
# "Nuovi" dati epidemiologici

5 giugno 2010

Claudia Galassi

CPO
CENTRO DI RIFERIMENTO PER L'EPIDEMIOLOGIA E LA PREVENZIONE ONCOLOGICA IN PIEMONTE

# Pubmed

**Bisphosphonate$ = 17298**

**ONJ = 195**

**Osteonecrosis AND jaw = 1059**

4 giugno 2010

J Clin Oncol. 2009 Nov 10;27(32):5356-62. Epub 2009 Oct 5.

**Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw.**

Vahtsevanos K, Kyrgidis A, et al.

Multivariate analysis demonstrated that use of dentures (aOR 2.02; 95% CI, 1.03 to 3.96), history of dental extraction (aOR 32.97; 95% CI, 18.02 to 60.31), having ever received zoledronate (aOR 28.09; 95% CI, 5.74 to 137.43), and each zoledronate dose (aOR 2.02; 95% CI, 1.15 to 3.56) were associated with increased risk for ONJ development. Smoking, periodontitis, and root canal treatment did not increase risk for ONJ in patients receiving BP.

**Conclusion**

…..however, randomized controlled trials are needed to validate these results.

Eur J Clin Pharmacol. 2010 Jun;66(6):547-54.
Epub 2010 May 1.

**Osteonecrosis of the jaw induced by clodronate, an alkylbiphosphonate: case report and literature review.**

Crépin S, Laroche ML, Sarry B, Merle L.

…The duration of exposure before onset was higher with alkylbiphosphonates than with aminobiphosphonates..

CONCLUSION: ..As these latter drugs (alkylbiphosphonates) are less potent, a high cumulative dose through long-term exposure would appear to be necessary and would favour ONJ.

BJU Int. 2009 Nov 13

**Frequency of zoledronic acid to prevent further bone loss in osteoporotic patients undergoing androgen deprivation therapy for prostate cancer**

Wadhwa VK, Weston R, Parr NJ.

Piccolo studio randomizzato, 58 pazienti con carcinoma prostatico non metastatico trattato con ormonoterapia e conseguente osteoporosi sono stati sottoposti a 5 somministrazioni di zoledronato 4mg (ogni 3 mesi, per un anno).

Furono registrati 2 casi di ONJ (**3.5%).**

# Frequenza di ONJ

Il reale tasso di incidenza di ONJ associata all'uso di DF è al momento sconosciuto.

Sono disponibili stime di frequenza, basate principalmente su studi retrospettivi tra loro eterogenei per disegno, definizione di caso...

Le stime di frequenza riportate negli studi osservazionali variano generalmente tra **l'1 e il 10%** sull'intera popolazione dei pazienti trattati con DF per via endovenosa (IV).

# Bisphosphonates in multiple myeloma (Review)

Mhaskar R, Redzepovic J, Wheatley K, Clark OAC, Miladinovic B, Glasmacher A, Kumar A, Djulbegovic B


***Cochrane Database Syst Rev. 2010 Mar 17;3:CD003188***

**Main results**
**17 trials with 1520 (**bisphosphonates) **1490** (control)

*Beneficial effect* on prevention of
-pathological vertebral fractures (RR= 0.74 ; 0.62-0.89)
-total skeletal related events (SREs) (RR= 0.80; 0.72-0.89)
-on amelioration of pain (RR = 0.75 ; 0.60-0.95)

*No significant effect* of bisphosphonates on
-overall survival (OS)
-progression-free survival (PFS),
-hypercalcemia
-reduction of non-vertebral fractures.

The indirect meta-analyses did not find the superiority of any particular type of bisphosphonate over others.

***Cochrane Database Syst Rev. 2010 Mar 17;3:CD003188***

## Main results

Only two RCTs reported ONJ.

We also identified seven observational trials evaluating 1068 patients for ONJ.

The identified observational studies suggested that ONJ may be a common event (range: 0% to 51%).

***Cochrane Database Syst Rev. 2010 Mar 17;3:CD003188***

# Dati derivanti da RCT

Maintenance therapy with thalidomide improves survival in patients with multiple myeloma

**Attal et al. (2006):** 597 pazienti di età inferiore ai 65 anni con MM sottoposti a trapianto erano stati randomizzati a ricevere uno di tre possibili trattamenti di mantenimento: A) nessuna terapia di mantenimento ; B) pamidronato IV 90 mg ogni 4 settimane; C) pamidronato + talidomide. Il trattamento era mantenuto fino alla progressione di malattia.

Gli autori riportano che si erano verificate ONJ nell'**1%** dei 196 soggetti inclusi nel gruppo B e nell'**1%** dei 201 inclusi nel gruppo C; nessun caso si era verificato nel gruppo A (200 pazienti).
La durata mediana di trattamento con pamidronato era stata di 21 mesi (range 0.2-51).

(Blood. 2006;108:3289-3294)

# Dati derivanti da RCT

## A Multicenter, Randomized Clinical Trial Comparing Zoledronic Acid Versus Observation in Patients With Asymptomatic Myeloma

**Musto et al. (2008):** 163 pazienti con mieloma asintomatico (smoldering o inactive), randomizzati a ricevere A) zoledronato 4mg ogni mese per 12 mesi, oppure B) **nessun trattamento**. Arruolamento tra 6/2001 e 6/2004.

Gli autori riportano un caso di ONJ nel braccio con zoledronato (81 pazienti) al termine del trattamento (1.2%); nessun caso nel gruppo B.

Gli autori riportano inoltre un caso successivo di ONJ, verificatosi in un paziente che aveva continuato il trattamento con zoledronato oltre i 12 mesi (violazione del protocollo).

*Cancer* 2008;113:1588-95.

**Stime di frequenza di ONJ in pazienti con Mieloma Multiplo trattati con DF IV nei 7 studi osservazionali inclusi nella RS Cochrane 2010***

| | Disegno | Pamidronato | Zoledronato | Pam+Zol. |
|---|---|---|---|---|
| ***Badros 2006*** | retrospettivo | 3/17 **(17.6%)** | 2/34 **(5.9%)** | 17/33 **(51.5%)** |
| ***Calvo-Villas 2006*** | NC | - | 7/64 **(10.9%)** | - |
| ***Corso 2007*** | retrospettivo | 0/20 **(0%)** | 5/37 **(11.9%)** | 2/42 **(4.5%)** |
| ***Dimopoulos 2006*** | | 7/93 **(7.5%)** | 1/33 **(3.0%)** | 6/66 **(9.1%)** |
| ***Garcia-Garay 2006*** | retrospettivo | 1/49 **(2.0%)** | 6/64 **(9.3%)** | 7/30 **(23.3%)** |
| ***Tosi 2006*** | retrospettivo | **-** | 6/225 **(2.7%)** | - |
| ***Zervas 2006*** | retrospettivo dal 1991, prospettico dal 2001-2006 | 1/78 **(1.3%)** | 6/91 **(6.6%)** | 21/85 **(24.7%)** |

** Mhaskar R et al. Bisphosphonates in multiple myeloma (Review). Cochrane Database Syst Rev. 2010 Mar 17;3:CD003188*

# A systematic review of bisphosphonate osteonecrosis (BON) in cancer

Cesar Augusto Migliorati · Sook-Bin Woo · Ian Hewson · Andrei Barasch · Linda S. Elting · Fred K. L. Spijkervet · Michael T. Brennan · Bisphosphonate Osteonecrosis Section, Oral Care Study Group, Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO)

*Support Care Cancer, 2010*

Stime di frequenza di ONJ in pazienti trattati con DF IV, nei 5 studi di coorte con follow-up documentato

| | Pamidronato | Zoledronato | Pam+Zol. |
|---|---|---|---|
| | 10.5% | 9.0% | 24.5% |

# Fattori di rischio

- Tipo di difosfonato usato (potenza) e via di somministrazione
  - IV DF >>> Oral DF
  - IV Zoledronato > IV Pamidronato
- Dose cumulativa

Fusco V et al. Osteonecrosis of the jaw (ONJ) risk in breast cancer patients after zoledronic acid treatment, The Breast (2010), doi:10.1016/j.breast.2010.03.008

**Table 1.**
ONJ incidence (or frequency) in patients treated with zoledronic acid and/or pamidronate.

| Author (reference) | ONJ in patients treated with zoledronic acid alone | ONJ in patients treated with pamidronate alone |
|---|---|---|
| Durie NEJM 2005[2] | ONJ incidence at 36 mo: 10%<br>Median time to ONJ: 18 mo | ONJ incidence at 36 mo: 4%<br>Median time to ONJ: 72 mo |
| Bamias JCO 2005[3] | ONJ frequency: 6.7% (7/105)[a]<br>Median time to ONJ: NR | ONJ frequency: 0% (0/58)[a]<br>Median time to ONJ: NR |
| Hoff JBMR 2008[4] | ONJ frequency 0.7% (9/1180)[b]<br>Median time to ONJ: 1.38 yrs | ONJ frequency 0.3% (7/2288)[b]<br>Median time to ONJ: 2.49 yrs |
| Ripamonti Ann Oncol 2009[5] (PRE group) | ONJ frequency 5.5% (7/127)[c]<br>Median time to ONJ: 15 inf | ONJ frequency 1.7% (10/567)[c]<br>Median time to ONJ: 25 inf |
| Vathsevanos JCO 2009[6] | ONJ frequency 8.0% (61/764)[d]<br>Median time to ONJ: NR | ONJ frequency 0.4% (1/236)[d]<br>Median time to ONJ: NR |

mo = months; yrs = years; inf = number of infusions; NR = not reported.

[a] 13% (9/69) if treated with pamidronate followed by zoledronate.

[b] 2.5% (13/526) if treated with pamidronate followed by zoledronate.

[c] 11.5% (9/78) if treated with pamidronate followed by zoledronate.

[d] 15.9% (15/94) if treated with pamidronate followed by zoledronate.

European Medicines Agency

EMEA/CHMP/292474/2009
EMEA/H/A-5(3)/1130

**OPINION OF THE COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE PURSUANT TO ARTICLE 5(3) OF REGULATION (EC) No 726/2004, ON BISPHOSPHONATES AND OSTEONECROSIS OF THE JAW**

EMEA, Settembre 2009

Whilst it is recognised that risk factors for ONJ are multiple and currently not fully elucidated, the most significant risk factors for the development of ONJ in association with bisphosphonates are considered to be bisphosphonate potency, route of administration and cumulative dose of bisphosphonate exposure. The impact of these parameters appears to be greater than the indication for treatment *per se*.

The history of dental disease and the nature of preceding dental procedures also seem to be of importance, with the majority of patients having had invasive dental procedures prior to the occurrence of ONJ. It should be highlighted though that it is under debate whether invasive dental procedure is a consequence of pre-existing ONJ rather than a precipitating factor.

For the remaining risk factors the literature findings are conflicting and the documentation less solid.

EMEA, Settembre 2009

Further clinical and epidemiological studies should also be performed aimed at obtaining further information regarding risk stratification and risk minimisation. The following recommendations are made regarding further research, including experimental, pre-clinical, clinical and epidemiologic studies:

Clinical and epidemiological studies

*First priority*

- A need for a unified pan-European database capturing all ONJ cases and allowing detailed analysis could help obtain further information on ONJ including: the background incidence of ONJ, the incidence of ONJ for individual drugs and indications, the time to onset, risk factors, possible genetic factors, the effects of drug holidays and alternative bisphosphonate dosing schedules, the effects of dental procedures and the prevention and treatment of ONJ.
- Prospective controlled randomised studies to examine alternative dosing schedules.

EMEA, Settembre 2009

# www.clinicaltrial.gov

**Found 7 studies with search of: Osteonecrosis AND bisphosphonates AND jaw**

| Rank | Status | Study |
|---|---|---|
| 1 | Active, not recruiting | **Bisphosphonate-Associated Jaw Osteonecrosis and PET Imaging**<br>Conditions: Bisphosphonate-Asscoiated ONJ; Osteomyelitis of the Jaw; Osteolytic Lesions of the Jaw; Osteoradionecrosis of the Jaw<br>Intervention:<br>Completion Date: October 2009 |
| 2 | Active, not recruiting | **Proposal For The Development Of A Well Defined Database For Patients With Oral Bisphosphonate-Related Osteonecrosis**<br>Condition: Osteonecrosis<br>Intervention: Other: alendronate<br>Completion Date: March 2010 |
| 3 | Recruiting | **Randomized Controlled Trial of Hyperbaric Oxygen in Patients Who Have Taken Bisphosphonates**<br>Condition: Osteonecrosis<br>Interventions: Device: hyperbaric oxygen; Device: non-treated control group<br>Completion Date: December 2012 |
| 4 | Completed | **CONDOR Study of Osteonecrosis of the Jaws (TMJ)**<br>Condition: Osteonecrosis of the Jaw<br>Intervention:<br>Completion Date: September 2008 |
| 5 | Active, not recruiting | **Long Term Efficacy and Safety of Zoledronic Acid Treatment in Patients With Bone Metastases**<br>Condition: Bone Neoplasms<br>Intervention: Drug: Zoledronic acid<br>Completion Date: |
| 6 | Recruiting | **Zoledronic Acid in Treating Patients With Metastatic Breast Cancer, Metastatic Prostate Cancer, or Multiple Myeloma With Bone Involvement**<br>Conditions: Breast Cancer; Metastatic Cancer; Multiple Myeloma and Plasma Cell Neoplasm; Musculoskeletal Complications; Pain; Prostate Cance<br>Urinary Complications<br>Intervention: Drug: zoledronic acid<br>Completion Date: |
| 7 | Recruiting | **Duration of Suppression of Bone Turnover Following Treatment With Zoledronic Acid in Men With Metastatic Castration Resistant Prostate Cancer**<br>Conditions: Metastatic Prostate Cancer; Bone Metastasis<br>Intervention: Drug: Zoledronic acid<br>Completion Date: January 2012 |

Study 2 of 7 for search of: onj

Previous Study | Return to Search Results | Next Study

Full Text View | Tabular View | No Study Results Posted | Related Studies

# Osteonecrosis of the Jaw in Patients With Cancer Receiving Zoledronic Acid for Bone Metastases

This study is currently recruiting participants.
Verified by National Cancer Institute (NCI), May 2010

First Received: April 1, 2009 Last Updated: May 28, 2010 History of Changes

| | |
|---|---|
| **Sponsor:** | Southwest Oncology Group |
| **Collaborator:** | National Cancer Institute (NCI) |
| **Information provided by:** | National Cancer Institute (NCI) |
| **ClinicalTrials.gov Identifier:** | NCT00874211 |

Estimated Enrollment:7200

Study Start Date:December 2008

Estimated Primary Completion Date: April 2015
(Final data collection date for primary outcome measure)

# Osteonecrosis of the Jaw in Patients With Cancer Receiving Zoledronic Acid for Bone Metastases. NCT00874211

PURPOSE: This randomized phase III trial is studying two different schedules of zoledronic acid to compare how well they work in treating patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma with bone involvement.

| Arms |
| --- |
| Arm I: Active Comparator<br>Patients receive zoledronic acid IV over ≥ 15 minutes. Courses repeat every 4 weeks for up to 2 years in the absence of disease progression or unacceptable toxicity. |
| Arm II: Experimental<br>Patients receive zoledronic acid IV over ≥ 15 minutes. Courses repeat every 12 weeks for up to 2 years in the absence of disease progression or unacceptable toxicity. |

# Interventions for the prevention of osteonecrosis of the jaws in patients receiving bisphosphonate therapy undergoing oral surgery (Protocol)

Oliver R, Badr M

THE COCHRANE COLLABORATION®

# OBJECTIVES

To determine whether a prophylactic intervention can prevent or reduce the incidence of development of bisphosphonate-related osteonecrosis of the jaws (BRONJ) in risk patients undergoing any oral surgical procedure when compared to another intervention, placebo or no intervention.

The null hypothesis will be: There is no reduction in the risk of BRONJ development in risk patients undergoing oral surgical interventions with any type of prophylactic intervention.

At risk patients are patients of all ages and from both sexes with current or history of taking bisphosphonates for any indication and undergoing an oral surgical intervention.