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Osteoporosis clinical practice guideline: romosozumab for treating severe osteoporosis – an update by the Egyptian Academy of Bone Health

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Abstract

Background: This is a Clinical Practice Guideline update released by the Egyptian Academy of Bone Health and Metabolic Bone Diseases. It does not replace the clinical practice guidelines published for the treatment of osteoporosis in 2021, but it entails specific recommendations and selective criteria for romosozumab as another pharmacological agent for treatment of postmenopausal osteoporosis. It has been issued, in part, due to the imminent approval of romosozumab in Egypt.

Main text: The guideline recommends the use of romosozumab, for up to 1 year, for the reduction of vertebral, hip, and non-vertebral fractures in postmenopausal women with severe osteoporosis at very high risk of fracture/imminent fracture risk: defined as *T*-score less than − 2.5 and a prior hip or vertebral fracture in the past 24 months or a very high fracture risk, as identified by FRAX (FRAX major osteoporosis fracture > 30%, FRAX hip fracture > 4.5%). The recommended dosage of romosozumab is 210 mg monthly by subcutaneous injection for 12 months. For osteoporotic postmenopausal women who have completed a 12-month course of romosozumab, treatment with an antiresorptive osteoporosis therapy is recommended to maintain bone mineral density gains and reduce fracture risk. The treatment is not recommended for women at high risk of cardiovascular disease and stroke, which includes those with prior myocardial infarction or stroke.

In conclusion, strategies to osteoporosis management have been highly diversified, with bone health specialists have become able to set up treatment plan tailored to the individual patient's requirement. Patients with severe osteoporosis at very high fracture risk need stronger therapeutic regimens to start with. Romosozumab endorses bone formation and suppresses bone resorption, leading to a greater anabolic window and a superior positive impact on bone mineral density.

Keywords: Romosozumab, Osteoporosis, Guidelines, Update, Egyptian Academy of Bone Health, Egyptian guidelines

Background

The recognition of imminent risk of fracture not only reflects a period during which the individual is at high risk of developing another low trauma fracture or categorizes a cohort of patients at very high risk of fracturing but also provides a window of opportunity for swift intervention to minimize the likelihood of developing

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subsequent new fractures. Furthermore, commencing the appropriate and timely management for these patients help to lower the mortality rate among a substantial proportion of the fractured patients which has been linked to refracture [1, 2].

Although many randomized controlled trials (RCT) have reported high anti-fracture efficacy induced by several anti-osteoporotic therapies, the management strategy for prevention of secondary fracture has generally adopted the "one-size fits all" approach. Consequently, most patients meeting the criteria for osteoporosis medical management are offered anti-resorptive agent, usually bisphosphonate, at standard dose as a first line treatment. In specific conditions and subject the treating healthcare professional or the patient preference, an alternative therapy, such as IV zoledronate or denosumab might be offered. Alternatively, anabolic therapy such as teriparatide, abaloparatide, or romosozumab might be offered particularly in patients with severe osteoporosis and very high fracture risk. All the recently published guidelines [3–6] as well as the Egyptian guidelines for osteoporosis [7] have endorsed a new policy to systematically personalize the pharmacological management strategy for osteoporotic patients based on refined risk stratification criteria [8]. Thus, the "anabolic first" approach has been endorsed for patients found to be at very high risk of fracture [9].

The Egyptian Academy of Bone Health and Metabolic Bone Diseases published clinical guidance including treatment algorithm for the management of osteoporosis, in January 2021, entitled "Egyptian consensus on treat-to-target approach for osteoporosis: a clinical practice guideline", which recommends the order of therapies based on the evaluation of the individual's fracture risk. This update has been issued, in part, in relation to the imminent approval of romosozumab, a monoclonal antibody targeting sclerostin for the management of osteoporosis in Egypt.

Methodology

Throughout the guideline update development process, the writing committee adhered strictly to the Conflict-of-Interest policy and procedures for The Egyptian Academy of Bone Health and Metabolic Bone Diseases. The literature search strategy was carried out following the same protocol of the "Clinical, Evidence-based, Guidelines" (CEG) program adopted in the Egyptian guidelines study carried out to develop Treat to Target osteoporosis management [7]. Inclusion criteria included systematic reviews, randomised controlled trials (RCTs), uncontrolled trials, observational studies such as cohort, case-control, and cross-sectional studies, as well as economic evaluations. Exclusion criteria included editorials, commentaries, conference abstracts, and non-evidence-based narrative/personal reviews. The final draft of this guideline update was subject to an expert review, carried out by specialists with expertise in the topic, without relevant conflicts of interest, and external to the writing committee.

Main text

Selection criteria for the prioritisation of eligible patients for romosozumab therapy in clinical practice

Postmenopausal women with severe osteoporosis at very high risk of fracture, defined as

- *T*-score <— 2.5 (at hip or spine) and
  - Vertebral or hip fracture in the past 24 months or history of > 2 osteoporotic vertebral fractures,

    or
  - Very high fracture risk (FRAX major osteoporosis fracture > 30%, FRAX hip fracture > 4.5%)

Romosozumab mechanism of action

Romosozumab is a humanized monoclonal antibody (IgG2) which binds and inhibits sclerostin, activating the bone lining cells which consequently enhances bone formation, thereby increase the obsteoblasts' bone matrix production, and recruitment of osteoprogenitor cells. Furthermore, romosozumab induces changes to expression of osteoclast mediators, thus decreasing bone resorption. Collectively, this dual effect of increasing bone formation and decreasing bone resorption results in rapid increases in trabecular and cortical bone mass, improvements in bone structure, as well as strength [10].

Romosozumab course of management

- Romosozumab treatment is recommended for up to 1 year for the reduction of vertebral, hip, and non-vertebral fractures.
- After completion of 12-month romosozumab course, treatment with anti-resorptive osteoporosis therapies is recommended to maintain bone mineral density gains and reduce fracture risk [7].

Hypocalcemia

Transient hypocalcaemia has been observed in patients receiving romosozumab.

- Prior to initiating therapy with romosozumab, serum calcium should be checked, and hypocalcemia should be corrected. Monitoring the patients for hypocalcemia symptoms and signs and symptoms is recommended.
- Transient hypocalcaemia has been observed in patients receiving romosozumab.
- Calcium levels should be measured if any patient presents with suspected symptoms of hypocalcaemia during treatment.
- Patients should be adequately supplemented with calcium and vitamin D
- Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 ml/min/1.73 m2) or on dialysis are at higher risk of developing hypocalcaemia and the safety data for these patients is limited. Therefore, serum calcium levels should be monitored in these patients.

Table 1 shows a list of the important risks reported in relation to romosozumab therapy.

Hypersensitivity

In clinical trials, clinically significant hypersensitivity reactions, including angioedema, erythema multiforme, and urticaria have been reported in the romosozumab cohort of patients. Appropriate therapy should be initiated if an anaphylactic or other clinically significant allergic reaction occurs, and the administration of romosozumab should be stopped.

Osteonecrosis of the jaw

- Rarely, osteonecrosis of the jaw (ONJ) has been reported in patients on romosozumab therapy.

Table 1 List of important risks linked to romosozumab therapy

List of risks	Risk
Important identified patient's risks	Serious cardiovascular disorders such as myocardial infarction and stroke
	Hypocalcemia
	Hypersensitivity
	Immunogenicity (development of antibodies to romosozumab)
Important identified treatment risks	Osteonecrosis of the jaw
	Atypical femoral fracture
	Serious infections
Post-treatment bone mineral density changes	Osteoporosis rebound effect

- The following risk factors should be considered when evaluating a patient's risk of developing ONJ:
  - Cancer, co-morbid conditions (e.g., anemia, coagulopathies, infection), smoking.
  - Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
  - Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures, e.g., tooth extractions.
- Maintaining good oral hygiene is recommended for all patients. It is advisable that all patients receive routine dental check-ups. Any oral symptoms such as dental mobility, pain, or swelling or non-healing of sores or discharge during treatment with romosozumab should be reported immediately.
- Patients who are suspected of having or who develop ONJ while on romosozumab should receive care by a dentist or an oral surgeon with expertise in ONJ. Discontinuation of romosozumab therapy should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Atypical femoral fractures

- Atypical low trauma fracture of the femoral shaft has been reported rarely in patients receiving romosozumab.
- Bearing in mind that the atypical femoral fracture may occur spontaneously, any patient who presenting with new or unusual thigh, hip, or groin pain should be suspected of having an atypical fracture and should be assessed to rule out an incomplete femur fracture.
- Patient presenting with an atypical femur fracture should also be evaluated for symptoms and signs of fracture in the contralateral limb.
- Interruption of romosozumab therapy should be considered, based on an individual benefit-risk assessment.

Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed with romosozumab. No pharmacokinetic drug interactions are expected with romosozumab.

Pre-Romosozumab Screening

Patient Name: **Age:** **Gender:**

National number: **Date:** / / 20

Blood Pressure: / **BMI**

هذه الأسئله تساعدنا في تقييم حالتك الصحيه وإختيار الدواء المناسب لك.

هل تعاني من اي من أمراض الاتية	نعم	لا	هل تعاني من اي من أمراض القلب الاتية	نعم	لا
هل اتشخصت في اي وقت بالسكته الدماغيه؟			جلطه في القلب		
هل اتبلغت في اي وقت من طبيبك المعالج انك مصاب بنوبة سكته موقته او سكتة دماغيه مصغرة			ألم الذبحة الصدرية		
هل في اي وقت حسيت بضعف من غير وجع في جانب من جسمك؟			هل تتناول الأدوية المضادة للذبحة الصدرية		
هل اصبت في اي وقت بتنميل مفاجئ او فقدان احساس في جانب من جسمك؟			هل عانيت من السكتة الدماغية (جلطة بالمخ) خلال العام الماضي		
هل فقدت مؤقتا جزء او كل نظرك؟			هل تعاني من جلطه قلبيه مزمنه و مستقرة		
هل في اى وقت و من غير ما تتوقع مافدرتش تفهم الكلام اللي حد بيقولهولك ؟			هل مات احد من عائلتك فجاه بسبب مرض في القلب		
هل في اي وقت و فجاة مابقتش قادر تعبر عن اللي انت عايز تقوله بالكلام او الكتابه؟			هل أجريت جراحة تحويل مسار الشريان التاجي		

العلاج الحالي

أوافق على إستخدام بياناتي الطبيه، بدون ذكر بياناتي الشخصيه في أغراض البحث العلمي: نعم□ لا:□

شكرا، فضلا إعط هذا الإستبيان للطبيب المعالج

الأسم التوقيع

التاريخ

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Imminent Fracture Risk: **Yes:** □ **No:** □

BMD:

Spine			Hip			Forearm		
	T-Score	BMD	Site	T-score	BMD	Site	T-score	BMD
L1-L4			Total Hip			Distal		
V. Morph			NoF			33%		

Past history of fracture:

Spine		Hip		Forearm	
Site	Date of Fracture	Site	Date of Fracture	Site	Date of Fracture

FRAX: 10-year probability of:

Major Osteoporosis Fracture %	Hip Fracture %

Lab Investigations

Serum total calcium		Serum Cholesterol	
Serum ionized calcium		Triglyceride	
Vitamin D		LDL	
Serum creatinine		HDL	

Medication reconciliation:

Current or previous treatment with any of the following drugs

Drug	Current	Previous	Dose	Duration
Calcium				
Vitamin D				
Antiresorptive (oral):				
Antiresorptive (IV)				
Denosumab				
Teriparatide				
Abaloparatide				

Comorbidities:

Treating physician: **Signature:**

Fig. 1 Pre-romosozumab, patient self-reported questionnaire to screen for possible risks. It also include the baseline bone health status as assessed by the treating healthcare professional

Measures to minimize the risks include

- Pre-romosozumab screening for cardiovascular or stroke risk using a patient self-reported questionnaire is advised (Fig. 1). This include self-reported questionnaire to be completed by the patient prior to therapy. The questionnaire includes seven questions to assess for stroke risk, which has been amended from Questionnaire for Verifying Stroke-Free Status (QVSFS) by neurological history and examination [11]. These questions are (1) have you at any time been diagnosed to have a stroke? (2) Have you at any time been told by your treating doctor that you have transient ischemic attack or ministroke? (3) Have you at any time developed painless weakness on one side of your body? (4) Have you at any time developed sudden numbness or lost sensation on one side of your body? (5) Have you ever temporarily lost part or all of your vision? (6) Have you at any time unexpectedly been unable to understand what someone is saying to you? And (7) Have you at any time unexpectedly been unable to say what you mean either in words or in writing?

In addition, there are seven questions to assess for the cardiovascular risk: (1) self-reported angina, (2) chronic stable ischemic heart disease, (3) coronary artery bypass, (4) myocardial infarction, (5) stroke, (6) do you take anti-anginal medication, and (7) family history of sudden cardiovascular death. Translation from English to Arabic was carried out following the guidelines proposed by Guillemin et al. [12].

- Romosozumab should not be considered for women at high cardiovascular or stroke risk pending further studies on cardiovascular risk associated with this treatment. High risk includes prior myocardial infarction or stroke. Measuring serum calcium is recommended as romosozumab is contraindicated in patients with hypocalcaemia.
- All patients should be provided with information card, providing information on how to use the medicine safely and how to identify and report side effects.
- Specific information, such as warnings, precautions, and advice on correct use, should be provided in the package leaflet and SmPC addressed to patients and healthcare professionals

- The medication should be provided by specialized centers; prescribed and monitored by bone health specialists with recognized experience in osteoporosis management (as identified in the Egyptian Guidelines for osteoporosis [7]).
- The way a medicine is supplied to the patient can help to minimize its risks.
- It is advisable that the patient have dental check-up and finish with his dental procedures before starting romosozumab.

Posology and method of administration

- Romosozumab is a humanized IgG2 monoclonal antibody produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells [13].
- Quantitative composition: Evenity 105 mg solution for injection in pre-filled pen

Each pre-filled pen contains 105 mg of romosozumab in 1.17 ml of solution (90 mg/ml)

- Dose: 210 mg once a month for 12 months
- Dose and administration:
  By subcutaneous injection-adult
  210 mg once a month for 12 months, to be administered as two consecutive 105 mg injections at different injection sites into the thigh, abdomen, or upper arm. This should be supplemented with calcium and vitamin D.
- Missed doses
  - If a romosozumab dose is missed, patient should administer it as soon as it is possible.
  - Thereafter, the next romosozumab dose should not be given earlier than 1 month after the last dose [13].

Special clinical conditions/populations

Older adults

No dose adjustment is necessary in older adult patients.

Renal impairment

No dose adjustment is required in patients with renal impairment. However, in patients with severe renal impairment or receiving dialysis, serum calcium should be monitored.

Hepatic impairment

No clinical trials have been conducted to evaluate the effect of hepatic impairment.

Pediatric population

Romosozumab safety and efficacy in children (age < 18 years) have not yet been established. No data are available [13].

Immunogenicity

In postmenopausal women receiving monthly doses of romosozumab, the incidence of anti-romosozumab antibodies was 18.6% (1162 of 6244) for binding antibodies and 0.9% (58 of 6244) for neutralizing antibodies. The earliest onset of anti-romosozumab antibodies was 3 months after first dosing. The majority of antibody responses were transient.

The presence of anti-romosozumab binding antibodies decreased romosozumab exposure by up to 25%. No impact on the efficacy of romosozumab was observed in the presence of anti-romosozumab antibodies. Limited safety data show that the incidence of injection site reactions was numerically higher in female patients with neutralizing antibodies [13].

Patient education: an information leaflet for the user has been produced in Arabic.

National register

- There should be a national register for all patients receiving romosozumab, including all reported side effects. This can be covered by the Egyptian Academy of Bone Health in cooperation with Amgen and providing centers.
- Services provided at the different Treating centers should be audited by the end of the year.

Personalizing osteoporosis management for patients at very high fracture risk

The concept of imminent fracture has become the corner stone for patients' stratification, according to their fracture risk with significant implications for the treatment choice. Thus, the patients' cohort at high risk of imminent fractures are those at urgent need of immediate treatment with anabolic agents. Ideally, this would be the agent that lessen the fracture risk most efficiently and as promptly as possible. Hence, the need to identify such agent, which according to the guidelines should be an anabolic agent [7]. However, site-specific changes in the BMD are also important in considering which anabolic agent to advice.

Published data revealed that after 1 year of teriparatide therapy, femoral BMD benefits have been consistently smaller than those reported in patients receiving anti-resorptive therapies, whereas there is decline in

the forearm BMD [14]. This is supported by the findings that teriparatide did not decrease significantly non-vertebral fractures, and that abaloparatide did not demonstrate clear-cut non-vertebral fractures prevention. Furthermore, neither teriparatide nor abaloparatide has shown evidence of efficacy against hip fractures in any single trial. Even, in a head-to-head comparative study, teriparatide showed only superiority for vertebral fractures in comparison to risedronate [15], meanwhile it did not show significant difference for non-vertebral fractures. Bearing in mind that non-vertebral fractures are the most common fractures and occur mainly in the cortical bone, such early impacts on the BMD are important, predominantly in the patients at high risk of sustaining hip fractures. In comparison, in the ARCH study [16], romosozumab improved all the fracture outcomes including hip as well as non-vertebral fractures in contrast to alendronate as the comparator agent.

Conclusion

In conclusion, romosozumab expands the management options in osteoporotic postmenopausal women who are at very high risk of fracture. Romosozumab modulate both bone formation and bone resorption and aims to achieve optimal fracture prevention. While romosozumab appears to have a generally manageable tolerability profile, extra clinical experience is required to more definitively establish its efficacy and safety. Romosozumab is contraindicated in patients with past history of myocardial infarction and stroke.

Abbreviations

DXA: Dual X-ray absorptiometry; ONJ: Osteonecrosis of the jaw; FRAX: Fracture Risk Assessment tool; BMD: Bone mineral density; ARCH: Active-contRolled FraCture Study in Postmenopausal Women with Osteoporosis at High Risk of Fracture; RCT: Randomized controlled trials; eGFR: Estimated glomerular filtration rate; CHO: Chinese hamster ovary.

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Consent for publication

NA

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The authors declare that they have no competing interests.

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