TERAPIAS SECUENCIALES Y TERAPIAS COMBINADAS DE LA OSTEOPOROSIS

XXX CONGRESO SOCIEDAD CHILENA DE OSTEOLOGÍA Y METABOLISMO MINERAL

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DISCLOSURE

SIN CONFLICTOS DE INTERES PARA ESTA PRESENTACION

TERAPIAS SECUENCIALES Y TERAPIAS COMBINADAS DE LA OSTEOPOROSIS

HOJA DE RUTA

- Farmacoterapia Osteoporosis 2023
- Estrategias Tratamiento Osteoporosis Pacientes Riesgo Fractura Muy Alto
- Terapias Combinadas y Terapias Secuenciales de la Osteoporosis

TRATAMIENTO OSTEOPOROSIS 2023

- Osteoporosis es una afección crónica que requiere manejo prolongado
- Beneficios esqueléticos terapias osteoporosis ↓ con discontinuación tratamiento ⇒ es importante desarrollar una estrategia para tratamiento prolongado
- Fármacos actuales terapia osteoporosis: diferentes mecanismos de acción, diferente potencia o efectividad, diferentes contraindicaciones
- Secuencia administración farmacoterapia osteoporosis puede tener importantes ramificaciones clínicas

TERAPIAS OSTEOPOROSIS APROBADAS 2022 FDA (*)

	Clase	Forma/Dosis	Aprobación FDA
Alendronato	Bifosfonato	oral semanal	Mujer y Hombre
Ibandronato	Bifosfonato	oral mensual	Mujer
Risedronato (#)	Bifosfonato	oral semanal	Mujer y Hombre
Ac. Zoledrónico	Bifosfonato	IV anual (o c/2 años)	Mujer y Hombre
Raloxifeno	SERM	oral diario	Mujer
Abaloparatide (#)	Análogo HPT	inyección sc diaria 2 años	Mujer
Teriparatide	Análogo HPT	inyección sc diaria 2 años	Mujer y Hombre
Denosumab	inhibidor RANKL	inyección sc c/ 6 meses	Mujer y Hombre
Romosozumab (#)	inhibidor Esclerostina	inyección sc mensual 12 meses	Mujer

(*) modif. S. Khandelwal, N. Lane Endocrinol Metab Clin NA 2022 (#) no disponible en Chile

Very High Risk Patients (AACE Criteria)

- Recent fracture or history of multiple fractures
- Fractures on approved osteoporosis medications or on medications known to cause skeletal harm
- Very low T-scores (< –3.0)
- High falling risk or history of injurious falls
- Very high fracture probability (FRAX >30% MOF, >4.5% hip fx)

Many of these patients are also at high imminent risk over the next 2 years

Camacho PM et al. Endocrine Practice 2020. AACE/ACE Guidelines 2020 Update.

F. Cosman, Conferencia Congreso ACR 2022

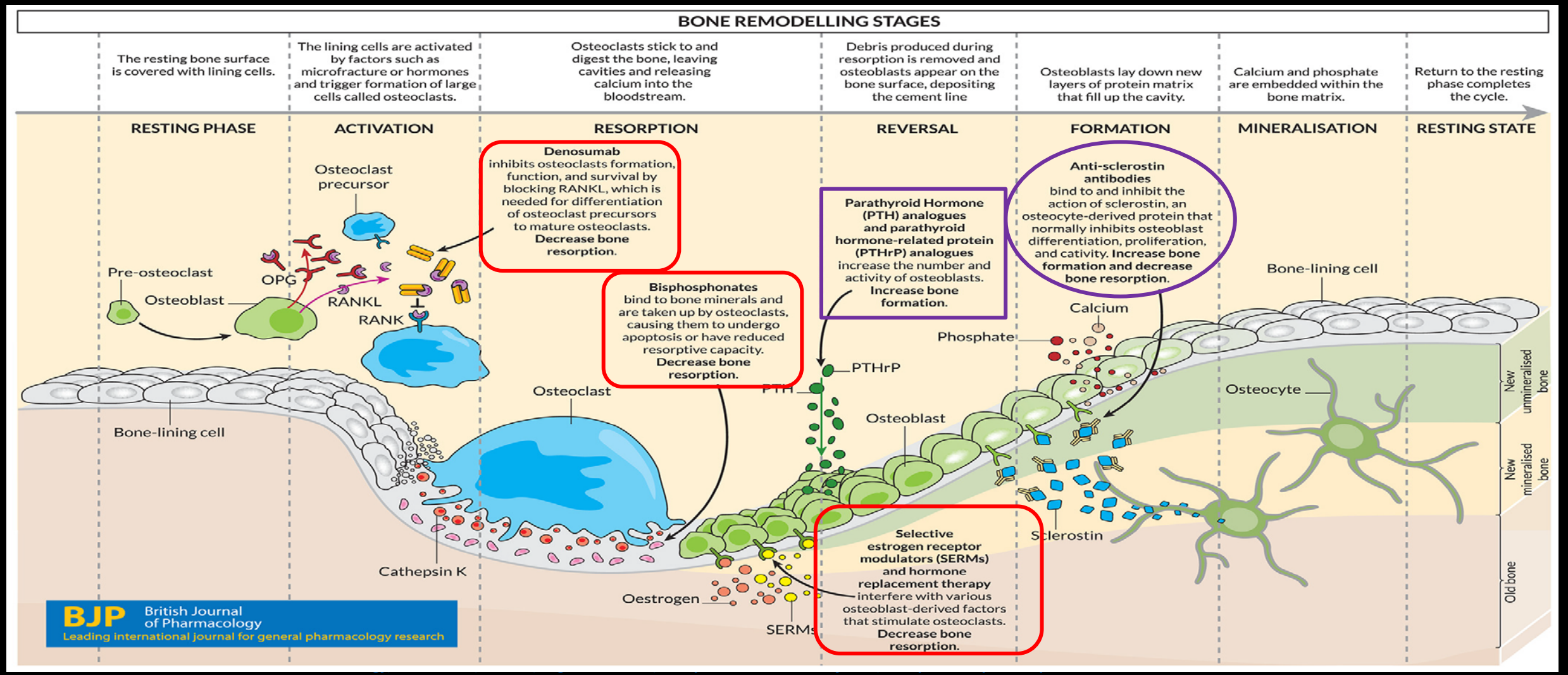
Treatment for Very High Risk Patients

- Treatment goals for very high risk women, especially at high imminent risk:
  - Reduce fracture risk rapidly and potently
  - Increase BMD rapidly and potently
- How do anabolic agents (teriparatide, abaloparatide and romosozumab) compare with antiresorptive agents toward these goals?
  - Speed of antifracture effect
  - Magnitude of antifracture effect
  - BMD Gain

Cosman F. Endo Practice 2020; 26:777-786

F. Cosman, Conferencia Congreso ACR 2022

Remodelación Osea y Efecto de diferentes tratamientos Osteoporosis (*)



(*) BL Langdahl, British J Pharmacol 2020

ELECCIÓN TERAPIA OSTEOPOROSIS DE ACUERDO AL NIVEL DE RIESGO

AACE & IOF sugieren categorización pacientes según Riesgo de Fractura: Bajo, Alto, o Muy Alto

AACE/ACE 2020 POSTMENOPAUSAL OSTEOPOROSIS TREATMENT ALGORITHM

Lumbar spine or femoral neck or total hip T-score of ≤ -2.5, a history of fragility fracture, or high FRAX® fracture probability*

Evaluate for causes of secondary osteoporosis

Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis

- Recommend pharmacologic therapy
- Education on lifestyle measures, fall prevention, benefits and risks of medications

High risk/no prior fractures**

- Alendronate, denosumab, risedronate, zoledronate***
- Alternate therapy: Ibandronate, raloxifene

Reassess yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate therapy

Resume therapy when a fracture occurs, BMD declines beyond LSC, BTM's rise to pretreatment values or patient meets initial treatment criteria

Progression of bone loss or recurrent fractures

- Assess compliance
- Re-evaluate for causes of secondary osteoporosis and factors leading to suboptimal response to therapy

- Switch to injectable antiresorptive if on oral agent
- Switch to abaloparatide, romosozumab, or teriparatide if on injectable antiresorptive or at very high risk of fracture
- Factors leading to suboptimal response

ABBREVIATIONS GUIDE

BMD – bone mineral density
LSC – least significant change
BTM – bone turnover marker

Very high risk/prior fractures**

- Abaloparatide, denosumab, romosozumab, teriparatide, zoledronate***
- Alternate therapy: Alendronate, risedronate

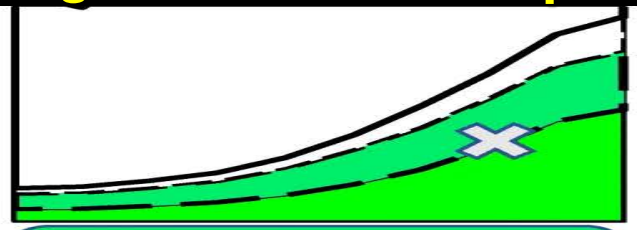
Reassess yearly for response to therapy and fracture risk

Denosumab	Romosozumab for 1 year	Abaloparatide or teriparatide for up to 2 years	Zoledronate
Continue therapy until the patient is no longer high risk and ensure transition with another antiresorptive agent.	Sequential therapy with oral or injectable antiresorptive agent	Sequential therapy with oral or injectable antiresorptive agent	• If stable, continue therapy for 6 years**** • If progression of bone loss or recurrent fractures, consider switching to abaloparatide, teriparatide or romosozumab

* 10-year major osteoporotic fracture risk ≥ 20% or hip fracture risk ≥ 3%. Non-US countries/regions may have different thresholds.
** Indicators of very high fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T scores, or increased fall risk.
*** Medications are listed alphabetically.
**** Consider a drug holiday after 6 years of IV zoledronate. During the holiday, an anabolic agent or a weaker antiresorptive such as raloxifene could be used.

Camacho PM et al. AACE Clinical Practice Guidelines for the Diagnosis & Treatment of Postmenopausal Osteoporosis-2020 Update. Endocr Pract 2020; 26 (Suppl.1):1-46

Algoritmo IOF Manejo Pacientes Riesgo bajo, alto, o muy alto de Fracturas Osteoporóticas

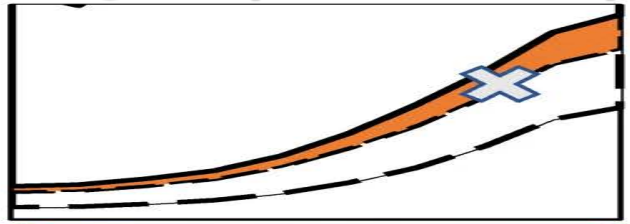


Low risk

Optimize calcium and vitamin D status

Risk appropriate exercise

Reassurance, lifestyle advice. Consider MHT and SERMs

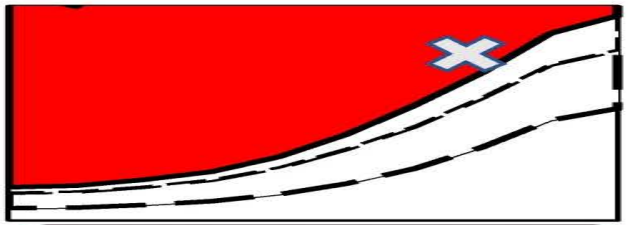


High risk

Optimize calcium and vitamin D status

Risk appropriate exercise and falls prevention

Consider oral bisphosphonate or other inhibitor of bone resorption*



Very high risk

Optimize calcium and vitamin D status

Risk appropriate exercise and falls prevention

Consider anabolic agent followed by inhibitor of bone resorption*. Consider LOEP

MHT, menopausal hormone therapy;
SERM, selective estrogen receptor modulator;
LOEP, local osteo-enhancement procedure
* See Appendix, table A2

Kanis JA et al. Algorithm for the management of patients at low, high & very high risk of osteoporotic fractures. Osteoporos Int 2020; 31:1-12

Choice of Treatment According to Level of Risk

Osteoanabolic therapies are recommended for patients at very high fracture risk

Very high risk

abaloparatide, romosozumab, teriparatide
alternatives: denosumab, zoledronate

1. Camacho PM et al. AACE Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2020 Update. *Endocr Pract* 2020;26(Suppl 1):1-46
2. Kanis JA et al. Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. *Osteoporos Int* 2020;31:1-12

M. McClung, IOF Bone Cast 2022

Benefits of Anabolic Medication First

- Anabolic agents reduce fracture risk faster and to a greater extent compared to antiresorptive treatment in head to head trials.
- Recent findings from FNIH/SABRE project suggest that the magnitude of BMD gain with osteoporosis treatment is associated with antifracture efficacy
  - BMD gains are larger when starting with anabolic vs antiresorptive agents
  - BMD gains are larger with anabolic/antiresorptive sequences compared to antiresorptive/anabolic sequences

1. Cosman F. Endo Practice 2020; 26:777-786
2. Bouxsein M, et al. JBMR 2019; 34: 632–642
3. Black DM, et al. Lancet Diab Endo 220; 8:672-682.

F. Cosman, Conferencia Congreso ACR 2022

ESTRATEGIAS TERAPIA OSTEOPOROSIS PACIENTES RIESGO FRACTURA MUY ALTO

- Monoterapia con Antiresortivos puede ser insuficiente para ↓ riesgo a niveles aceptables en estos pacientes
- Podría considerarse terapia mas agresiva medicamentos anti fractura:
  - -Terapia Combinada
  - -Terapia Secuencial

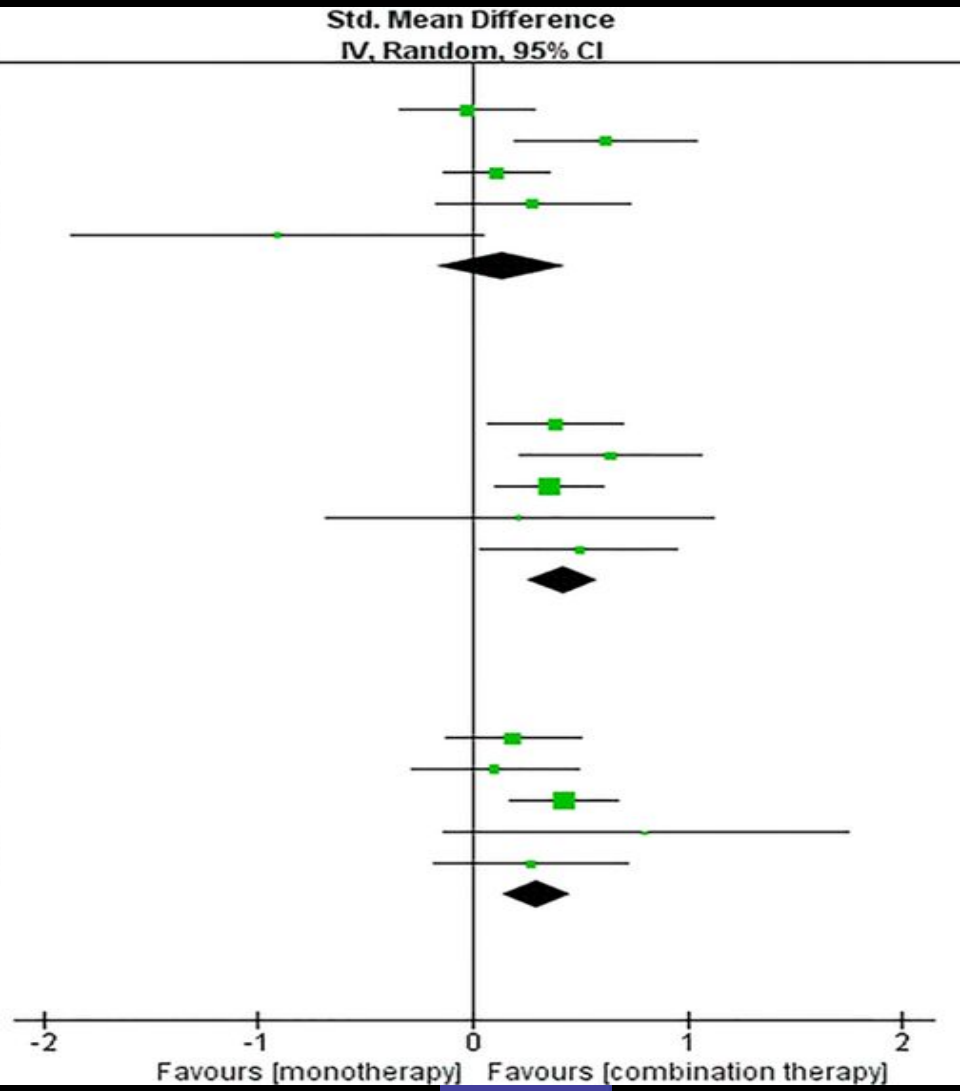
TERAPIAS COMBINADAS DE LA OSTEOPOROSIS

- Coadministración agente Anabólico + agente Antiresortivo puede ser apropiada en pacientes riesgo muy alto de fractura
- Aunque terapia combinada puede beneficiar algunas MPM, para muchas pacientes (y particularmente tto-naive) la mejor opción seria iniciar terapia anabólica sin terapia antireabsortiva concomitante
- Se han evaluado en estudios con DMO como endpoint (no de Fractura como endpoint) *(Lou S, Lv H, Li Z, Tang P (2018) Combination therapy of anabolic agents & bisphosphonates on BMD in patients with osteoporosis: a meta-análisis of RCTs. BMJ Open 8:e015187*

Combination therapy of Anabolic Agents & Bisphosphonates on BMD in patients with osteoporosis
Meta-Análisis of RCTs

Forest plot for the BMD variation of the 6 to 12 months duration. IV, inverse variance

Study or Subgroup	combination therapy Mean	SD	Total	monotherapy Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
1.1.1 Lumbar spine									
Black 2003	6.1	4.43	59	6.3	7.12	119	25.0%	-0.03 [-0.34, 0.28]	2003
Cosman 2009	4.5	4	45	2	4	45	20.4%	0.62 [0.20, 1.04]	2009
Cosman 2011	7.5	4.4	122	7	4.6	131	27.8%	0.11 [-0.14, 0.36]	2011
Muschitz 2013	5	6.3	39	2.8	9.3	37	19.3%	0.28 [-0.18, 0.73]	2013
Walker 2013	2.82	4.7	10	7.21	4.5	9	7.6%	-0.91 [-1.87, 0.05]	2013
Subtotal (95% CI)			**275**			**341**	**100.0%**	**0.13 [-0.17, 0.43]**	
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 11.11$, df = 4 (P = 0.03); $I^2 = 64\%$									
Test for overall effect: Z = 0.87 (P = 0.39)									
1.1.2 Total hip									
Black 2003	1.9	3.3	59	0.3	4.5	119	26.7%	0.38 [0.07, 0.70]	2003
Cosman 2009	1.4	3.4	45	-0.8	3.4	45	14.7%	0.64 [0.22, 1.07]	2009
Cosman 2011	2.3	3.3	123	1.1	3.4	129	42.7%	0.36 [0.11, 0.61]	2011
Walker 2013	2.19	3.1	10	1.5	3	9	3.2%	0.22 [-0.69, 1.12]	2013
Muschitz 2013	4	5.3	39	1.4	5.1	37	12.7%	0.49 [0.04, 0.95]	2013
Subtotal (95% CI)			**276**			**339**	**100.0%**	**0.42 [0.26, 0.58]**	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.64$, df = 4 (P = 0.80); $I^2 = 0\%$									
Test for overall effect: Z = 5.05 (P < 0.00001)									
1.1.3 Femoral neck									
Black 2003	1.7	3.8	59	0.8	5.3	119	26.3%	0.18 [-0.13, 0.50]	2003
Cosman 2009	0.7	6	52	0.1	6	50	17.0%	0.10 [-0.29, 0.49]	2009
Cosman 2011	2.2	5	123	0.1	4.9	129	41.2%	0.42 [0.17, 0.67]	2011
Walker 2013	8.45	5.7	10	3.89	5.1	9	2.9%	0.80 [-0.14, 1.75]	2013
Muschitz 2013	4.6	9	39	2.4	6.9	37	12.6%	0.27 [-0.18, 0.72]	2013
Subtotal (95% CI)			**283**			**344**	**100.0%**	**0.30 [0.14, 0.46]**	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.58$, df = 4 (P = 0.47); $I^2 = 0\%$									
Test for overall effect: Z = 3.63 (P = 0.0003)									



Shenghan Lou et al. BMJ Open 2018;8:e015187

BMJ Open

TERAPIAS SECUENCIALES DE LA OSTEOPOROSIS

- Agente Anti-Resortivo seguido por Agente Anti-Resortivo
- Agente Anti-Resortivo seguido por Terapia Anabólica
- Terapia Anabólica seguida por Terapia Anti-Resortivo

TERAPIAS SECUENCIALES DE LA OSTEOPOROSIS

- Agente Anti-Resortivo seguido por Agente Anti-Resortivo:

- RCT 650 MPM Osteoporosis-DXA previamente tratadas con ALN promedio 6,3 años y randomizados a DEN o ZOL por 12 meses: ↑DMO-CL/Cadera y ↓MRO fueron mayores en tto-DEN *(Miller PD, et al. JCEM 2016:3163-70)*

TERAPIAS SECUENCIALES DE LA OSTEOPOROSIS

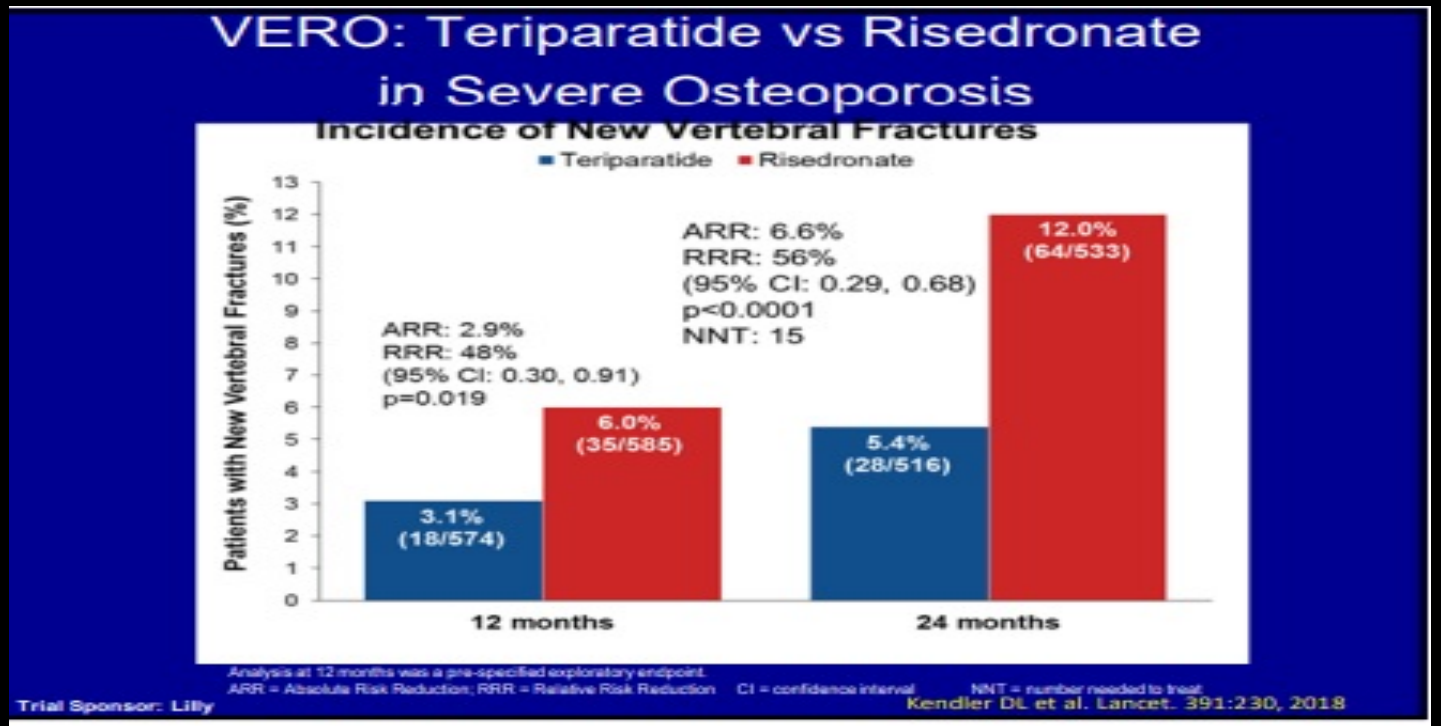
- Agente Anti-Resortivo seguido por Terapia Anabólica:

Cuando se considera Terapia Antiresortiva vs. Terapia Anabólica, la secuencia utilizada puede tener efectos en el aumento DMO: aunque en general es preferible la terapia anabólica antes que la terapia antiresortiva, en la practica clínica no siempre es posible debido a las compañías de seguro frecuentemente requieren falla previa tratamiento antiresortivo

TERAPIAS SECUENCIALES DE LA OSTEOPOROSIS

- Agente Anti-Resortivo seguido por Terapia Anabólica:

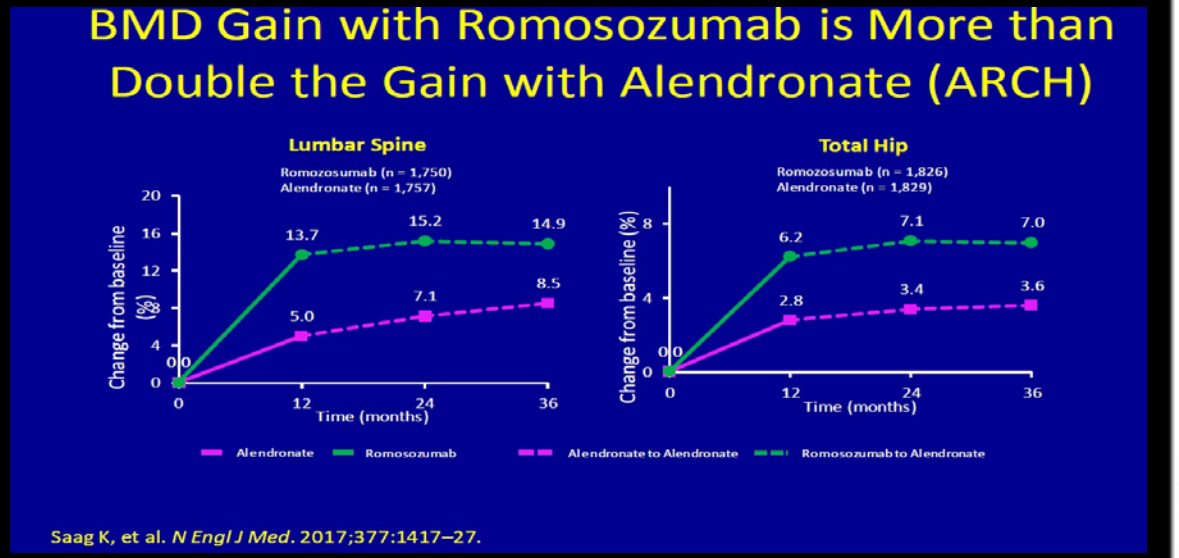
- VERO Trial: MPM-Osteoporosis randomizadas a tto. 24 meses TER diario + placebo o placebo + Risedronato (RIS). Solo 60% grupo tto TER y grupo tto RIS habían recibido previamente tto BIF χ 3,7 años. Tto. TER se asocio con significativa $\downarrow$ riesgo de nuevas fracturas vertebrales (56%) y fracturas clínicas (34%) (Kendler DL, et al. Lancet 2018; 391: 230-40

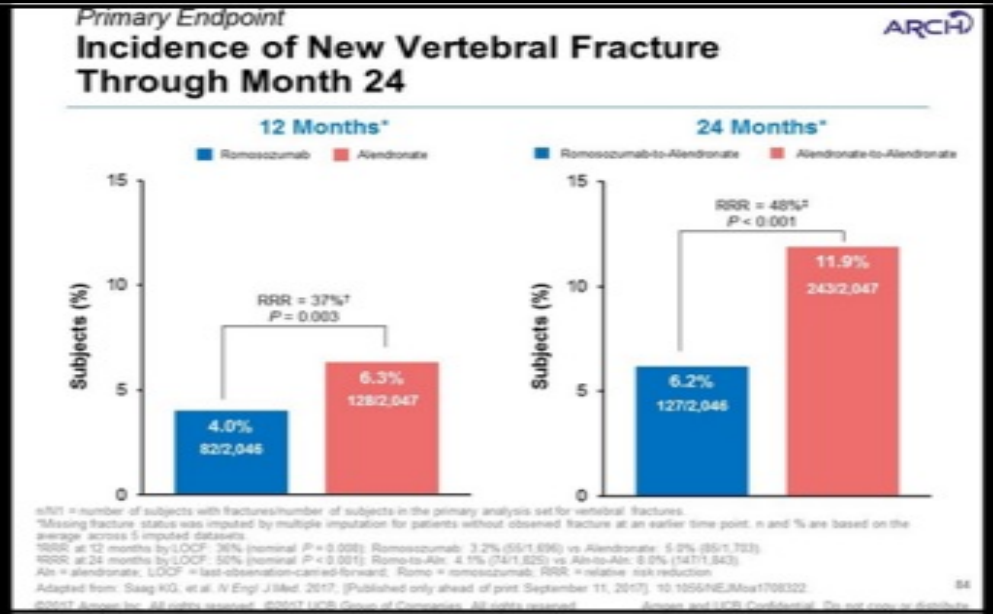


TERAPIAS SECUENCIALES DE LA OSTEOPOROSIS

- Terapia Anabolica seguida por Terapia Anti-Resortivo:

- ARCH Study: 4100 MPM con riesgo fractura alto se randomizaron a tto ROM vs. ALN por 1 año, seguido por ALN por 1 año adicional en ambos grupos: tto ALN mantuvo ↑DMO mediado por ROM y la ↓riesgo fractura vertebral (Saag KG, et al. NEJM 2017;377:1417-27. Cosman F, et al. JBMR 2020





TERAPIAS SECUENCIALES DE LA OSTEOPOROSIS

- DMO y fracturas son influidos significativamente por el orden de administración agentes antifracturas: *administración agente anabólico luego de terapia antiresortiva tiene menos impacto DMO que si anabólico se administra primero*
- Cuando se considera terapia secuencial se recomienda iniciar con terapia anabólica y luego agente antiresortivo
- Múltiples variables afectan los resultados, ej.: agente prescrito, características paciente, duración tratamiento
- Se necesita mas investigación para determinar el mejor orden y los fármacos mas apropiados para terapia combinación y terapia secuencial en pacientes individuales.

Medicamentos aprobados en USA para Tratamiento Osteoporosis (*)

Table. Medications Licensed in the United States for Treatment of Osteoporosis

Drug Name (Class)	Route; Frequency	Types of Fractures Examined in Randomized Clinical Trials at Long-Term Follow-up (>36 mo)				Average Annual Medicare Spending Per Beneficiary in 2019	FDA Warning
		Hip	Clinical Vertebral	Any Clinical	Radiographic Vertebral		
Antiresorptive drugs							
Alendronate (bisphosphonate)*†‡	By mouth (tablet or solution); once a day (10 mg) or once a week (70 mg)§	Yes	No	Yes	Yes	$793-$1306 (brand-name); $39 (generic)	Upper gastrointestinal irritation; osteonecrosis of the jaw; atypical femur fractures; severe bone, joint, and muscle pain
Risedronate (bisphosphonate)*†‡	By mouth; once a day, once a week, or 2 d in a row once per month§	Yes	No	No	Yes	$2036-$2732 (brand-name); $604 (generic)	Upper gastrointestinal irritation; osteonecrosis of the jaw; atypical femur fractures; severe bone, joint, and muscle pain
Ibandronate (bisphosphonate)*‡	By mouth; once a month§	No	No	No	Yes	$1379 (brand-name); $220 (generic)	Upper gastrointestinal irritation; osteonecrosis of the jaw; atypical femur fractures; severe bone, joint, and muscle pain
Zoledronate (bisphosphonate)*†‡	Intravenous; once a year§	Yes	Yes	Yes	Yes	$855 (brand-name); $316-$987 (generic)	Osteonecrosis of the jaw; atypical femur fractures; severe bone, joint, and muscle pain
Denosumab (RANK ligand inhibitor)‡‖	By injection (subcutaneous); every 6 mo¶	Yes	Yes	Yes	Yes	$1913-$12 241 (brand-name)	Dermatologic reactions and serious infection, including skin infections; suppression of bone turnover contributing to adverse outcomes, such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing
Anabolic drugs							
Abaloparatide (parathyroid hormone–related protein)‖	By injection (subcutaneous); once a day	No	No	Yes**	Yes**	$9873 (brand-name)	Hereditary osteosarcoma disorders††
Teriparatide (recombinant human parathyroid hormone)‖‡	By injection (subcutaneous); once a day	Yes**	Yes**	Yes**	Yes**	$22 156 (brand-name)	Hereditary osteosarcoma disorders††
Romosozumab (sclerostin inhibitor)‖	By injection (subcutaneous); once a month for 12 mo§§	No	Yes**	Yes**	Yes**	$5574 (brand-name)	Cardiovascular risk; Stroke history or risk‖‖
Estrogen agonist on bones							
Raloxifene (selective estrogen receptor modulator)*‡	By mouth; once a day	Yes	Yes	Yes	Yes	$1730 (brand-name); $593 (generic)	Stroke history or risk; Thromboembolism history or risk¶¶

(*) modif. A. Qaseem, L. Hicks, et als. Pharmacologic Treatment of Primary Osteoporosis or Low Bone Mass to prevent Fractures in Adults: A Living Clinical Guideline from the ACP. Ann Intern Med. Feb/2023:224-238

MEDICAMENTOS APROBADOS EN USA TRATAMIENTO OSTEOPOROSIS 2022*

Nombre	Gasto Anual promedio (U$)/Beneficiario Medicare 2019
Drogas Antiresortivas:	
Alendronato oral semanal	793 -1.306 #, 39 ##
Risedronato oral semanal	2.036 - 2.732 #, 604 ##
Ibandronato oral mensual	1.379 #, 220 ##
Zoledronato iv anual	855 #, 316-987 ##
Denosumab sc semestral	1.913 – 12.241 #
Drogas Anabólicas:	
Abaloparatide sc diario	9.873 #
Teriparatide sc diario	22.156 #
Romosozumab sc mensual	5.574 #
SERM:	
Raloxifeno oral diario	1.730 #, 593 ##

modif. A. Qaseem, L. Hicks, et als. Pharmacologic Treatment of Primary Osteoporosis or Low Bone Mass to prevent Fractures in Adults: A Living Clinical Guideline from the ACP. Ann Intern Med. Feb/2023:224-238

#= brand name ##= genérico

TERAPIAS SECUENCIALES Y TERAPIAS COMBINADAS DE LA OSTEOPOROSIS

RESUMEN

- En mujeres postmenopáusicas sin contraindicaciones los bifosfonatos son piedra angular de la terapia en muchos pacientes
- En pacientes con riesgo alto de fractura la terapia anabólica esquelética frecuentemente es la mejor opción para limitar riesgo de fracturas futuras
- Terapia combinada de osteoporosis es prometedora pero su financiamiento es un gran desafío

GRACIAS