Consensus Advisory Statement from the National Osteoporosis Guideline Group (NOGG) and Royal Osteoporosis Society (ROS) on the use of romosozumab, following the 2022 NICE Appraisal.

30th May 2022

Following NICE 2022 recommendations for treatment with the bone-forming agent romosozumab in a subset of patients at very high risk of fracture (see below), this statement reprises NOGG 2021 recommendations concerning the management of patients at very high risk of fracture in the UK.

NICE 2022 Recommendation

NICE recommends romosozumab as an option for treating severe osteoporosis in people after menopause who are at high risk of fracture, only if they have had a major osteoporotic fracture (MOF) within 24 months (so are at imminent risk of another fracture) and the [manufacturing] company provides romosozumab according to the commercial arrangement. [1]

NICE defines a MOF according to the manufacturing company submission as a fragility fracture of the spine, hip, forearm or humerus.

NOGG/ROS Advisory statement on the prioritisation of romosozumab in clinical practice

Building on NOGG 2021 recommendations, [2] we suggest that referral for, and consideration of treatment with romosozumab, is prioritised **in postmenopausal women who have had a MOF within 24 months, with any one of the following:**

- a BMD T-Score ≤-3.5 (at the hip or spine), or
- a BMD T-score ≤-2.5 (at the hip or spine) and either
    - vertebral fractures (either a vertebral fracture within 24 months or a history of ≥2 osteoporotic vertebral fractures), or
    - very high fracture risk (*e.g.*, as quantified by FRAX).

Following the approved duration of treatment with romosozumab (12 months), treatment with alendronate, zoledronate or denosumab should be initiated without delay.

Warnings and precautions for the use of romosozumab

- Previous myocardial infarction or stroke

  Romosozumab is contraindicated in patients with previous myocardial infarction or stroke. When determining whether to use romosozumab for an individual patient, consideration should be given to her fracture risk over the next year and her cardiovascular risk based on risk factors (*e.g.*, established cardiovascular disease, hypertension, hyperlipidaemia, diabetes mellitus, smoking, severe renal impairment, advanced age). Romosozumab should only be used if the prescriber and patient agree that the benefit outweighs the risk. If a patient experiences a myocardial infarction or stroke during therapy, treatment with romosozumab should be discontinued.

- Hypocalcaemia

  Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 ml/min/1.73 m^2) or receiving dialysis are at greater risk of developing hypocalcaemia and the safety data for these patients is limited. Calcium levels should be monitored in these patients.

- Hypersensitivity

  Clinically significant hypersensitivity reactions, including angioedema, erythema multiforme, and urticaria occurred in the romosozumab group in clinical trials. If an anaphylactic or other clinically significant allergic reaction occurs, appropriate therapy should be initiated and use of romosozumab should be discontinued.

Further considerations

- Romosozumab is given as a subcutaneous injection in a dose of 210 mg (administered as two subcutaneous injections of 105mg each) once monthly. The duration of treatment is limited to 12 months.
- The manufacturing company provides a patient support programme for those treated with romosozumab which includes a homecare service, an adherence support program and training on delivering injections.
- Bone-forming treatment needs to be followed by anti-resorptive treatment (*e.g.*, intravenous zoledronate, subcutaneous denosumab or oral alendronate). Contraindications to, or intolerance of, these treatments should be considered prior to prescribing bone-forming agents.
- Romosozumab is not yet approved for use in men, nor specifically in those with glucocorticoid induced osteoporosis.
- Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis.
- Specialists should consider keeping local registers of patients being treated with romosozumab to enable local audits of practice.

Identifying a recent vertebral fracture

- A recent vertebral fracture can be identified by the combination of (i) a vertebral fracture visualised on a plain radiograph, lateral spine DXA or other imaging **and** (ii) a history consistent with vertebral fracture occurring within the last 24 months **or** a previous image within the last 24 months with no evidence of fracture at that vertebral level. The history would characterise new onset back pain, in an older person at risk of osteoporosis, precipitated by mild, or sometimes no, trauma, severe enough to limit function, and which often prompts the seeking of medical attention.
- **Of note**, multiple vertebral fractures indicate severe osteoporosis irrespective of measured LS BMD, as the loss in lumbar vertebral volume artefactually increases LS BMD to hide a previously low T-Score.

References

1. National Institute for Health and Care Excellence (NICE), *Technology appraisal guidance – Romosozumab for treating severe osteoporosis*. TA791. 25th May 2022.
2. Gregson, C.L., et al., *UK clinical guideline for the prevention and treatment of osteoporosis.* Arch Osteoporos, 2022. **17**(1): p. 58.

NOGG guideline available at: www.nogg.org.uk

Examples of clinical cases suitable for treatment with romosozumab

Below are provided three example clinical cases which characterise the patients who should be prioritised for treatment with romosozumab.

Case 1, Anne, age 65

Presentation and initial assessment

- Anne attends A&E after developing a sudden onset of severe pain between her shoulders and around her chest when she was hanging out her washing
- On examination, she is tender to percussion over the mid-thoracic spine and X-rays show a severe wedge fracture at T8
- She is prescribed analgesics and referred urgently to the Fracture Liaison Service (FLS)

FLS assessment

- Anne reports a wrist fracture aged 60 in a fall on the ice but has not previously been investigated or treated for osteoporosis. She recalls that her mother was disabled by severe back pain in her later years and became very stooped
- She is very slim (BMI 19.5), smokes 15 cigarettes daily and did not take HRT after her menopause at the age of 44. She has no other risk factors for fracture
- FRAX shows 10-year probabilities of 20% for major osteoporotic fracture (MOF) and 8.6% for hip fracture. Probabilities increase slightly to 21% and 9.2% respectively on inclusion of her DXA scan results (LS T-score -3.5, FN T-score -2.7)
- If these FRAX probabilities are adjusted to take account of the recency of fracture, 10-year probabilities increase to 39% for MOF and 16% for hip
- Laboratory tests do not identify any additional underlying causes for her osteoporosis

Discussion about management

- Anne is advised that her recent vertebral fracture and BMD results indicate a very high risk of further vertebral fracture – which will have been underestimated by FRAX as this does not take account of the spine BMD
- She is keen to consider any treatment that could prevent her "ending up like her Mum" but is initially cautious about the possibility of cardiovascular events with romosozumab because her father died after a heart attack when he was 75
    - Calculation of her cardiovascular risk using QRisk [1] indicates a 10-year risk of heart attack/stroke of 12.8% compared to a risk of 7.8% in a healthy woman matched for age and ethnicity
    - If she were to stop smoking, QRisk suggests her risk would reduce to 8.7%
    - Anne would like to stop, but has been unsuccessful with previous attempts

Management plan agreed following discussion:

- Romosozumab for 12 months with a plan to transition to annual IV zoledronate on completion
- Calcium and vitamin D supplementation
- Referral to smoking cessation clinic
- Appointment arranged with physiotherapist for pain management and advice on rehabilitation and safe exercise

[1] QRISK®3 is freely available online tool (https://qrisk.org/three/) commonly used in primary care to estimate cardiovascular risk in people who don't already have cardiovascular disease. QRISK®3 presents a 10-year probability of heart attack or stroke, alongside the average probability of a person with the same age, sex and ethnicity to inform clinical decision making.

Case 2 – Geeta, age 69

Presentation and initial assessment

- Geeta visits her GP asking for painkillers after slipping in the garden and fracturing her humerus during a visit to her daughter
- Her GP sees in her records that she had been prescribed alendronate 5 years ago after a wrist fracture but did not ask for further prescriptions
- Geeta remembers that the tablets had caused terrible heartburn which went away when she stopped them. She wasn't aware there were any other treatment options so didn't want to bother her GP by going back
- FRAX assessment, taking into account her fracture history and the fact her father fractured his hip, confirms that treatment is indicated
- Geeta and her GP agree she should avoid further oral treatment. She is happy to accept her GP's offer of referral to the osteoporosis clinic at the hospital to discuss an injectable treatment

Osteoporosis clinic evaluation

- Clinical assessment doesn't reveal any additional risk factors for osteoporosis apart from low dietary calcium intake, but bone densitometry shows very low BMD with T-scores of -3.5 at the spine and -3.4 at the hip
- Laboratory tests show vitamin D insufficiency but that she is normocalcaemic with no secondary hyperparathyroidism. There are no other abnormal findings
- Geeta is very worried by her BMD results, especially on hearing that FRAX assessment suggests a 47% 10-year risk of MOF and 23% risk of hip fracture
    - Her consultant explains that Geeta will need to take calcium and vitamin D supplements and that there is a range of injectable treatment options which can all substantially reduce her risk of fracture
    - She also explains that there is evidence suggesting that the treatments that build bone are more effective when they are used as the first treatment
    - After discussion about the risks and benefits of each treatment as they apply to her, including QRisk assessment of her cardiovascular risk, Geeta and her consultant agree she will have initial treatment with romosozumab which will be followed by either zoledronate or denosumab.

Case 3 – Maria, age 74

Presentation and initial assessment

- Maria calls 999 after missing the last step coming downstairs, falling awkwardly and being unable to get up
    - X-rays in A&E confirm fractures of her wrist and pelvis (bilateral pubic rami)
    - She has surgical fixation of her wrist but is unable to mobilise and is admitted for pain management and FLS assessment

FLS assessment

- Maria does not report any broken bones in the past. She developed rheumatoid arthritis 10 years ago which is well controlled on biologic treatment
    - Her rheumatologist assessed her osteoporosis risk with FRAX and DXA a few years ago and she was told she had "osteopenia" and advised to take vitamin D but that she did not need any other treatment
    - The planned follow-up assessment 5 years later was cancelled because of COVID-19 and had not been rearranged
- DXA now shows osteoporosis: FN T-score -2.9 and FRAX indicates 10-year probabilities of 34% for MOF and 13% for hip
    - Spine BMD could not be assessed reliably because of appearances suggesting degenerative change
    - If the FRAX probabilities are adjusted to take account of the recency of fracture, 10-year probabilities increase to 47% for MOF and 20% for hip
    - VFA (vertebral fracture assessment) DXA scans suggest three vertebral fractures at the thoraco-lumbar junction
- Vertebral fractures (T10, 11 and 12) and degenerative change are confirmed on spine radiographs but there is no previous imaging to help identify the timing of the fractures
    - Maria has longstanding back pain and remembers this increased about 3-4 years ago after she was knocked over by a dog in the park. The severe pain took several weeks to improve but she thought it was part of her arthritis and didn't report it at her next appointment as it had improved by that time
    - Laboratory tests show she is calcium and vitamin D replete on her supplements. No other abnormalities are identified

Management discussion

- Maria is advised that the presence of vertebral fractures indicates that her risk of further fracture is higher than suggested by her FRAX score
- Her risk of vertebral fracture justifies first-line treatment with an anabolic treatment and although the vertebral fractures probably occurred a few years ago, the recent MOF makes her eligible for romosozumab treatment
- Because of her rheumatoid arthritis, Maria's 10-year cardiovascular risk at 22% is higher than the age-matched risk of 16%. After discussion about the potential benefits and risks of both romosozumab and teriparatide, she decides that daily teriparatide injections would be difficult, and although her cardiovascular risk is higher over a 10 year period, she has never had a heart attack or stroke, and on balance she would rather have romosozumab for one-year followed directly by antiresorptive treatment.