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Unit No. 3

CURRENT CHALLENGES IN OSTEOPOROSIS TREATMENT DISCONTINUATION

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ABSTRACT

Osteoporosis is a chronic disease that may require lifelong therapy. Therefore, evidence-based approach regarding the efficacy and safety of long-term osteoporosis therapy and therapy discontinuation is important. The most important goals for osteoporosis and fragility fracture patients are the recovery of pre-fracture functional level and reduction of fracture risk. There has been increasing consensus that a treat-to-target (T2T) strategy is applicable to osteoporosis and that bone mineral density (BMD) is currently the most clinically appropriate target. However, there is no clear consensus with regard to the definition of a specific BMD treatment target and timeframes applicable to T2T in osteoporosis, and these would need to be individually determined. Treatment with bisphosphonates may be interrupted after 3-5 years, only in patients in whom fracture risk is low or lowered because of the treatment itself. It is recommended never to discontinue treatment in patients with one or more prevalent osteoporotic fractures or in whom the BMD values are still below -2.5 (T score). Recent reports imply that denosumab discontinuation may lead to an increased risk of multiple vertebral fractures. Patients considered at high fracture risk should either continue denosumab therapy for up to ten years or be switched to an alternative treatment. For patients at low-risk, a decision to discontinue denosumab could be made after five years, but bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover.

Keywords: Osteoporosis, treatment discontinuation, fracture care

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INTRODUCTION

Fragility fractures will affect one-third of women and one-fifth of men 50 years old and older worldwide.[1] Because of its rapidly ageing population, the Asia-Pacific (AP) region will have a disproportionately high number of fragility fractures: It has been estimated that by 2050, more than 50 percent of osteoporosis-related hip fractures will occur in the AP region.[1] In Singapore, the proportion of people 50 years and older is expected to make up almost 1 in 2 people by 2050.[1] With the concerted efforts of hospitals, family physicians and the community, there is increasing identification, lifestyle modification and treatment adherence of patients with osteoporosis[2], and reduction of age standardised hip fracture rates in Singapore.[3] With more patients receiving appropriate medications for osteoporosis to prevent fractures, questions on when and how to discontinue various medications in a safe and appropriate manner become important.

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WHEN TO STOP OSTEOPOROSIS MEDICATIONS?

The most important goals for osteoporosis and fragility fracture patients are the recovery of pre-fracture functional level and reduction of fracture risk. There has been increasing consensus that a treat-to-target (T2T) strategy applies to osteoporosis and that bone mineral density (BMD) is currently the most clinically appropriate target.[4] However, there is no clear consensus regarding the definition of a specific BMD treatment target and timeframes applicable to T2T in osteoporosis, and these would need to be individually determined.[4] The target T-score should be set at a level associated with no increase in fracture risk for the same age population. These levels will have to be determined by each country using data on mortality and fracture risk by age groups. Singapore is also making efforts in determining these levels, especially for treatment threshold by Fracture Risk Assessment Tool (FRAX) risk of fracture for different age groups.[5] In addition, the target BMD's determination should also consider the patient characteristics, care goals, and selecting a reasonable and achievable value. The time point to assess whether the treatment target has been achieved should be established on an individual basis after starting treatment.[4] All these should be determined with a shared decision-making approach with the patient, with the involvement of patient's family if the patient prefers.

There is increasing evidence that the concept of drug holiday for osteoporosis medication should be approached with caution and perhaps only suitable for a select group of patients with low to moderate risk of osteoporosis when they were started on treatment. Studies that considered the long-term continuation of osteoporosis medications did not identify increased fracture risk and reported only very low rates of adverse skeletal events such as an atypical femoral fracture.[6] In other words, for patients with moderate to high risk of fractures, the benefit of preventing fractures by continuing therapy is much greater than the potential harm of rare adverse effects.

HOW TO STOP OSTEOPOROSIS MEDICATIONS?

Bisphosphonates, when discontinued, are associated with a prolonged reduction in bone turnover markers (BTMs), with a very gradual increase to pre-treatment levels within 3 to 60 months of treatment cessation, depending on the bisphosphonate used and the prior duration of therapy.[7] Although the prolonged effect of some bisphosphonates on BTMs and BMD may contribute to residual benefit on bone strength, it may also raise safety concerns. These evaluations are the basis of the recommendations recently published by NIH.[8] Treatment with ALN or ZOL may be interrupted after 3-5 years, only in patients in whom fracture risk is low or lowered because of the treatment itself. It is recommended to never discontinue treatment in patients with one or more prevalent osteoporotic fractures or in whom the BMD values are still below -2.5 (T score).[7]

In contrast to the discontinuation of bisphosphonates, withdrawing other bone active drugs results in rapid loss of their effects on BMD and BTMs. BMD gains achieved with oestrogens, SERMs, denosumab or teriparatide therapy are lost over 1–2 years. Regarding denosumab, markers of bone turnover rebound to values well above baseline for 1–2 years after stopping therapy, corresponding to the interval of rapid decrease of the significant gains in BMD. There appears to be an increased risk of multiple vertebral fractures after discontinuation of denosumab, although strong evidence for such an effect and for measures to prevent the occurring bone loss is lacking.[9] Clinicians and patients should be aware of this potential risk. Based on available data, a re-evaluation should be performed after five years of denosumab treatment. Patients considered at high fracture risk should either continue denosumab therapy or be switched to an alternative treatment (e.g. oral or IV bisphosphonates).[9] For patients at low-risk, a decision to discontinue denosumab could be made after five years, but bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover, especially if the patients are naive to bisphosphonates prior to starting denosumab.[9] However, since the optimal bisphosphonate regimen post-denosumab is currently unknown, continuation of denosumab can also be considered until results from ongoing trials become available. Based on current data, denosumab should not be stopped without considering alternative treatment in order to prevent rapid BMD loss and a potential rebound in vertebral fracture risk.

Ideally, studies evaluating the effects of long-term treatment and treatment discontinuation should be designed to provide head-to-head "offset" data between bisphosphonates and non-bisphosphonate antiresorptive agents. In the absence of this, a clinical recommendation for physicians may be to periodically assess the benefits/risks of continuation versus discontinuation versus alternative management strategies.

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LEARNING POINTS

- **The most important goals for osteoporosis and fragility fracture patients are the recovery of pre-fracture functional level and reduction of fracture risk. There has been increasing consensus that a treat-to-target (T2T) strategy is applicable to osteoporosis and that bone mineral density (BMD) is currently the most clinically appropriate target.**
- **Treatment with bisphosphonates may be interrupted after 3-5 years, only in patients with low or lowered fracture risk because of the treatment itself.**
- **Patients considered at high fracture risk should either continue denosumab therapy for up to ten years or be switched to an alternative treatment. For patients at low-risk, a decision to discontinue denosumab could be made after five years, but bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover.**

ASSESSMENT OF 15 MCQS

FPSC NO : 91
MCQS ON OSTEOPOROSIS: A GROWING PRIMARY CARE CONCERN 2021
Submission DEADLINE: 25 May 2021, 12 NOON

INSTRUCTIONS
- **To submit answers to the following multiple choice questions, you are required to log on to the College Online Portal (www.cfps2online.org)**
- **Attempt ALL the following multiple choice questions.**
- **There is only ONE correct answer for each question.**
- **The answers should be submitted to the College of Family Physicians Singapore via the College Online Portal before the submission deadline stated above.**
- **There will be NO further extension of the submission deadline**

1. Which these patients should be screened for osteoporosis?

A. A postmenopausal woman with type 1 or type 2 diabetes
B. A postmenopausal women with a history or rheumatoid arthritis
C. A postmenopausal women with a current history of primary hyperparathyroidism
D. 45-year-old postmenopausal women with the cessation of menses since 35 years old due to premature menopause
E. A premenopausal woman who has hyperthyroidism and no fracture history

2. Which of these are not fields that are found when calculating the FRAX score?

A. Alcohol intake
B. Smoking history
C. Lack of exercise
D. Hip fracture in a parent
E. Secondary osteoporosis

3. Which of these statements are true with regards to interpreting the bone mineral density (BMD) report of a 55-year-old postmenopausal female?

A. T-score of spine is -0.9, total hip -2.0, neck of femur -2.6 – this patient has osteopenia
B. T-score of spine is -0.9, total hip 0.9, neck of femur -1.0- this patient has normal bone mineral density
C. T-score of spine is -0.9, total hip -2.4, neck of femur -2.0 – this patient has osteoporosis
D. US heel shows a T-score of -2.8 – this patient has osteoporosis
E. Two regions of interest in a BMD assessment of the hip and spine need to be taken into account when interpreting it

4. Which of these statements are false?

A. FRAX score takes into account only current alcohol and smoking habits
B. OSTA helps to identify patients who are at low, moderate and high risk of osteoporosis
C. Low risk of osteoporosis connotes a three percent risk of osteoporosis
D. Both low and moderate risk of osteoporosis means you can defer investigating further with BMD
E. Secondary causes of postmenopausal osteoporosis include endocrine causes such as hyperparathyroidism, premature menopause and hyperthyroidism

5. Which of these is not a risk factor for osteoporosis?

A. Prolonged immobilisation
B. Early menopause
C. Family history of osteoporosis
D. Height loss of > 2cm
E. BMI 22.5 kg/m^2

6. Thresholds for Intervention based on FRAX can be

A. Age-dependent
B. Weight-dependent
C. Height-dependent
D. Fixed, at ten percent for Major Osteoporotic Fractures and three percent for Hip Fractures
E. Hybrid, with choice of age-dependent curves and fixed thresholds groups for the same age groups

7. The risk of fracture with Type 2 Diabetes Mellitus is equivalent to that of

A. Age 65 years
B. Rheumatoid arthritis
C. Prednisolone 5 mg daily
D. Hyperthyroidism
E. Smoking

8. A 75-year-old patient who has suffered two fragility fractures of the spine seven months ago, with DXA BMD T-score -3.1 in the spine and -3.5 in the hip is classified as:

A. Low-risk
B. Low-medium risk
C. High-risk

D. High-Very high risk
E. Very High-risk

9. The patient in Question 10 should be offered, as first line therapy, if there are no contraindications:

A. Menopausal hormone therapy - HRT or Tibolone
B. A SERM such as Raloxifene or Bazedoxifene
C. Oral bisphosphonates such as Alendronate or Risedronate
D. Anabolic therapy such as Teriparatide or if not feasible, SC Denosumab or IV Zoledronate
E. Vertebroplasty or kyphoplasty

10. A 55-year-old female patient with T2DM has DXA T-scores of -2.2 in the spine and -1.0 in the femoral neck. Which of the following statements is true?

A. If there are no fragility fractures, she has Osteopaenia in the spine and normal BMD in the hip
B. If there are no fragility fractures, she has Osteopaenia and needs calculation of FRAX scores to decide on whether to treat pharmacologically
C. If there are no fragility fractures, she has Osteoporosis on DXA and requires pharmacological treatment
D. If she has a fragility fracture, and her FRAX scores are low, she does not require pharmacological treatment
E. If she has a fragility fracture of the spine, she can be offered Raloxifene as she is young and Raloxifene is good for improving spinal BMD and reducing spinal fractures

11. What are the most important goals for osteoporosis and fragility fracture patients?

A. Affordable bone mineral density (BMD) to allow early diagnosis and monitor treatment response
B. Recovery of pre-fracture functional level and reduction of fracture risk
C. Affordable effective therapy so that every patient can be treated
D. Empower patient through health literacy improvement and self-management training
E. Accessible and convenient care provided by a family physician

12. The most appropriate target for the treat-to-target (T2T) strategy for osteoporosis is:

A. Bone turnover markers
B. Fracture Risk Assessment Tool
C. Bone Mineral Density
D. Trabecular bone score
E. Bone strength measurement

13. Treatment with bisphosphonates may be interrupted after 3-5 years,

A. In patients who has a previous hip fracture, but the BMD Neck of Femur T-score has improved to greater than -2.0
B. In patients who has previous vertebra fracture but the BMD L2-4 T-score has improved to greater than -2.0
C. In patients who are fearful of bisphosphonate side effects
D. In patients in whom fracture risk is low or lowered because of the treatment itself
E. In a patient who requests for a drug holiday

14. Patients who are at high risk of fracture can safely stop denosumab therapy if

A. They have prior exposure to bisphosphonate therapy
B. They continue alternative osteoporosis therapy
C. They have low bone turnover markers
D. They do not have fractures before
E. They are adherent to lifestyle measures for falls prevention

15. Patient can stop osteoporosis treatment when their BMD T score is:

A. -1.0
B. -1.5
C. -2.0
D. -2.5
E. Associated with no increase in the risk of fracture for the same age population