Session 4

골다공증 약물치료 II

좌장: 유병연 (건양의대), 서형연 (전남의대)

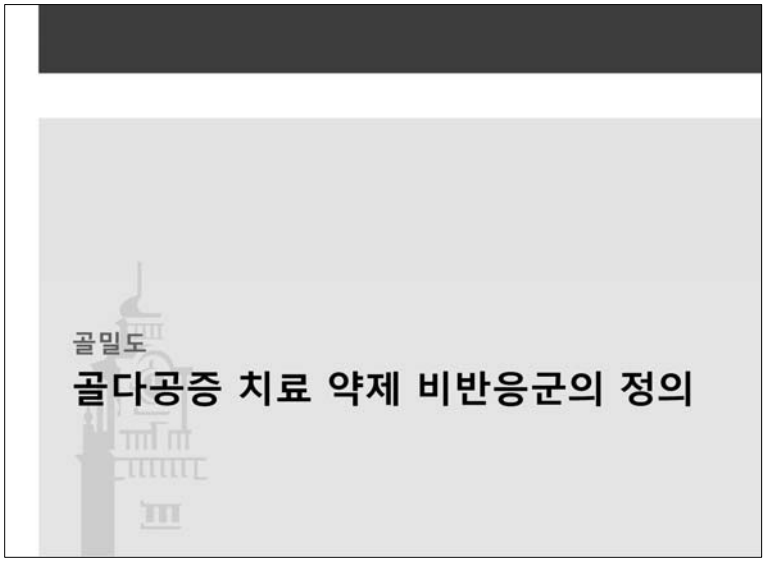
대한골다공증학회

제47회 연수강좌

골다공증 비반응군에 대한 치료전략

오 범 조

서울대학교 의과대학 가정의학과



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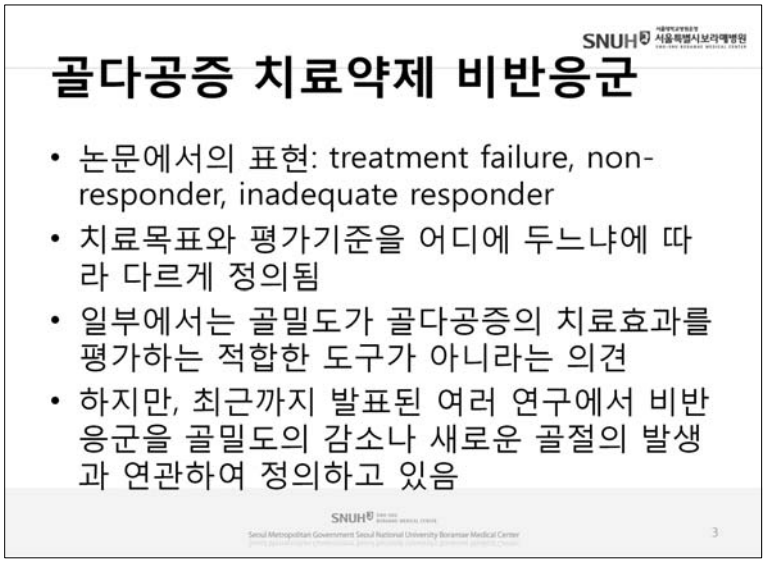

비반응군의 골밀도 평가

1. 같은 골밀도측정기로 동일한 조건에서 얻은 결과인가?
2. 골밀도 측정과 평가에서 기술적 오류는 없는가 ?
3. LSC를 상회하는 유의한 변화인가 ?
   → SDD (smallest detectable difference)라는 개념
   → 골다공증 치료 후 골밀도가 2% 이상 감소하였거나 절대 수치로 척추골밀도가 0.05 g/cm^2, 대퇴골 전체가 0.04 g/cm^2 이상 감소하면 비반응군으로 평가
4. 검사 기간 사이에 체중 변화, 퇴행성 변화나 압박골절을 비롯한 해부학적 구조 변화, 측정 부위의 시술 등 골밀도에 영향을 미칠 변화가 있는가 ?
5. 골밀도측정기의 질관리 (quality control, QC)가 제대로 이루어지고 있는가 ?

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골다공증 치료 약제의 진성 비반응군

약제에 대한 비반응군 (Non-responder)

- 약제 비반응군을 선별하는 목적은

1) 치료약제 선택의 적절성에 대한 평가
2) 약제의 변경
3) 약제 비반응군에 대한 재고찰 (2nd 원인)
4) 비반응군의 골절 예방

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비반응군 평가수단

1) 골절
   → 약물치료시 척추 골절은 30~70%, 대퇴골 골절은 40~50%, 비척추골절은 15~20% 정도 감소 효과 기대
2) 골밀도 (BMD)
   → 골다공증 치료후 골강도의 강화나 골절 예방 효과를 평가하는데 있어 BMD의 변화는 민감한 지표가 되지 못한다는 보고
3) 생화학적 골표지자 (BTM)
   → 치료반응의 평가에 있어 골표지자의 장점은 약제 시작후 짧은 시간내에 반응을 판단할 수 있으며, 반복 측정을 통해 변동성을 최소화할 수 있다는 점

약제에 대한 비반응군 (Non-responder)

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4) 비반응군의 골절 예방

Position statement from IOF CSA Inadequate Responders Working Group

- 2012년 IOF position statement에서 표방한 **inadequate responder**에 대한 정의

1) 2 부위 이상의 취약 골절 발생
2) 1 부위 골절+ BTM (βCTX or P1NP)의 유의한 차이가 없는 경우 and/or BMD의 유의한 감소
3) BTM (βCTX or P1NP)의 유의한 차이가 없으면서, BMD의 유의한 감소

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골다공증 치료약제 비반응군에 대한 대처

- 골다공증 약물 치료에 실패했을 때 (비반응군), 대안 치료 방안에 대한 임상적 근거는 확보되어 있지 않음 → 현재로서 제시할 수 있는 기본적 방침을 요약하면,

1) 보다 약한 골흡수억제제에 반응하지 않는 경우 보다 강한 골흡수억제제로 전환
2) 경구 약제에 반응하지 않는 경우 정맥 투여 약제로 전환
3) 강한 골흡수억제제에 반응하지 않는 경우 골형성 촉진제로 전환

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약물 순응도와 비반응군

약물 순응도

약물 순응도

: 약제를 꾸준히 지속적으로 사용하는 것

- 일정 기간(예를 들어 365일) 동안 실제 약제를 사용한 기간의 비로 표현되는 MPR (medication possession ratio)
- 약제를 중간에 끊지 않고 지속하여 사용한 기간으로 표현되는 지속도(persistence) 로 평가

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약제의 순응도에 영향을 미치는 요인

- 약제와 관련된 요인
  → 약제의 종류에 따라
- 환자 특성에 관련한 요인
  → 사회 경제적 수준, 성별, 나이에 따라
- 처방 의사에 관련한 요인
  → 어느 과 의사가 처방하는지에 따라

이차성 골다공증과 비반응군

이차성 골다공증과 비반응군

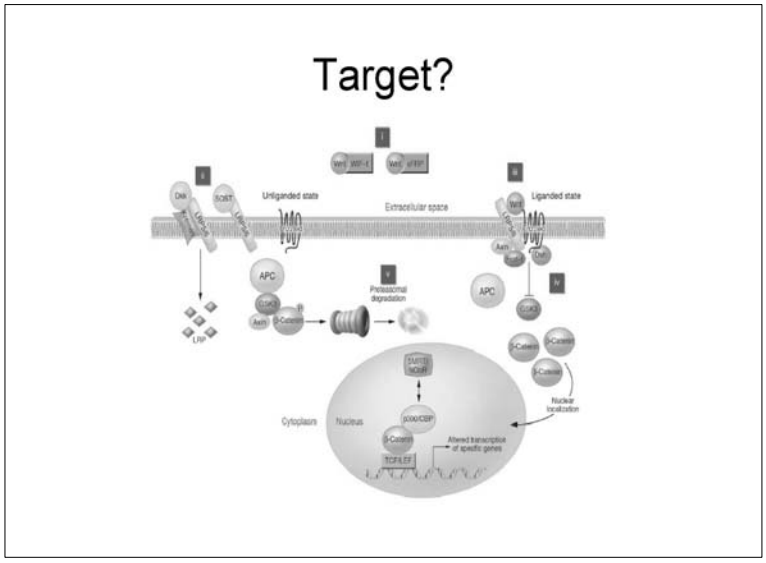
[권고안]

1. 치료 반응을 관찰하기 위해 새로운 골절 여부, 골밀도, 생화학적 골표지자를 측정할 수 있다.
2. 치료 반응을 평가하기 전에 다음을 확인해야 한다.
   - ✓ 약물복용은 규칙적으로 권고된 방법으로 투여되어야 한다.
   - ✓ 적절한 칼슘과 비타민D의 섭취를 포함하여 좋은 생활습관을 유지한다.
3. 폐경후 골다공증에서 1회 골절의 발생이 치료실패의 증거로 생각되지 않는 것을 고려 시 치료 기간 중 발생한 한번의 골절이 비반응군을 의미하지는 않는다. 그러나 현 시점에서 기존 연구의 부족으로 비반응군을 정의할 검사법, 골절 발생 횟수에 대해서 정의하기 어렵다. 향후 기저질환을 고려하고 개별화하여 판정하는 것이 필요할 것으로 생각된다.

골다공증 치료의 Target은 무엇일까?
(T-score or Fx Prevention or Bone Turnover Marker?)

김 광 준

연세대학교 의과대학 노년내과




PERSPECTIVE

JBMR

Goal-Directed Treatment of Osteoporosis

Steven R Cummings,[1] Felicia Cosman,[2,3] Richard Eastell,[4] Ian R Reid,[5] Mona Mehta,[1] and E Michael Lewiecki[6]

[1]San Francisco Coordinating Center, California Pacific Medical Center Research Institute and the Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA
[2]Regional Bone Center, Helen Hayes Hospital, West Haverstraw, NY, USA
[3]Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY, USA
[4]Department of Bone Metabolism, University of Sheffield, Sheffield, United Kingdom UK
[5]Department of Medicine, University of Auckland, Auckland, New Zealand
[6]New Mexico Clinical Research & Osteoporosis Center and the University of New Mexico School of Medicine, Albuquerque, NM, USA

SPECIAL FEATURE

JCEM

Position Statement

Treat-to-target for Osteoporosis: Is Now the Time?

E. Michael Lewiecki, Steven R. Cummings, and Felicia Cosman

New Mexico Clinical Research & Osteoporosis Center (E.M.L.), Albuquerque, New Mexico 87106; San Francisco Coordinating Center (S.R.C.), California Pacific Medical Center Research Institute and the Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California 94115; Regional Bone Center (F.C.), Helen Hayes Hospital, West Haverstraw, New York 10993; and Department of Medicine (F.C.), Columbia University College of Physicians and Surgeons, New York, New York 10032

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Goal or target to treat

1. 치료의 목표
2. 어디까지, 언제까지, 어떻게 치료할것인지?

What is a goal?

What do we have to consider when we treat the patients with osteoporosis?

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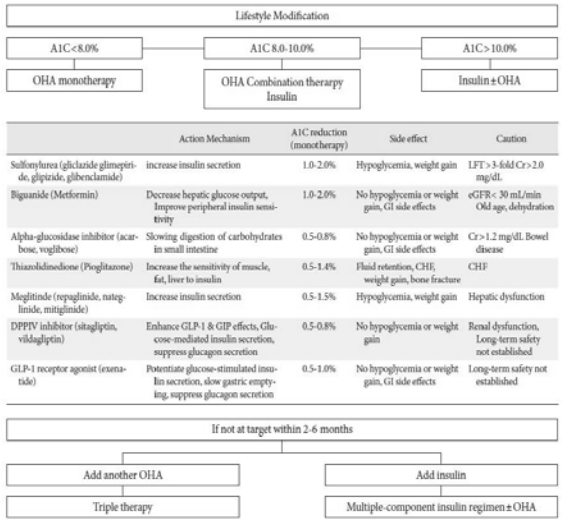

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AGS: American Geriatrics Society
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Treat-to-Target Example

- Hypertension

  Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

  target BP

  140/90 mm Hg to reduce the risk of CVD

  130/80mm Hg when DM or renal disease

- Hypercholesterolemia

  Coordinating Committee of the National Cholesterol Education Program

  LDL-C

  < 100 mg/dL CHD

  < 130 mg/dL ≥2 risk factors

  < 160 mg/dL 1 or none

  J Clin Endocrinol Metab, March 2013,

MEMO

Indicator

1. Diabetes: A1c
2. Hypercholesterolemia: LDL cholesterol
3. Hypertension: BP
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How about osteoporosis?

1. BMD?
2. BTM?
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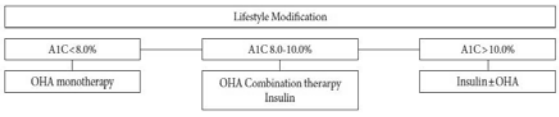

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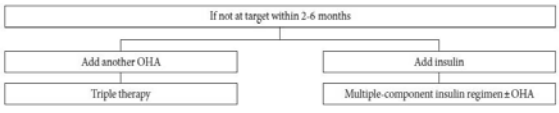

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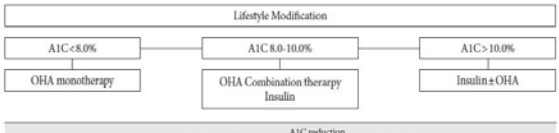

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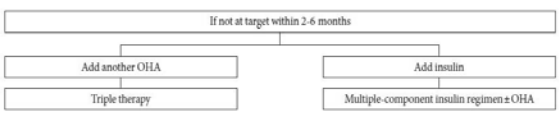
Meglitinde (repaglinide, nateglinide, mitiglinide)	Increase insulin secretion	0.5-1.5%	Hypoglycemia, weight gain	Hepatic dysfunction
DPPIV inhibitor (sitagliptin, vildagliptin)	Enhance GLP-1 & GIP effects, Glucose-mediated insulin secretion, suppress glucagon secretion	0.5-0.8%	No hypoglycemia or weight gain	Renal dysfunction, Long-term safety not established
GLP-1 receptor agonist (exenatide)	Potentiate glucose-stimulated insulin secretion, slow gastric emptying, suppress glucagon secretion	0.5-1.0%	No hypoglycemia or weight gain, GI side effects	Long-term safety not established



A New Consensus Statement from the ADA and AGS for Older Adults (2012)

Patient Characteristics/ Health Status	Rationale	Reasonable A1C Goal (A Lower Goal May Be Set for an Individual if Achievable without Recurrent or Severe Hypoglycemia or Undue Treatment Burden)	Fasting or Preprandial Glucose (mg/dL)	Bedtime Glucose (mg/dL)	Blood Pressure (mmHg)	Lipids
Healthy (Few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5%	90–130	90–150	<140/80	Statin unless contraindicated or not tolerated
Complex/intermediate (Multiple coexisting chronic illnesses[a] or 2+ instrumental ADL impairments or mild to moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0%	90–150	100–180	<140/80	Statin unless contraindicated or not tolerated
Very complex/poor health (Long-term care or end-stage chronic illnesses[b] or moderate to severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%[c]	100–180	110–200	<150/90	Consider likelihood of benefit with statin (secondary prevention more so than primary)

AGS: American Geriatrics Society
1. M.Sue Kirkman, et al. Diabetes in older adults. DOI:10.1111/jgs.12035

Treat-to-Target Example

- Hypertension
  Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
  target BP
  140/90 mm Hg to reduce the risk of CVD
  130/80mm Hg when DM or renal disease

- Hypercholesterolemia
  Coordinating Committee of the National Cholesterol Education Program
  LDL-C
  < 100 mg/dL CHD
  < 130 mg/dL ≥2 risk factors
  < 160 mg/dL 1 or none

J Clin Endocrinol Metab, March 2013,

Indicator

1. Diabetes: A1c
2. Hypercholesterolemia: LDL cholesterol
3. Hypertension: BP
4. CRF: GFR, Creatinine

MEMO

MEMO

How about osteoporosis?

1. BMD?
2. BTM?
3. Vitamin D?
4. Calcium?
5. Fracture?

- 치료의 목표를 어디에 둘것인가?

골다공증의 정의

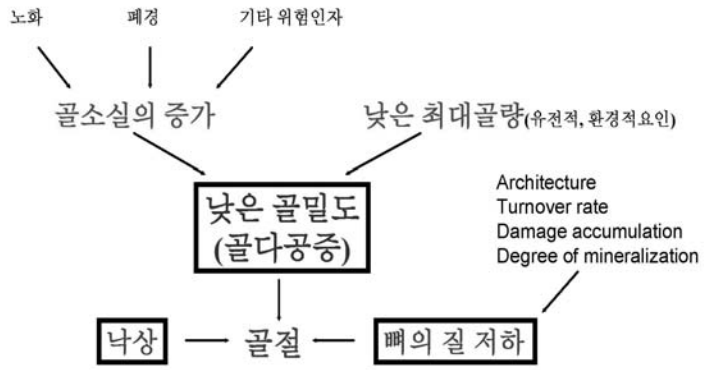
reduction in the strength of bone that leads to an increased risk of fractures

Bone Strength = Bone Quality + Bone Mineral Density

Architecture
Turnover rate
Damage accumulation
Degree of mineralization

NIH Consensus Development Panel on Osteoporosis. JAMA 285:785-95,2001

골다공증 골절의 발병기전



MEMO

Goal of osteoporosis therapy

- Prevent first fragility fracture or future fractures if one has already occurred
- Stabilize/increase bone mass
- Relieve symptoms of fractures and/or skeletal deformities
- Improve mobility and functional status
- Initiate lifestyle changes to enhance prevention of fractures

Prevention of Fracture!

Vitamin D

ORIGINAL ARTICLE
Endocrine Care

Vitamin D Insufficiency in Korea—A Greater Threat to Younger Generation: The Korea National Health and Nutrition Examination Survey (KNHANES) 2008

Han Seok Choi, Han Jin Oh, Hoon Choi, Woong Hwan Choi, Jung Gu Kim, Kyoung Min Kim, Kwang Joon Kim, Yumie Rhee, and Sung-Kil Lim

TABLE 2. Mean serum 25 (OH)D levels by participant characteristics in adults (n = 5,921)[a]

Factors	Male		Female	
	Serum 25(OH)D Level, ng/ml	P value[b]	Serum 25(OH)D Level, ng/ml	P value[b]
Age group, yr				
20–29	18.1 (7.0)		16.1 (5.7)	
30–39	20.6 (7.3)		17.3 (6.2)	
40–49	21.4 (7.0)		17.4 (6.5)	
50–59	22.9 (7.6)		19.9 (7.5)	
60–69	23.8 (7.5)		20.0 (7.9)	
70–79	23.0 (8.3)		19.0 (8.0)	
≥80	20.7 (8.1)	<0.001	17.6 (8.0)	<0.001

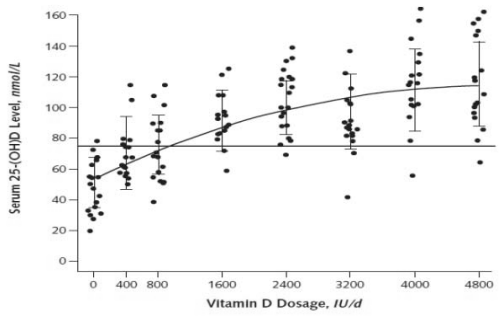
Age, yr

FIG. 1. Change of mean serum 25(OH)D levels stratified by 10-year age categories. To convert 25(OH)D levels to nanomoles per liter, multiply by 2.496.

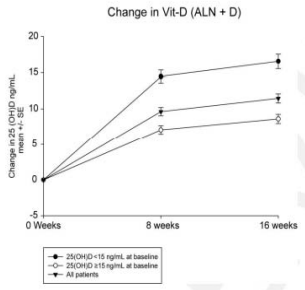
MEMO

Vitamin D supplement

- 100IU vitamin D supplement -> 1.0ng/ml 상승



Group	Baseline		Week 8		Week 16	
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD
ALD/D5600						
Vit D insufficiency at baseline	49	12.28 ± 1.46	46	26.70 ± 5.56***	49	28.84 ± 6.77***
Vit D non-insufficiency at baseline	87	22.15 ± 5.39	87	29.22 ± 4.52***	87	30.77 ± 5.22***
Total	136	18.60 ± 6.48	133	28.35 ± 5.03***	136	30.08 ± 5.87***



IOF position statement : Recommendations

target 25(OH)D level : 30 ng/mL
vitamin D requirement : 800-1000IU / day
intake increase to 2000IU per day
obese/ osteoporosis
limited sun exposure (요양원등)
mal-absorption

Dawson-Hughes Osteoporosis Int 2010

ESCEO 2013 Recommendations

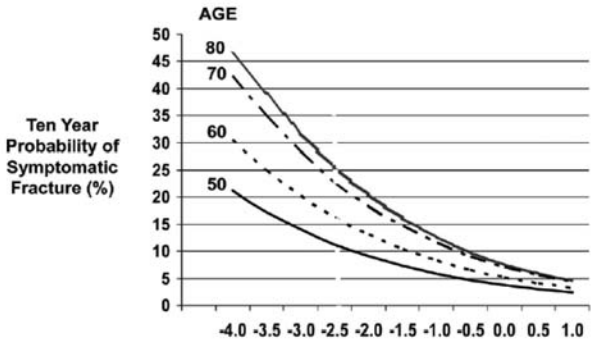
target level : 20ng/mL
fragile elderly with ↑ risk for fall& Fx : 30ng/ml
동일 요구량/ UL of safety 10,000IU / day

Current Medical Research & Opinion 2013

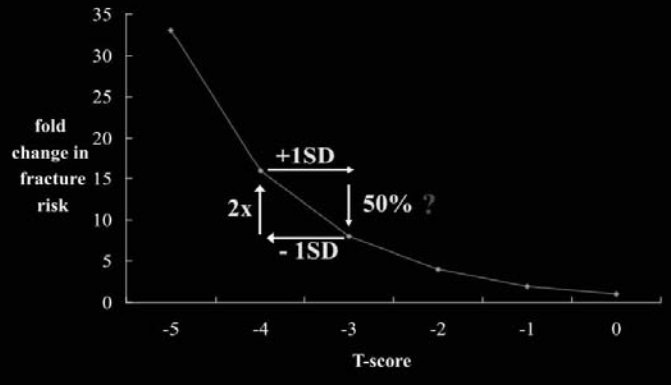
MEMO

BMD

BMD PREDICTS FRACTURES

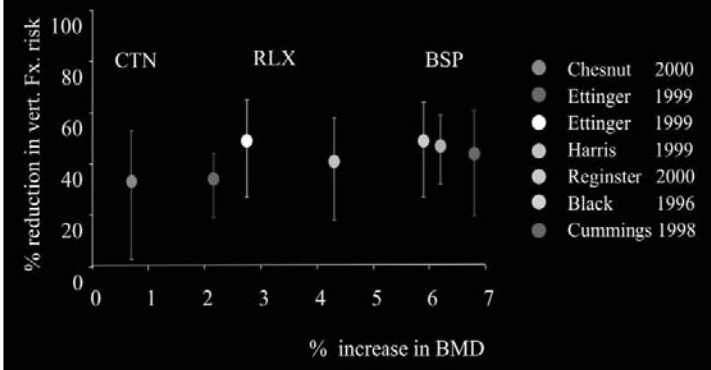


relationship btw BMD change and fx risk



MEMO

increase in BMD & risk of vertebral fx



… the mechanism by which antiresorptive drugs reduce skeletal fragility is explained only partially by changes in BMD…

Delmas PD. Bone 2000

… the relationship between BMD changes and fracture risk reduction with antiresorptive therapies is uncertain….

Marcus R. Endocrine Review 2002

BMD as a treatment target

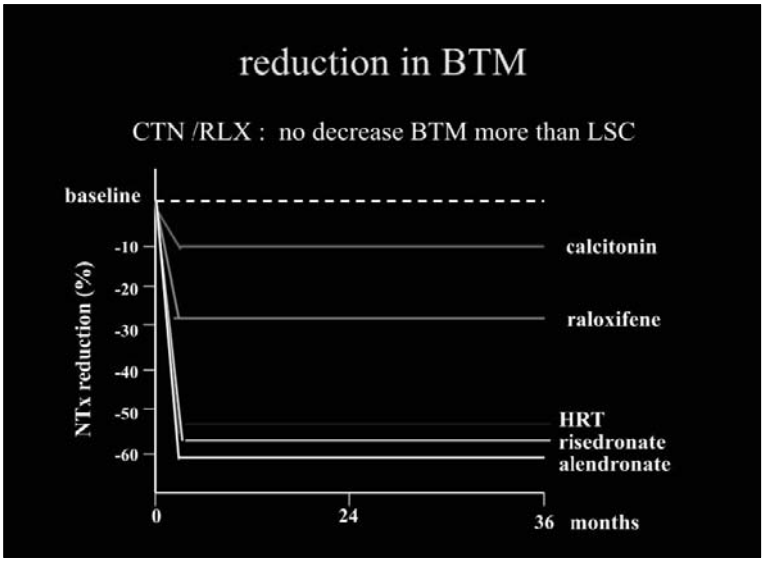
- Confounding factors: trabecular bone, cortical bone, geometry…
- ISCD recommendation: use BMD, not T-score for quanatative comparison

MEMO

BMD increase does not reflect a proportional to reduction of relative risk of fracture

Studies	Δ BMD (%)	%reduction of fracture risk
PROOF (Chesnut et al., Am.J.Med.2000)	0.5	36
MORE (Ettinger et al., JAMA 1999)	2.6	30
FIT1 (Black et al., Lancet 1996)	6.2	47
FIT2 (Cummings et al., JAMA 1998)	6.8	44
VERT-NA (Harris et al., JAMA 1999)	5.2	41
VERT-MN (Reginster et al. , Osteoporosis Int 2000)	6.3	49

Bone turnover marker



MEMO

BTM as a treatment target

- Monitor the effect of antiresorptive Tx
- Restarting Tx after drug holiday

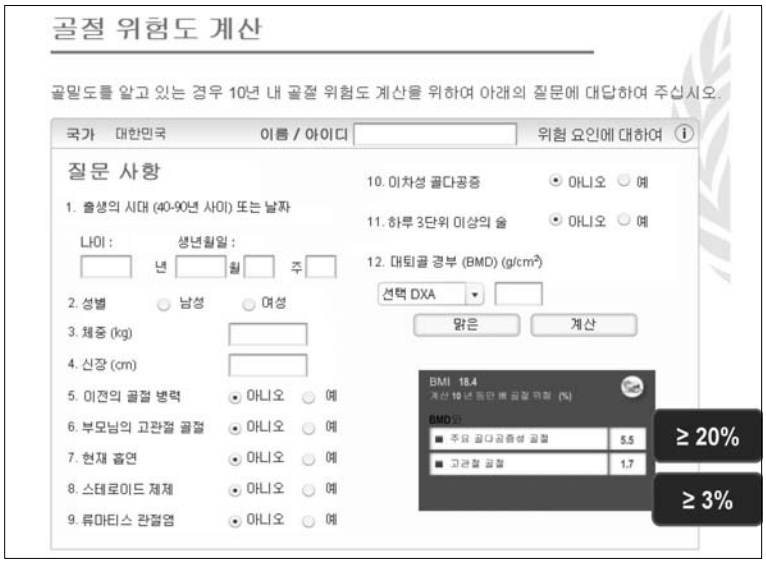
- Limitations

1. Assay variability/optimal BTM?
2. Availability/Affordability

BTM

	Assess baseline BTM levels: fasting serum BSALP or CTX or P1NP
	↓
Day 0	Start bisphosphonate therapy
3 months	Control BTM levels: decrease ≥ 30%
	If not:
	Check compliance
	Check if drug is taken properly (for instance, not with milk or calcium supplement, or waters rich in calcium)
	Drug storage
6 months	Control BTM levels: decrease > 30% + return to premenopausal state
1 year	Reassess BTM

Fracture risk



Fx risk as a treatment target

Measurement	Parameter	Pros	Cons
Fracture risk	Absolute value	FRAX is often used to select patients for initiation of therapy	FRAX is an algorithm that is still not familiar to many physicians and patients. FRAX requires extra effort to use and fully understand. FRAX does not account for all risk factors for fracture
	Change in value	Using a change in fracture risk as a target would account for differences among patients in the initial level of risk	FRAX value may not change, or even worsen with age, when an effective drug stabilizes but does not increase BMD

MEMO

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Indicator?

Table 1. Potential Indicators of Suboptimal Response to Osteoporosis Therapy

Indicator	Comments
No change in BMD	This is sometimes perceived as a treatment failure, although clinical trials have shown that stability of BMD on therapy is associated with a reduction in fracture risk.
Decrease in BMD	A statistically significant BMD decrease is cause for concern and should trigger evaluation for contributing factors. Possible causes include poor adherence to therapy, malabsorption, and taking medications or developing a disease or condition with harmful skeletal effects.
BMD initially increases but then remains stable	This is a typical response to treatment with bisphosphonates. When the BMD plateaus at a low level, it is not known whether a change in therapy that results in further increase in BMD provides additional antifracture benefit.
Failure of BTM to change as expected (decrease with antiresorptive therapy, increase with osteoanabolic therapy)	Although BTMs may have a role in monitoring therapy, their use in clinical practice is confounded by factors that include assay variability and uncertainty on which BTM is best for each drug. BTM changes occur sooner than BMD changes. BTMs are not covered by some major health insurance companies in the United States.
Failure to achieve an acceptable level of fracture probability	The goal of therapy is to reduce fracture risk. There is some evidence that FRAX generates a similar risk of major osteoporotic fracture in patients receiving prescriptions for oral antiresorptives. Other indices may be developed that are based on data from treated patients, taking into account changes on treatment.
Fracture	A fracture on therapy is an undesirable event that identifies the patient as being at higher risk for future fracture than previously recognized.

Target?

Table 2. Considerations for Osteoporosis Treatment Targets

Measurement	Parameter	Pros	Cons
BMD/T-score	Absolute value	DXA is widely available and currently used to monitor therapy. T-scores are used for diagnostic classification and to determine when treatment is indicated. Physicians and patients are already generally familiar with T-scores.	BMD is one of many risk factors for fracture. Other risk factors, particularly age and previous fragility fracture, are also important predictors of fracture risk. BMD values vary with different instruments and at different skeletal sites. An absolute target may not account for improvement when the baseline fracture risk is very high.
	Change in value	Osteoporosis therapy is often monitored by quantitative comparison of BMD. An increase in BMD is associated with reduction in fracture risk.	No change in BMD with therapy is also associated with reduction in fracture risk. There is debate on the magnitude of BMD change and reduction of fracture risk with therapy. A change in the reference database is a confounding factor in comparing T-scores.
BTM	Absolute value	A target level below or above the mean value for a healthy reference population might be used for antiresorptive and anabolic therapy, respectively.	An absolute value target may not recognize improvement from an extreme baseline level. It is not clear which BTM is best for which drug. Assay variability. Timing of specimen collection.
	Change in value	Looking for a significant change from the baseline value might avoid difficulties in assessing effect of therapy when the baseline value is extremely high or low.	Assessing the significance of a change in value requires knowledge of the LSC, which may vary for each BTM.
Fracture risk	Absolute value	FRAX is often used to select patients for initiation of therapy.	FRAX is an algorithm that is still not familiar to many physicians and patients. FRAX requires extra effort to use and fully understand. FRAX does not account for all risk factors for fracture.
	Change in value	Using a change in fracture risk as a target would account for differences among patients in the initial level of risk.	FRAX value may not change, or even worsen with age, when an effective drug stabilizes but does not increase BMD.

Summary

1. Vitamin D: 30ng/ml 라는 명확한 target, baseline 에 따라서 투여시 수치변화에 대한 근거가 있음. 3개월, 6개월 후 재검가능
2. BMD: 약제별로 변화의 차이가 있음. 어떠한 약제를 사용했는가에 대한 고려가 필요함. 감소시에는 반드시 compliance 등을 확인해 보아야 함.
3. BTM: anti-resorptive agent 의 효과 monitoring 에는 효과적임. 30% 이상 감소시에는 약제를 잘 유지하고 있음을 파악가능.
4. FRAX: 제한점이 있으나 보조적인 도구로는 가능

Conclusion

- 궁극적인 치료 목표는 골절의 예방이다.
- 골절을 예방하기 위한 골다공증의 치료에 있어서 현재까지 어느 한가지 indicator 를 가지고 치료 효과를 평가할 수는 없다.
- 때문에 현재 사용이 가능한 BMD, BTM, FRAX 를 복합적으로 이용해야 한다.
- 골다공증성 골절의 위험성을 평가할 수 있는 명확안 Indicator 의 개발과 이를 위한 임상연구등이 계속 이루어져야 한다.

MEMO

Thanks For Listening. Questions Welcome!

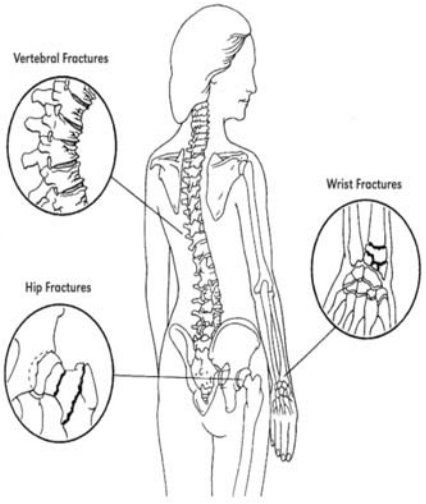
치료 약제의 순차적 사용

홍 상 모

한양대학교 의과대학 내분비대사내과

Definition of Osteoporosis

골다공증은 말 그대로 뼈에
구멍이 많이 생겨 뼈가 약하게
되어서 가볍게 넘어지거나
부딪히는 정도의 약한
충격에도 부러지기 쉬운 상태



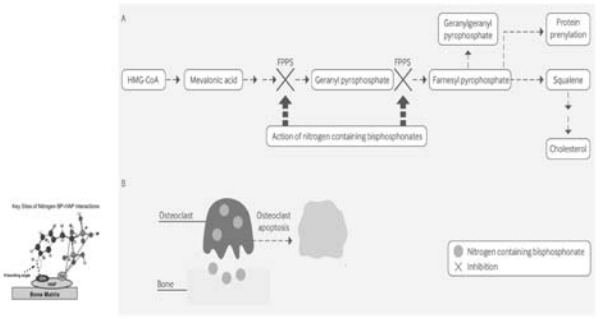
MEMO

Osteoporosis Medication

기전	계열	해당 성분
골흡수억제제	비스포스포네이트	alendronate, risedronate, pamidronate, ibandronate, zoledronic acid 등
	여성 호르몬	estrogen±progestogen, tibolone
	선택적 에스트로겐 수용체 조절제 (SERM)	raloxifene, bazedoxifene
	RANKL 억제제	denosumab
골형성촉진제	부갑상선호르몬제	teriparatide, teriparatide acetate
	Anti-sclerotin antibody	**Romosuzumab**

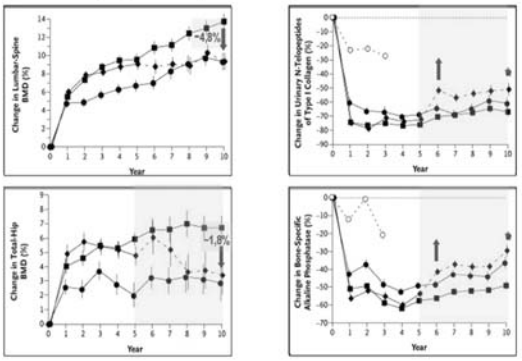
MEMO

Actions of Bisphosphonates



Mechanism of action of nitrogen containing bisphosphonates. (A) Nitrogen containing bisphosphonates selectively inhibit farnesyl pyrophosphate synthase (FPPS) within osteoclasts, which disrupts the HMG CoA-reductase pathway. (B) Osteoclast endocytosis of bisphosphonate from the bone surface leads to inhibition of FPPS and osteoclast apoptosis. HMG-CoA=3-hydroxy-3-methylglutaryl coenzyme A

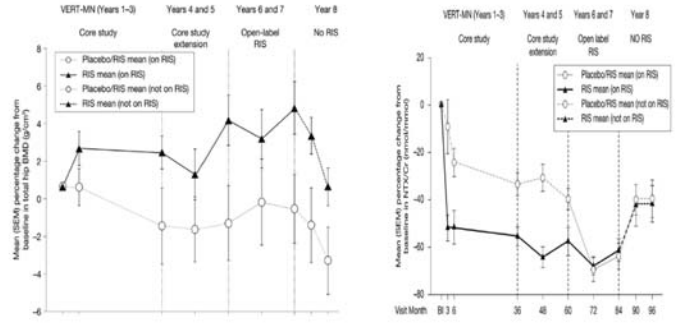
Variations of femoral or lumbar spine BMD and of two bone turnover markers (urine NTX or bone alkaline phosphatases) in the extension of phase 3 study with Alendronate in postmenopausal osteoporosis



Adami, S., Idolazzi, L., Fracassi, E., Gatti, D., & Rossini, M. (2013). Osteoporosis treatment: when to discontinue and when to re-start. *Bone research*, *1*(1), 323-335.

Changes in femoral neck BMD and urine NTX in patients of VERT-MN study participating in the extension study.

the return to pre-treatment levels of bone turnover and BMD occurs after about one year in patients treated with RIS and five years in those treated with ALN for 4 years.



Adami, S., Idolazzi, L., Fracassi, E., Gatti, D., & Rossini, M. (2013). Osteoporosis treatment: when to discontinue and when to re-start. *Bone research*, *1*(1), 323-335.

MEMO

IMPACT OF FDA'S SAFETY ANNOUNCEMENTS ON BISPHOSPHONATE USE

FDA safety announcements

Osteonecrosis of the jaw (ONJ) in May 2005

Atrial fibrillation in October 2007

Atypical femur fracture in March 2010

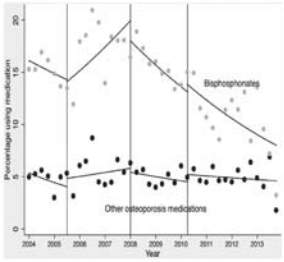
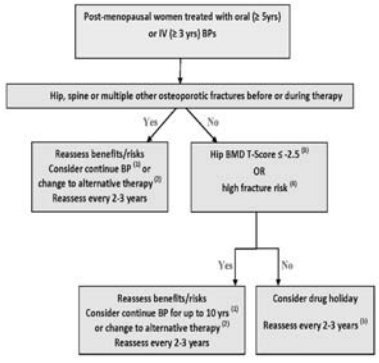


Fig. 1. Impact of FDA safety announcements on the use of osteoporosis medications following hip fracture. Dots represent the observed values. The solid lines are the predicted values from the regression models fit to the person-level data. Three vertical lines indicate the quarters immediately after the three FDA announcements (far left for osteonecrosis of the jaw, middle for atrial fibrillation and far right for atypical femur fracture) were released.

J Bone Miner Res. 2016 Mar 11. doi: 10.1002/jbmr.2832

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

Approach to the management of postmenopausal women on long-term bisphosphonate therapy.



However, there is no real evidence that the interruption of therapy prevents complications, and the optimal length of the interruption is

Increased risk (40%) for fractures during the drug ho

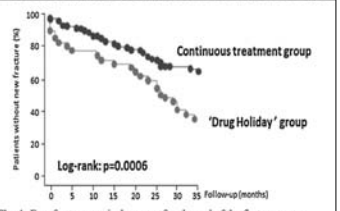
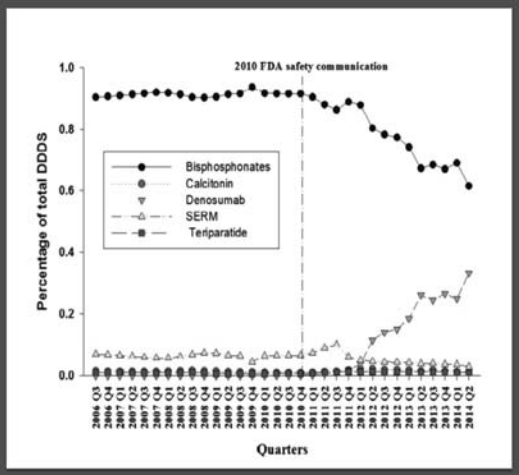


Fig. 4 Free-fracture survival curves after the end of the first sequence

Journal of Bone and Mineral Research, Vol. 31, No. 1, January 2016, pp 16–35
Osteoporos Int (2017) 28:3431–3438

따라서 다른 골다공증 약에 대해서 관심과 처방이 증가.....

MEMO



Market share of osteoporosis drug defined daily dose in the medicaid fee-for-service program (Q3 2006-Q2 2014).

Saudi Pharm J. 2018 Feb;26(2):238-243. doi: 10.1016/j.jsps.2017.12.005.

Osteoporosis Medication

기전	계열	해당 성분
골흡수억제제	비스포스포네이트	alendronate, risedronate, pamidronate, ibandronate, zoledronic acid 등
	여성 호르몬	estrogen±progestogen, tibolone
	선택적 에스트로겐 수용체 조절제 (SERM)	raloxifene, bazedoxifene
	RANKL 억제제	denosumab
골형성촉진제	부갑상선호르몬제	teriparatide, teriparatide acetate
	Anti-sclerotin antibody	Romosuzumab

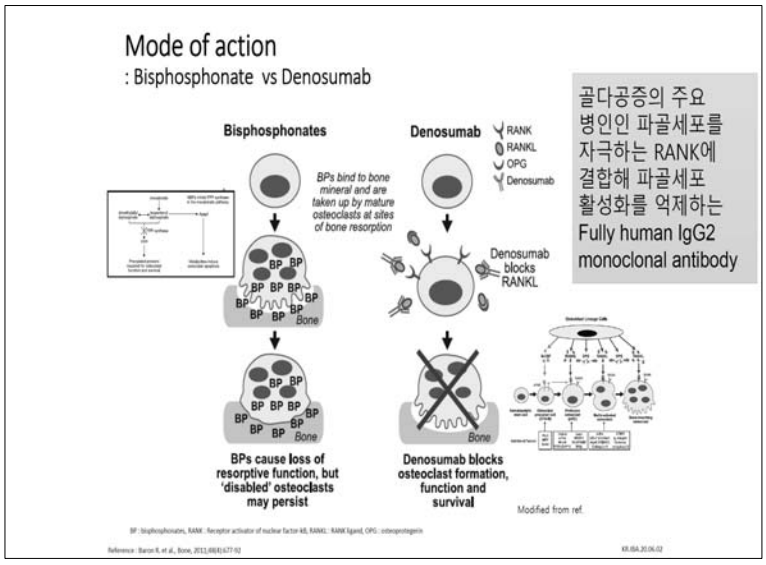
Denosumab (Prolia)

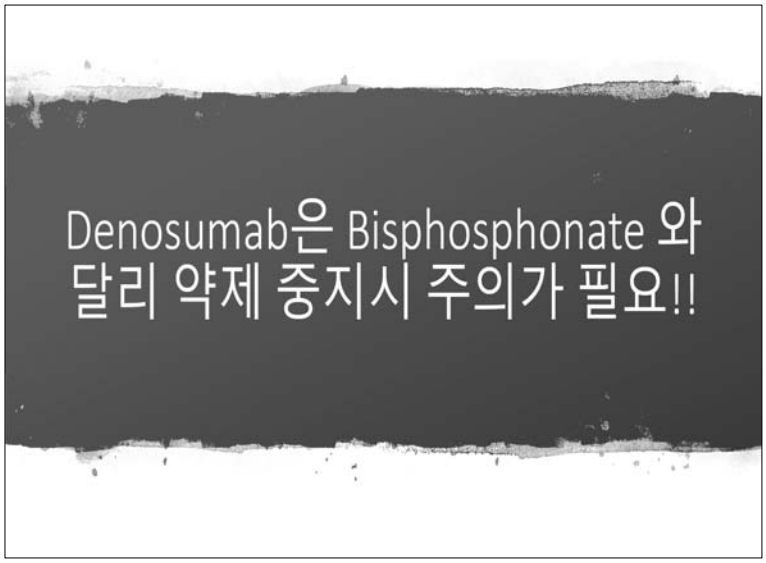
6개월 마다 주사 맞고 빠르게 효과가 나타나며 가역적인 골흡수억제제

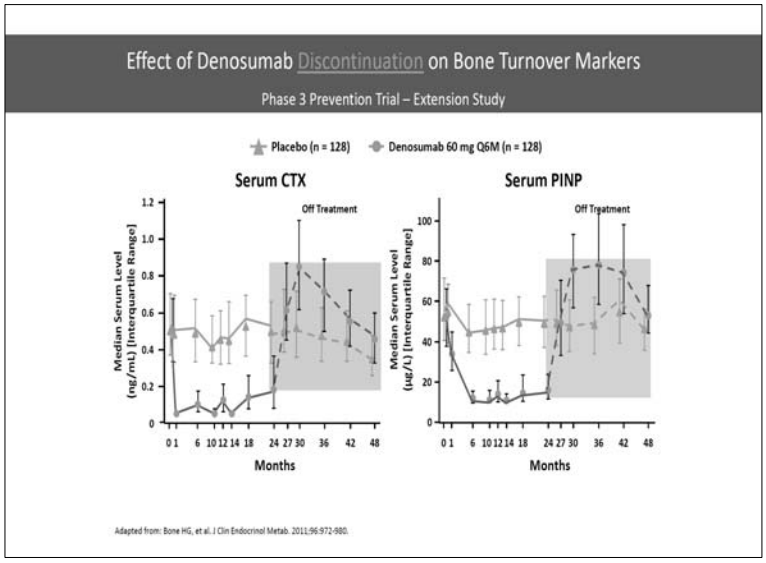
- 치료 적응증
  1. 폐경 후 여성 골다공증 환자의 치료
  2. 남성 골다공증 환자의 골밀도 증가를 위한 치료
  3. 안드로겐 차단요법을 받고 있는 비전이성 전립선암 환자의 골 소실 치료
  4. 아로마타제 저해제 보조요법을 받고 있는 여성 유방암 환자의 골 소실 치료
- 치료전 주의 사항
  - 저칼슘혈증이 있으면 치료 시작 전에 반드시 교정해야 한다.
  - 비타민D 결핍이 있으면 치료 시작 전 보충을 시작해야 한다.
  - 임산부 금기
- 용법
  - 6개월 마다 상완 허벅지 또는 복부에 피하 (Subcutaneous) 주사 한다.
  - 모든 환자는 칼슘 1000 mg과 비타민D 400 IU 이상을 매일 복용해야 한다.

https://www.amgen.co.kr/~/media/amgen/full/www-amgen-com/www-amgen-co-kr/downloads/products/prolia_pi_korean.ashx?la=ko-KR

MEMO

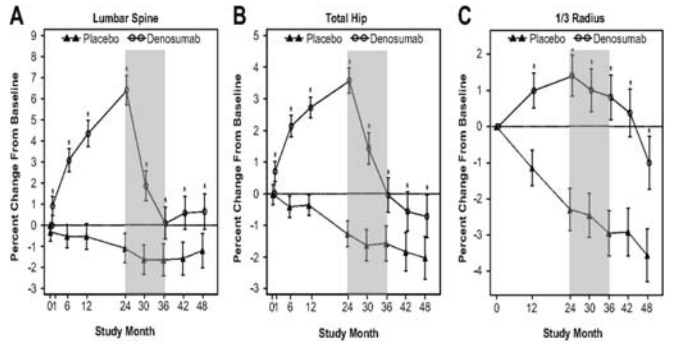

Mode of action
: Bisphosphonate vs Denosumab
Bisphosphonates
Denosumab
RANK
RANKL
OPG
Denosumab
BPs bind to bone mineral and are taken up by mature osteoclasts at sites of bone resorption
Denosumab blocks RANKL
Bone
BPs cause loss of resorptive function, but 'disabled' osteoclasts may persist
Denosumab blocks osteoclast formation, function and survival
Modified from ref.
골다공증의 주요 병인인 파골세포를 자극하는 RANK에 결합해 파골세포 활성화를 억제하는 Fully human IgG2 monoclonal antibody


Denosumab은 Bisphosphonate 와
달리 약제 중지시 주의가 필요!!


Effect of Denosumab Discontinuation on Bone Turnover Markers
Phase 3 Prevention Trial – Extension Study
Placebo (n = 128)
Denosumab 60 mg Q6M (n = 128)
Serum CTX
Serum PINP
Off Treatment
Median Serum Level (ng/mL) [Interquartile Range]
Median Serum Level (µg/L) [Interquartile Range]
Months
Adapted from: Bone HG, et al. J Clin Endocrinol Metab. 2011;96:972-980.

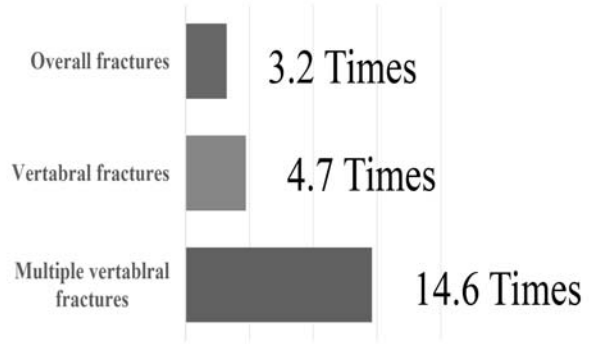
MEMO

Percentage change from month 0 in Lumbar Spine (A), Total Hip (B), and 1/3 Radius (C) BMD over 48 months



Henry G Bone et al. J Clin Endocrinol Metab. 2011 Apr;96(4):972-80.

Incident rate ratios per 100 patients-years among denosumab discontinuer vs. persistent user: Real-world data from a large healthcare provider



Bone 2020 Jan;130:115150.

Clinical Guideline for Denosumab

- **Position statement by A systematic review and position statement by ECTS (2017)**
  - Patients and physicians should be aware that treatment with denosumab should not be stopped without considering an alternative (antiresorptive) treatment.
- **Endocrine Society (2019)**
  - In postmenopausal women with osteoporosis taking denosumab, administration of denosumab should not be delayed or stopped without subsequent antiresorptive.
- **AACC/ACE Guideline 2020 update**
  - If treatment is discontinued, patients should be transitioned to an alternative antiresorptive therapy.

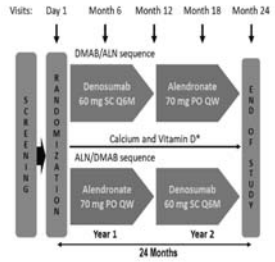
따라서 Prolia 처방 전에 prolia 치료 후 다른 골흡수억제제의
비급여 치료에 대해서 설명이 필요 합니다.

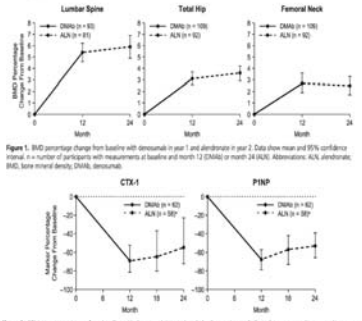
MEMO

Limited data are available on patients transitioning from denosumab to bisphosphonates, such as alendronate

Bone Mineral Density After Transitioning From Denosumab to Alendronate

Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women





Osteoporos Int (2012) 23:317–326
J Clin Endocrinol Metab 105: e255–e264, 2020

Bone Mineral Density After Transitioning From Denosumab to Alendronate

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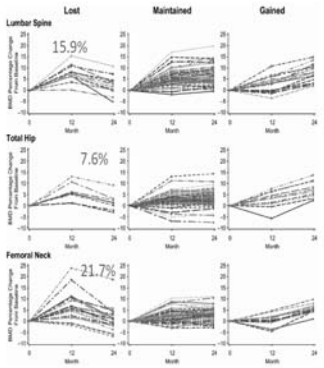


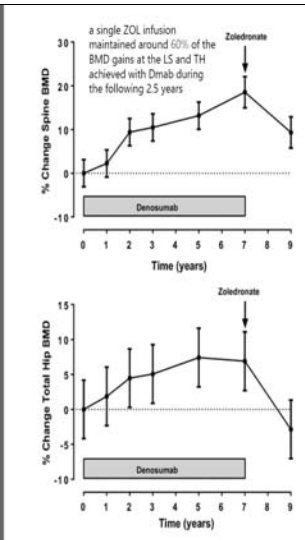
Osteoporos Int (2012) 23:317–326
J Clin Endocrinol Metab 105: e255–e264, 2020

MEMO

Bone loss after denosumab: only partial protection with zoledronate.

Effects of denosumab followed by zoledronate on BMD in postmenopausal women with osteoporosis. Changes in BMD from the time that denosumab was initiated are shown as mean and 95% confidence intervals. Denosumab was administered, 60 mg every 6 months, from 0 to 7 years, then a single infusion of zoledronate 5 mg, given at year 7. BMDs were measured 18–23 months after zoledronate treatment. No osteoporosis treatments were given between years 7 and 9

Calcified Tissue International volume 101, pages371–374(2017)



Zoledronate was given after a median delay of 65 days from trial-end : in the hope that this might increase skeletal uptake of the drug

Calcified Tissue International volume 103, pages55–61(2018)

achieved 73% retention of the BMD gains at the LS and 87% retention of the gains at the TH

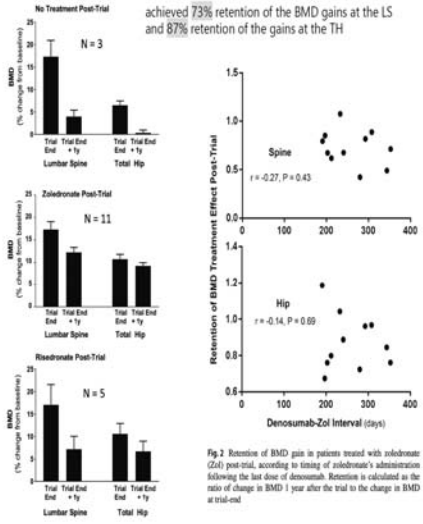


Fig. 2 Retention of BMD gain in patients treated with zoledronate (Zol) post-trial, according to timing of zoledronate's administration following the last dose of denosumab. Retention is calculated as the ratio of change in BMD 1 year after the trial to the change in BMD at trial-end

Treatment with Zoledronate Subsequent to Denosumab in Osteoporosis: a Randomized Trial

Solling, A. S., et al. (2020). *Journal of Bone and Mineral Research*. https://doi.org/10.1002/jbmr.4098

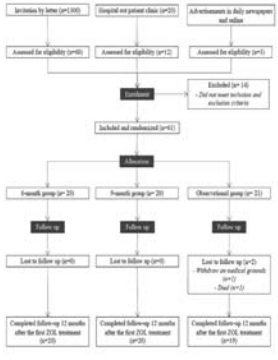


Table 1. Baseline Characteristics

Study population (n = 61)	6-month group (n = 20)	9-month groups (n = 20)	Observation group (n = 21)
Gender, n (%)			
Male	2 (10)	3 (15)	2 (10)
Female	18 (90)	17 (85)	19 (90)
Age (years), mean ± SD	68 ± 8	65 ± 7	69 ± 9
Height (cm), mean ± SD	162 ± 6.8	166 ± 8.8	165 ± 8.3
Weight (kg), mean ± SD	62.9 ± 11.4	67.0 ± 14.3	66.8 ± 13.2
Body mass index (kg/cm²), mean ± SD	24.0 ± 4.2	24.4 ± 4.6	24.3 ± 2.9
Prior fracture, n (%)	10 (50)	10 (50)	11 (52)
Years with osteoporosis, mean ± SD	8.0 ± 4.1	5.9 ± 3.3	6.2 ± 3.2
Years treated with DMAB, mean ± SD (range)	5.2 ± 1.8 (2–7)	4.4 ± 1.5 (2–7)	4.4 ± 1.5 (2–8)
Prior treatment with ALN, n (%)	14 (70)	11 (55)	18 (86)
Years treated with ALN, mean ± SD (range)	0.86 ± 0.9 (0.08–2.8)	0.70 ± 0.7 (0.08–2.0)	0.82 ± 0.6 (0.08–2.0)
Prior treatment with other BP, n (%)	4 (20)	4 (20)	1 (5)
Years treated with other BP, mean ± SD (range)[a]	1.1 ± 1.9 (0.08–4)	1.3 ± 1.7 (0.08–4)	7
Bone mineral density (g/cm²), mean ± SD			
Lumbar spine (L_1–L_4)	0.860 ± 0.055	0.878 ± 0.063	0.871 ± 0.089
Total hip	0.791 ± 0.104	0.779 ± 0.078	0.803 ± 0.072
Femoral neck	0.656 ± 0.102	0.668 ± 0.062	0.677 ± 0.088
T-scores, mean ± SD			
Lumbar spine (L_1–L_4)	−1.6 ± 0.5	−1.6 ± 0.6	−1.8 ± 0.7
Total hip	−1.3 ± 0.7	−1.4 ± 0.6	−1.2 ± 0.5
Femoral neck	−1.8 ± 0.9	−1.7 ± 0.6	−1.6 ± 0.7
TBS, mean ± SD[b]	1.24 ± 0.07	1.25 ± 0.07	1.25 ± 0.08
p-CTX (µg/L), mean ± SD[c]	0.21 ± 0.20	0.21 ± 0.17	0.26 ± 0.17
p-P1NP (µg/L), mean ± SD[c]	21 ± 10	21 ± 11	24 ± 11
p-osteocalcin (µg/L), mean ± SD[c]	9 ± 3	9 ± 3	9 ± 2

ALN = alendronate; BP = bisphosphonate; DMAB = denosumab; p-CTX = p-C-terminal collagen crosslinks; p-P1NP = p-procollagen type I N-terminal propeptide; TBS = trabecular bone score.
[a]TBS reference value for postmenopausal women: ≥1.350: normal; TBS = 1.20–1.35: partially degraded microarchitecture; TBS ≤1.200: degraded microarchitecture.
[b]Bisphosphonate: n = 6, risedronate: n = 2, etidronate followed by risedronate: n = 1.
[c]Reference intervals for premenopausal women: p-CTX <0.39 µg/L, p-P1NP 17–124 µg/L, p-osteocalcin 10–47 µg/L.

MEMO

Treatment with Zoledronate Subsequent to Denosumab in Osteoporosis: a Randomized Trial

Sølling, A. S., et al. (2020). *Journal of Bone and Mineral Research*. https://doi.org/10.1002/jbmr.4098

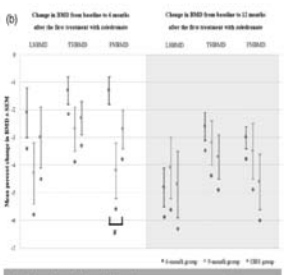


Table 2. The Proportion of Patients Who Failed to Maintain BMD

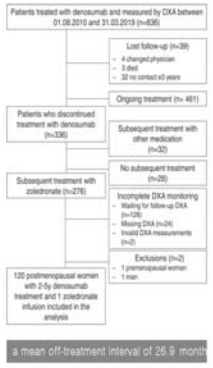
	6 months after the first ZOL, n (%)			12 months after the first ZOL, n (%)		
Group	LSBMD	THBMD	FNBMD	LSBMD	THBMD	FNBMD
6-month group (n = 20)	6 (30)	1 (5)	0 (0)	13 (65)	3 (15)	4 (20)
9-month group (n = 20)	9 (45)	5 (25)	8 (40)	13 (65)	7 (35)	6 (30)
Observation group (n = 19)	9 (47)	2 (11)	3 (16)	12 (63)	7 (37)	7 (37)
p	0.50	0.17	0.004*	0.99	0.25	0.52

BMD loss beyond the least significant change: ±3% LS and ±5% loss at TH or FN. Values of *p* are between-group differences (ANOVA).
BMD = bone mineral density; FNBMD = femoral neck BMD; LSBMD = lumbar spine BMD; THBMD = total hip BMD.

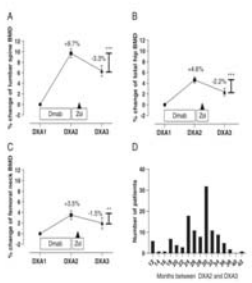
In patients discontinuing DMAB after long-term treatment a single intravenous infusion of ZOL 5 mg given 6 or 9 months after the last DMAB injection or when bone turnover is increased is not sufficient to completely prevent bone loss.

Incident vertebral fractures were seen in two women in the 9M group.

A Single Infusion of Zoledronate in Postmenopausal Women Following Denosumab Discontinuation Results in Partial Conservation of Bone Mass Gains



a mean off-treatment interval of 26.9 month



A single infusion of 5 mg zoledronate after a 2- to 5-year denosumab treatment cycle retained more than half of the gained BMD and was not associated with multiple vertebral fractures, as reported in patients who discontinued denosumab without subsequent bisphosphonate

J Bone Miner Res. 2020 Jul;35(7):1207-1215. doi: 10.1002/jbmr.3962. Epub 2020 Feb 11.

Effect of risedronate on bone loss at discontinuation of denosumab

Laroche, M., et al. (2020). Effect of risedronate on bone loss at discontinuation of denosumab. *Bone Reports*, 100290.

- The patients started risedronate (RIS) treatment six months after the last denosumab injection.
- The risedronate regimen was one 35 mg ta-blet per week for 3 months.

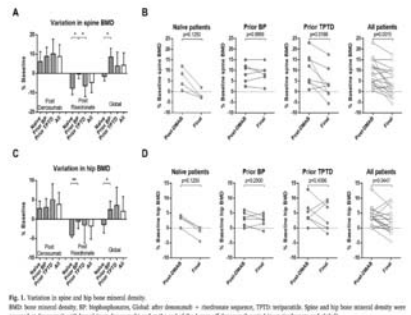
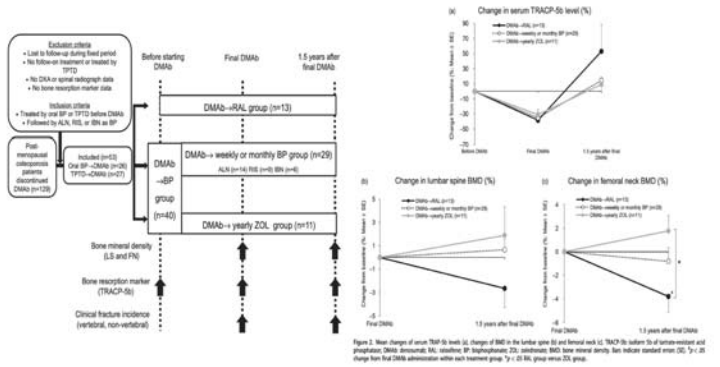


Fig. 1. Variation in spine and hip bone mineral density.
BMD: bone mineral density; BP: bisphosphonate; Global: after denosumab → risedronate sequence; TPTD: teriparatide. Spine and hip bone mineral density were assessed at denosumab withdrawal (post-denosumab) and at the end of the 1-year off-denosumab period (post-risedronate and global).

Three months of risedronate treatment does not prevent bone loss in patients who have not been treated with bisphosphonates before denosumab.

MEMO

Effects of follow-on therapy after denosumab discontinuation in patients with postmenopausal osteoporosis



Ebina, Kosuke, et al. *Modern Rheumatology* just-accepted (2020): 1-21.

Denosumab 중단 후 어떻게 해야 하나요? (정리)

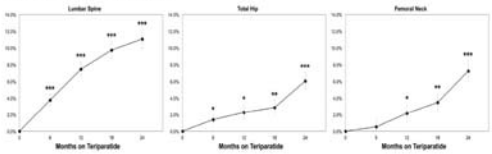
- Bisphosphonate와 같은 강력한 골다공증 약제를 추가 사용해야 한다
- Bisphosphonate 투여 후에도 골밀도나 bone turnover maker등을 지속적으로 추적 해야 한다.

Teriparatide 도.....

MEMO

Bone Density After Teriparatide Discontinuation in Premenopausal Idiopathic Osteoporosis

a Change in BMD on Teriparatide



b Change in BMD after Teriparatide Cessation

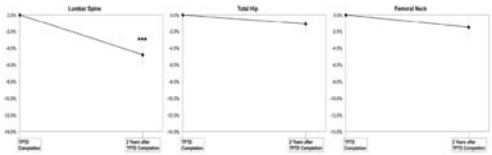


Figure 1. A, Change in BMD on teriparatide for the 15 women included in this study. B, Change in BMD 2.0 ± 0.6 y after teriparatide cessation. Graphs are shown ± SE. For percent change vs baseline: *, P < .05; **, P < .01; ***, P < .001.

Compared with the time of teriparatide completion, BMD measured at the follow-up timepoint 2.0 0.6 years after teriparatide cessation had declined significantly at the LS (-4.8±4.3%; P = .0007) but remained stable at the FN (-1.5± 4.2%), TH (-1.1±3.7%), and 1/3 radius (+0.2±2.5%); Figure 1B.

J Clin Endocrinol Metab. 2015 Nov; 100(11): 4208–4214.

Bone Density After Teriparatide Discontinuation in Premenopausal Idiopathic Osteoporosis

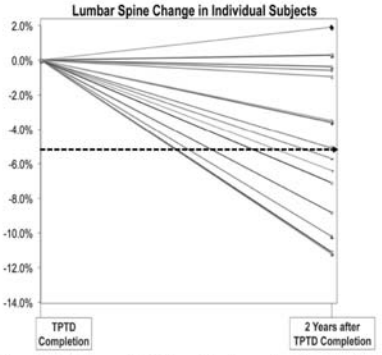
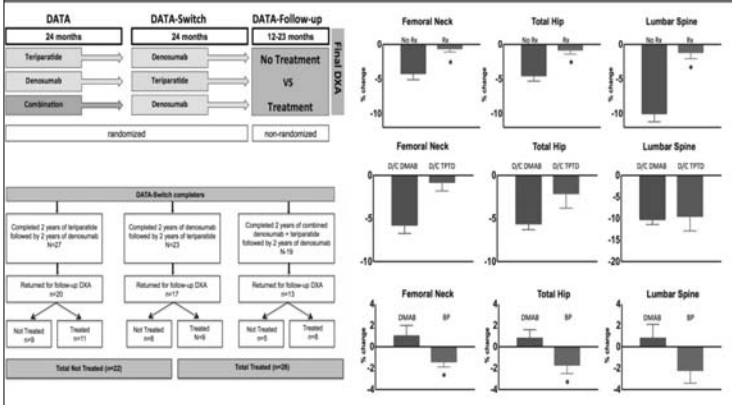


Figure 2. BMD loss at the LS 2.0 ± 0.6 y after teriparatide cessation was quite variable.

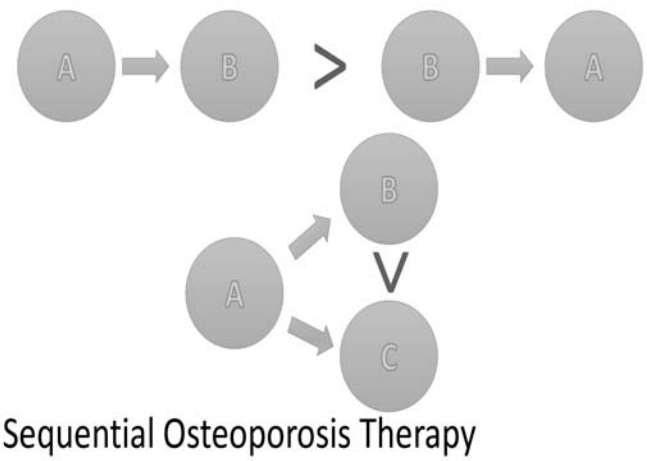
J Clin Endocrinol Metab. 2015 Nov; 100(11): 4208–4214.

Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial



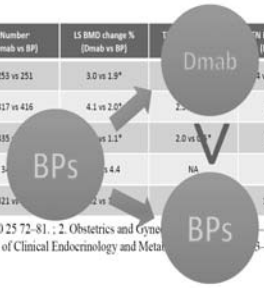
Leder, B. Z., et al. (2017). *Bone*, *98*, 54-58.

MEMO



The effect of switching from BPs to denosumab or continuing on the same or other BP on BMD and BTM in women with postmenopausal osteoporosis

Study	Comparison (duration)	Number (Dmab vs BP)	LS BMD change % (Dmab vs BP)	TH BMD change % (Dmab vs BP)	Radius BMD change % (Dmab vs BP)	Suppression of BTMs
1	From ALN to Dmab or ALN (1 year)	253 vs 251	3.0 vs 1.9*	4 vs 0.4* (approx)	0.8 vs 0.1* (approx)	Greater with Dmab
2	From oral BPs to Dmab or IBN (1 year)	417 vs 416	4.1 vs 2.0*	1.7 vs 0.7*	NA	Greater with Dmab
3	From ALN to Dmab or RIS (1 year)	435	vs 1.1*	2.0 vs 0.3*	1.4 vs 0.0*	NA	Greater with Dmab
4	From ZOL to Dmab or ZOL (1 year)	3	s 4.4	NA	NA	NA	Greater with Dmab
5	From oral BPs to Dmab or ZOL (1 year)	321 vs	2 vs	1.2 vs −0.1*	0.6 vs 0.0*	Greater with Dmab



1. Journal of Bone and Mineral Research 2010 25 72–81. ; 2. Obstetrics and Gyne –1299. ; 3. Bone 2014 58 48–54. ; 4. Osteoporosis International 2015 26 2521–2527. ; 5. Journal of Clinical Endocrinology and Meta 3–3170.

Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial

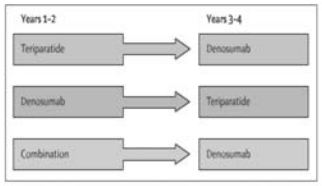
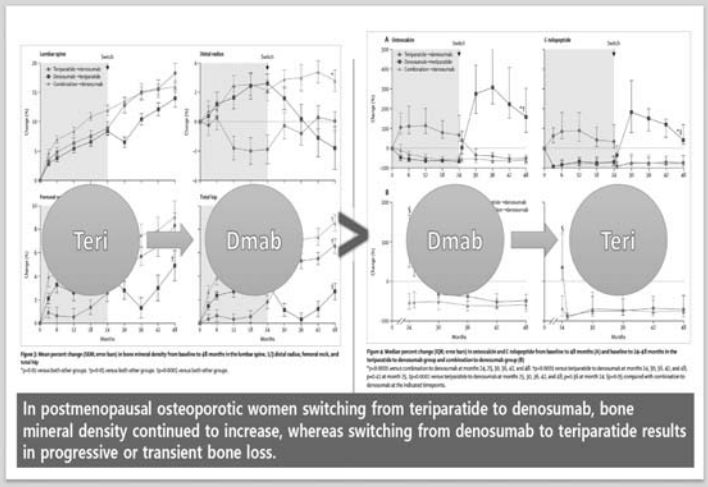


Figure 1: DATA-Switch study design

Lancet 2015; 386: 1147–55

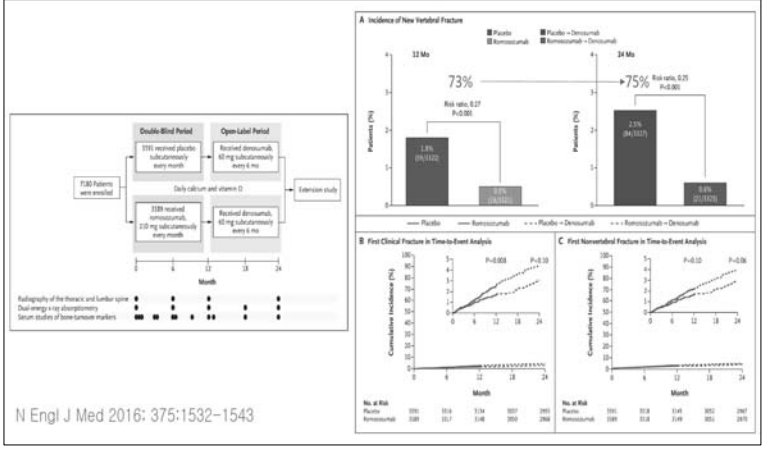
Figure 2: Trial profile
ITT=intention to treat.

MEMO



In postmenopausal osteoporotic women switching from teriparatide to denosumab, bone mineral density continued to increase, whereas switching from denosumab to teriparatide results in progressive or transient bone loss.

Romosozumab Treatment in Postmenopausal Women with Osteoporosis



N Engl J Med 2016; 375:1532–1543

Take home massage

- Denosumab 치료를 중단할 때 대체 골 흡수억제 제재 치료법으로 전환해야 한다.
- 기존의 비스포스포네이트로 치료 목표에 도달하지 못한 환자에서 추가적인 골밀도 상승을 위해 denosumab 약제로의 전환 고려 해야 한다.
- 골 형성제 치료에 적응증 환자라면 먼저 골형성제 치료 후 denosumab 치료을 이어서 처방하는 것이 골밀도 증가에 효과 적이다.