骨質疏鬆的治療策略與挑戰案例報告

臺北榮民總醫院 藥學部
吳汶儒 藥師

Patient information

Patient Information

- Ms. W, **75** y/o, **146.1**cm, **48.1** kg, BSA 1.998
- A case in META since 2022/05/04 to 2024/05/20

Active disease

- **Severe osteoporosis** with T7,T11,T12 & L2 compression fracture

Gynecological History

- Menopause: 47 y/o

Family History

- Mom has DM at 80+ y/o & Pancreatic cancer

Personal History

- Alcohol: denied
- Allergy: denied
- Betal nuts: denied
- Cigarette: denied

Clinical course

Examination and Lab Data

- **DXA**- absorptiometry of bilateral hips:
  BMD **R't** total hip=0.530 g/cm2, **T-score=-3.4**; Z-score=-1.3
  BMD **L't** total hip=0.516 g/cm2, **T-score=-3.5**; Z-score=-1.4
- **T7,T11,T12 & L2 compression fracture**
- PE: Goiter (-)
- Crea 0.79 mg/dl
- TSH 1.82 uIU/mL (Ref:0.270~4.2)
- Free T4 1.07 ng/dL (Ref:0.93~1.7)
- 2021/09 Ca:9.0 mg/ dl, Vit.D3: 22.5 ng/ml
- 2021/04 MRI-whole body: Several well-circumscribed nodules at both lobes of thyroid gland, the largest one about 5.7x3.4mm at left gland.

2022/05/04
→1st Prolia & Cal tablet

2022/11/30
→2nd Prolia

2023/05/24
→3rd Prolia
→F/U thyroid sono for goiter

2023/11/30
→ 4th Prolia
→ F/U neck sono for LAPs

2024/05/20

Clinical course

Examination and Lab Data

- **DXA**- absorptiometry of bilateral hips:
  BMD **R't** total hip=0.530 g/cm2, **T-score=-3.4**; Z-score=-1.3
  BMD **L't** total hip=0.516 g/cm2, **T-score=-3.5**; Z-score=-1.4
- **T7,T11,T12 & L2 compression fracture**
- Crea 0.79 mg/dl
- PE: Goiter (-)
- TSH 1.82 uIU/mL (Ref:0.270~4.2)
- Free T4 1.07 ng/dL (Ref:0.93~1.7)
- 2021/09 Ca:9.0 mg/ dl, Vit.D3: 22.5 ng/ml
- 2021/04 MRI-whole body: Several well-circumscribed nodules at both lobes of thyroid gland, the largest one about 5.7x3.4mm at left gland.

Protein electrophoresis

項目名稱	H/L	結果	單位	參考區間
Albumin	L	53.9	%	55.8 ~ 66.1
Alpha-1 globulins		3.3	%	2.9 ~ 4.9
Alpha-2 globulins		8.0	%	7.1 ~ 11.8
beta-1 globulins		5.3	%	4.7 ~ 7.2
beta-2 globulins	H	6.9	%	3.2 ~ 6.5
Gamma globulins	H	22.6	%	11.1 ~ 18.8
M-protein		0	%	N/A
M-protein		0	%	N/A

項目名稱	H/L	結果	單位	參考區間
Total protein		7.7	g/dL	6.6 ~ 8.7
Albumin		4.2	g/dL	N/A
Alpha-1 globulins		0.3	g/dL	N/A
Alpha-2 globulins		0.6	g/dL	N/A
beta-1 globulins		0.4	g/dL	N/A
beta-2 globulins		0.5	g/dL	N/A
Gamma globulins		1.7	g/dL	N/A
M-protein		0	g/dL	N/A
M-protein		0	g/dL	N/A

Urine routine

項目	H/L	結果	單位	參考值
Chemical Strip Color		Yellow	N/A	Yellow
Clarity		clear	N/A	Clear
Sugar		-	g/dL	Negative
Bilirubin		-	N/A	Negative
Ketone		-	N/A	Negative
Specific gravity		1.011	N/A	1.003~1.035
Occult Blood		-	N/A	Negative
pH		5.5	N/A	5.0~8.0
Protein		-	mg/dL	Negative
Urobilinogen		<=1.5 EU/dL	E.U./dL	<=1.5
Nitrite		-	N/A	Negative

2022/05/04
→1st Prolia & Cal tablet

2022/11/30
→2nd Prolia

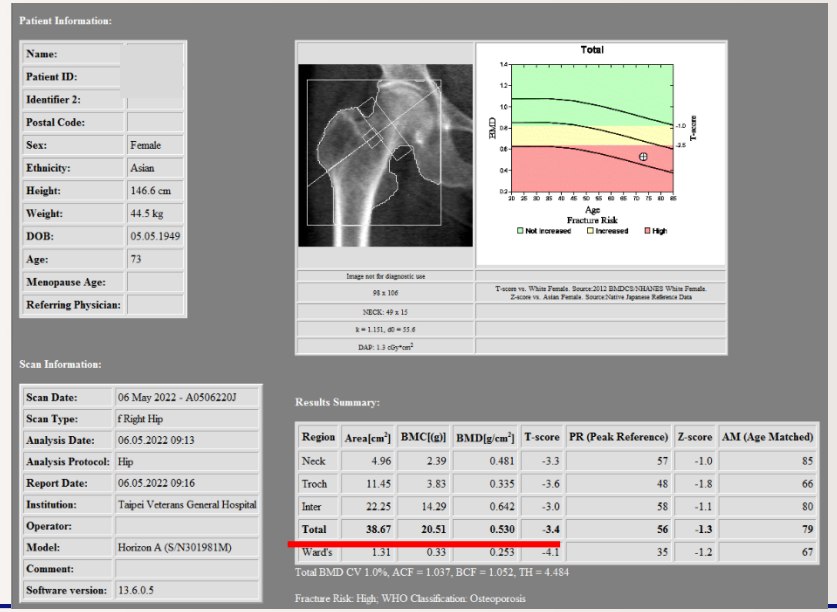
2023/05/24
→3rd Prolia
→F/U thyroid for goiter

20

T- score

Ms. W 2022-05-25 DXA-hip R't:-3.4 & L't:-3.3　T7, T11, T12 & L2 comp Fx (acute T12 & L1 Fx)

	T- score
Normal	≧-1.0
Osteopenia/ low bone mas	-1.0~-2.5
Osteoporosis	≦-2.5
Severe osteoporosis	≦-2.5 + non-traumatic FX ✓



Patient Information:

Name:	
Patient ID:	
Identifier 2:	
Postal Code:	
Sex:	Female
Ethnicity:	Asian
Height:	146.6 cm
Weight:	44.5 kg
DOB:	05.05.1949
Age:	73
Menopause Age:	
Referring Physician:	

Total

Age

Fracture Risk

Not increased　Increased　High

Scan Information:

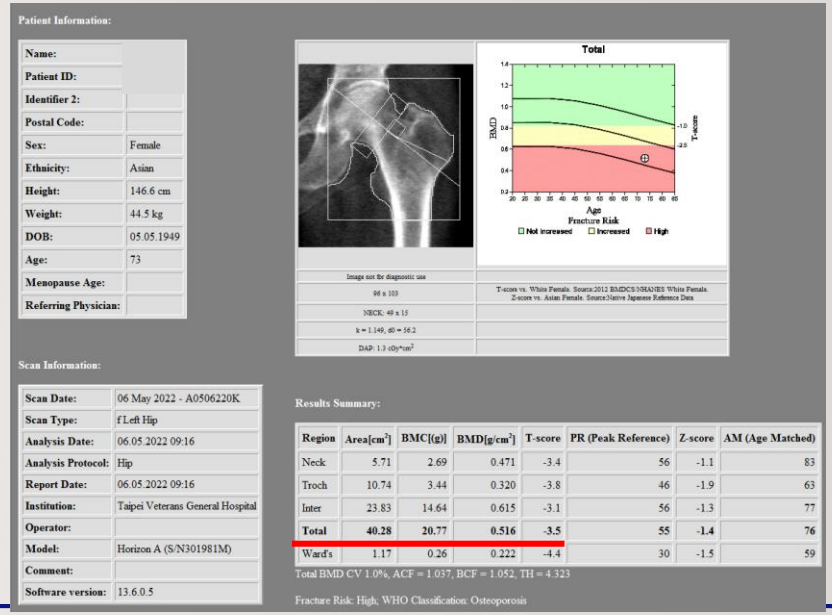
Scan Date:	06 May 2022 - A0506220J
Scan Type:	f Right Hip
Analysis Date:	06.05.2022 09:13
Analysis Protocol:	Hip
Report Date:	06.05.2022 09:16
Institution:	Taipei Veterans General Hospital
Operator:	
Model:	Horizon A (S/N301981M)
Comment:	
Software version:	13.6.0.5

Results Summary:

Region	Area[cm²]	BMC[(g)]	BMD[g/cm²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
Neck	4.96	2.39	0.481	-3.3	57	-1.0	85
Troch	11.45	3.83	0.335	-3.6	48	-1.8	66
Inter	22.25	14.29	0.642	-3.0	58	-1.1	80
Total	**38.67**	**20.51**	**0.530**	**-3.4**	**56**	**-1.3**	**79**
Ward's	1.31	0.33	0.253	-4.1	35	-1.2	67

Total BMD CV 1.0%, ACF = 1.037, BCF = 1.052, TH = 4.484

Fracture Risk: High, WHO Classification: Osteoporosis



Patient Information:

Name:	
Patient ID:	
Identifier 2:	
Postal Code:	
Sex:	Female
Ethnicity:	Asian
Height:	146.6 cm
Weight:	44.5 kg
DOB:	05.05.1949
Age:	73
Menopause Age:	
Referring Physician:	

Total

Age

Fracture Risk

Not increased　Increased　High

Scan Information:

Scan Date:	06 May 2022 - A0506220K
Scan Type:	f Left Hip
Analysis Date:	06.05.2022 09:16
Analysis Protocol:	Hip
Report Date:	06.05.2022 09:16
Institution:	Taipei Veterans General Hospital
Operator:	
Model:	Horizon A (S/N301981M)
Comment:	
Software version:	13.6.0.5

Results Summary:

Region	Area[cm²]	BMC[(g)]	BMD[g/cm²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
Neck	5.71	2.69	0.471	-3.4	56	-1.1	83
Troch	10.74	3.44	0.320	-3.8	46	-1.9	63
Inter	23.83	14.64	0.615	-3.1	56	-1.3	77
Total	**40.28**	**20.77**	**0.516**	**-3.5**	**55**	**-1.4**	**76**
Ward's	1.17	0.26	0.222	-4.4	30	-1.5	59

Total BMD CV 1.0%, ACF = 1.037, BCF = 1.052, TH = 4.323

Fracture Risk: High, WHO Classification: Osteoporosis

Date	CREA	BILIT	ALT	AST	eGFR(C-G)
2022/07/26	0.52	-	-	-	115.59
2022/11/30	-	0.50	20	-	-

2023/05/24 TSH,T4 Free

項目	H/L	結果	單位	參考值
T3				
T4				
TSH		1.570	uIU/mL	0.270~4.20
FREE T3				
FREE T4		1.20	ng/dL	0.93~1.7

2023/05/24 SONOGRAM- THYROID GLAND

> Several variable sized lymph nodes in bilateral lower neck, up to 1cm in right lower neck and 0.9 cm in left supraclavicular region, suspicious of lymphadenopathy, suggest further evaluation.
> Several heterogeneous low echogenicity nodules in bilateral thyroid glands, probably nodular goiter. The size range from 0.2 to 0.6cm.

2023/11/30 SONOGRAM- NECK

> Several nodules are noted in both lobes thyroid, with largest one measured 0.6 cm in left lobe thyroid, probably nodular goiter. Recommend follow up.
> Several lymph nodes are noted in bilateral lower neck, with largest one measured 1.5 cm in right lower neck, probably reactive lymph nodes or lymphadenopathy. Recommend clinical correlation and follow up.

2022/05/25
→1st Prolia & Cal tablet

2022/11/30
→2nd Prolia

2023/05/24
→3rd Prolia
→F/U thyroid sono for goiter

2023/11/30
→ 4th Prolia
→ F/U neck sono for LAPs

2024/05/20
→5th Prolia

Osteoporosis risk factors

Ms. W, 75 y/o, 146.1cm, 48.1 kg, BSA 1.998 Menopause: 47 y/o

Risk factors for osteoporosis:

- ☑ Age >50
- ☑ Gender
- ☐ Low body mass index (BMI)
- ☑ Fractures, especially hip, vertebrae, and wrist fractures
- ☐ Reduced height (more than 4 cm)
- ☐ Parental history of hip fracture
- ☐ Current smoker
- ☐ Excessive alcohol consumption
- ☐ Secondary osteoporosis
- ☐ Medications
- ☐ Bedridden, debilitating, or hypermobile (e.g., spinal cord injury, Parkinson's disease, stroke, muscular dystrophy, rigid spondylitis, etc.)Translated with DeepL.com (free version)

FRAX® FRAX骨折風險評估工具

Ms. W, 75 y/o, 146.1cm, 48.1 kg

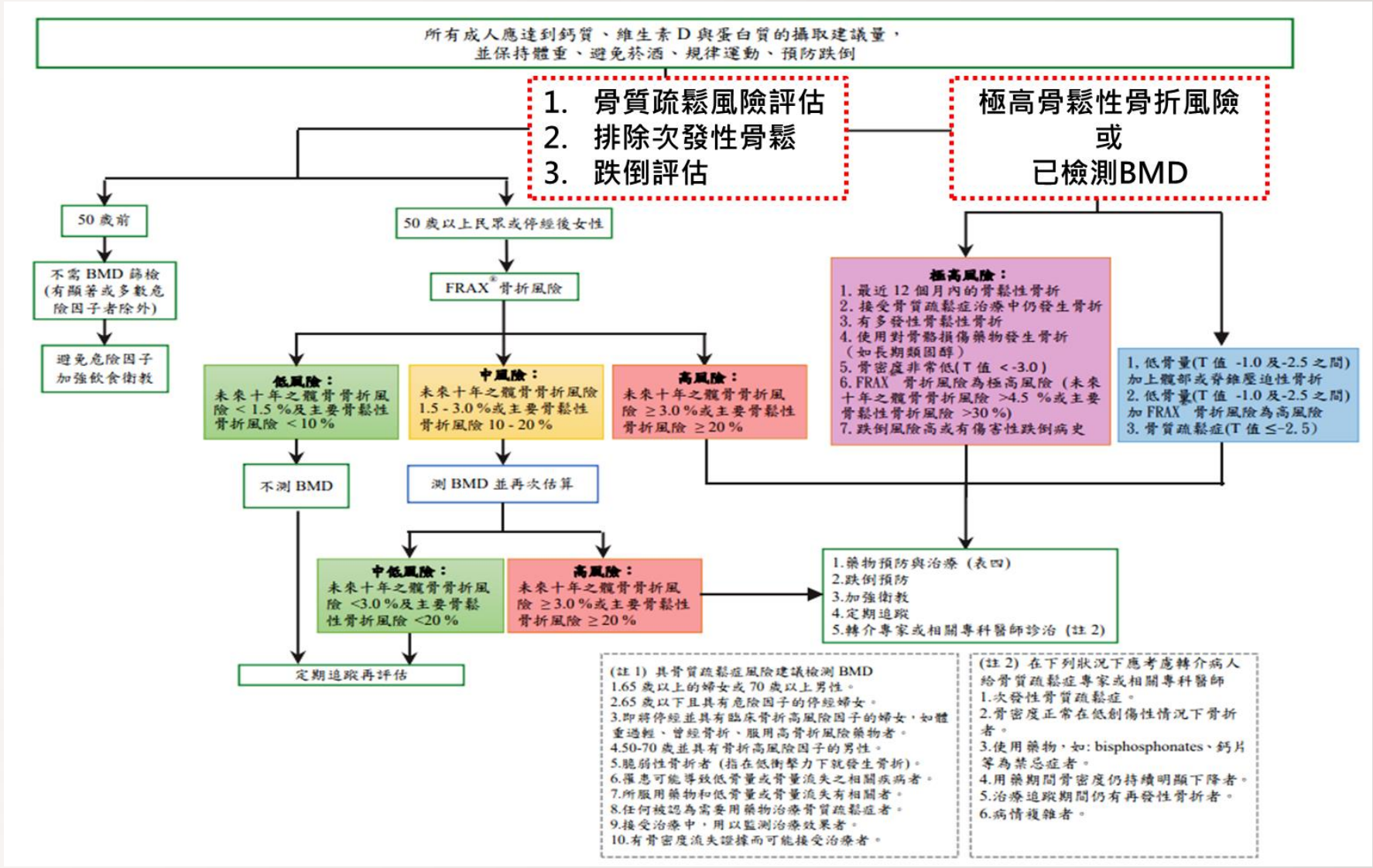
- **High risk group**
  - **Hip fracture ≧ 3%**
  - **Major osteoporosis fractures ≧ 20%**

- **Moderate risk group**
  - **Hip fracture 1.5~3 %**
  - **Major osteoporosis fractures 10 ~ 20%**

- **Low risk group**
  - **Hip fracture < 1.5**
  - **Major osteoporosis fractures <10 %**

https://frax.shef.ac.uk/FRAX/tool.aspx?lang=cht

台灣成人骨質疏鬆症之評估與治療流程



台灣成人骨質疏鬆症之評估與治療流程

極高骨鬆性骨折風險 或
已檢測BMD ✓

極高風險

1. 最近 12 個月內的骨鬆性骨折
2. 接受骨質疏鬆症治療中仍發生骨折
3. 有多發性骨鬆性骨折 ✓
4. 使用對骨骼損傷藥物發生骨折(如長期類固醇)
5. 骨密度非常低 (T 值 < -3.0) ✓
6. FRAX®骨折風險為極高風險 (未來十年之髖骨骨折風險 >4.5 % 或主要骨或主要骨鬆性骨折風險 >30 %) ✓
7. 跌倒風險高或有傷害性跌倒病史

1. 低骨量(T 值 -1.0 及-2.5 之間) 加上髖部或脊錐壓迫性骨折
2. 低骨量(T 值 -1.0 及-2.5 之間)加 FRAX®骨折風險為高風險
3. 骨質疏鬆(T 值≦ -2.5) ✓

1. 藥物預防與治療
2. 跌倒預防
3. 加強衛教
4. 定期追蹤
5. 轉介專家或相關專科醫師診治

Hip fracture 20 %
Major osteoporosis fractures 36%

Medication Selection

Very high fracture risk (Multiple spine fractures/hip fracture + T-score < − 2.5)

- 2022 BHOF- Initial treatment with an anabolic agent Teriparatide treatment for up to 2 years or romosozumab for 1 year.
- 2020 AACE- Recommended initial therapy: Abaloparatide, **Denosumab**, Romosozumab, Teriparatide, Zoledronate.

健保給附規範

第二線用藥：Teriparatide / Romosozumab

1) **限用於停經後婦女**
2) 需符合下列條件：
   - **T score ≦ -3+hip 或 spine fracture ≧二處 +使用第一線藥物 ≧12個月又發生新骨折或不耐受**
3) 使用不得超過24支並於一年內使用完畢，使用期間內不得併用其他骨質疏鬆症治療藥物。
4) 與 teriparatide 僅得擇一使用，除因耐受性不良，不得互換。

Comparison of anti-fracture effectiveness of zoledronate, ibandronate and alendronate versus denosumab in a registry-based cohort study

Judith Everts-Graber[1,2] · Harald Bonel[3,4,5] · Daniel Lehmann[6] · Brigitta Gahl[7] · HansJörg Häuselmann[8] · Ueli Studer[1] · Hans-Rudolf Ziswiler[1] · Stephan Reichenbach[2,9] · Thomas Lehmann[1]

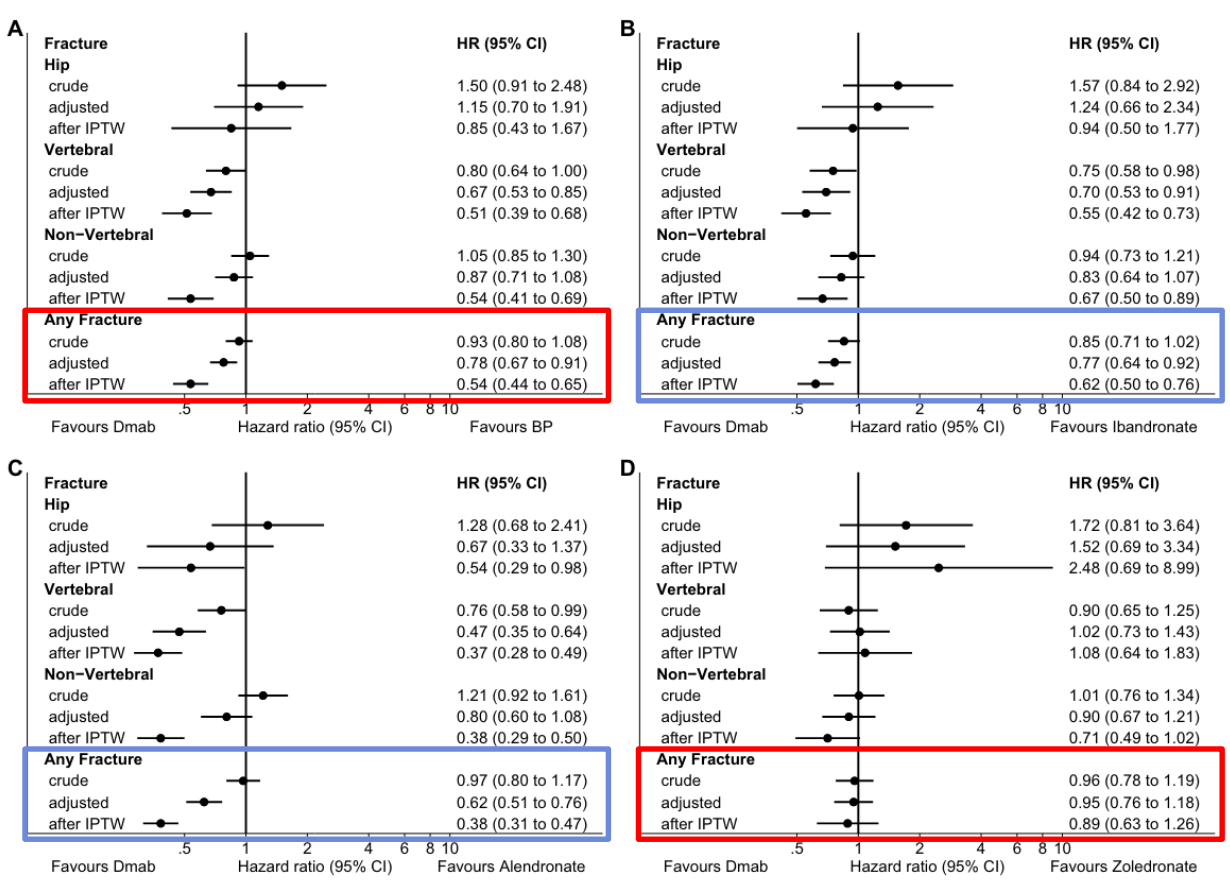
Received: 21 November 2022 / Accepted: 13 July 2023 / Published online: 26 July 2023

- **Retrospective Cohort Study**
- PICO
  - **P:** total of 3,068 patient >50 y/o,
  - **I:** Bisphosphonate (41% alendronate, 36% ibandronate, 23% zoledronate)
  - **C:** Denosumab
  - **O:** Fracture risk

Comparison of anti-fracture effectiveness of zoledronate, ibandronate and alendronate versus denosumab in a registry-based cohort study

Judith Everts-Graber[1,2] · Harald Bonel[3,4,5] · Daniel Lehmann[6] · Brigitta Gahl[7] · HansJörg Häuselmann[8] · Ueli Studer[1] · Hans-Rudolf Ziswiler[1] · Stephan Reichenbach[2,9] · Thomas Lehmann[1]

Received: 21 November 2022 / Accepted: 13 July 2023 / Published online: 26 July 2023



- This registry-based study of 3068 patients with osteoporosis compared the anti-fracture effectiveness of denosumab versus bisphosphonates.
- Denosumab was associated with significantly greater risk reduction than alendronate or ibandronate for vertebral and any fractures.
- No difference in fracture risk reduction was found between zoledronate and denosumab.

Comparison of Osteoporosis Drugs

		途徑	使用劑量/頻率	脊椎骨折	脊椎外骨折	男性骨鬆	類固醇骨鬆	骨鬆預防
Anti-resorptive	**雙磷酸鹽類 (bisphosphonates)**							
	Alendronate	po	70 mg/ 每週	++	++	++	++	++
	Risedronate	po	150mg/ 每月	++	++	++	++	++
	Ibandronic acid	IV	3 mg/ 每3個月	++	+	N/A	N/A	N/A
	Zoledronic acid	IV	5 mg/ 每年	++	++	++	++	++
	細胞核κB受體活化劑 (RANKL)							
	Denosumab	SC	60 mg/ 每6個月	++	++	+	+	N/A
	雌激素、選擇性雌激素受體調節劑 (selective estrogen receptor modulators, SERMs)							
	Estrogen	PO	0.625 mg/ 每日	++	++	不宜	不宜	++
	Raloxifene (SERM)	PO	60mg/ 每日	++	+	不宜	N/A	++
	Bazedoxifene (SERM)	PO	20mg/ 每日	++	+	不宜	N/A	N/A
Anabolic	**副甲狀腺素衍生物 (parathyroid hormone analog)**							
	Teriparatide	SC	20 mcg/ 每日	++	++	++	++	N/A
	Sclerostin單株抗體							
	Romosozumab	SC	210 mg/ 每月	++	++	+	N/A	N/A

N/A:目前尚無證據

Drug profile

Drug	Dosage	Route	Frequency	Start	End
Prolia inj 60 mg (Denosumab)	1 SYRG	SC	STAT	2022-05-25	2022-05-26
Cal. acetate "U.L."* tab 667 mg	1TAB	PO	TIDCC		
Prolia inj 60 mg (Denosumab)	1 SYRG	SC	STAT	2022-11-30	2022-12-01
Prolia inj 60 mg (Denosumab)	1 SYRG	SC	STAT	2023-05-24	2023-05-25
Prolia inj 60 mg (Denosumab)	1 SYRG	SC	STAT	2023-11-30	2023-12-01

骨鬆藥品健保給附規範

- 第一線用藥 (Teriparatide、Romosozumab 以外)

  Hip 或 spine fracture 一處 + T score ≦ -2.5　or
  Hip 或 spine fracture ≧二處 + T score ＜ -1

1. 抗骨質再吸收劑（anti- resorptive）
   1) 限用於停經後婦女（alendronate、zoledronate、denosumab 及risedronate 35mg 亦可使用於男性，risedronate 150mg 不可使用於男性）
   2) 治療時，一次限用一項藥物，不得併用其他骨質疏鬆症治療藥物
   3) 使用雙磷酸鹽類藥物，須先檢測病患之血清 creatinine 濃度，符合該項藥物仿單之建議規定。

Discussion

- Duration of denosumab therapy
- Risk of multiple vertebral fractures after discontinuation
- Sequential osteoporosis therapy
- Hypocalcemia with denosumab use

Denosumab

RANKL（Receptor activator of nuclear factor kappa beta）

(Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months)

The FREEDOM Trial (3-year)

Primary endpoint: Rate of new vertebral fracture after 3 years of treatment

7868
Postmenopausal women with osteoporosis

3906
placebo

3902
Denosumab 60 mg

Fracture, relative risk
Reduction vs. placebo

New vertebral	↓ 68%,
Nonvertebral	↓ 20%
hip	↓ 40%
wrist fractures	↓ 16%

BMD T-score, mean%
Change vs placebo

lumbar spine	9.2% ↑
total hip	6.0%

FREEDOM Extension (7 or 10 years)

Primary endpoint: Evaluate safety and tolerabiblity of denosumab for up to 7 or 10 years

2270
Crossover group

BMD VS Extension baseline
- Lumbar spine ↑ 16.5%
- Total hip ↑ 7.4 %

Annualized incidence of fractures
- New vertebral 0.90~1.86%
- Nonvertebral 1.18~2.55%

2343
Long-term group

BMD VS FREEDOM baseline
- Lumbar spine ↑ 21.7%
- Total hip ↑ 9.2 %

Annualized incidence of fractures
- New vertebral 1.16~1.47%
- Nonvertebral 0.84~1.91%

Yearly exposure-adjusted incidence of select adverse events of interest (combined denosumab treatment groups) :
Atypical femoral fractures <0.1 per 100 participation-years
Osteonecrosis of the jaw <0.1-0.2 per 100 participation-years

Denosumab treatment for up to 10 years was associated with low rates of adverse events, low fracture incidence compered with that observed during the original trial, and continued increases in BMD without plateau.

Can Fam Physician. 2011 Apr; 57(4): 438–441. Lancet Diabetes Endocrinol. 2017 Jul;5(7):513-523.

Duration of therapy

- Osteoporosis is a chronic condition that generally requires long-term monitoring and therapy.
- The maximum follow-up time for published clinical data on the long-term effects of denosumab treatment is **10 years**, there is **no absolute limit on treatment duration**.
- Patients at continued high risk for fracture, treatment with denosumab should be continued indefinitely.

Denosumab discontinuation might be considered in several clinical circumstances:

1) Patient has suboptimal response to denosumab with incident fracture, declining BMD, or persistently low BMD.
2) Patient develops hypersensitivity or other adverse effects to denosumab such as ONJ or AFF.
3) In some cases, patients may request to discontinue denosumab for cost or other reasons.

Atypical femoral fractures (AFF)
Osteonecrosis of the jaw (ONJ)

Lancet Diabetes Endocrinol. 2017 Jul;5(7):513-523.

Risk of Multiple Vertebral Fractures After Discontinuation

Bone tissue leading to a mass increase in osteoclastogenesis and RANKL release after stopping Denosumab.

CTX Rising within an average of 3 months after stopping Denosumab (9 months after last injection), peaking after an average of 6 months.

Increased **Multiple vertebral fractures (MVF)**

Alendronate/ Zoledronic acid has been shown to maintain bone density after discontinuation of denosumab.

CTx:Serum Beta-C-Terminal Telopeptides

J Clin Med. 2021 Jan; 10(1): 152.

Osteoporosis Drugs

	途徑	使用劑量/頻率	脊椎骨折	脊椎外骨折	男性骨鬆	類固醇骨鬆	骨鬆預防
Anti-resorptive	**雙磷酸鹽類 (bisphosphonates)**						
Alendronate	po	70 mg/ 每週	++	++	++	++	++
Risedronate	po	150mg/ 每月	++	++	++	++	++
Ibandronic acid	IV	3 mg/ 每3個月	++	+	N/A	N/A	N/A
Zoledronic acid	IV	5 mg/ 每年	++	++	++	++	++
	細胞核κB受體活化劑 (RANKL)						
Denosumab	SC	60 mg/ 每6個月	++	++	+	+	N/A
	雌激素、選擇性雌激素受體調節劑 (selective estrogen receptor modulators, SERMs)						
Estrogen	PO	0.625 mg/ 每日	++	++	不宜	不宜	++
Raloxifene (SERM)	PO	60mg/ 每日	++	+	不宜	N/A	++
Bazedoxifene (SERM)	PO	20mg/ 每日	++	+	不宜	N/A	N/A
Anabolic	**副甲狀腺素衍生物 (parathyroid hormone analog)**						
Teriparatide	SC	20 mcg/ 每日	++	++	++	++	N/A
	Sclerostin單株抗體						
Romosozumab	SC	210 mg/ 每月	++	++	+	N/A	N/A

N/A:目前尚無證據

Sequential osteoporosis therapy (Initiated 6 months after the last denosumab)

- Denosumab→ Alendronate

  DAPS stady

  1) Oral alendronate has been shown to maintain bone density after discontinuation of denosumab.
  2) Effective after 1-2 years. Osteoporos Int. 2012 Jan;23(1):317-26.

- Denosumab→ Zoledronate

  1) Shorter durations (denosumab treatment <2.5 years): **more effective** in preventing bone loss.

  - In a trial Postmenopausal women who received denosumab 2.5 years, using zoledronate 6 months after the last denosumab inj can maintain increasd BMD in about 80% for 3 years. Bone 2020, 138:115478.

  2) Longer durations (denosumab treatment >3 years): some bone loss may be expected even after a single dose of zoledronate administered.

  - In a trial postmenopausal women who received denosumab average of 3 years (range 2-5 years), single dose of Zoledronate injection resulted in the preservation of BMD at the lumbar spine 66% and total hip 49%. J Bone Miner Res 2020, 35(7):1207-1215.
  - In a multicenter study, postmenopausal patients received zoledronic acid six months after denosumab. At 12 months, lumbar spine BMD significantly decreased in >3 years group but remained stable in ≤3 years group. J Clin Endocrinol Metab 2021; 106:e4155.

Sequential osteoporosis therapy

- If a decision has been made to administer **Zoledronate** to prevent bone loss after discontinuation of denosumab, **measure** a fasting serum **C-telopeptide (CTX)** 3 and 6 months after the infusion, if serum **CTX is >350 pg/mL may require a second infusion**.

- If denosumab is discontinued (or delayed beyond 2~3 months), suggest administering a bisphosphonate to prevent rapid bone loss and vertebral fracture.

- Denosumab→ Teriparatide
  - A study on postmenopausal women undergoing "Teriparatide to Denosumab transition therapy" and "Denosumab to Teriparatide transition therapy" compared bone density differences.
  - Teriparatide to Denosumab group, bone density increased, while in the Denosumab to Teriparatide group, progressive or transient bone loss occurred.

Switching from denosumab to teriparatide (and presumably abaloparatide) does NOT prevent the rebound in remodeling, and significant bone loss occurs

Lancet 2015, 386(9999):1147-1155.

	途徑	使用劑量/頻率	脊椎骨折	脊椎外骨折	男性骨鬆	類固醇骨鬆	骨鬆預防
Anti-resorptive	**雙磷酸鹽類 (bisphosphonates)**						
	Alendronate	po	70 mg/ 每週	++	++	++	++	++
	Risedronate	po	150mg/ 每月	++	++	++	++	++
	Ibandronic acid	IV	3 mg/ 每3個月	++	+	N/A	N/A	N/A
	Zoledronic acid	IV	5 mg/ 每年	++	++	++	++	++
	細胞核κB受體活化劑 (RANKL)						
	Denosumab	SC	60 mg/ 每6個月	++	++	+	+	N/A
	雌激素、選擇性雌激素受體調節劑 (selective estrogen receptor modulators, SERMs)						
	Estrogen	PO	0.625 mg/ 每日	++	++	不宜	不宜	++
	Raloxifene (SERM)	PO	60mg/ 每日	++	+	不宜	N/A	++
	Bazedoxifene (SERM)	PO	20mg/ 每日	++	+	不宜	N/A	N/A
Anabolic	**副甲狀腺素衍生物 (parathyroid hormone analog)**						
	Teriparatide	SC	20 mcg/ 每日	++	++	++	++	N/A
	Sclerostin單株抗體						
	Romosozumab	SC	210 mg/ 每月	++	++	+	N/A	N/A

s therapy

ate to prevent bone loss after
rum **C-telopeptide (CTX)** 3 and 6
nL may require a second infusion.

3 months), suggest administering a
bral fracture.

- Denosumab→ Teriparatide
  - A study on postmenopausal women undergoing "Teriparatide to Denosumab transition therapy" and "Denosumab to Teriparatide transition therapy" compared bone density differences.
  - Teriparatide to Denosumab group, bone density increased, while in the Denosumab to Teriparatide group, progressive or transient bone loss occurred.

Switching from denosumab to teriparatide (and presumably abaloparatide) does NOT prevent the rebound in remodeling, and significant bone loss occurs

Lancet 2015, 386(9999):1147-1155.

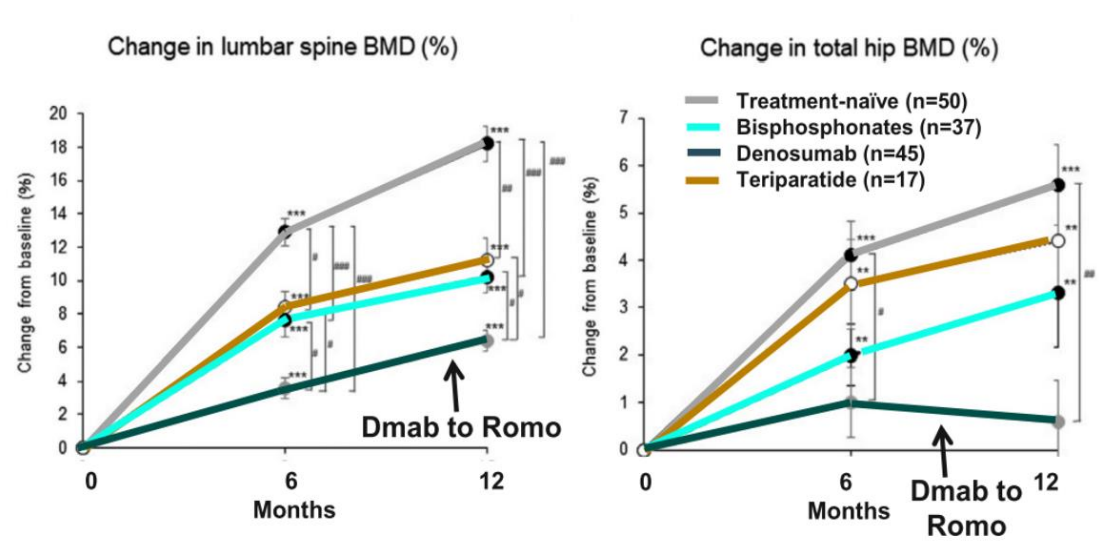
Sequential osteoporosis therapy

- Denosumab→ Romosozumab (Evenity®)

Switching from short-term denosumab to romosozumab results in stable or increased BMD.

➢ BMD response to romosozumab for 12 months was evaluated in patients with various previous treatments: bisphosphonates 2.5 years; denosumab 2 years; teriparatide 11 months.

➢ BMD remained stable or increased slightly.



No data yet about effect of that sequence after long-term denosumab change in lumbar spine BMD (%)

Adapted from Ebina K et al. Osteoporos Int 2022;33:1807-13

Back to the patient

Ms. W, 75 y/o
Currently using Prolia for 2.5 years → Shorter durations

1	2	3	4	5
2022/05/25	2022/11/30	2023/05/24	2023/11/30	2024/05/20

- **If discontinued, the following medications may be considered:**

1) **Alendronate**
2) **Zoledronate**
3) **Romosozumab**

Teriparatide

Hypocalcemia

Normal kidney function

serum calcium (Ref: 8.5-10.5 mg/ dl)

- In a trial all women were supplemented with daily calcium (1000 mg) and vitamin D (400~ 800 IU). A small proportion of women had a decrease in the serum calcium level to <8.5 mg/dL. The decrease was transient, and there were no episodes of symptomatic hypocalcemia that required discontinuation of denosumab.

When calcium and vitamin D are adequately supplemented, hypocalcemia is typically not a concern.

Impaired kidney function or other risk factors for hypocalcemia

- **CKD**, malabsorption syndromes, or **hypoparathyroidism**, severe hypocalcemia may occur.
- The **US FDA has added a boxed warning** about risk of severe hypocalcemia in individuals with **advanced chronic kidney disease** for denosumab (Prolia).
- A study, 607 of 1523 denosumab-treated patients and 23 of 1281 oral bisphosphonate–treated patients developed severe hypocalcemia. The **12-week** weighted cumulative incidence of severe hypocalcemia was 41.1% with denosumab *vs* 2.0% with oral bisphosphonates. [95% CI, 13.2-41.2]

In dialysis-dependent female patients aged >65, there is a heigh risk of hypocalcemia with denosumab use, requiring careful monitoring.

JAMA. 2024 Feb 13;331(6):491-499.

US Food and Drug Administration (FDA)

Back to the patient

Ms. W, 75 y/o
Prolia for 2.5 years

1 — 2022/05/25
2 — 2022/11/30
3 — 2023/05/24
4 — 2023/11/30
5 — 2024/05/20

Date	CREA	BILIT	ALT	AST	eGFR(C-G)
2022/07/26	0.52	-	-	-	115.59
2022/11/30	-	0.50	20	-	-

2023/05/24 TSH,T4 Free

項目	H/L	結果	單位	參考值
T3				
T4				
TSH		1.570	uIU/mL	0.270~4.20
FREE T3				
FREE T4		1.20	ng/dL	0.93~1.7

2023/05/24 SONOGRAM- THYROID GLAND

> Several variable sized lymph nodes in bilateral lower neck, up to 1cm in right lower neck and 0.9 cm in left supraclavicular region, suspicious of lymphadenopathy, suggest further evaluation.
> Several heterogeneous low echogenicity nodules in bilateral thyroid glands, probably nodular goiter. The size range from 0.2 to 0.6cm.

2023/11/30 SONOGRAM- NECK

> Several nodules are noted in both lobes thyroid, with largest one measured 0.6 cm in left lobe thyroid, probably nodular goiter. Recommend follow up.
> Several lymph nodes are noted in bilateral lower neck, with largest one measured 1.5 cm in right lower neck, probably reactive lymph nodes or lymphadenopathy. Recommend clinical correlation and follow up.

Comparison of Common Calcium Supplements

鈣質種類	吸收率	含鈣元素比率	其他
碳酸鈣 Calcium carbonate	500 mg 2~3 times daily	40%	• 須隨餐(飯後)服用 • 胃酸會增加吸收率 (PH↓吸收↑) • 可能會胃脹氣
檸檬酸鈣 Calcium Citrate	950-1000 mg 2~3 times daily	21%	• 不受PH質影響 • 適用於長期使用制酸劑(PPI)病人 • 鋁中毒風險
磷酸鈣 Tricalcium phosphate	1200 mg 2 times daily	39%	• 與人體最接近的鈣質 • 腎功能不全者須謹慎使用
葡萄糖酸鈣 Calcium gluconate	參閱包裝	9%	• 含鈣量少
乳酸鈣 Calcium lactate	參閱包裝	13%	
醋酸鈣 Calcium acetate	1~3 tablets 3 times daily	25%	• 空腹 (補鈣) • 隨餐 (降磷)

Physiol Rev 2013;93:189- 268.

Dietary Reference Intakes for calcium and vitamin D

- The Bone Health and Osteoporosis Foundation (BHOF) and the International Osteoporosis Foundation (IOF) recommend that:

Dietary Calcium Intake:

>50 years old	**1200 mg/daily**
< 50 years old Adult	**1000 mg/daily**
Postmenopausal women with osteoporosis	**1200 mg/daily**

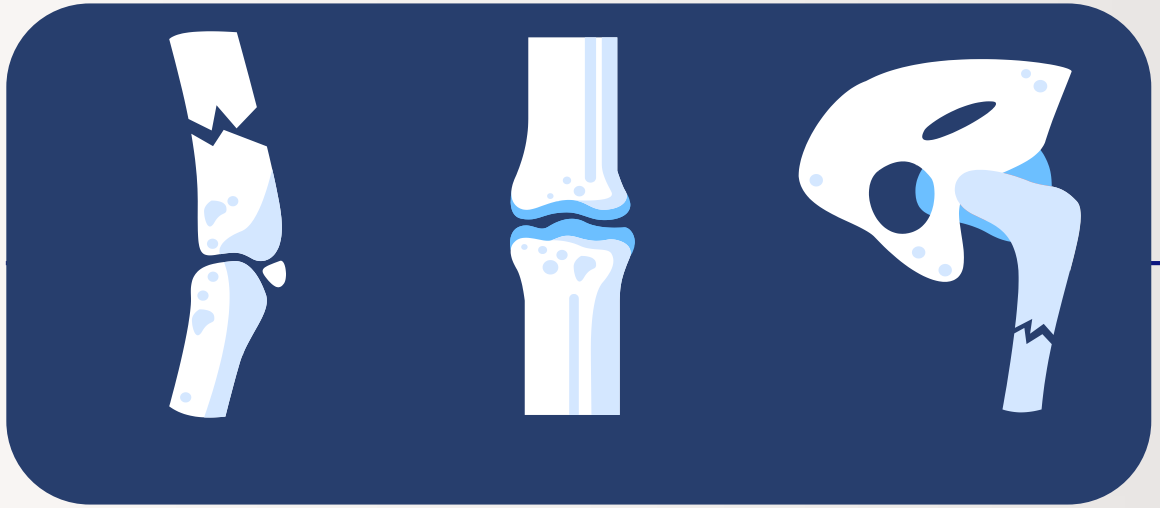
VitD intake:

>50 years old	**800-1000 IU/daily**
< 50 years old Adult	**400-800 IU/daily**
Osteoporosis	**At least 800 IU/daily**

- ◆ Excessive calcium intake (>1,500 mg) is not beneficial and may carry a potential risk of stones or cardiovascular disease.
- ◆ Calcium and vit.D supplementation cannot replace medication.

Take home massage

- Denosumab treatment is 10 years, there is no absolute limit on treatment duration.
- Risk of Multiple Vertebral Fractures After Discontinuation.
  - Alendronate/ Zoledronic acid has been shown to maintain bone density after discontinuation of denosumab.
  - Switching from denosumab to teriparatide does not prevent the rebound.
  - Switching from short-term denosumab to romosozumab results in stable or increased BMD.
- US FDA has added a boxed warning about risk of severe hypocalcemia in individuals with advanced kidney disease for brand name denosumab (Prolia).
- Follow-up dual-energy x-ray absorptiometry (DXA) of the hip and spine after one to two years.



Thanks

Romosozumab 健保給附規範

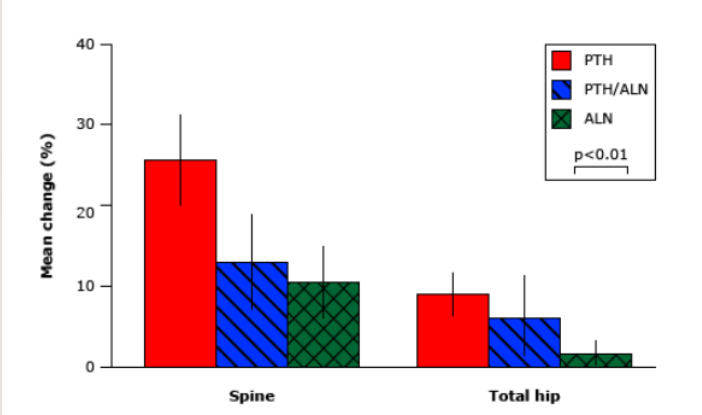
- 第二線用藥：Romosozumab (ex Evenity®)

1) **限用於停經後婦女**
2) 需符合下列條件：
   - **T score ≦ -3+hip 或 spine fracture ≧二處 + 使用第一線藥物 ≧12個月又發生新骨折或不耐受**
3) 使用不得超過24支並於一年內使用完畢，使用期間內不得併用其他骨質疏鬆症治療藥物。
4) 與 teriparatide 僅得擇一使用，除因耐受性不良，不得互換。

Combination therapy

PTH analog plus denosumab

- Several trials have reported that PTH + alendronate (either started concurrently or + 6 months prior to PTH analog) resulted in **no additional benefit** for **spine or hip BMD** compared with PTH analog alone.



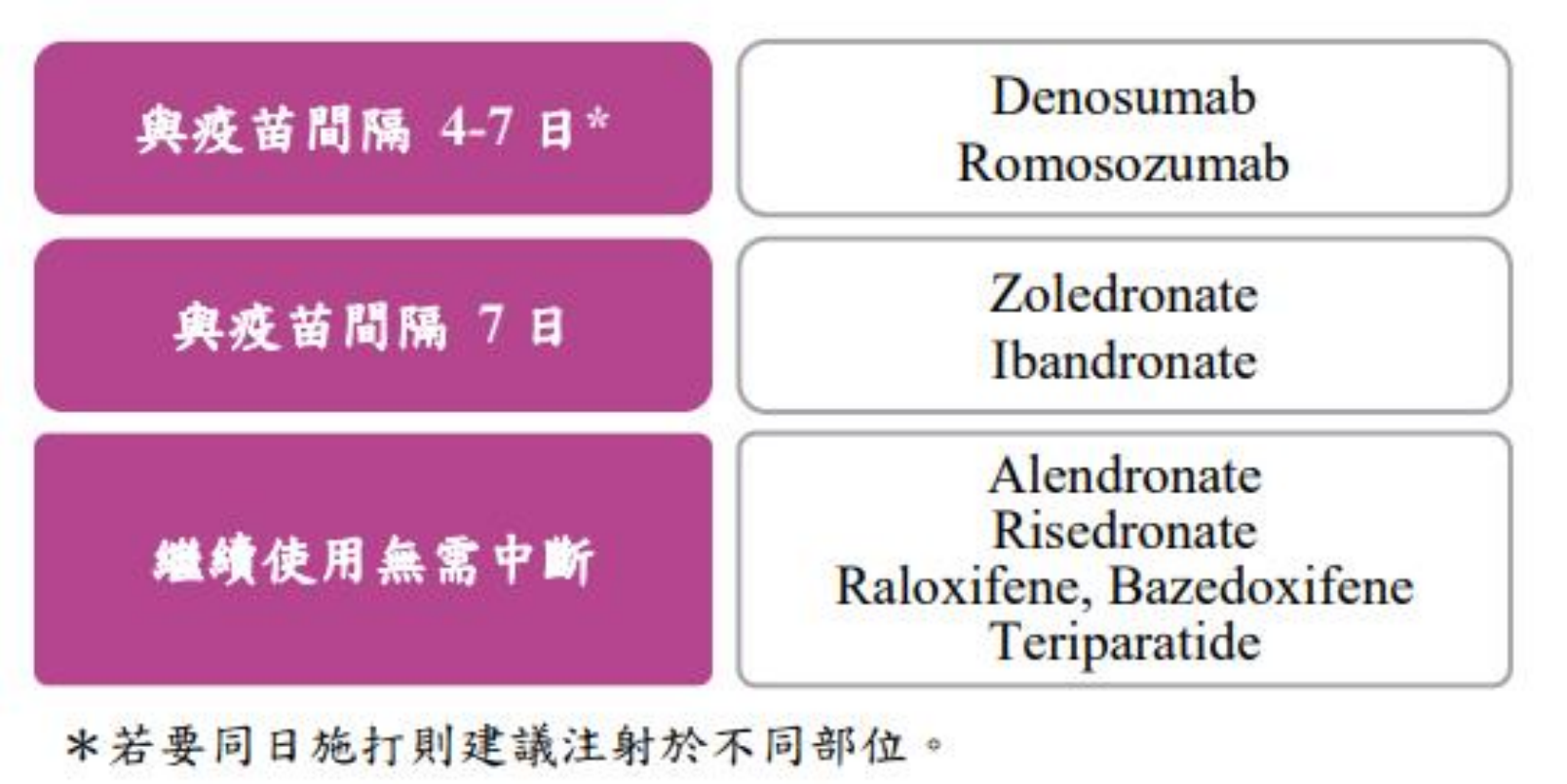
PTH analog plus denosumab

- Combination therapy seems to enhance BMD more than either therapy alone, but fracture data are lacking, and optimal post-treatment consolidation strategies remain undetermined.
  - ➢ In a trial comparing teriparatide (20 mcg subcutaneously daily), denosumab (60 mg subcutaneously every six months), or both in postmenopausal women with a high risk for fracture (BMD T-score <-2.5 or T-score <-2.0 with other fracture risk factor)

We do not suggest combination therapy with denosumab and teriparatide or any another osteoporosis therapy. Combination therapy with denosumab and teriparatide is reviewed separately

Lancet Diabetes Endocrinol. 2019 Oct;7(10):767-775.

COVID-19 Vaccination and Osteoporosis Treatment



骨鬆藥品健保給附規範

- 第一線用藥 (Teriparatide、Romosozumab 以外)

  - 抗骨質再吸收劑（anti- resorptive）

1) 限用於停經後婦女（alendronate、zoledronate、denosumab 及 risedronate 35mg 亦可使用於男性，risedronate 150mg 不可使用於男性）

   - **Hip 或 spine fracture 一處 + T score ≦ -2.5　or**
   - **Hip 或 spine fracture ≧二處 + T score ＜ -1**

2) 治療時，一次限用一項藥物，不得併用其他骨質疏鬆症治療藥物
3) 使用雙磷酸鹽類藥物，須先檢測病患之血清 creatinine 濃度，符合該項藥物仿單之建議規定。

骨鬆藥品健保給附規範

- 第二線用藥 : Teriparatide (ex Forteo®)

1) 限用於停經後婦女 **或** 原發性或次發於性腺功能低下症造成骨質疏鬆之男性

2) 需符合下列條件：

   - **T score ≦ -3+hip 或 spine fracture ≧二處 +使用第一線藥物≧12個月又發生新骨折或不耐受**

3) 使用不得超過18支並於二年內使用完畢，使用期間內不得併用其他骨質疏鬆症治療藥物。

骨鬆藥品健保給附規範

- 第二線用藥 : Romosozumab (ex Evenity®)

1) **限用於停經後婦女**
2) 需符合下列條件：
   - **T score ≦ -3+hip 或 spine fracture ≧二處 +使用第一線藥物 ≧12 個月又發生新骨折或不耐受**
3) 使用不得超過24支並於一年內使用完畢，使用期間內不得併用其他骨質疏鬆症治療藥物。
4) 與 teriparatide 僅得擇一使用，除因耐受性不良，不得互換。