

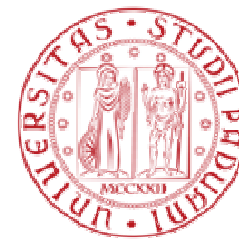


VI Congresso Nazionale ISO  
14-15 novembre 2017, Palazzo Zacco -Padova

## Nuovi farmaci molecolari e inibitori del riassorbimento osseo: Rischio osteonecrosi mascellare (ONJ) - Il punto di vista del Chirurgo



**Alberto Bedogni, MD, FEBOMS**



*Regional Center for Prevention, Diagnosis and Treatment of Medication and Radiation-related Bone Diseases of the Head and Neck (DGR 2707, 12/2014)*

*Unit of Maxillofacial Surgery, Dept. of Neuroscience-DNS, University of Padua*

## Nuovi farmaci molecolari e inibitori del riassorbimento osseo: Rischio osteonecrosi mascellare (ONJ) - Il punto di vista del Chirurgo

- Targeted therapies: What is their role in MRONJ?
- Drug holiday: Should the antiresorptive treatment be paused or stopped when MRONJ is diagnosed? What do we know today?

# Targeted therapies: What is their role in MRONJ?

Starting from 2008, “ONJ cases have been reported in cancer patients after treatment including **antiangiogenic agents and other targeted therapy**, with and without antiresorptive drugs (NBP, denosumab)”.

EXPERT OPINION ON DRUG SAFETY, 2016  
VOL. 15, NO. 7, 925–935  
<http://dx.doi.org/10.1080/14740338.2016.1177021>



---

## REVIEW

## Osteonecrosis of jaw beyond antiresorptive (bone-targeted) agents: new horizons in oncology

Vittorio Fusco<sup>a</sup>, Daniele Santini<sup>b</sup>, Grazia Armento<sup>b</sup>, Giuseppe Tonini<sup>b</sup> and Giuseppina Campisi<sup>c</sup>



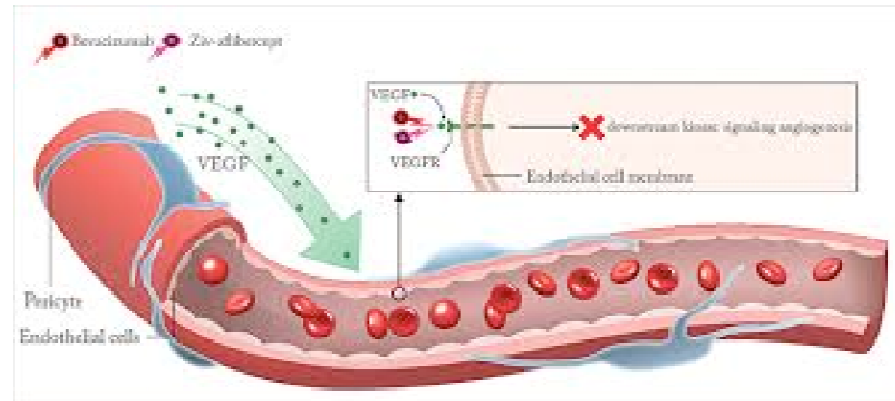
EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

The European Medical Agency (EMA) released alerts in 2010 regarding the risks of ONJ after treatment including **bevacizumab** or **sunitinib**.

MHRA. Bevacizumab and sunitinib: risk of osteonecrosis of the jaw. Drug Safety Update. 2011. Available from: <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON105745>

# Anti-vascular endothelial growth factor (VEGF)

- Bevacizumab
- Aflibercept



**Action:** inhibition of angiogenesis and tumor growth

**Indications:** colorectal cancer, renal cell cancer, lung cancer, breast cancer, cervical and ovarian cancer, glioblastoma *and macular degeneration*

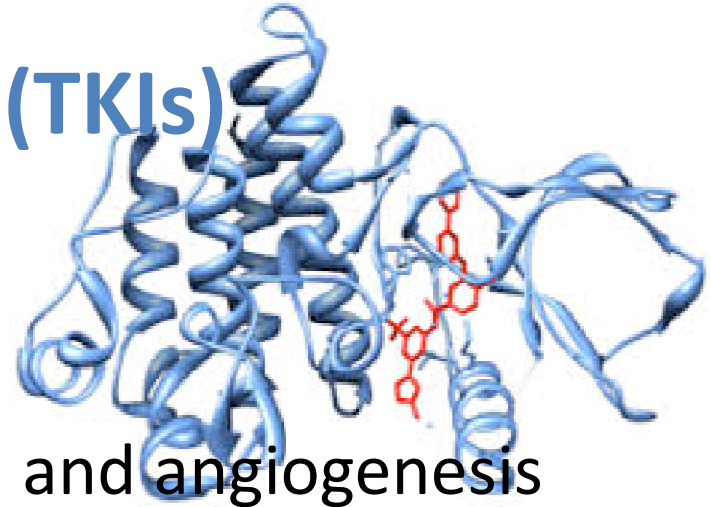
## Oral toxicity

1. Increased risk of infection
2. Impaired wound healing



# Tyrosine Kinase inhibitors (TKIs)

- Sunitinib
- Sorafenib



**Action:** inhibition of tumor growth and angiogenesis through multi-target mechanisms.

**Indications:** renal cell cancer, soft-tissue sarcoma, lung cancer, pancreatic neoplasms, gastrointestinal stromal tumors (GISTs), hepatocellular cancer, melanoma, thyroid cancer, colon cancer.

## Oral toxicity:

1. Oral mucositis /stomatitis
2. Oral ulcerations
3. Oral pain



# Mammalian target of rapamycin (mTOR) inhibitors

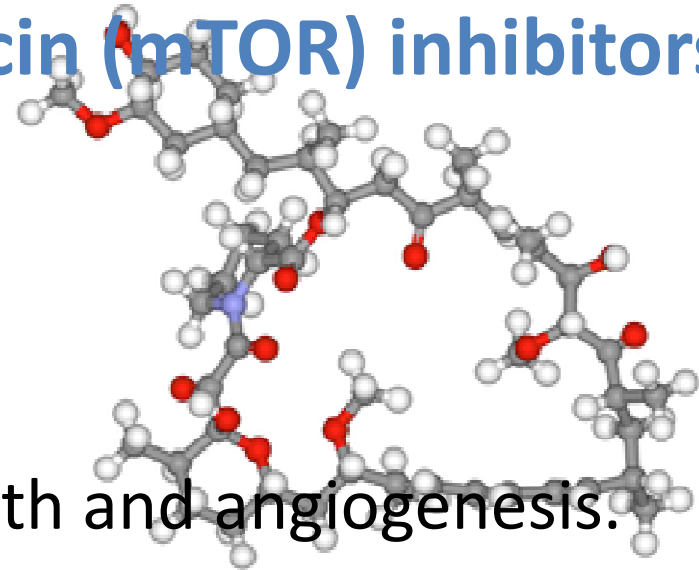
- Everolimus
- Temsirolimus

**Action:** inhibition of tumor growth and angiogenesis.

**Indications:** renal cell cancer, breast cancer, pancreatic neuroendocrine tumors, and prevention of solid organ rejection

## Oral toxicity:

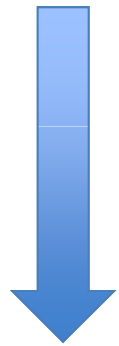
1. Oral ulcerations
2. Increased risk of infection
3. Impaired healing



## Unsolved questions

Who are the patients at higher risk of MRONJ during or after treatment with antiangiogenic agents (alone/combination)?

- **Breast and prostate CANCER pts, MM pts.** **2003**



Long-term courses of antiangiogenic drugs  
Longer survival rates  
Expanding indications

- mRCC pts.
- Lung cancer pts.
- Colorectal cancer pts.
- Ovarian cancer pts
- Others...

**2017**





# Targeted therapies: What is their role in MRONJ?

## Concomitant or sequential use of antiresorptive agents



- ☐ Increased risk of developing ONJ
- ☐ Earlier onset
- ☐ Faster disease progression
- ☐ Worse prognosis

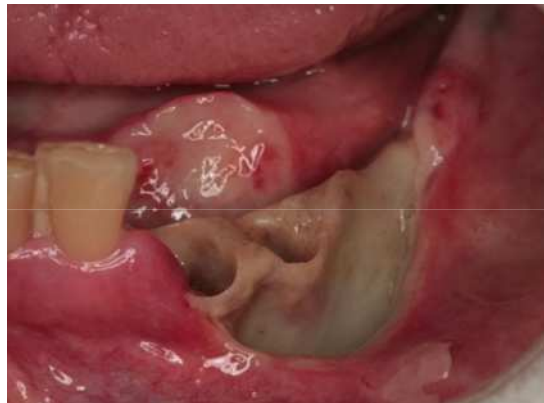
Lescaille G et al. Clinical study evaluating the effect of bevacizumab on the severity of zoledronic acid-related osteonecrosis of the jaw in cancer patients. Bone. 2014, 58:103-7

## Unsolved questions

Do **clinical** and **radiological** features of **ONJ** related to anti-angiogenic drugs and '**targeted therapy**' differ from those observed with antiresorptive treatment?



- NBP



- Anti-VEGF



- mTOR Inhibitors

- Non specific clinical and radiological signs of MRONJ
- *Differential diagnosis between Oral mucosa toxicity and early ONJ is challenging*

# MRONJ: i.v. NBP + sunitinib



**Fig. 2.** Situation after resumption of sunitinib: increased exposure of bone, loss of a canine tooth and cervical cutaneous sinus-track formation.

(Fig. 4). The bone infection improved with another cycle of oral amoxicillin-clavulanic acid and metronidazole, and gingival repair occurred.

This is the first report of osteonecrosis of the jaw in a patient receiving a novel antiangiogenic drug who had been previously treated with i.v. bisphosphonates. The consecutive episodes of painful jaw infection with cutaneous fistula and bone sequestration in our patient were likely correlated with sunitinib therapy, occurring during active treatment, significantly improving after sunitinib discontinuation and antibiotic therapy, then rapidly worsening with resumption of treatment.



**Fig. 4.** At sunitinib re-challenge: painful swelling, bone exposure in the right body of the mandible with spontaneous tooth loss.

Brunello et al, Bone 2009

## Unsolved questions

What dental preventive measures could be taken in patients receiving antiangiogenic and targeted therapies?

Local risk factors remain the same as for patients receiving antiresorptive medications

- tooth extraction and alveolar surgery
- implants,
- ill- fitting dentures
- Poor oral health



In general, the preventive protocols already adopted for the antiresorptive agents might be used for these new drugs.

## ONJ in RCC cancer patients

### Combination of Zoledronic Acid and Targeted Therapy Is Active But May Induce Osteonecrosis of the Jaw in Patients With Metastatic Renal Cell Carcinoma

*Torben Smidt-Hansen, MD, <sup>\*</sup>Troels B. Folkmar, DDS, <sup>†</sup>Kirsten Fode, MD, <sup>‡</sup>Mads Agerbaek, MD, <sup>§</sup> and Frede Donskov, MD, DMSc<sup>||</sup>*

ONJ:     **6/21 (29%)**   no pretherapy oral examination  
          **1/9 (11%)**     with pretherapy oral examination

**Conclusion:** The combination of ZA and TT resulted in high, clinically meaningful activity. ONJ may be exacerbated by concomitant ZA and sunitinib. Regular OM examinations before and during treatment are recommended.

© 2013 American Association of Oral and Maxillofacial Surgeons

Smidt-Hansen et al – JOMS 2013

# New drugs: Tyrosine Kinase Inhibitors and other new drugs: What is their role in MRONJ?

---

## Conclusions

As novel drugs with antiangiogenic properties become available in the anticancer armamentarium, it is likely that longer drug(s) treatment duration and longer survival rates will be associated with **higher ONJ rates** in cancer patients.

**KEEP YOURSELF INFORMED**

The **clinical/radiological aspects** and especially the prognosis of ONJ associated with targeted therapies seem to be unlike those used in BRONJ



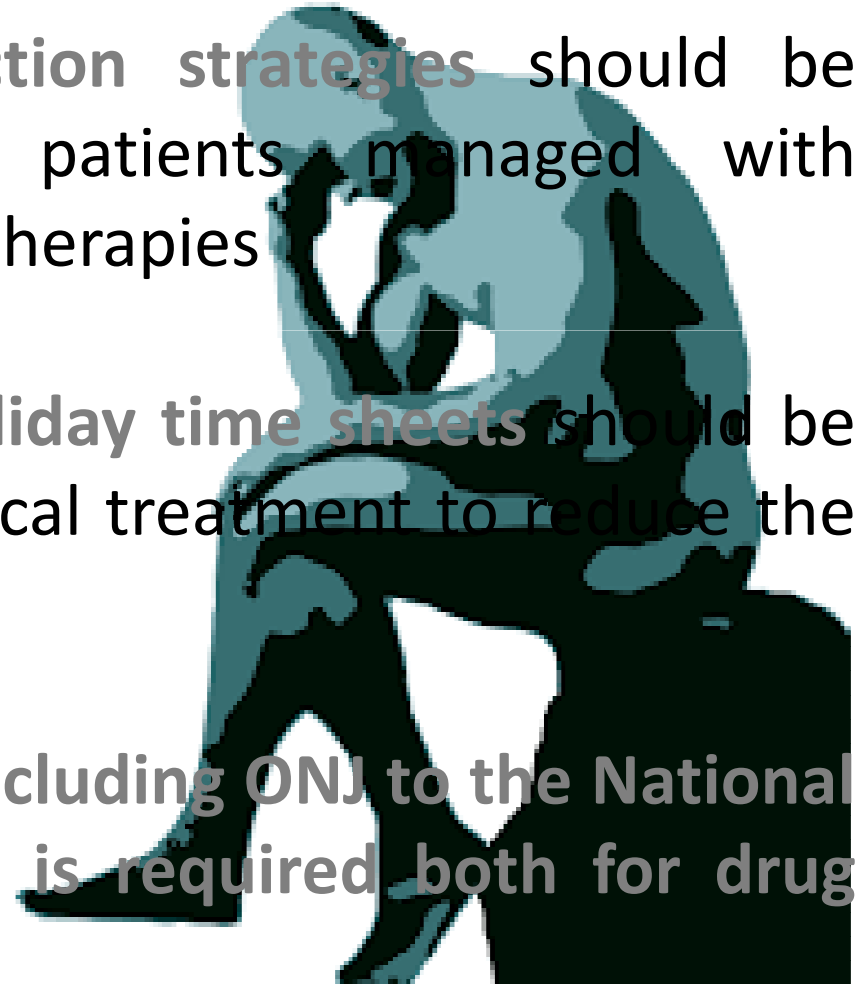
## New drugs: Tyrosine Kinase Inhibitors and other new drugs: What is their role in MRONJ?

---

Prevention and risk reduction strategies should be implemented for cancer patients managed with antiangiogenic and targeted therapies

Medication-specific drug-holiday time sheets should be applied before any oral surgical treatment to reduce the risk of ONJ occurrence

Reporting oral side effects including ONJ to the National Safety Surveillance Systems is required both for drug prescribers and dentists.







## Drug holiday: temporary interruption of a given medication

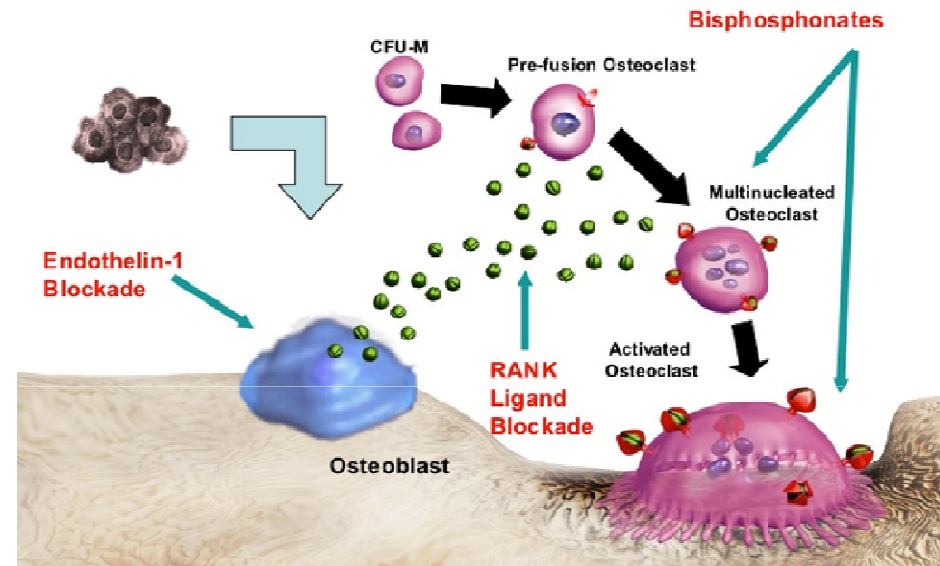
- It refers to the deliberate interruption of pharmacotherapy for a **defined period** and **for a specific clinical purpose**:
  1. for the assessment of efficacy and tolerability of a drug therapy.
  2. **for a therapeutic benefit such as:**
    - a. **alleviating adverse effects.**
    - b. Prevent impaired wound healing after surgery
      - Risk reduction strategies






## TRONEN-CONTAINING BISPHOSPHONATES BPs)

- Solid tumors
- Multiple myeloma
- Osteoporosis
- Rheumatoid arthritis



- Avid mineral binding  **SKELETAL RETENTION**
- Very short half-life in plasma
- *Embedded in bone, inactive, with long-term release*
- *Unpredictable duration of the effect after discontinuation*



## ITROGEN-CONTAINING BISPHOSPHONATES (NBPs)

- “bisphosphonates are deposited in bone for at least ten years, and when bone containing bisphosphonate is resorbed, the NBP recirculates locally and systemically and is able to bind again to bone surfaces”.
- “Bone resorption continues to be inhibited over time, and the antiresorptive effect persists after the drug has been stopped”.

Ro C, et al. Bisphosphonate drug holiday: choosing appropriate candidates. Curr Osteoporos Rep. 2013 Mar; 11(1): 45–51.



## • NITROGEN-CONTAINING BISPHOSPHONATES (NBP<sub>s</sub>)

### OSTEOPOROSIS and drug holiday

1. *for the assessment of efficacy and tolerability of a drug therapy.*

### Position of Prescribers

**As RCT evidence is not yet available on who may qualify for a drug holiday**, there is considerable controversy regarding the selection of candidates for the drug holiday and monitoring during a drug holiday, both of which **should be based on individual assessments of risk and benefit.**

Lee Sh, et al. Position Statement: Drug Holiday in Osteoporosis Treatment with Bisphosphonates in South Korea. J Bone Metab, 2015 Nov;22(4):167-74.



## NITROGEN-CONTAINING BISPHOSPHONATES (NBPs)

### OSTEOPOROSIS and drug holiday

1. *for the assessment of efficacy and tolerability of a drug therapy.*

### Position of Prescribers

- For patients at low risk for fracture who had been on:
  - an oral bisphosphonate for 5 years
  - an intravenous bisphosphonate for 3 years (Zol)
- Evidence is too limited to suggest a drug holiday after ibandronate use.

Adler RA et al. Report of a Task Force of the **American Society for Bone and Mineral Research**. J Bone Miner Res. (2016)

Anagnostis P, et al. **Drug holidays** from bisphosphonates and **denosumab** in **postmenopausal osteoporosis**: EMAS position statement. Maturitas. 2017 Jul;101:23-30 30 (European Menopause and Andropause Society)



## NITROGEN-CONTAINING BISPHOSPHONATES (NBPs)

### OSTEOPOROSIS and drug holiday in established MRONJ

1. *for a therapeutic benefit such as:*
  - a. *alleviating adverse effects.*

#### Position of Prescribers

#### REVIEW

JBMR®

#### Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research

Robert A Adler,<sup>1\*</sup> Ghada El-Hajj Fuleihan,<sup>2\*</sup> Douglas C Bauer,<sup>3</sup> Pauline M Camacho,<sup>4</sup> Bart L Clarke,<sup>5</sup> Gregory A Clines,<sup>6</sup> Juliet E Compston,<sup>7</sup> Matthew T Drake,<sup>5</sup> Beatrice J Edwards,<sup>8</sup> Murray J Favus,<sup>9</sup> Susan L Greenspan,<sup>10</sup> Ross McKinney Jr,<sup>11</sup> Robert J Pignolo,<sup>12</sup> and Deborah E Sellmeyer<sup>13</sup>

“When **ONJ** or an Atypical femoral fracture FF occurs in a patient on chronic **BPs** for osteoporosis, **discontinuation of the BP is recommended**”.



## NITROGEN-CONTAINING BISPHOSPHONATES (NBPs)

### Drug holiday to prevent MRONJ

1. *for a therapeutic benefit such as:*
  - a. *alleviating adverse effects.*
  - b. *Prevent impaired wound healing after surgery*
    - *Risk reduction strategies*

### Position of Specialists who manage MRONJ

**American Association of Oral and  
Maxillofacial Surgeons Position Paper on  
Medication-Related Osteonecrosis of the  
Jaw—2014 Update**

Salvatore L. Ruggiero, DMD, MD, \*Thomas B. Dodson, DMD, MPH, †  
John Fantasia, DDS, ‡Reginald Goodday, DDS, MSc, §Tara Agbaloo, DDS, MD, PhD, ||  
Bhoomi Mebrotra, MD, ¶ and Felice O’Ryan, DDS\*

### *Expert Opinion!*

**Osteoporotic patients:** a theoretical benefit may still apply for those patients with extended exposure histories (>4 yr)... before an invasive dental procedure.

**Cancer patients:** if ONJ develops, the oncologist may consider discontinuing antiresorptive therapy until soft tissue closure has occurred, depending on disease status.



## NITROGEN-CONTAINING BISPHOSPHONATES (NBPs)

### Drug holiday to prevent MRONJ

1. *for a therapeutic benefit such as:*
  - a. *Prevent impaired wound healing after surgery*
    - *Risk reduction strategies*

### Position of Specialists who manage MRONJ

#### *Expert Opinion!*



REVIEW

2015

JBMR®

#### **Diagnosis and Management of Osteonecrosis of the Jaw: A Systematic Review and International Consensus**

Aliya A Khan, Archie Morrison, David A Hanley, Dieter Felsenberg, Laurie K McCauley, Felice O'Ryan, Ian R Reid, Salvatore L Ruggiero, Akira Taguchi, Sotirios Tetradis, Nelson B Watts, Maria Luisa Brandi, Edmund Peters, Teresa Guise, Richard Eastell, Angela M Cheung, Suzanne N Morin, Basel Masri, Cyrus Cooper, Sarah L Morgan, Barbara Obermayer-Pietsch, Bente L Langdahl, Rana Al Dabagh, K. Shawn Davison, David L Kendler, George K Sándor, Robert G Josse, Mohit Bhandari, Mohamed El Rabbany, Dominique D Pierroz, Riad Sulimani, Deborah P Saunders, Jacques P Brown, and Juliet Compston, on behalf of the International Task Force on Osteonecrosis of the Jaw

Clinical judgment is always essential...it may be advisable to stop antiresorptive therapy before surgery if it is possible to do so without adverse consequences for bone health. In such circumstances the Task Force **recommends stopping antiresorptive therapy.**





## NITROGEN-CONTAINING BISPHOSPHONATES (NBPs)

Drug holiday in established MRONJ

### Position of Specialists who manage MRONJ

How important is stopping bisphosphonates once BRONJ is present in view of the long “half-life” of these drugs?



**Unknown!**

Interventions for treating bisphosphonate-related  
osteonecrosis of the jaw (BRONJ) (Review)

Rollason V, Laverrière A, MacDonald LCI, Walsh T, Tramèr MR, Vogt-Ferrier NB

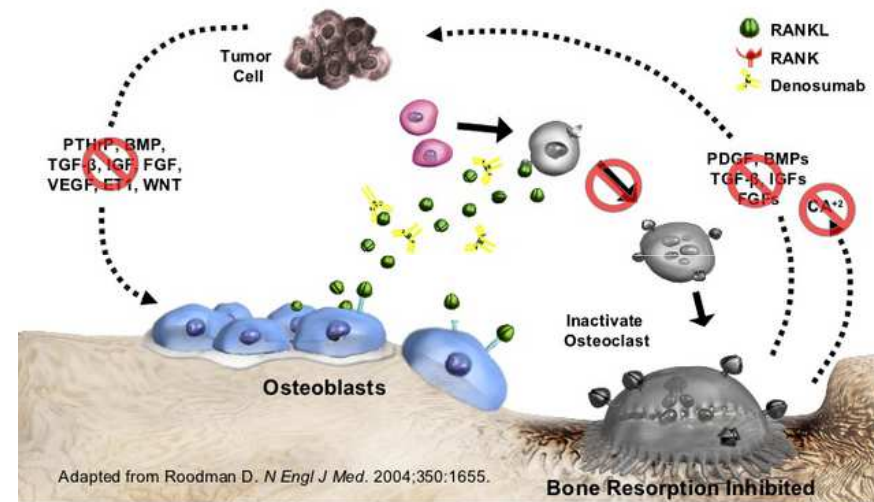
Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Review) Copyright © 2016 **The Cochrane Collaboration**. Published by John Wiley & Sons, Ltd.



## DENOSUMAB

- Solid tumors (XGEVA)
- Osteoporosis (PROLIA)

### Denosumab Binds RANK Ligand and Inhibits Osteoclast Formation, Function and Survival



- Bone tropism ➡ Absent skeletal retention
- Short half-life in plasma
- *Back to normal cell function after discontinuation*



# DENOSUMAB

## OSTEOPOROSIS and drug holiday

### Position of Prescribers

- Evidence is too limited to suggest a drug holiday after denosumab use.

Adler RA et al. **Report of a Task Force of the American Society for Bone and Mineral Research.** J Bone Miner Res. (2016)

Anagnostis P, et al. **Drug holidays** from bisphosphonates and **denosumab** in **postmenopausal osteoporosis: EMAS position statement.** Maturitas. 2017 Jul;101:23-30 (European Menopause and Andropause Society)



# DENOSUMAB

## OSTEOPOROSIS and drug holiday

### Position of Prescribers

“Rebound in fracture risk make it clear that a **holiday from denosumab therapy is not justified** in patients with osteoporosis”



Osteoporos Int (2016) 27:1677–1682  
DOI 10.1007/s00198-016-3553-3

EDITORIAL

### Cancel the denosumab holiday

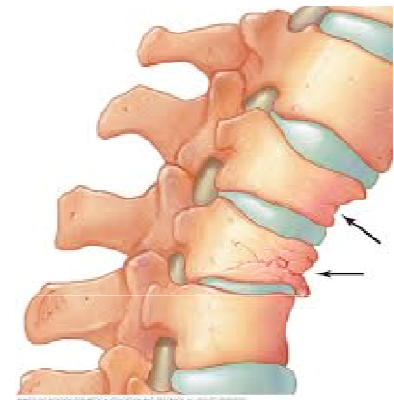
M. R. McClung<sup>1</sup>



## DENOSUMAB

### OSTEOPOROSIS and drug holiday

#### Position of Prescribers



#### Occurrence of severe vertebral fractures after discontinuation

- Aubry-Rozier B, et al. Severe spontaneous vertebral fractures after denosumab discontinuation: three case reports. *Osteoporos Int*, **2015**.
- Popp AW, et al. Rebound-associated vertebral fractures after discontinuation of denosumab—from clinic and biomechanics. *Osteoporos Int*, **2015**.
- Anastasilakis AD, Makras P. Multiple clinical vertebral fractures following denosumab discontinuation. *Osteoporos Int*, **2015**.



# DENOSUMAB

## OSTEOPOROSIS and drug holiday

### Position of Prescribers

CLINICAL TRIALS

---

JBMR

#### **Discontinuation of Denosumab and Associated Fracture Incidence: Analysis From the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) Trial**

Jacques P Brown,<sup>1</sup> Christian Roux,<sup>2</sup> Ove Törring,<sup>3</sup> Pei-Ran Ho,<sup>4</sup> Jens-Erik Beck Jensen,<sup>5</sup> Nigel Gilchrist,<sup>6</sup> Christopher Recknor,<sup>7</sup> Matt Austin,<sup>4</sup> Andrea Wang,<sup>4</sup> Andreas Grauer,<sup>4</sup> and Rachel B Wagman<sup>4</sup>

“there does not appear to be an excess in fracture risk after treatment cessation with denosumab compared with placebo during the off-treatment period for up to 24 months”.



## DENOSUMAB

### Drug holiday in established MRONJ



#### **American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw—2014 Update**

*Salvatore L. Ruggiero, DMD, MD, \*Thomas B. Dodson, DMD, MPH, †  
John Fantasia, DDS, ‡Reginald Goodday, DDS, MSc, §Tara Agbaloo, DDS, MD, PhD, ||  
Bboomi Mebrotra, MD, ¶ and Felice O'Ryan, DDS\**

### **Position of Specialists involved in MRONJ treatment**

“the antiresorptive effects of denosumab should be mostly dissipated within 6 months of stopping the drug...However, there are **no studies to support or refute the strategy of stopping denosumab therapy in the prevention or treatment of MRONJ.**

# Drug holiday: Should the antiresorptive treatment be paused or stopped when MRONJ is diagnosed?

## What do we know today?

### Recent insights:

### Animal studies

de Molon RS et al. J Bone Miner Res. 2015 Sep;30(9):1627

“RANKL inhibitor, but not a bisphosphonate, reverses features of osteonecrosis in mice”



M. Zandi et al. J Cranio-Maxillofac Surg, 2015; 43: 1823-1

“Zoledronate discontinuation significantly decreased the incidence and severity of BRONJ in rats”





# Drug holiday: Should the antiresorptive treatment be paused or stopped when MRONJ is diagnosed?

## What do we know today?

### Recent insights:

### Clinical studies

- Regardless of treatment modality and MRONJ stage at presentation, discontinuing the agent at the beginning of treatment is associated with faster resolution of MRONJ symptoms

Hinson A, et al.. J Oral Maxillofac Surg, 2015; 73: 53-56

- A correlation between timely discontinuation of antiresorptives and MRONJ healing has been showed for the first time.

Martins AS, et al. J Cranio Maxillofac Surg 2017. In press

Drug holiday: Should the antiresorptive treatment be paused or stopped when MRONJ is diagnosed?  
What do we know today?

## Conclusions

- Data on DRUG HOLIDAY are elusive
- Temporary suspension of NBP is unlikely to improve the natural course of MRONJ in the short-term, due to their skeletal retention.
- Temporary suspension of Denosumab may improve the natural course of MRONJ but pose the patient at high risk of SRE/fractures.
- *DRUG HOLIDAY endorsed by the prescriber's final decision, based on the individual risk/benefit ratio*

Drug holiday: Should the antiresorptive treatment be paused or stopped when MRONJ is diagnosed?  
What do we know today?

---

...why more and more MRONJ patients have their antiresorptive therapy withdrawn by the prescribers before the diagnosis has been achieved?

...I have no answer yet



Prejudice is a great  
time-saver. You can form  
opinions without having to  
get the facts. Prejudice not  
being founded on reason  
cannot be removed by  
argument.

Samuel Johnson

**THANK'S FOR YOUR ATTENTION**

[alberto.bedogni@unipd.it](mailto:alberto.bedogni@unipd.it)

