ABSTRACT

Based on WHO Criteria-1997, osteoporosis (OST) can be diagnosed clinically when the BMD (by DEXA) of the spine, hip or mid-radius is over-2.5 standard deviation (SD) below that of the young adult. In clinical practice, the most frequent OSTs can be categorized into 3 types, Type I-OST (PMO: Post Menopause OST), Type II-OST (ARO: Age-Related OST), and Type III-OST (CIO: Corticosteroid-Induced OST). Diabetic osteopenia and osteoporosis become major issues in daily clinical experiences. Recent studies indicated that the probable causes of diabetic osteopenia can be suggested: 1 AGE-modified collagen affected osteoblastic cell differentiation and function; 2. could be responsible for osteopenia-osteoporosis (esp. in post-menopause) in patients with diabetes mellitus. One of the 3 Missions of International Osteoporosis Foundation is to motivate people to take action to prevent, diagnose, and treat Ost. The Treatment Update of OST can also be grouped into three interventions: 1 Healthy Life Style as mentioned in the Prevention, 2 Calcium Supplement 1-1.5 g/day, 3A Drugs (Estrogen, Bisphosphonates, Calcitonin, Growth Hormone, SERMs, Strontium Ranelate (SR), Vitamin D, Fluoride, PTH-PTHRP, and 3B Symptomatic (Lumbar Support etc). The 3rd Generation (Gen.) Bisphosphonates (BISPs) investigated in humans, numbered in increasing order of potency are: Neridronate, Aledronate, Olpadronate, Risedronate, Iblandronate, Zoledronate. Alendronate (ALE) and Risedronate (RIS) are available in Indonesia. The novel BISP, Risedronate (RIS) is 5-fold more potent than ALE. Most recent studies on PMO demonstrated that RIS of 35 mg, or 50 mg Once a Week (OaW) provided the same efficacy and safety as the daily 5 mg regimen; therefore, the lower dose, 35 mg OaW can be considered as optimal dose for PMOs or other osteoporotic patients who desire OaW regimen. In addition, RIS can be prescribed without dosage adjustment for patients with mild or moderate renal impairment (creatinine clearance more than 20 ml/minute). Conclusions: OST, such as PMO, ARO, CIO, and diabetic osteopenia are the most prevalent bone disorders affecting ageing adults in Indonesia. Motivation of people to take action of prevention and treatment of OST should be intensified and socialized. RIS, a novel 3rd Gen-BISP has been proven to be effective and safe to prevent and to treat OST in a dosage of 5 mg OD, even with the same efficacy and safety if such a drug to be given 35 mg once a week. Importantly, it can be given safely without dosage adjustment as long as creatinine clearance of patients is more than 20 ml/min.

Keywords: osteoporosis, diabetic osteopenia, bisphosphonates, Risedronate

INTRODUCTION

Osteoporosis (OST) can be defined as a bone disease characterized by five features: systemic, low BMD (T score > -2.5), microarchitectural deterioration of bone tissue, leading to enhanced bone fragility, and increase in fracture risk. Indications for BMD measurements and biochemical markers based on guidelines established in consensus conference held by the Asian Pacific Osteoporosis Foundation and the International Osteoporosis Foundation on January 18, 2004 in Hong Kong will be summarized. Biomechanical competence of trabecular bone depends on the amount of bone in microarchitecture. Altered bone trabecular architecture may play a key-role in fracture risk. Hence, bone architecture may be assumed as significant predictor of the presence of fracture (Borah et al 2001, Seeman 2002). Material and structural strength are maintained in early adulthood by remodeling (the focal replacement of old with new bone). The disease affects an estimated 75 million people in United State, Europe, and Japan (Consensus 1991). In the United State alone, an estimated 1.3 million Osteoporosis-related fracture occur each year, with attended costs exceeding $ 10 billion per year. Vertebral fracture, and impair both the quality of life and functioning of Osteoporosis subjects (Hall et al 1999)

One of the 3 Missions of IOF (International Osteoporosis Foundation) is to motivate people to take action to prevent, diagnosis, and treat Osteoporosis. Prevention and Treatment of OST include: Healthy Life...
Style, Calcium Intake 0.5 - 1.5 g/day, Early Intervention (for prevention), and Drugs & Symptomatics (Lumbar Support, Orthopedic Intervention, Etc.) for treatment. Drugs, especially the 3rd Gen. Bisphosphonates (BISPs) are the most frequent ones reported in many recent studies and can be regarded as promising drugs in the Prevention and Treatment of OST. Alendronate (ALE) and Risedronate (RIS) are the 3rd Gen. BISPs that have Nitrogen or Amino Compound can be used in the Prevention and Treatment of OST. However, RIS has 5 times greater potency than ALE. The aim of this paper and presentation are to give the basic and clinical knowledge (in brief) of OST including Prevention and Treatment, and the current understandings of BISPs especially a Novel 3rd Gen. BISP (RIS) to GPs, Internists, Gynecologists, Orthopedic Surgeons, and other associated Specialists.

SUMMARIZED GUIDELINES OF DIAGNOSIS, PREVENTION OF OSTEOPOROSIS IN ASIA

Indications for BMD measurements

BMD measurements should be performed only if the decision to treat is influenced by the result of the test. Population-based BMD screening is not cost-effective. The National Osteoporosis Foundation recommends that DEXA measurements be performed in the following subjects. Asian countries can use this as a reference for establishing country specific guidelines.

1. Postmenopausal women 65 years or older, regardless of additional risk factors. This recommendation includes women 65 year or older who have been taking osteoporosis therapy and have not had a BMD test
2. Postmenopausal women younger than 65 years and with 1 or more of the following additional risk factors for osteoporosis. These risk factors include parental history of hip fracture, current cigarette smoking, a body weight less than 57.2kg for Caucasians, (or BMI<19 for Asians) use of (or plans to use) oral corticosteroids longer than 3 months, or serious long-term conditions thought to increase fracture risk, such as hyperthyroidism or malabsorption.
3. Postmenopausal women who have had a fracture of any type as an adult after age 45 years.

The guidelines on the diagnosis, prevention and treatment of osteoporosis in Asia-2004 include the measurement of biochemical markers of bone turnover.

Biochemical markers of bone turnover

The following biochemical markers of bone turnover can be measured in serum and urine

1. Biochemical markers of bone formation (in serum)  
   a. Bone specific alkaline phosphatase  
   b. Procollagen type I propeptides (PINP)  
   c. Osteocalcin
2. Biochemical markers of bone resorption  
   a. Deoxypridinoline cross-link (in urine)  
   b. C and N-telopeptides of type I collagen cross-link (in serum and urine)

In clinical trials, the percentage decrease in bone turnover markers correlates with the change in BMD at 2 years. However, there is no good evidence that reduce levels of bone-turnover markers, in response to therapy, predict fracture risk reduction. In women aged 75 years or older, urine C-telopeptide and free deoxypyridinoline cross-link of type I collagen have been shown to be independent predictors of an increased risk of hip fracture, and their combination with low BMD is an even stronger predictor. Biochemical markers can hence be used to complement BMD testing for assessment of fracture risk.

OSTEOPOROSIS IN PRACTICE  AS OBSERVED IN INDONESIA

Osteoporosis (OST) results from the bone loss over period of time due to bone resorption (by Osteoclast) has exceeded bone formation (by Osteoblast). To date, all effective therapies of OST are inhibitors of Osteoclast's recruitment, differentiation, maturation and activity. However, the promising drug such as Strontium Ranelate (SR) which has novel mechanisms (dual effects) appear to be operating on replication of preosteoblasts and their synthesis of collagen and non-collagens protein, and this drug also inhibits bone resorption. As observed in Indonesia, in clinical practice there are 3 types of OST, such as type I - OST (PMO: Post Menopausal Osteoporosis), type II - OST (ARO: Age Related Osteoporosis), and type III - OST (CIO: Corticosteriod-Induced Osteoporosis) in which its short descriptions of each can be seen in Table 1.
**TABLE I - Osteoporosis in Clinical Practice in Indonesia**

<table>
<thead>
<tr>
<th>Type I: PMO</th>
<th>Type II: ARO</th>
<th>Type III: CIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Menopausal Osteoporosis</td>
<td>Age Related Osteoporosis</td>
<td>Corticosteroid-Induced Osteoporosis</td>
</tr>
<tr>
<td>Estrogen Deficiency</td>
<td>Intestinal and Kidney Aging</td>
<td>Corticosteroid Induced</td>
</tr>
</tbody>
</table>

**Osteoclastogenic Cytokines:**
- TNFα↑, IL-1↑, IL-6↑, IL-11↑,
- RANKL↑, GM-SCF↑

- Ca Malabsorption
- Vit. D. Receptor ↓
- PTH-Receptor N or ↑
- Calcitriol N or ↓

Ca Absorption ↓
- 1 Alpha Hydroxylase ↓
- 1,25-(OH)2D3 ↓

- Osteogenic Progenitor Cells ↓
- Osteoblast ↓
- Muscle Strength ↓
- Physical Activity ↓
- Parathormone ↑
- Aromatase ↓
- SHBG ↑, GH ↓, IGF-1 ↓

F: 55 – 70 yrs

M: F = 1:2
Age 70 – 90 yrs

Chronic Usage of Corticosteroid (more than 2.5 - 7.5 mg/day)

Reduced physical activity and stability of patients with diabetes could increase the risk of falls and bone fracture; in diabetic patients fracture repair is prolonged. One of possible reason could be the accelerated bone collagen ageing in diabetes mellitus. Decreased BMD in diabetes mellitus type 1, i.e., diabetic patient of higher risk for osteopathy, is mainly caused by presence of: decreased IGF and insulin levels; an autoimmune process accompanied with inflammation reaction; decreased testosterone; decreased body weight. In contrast, patients with type 2 diabetes mellitus, which is characterized by insulin resistance and hyperinsulinemia in overweight person, have a normal (or even increased) BMD. Katayama et al (1996) reported that AGE-modified collagen type 1 affected osteoclastic cell differentiation and function in patients with diabetes mellitus might contribute to diabetic osteopenia.

**PREVENTION AND TREATMENT OF OSTEOPOROSIS**

**A.** The Prevention Program of Osteoporosis comprises 3 interventions: Healthy Life Style, Good Diet, and Early Intervention.

1. Healthy Life Style for Osteoporosis should be implemented, such as weight bearing physical activity and 6-NOs. The latter (6-NOs) means NO smoking (1), NO coffee (2), NO alcohol (3), and NO intake of protein (4), fats (5), and sodium or salt (6).
2. Calcium intake 500-1000 mg daily is a good diet for prevention.
3. Early Interventions of PMO, ARO, and CIO should be carried out, and also (if present) excellent control of Diabetes Mellitus (diabetic osteopenia), Thyroxicosis, Hyperparathyroidism, Hypogonadism, etc.

**B.** The Treatment Update of Osteoporosis includes: items a and b as mentioned above with c: "Anti-Resorptive Agents: Estrogen, Calcitonin, SERMs (Selective Estrogen Receptor Modulators), Bisphosphonates (Risedronate, etc), and or "Bone Formation Activators" such as Vitamin D, Fluoride, Anabolic Steroids, PTH & PTHRP, and Strontium Ranelate (newest anti-osteoporotic drug with dual effects).

Summarized Recent Advances in the Prevention and Treatment of Osteoporosis can be summarized and seen in Table 2.
### TABLE 2 - Osteoporosis: Recent Advances in Prevention and Treatment  

<table>
<thead>
<tr>
<th>PREVENTION</th>
<th>TREATMENT</th>
</tr>
</thead>
</table>
| I.  
1. Life Style: Weight-Bearing Exercise  
2. 6-NOs:  
1. No Smoking, 2. No Coffee, 3. No Alcohol  
No-Excess Intake of:  
4. Protein, 5. Fat, 6. Na (Salt) | I.  
1. Life Style: Weight-Bearing Exercise  
2. 6-NOs  
3. Weight Gain if Underweight |
| II. Good Diet: Calcium Intake (0.5 – 1 g/day)                             | II Calcium Supplement (1-1.5 g/day)                              |
| III. Early Intervention:  
1. Menopause  
2. Andropause  
3. CS-Induced Osteoporosis  
4. Diseases: DM, Chusing's syndrome, Thyrotoxicosis, Hyperparathyroidism, Hypogonadism, Etc. | III③ Drugs:  
1. Estrogen  
2. Bisphosphonates  
3. Calcitonin  
4. GH  
5. SERMs  
6. Vit. D  
7. Fluoride  
8. Steroids  
9. PTH-PTHrP  
10. Strontium Ranelate (SR)  
⑤ Symptomatic: Lumbar Support |

### RECENT INFORMATION ABOUT DRUG TREATMENT OF OSTEOPOROSIS

These information are summarized from several studies and publications. Most Studies reported that Bisphosphonates continuously be used in treating Paget's disease and the hypercalcemia of malignancy, however, the recent uses include prevention and treatment of PMO, ARO, CIO, and post-transplantation bone loss, and decrease of bone pain and inhibition of bone metastases in patients with cancer.

I. Bisphosphonates investigated in humans, numbered in increasing order of potency can be abbreviated as E, TPC, and NAORIZ (Tjokroprawiro 2001, 2002). The First Generation (E) is Etidronate; the Second Generation (TCP) are Tiludronate, Clodronate, and Pamidronate; and the Third Generation (NAORIZ and MICE) are Alendronate (ALE), Olpadronate, Risedronate (RIS), Ibandronate, Zoledronate; as well as Minodronate, Incadronate, Cinadronate, and EB-1053.

Alendronate (ALE) is approximately 10-fold more potent than Pamidronate, 100-fold more potent than Clodronate, and 1000-fold more potent than Etidronate; however, Risedronate (RIS) as a novel Pyridinyl Bisphosphonate is 5-fold more potent than ALE. Bisphosphonates inhibit Osteoclast activity through several mechanisms, i.e., reducing lactic acid production, prostaglandins formation, lysosomal and other enzymes, membrane permeability, and suppressing Osteoblast Lineage Cells (decrease in Osteoclast number, lowered Osteoclast recruitment, induce apoptosis). Risedronate (RIS) is a Pyridinyl Bisphosphonate, has an affinity to hydroxyapatite crystals in bone (for mineralisation) and inhibits osteoclast activity and kills mature Osteoclast by triggering apoptosis. Risedronate (RIS) is a Pyridinyl Bisphosphonate, has an affinity to hydroxyapatite crystals in bone (for mineralisation) and inhibits osteoclast activity and kills mature Osteoclast by triggering apoptosis.

The five sequential steps of Osteoclast maturation and functions (Teitelbaum 2000, adapted from: Tjokroprawiro 2001, 2002): Phase I (Recruitment), Phase II (Proliferation and Survival), Phase III (Differentiation), Phase IV (Polarization), and Phase V (Resorption). Biomolecular mechanisms of RIS include: inhibits recruitment (Phase I), differentiation (Phase III), and maturation - attachment (Phase V) of Osteoclast to bone for resorption. Biomolecular mechanisms of RIS include: inhibits recruitment (Phase I), differentiation (Phase III), and maturation - attachment (Phase V) of Osteoclast to bone for resorption.

Martin (2002) reported that Nitrogen-containing BISPs, (almost all BISPs of 3rd Generation, such as ALE, RIS, Etc) are taken up by Osteoclasts, where they inhibit Farnesyl Disphosphate Synthase, an enzyme in the Mevalonate Pathway of cholesterol synthesis. This process result in the reduction of
Geranylgeranyl Disphosphat e, the substance required for prenylation of GTP-BPs = Guanosine Triphosphate-Binding Proteins (such as Rho, Rab, and Cdc42). The GTP-BPs (also M-CSF in Phase II) are essential for Osteoclast activity, proliferation and survival. This process leads the inactivation of Osteoclasts, hence, apoptosis may pursue, and resulting in reduced bone resorption. Vertebral-Efficacy with Risedronate Therapy-Multi national (VERT-MN) Study (one tablet daily: placebo or 5.0 mg RIS for 3 years, 1000 mg Calcium/day, vitamin D 500 IU/day) enrolled almost 4000 postmenopausal women (Harris et al 1999). Summarized results showed that RIS 5.0 mg daily significantly reduced the incidence of new and worsening vertebral fractures and of new vertebral fractures. RIS therapy in PMO proven to a fracture reduction by 65% after the first year and sustains non-vertebral fracture reduction by 39% over 3 years.

Cohen et al (1999) reported the result of a 12 month, multicentre, randomized, double-blind, placebo-controlled, parallel-group study that RIS therapy in a dosage of 5 mg/day was able to prevent bone loss in patients initiating corticosteroid treatment (prednisone or its equivalent = 7.5 mg/day with mean previous 3 months and were expected to continue treatment for another 12 months). Brown et al (2002) in their study evaluated the efficacy and tolerability of the RIS Once a Week (OaW), 35 mg and 50 mg, compared with RIS 5mg OD in PMO for 12 months. The results showed that RIS 35 mg and 50 mg OaW provided the same efficacy and safety as the daily 5 mg regimen. It can be implicated that the dose 35 mg OaW is considered as an optimal regimen for women with PMO who prefer OaW-regimen. These results are in line with the result of study published in Osteo Int 2000 (Suppl.2): S204 (Anonymous 2000), in which the dose of RIS in the latter is 30 mg OaW. Risedronate also showed its efficacy in Prevention of the first vertebral fractures (Heaney 2002). RIS treatment therefore significantly reduced the risk of first (without prevalent fracture) in postmenopausal women with Osteoporosis, with a similar magnitude of effect early and late after the menopause.

Such a novel Bisphosphonate also shows 74% vertebral fracture reduction after one year of treatment in CIO and prevents bone loss in patients with Corticosteroid therapy. This Bisphosphonate has been well accepted as a drug for treating Osteoporosis in patients over 65 years with fracture risks (ARO). Heaney et al (2002) demonstrated that RIS produced a clinically and statistically significant reduction in the risk of first vertebral fracture in women with osteoporosis (mean lumbar spine T-score = -3.3) who have no prevalent vertebral fractures, and it did so in both younger and older postmenopausal women. Hence, RIS treatment should be considered in women with low spinal bone mass to prevent the occurrence of first vertebra fracture and thereby to inhibit the progression of osteoporosis, regardless of age. Additionally, RIS can be prescribed without dosage adjustment for patients with mild or moderate renal impairment in which creatinine clearance is still more than 20 ml/min (Mitchell et al 2000). Extent of RIS absorption was comparable in subject dosed 2 hours after dinner and 0.5 hour before breakfast; however, a significantly greater extent of absorption occurred when RIS was given 1 or 4 h prior to a meal (1.4 to 2.3 fold greater, respectively).

2. There is a great deal of evidence supporting the notion that intermittent low dose of PTH results in the formation of new bone on the outside surface of the bone, increases the deposition of bone in the inside of cortex and thickness of trabecular architecture of the bone. However, continuous high dose of PTH will stimulate bone resorption. It was recently reported the results of a multinational study of 1637 postmenopausal women prior vertebral fracture to PTH. The risk of a spine fracture as reduced by 70% within 18 months of treatment. Non-Vertebral fracture risk was reduced by 50%.

3. A new class of agents, the SERMs has been recently developed. The first agent in this class to be widely available isRaloxifene. This agent prevents postmenopausal bone loss, induces early (1 year) and sustained (up to 4 years), reduction of new vertebral fracture. In contrast to estrogen, Raloxifene does not stimulate the endometrium and reduces markedly (-70%) the risk of breast cancer. Multiple Outcome of Raloxifene Evaluation (MORE) study reported that Raloxifene had a sustained effect, decreasing the risk of spine fractures in the fourth year. Minimally, 14 SERMs (Selective Estrogen Receptor Modulators) can be summarized, such as (Tjokroprawiro 2002):

1. Tamoxifene
2. Droloxifene
3. Clomifene
4. Raloxifene
5. LY353381
6. Levorelaxifene
7. Idoxifene
8. Toremifene
9. Miproxifene
10. Lasofoxifene
11. Ormeloxifene
12. Nafoxidine
13. Centchroman
14. Fasioidex

4. Nasal Calcitonin is a safe alternative for the treatment of Osteoporosis, but the data demonstrating an anti fracture efficacy are less convincing. The PROOF study suggested that the dose of 200 IU/day but not
other dose-reduced the risk of new fractures by 30%,
without an effect on non-vertebral fractures.

5. Fluoride is a potent mitogen for the osteoblasts and
increases markedly axial bone mass, but does not
reduce vertebral fracture rate.

6. Vitamin D supplementation can help reduce the risk
of hip fracture and the risk of falling because Vitamin D
improves muscle function in addition to its actions
on bone metabolism. It was reported that 21,000 IU
Vitamin D3 once per month given to women (mean age 85 years) resulted in reduction of hip fracture by
34% after 12 months.

7. Strontium Ranelate (SR) is the newest anti-
osteoporotic drug in late clinical trial, which in
preclinical studies appear to show dual effects, bone
formation and resorption (Martin 2002). In organ
cultures, bone resorption is inhibited, whereas SR
stimulates replication of preosteoblasts and their
synthesis of collagen and non-collagenous proteins.
The mechanism of resorptive inhibition is unclear.
The primary effect of the drug could be on the
Osteoblast Lineage (Phase I, Recruitment?), with
changes taking place that could influence the ability
of those cells to recruit Osteoclast formation and/or
activity.

8. Whatever the probable causes of diabetic osteopenia
(decreased IGF, roles of nonenzymatic glycosylation
of type 1 collagen, etc), irrespective of the types of
diabetes (either T1DM or T2DM), excellent glycemic
control is really essential.

CONCLUSIONS

Risedronate (RIS) is a novel 3rd Gen. Bisphosphonate
which shows its efficacy and safety in the Prevention
and Treatment of Osteoporosis, either in Type I-
Osteoporosis (PMO) and Type III-Osteoporosis (CIO),
or in Type II-Osteoporosis (ARO). RIS has an affinity
to hydroxyapatite crystals of bone for mineralisation
and also attach to Osteoclast in inhibiting its
recruitment, proliferation & survival, differentiation,
and resorption. Due to the inhibition effect of RIS to
Farnesyl Diphosphate Synthase, this leads to reduction
of Geranyl geranyl Diphosphate, and then followed by
decreased GTP-BPs (such as Rho, Rab, and Cdc42) that
are essential for Osteoclast activity and survival; hence,
apoptosis of Osteoclast may pursue. Conclusively, RIS
has triple effects: anti resorption, bone mineralisation,
and may induce apoptosis of Osteoclast. RIS treatment
significantly reduces the risk of first vertebral fracture,
and in variety doses of 35 mg, or 50 mg Once a Week
(OaW) provide the same efficacy and safety as the daily
dose of 5 mg. Therefore, 30 mg RIS OaW will be more
adhered to by the treated patients. On the basis of
clinical experience, after the daily dose of 5 mg for one
year a regimen 35 mg OaW for another two years is
being on trial in Surabaya. In addition, RIS therapy is
effective and well tolerated (up to creatinine clearance
more than 20 ml/min) in the prevention and treatment of
PMO, CIO, and ARO.

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