# FARMACOVIGILANZA E UPDATE PROGETTO AIFA

Alessandria 10 maggio 2014

# OBIETTIVI DELLA FARMACOVIGILANZA

- **individuare nel più breve tempo possibile nuove, in particolare gravi, reazioni avverse da farmaci recentemente immessi in commercio;**
- **documentare l'incidenza degli effetti avversi da farmaci;**
- **valutare la reale utilità di un medicamento, anche sotto il profilo di nuove possibili indicazioni;**
- **promuovere un modo di prescrivere sempre più razionale (e quindi anche più economico).**

# Metodiche in farmacovigilanza

- Approccio descrittivo
  - Case report
  - **Segnalazione spontanea**
- Approccio analitico
  - Studi clinici randomizzati
  - Studi di coorte
  - Studi caso-controllo
- Ulteriori metodologie
  - Prescription Event Monitoring
  - Record-Linkage
  - Metanalisi

The first three cases of bisphosphonate-associated osteonecrosis of the jaw were spontaneously reported to the FDA by an oral surgeon in 2002, with the toxic effect being described as a potentially late toxic effect of chemotherapy. In 2003, and 2004, three oral surgeons independently reported to the FDA information on 104 patients with cancer with bisphosphonate-associated osteonecrosis of the jaw seen in their referral practices in California, Florida, and New York, USA.

# Pharmacovigilance and reporting oversight in US FDA fast-track process: bisphosphonates and osteonecrosis of the jaw

*Beatrice J Edwards, Mrinal Gounder, June M McKoy, Ian Boyd, Mathew Farrugia, Cesar Migliorati, Robert Marx, Salvatore Ruggiero, Meletios Dimopoulos, Dennis W Raisch, Seema Singhal, Ken Carson, Eniola Obadina, Steve Trifilio, Dennis West, Jayesh Mehta, Charles L Bennett*

*Lancet Oncol* 2008; 9: 1166–72

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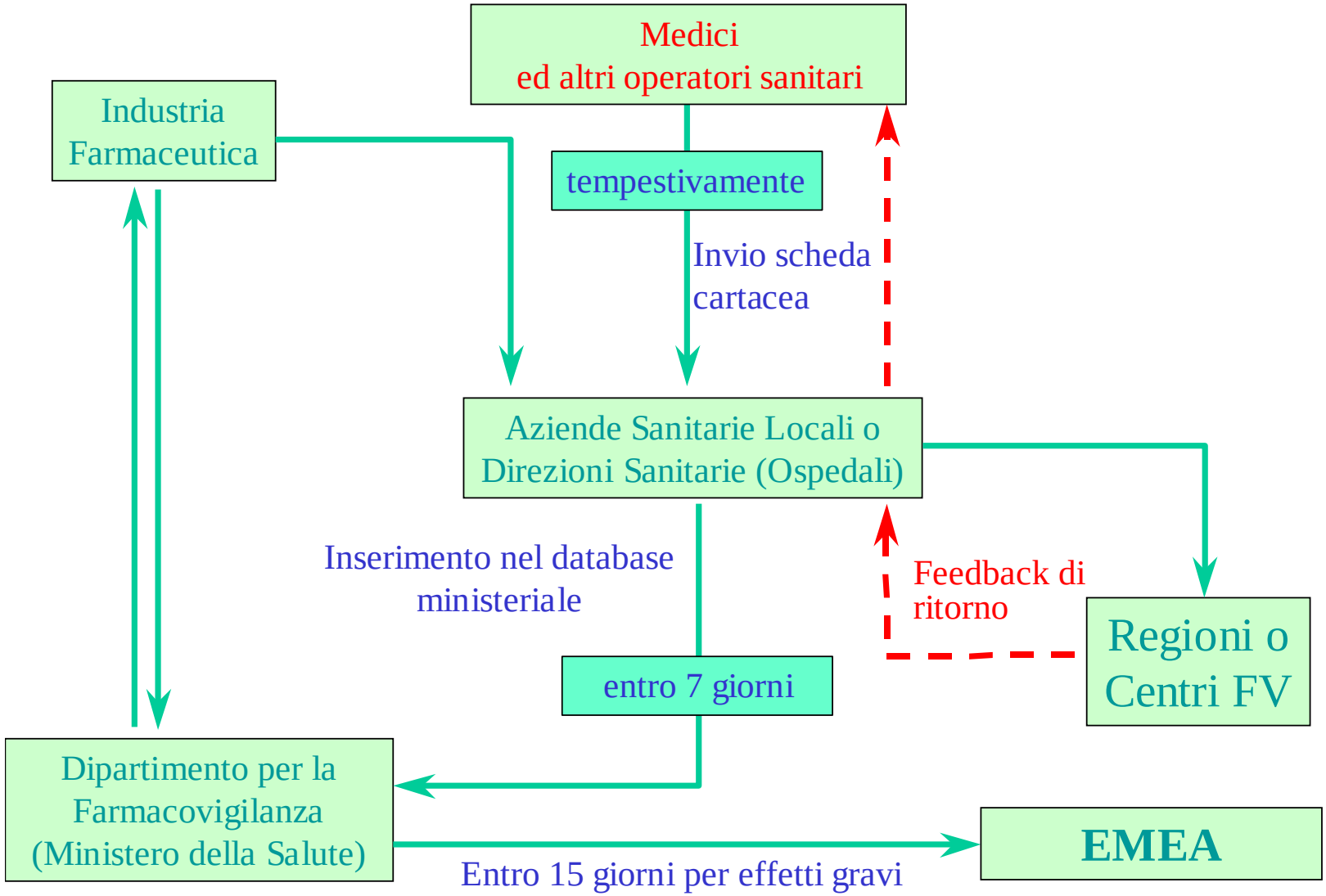
More than half of all serious adverse reactions are identified 7 or more years after a drug receives approval from the US Food and Drug Administration (FDA). In 2002, 9 months after the intravenous bisphosphonate zoledronic acid received regulatory approval for marketing, the FDA received reports of nine patients with cancer, who were treated with zoledronic acid, who unexpectedly developed osteonecrosis of the jaw. During the next 2 years, three oral surgeons described 104 patients with cancer with osteonecrosis of the jaw in the medical literature and identified intravenous bisphosphonate therapy as being common to the care of these patients. In subspecialty medical, radiology, and dental journals, case reports and case series described clinical features of osteonecrosis of the jaw in patients with cancer who were treated with bisphosphonates. Manufacturer-sponsored epidemiological studies reported the first estimates of the incidence of this toxic effect, ranging from 0·1% to 1·8%. By contrast, independent epidemiological efforts from clinicians and the International Myeloma Foundation reported incidence estimates between 5% and 10%. Between 2003 and 2005, warnings about the risks of bisphosphonate-associated osteonecrosis were disseminated by national regulatory agencies, the manufacturers of bisphosphonates, and the International Myeloma Foundation. From 2006, independent clinical recommendations for diagnosis, prevention, and treatment of this toxic effect have been disseminated by manufacturers, national regulatory authorities, the International Myeloma Foundation, and medical specialty organisations. Furthermore, independent efforts by pharmaceutical manufacturers, dental and medical professionals, a non-profit organisation (the International Myeloma Foundation), patients, and regulatory authorities has led to the rapid identification and dissemination of safety information for this serious adverse reaction. Better coordination of safety-related pharmacovigilance initiatives is now needed.

# Schema del sistema di farmacovigilanza in Sicilia



# Progetto di Farmacovigilanza Attiva “Farmaci anti-angiogenetici e rischio osteonecrosi dei mascellari. Progetto multicentrico su dati retrospettivi, ottimizzazione della farmacovigilanza e della prevenzione secondaria, studi genetici”

# CENTERS

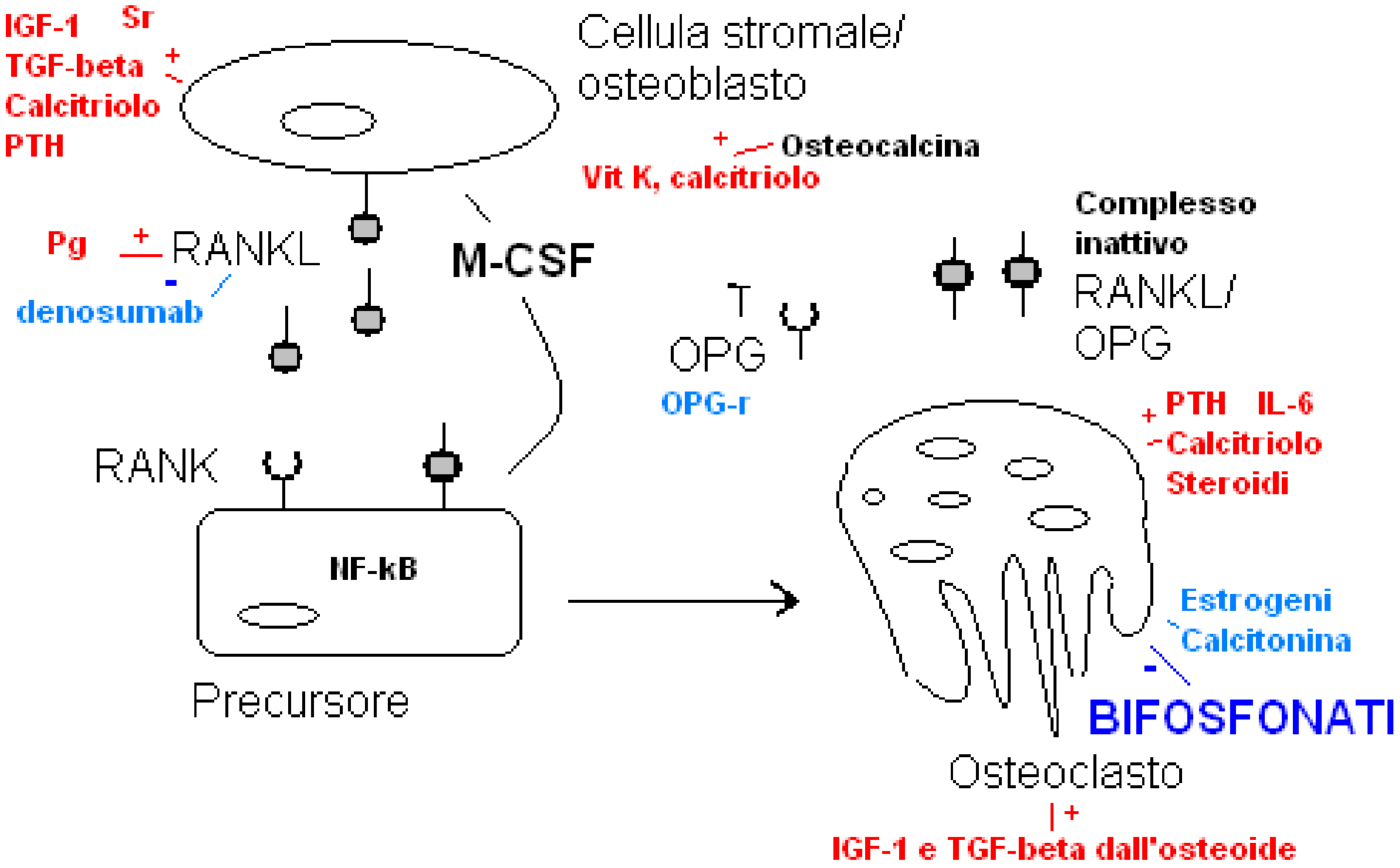
- Centro regionale siciliano di consulenza e informazione sugli effetti tossici da farmaci antitumorali e sulle ADR nei pazienti neoplastici – U.O.C. di Farmacologia Clinica – Policlinico Universitario “P. Giaccone” di Palermo (N. D’Alessandro)
- Centro P.R.O.M.A.B. (**P**revenzione e **R**icerca sull’**O**steonecrosi dei **M**ascellari da **B**isfosfonati) - Policlinico Universitario “P. Giaccone” di Palermo (G. Campisi)
- Centro Regione Sicilia per la segnalazione spontanea di Messina (A. Caputi)
- Centro di riferimento per la diagnosi e la prevenzione delle osteonecrosi dei mascellari – AOUP “G. Martino” di Messina (D. Cicciù)
- Rete oncologica Piemonte e Valle d’Aosta – Centro osteonecrosi – (V. Fusco)
- Società Italiana di Patologia e Medicina Orale

# Obiettivi

- **migliorare le conoscenze sui fattori di rischio, tra cui l'uso di farmaci anti-angiogenetici), per l'osteonecrosi delle ossa mascellari;**
- **eseguire e validare una campagna di prevenzione secondaria odontoiatrica per l'osteonecrosi delle ossa mascellari nelle Regioni Sicilia, Piemonte e Val d'Aosta;**
- **-implementazione della segnalazione spontanea nel campo dell'osteonecrosi delle ossa mascellari;**
- **creare e validare una scheda di segnalazione di ADR specificamente rivolta all'osteonecrosi delle ossa mascellari (in aggiunta a quella standard della Rete Nazionale di Farmacovigilanza) ai fini di un ottimale inquadramento delle singole manifestazioni;**
- **condurre uno studio farmacogenetico che permetterà di chiarire meglio il ruolo di modificazioni genetiche nel determinismo della osteonecrosi delle ossa mascellari indotta da anti-angiogenetici, bisfosfonati, altri farmaci contro il riassorbimento osseo (come il denosumab) o dalla loro combinazione.**

# Potential mechanisms of ONJ

- Inhibition of bone remodeling: compromised bone microenvironment functioning affecting bone remodeling and repair.
- Vascular: anti-angiogenic effects delaying wound healing and/or affecting micro-infarction in bone and/or soft tissues.
- Infection and inflammation: microorganisms of the oral cavity promoting cell death in the bone and/or oral soft tissues.
- Genetic predisposition: genetic polymorphisms affecting drug metabolism, excretion, or drug targets within pathways of bone metabolism and/or wound healing.
- Drug interactions: drug interactions between chemotherapy and bisphosphonate selectively promoting cell death.


IGF-1
Sr
TGF-beta
Calcitriolo
PTH
+
Cellula stromale/
osteoblasto
+
Osteocalcina
Vit K, calcitriolo
Pg
+
RANKL
-
denosumab
M-CSF
T
OPG
OPG-r
Complesso
inattivo
RANKL/
OPG
RANK
NF-kB
+
PTH
IL-6
-
Calcitriolo
Steroidi
Estrogeni
Calcitonina
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BIFOSFONATI
Precursore
Osteoclasto
| +
IGF-1 e TGF-beta dall'osteoide

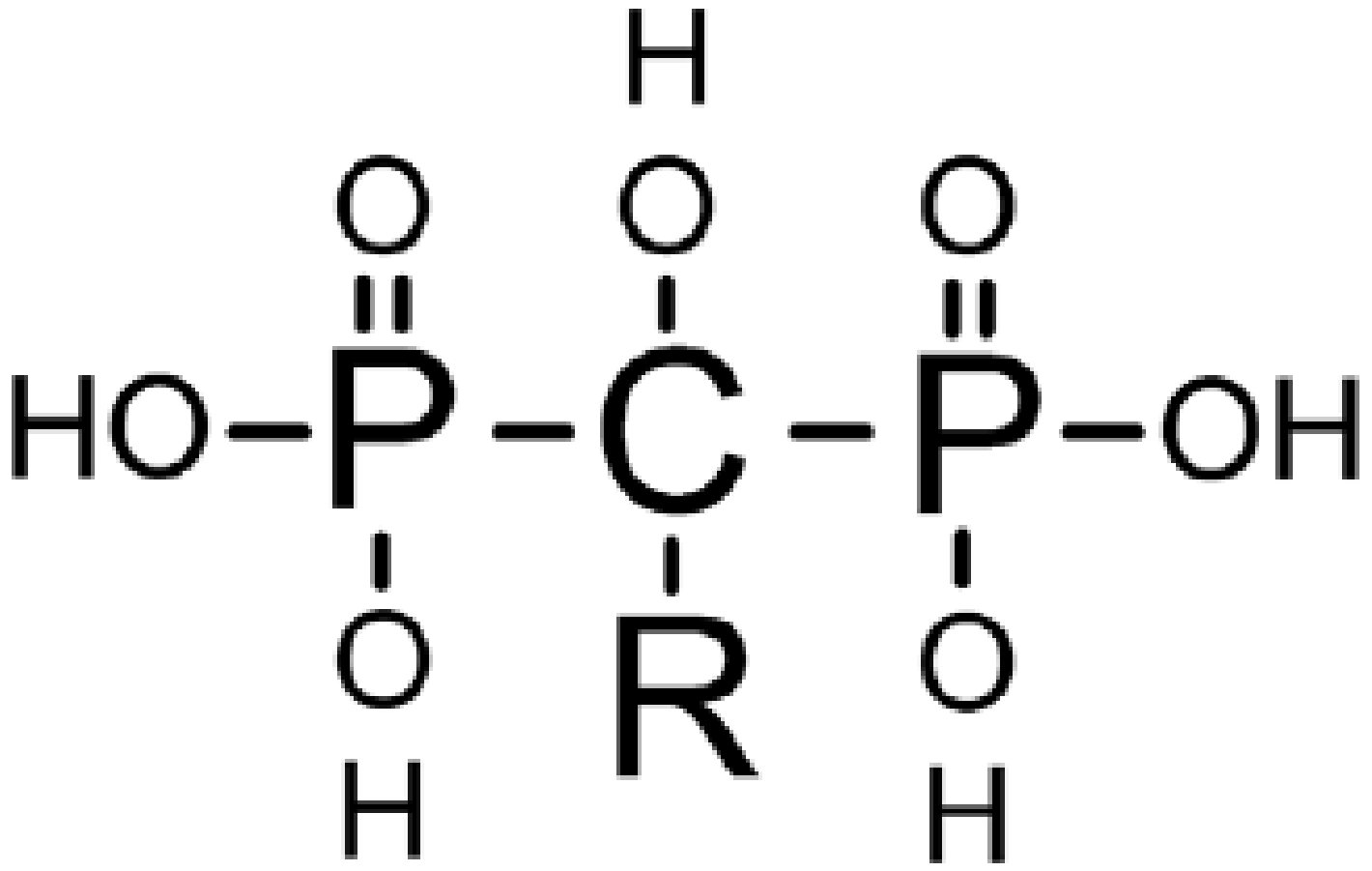



**Figure 1.** Bisphosphonates used most frequently in the clinic today have a characteristic structure. All have a hydroxyl group on the carbon atom that confers high affinity for calcium and the skeleton. They vary only at the R-group, which always contains a nitrogen atom that is in either an alkyl or a heterocyclic structure.

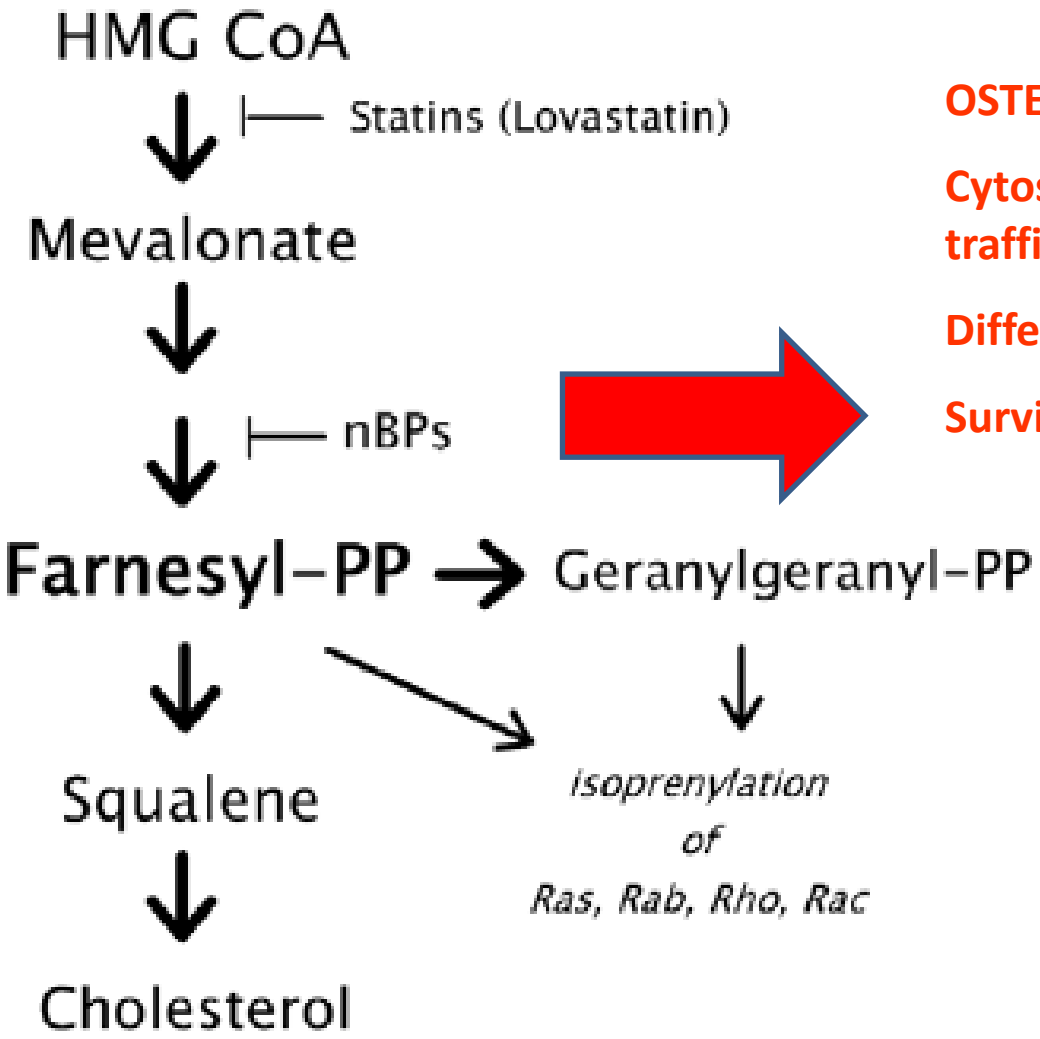



**Figure 2.** Nitrogen-containing bisphosphonates inhibit farnesyl diphosphate (FPP) synthase, an enzyme in the mevalonate pathway. FPP synthase is responsible for isoprenylation of small GTPases that promote an array of activities in the osteoclasts that control bone resorption. Without this activity, bone resorption is slowed.

**OSTEOCLASTS**

**Cytoskeleton, vesicular trafficking, brush border**

**Differentiation**

**Survival**

!

BPPs differ in their potency in inhibiting FPPS

# Potenza relativa dei vari bisfosfonati nell'inibire gli osteoclasti

- ETIDRONATO 1
- CLODRONATO/TILUDRONATO 10
- PAMIDRONATO/NERIDRONATO 100
- ALENDRONATO 500-1000
- RISEDRONATO 3000-5000
- IBANDRONATO 10000
- ZOLEDRONATO> 10000

# Atypical subtrochanteric and diaphyseal femoral fractures (AFFs)

**Although the relative risk of patients with AFFs taking BPs is high, the absolute risk of AFFs in patients on BPPs is low, ranging from 3.2 to 50 cases per 100,000 person-years. However, long-term use may be associated with higher risk (~100 per 100,000 person-years)**

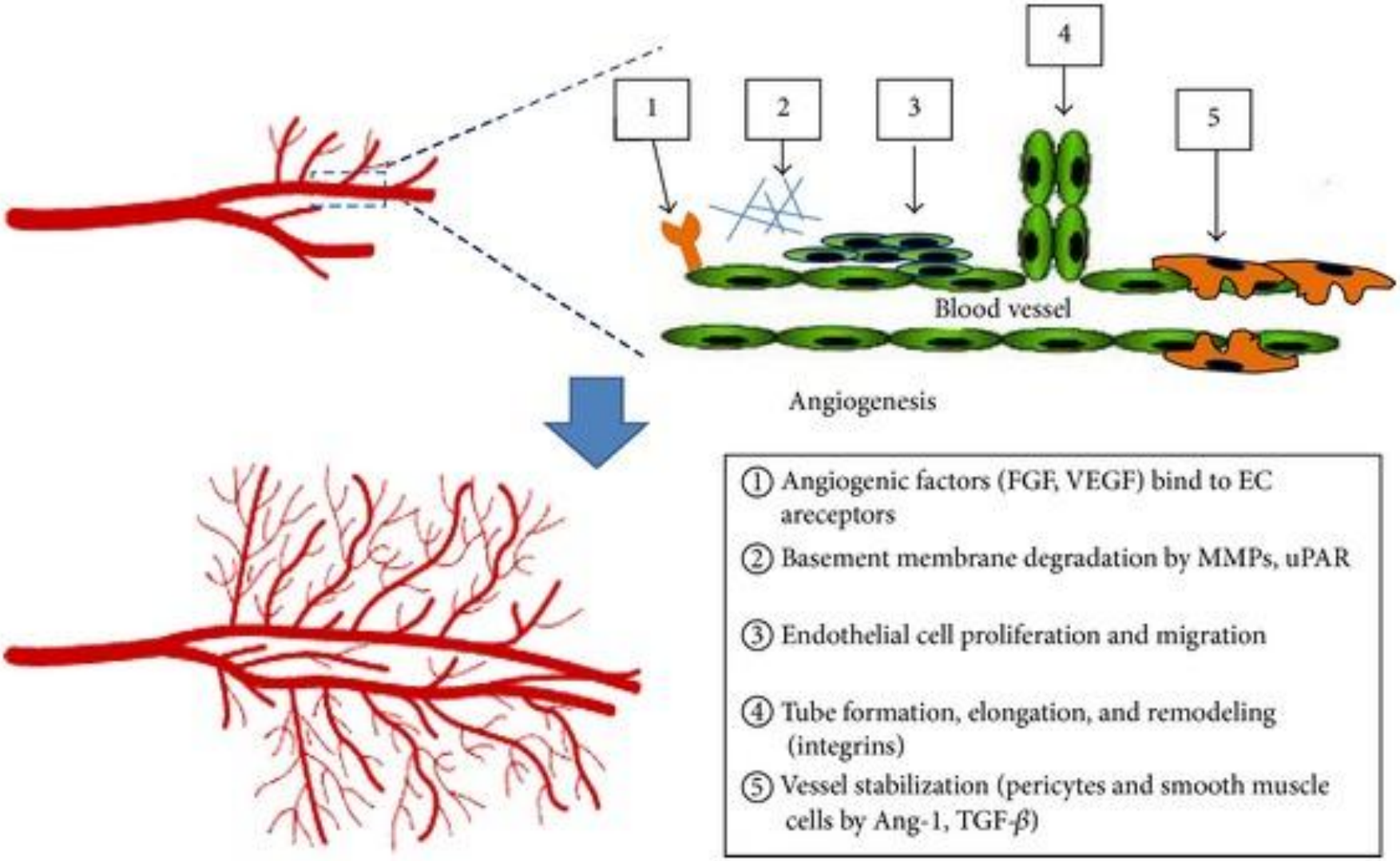
**Bisphosphonate-associated osteonecrosis of the auditory canal**

1.Mark N. Polizzotto[1],
2.Vincent Cousins[2] and
3.Anthony P. Schwarer[1]

**British Journal of Haematology**
Volume 132, Issue 1, page 114, January 2006

# Risk factors (other than local) for ONJ

- Drug (BPP) : molecule (+++), route of administration (++), cumulative dose (+++), duration of treatment (+++)
- Indication for BPP: multiple myeloma (++), solid tumors (++), osteoporosis (+)
- Concomitant therapies: chemotherapy (-/+), others
- Life style: smoking (+/-), alcohol (-/+), overweight (+/-)
- Anagraphy: sex (+/-), age (+/-), ethnicity (+/-),genetic factors (+/-)
- Comorbidities: diabetes (+/-), rheumatoid arthritis (+), hypocalcemia - hyperparathyroidism (+), osteomalacia - hypovitaminosis D (+), renal insufficiency in dialysis (+), anemia (+/-)




① Angiogenic factors (FGF, VEGF) bind to EC areceptors

② Basement membrane degradation by MMPs, uPAR

③ Endothelial cell proliferation and migration

④ Tube formation, elongation, and remodeling (integrins)

⑤ Vessel stabilization (pericytes and smooth muscle cells by Ang-1, TGF-$\beta$)

Pro-angiogenic mediators implicated in tumour angiogenesis

| Category | Examples | References |
|---|---|---|
| Growth factors | VEGFs | Bouis *et al.*, 2006 |
| | FGFs | Bouis *et al.*, 2006 |
| | TGFs | Bouis *et al.*, 2006 |
| | PDGFs | Bouis *et al.*, 2006 |
| | Insulin-like growth factors | Lopez-Lopez *et al.*, 2004; Bid *et al.*, 2011 |
| | ANGs | Fagiani and Christofori, 2013 |
| Cytokines | IL-8 | Strieter *et al.*, 2004 |
| | CSF-1 | Lin *et al.*, 2006 |
| Bioactive lipids | PGE2 | Wang and Dubois, 2010 |
| | S1P | Murakami, 2011 |
| Matrix-degrading enzymes | MMPs | Bourboulia and Stetler-Stevenson, 2010 |
| | Heparanases | Vlodavsky and Friedmann, 2001 |
| Small mediators | NO | MacLauchlan *et al.*, 2011 |
| | Peroxynitrite | El-Remessy *et al.*, 2007 |
| | Serotonin | Qin *et al.*, 2013 |
| | Histamine | Qin *et al.*, 2013 |

Asmaa E El-Kenawi[1] and Azza B El-Remessy[2,3,4]
British Journal of Pharmacology (2013) **170** 712–729

## Major categories of angiogenesis inhibitors and molecular targets

- *Chemotherapeutic agents*

**Cyclophosphamide (EC apoptosis, decreased circulating EPC)**
**Paclitaxel (Microtubules)**

- *VEGF-targeted therapy*

**Bevacizumab (VEGF)**
**VEGF-Trap (VEGF-A, VEGF-B and PlGF)**
**Sunitinib (VEGFR1–3, PDGFR-α, PDGFR-β, c-Kit, CSF-1R and Flt-3)**
**Sorafenib (VEGFR1–3, PDGFR-β, Raf-1, B-Raf)**
**Pazopanib (VEGFR1-3, PDGFR-α-β and c-Kit)**
**Vatalanib (VEGFR1–3, PDGFR-β and c-Kit)**
**Axitinib (VEGFRs, PDGFR-β and c-Kit)**
**SU6668 (VEGFR2, FGFR1 and PDGF-β)**

- *FGF-targeted therapy*

**AZD4547 (FGFR1–3)**
**Ponatinib (FGFR1–4)**
**SSR (FGFRs)**
**Brivanib (VEGFRs and FGFRs)**
**Dovitinib (FEGFRs, VEGFRs and PDGFR)**
**Nintedanib (VEGFRs, FGFRs and PDGFR)**

- ***Oncogene-targeted therapy/signalling transduction-targeted therapy***

**Dasatinib (Src and indirectly VEGF, IL-8)**
**Tipifarnib (MMP-1)**
**NVP-AUY922 (Hsp90)**
**Bortezomib (NF-κB-dependent release of VEGF and IL-8)**
**Gossypol (VEGF and IL-8 release)**
**Dacinostat (Histone deacetylase)**

- ***Matrix degrading and remodelling-targeted therapy***

**DX-2400 (MMP-14)**
**PI-88 (Heparanase)**

- ***Tumour-associated stromal cell-targeted therapy***

**JNJ-28312141 (CSF-1R)**
**Zoledronic acid (TAM-associated production of VEGF)**
**Anti-BV8 antibody (Neutrophils recruitment)**

- ***CAMs-targeted therapy***

**Cilengitide (αvβ3 and αvβ5 integrins ligation to matrix proteins)**
**Volociximab (αvβ1 integrin interaction with fibronectin)**
**ADH-1 (N-cadherin)**

- ***Inflammatory angiogenesis-targeted therapy***

**Ibuprofen(COX1/2)**
**Celecoxib (COX-2)**
**Repertaxin (CXCR1 and CXCR2)**

# REPORTS OF ONJ IN SICILY – NEOPLASTIC PATIENTS

- 148 cases of ONJ (103 reported by A.O.U.P. “P. Giaccone” of Palermo) in neoplastic patients
- in 112 cases (75.6%), zoledronic acid was the only suspected medication; in 28 cases (18.9%) there was an additional BPP (21 cases) or other agent (7 cases) as a suspected medication
- in 2 cases (1.3%) ibandronate was the only suspected medication
- in 1 case (0.6%) pamidronate was the only suspected medication
- in 1 case (0.6%) sunitinib was the only suspected medication
- in 1 case (0.6%) bevacizumab was the only suspected medication
- in 1 case (0.6%) rituximab was the only suspected medication

- Jaw 97 (65.5%); Maxilla 34 (22.9%); Jaw & Maxilla 14 (9.4%); N.S. 3 (2.0%)
- Males 50 (33.7%), Females 98 (66.3%)
- Breast cancer 62 (41.8%); Multiple myeloma 39 (26.3%); Prostate cancer 21 (14.1%); Renal cancer 6 (4.0%); Lung cancer 5 (3.3%); Other tumors 7(4.7%); N.S. 8 (5.4%).
- In Multiple myeloma: Males 14 (35.8%), Females 25 (64.1%)

# REPORTS OF ONJ IN SICILY – OSTEOPOROROTIC PATIENTS

- 68 cases of ONJ (48 reported by A.O.U.P. P. Giaccone of Palermo) in osteoporotic patients
- in 34 cases (50.0%) alendronate was the only suspected medication
- in 13 cases (19.1%) ibandronate was the only suspected medication
- in 4 cases (5.8%) clodronate was the only suspected medication
- in 4 cases (5.8%) zoledronic acid was the only suspected medication
- in 4 cases (5.8%) risedronate was the only suspected medication
- in 1 case (1.4%) pamidronate was the only suspected medication
- in 8 cases (11.7%) two BPPs were suspected together (in one case plus denosumab)

# CASES (5) OF ONJ ASSOCIATED TO BEVACIZUMAB

- in one case (Cancer of the uterus) bevacizumab was the only suspected medication (among the concomitant medications there are paclitaxel and lansoprazole)
- in one case (Breast cancer) zoledronic acid (but for only 2 administrations) was also a suspected medication (among the concomitant medications there was paclitaxel; there was diabetes)
- in one case (Breast cancer) zoledronic acid was also a suspected medication (among the concomitant medications there are paclitaxel, lansoprazole and furosemide)
- in one case (Breast cancer) zoledronic acid was also a suspected medication (among the concomitant medications there were paclitaxel, omeprazole and prednisone)
- in one case (Breast cancer) bevacizumab is a concomitant medication and zoledronic acid was the suspected drug (among the concomitant medications there was also paclitaxel)

# CASES (4) OF ONJ ASSOCIATED TO SUNITINIB

- in one case (Renal cancer) sunitinib was the only suspected medication
- in two cases (Renal cancer) zoledronic acid was also a suspected medication (pantoprazole was a concomitant medication in one case)
- in one case (Renal cancer) pamidronate was also a suspected medication (furosemide and omeprazole were concomitant medications)

# CASES OF ONJ ASSOCIATED TO OTHER ANTI-ANGIOGENIC DRUGS

- THALIDOMIDE as a suspected medication in 1 case and as a concomitant medication in 9 cases
- EVEROLIMUS as a suspected medication in 1 case and concomitant in 2 cases
- RITUXIMAB as a suspected medication in 1 case
- PACLITAXEL as a concomitant medication in 7 cases
- DOCETAXEL as a concomitant medication in 7 cases
- BORTEZOMIB as a concomitant medication in 4 cases
- LENALIDOMIDE as a concomitant medication in 2 cases

# AIMS OF PHARMACOGENETIC STUDIES

- PREDICTION
- DIAGNOSIS
- IDENTIFICATION OF THE MECHANISM >TREATMENT

# Gene variants associated with ONJ

- *RBMS3* (rs10510628): binding protein for Prx1, a homeobox transcriptional factor that upregulates collagen type I in fibroblasts
- *IGFBP7* (rs11934877): Insulin-like growth factor-binding protein 7
- *FPS* (A/C rs2297480): Farnesyl Pyrophosphate Synthetase
- *Aromatase* (g.132810C>T)
- *CYP2C8* (rs1934951, rs1934980, rs1341162 and rs17110453): synthesis of EETs > angiogenesis, HMG-CoAR > osteoblast differentiation.
- *ABCC4 (MRP4)*: transporter of multiple endogenous and foreign substrates
- *COL1A1* (rs1800012), *RANK* (rs12458117), *MMP2* (rs243865), *OPG* (rs2073618) and *OPN* (rs11730582).

# A search for candidate drugs in the same way as for candidate genes

| Agents | Mechanism | Evidence |
|---|---|---|
| Glucocorticoids | Reduced proliferation and differentiation of osteoblasts. Decreased function and induction of apoptosis in osteocytes. Increased osteoclast generation. Decreased calcium absorption by the gastrointestinal tract and renal calcium loss. Secondary hyperparathyroidism. Muscle weakness. | Strong: 25% of patients on long-term corticosteroids may suffer a fracture. |
| Proton pump inhibitors | Chronic hypergastrinemia induced by PPI therapy may lead to parathyroid hyperplasia, resulting in increased loss of calcium from the bone. In addition, profound gastric acid suppression may reduce the bioavailability of calcium for intestinal absorption. Block of acid secretion and thus of bone resorption by osteoclasts by inhibiting vacuolar $H^+$-ATPase (at high concentrations). | The majority of observational studies report a significant increase in low to moderate risk (OR 1.2 to 3.1) of fractures, correlated with the dose and duration of treatment. Concurrent PPIs use appears to be associated with a loss of protection against hip fractures given by BPP. |

| Agents | Mechanism | Evidence |
|---|---|---|
| Selective Serotonin Reuptake Inhibitors | Functional serotonin receptors and transporters are present in osteoclasts, osteoblasts and osteocytes, and serotonin can influence bone metabolism. The higher the affinity of an antidepressant for serotonin, the higher the risk of fracture. | The preponderance of evidence points to a negative effect of SSRIs on BMD and fracture risk. |
| Thiazolidinediones | Competition of lineage commitment between osteoblasts and adipocytes for a common precursor cell, resulting in decreased osteoblast numbers. | Long-term treatment with thiazolidinediones increases the risk of fractures by up to 4-fold in postmenopausal women and in men. This risk correlates with the duration of treatment with thiazolidinediones and is significant after 12 to 18 months. |
| Loop diuretics | Increased renal calcium loss. | Sufficient evidence of decreased BMD and increased risk of fractures in men and postmenopausal women on long-term treatment with these drugs. |

| Agents | Mechanism | Evidence |
| --- | --- | --- |
| Heparin | In vivo, heparin decreases bone formation and increases bone resorption, the latter by inhibiting the expression of osteoprotegerin. | Long-term use of unfractioned heparin has been associated with a 2.2-5% incidence of heparin-induced osteoporotic fracture, but for low-molecular-weight heparin (LMWH) data are scarce and there is lack of clarity of the risks of osteoporosis and osteoporotic fractures. |
| Aromatase inhibitors | Reduction in estrogen concentrations caused by the suppression of androgen aromatization causes bone loss. | Letrozole and anastrozole, decrease BMD and increase the relative risk of vertebral and nonvertebral fractures by 40%, when compared with tamoxifen. The effect is more prevalent in women starting aromatase inhibitors early after menopause. Bone loss with increased risk of fragility fractures also is observed in women receiving exemestane. |

| Agents | Mechanism | Evidence |
| --- | --- | --- |
| Gonadotrophin-releasing hormone analogs | Reduced serum testosterone and estradiol levels. | A decrease of about 6%/year in BMD is observed in premenopausal women on GnRH agonists with a recovery of bone mass after discontinuation. GnRH agonists may not increase the risk of fragility fractures in women with normal BMD. In men with carcinoma of the prostate, the risk of fractures correlates with the degree and rate of BMD decrease, patient age, and duration of therapy, but not with tumor stage. |
| Thyroxine | Thyroid hormones increase bone resorption directly and indirectly by inducing the production of bone-resorbing cytokines. Recently, TSH was reported to inhibit bone resorption directly, suggesting that the suppression of TSH itself may cause bone loss. | Subclinical thyrotoxicosis causes bone loss in elderly subjects and postmenopausal women. |

| Agents | Mechanism | Evidence |
|---|---|---|
| Antiretroviral drugs (NRTIs, NNRTIs and PIs) | NRTI class may produce perturbation of gene osteoblast expression and changes implying osteoblast dysfunction. | Several studies have shown a higher prevalence of reduced BMD and a higher incidence of fracture among HIV-infected persons, aggravated by the beginning of ART. All the three different classes lead to BMD loss but NRTIs are associated with a significantly greater BMD loss in the hip and spine. |
| Warfarin and other vitamin K antagonists | Reduced levels of the vitamin K-dependent gamma-carboxylated forms of osteocalcin and of bone Gla protein. | Observational cross-sectional studies describing their effects on bone mineral density have reported conflicting results. Overall, long-term vitamin K antagonists might be associated with no more than a modest increase in osteoporotic fracture risk, but this should be verified in future longitudinal studies. |

| Agents | Mechanism | Evidence |
|---|---|---|
| Antiepilectic drugs | Induction of liver enzymes which leads to vitamin D deficiency. Actually, AEDs that decrease seizure frequency may result in a net decrease in fracture risk. | Some AEDs, especially among the older drugs, are *per se* associated with a small increase in fracture risk Overall, most AEDs, especially among the newer AEDs, seem relatively safe in terms of fracture risk. |
| Immunosuppressive drugs (Calcineurin inhibitors) | Alterations of the balance between RANKL and osteoprotegerin. | Bone loss in transplant recipients who are treated with little or no glucocorticoid and with calcineurin inhibitors as the backbone therapy has been very low. |
| Laxatives, Anxiolytics, Neuroleptics, Opioids, NSAIDs | Probably increased risk of falls. | Limited increase in fracture risk. |

# Bone protective drugs?