Traitements de l'ostéoporose chez l'insuffisant rénal chronique

Dr. Luc Radermacher

Plan

- Ostéoporose post ménopausique.
- Reins et Os.
- Reins et médicaments.
- Os et médicaments.
- Reins, Os et médicaments.

Clinical Practice

Postmenopausal Osteoporosis

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Case Vignette

- A 73-year-old asymptomatic white woman with a history of a Colles fracture of the left radius 10 years earlier presents for evaluation.
- Dual-energy x-ray absorptiometry reveals a bone mineral density (BMD) T score of −2.8 in the lumbar spine and −2.5 in the total hip.
- How should this case be managed?

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Guidelines from Professional Organizations for the Treatment of Osteoporosis.

Table 1. Guidelines from Professional Organizations for the Treatment of Osteoporosis.*

Organization	Whom to Treat	Nonpharmacologic Approaches	Pharmacologic Approaches
National Osteoporosis Foundation (United States)[7]	Women with a previous hip or vertebral fracture, a T score of –2.5 or less at the hip, lumbar spine, or femoral neck, or a T score between –1.0 and –2.5 and a 10-yr probability of hip fracture >3% or of major osteoporotic fracture >20%	Total daily intake (diet plus supplements) of 1200 mg of calcium and 800–1000 IU of vitamin D, regular weight-bearing exercise, fall-prevention strategies, muscle strengthening, and avoidance of smoking and excess alcohol intake	Antiresorptive or anabolic agents, with reassessment after 2–5 yr
National Osteoporosis Guideline Group (United Kingdom)[8]	Women with previous fragility fracture; if risk factors are present, use FRAX with or without BMD measurement; treat if FRAX score exceeds age-specific criteria	Maintenance of mobility and correction of nutritional deficiencies, particularly of calcium, vitamin D, and protein†	First-line therapy: generic alendronate; second-line therapies: ibandronate, risedronate, zoledronic acid, denosumab, and raloxifene; teriparatide should be reserved for patients at very high risk for fractures, especially vertebral fractures
Scientific Advisory Council, Osteoporosis Canada[9]	Women with previous hip or spine fracture or multiple fractures or a T score of –2.5 or less at the spine or total hip; assess risk with the 2010 tool of the Canadian Association of Radiologists and Osteoporosis Canada; treat if 10-year risk of major osteoporotic fractures is >20%	Resistance exercise, core-stability training, and balance measures; total daily intake of 1200 mg of calcium and 400–1000 IU of vitamin D; aim for serum level of 25-hydroxyvitamin D of ≥30 ng/ml‡	First-line therapies: alendronate, risedronate, zoledronic acid, and denosumab for prevention of hip, nonvertebral, and vertebral fractures and raloxifene for prevention of vertebral fractures; estrogen for postmenopausal symptoms and prevention of fractures in patients at high risk

* BMD denotes bone mineral density, and FRAX Fracture Risk Assessment Tool.
† Adequate protein intake is essential for maintenance of bone mass.
‡ The preferred serum level of 25-hydroxyvitamin D is not firmly established, and other guidelines include levels of 20 ng per milliliter or more.

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Drugs Approved by the Food and Drug Administration for the Treatment and Prevention of Osteoporosis.

Table 2. Drugs Approved by the Food and Drug Administration for the Treatment and Prevention of Osteoporosis.*

Drug Class and Agent	Method and Frequency of Administration	Type of Fracture Risk Reduction	Side Effects	Approved Use for Osteoporosis
Bisphosphonates†				
Alendronate	Oral: 35–70 mg/wk	Vertebral, nonvertebral, hip	Common: esophagitis, musculoskeletal symptoms; rare: ONJ, atypical femur fractures	Treatment and prevention
Risedronate	Oral: 35 mg/wk or 150 mg/mo (in a single dose or in two 75-mg doses on consecutive days)	Vertebral, nonvertebral, hip	Common: esophagitis, musculoskeletal symptoms; rare: ONJ, atypical femur fractures	Treatment and prevention
Ibandronate	Oral: 150 mg/wk; intravenous: 3 mg every 3 mo	Vertebral	Common: first-dose (intravenous) reaction, esophagitis, musculoskeletal symptoms; rare: ONJ, atypical femur fractures	Treatment and prevention
Zoledronic acid	Intravenous: 5 mg/yr	Vertebral, nonvertebral, hip	Common: acute-phase response (most often after first dose),‡ musculoskeletal symptoms; rare: ONJ, atypical femur fractures	Treatment and prevention
Biologic: denosumab	Subcutaneous: 60 mg every 6 mo	Vertebral, nonvertebral, hip	Common: cellulitis or skin reactions; rare: ONJ, atypical femur fractures	Treatment
Anabolic: teriparatide	Subcutaneous: 20 μg/day	Vertebral, nonvertebral	Common: nausea, leg cramps; rare: hypercalcemia, osteosarcoma§	Treatment
Calcitonin¶	Intranasal: 200 IU/day	Vertebral	Nasal congestion	Treatment
SERM: raloxifene	Oral: 60 mg/day	Vertebral	Venous thromboembolism, hot flashes, leg cramps, nausea	Treatment and prevention
Estrogens‖			Venous thromboembolism, increased risk of breast cancer and cardiovascular disease	Prevention
Conjugated equine estrogen	Oral: 0.15–1.25 mg/day	Vertebral, nonvertebral, hip		
17β-estradiol	Oral: 0.025–0.10 mg/day; transdermal: 2 times/wk	No data from randomized trials		
Ultra-low-dose 17β-estradiol	Oral: 0.014 mg/day	No data		

* ONJ denotes osteonecrosis of the jaw, and SERM selective estrogen-receptor modulator.
† Oral bisphosphonates are also approved in smaller doses for daily use to prevent osteoporosis, but currently those doses are seldom prescribed.
‡ Flulike symptoms including fever, arthralgia, or headache may occur after the first administration in up to one third of patients. Symptoms do not last more than 3 days after infusion.[8]
§ There is a black box warning about a risk of osteosarcoma, which has been reported with long-term teriparatide administration in rodents, but only one case in humans has been conclusively related to teriparatide administration.
¶ Calcitonin is no longer approved for the treatment of osteoporosis in Europe.
‖ Tibolone, which has estrogenic action, is approved for the treatment of postmenopausal osteoporosis in Europe.

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Number of Patients Who Would Need to Be Treated for 3 Years with Bisphosphonates to Prevent One Fracture versus the Hypothetical Number Associated with an Increase of One Atypical Femur Fracture.

Table 3. Number of Patients Who Would Need to Be Treated for 3 Years with Bisphosphonates to Prevent One Fracture versus the Hypothetical Number Associated with an Increase of One Atypical Femur Fracture.*

Variable	No. Needed to Treat (3 yr)†	No. of Events Prevented per 1000 Patients Treated (3 yr)
Type of fracture		
Any nonvertebral, including hip	35	29
Hip	90	11
Vertebral fracture (morphometric)	14	71
Any fracture		100
	No. Needed to Harm (3 yr)‡	**No. of Atypical Femur Fractures Associated with Treating 1000 Women for 3 Yr**
Hypothetical relative risk of atypical femur fracture		
1.2	43,300	0.02
1.7	12,400	0.08
2.4	6,200	0.16
11.8	800	1.25

* Adapted from Black et al.[47]

† The estimated numbers of patients who would need to be treated with bisphosphonates in order to prevent one fracture were derived from fracture rates, in the active-treatment group as compared with the placebo group, in the Fracture Intervention Trial (for patients with either a vertebral fracture or a BMD T score of less than −2.5 at the hip) for alendronate[28] or in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial for zoledronic acid.[35] The number of events prevented per 1000 patients treated for 3 years refers to fractures that would be prevented by bisphosphonate treatment.

‡ The calculation of the number needed to harm requires the incidence rate among untreated women with osteoporosis as well as the relative risk associated with treatment. The incidence estimate for atypical femur fracture among untreated women with osteoporosis was estimated as 11.5 per 100,000 women followed for 3 years. This was estimated as follows: in the placebo groups from two large randomized trials,[28,35] the 3-year incidence of hip fractures was approximately 2.5%, which would yield an expected number of 25 hip fractures in 1000 untreated women with osteoporosis followed for 3 years. Then, applying a ratio of 4.6 atypical femur fractures per 1000 hip fractures to the 25 hip fractures yields an expected number of 0.115 atypical fractures over a period of 3 years (11.5 per 100,000 women). The ratio of 4.6 is derived from Schilcher et al.[44] (59 atypical femur fractures among 12,777 femur fractures) and is consistent with another population-based study[46] (22 atypical femur fractures among 5419 femur fractures). We assume four possible relative risks taken from a meta-analysis of bisphosphonates and atypical femur fracture.[45] These include the relative-risk estimate from the full set of studies in the meta-analysis and its lower and upper confidence bounds (relative risk, 1.7; 95% confidence interval, 1.2 to 2.4). In addition, from that same meta-analysis, we include the relative risk (11.8) calculated from the two studies that assessed radiographs of atypical femur fractures according to 2013 American Society for Bone and Mineral Research criteria.[24,45]

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Summary and Recommendations

- The woman in the vignette has a low BMD and a fracture history, which are factors that are consistent with osteoporosis.
- We would recommend increased physical activity, avoidance of smoking and excess alcohol intake, a total calcium intake of 1000 to 1500 mg per day and a total vitamin D intake of 600 to 800 IU per day, and the use of an antiresorptive agent.
- We would generally recommend a bisphosphonate as first-line therapy if there are no contraindications; we would discuss with the patient the rare potential risks of atypical femur fracture or osteonecrosis of the jaw but also the much greater anticipated benefits in terms of overall reduction in the risk of fractures.
- Depending on the results of follow-up BMD measurement, we would discuss the possibility of temporarily discontinuing the bisphosphonate after 5 years of treatment.

Actualisation 2012 des recommandations françaises du traitement médicamenteux de l'ostéoporose post-ménopausique.

Briot K, Cortet B et Coll.

Joint Bone Spine 2012 May;79(3):304-13

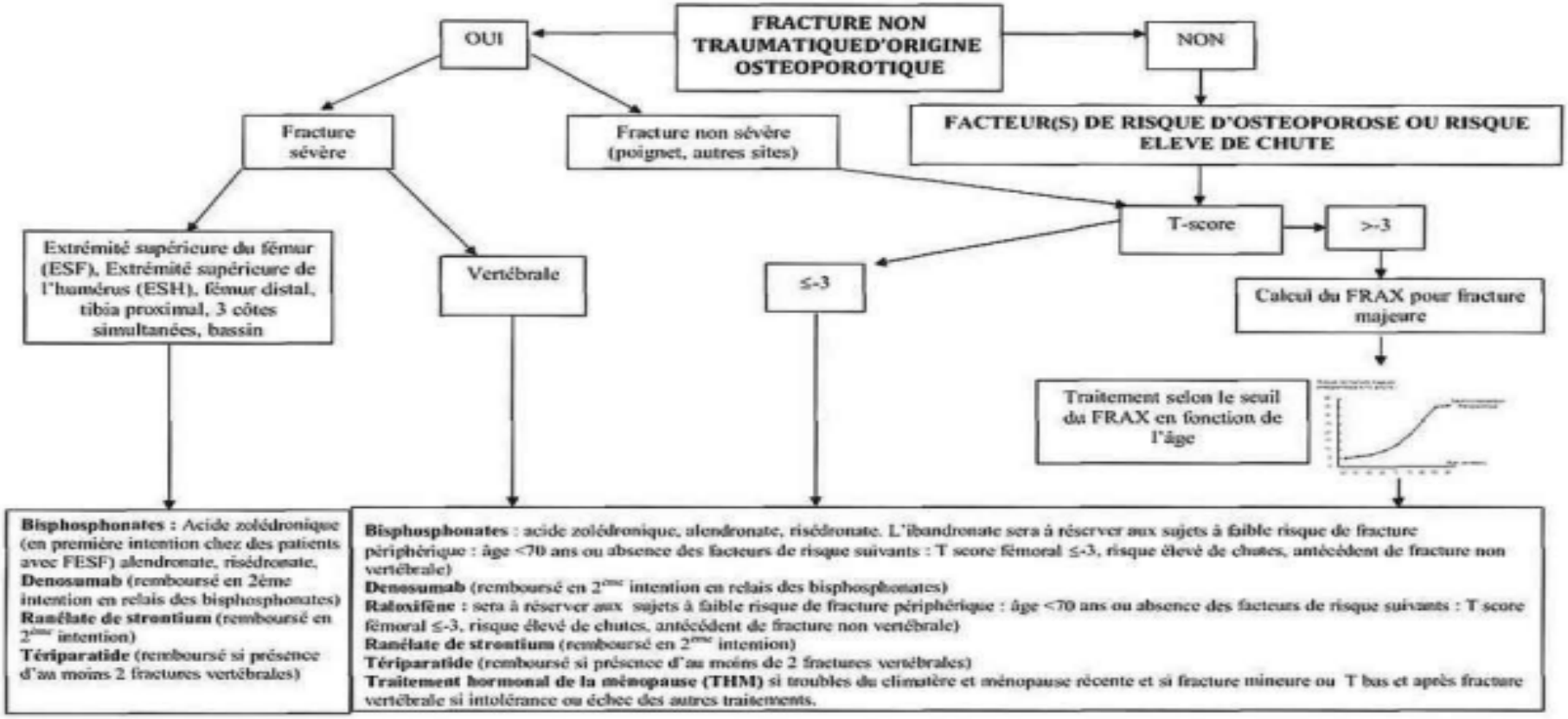
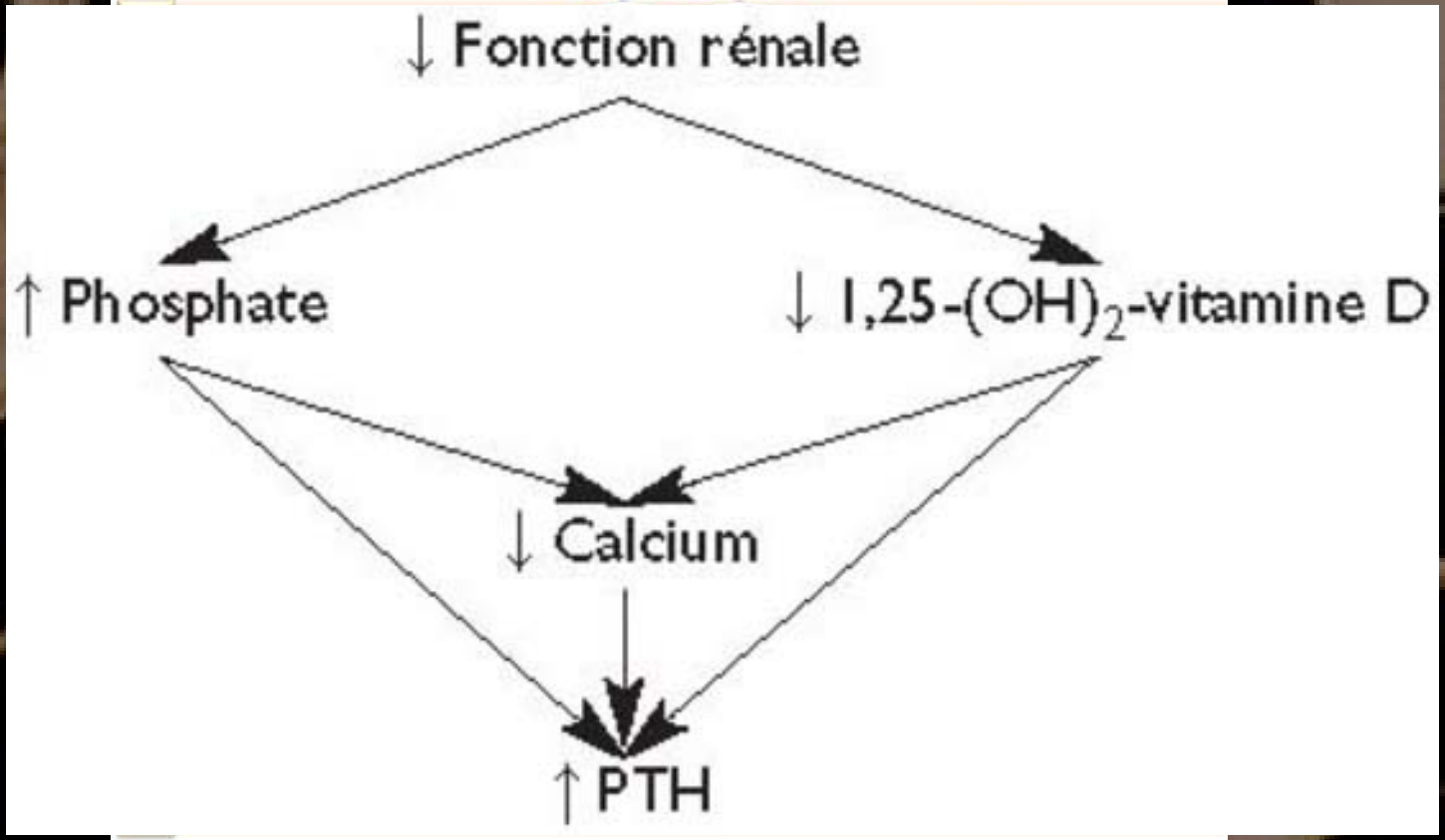


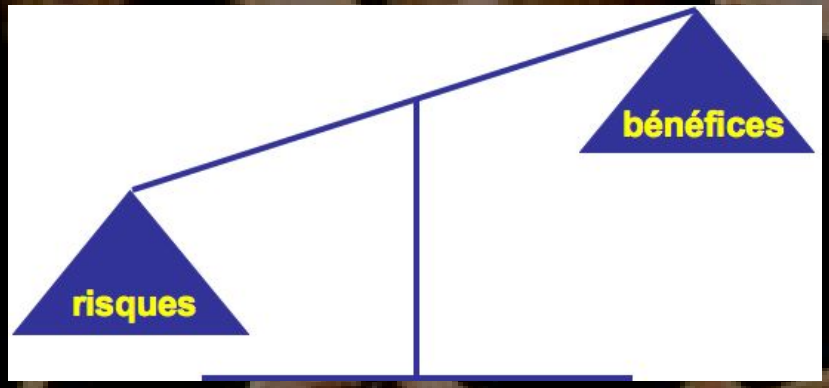
Fig. 2. Stratégies thérapeutiques dans l'ostéoporose post-ménopausique.

Reins et os :
L'ostéodystrophie rénale



→ **Ostéopénie + Calcifications métastatiques**

Reins et médicaments : Particularités de l'IRC



- Modifications de la pharmacocinétique : Excrétion rénale réduite avec T1/2 allongé. → Risque d'accumulation / intoxication.
- Toxicité rénale.
- Sensibilité accrue aux effets secondaires (Na, K, Ca↓, Coag., Hémato, Cardio, Neuro, Rhumato, Immuno, Gastro, Dermato, …).
- Comorbidité → Polymédication → Interactions médic.

→ Population particulière à hauts risques (stades ≥ 3)

→ Nécessité d'ajustement des doses et/ou respect de C.I. spécifiques qui concerne 50% des médicaments.

Os et médicaments : Traitements de l'ostéoporose

- Ca et Vit D
- <u>Modulateurs du remodelage osseux :</u>
  - Oestrogènes, oestroprogestatifs et Tibolone : ne sont plus recommandés.
  - Raloxifène, Basedoxifène.
  - Bisphosphonates
  - Strontium
  - Dénosumab
  - Tériparatide
  - Calcitonine : n'est plus recommandé.

Os et médicaments : Calcium et vit D

- **Calcium :**
  - Indications : Toutes ostéoporoses. 1lère intention.
  - Mode d'action : Matière première de la matrice os.
  - Doses : 0,5 – 1,5 g Ca++ /24h, selon calcémie.
  - ES : Constipation, lithiases rénales, hyperCa.

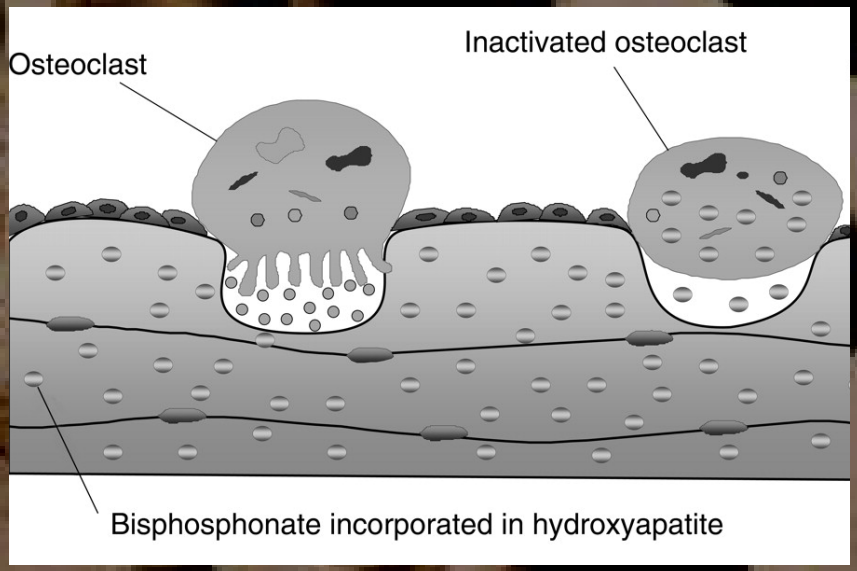
- **Vitamine D :**
  - Indication : Toutes ostéoporose. 1lère intention.
  - Mode d'action : ↑ Abs. digestive et rénale du Ca.
  - Doses : 200 – 50 000 U.I./24h, selon taux vitD et Ca
  - ES : Diarrhée, lithiases rénales, hypercalcémie.

Os et médicaments : Raloxifène - Basedoxifène

- **Indication :** Ostéoporose post-ménopausique, 2ième intention
- **Mode d'action :** Agonistes des œstrogènes sur récepteurs osseux. Antagonistes sur récepteurs mammaires et endométriaux.
- **Doses :**
  - Raloxifène (Evista°) : 60 mg, 1x/24h.
  - Basédoxifène (Conbriza°) : 20 mg, 1x/24h.
- **ES :** Bouffées de chaleurs, crampes, TVP/EP.
- **CI :** TVP/EP, Néo gynéco.
- **PK :** Elimination extrarénale (hépatique).

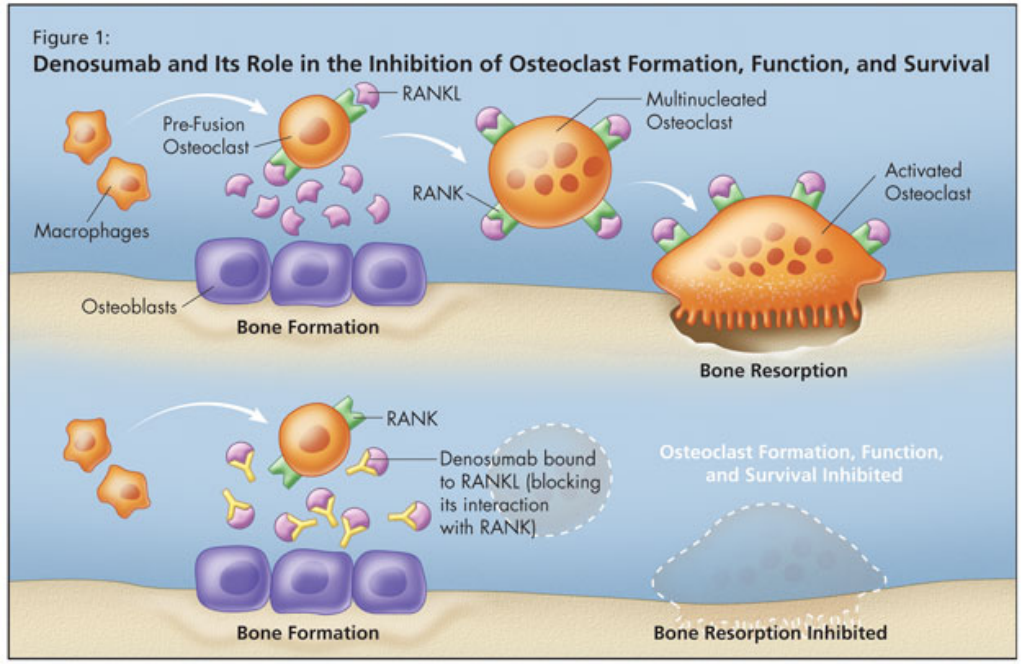
Os et médicaments : Bisphosphonates

- **Indications :** Toutes ostéoporoses (T-score < -2,5). 2ième intention. Maximum 5 ans.
- **Mode d'action :** se fixe de manière durable à la matrice osseuse et inhibe l'activité des ostéoclastes matures.
- **Dosages (PO) :**
  - Alendronate (Fosamax°) : 70 mg / semaine.
  - Risédronate (Actonel°) : 35 mg / semaine.
  - Ibandronate (Bonviva°) : 150 mg oral 1x/mois ou 3mg IV / 3 mois
  - Zolédronate (Aclasta°) : 5 mg IV, 1x/an.
- **ES :** (même après des mois) : Symptômes G.O., Hypocalcémie, Ostéonécrose (1/10000), Néphrotoxicité (IRA-IRC).
- **CI :** Hypocalcémie sévère, IRC stade 4.
- **PK :** Elimination rénale



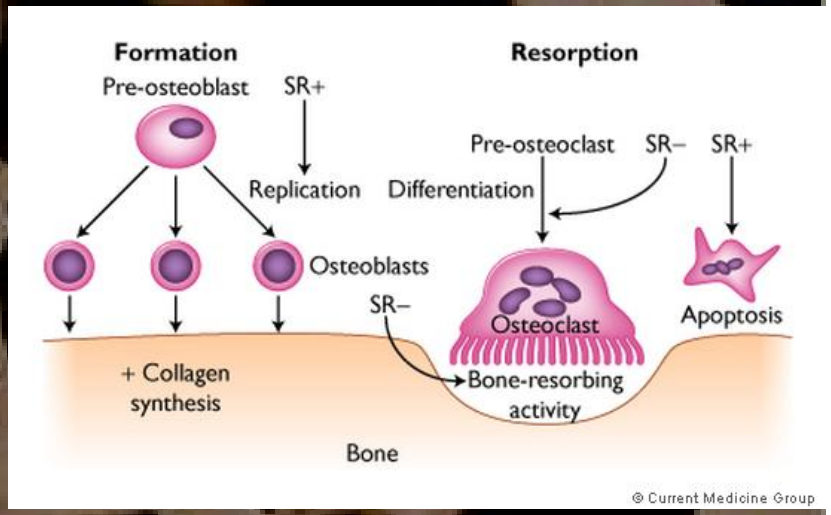
Os et médicaments : Denosumab (Prolia°)

- **Indications :** Toutes ostéoporoses. 2ième intention.
- **Mode d'action :** Inhibiteur du Rank ligand → inhibition de la maturation des ostéoclastes.
- **Dosage :** 60mg SC 1x/6 mois
- **ES :** Infections, Cataracte, Hypocalcémie, Ostéonécrose (1/10000).
- **CI :** Hypocalcémie sévère.
- **PK :** Elimination extrarénale (anticorps monoclonal)



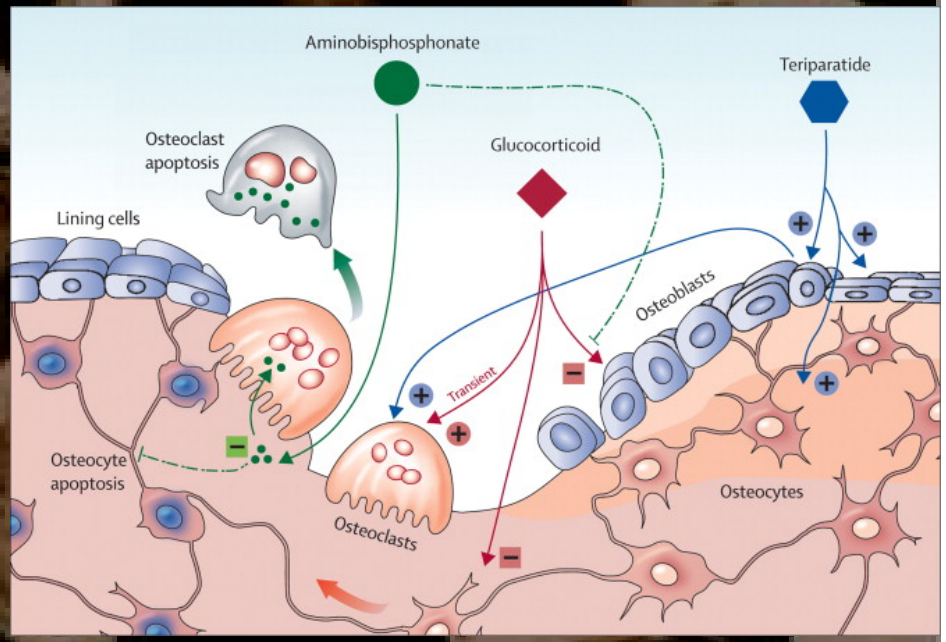
Os et médicaments : Ranelate de Strontium (Protelos°)

- **Indications :** Toutes ostéoporoses. 2ième intention.
- **Mode d'action :** Stimule les ostéoblastes et inhibe les ostéoclastes
- **Dosage :** 2g, 1x/24h
- **ES :** TPP/EP, Infarctus, ostéomalacie.
- **CI :** Maladies thrombo-emboliques, IRC stade 4.
- **PK :** Elimination rénale > 60%



Os et médicaments : Tériparatide (Forstéo°)

- **Indications :** Toutes ostéoporoses. 3ième intention.
- **Mode d'action = PTH :** Stimulation de l'activité ostéoblastique.
- **Dosage :** SC 20µg, 1x/24h (Max 2 ans)
- **ES :** Hypercalcémie, ostéosarcome.
- **CI :** Maladies thrombo-emboliques.
- **PK :** Elimination rénale et hépatique (50/50 %)



Reins, Os et médicaments : Ostéoporose et IRC

- IRC (dès stade 3) + Ostéoporose = Ostéodystrophie rénale, jusqu'à preuve de contraire.

- **<u>Deux types de traitements :</u>**
  → Traitement de l'ostéoporose simple (sans troubles phosphocalciques)
  → Traitement de l'ostéodystrophie rénale ± complètes, avec HypoCa, HyperPO4 et HyperPTH

- Modification PK de 50% des médicaments dès stade 3. !!! C.I. spécifiques !!!

Reins, Os et médicaments :

Traitement ostéoporose simple

- 1° **Ca + VitD**

- 2° **Raloxifène (Evista°) Bazédoxifène (Conbriza°)** pour ostéoporose lombaire simples, post ménopausique.

  3° **Denosumab (Prolia°)**

  Critères de remboursements INAMI :
  La spécialité fait l'objet d'un remboursement s'il est démontré qu'elle est administrée pour le traitement de l'ostéoporose chez une **femme ménopausée** qui répond à au moins une des conditions suivantes:
  - soit un antécédent de fracture vertébrale définie par une réduction d'au moins 25% et d'au moins 4 mm en valeur absolue, de la hauteur du bord antérieur ou postérieur ou du centre de la vertèbre considérée, démontré par un examen radiologique;
  - soit un **T-score**, calculé par rapport à une population de référence féminine, **< - 2.5** au niveau de la colonne lombaire (L1-L4 ou L2-L4) ou de la hanche (zone totale ou zone propre du col) lors d'un examen réalisé par la technique de l'absorptiométrie radiologique à double énergie = Densitométrie osseuse.

- **Bisphosphonates, Strontium : C.I. si IRC stade 3 - 4**

Reins, Os et médicaments :
Traitements de l'ostéodystrophie rénale

- 1°: **Ca + VitD.**

- 2°: **Traitements de l'hyperphosphorémie :**
  - Conseils diététiques.
  - Sels de Ca (Phoslo°) ou Mg (Renepho°) aux repas.
  - Sevelamer (Renvela°), Lanthanum (Fosrenol°), oxyhydroxide sucroferrique (Velphoro°) (remb. Bf).

- 3°: **Traitements de l'hypocalcémie :**
  - ↑ Sels de Ca en dehors des repas.
  - Vitamine D activée (Rocaltrol°).

- 4° : **Traitements de l'hyperparathyroïdie :**
  - Sels de Ca + VitD activée si pas d'hyperPO4
  - Sels de Ca + Cinacalcet (Mimpara°) ou Etelcalcetide (Parsabiv°).
  - PTX

- 5° : **Denosumab, Teriparatide** selon remboursements INAMI …

Merci de votre attention