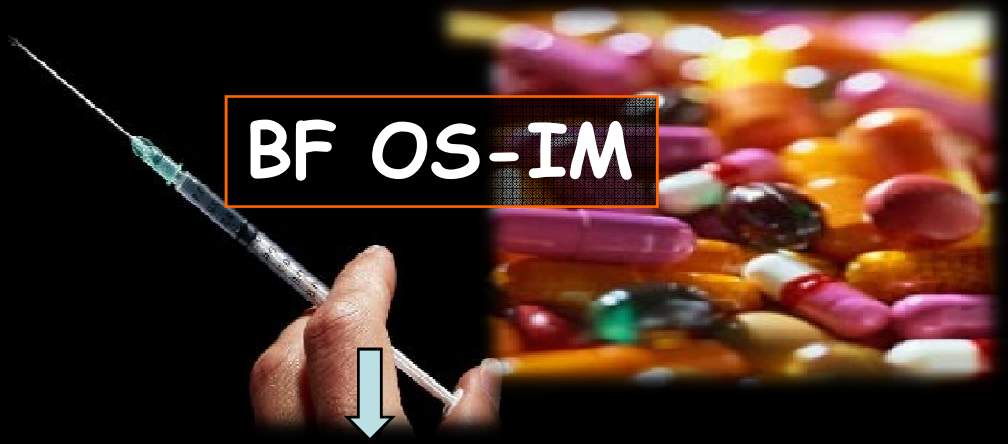
Pharmacotherapy 2008;28(5):667-677

SOSPENDERE il BF potrebbe: (AAOMS)



- Prevenire la progressione dell'ONJ
- Diminuire i sintomi

Considerazioni ipotetiche, basate su osservazioni cliniche, non fondate su studi scientifici

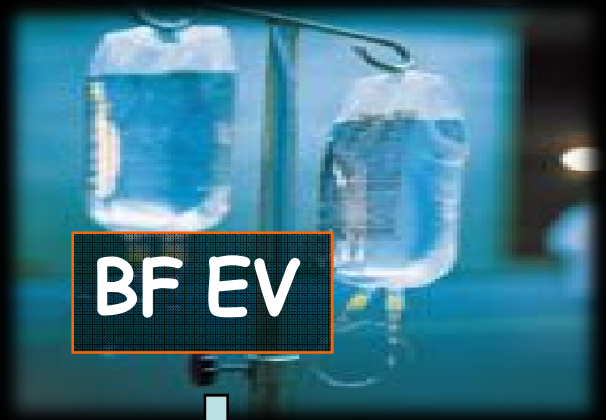


BF OS-IM

La sospensione del BF comporta POCHI RISCHI per la progressione dell'OSTEOPOROSI

STOP:

3 MESI PRIMA
3 MESI DOPO



BF EV

I BENEFICI dati dal BF valgono più del RISCHIO di progressione dell'ONJ

CONTATTARE L'ONCOLOGO

Amber E.King, Pharm D., and Elena M, Umland, Pharm D.

Pharmacotherapy 2008;28(5):667-677

SI

Ostéonécrose des maxillaires et bisphosphonates en cancérologie

René-Jean BENSADOUN, Jean-Louis BLANC, Cyril CONFAVREUX, René GOURMET, Jean-Michel MAES, Guillaume PENEL, Marie-Hélène VIEILLARD, Anne WOELLER

Bull Cancer 2008 ; 95 (4) : 413-8

La SOSPENSIONE del BF è indicata FINO ALLA COMPLETA CICATRIZZAZIONE

nel caso in cui NON SIA POSSIBILE sospendere

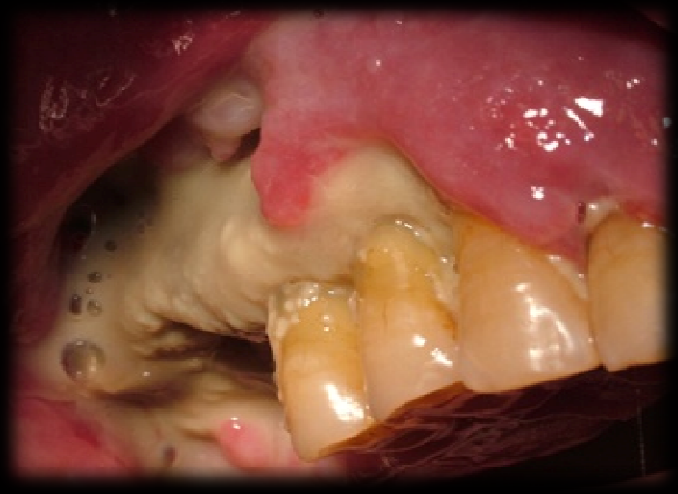
- Eseguire le cure odontoiatriche necessarie prima dell'inizio del trattamento
- Mantenere una buona igiene
- Controllare periodicamente il paziente

NECESSITA' DI UN TRATTAMENTO INVASIVO

Ritardare la successiva somministrazione del BF (non nei pz ad alto rischio)

Effettuare le estrazioni dentarie con terapia antibiotica prima e dopo la chirurgia per almeno 10 gg

Riprendere il BF dopo la cicatrizzazione completa



COMPARSA DELL'ONJ

Prendere in considerazione la componente infettiva (ATB mirati?)

Valutare la scelta chirurgica più conservativa possibile

- Stop al BF (non nei pz ad alto rischio)
- Risomministrare il BF in funzione dell'evoluzione della malattia sistemica

SI

Bisphosphonate-Induced Osteonecrosis of the Jaw

Courtney D.Krueger, Patricia M.West, Matthew Sargent, Amy E.Lodolce, and A Simon Pickard

SOSPENDERE IL BF NEI PZ EV

(Da 1 mese prima a guarigione completata)

(Nessuna presa di posizione per OS e IM)

***The Annals of Pharmacotherapy*, 2007 February (41) 276-284**

SI

Clinical Investigation of C-Terminal Cross-Linking Telopeptide Test in Prevention and Management of Bisphosphonate-Associated Osteonecrosis of the Jaws

J Oral Maxillofac Surg 67:1167-1173, 2009

Ranjit Kunchur, BDS, MDS, Allan Need, MD, FRACP,†*

Table 3. PATIENTS WITH ONJ

Route	Age (yr)	Gender	Comorbidity Group	Bone Disease	Bisphosphonate Type	Bisphosphonate Duration (mo)	CTX	Event	Onset ONJ to CTX (mo)	Drug Stopped (mo)
Oral (n = 9)	80	Female	II	Osteoporosis	Alendronate	60	<70	Extraction	3	Ongoing
	72	Female	II	Osteoporosis	Risedronate	42	137	Extraction	2	Ongoing
	81	Female	II	Osteoporosis	Alendronate	60	148	Extraction	23	Ongoing
	88	Female	II	Paget's	Alendronate	120	261	Extraction	6	Ceased 6
	65	Female	I	Osteoporosis	Alendronate	60	341	Extraction	23	Ceased 5
	77	Female	I	Osteoporosis	Alendronate	60	539	Extraction	48	Ceased 6
	77	Female	I	Osteoporosis	Alendronate	60	576	Extraction	24	Ceased 6
	71	Female	I	Osteoporosis	Risedronate	24	450	Extraction	6	Ceased 12
	61	Female	II	Osteoporosis	Risedronate	24	1391	Extraction	24	Ceased 24
Intravenous (n = 6)	50	Male	II	Prostate metastases	Zoledronic acid	6	<70	Extraction	12	Ongoing
	61	Male	II	Myeloma	Zoledronic acid	8	<70	Spontaneous	1	Ongoing
	62	Male	III	Myeloma	Zoledronic acid	7	112	Spontaneous	2	Ongoing
	76	Male	I	Prostate metastases	Zoledronic acid	120	208	Spontaneous	1	Ongoing
	81	Female	II	Paget's	Pamidronate	12	418	Extraction	48	Ceased 6
	80	Male	I	Prostate metastases	Pamidronate	22	1107	Extraction	40	Ceased 24

"RISK ZONE"

CTX < 150-200 pg/mL

Se il Bf viene sospeso, il valore del CTX incrementa circa 25 pg/mL al mese

If medically appropriate, the bisphosphonate can be ceased so that the CTX value increases to bring the patient out of the "risk zone."

SI

NO

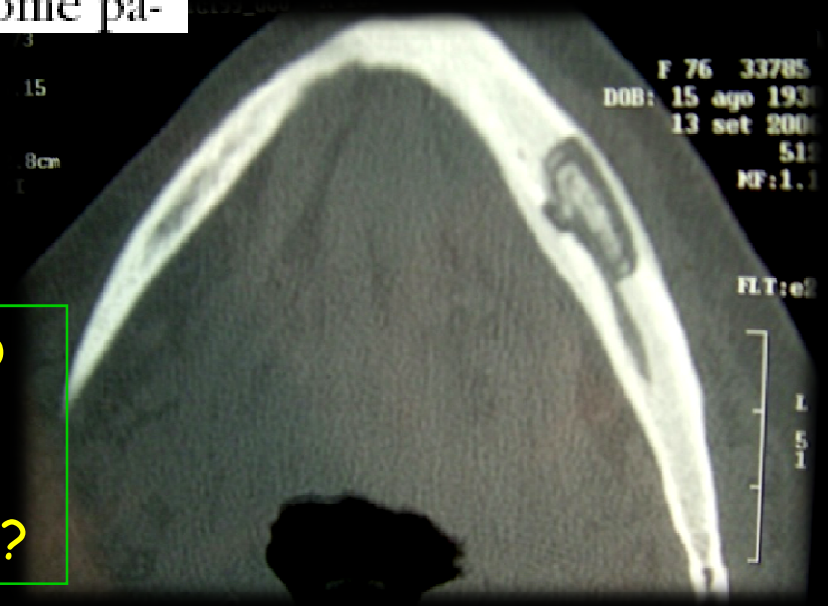
J Oral Maxillofac Surg
67:53-60, 2009, Suppl 1

Bisphosphonates—What the Dentist Needs to Know: Practical Considerations

*John E. Fantasia, DDS**

BRONJ is a difficult condition to treat. Some patients have resolution with discontinuation of their nBP medications, with sequestration of necrotic bone and healing of the involved site. However, some pa-

Diversi Autori concordano con questa evidenza clinica



- ✓ Perché tende a crearsi un sequestro spontaneo?
- ✓ Riattivazione del metabolismo osseo?

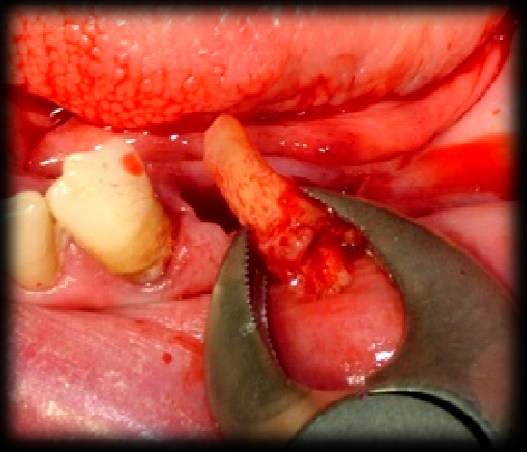
SI

NO

Recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw (ONJ) in cancer patients treated with bisphosphonates

José Bagán, Juan Blade, Jose Manuel Cozar, Manuel Constela, Ramón García Sanz, Francisco Gómez Veiga, Juan José Lahuerta, Ana Lluch, Bartomeu Massuti, Juan Morote, Jesús F. San Miguel, Eduardo Solsona

Med Oral Patol Oral Cir Bucal 2007;12:E336-40.



ESTRAZIONI (ONJ-)

NON C'E' EVIDENZA CHE LA SOSPENSIONE DIA BENEFICI

CHIRURGIA RESETTIVA PER GROSSE ONJ

IL BF DOVREBBE ESSERE SOSPESO (VALUTARE RISCHI/BENEFICI)

NO

Bisphosphonate-associated osteonecrosis of the jaw: does it occur in children?

J. J. Brown, L. Ramalingam and M. R. Zacharin

Clinical Endocrinology (2008) **68**,863–867

- 11/42 bambini in terapia con BF
- BF prev x osteogenesi imperfetta
- hanno subito estrazioni senza alcun protocollo particolare

NO ONJ

Turn over osseo aumentato
Maggiore vascolarizzazione
Miglior risposta ai traumi (dentizione permanente)

NON SOSPENDERE

NO

Summary of ASBMR Task Force on ONJ

D.B. Burr

J Musculoskelet Neuronal Interact 2007; 7(4):354-355

or delayed. There are no data to suggest that stopping BP therapy will allow the ONJ to resolve, nor is there evidence that halting BP therapy prior to dental procedures is effective, because of the long half-life of BPs in the skeleton. The best management

Emi-vita
molto lunga

NON SOSPENDERE

NO

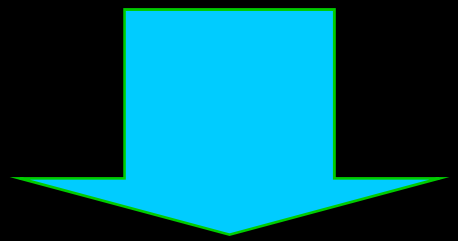
E.Nastro, C.Musolino, A.Allegra, G.Oteri, M.Cicciù,
A.Alonci, E.Quartarone, C.Alati, F.S.DePonte

Acta Haematol 2007;117:181-187

Bisphosphonate-Associated Osteonecrosis of the Jaw in Patients with Multiple Myeloma and Breast Cancer

Studio piccolo :

- 12 pz
- tutti ONJ+
- tutti pz oncologici (ZOL-PAM)



NON SOSPENDERE

[..] Anche se: in assenza di rischi di ipocalcemia severa sarebbe plausibile considerare lo stop [..]

Azienda Ospedaliera
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Direttore Prof Carossa S.

S.S.C.V.D. Chirurgia Stomatologica
Responsabile Dr. Marco Mozzati

ESTRAZIONI IN PZ BF

[Aggiornato a Aprile 2009]

359

os im

Totale pazienti	Totale estrazioni	CTR 1 MESE	CTR 3 MESI	CTR 6 MESI	CTR 12 MESI	CTR 18 MESI	COMPLICANZE
79	249	82	45	89	33	0	0

ev

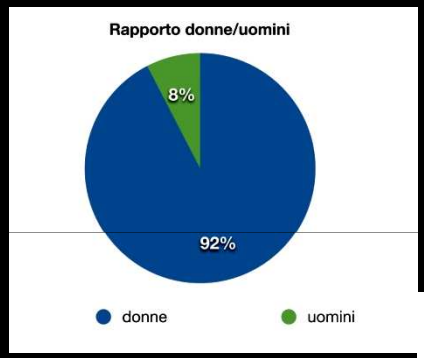
Totale pazienti	Totale estrazioni	CTR 1 MESE	CTR 3 MESI	CTR 6 MESI	CTR 12 MESI	CTR 18 MESI	COMPLICANZE
35	110	26	48	33	3	0	1

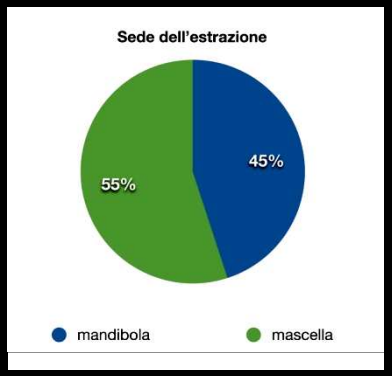
TOT

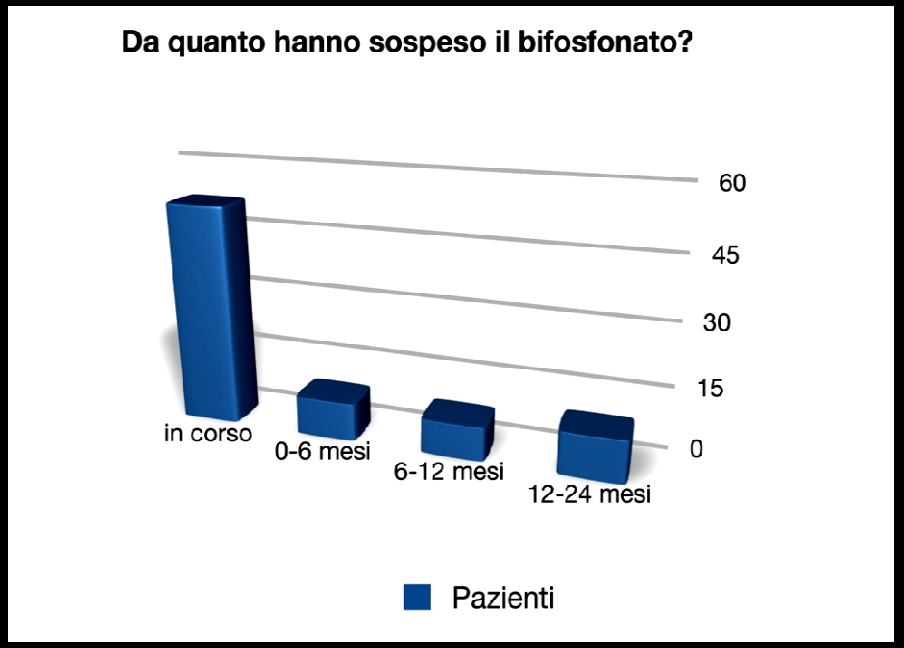
Totale pazienti	Totale estrazioni	CTR 1 MESE	CTR 3 MESI	CTR 6 MESI	CTR 12 MESI	CTR 18 MESI	COMPLICANZE
114	359	108	93	122	36	0	1

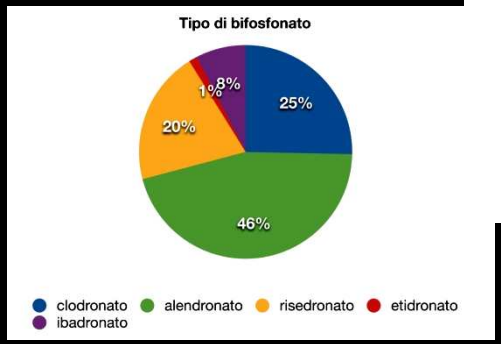
ESTRAZIONI: BF OS - IM

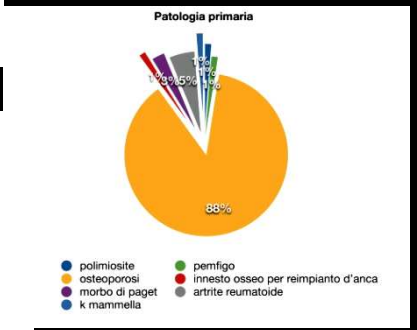
[Aggiornato a Aprile 2009]







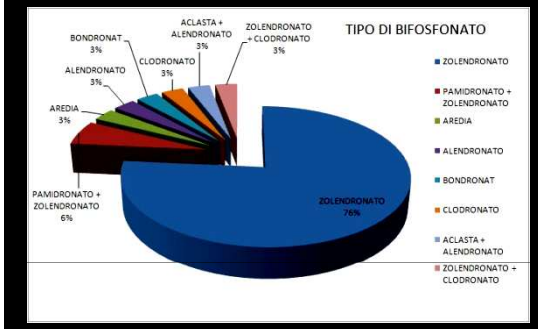


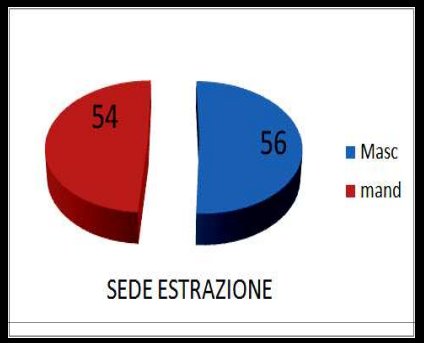


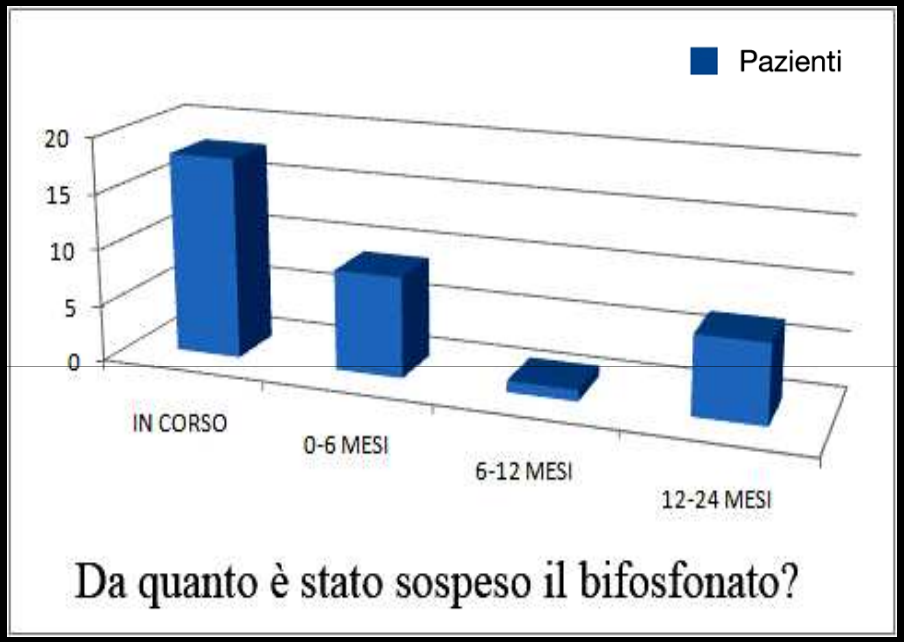
Totale pazienti	Totale estrazioni	CTR 1 MESE	CTR 3 MESI	CTR 6 MESI	CTR 12 MESI	CTR 18 MESI	COMPLICANZE
79	249	82	45	89	33	0	0

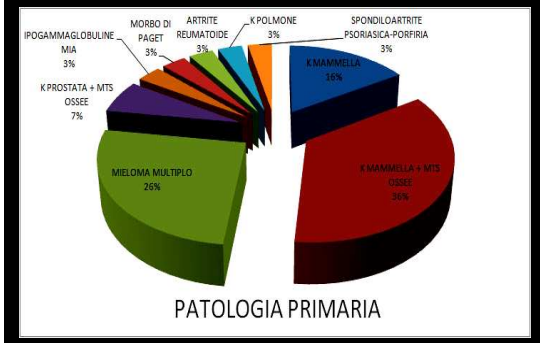
ESTRAZIONI: BF EV

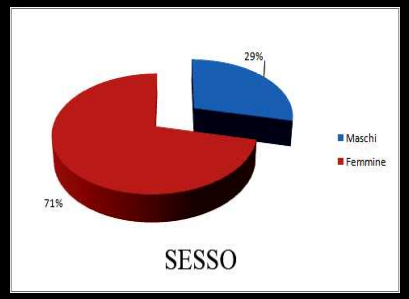
[Aggiornato a Aprile 2009]







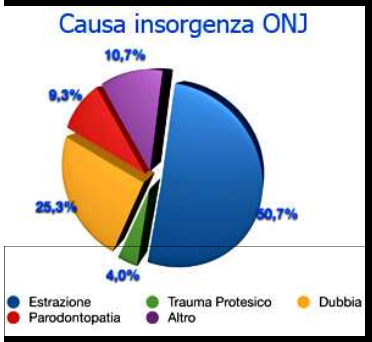


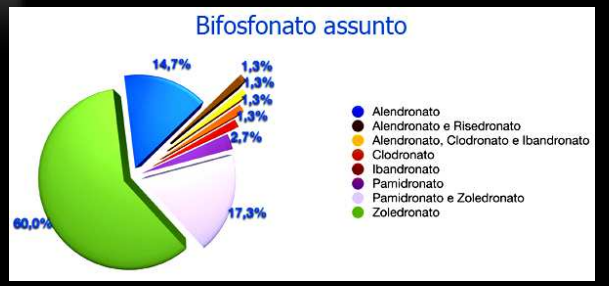


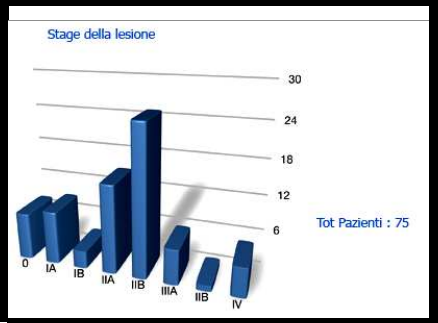
Totale pazienti	Totale estrazioni	CTR 1 MESE	CTR 3 MESI	CTR 6 MESI	CTR 12 MESI	CTR 18 MESI	COMPLICANZE
35	110	26	48	33	3	0	1

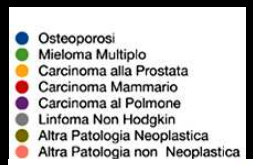
ONJ +

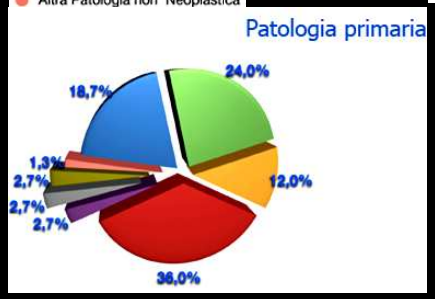
[Aggiornato a Aprile 2009]

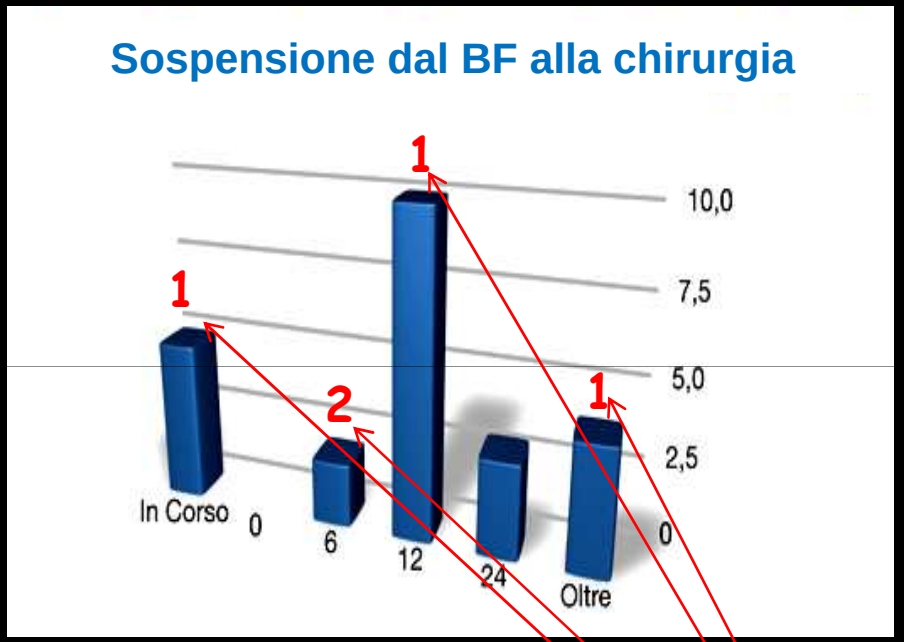












Totale Pz ONJ+	Totale ONJ Operate	Recidive 1 Mese	Recidive 3 Mesi	Recidive 6 Mesi	Recidive 12 Mesi	Recidive 18 Mesi	Totale Recidive
75	24	1	2	0	2	0	5

Accepted in March 2009

ORAL DISEASES

Dental management of patients at risk of osteochemonecrosis of the jaws: a critical review

Dr. Stefano Fedele DDS, PhD

UCL Eastman Dental Institute

appropriate risk groups. Marx and coworkers suggested that patients with a history of fewer than 3 years of exposure to oral BP are at extremely low risk of BOJ and can safely receive surgical procedures (Marx et al, 2007). They also suggested that in individuals with a history of greater than 3 years of oral BP use (or less than 3 years with concomitant corticosteroid or chemotherapy use) the evaluation of degree of bone turnover inhibition (*via* serum C-terminal telopeptide [CTX] levels) could help in identifying subgroups of patients at different degrees of risk (Marx et al, 2007). They recommended deferring the surgery in patients with CTX level lower than 150 pg/mL (this indicates that bone turnover is highly impaired and the risk of ostenecrosis is greater) and planning, together with the prescribing physician, discontinuation of oral BP for 6-9 months (described as a "drug holiday") to allow the CTX value to rise and surgery to be safely performed (Marx et al, 2007). Other researchers have suggested that the discontinuation of oral BP for 1-3 months could help in any case (regardless of the length of exposure and evaluation of bone turnover markers) as the anti-angiogenic effect of BP would be reduced and, consequently, wound healing after surgery would

- BF os < 3 anni: bassissimo rischio.
- BF os > 3 anni o < 3 anni + corticost.: valutare CTX (C-terminal telopeptide).
- CTX < 150 pg/mL: stop BF x 6-9- mesi.
- In ogni caso, se possibile: stop BF x 1-3 mesi potrebbe diminuire l'effetto anti-angiogenetico dei BF (x la mucosa)

2008). In cases where planned surgery involves multiple quadrants, they recommend commencing with one quadrant, waiting for 2 months, and if no complication occurs, considering it is safe to treat the remaining quadrants at one time (American Dental Association Council on Scientific Affairs, 2006; Edwards et

- Se necessaria chirurgia nei 4 quadr: prima 1 quadr – ctr x 2 mesi – poi altri quadr (eventualmente anche in contemporanea).

McLeod et al, 2007). The evaluation of degree of bone turnover inhibition, as indicated by serum C-terminal telopeptide [CTX] levels, was found to be not relevant in estimating the risk of BOJ in patients on intravenous BP by two separate studies (Bagan et al, 2008; Marx et al, 2007). Other researchers have recommended the discontinuation of oral BP for 1-3 months in order to allow osteoclast recovery (Van den Wyngaert et al, 2007) and reduce the anti-angiogenic effect of BP (Campisi et al, 2007). They suggested that this would

- BF ev: il CTX non sembra essere un buon parametro di valutazione del rischio di comparsa di ONJ.
- BF ev: in ogni caso interrompere 1-3- mesi in accordo con il Curante per ridurre gli effetti anti-angiogenetici.

CONCLUSIONI ?

significant. For both oral and intravenous BP, none of the suggested risk-reduction strategies have been demonstrated effective and therefore only sensible and practical precautions to reduce bone trauma and to minimize the risk of infection can be recommended. Most importantly, there is need to ensure that patients taking BP are well informed of the oral risks and triggers for BOJ, so they can make informed decisions about undergoing any dental procedures. The

Grazie

matteo.scoletta@libero.it