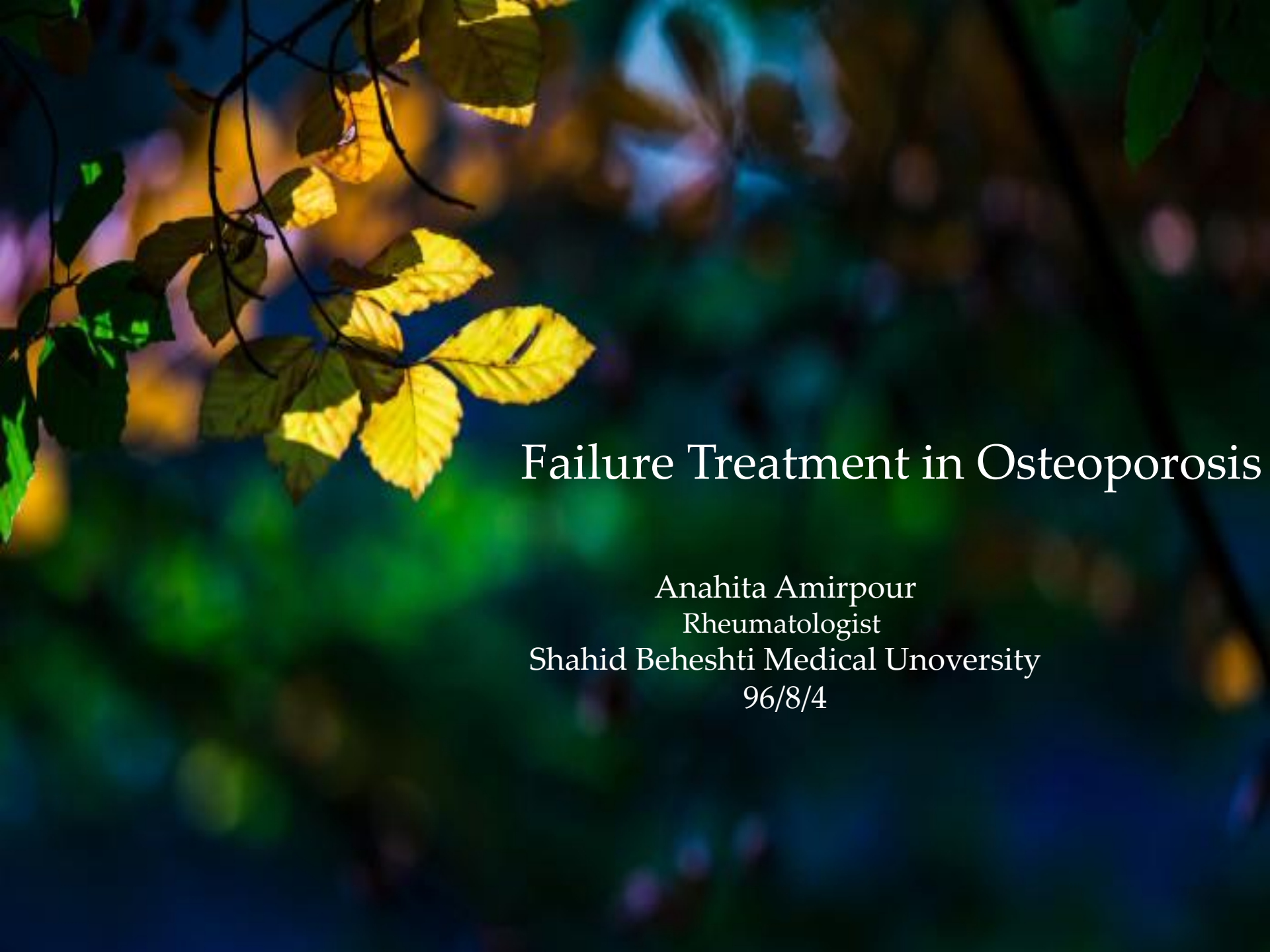




Failure Treatment in Osteoporosis

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96/8/4

Goal-Directed Treatment of Osteoporosis

- Goal of treatment is to reduce the 5-year risk of all clinical FX to less than 10%
- BPs have more than a 50% probability of decreasing FX risk less than 10% within 3 years of treatment.
- ❖ Goal of treatment is to reach BMD at Fn T-score higher than -2.0 in all and >-1.5 , if a patient has a vertebral FX or 2 strong risk factors.
- ❖ BPs have 30% chance of reaching that goal within 3 years.

BMD decreased or FX during therapy

- Evaluate additional factors (Poor adherence, Inadequate GI absorption, Inadequate intake of Ca/vit D, the development of another disease)

- Some clinicians believe decrease in BMD:

Truly reflects

Not necessarily imply

(measurement error, repeat BMD one year later)

} Treatment Failure

Occurrence of FX

FX occurring during treatment is not necessarily evidence of treatment failure.

1. FX may occur shortly after treatment initiation.

Data from phase III trials of AOM indicate:

FX within the first year cannot evidence of drug inefficacy.

2. Osteoporosis treatment may preventing multiple FX with severe disabilities but not minor FX with little functional impact

Overall AOM decreased FX Risk only 40% to 70%

Decreasing FX Risk with AOM

Molecules	Duration	Vertebral fracture risk reduction (%)	References
SERM	3 years	50% (if no prevalent VF)	Ettinger, JAMA 1999 [43]
Oral bisphosphonates	3 years	±50%	Chapurlat et al., Nat Clin Pract Endoc Metab 2006 [17]
IV bisphosphonates	3 years	75% (HORIZON) 62% (BONE, DIVA)	Black et al., NEJM 2007 [18] Chestnut et al., JBMR 2004 [19] Delmas et al., Arth Rhum 2006 [20]
Strontium ranelate	3 years	39% (TROPOS) 41% (SOTI)	Reginster et al., Arth Rheum 2008 [23] Meunier et al., NEJM 2004 [22]
Teriparatide	18 months	65%	Neer et al., NEJM 2001 [21]

Must be Consider

1. Satisfactory treatment compliance
2. Needs to certain length of time for producing the desired effect(1 year)
3. Full activity time of a drug (up to 5 years)
4. Appropriate levels of vitamin D and Calcium intake

Adherence

- **Compliance**, defined as the proportion of drug doses taken as prescribed : dosing time, modality of dosage, and frequency
(80% of doses taken)
- **Persistence**, defined as duration of treatment taken as prescribed
(1 year persistency is lower than 50%)

Adequacy of the treatment response can be evaluated only in patients who have adhered to their treatment regimen (80% of doses taken as prescribed) for at least 1 year, appropriate Ca & vitamin D consumption.

Fracture incidence and changes in quality of life in women with an inadequate clinical outcome from osteoporosis therapy

In the Observational Study of Severe Osteoporosis (OSSO)

(a prospective observational study conducted in Europe)

- In a study of 11 248 PMW , 51% were poorly compliant, had a 16% greater risk of FX than compliant patients.

IR: Bone FX despite good adherence to therapy for at least 1 year

- 8%- 18% of patients sustained a new FX after 3–5 years while on therapy
- FX on therapy is indicating poor response
- FX on therapy may not be indicative of treatment failure.
- Quality of life was poorer in IR

Guidelines for Monitoring Response to Therapy

DXA

- **ISCD** (International Society for Clinical Densitometry)
One to two years  longer intervals
- **NOF** (National Osteoporosis Foundation)
One to two years  every 2 Y
- **AACE** (The American Association of Clinical Endocrinologists)
One to two years  every 2 y or less
- **NAMS** (The North American Menopause Society)
One to two year  less frequently
- **ACP** (The American College of Physicians)
Recommendation against monitoring during therapy

Magnitude Change of BMD

“least significant change” (LSC) (95% CI) In the best-case scenario = 3%
(LSC=2.8 × precision error)

“Trend Assessment Margin” (TAM) (90%CI) = 2%
(TAM=1.8 × precision error)

“Smallest Detectable Difference” (SDD) = ± 0.05 g/cm₂ at L1–L4 & ± 0.04 g/cm₂ at Ft

NOGG 2017: Clinical guideline for the Prevention and Treatment of Osteoporosis

(Postmenopausal women and men aged 50 years or more)

Clinical risk factors considered in the FRAX assessment of FX probability

- Age
- Sex
- Low body mass index (≤ 19 kg/m²)
- Previous fragility fracture, including morphometric vertebral fracture
- Parental history of hip fracture
- Current glucocorticoid treatment (any dose, by mouth for 3 mo or more)
- Current smoking
- Alcohol intake 3 or more units daily

Evaluation of Secondary Osteoporosis

Co-morbid condition:

Anorexia Nervosa
Chronic Kidney Disease
Chushing' Syndrome
Carcinomatosis
Ehler-Danlos Syndrome
Homocystinuria
Hyperparathyroidism
Hyperprolactinemia
Hypophosphatasia
Marfan Syndrome
Multiple Myeloma
Osteogenesis Imperfecta
Neurological/ psychiatric disease
Myositis, Myopathies, Dystrophies
Renal Tubular Acidosis

Chronic Liver Disease
Inflammatory Bowel Disease
Celiac Disease
Malabsorption State
Hemochromatosis
Hypercalciuria
Organ Transplant
COPD
Malignancy
CVD
Asthma
HIV infection
Hypomagnesiumia
AS

Hyperparathyroidism	Intact PTH Serum Calcium
Hyperthyroidism	TSH T ₄ and FTI T ₃
Hypogonadism	Testosterone in men Estradiol in females LH and FSH
Osteomalacia	25-hydroxyvitamin D
Cushing's syndrome	24-hour free urinary cortisol Dexamethasone suppression test
Addison's disease	ACTH stimulation test
Renal disease	Serum creatinine Glomerular filtration
Liver disease	Liver function tests
Malabsorption	24-hour urinary calcium excretion Serum albumin level Serum calcium Serum carotene
Multiple myeloma	Serum protein electrophoresis Urine for Bence Jones proteinuria Serum calcium Intact PTH Erythrocyte sedimentation rate
Hemochromatosis	Serum iron panel
Hyperprolactinemia	Serum prolactin
Acromegaly	Serum IGF-1
Renal tubulopathy	Urinalysis including pH Acid-base studies Urine calcium, phosphorus, amino acid, and glucose
Mastocytosis	Serum tryptase Urine N-methylhistamine Iliac bone biopsy with double tetracycline labeling
Inflammatory and rheumatic diseases	Erythrocyte sedimentation rate ANA Anti DNA antibodies RF

Evaluation of Secondary Osteoporosis

Medications:

Cyclosporine

Excess Thyroid Hormone

GnRH Agonist

Aromatase Inhibitors

Depo Medroxyprogesterone Acetate

Heparin

MTX

Chemotherapy

Phenobarbital

Phenothiazines

Phenytoin

Steroid

PPI

Evaluation of Secondary Osteoporosis

Nutritional Deficiencies

- Alcoholism
- Calcium Deficiency
- Gastric & Bowel Resection
- Malabsorption Syndrome
- Vitamine D deficiency
- High Sodium & Protein Diet
- Low Albumin & Callery Diet
(Falling- FX)

Other Causes

- Low Body Weight
- Estrogen – Deficiency
- Smoking
- Athletic Amenorrhea
- Pregnancy

Other Causes

- **2/3 of the risk for FX** in PMW is determined by premenopausal **PBM**

Peak bone mass Blacks > Whites & Asians, M>F

- **1/2** of the bone mass is accumulated during puberty

(Minimal additional accumulation of the BM during the next 5 to 15 years)

- **40% to 80%** of the variability in the bone mass is determined by genetic factors
(Estrogen receptor, TGF- β , Apolipoprotein E & collagen)

Risk Factors for Treatment Failure With Antiosteoporosis Medication

The Global Longitudinal Study of Osteoporosis in Women (GLOW)

Treatment Failure: Two or more FX while on AOM.

GLOW is a prospective, observational cohort study of women aged ≥ 55 years, in 10 countries over 3 years. Data from 26,918 women were available, of whom 5550 were on AOM.

Three variables remained **predictive of treatment failure** :

1. Worse SF-36 vitality score (OR per 10-point increase, 0.85; 95% CI, 0.76–0.95; $p = 0.004$)
2. Two or more falls in the past year (OR, 2.40; 95% CI, 1.34–4.29; $p = 0.011$),
3. Prior fracture (OR, 2.93; 95% CI, 1.81–4.75; $p < 0.0001$)

Treatment Failure in Osteoporosis

A significant minority of patients who adhere to treatment fail to respond to available treatments. The reasons for this remain uncertain.

In some cases, treatment has failed perhaps :

- The bone is too severely disrupted (High TBS)
- The treatment may be inappropriate
- Perhaps failing to access remodelling sites in bone.

Factors associated with bisphosphonate treatment failure in postmenopausal women with primary osteoporosis

International Osteoporosis Foundation and National Osteoporosis Foundation 2014

- Risk of IR to the BP with ALP values in the upper ½ NL range increased **4 fold**
- Risk of IR to the BP with combination of current smoking & ALP ≥66.5 u/L increase **8 fold**

High Bone Turnover

is a known risk factor for osteoporotic FX, independent of BMD .

Changes in ALP levels between baseline and the end of the follow-up were not associated with a better response to the therapy

Factors associated with bisphosphonate treatment failure in postmenopausal women with primary osteoporosis

International Osteoporosis Foundation and National Osteoporosis Foundation 2014

BMD (Hologic Discovery)

lumbar spine (LS; in vivo precision 1.0 %)

Total femur (FT; in vivo precision 1.7 %)

Femoral neck (FN; in vivo precision 1.8%)

BMD changes were considered significant if they were above the LSC;

Calculated by the formula : **$2.8 \times \text{precision error}$**

LS 2.8 %, TF 4.8 %, FN 5.0 %

Factors associated with bisphosphonate treatment failure in postmenopausal women with primary osteoporosis(cont)

International Osteoporosis Foundation and National Osteoporosis Foundation 2014

- The 25.8 % of PMW inadequately responds to BP, despite a good compliance to therapy and normal 25OHVitD level.
- Treatment failure was associated with:
 1. **Current smoking** (OR 3.22, 95 % CI 1.10–9.50, P=0.034)
 2. **Baseline alkaline phosphatase levels ≥ 66.5 U/L** (OR 4.22, 95 %CI 1.48–12.01, P=0.007)

Trabecular Bone Score (TBS)

- Low TBS is associated with an increase in both prevalent / incident FX (Independent of both clinical risk factors & BMD at the LS and Fn)
- Magnitud changes of TBS is less than that of BMD with osteoporosis treatment, it is not clear how change in TBS relates to FX risk reduction.
- TBS may also have a role in the assessment of FX risk in :
DM, hyperparathyroidism , G/C-induced osteoporosis

Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice
(ESCEO) Bone. 2015 Sep; 78: 216-224.

- **lower TBS** values are associated with **increased risk factor** for major osteoporotic FX in PMW & older men, independent of BMD & other clinical risk factors & FRAX®.

Bone. 2017 Nov;104:66-72

- TBS gives lower values in PMW and in men with previous fragility FX than without FX patients.
- TBS results are lower in women who experience fragility fx with normal BMD.

J Bone Miner Res. 2014 Mar;29(3)

- Increase LS TBS over time with BPs treatment
(changes less than that of BMD)
- Preserve for years after stopping treatment
- Significant correlation during treatment between BMD & TBS
(Not during drug withdrawal)

	TBS	BMD
Precision	2.1%	1.7%
LSC	4.8%	4.2%
MTI	10–15 y	2.5 y

Only 12 % increase in TBS more than LSC

Risk Factors for Prediction of Inadequate Response to Antiresorptives

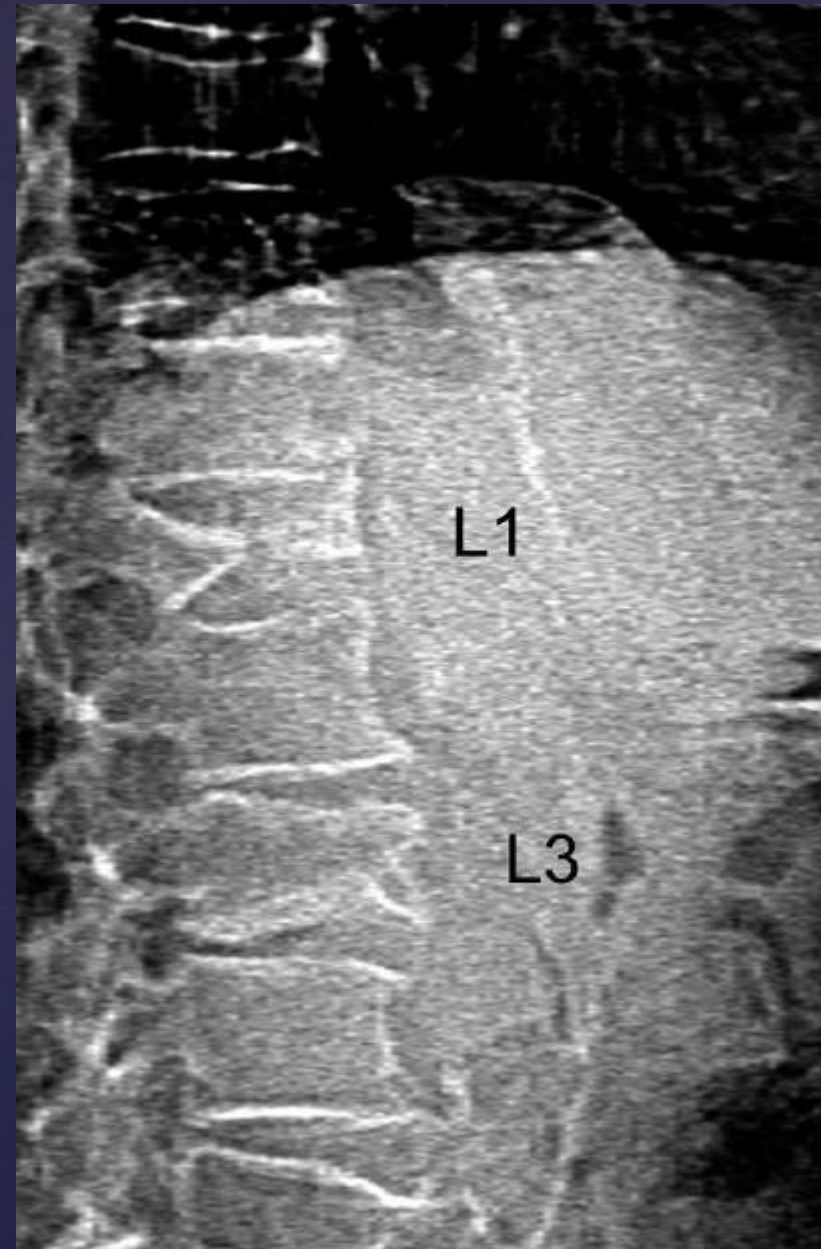
Deep microarchitectural weakening or advanced deterioration TBS
may be the “therapeutic ceiling” for drugs.

New vertebral FX are asymptomatic in 2/3 of cases.

Height loss >2 cm or back pain should prompt a radiographic evaluation.

Vertebral fracture assessment (VFA) involves lateral scanning of the T.L spine by the C-arm of a DEXA.

VFA can be performed independently from BMD measurements with a good negative predictive value



Bone Turnover Markers

Change in BTM to be clinically meaningful, it must exceed the LSC

(2.8 times the precision error)

50 % decline in U excretion of NTX  Improvement in BMD & FX risk

30 % decline in S CTX, P1NP, BALP  Improvement in BMD & FX risk

Monitoring the Response to Therapy

BTM

[Routine monitoring is not necessary]

Evaluation of:

- Drug Malabsorption
- Efficacy
- Reluctance to take anti-osteoporosis drugs regularly

(Fasting U NTX or S CTX before & after 3 to 6 mo)

Decrease > 50 in U NTX or > 30 % in S CTX  Compliance / Efficacy

Decrease < 30 % may not necessarily indicate treatment failure.

Markers of Bone Turnover

BTMs Not Routinely measure

There is **no role for BTMs** in selecting candidates for BMD or treatment.

There are insufficient data to support the use of BTMs for deciding whether or when to discontinue BP therapy or whether or when to restart another.

Bone turnover markers

Resorption markers

Type I collagen degradation products

Pyridinium crosslinks (PYD and DPD)

C- and N-telopeptides (CTX, ICTP, NTX)

Enzymes

Tartrate-resistant acid phosphatase (TRACP) 5b*

Cathepsin K

Matrix metalloproteinases (MMPs)

Formation markers

Matrix proteins

Procollagen type I propeptides

C-terminal (PICP)

N-terminal (PINP)*

Osteocalcin (OC)

Enzymes

Bone isoform of alkaline phosphatase (BALP)*



Inadequate Responders to Osteoporosis Treatment: proposal for an operational definition

Classifying Patient's Response as:

Inadequate—Incident FX *and* a decrease in BMD greater than Trend Assessment Margin (TAM), 2%

Possibly inadequate—Incident FX *or* a decrease in BMD greater than a TAM ,2%

Appropriate—No FX *and* no decrease in BMD greater than TAM ,2%

Definition of an Inadequate Treatment Response

- Sawka et al. (CANDOO):

Incident FX after 2 years or as a loss of 3% or more in BMD, 13 - 24 mo therapy(18%)

Sawka AM, Adachi JD, et al What predictsearly fx or bone loss on bisphosphonate therapy. J ClinDensitom(2003)

- Lewiecki et al.

Nonresponders Decrease in BMD greater than the LSC

Lewiecki EM: Nonresponders to osteoporosis therapy. J Clin Densitom (2003)

- The National Institute for Health and Clinical Excellence (NICE) in the UK :
BMD decrease combined with a bone insufficiency FX during 1 y

National Institute for Clinical Excellence (2004) Final appraisal determination—secondary prevention of osteoporotic fragility fractures in postmenopausal women

Definition of an Inadequate Treatment Response

- Puente A, et al: BMD gain $< 2\%$ within 1 year was (28%)

Intramuscular clodronate in nonresponders to oral alendronate therapy for osteoporosis. J Rheumatol 2000;.

- Adami et al. in the **ICARO** study: New fragility FX after at least 6 months (25%)

Adami S, Isaia G et al (2006) Fracture incidence and characterization in patients on osteoporosis treatment: the ICARO study. J Bone Miner Res 21:1565–1570

- Obermayer-Pietsch In the **EUROFORS** trial:
New fragility FX after 12 mo of treatment, a T-score < -3 or a decrease in BMD of $>3.5\%$ after 24 mo

Obermayer-Pietsch B et al (2006) Response of BMD to 24 months of teriparatide in patients with and without prior antiresorptive treatment: the EUROFORS Study. J Bone Miner Res 21

Absorptiometry Criteria

No benefits = BMD decreased more than 4%

The inadequate response rate defined as a BMD gain smaller than 2% within 1 year was 28%

Puente A, Scognamiglio A, et al. Intramuscular clodronate in nonresponders to oral alendronate therapy for osteoporosis. J Rheumatol 2000;.

35% of patients had an inadequate response defined as a BMD decline or FX

Heckman GA, Papaioannou, et al. Effect of vitamin D on BMD of elderly patients with osteoporosis responding poorly to bisphosphonates. BMC Musculoskelet Disord 2002;3:6.

Inadequate response defined as a BMD decrease greater than 3% after 2 years occurred in 18% of patients

Sawka AM, Adachi JD, et al. What predicts early fracture or bone loss on bisphosphonate therapy? J Clin Densitom 2003;.

Consensus Definition of an Inadequate Treatment Response

(Osteoporosis Diagnosis and Surveillance of SEvErity, ODISSEE)

An inadequate response was defined as any of the following:

- major insufficiency fracture (after at least 1 year of treatment)
- multiple minor insufficiency fractures
- BMD decrease greater than the LSC (0.03 g/cm^2) after 5 years or earlier in patients with minor FX

Major fractures: FX of the spine, femoral neck, wrist, proximal humerus caused by low-energy trauma.

Working Group of the Committee of Scientific Advisors of the International Osteoporosis Foundation (IOF) published:

Criteria to Define Failure :

- Two or more incident fragility FX
- One incident FX and elevated BTM at baseline with no significant reduction with an antiresorptive, a significant decrease in BMD, or both
- Both no significant decrease in bone markers and a significant decrease in BMD.

{Decrease in BTM less than the LSC; decrease of less than 20%–30% from baseline}

{Decrease in BMD greater than the LSC = a decrease of more than 4%–5% from baseline}

Definition of treatment failure is not strongly evidence based.

Decline in BMD , 5 % or more in at least two serial BMD at the lumbar spine or 4 % at the proximal femur is infavor of IR.

A significant response in BTM is :

- Decline of 25 % from baseline for anti-resorptive treatments
 - Increase of 25 % from baseline for anabolic agents (PTH)
- } After 6 months

For anti-resorptive treatments, if baseline levels are not known, a positive response is a decrease below the average value of young adult.

Three general rules in treatment of IR:

- (1) A **weaker** anti-resorptive is reasonably replaced by a **more potent** drug of the same class.
- (2) An **oral** drug is reasonably replaceable by an **injected** drug.
- (3) A strong **anti-resorptive** is reasonably replaceable by an **anabolic agent**.

Clinical Challenges in the Management of IR

No published studies demonstrated the efficacy of **Switching** from one to another medication will be beneficial.

Change oral BPs to IV form

Patients with:

Zolendronic Acid

Inability to swallow
a pill



Esophageal disorders
(achalasia, scleroderma,
esophageal strictures,
varices), Intolerance to
oral BPs

Inability to sit upright
for 30 to 60 minutes

History of Roux-en-Y
gastric bypass

Inability to follow dosage
of oral BP

Contraindications/intolerance to oral bisphosphonates

Alternatives for patients with intolerance to oral bisphosphonates :

(IV) Bisphosphonates (except CKD) [Zoledronic acid > Ibandronate]

Denosumab

Teriparatide (except in CKD)

SERMs

Allergy or Bone Pain with BPs

In patient with:

Osteoporosis (Not Sever) **plus** fragility FX

Treat with **Denosumab** rather than PTH (Grade 2B)

In patient with:

Osteoporosis (Not Sever) **without** fragility FX

Raloxifen, particularly in woman at high risk of Breast Cancer

Decline in BMD

- When the change in BMD is <5 percent & take the drug correctly & no contributing factors



Continuing the same therapy & repeating the BMD two years later

- When the decline in BMD is ≥ 5 percent

Switch from an oral BP to an IV BP
(typically zoledronic acid)

Poor absorption  Switching to an IV  more favorable response

Other alternatives

Switching to Denosumab or Teriparatide.

Treatment in IR Osteoporotic Patients

- For PMW with severe osteoporosis (T-score of -2.5 or below plus a fragility FX) who continue to fracture after one year of BPs therapy:

Treat with **PTH** (Grade 2B)

- An alternative option for patients who are unresponsive to other therapies & In patient with Impaired renal function & high risk for FX

Treat with **Denosumab**(Grade 2B)

- For some patients with severe osteoporosis & IR :

Treat with Teriparatide first (maximum of 2 years), followed by Denosumab

(preserve the gains in BMD achieved with Teriparatide)

Augmentation of therapy

Currently published data are inconclusive.



Combining two anti-resorptive agents together
(bisphosphonate plus Estrogen, Raloxifene or Calcitonin)

Greater BMD increases than one anti-resorptive agent

(Lindsay et al 1999)

No published studies demonstrating that combinations of two anti-resorptive agents reduce the occurrence of low trauma FX more than or even as well as anti-resorptive agent monotherapy

Combining an anti-resorptive agent with an anabolic

Two major studies utilizing the combination of Alendronate and PTH :

BMD gains were similar to Alendronate monotherapy & less than PTH monotherapy
([Black et al 2003](#); [Finkelstein et al 2003](#)).

No studies have adequately evaluated **FX reduction** with combined anti-resorptive/anabolic agent regimens.

Using anti-resorptive agents & anabolic agents sequentially, rather than concurrently, appears to have more promise, but remains under investigation.

([Black et al 2005](#))

Suggested therapy changes when initial osteoporosis medication is not efficacious

Current agent

Raloxifene

Estrogens

Calcitonin

Oral bisphosphonate

IV bisphosphonate

Teriparatide

New agent

Oral or IV BPs, teriparatide, Denosumab

Oral or IV bisphosphonate,
Denosumab, teriparatide

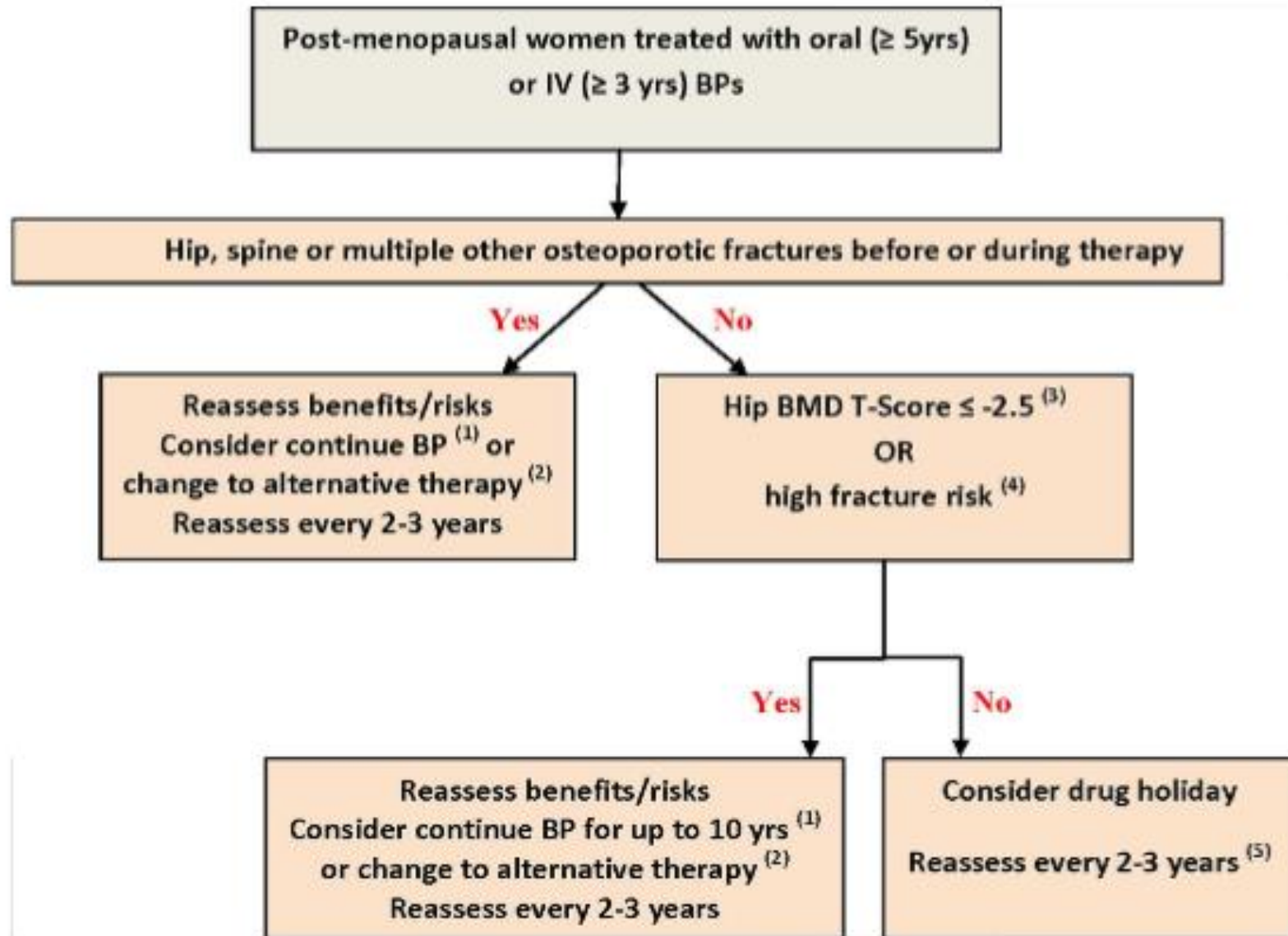
Oral or IV bisphosphonate,
Denosumab, teriparatide

IV bisphosphonate, Denosumab,
teriparatide

Denosumab, Teriparatide

Oral or IV BP, Denosumab

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



Bone-Forming Agents in Non-Responders to Bisphosphonates

Romosozumab (sclerostin monoclonal Ab) versus PTH in PMW with osteoporosis transitioning from oral BPs therapy

Bente Langdahl and colleagues in a randomised openlabel study in 436 PMW, who were IR to oral BPs (6 ± 2 y), compared the effect 12 mo treatment with Teriparatide & Romosozumab.

Romosozumab was significantly superior to PTH (change +2 ± 6% vs -0.6%; $p < 0.0001$) on Ft BMD

Cortical hip volumetric BMD increased at 6 and 12 mo in Romosozumab group, but decreased in PTH group.

Hip strength, was significantly increased in the Romosozumab group, whereas a significant decline was seen at 6-12 mo in PTH group.

Bone-forming agents in non-responders to bisphosphonates

The anabolic effects in 12 mo evaluation:

Drug	Effect	Result
PTH	pro-remodelling activity	- Decline in hip cortical BMD - Increase cortical porosity - Reduced mineralisation
Romosozumab	Modelling activity	- Increase bone formation - Inhibite bone resorption - Suppresse bone remodelling

New insights into treatment of osteoporosis in PMW

Odanacatib

Specific inhibitor of Cathepsin-K

Degrades bone collagen type I, inhibits bone resorption / bone formation

Blosozumab

Monoclonal Ab against Sclerostin

Stimulate bone formation / Decrease bone resorption.



Thanks for Your Attention