

골다공증 약물의 안전한 사용 (경구제, 주사제)

김 범 택

아주의대 가정의학과

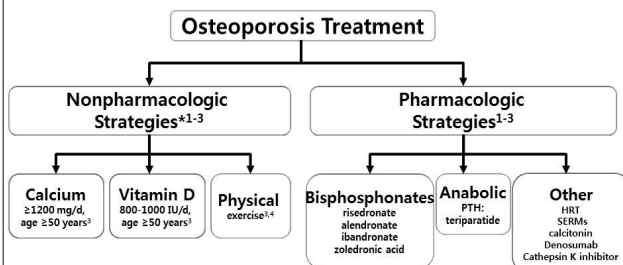
강의 내용

- ◆ Principles of Osteoporosis Treatment
- ◆ Factors to consider for osteoporosis medications
- ◆ Adverse effects of osteoporosis medications
- ◆ Give the Best you have



Principles of Osteoporosis Treatment

Osteoporosis Treatment Strategies



SERM=selective estrogen receptor modulator; RANK-L=RANK ligand.

*Including supplements if necessary.

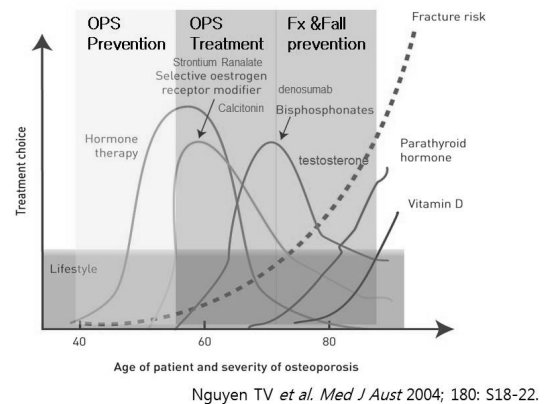
1. NIH, JAMA. 2001;285:785-795.

2. AACE. Endocr Pract. 2003;9:544-564.

3. NOF. Clinician's Guide to Prevention and Treatment of Osteoporosis. NOF; 2010.

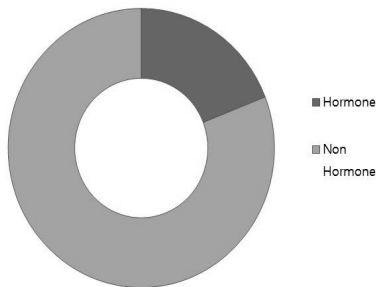
4. US DHHS. Bone Health and Osteoporosis: A Report of the Surgeon General. Office of the Surgeon General; 2004.

What options do we have?

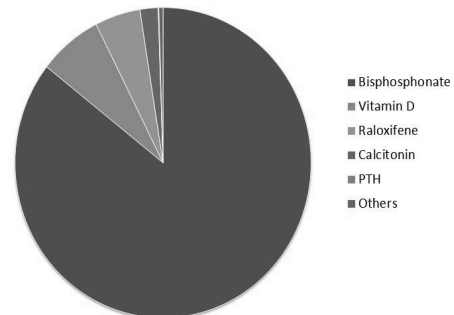


Nguyen TV et al. Med J Aust 2004; 180: S18-22.

HRT vs. Non-HRT



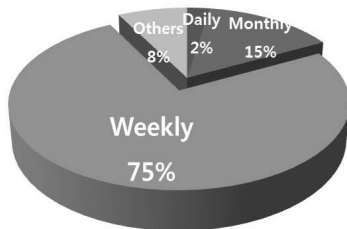
Bisphosphonates Rule !



J Korean Soc Menopause. 2010 Dec;16(3):170-175

The Most Commonly Prescribed BPs

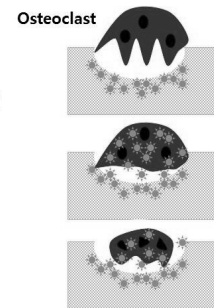
Total Prescriptions for Traditional Bisphosphonates, %*



2011 2Q IMS data

Why Bisphosphonates ?

- Proven efficacy
- Interval of medication
- Low cost
- Safety



Less Frequent Dosing

❖ Alendronate

- 5mg daily
- 10mg daily
- 70mg weekly, 70mg weekly

❖ Risedronate

- 5mg daily
- 35mg weekly
- 150mg monthly

❖ Ibandronate

- 2.5mg daily
- 150mg monthly
- 3mg q 3month (IV)

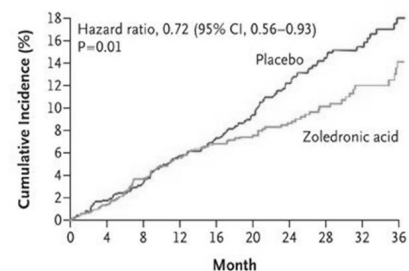
❖ Zoledronate

- 5mg q 1year (IV)

❖ Palmidronate

- 15mg q 3 month (IV)

Mortality after fracture

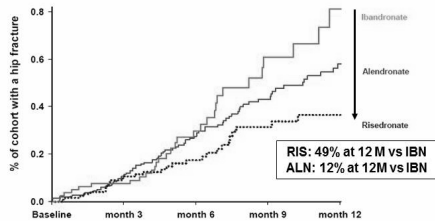


No. at Risk

Zoledronic acid	1054	1029	987	943	806	674	507	348	237	144
Placebo	1057	1028	993	945	804	681	511	364	236	149

Real life data show the consistency with RCTs
- REAL (IBN addition) study – Hip fracture

Incidence of hip fracture during 12 months of bisphosphonate use



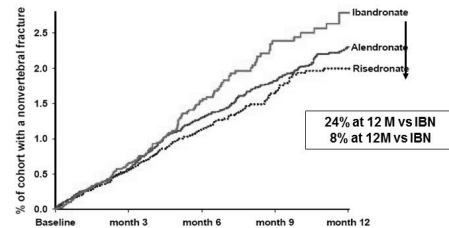
Patients at risk (fracture events)

Alendronate	21615 (0)	21590 (25)	12993 (54)	8677 (69)	5582 (80)
Risedronate	12215 (0)	12202 (13)	6847 (19)	4319 (27)	2584 (29)
Ibandronate	7850 (0)	7844 (6)	3745 (16)	2151 (27)	1163 (30)

Ringe JD et al. Effectiveness of Bisphosphonate treatment on hip fractures: an observational cohort study of risedronate and alendronate with the addition of ibandronate. [Abstract] Calcif Tissue Int 2008; 82 (suppl 1): S245, Abs. Tu-P483. 39th ECTS

Real life data show the consistency with RCTs
- REAL (IBN addition) study – Non-vertebral fracture

Nonvertebral fracture incidence during 12 months of bisphosphonate use

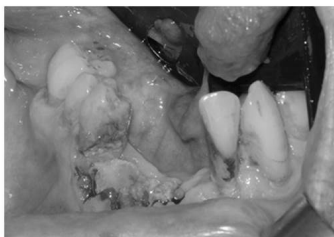


Patients at risk (fracture events)

Alendronate	21615 (0)	21489 (126)	12794 (253)	8439 (308)	5319 (343)
Risedronate	12215 (0)	12147 (68)	6743 (123)	4196 (162)	2449 (164)
Ibandronate	7850 (0)	7799 (51)	3699 (99)	2113 (123)	1145 (129)

Ringe JD et al. Effectiveness of Bisphosphonate treatment on hip fractures: an observational cohort study of risedronate and alendronate with the addition of ibandronate. [Abstract] Calcif Tissue Int 2008; 82 (suppl 1): S245, Abs. Tu-P483. 39th ECTS

BRONJ and Atypical fracture



골다공증을 치료하는 의사의 어려움



Factors to consider for osteoporosis medications

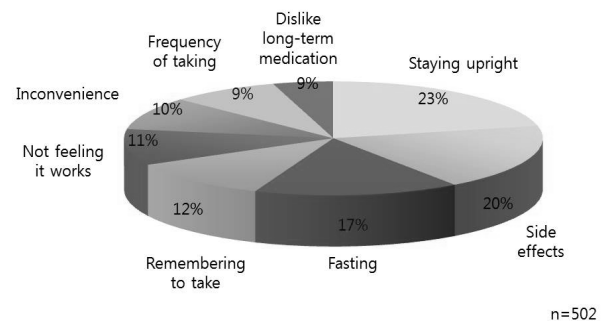
When Should We Stooooop?



Long Term Treatment



Why Pts Stop?



IOF, 2005
http://www.osteofound.org/publications/pdf/adherence_gap_report.pdf

Ideal OPS medication

	Easy	to Take
	Greatest	Efficacy
The	Long-term	Prevention
	Least	Adverse Effects
	Reasonable	Cost

Adverse effects of osteoporosis medications

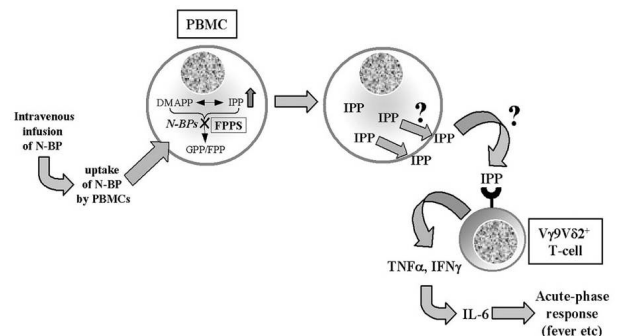
Are BPs Safe?

Short term vs. Long term

- | | |
|---|--|
| <ul style="list-style-type: none"> • Acute phase reaction • Upper GI trouble • Musculoskeletal pain • Hypocalcemia • Ocular inflammation • Skin reactions | <ul style="list-style-type: none"> • BRONJ • Atypical Fracture • Renal Toxicity • Atrial Fibrillation(?) • Esophageal cancer(?) |
|---|--|

Drugs. 2011;71(6):791-814

Flu like reaction (Acute phase reaction)



Renal Toxicity

• Restrain of Use when

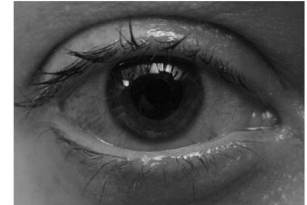
- Risedronate : CCR < 30 mL/min
- Ibandronate : CCR < 30 mL/min
- Alendronate : CCR < 35 mL/min
- Zoledronate : CCR < 35 mL/min



Manufacturer's instructions

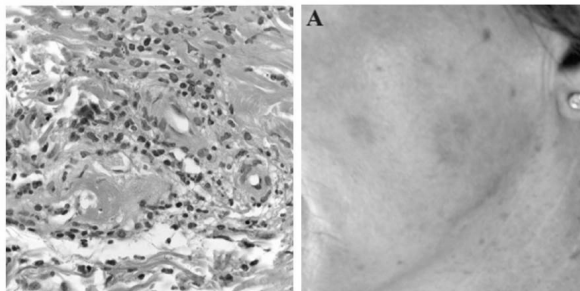
Ocular inflammation

- Iritis, Uveitis, Scleritis
- Ocular pain & photo sensitivity
- Variable duration



Mayo Clin Proc. 2009;84(7):632-8

Ibandronate related dermatitis



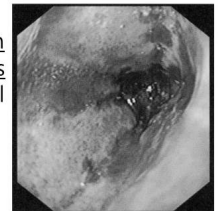
Eur J Dermatol. 2011;21(4):591-4

Erosive esophagitis

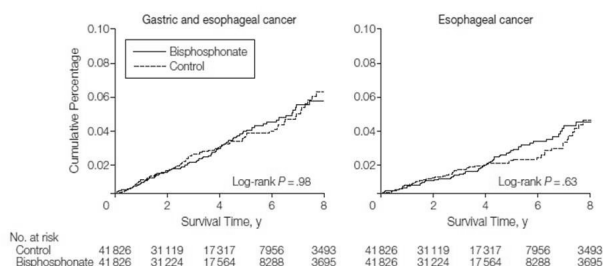
Most common reason for patient intolerance to oral BPs

Resulting from failure to maintain an upright posture for 30 to 60 minutes after ingesting medication with a full glass of water

IV BPs or SERMs



BPs and Esophageal cancer



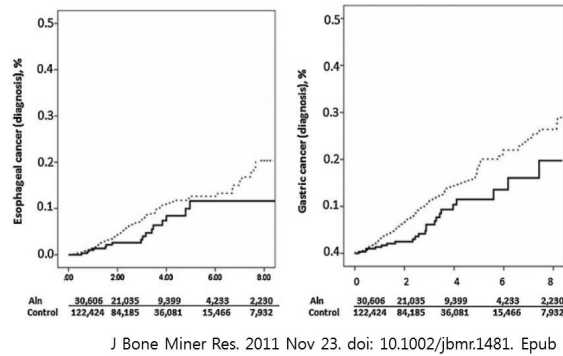
JAMA. 2010 ;304(6):657-63.

BPs and Esophageal cancer

Category	Cases (0 prescriptions/ ≥10 prescriptions)	Relative risk (95% CI)	Relative risk (95% CI)
All women	2864/50		1.93 (1.37 to 2.70)
Age at index date			
40-69 years	1220/9		3.14 (1.32 to 7.46)
≥70 years	1644/41		1.77 (1.22 to 2.56)
P for heterogeneity=0.2			
Sex			
Men	1856/12		1.57 (0.81 to 3.04)
Women	1008/38		2.08 (1.40 to 3.08)
P for heterogeneity=0.5			
Smoker			
Yes	1366/22		1.55 (0.94 to 2.58)
No	1166/26		2.22 (1.40 to 3.52)
P for heterogeneity=0.3			
Alcohol drinker			
Yes	1879/33		2.08 (1.36 to 3.16)
No	406/8		1.18 (0.54 to 2.60)
P for heterogeneity=0.2			

Green J et al. BMJ 2010;341:bmj.c4444

Alendronate and UGI cancers

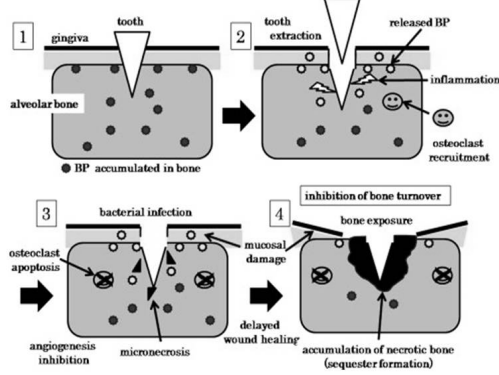


Alendronate and UGI cancers

	No. of prescriptions	Crude		Adjusted	
		OR	95% CI	OR	95% CI
Esophageal cancer	Any	0.75	(0.46-1.22)	0.71	(0.43-1.19)
	1	2.12	(0.86-5.22)	1.96	(0.79-4.89)
	2-9	0.85	(0.34-2.08)	0.81	(0.32-2.04)
	10+	0.53	(0.27-1.05)	0.51	(0.25-1.02)
Gastric cancer	Any	0.58	(0.37-0.91) ^a	0.61	(0.39-0.97) ^a
	1	1.06	(0.39-2.88)	1.15	(0.42-3.13)
	2-9	0.91	(0.44-1.85)	0.99	(0.48-2.05)
	10+	0.40	(0.21-0.75) ^a	0.42	(0.22-0.81) ^a
Combined outcome	Any	0.61	(0.44-0.84) ^a	0.63	(0.45-0.87) ^a
	1	1.32	(0.68-2.57)	1.36	(0.70-2.67)
	2-9	0.86	(0.50-1.47)	0.90	(0.52-1.56)
	10+	0.42	(0.27-0.66) ^a	0.44	(0.27-0.69) ^a

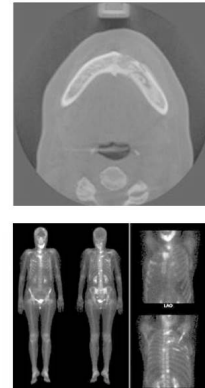
J Bone Miner Res. 2011 Nov 23. doi: 10.1002/jbmr.1481. Epub

Pathophysiology of BRONJ



BRONJ diagnosis

- No X-ray
- CT
- MRI
- Bone Scan

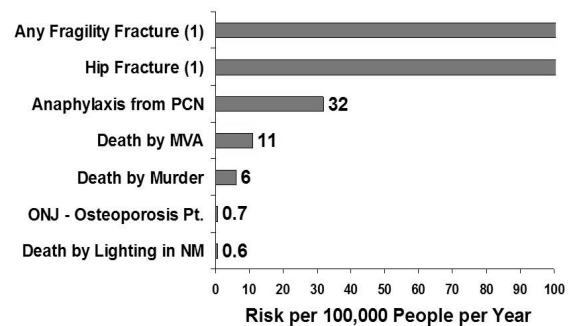


Stage of BRONJ

At risk category	No apparent exposed/necrotic bone in patients who have been treated with either oral or IV bisphosphonates
Stage 0	Nonspecific clinical findings and symptoms such as jaw pain or osteosclerosis but no clinical evidence of exposed bone
Stage 1	Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage
Stage 3	Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border or sinus floor

Ann N Y Acad Sci. 2011 Feb;1218:38-46

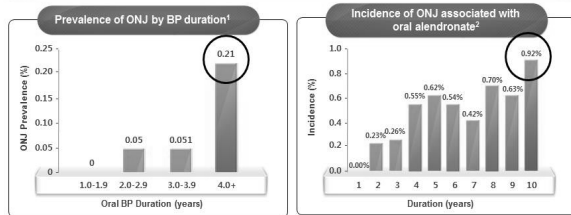
ONJ Comparative Risks



[M. Lewiecki 2007]

Increase of Incidence of ONJ in Long-term BP Therapy

- BP 복용 시 절대적인 발병률은 높지 않으나, BP를 오래 복용할수록 발병률 증가¹
- Alendronate를 4년 이상 복용 시 발병률이 급증함²
- 10년 이상 복용 시 발병률이 0.92%까지 증가함²



Study design: 1. The "Predicting Risk of Osteonecrosis with Bisphosphonate Exposure" (PROBE) study was a cross-sectional study conducted to determine the prevalence of ONJ among patients using oral bisphosphonates and to examine other possible risk factors and effect modifiers for the development of ONJ among patients with oral bisphosphonate exposure. 2. Using an electronic medical records system and manual confirmation of ONJ, patients who began taking osteoporosis treatment and developed ONJ were identified between January 2000 and April 2012.

1. Lo JC, et al. J Oral Maxillofac Surg 2010;68:243-53. 2. Chiu WY, et al. J Clin Endocrinol Metab 2014;99:2729-35

Management Strategies of MRONJ

- 여러 기관에서 MRONJ의 관리에 대해 서로 다른 견해를 보임
- 최근 ONJ Task Force에서는 BP에 장기 노출 시 ONJ의 위험이 높다고 발표함

2011 : the ADA Council on Scientific Affairs¹

- Patients receiving lower cumulative doses of BP (<2 years) or denosumab may continue antiresorptive therapy during invasive dental treatment

2015 : International ONJ Task Force²

- Recommended drug holiday in higher risk patients for developing ONJ
 - greater cumulative bisphosphonate exposure (>4 years)³
 - multiple risk factors (diabetes, periodontal disease, glucocorticoid treatment, immune deficiencies, smoking, etc.)²

2014 : AAOMS Position Paper on MRONJ³

- No evidence that discontinuing oral bisphosphonates for 3 months prior to and 3 months following invasive dental surgery alters the risk of ONJ patients
- Patients who have taken oral BP ≥ 4 years, discontinuation (drug holiday) for 2 month before surgery

MRONJ = medication-related osteonecrosis of the jaw; AAOMS = American association of oral and maxillofacial surgeons; ADA = American dental association; DM = Diabetes mellitus; RA = Rheumatic Arthritis

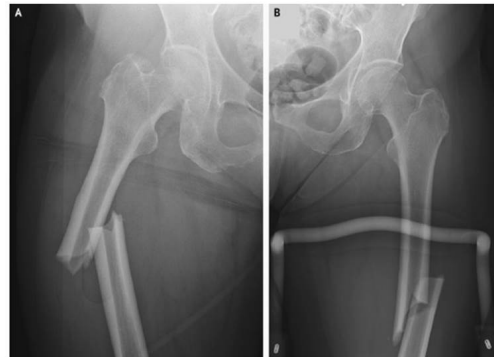
1. Hellstein JW, et al. J Am Dent Assoc 2011;142:1243-1251.
2. Khan AA, et al. JBM 2015; 30(1):3-23
3. MRONJ Position Paper- 2014 update.

Duration of Bisphosphonate Therapy				
	Transient, <100 days	Short-term Use, 100 days to 3 years	Intermediate Use, 3 to 5 Years	Long-Term Use, ≥5 Years
No. (%) of patients				
Case (n = 9723)	817 (8.4)	5587 (57.5)	2438 (25.1)	881 (9.1)
Control (n = 48 564)	3434 (7.1)	27 086 (55.8)	13 148 (27.1)	4896 (10.1)
Odds Ratio (95% CI)				
Crude	1.0 [Reference]	0.87 (0.80-0.94)	0.72 (0.65-0.79)	0.65 (0.58-0.74)
Adjusted ^a	1.0 [Reference]	0.93 (0.81-1.07)	0.86 (0.73-1.00)	0.76 (0.63-0.93)

Duration of Bisphosphonate Therapy				
	Transient, <100 days	Short-term Use, 100 days to 3 years	Intermediate Use, 3 to 5 Years	Long-Term Use, ≥5 Years
No. (%) of patients				
Case (n = 716)	42 (5.9)	349 (48.7)	204 (28.5)	121 (16.9)
Control (n = 3580)	218 (6.1)	1832 (51.2)	1070 (29.9)	460 (12.9)
Odds Ratio (95% CI)				
Crude	1.0 [Reference]	1.00 (0.70-1.43)	1.08 (0.73-1.59)	1.74 (1.11-2.73)
Adjusted ^a	1.0 [Reference]	0.90 (0.48-1.68)	1.59 (0.80-3.15)	2.74 (1.25-6.02)

JAMA. 2011 Feb 23;305(8):783-9.

Atypical Fracture



Diagnostic Criteria

Characteristics	Sensitivity (%)	Specificity (%)	Accuracy (%)
Reader 1			
Focal lateral cortical thickening	100 (19/19)	89.5 (17/19)	94.7 (36/38)
Transverse fracture	89.5 (17/19)	84.2 (16/19)	86.8 (33/38)
Medial spike	79.0 (15/19)	73.7 (14/19)	76.3 (29/38)
Comminution	73.7 (14/19)	73.7 (14/19)	73.7 (28/38)
Reader 2			
Focal lateral cortical thickening	100 (19/19)	68.4 (13/19)	84.2 (32/38)
Transverse fracture	89.5 (17/19)	79.0 (15/19)	84.2 (32/38)
Medial spike	73.7 (14/19)	73.7 (14/19)	73.7 (28/38)
Comminution	79.0 (15/19)	63.2 (12/19)	71.1 (27/38)
Reader 3			
Focal lateral cortical thickening	94.7 (18/19)	89.5 (17/19)	92.1 (35/38)
Transverse fracture	94.7 (18/19)	79.0 (15/19)	86.8 (33/38)
Medial spike	84.2 (16/19)	84.2 (16/19)	84.2 (32/38)
Comminution	79.0 (15/19)	79.0 (15/19)	79.0 (30/38)

AJR Am J Roentgenol. 2011;197(4):954-60

ASBMR Task Force 2013 Definition of AFF

- To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare.
- In addition, at least four of five major features must be present. None of the Minor Features is required but have sometimes been associated with these fractures.

ASBMR Task Force 2013

Major features

- Minimal/no trauma: The fracture is associated with minimal or no trauma, as in a fall from a standing height or less
- Transverse fracture line: The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur
- Medial Spike: Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
- Noncomminuted: The fracture is noncomminuted or minimally comminuted
- Beaking/Flaring: Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring")

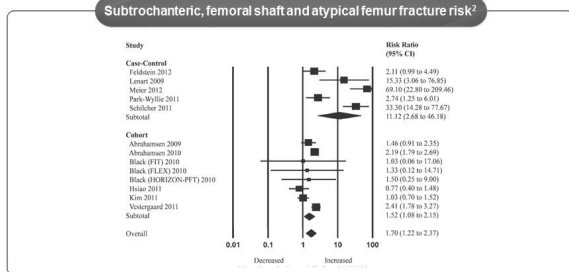
AFF=Atypical femoral fracture; ASBMR=American society for bone and mineral research

Shane E, et al. JBM 2014;29:1-23

Risk Factors of Atypical Fracture – BP Use

- BP 사용 시 AFF, subtrochanteric 및 femoral shaft 골절이 증가함¹

ASBMR Task Force 2013



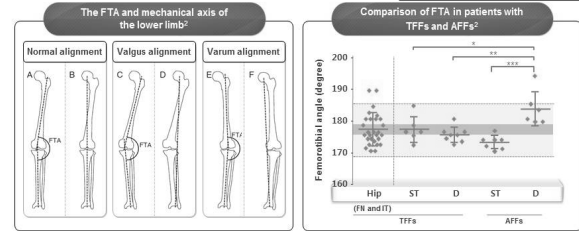
Study design: Searched MEDLINE and EMBASE databases (January 1, 1990 to October 19, 2012) for studies examining the association of bisphosphonate use and AFF, as well as subtrochanteric and femoral shaft fractures.

1. Shane E, et al. JBM 2014;29:1-23
2. Giedraitis L, et al. Bone Miner Res, 2013;28:1729-37

Risk Factor of Atypical Fracture – Ethnicity

- FTA (Femorotibial angle): atypical fracture 환자가 typical fracture 환자보다 평균값(175.1~178.0°)에서 더 많이 벗어남²
➢ 아시아인에서 FTA가 더 큰 변형(bowing)을 보이므로 AFF의 위험성이 더 큼¹

ASBMR Task Force 2013



Study design: To examine the weight-bearing alignment of the lower limb, standing radiographs of the lower limbs were obtained in the patients with AFFs. The standing femorotibial angle (FTA) was measured in the anteroposterior view, as previously described.
*p<0.05, **p<0.01. FN, femoral neck fractures; IT, intertrochanteric fractures; ST, subtrochanteric fractures; D, femoral diaphyseal fractures.
FTA=femorotibial angle; AFF=atypical femoral fracture; TFF=typical femoral fracture

1. Shane E, et al. JBM 2014;29:1-23
2. Y. Sato, et al. Bone 2014;66:105-10

Atypical Fracture Incidence in Korea

Atypical femoral fractures after anti-osteoporotic medication: a Korean multicenter study

Kang JS, et al. Int Orthop, 2014;38(6):1247-53

Aim

- To investigate the clinical features of atypical femoral fractures among BP users
➢ To clarify the association between long-term (>3 years) BP therapy and characteristics of atypical femoral fractures

Methods

- A total of 108 consecutive patients with displaced atypical femoral fracture
➢ Retrospectively reviewed based on images and the medical records from eight tertiary referral hospitals

Study duration

- January 2005 and June 2011

Kang JS, et al. Int Orthop, 2014;38(6):1247-53

Delayed Union After Atypical Fracture

- 연구에 포함된 모든 환자는 BP를 복용했으며, 그 중 75%가 3년 이상 BP를 복용함
➢ BP를 장기 복용할 수록 (3년 이상) union 기간이 유의하게 증가함

Characteristics of medications

Characteristic	Patients (n=70)
Medication duration (months)	36.8 ± 50.8 months (range, 1-204)
>3 year medication (n)	57 (75%)
Alendronate (n)	41 (53.0%)
Risedronate (n)	18 (23.6%)
Ibandronate (n)	10 (13.1%)
Pamidronate (n)	1 (1.3%)
Zoledronate (n)	1 (1.3%)
Mixed (n)	5 (6.5%)

Characteristics of fractures according to the duration of therapy

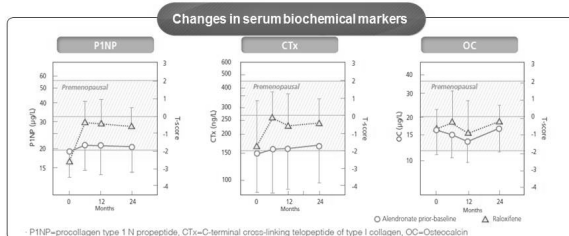
Characteristic	<3 year medication (n=19)	>3 year medication (n=57)	P-value
Duration of union	4.8 ± 2.5 months	9.3 ± 3.7 months	0.017
Delayed union (n=43)	5	38	0.021
Bilateral fracture (n=23)	2	21	0.039

Atypical femoral fracture: A fracture located along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare, associated with minimal or no trauma history, transverse or short oblique configuration, non-comminuted or minimal comminuted, complete fractures extending through both cortices or incomplete fracture involving only the lateral cortex, localized periosteal or endosteal thickening of the lateral cortex (ASBMR Task Force 2013).
Delayed union: A fractured bone that did not completely heal within six months of injury.

Kang JS, et al. Int Orthop, 2014;38(6):1247-53

Recovery of Turnover Rate after Switching from BP to Raloxifene

- Raloxifene 1년 투약 후 생화학적 지표들이 유의하게 증가하여 premenopausal level까지 증가함



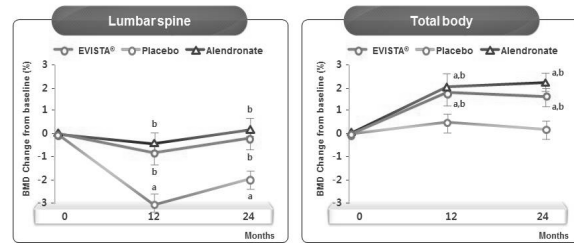
PINP=procollagen type I N propeptide, CTx=C-terminal cross-linking telopeptide of type I collagen

Study design: Ninety-nine ambulatory women were randomized to double-blind raloxifene (60 mg/d; n=33), placebo (n=33), or continuation of open-label alendronate (n=33) for 12 months. Patients continued their assigned treatment in a subsequent 12-month open-label extension phase. All patients received supplemental calcium (500 mg/d) and vitamin D (800 IU/d). * Before randomization, patients were treated with alendronate (10 mg/d) for 43 ± 7 months.

Michalska D, et al. J Clin Endocrinol Metab 2006;91:870-7

BMD Maintenance after Switching from BP to Raloxifene

- Raloxifene 및 alendronate를 1년간 투약한 결과 LS BMD 감소세를 방지함
➢ Total Femur BMD도 유사하게 증가함

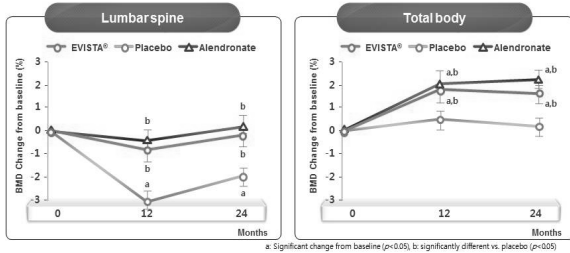


Study design: Ninety-nine ambulatory women were randomized to double-blind raloxifene (60 mg/d; n=33), placebo (n=33), or continuation of open-label alendronate (n=33) for 12 months. Patients continued their assigned treatment in a subsequent 12-month open-label extension phase. All patients received supplemental calcium (500 mg/d) and vitamin D (800 IU/d).

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Alternatives

- Change Dose and Route
- Change medication
- Drug Holidays

Alternative Drugs

- SERM
- Denosumab
- Teriperatide
- Strontium Ranelate
- HRT

Holiday for BPs

- Efficacy
 - Residual in Bone
 - Over suppression
 - Slow recovery of bone turnover
- Adverse Effect
 - BRONJ
 - Atypical Fracture
 - Esophageal cancer



Prevention and Management of MRONJ

Position Statement of KSBMR (2015)

비스포스포네이트 장기 투여(3년 이상)에 따른 MRONJ 예방 및 관리 방안 제시

투여 기간이 4년 이하이고 임상적 위험요소가 없는 환자

- ▶ 대부분 치과치료계획의 변경은 필요치 않다.
- ▶ 치과임플란트 식립이 예정된 경우 낮은 가능성에도 불구하고 MRONJ의 위험성이 포함된 동의서가 권장된다.
- ▶ 약제를 처방한 의사와 연락하여 용량 조절이나 휴약, 다른 골다공증약으로의 약물 전환 등을 타진해본다.

3투여 기간이 4년 이하이지만 스테로이드 혹은 혈관형성억제제 등 투여되고 있거나 당뇨 등 임상적 위험요소가 동반된 환자나 임상적 위험요소 동반 여부에 관계없이 경우 투여 기간이 4년 이상인 환자

- ▶ 약제를 처방한 의사와 상의하여, 환자의 전신상태가 허락할 경우 가능한 2개월 이상의 휴약 기간을 거쳐서 발치나 수술 등이 포함된 치과치료를 시행할 수 있다.
- ▶ 약제의 재투여는 골치유가 완성된 후에 시행한다.

MRONJ : medication-related osteonecrosis of the jaw

Position Statement of KSBMR, 2015

Recent Guideline Update – NOF 2014

- ▶ 2014년 NOF guideline update에서는 3~5년 간 BP 복용 시 휴약기를 권장함

2014 CLINICIAN'S GUIDE TO PREVENTION AND TREATMENT OF OSTEOPOROSIS

Duration of Treatment

Evidence of efficacy beyond five years is limited, whereas rare safety concerns such as ONJ and atypical femur fractures become more common beyond five years.^{96,97} Since there is no extensive evidence base to guide treatment duration decisions, duration decisions need to be individualized.⁹⁸ After the initial three to five year treatment period, a comprehensive risk assessment should be performed. This should include interval clinical history, particular with respect to intercurrent fracture history and new chronic diseases or medications, as well as height measurement, BMD testing and vertebral imaging if there has been any documented height loss during the treatment period. It is reasonable to discontinue bisphosphonates after three to five years in people who appear to be at modest risk of fracture after the initial treatment period. In contrast, for those who appear to be at high risk for fracture, continued treatment with a bisphosphonate or an alternative therapy should be considered.⁹⁹

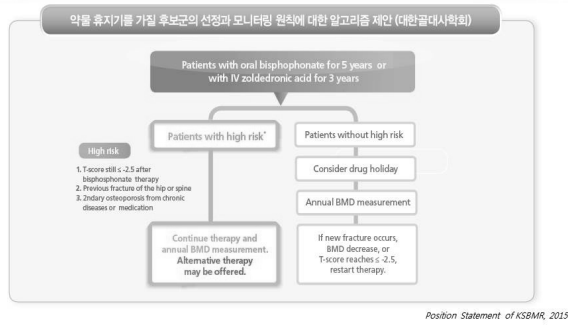
NOF=national osteoporosis foundation



NOF, Clinician's guide to prevention and treatment of osteoporosis, 2014

Recent Guideline Update – KSBMR 2015

대한골대사학회 권고안에서도 Bisphosphonate를 처방 받는 환자는 치료의 장기 안전성을 위하여 Drug holiday 혹은 다른 치료제로 전환을 권고함



Take Home Message!

Lift Up
Your
Scale !

