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Romosozumab: confusion regarding its indications

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Abstract

Romosozumab is undoubtedly an excellent drug to treat osteoporosis. However, its high price—much higher than antiresorptive drugs—initially led to accepting that its indication should be limited to patients with particularly high risk of fracture. However, the implementation of this idea into the routine clinical practice has been challenging. Firstly, different terms ("very high risk", "high risk", "severe osteoporosis") have been used to describe such indications, and the specific meaning of each term changes from one author to the next. On the other hand, without enough scientific basis, concepts have been introduced to expand the drug indications to the point of proposing its universal or near-universal use ("imminent risk", initiation of anabolic treatment for osteoporosis universally or quasi-universally). All this has created confusion among prescribing physicians and led to overly restrictive regulations imposed by health authorities regarding its use. This manuscript delves into these and other ideas in detail.

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INTRODUCTION

The marketing of romosozumab has been accompanied by a certain degree of confusion regarding the type of patient for whom it is indicated. Several factors contribute to this confusion. For example, the fact that the ARCH study (1) found a higher rate of serious cardiovascular events has led to its contraindication in patients who had previously experienced acute myocardial infarctions or strokes. Understandably, it is also advised to avoid it in patients with an equivalent cardiovascular risk. This raises the problem of how to define and determine this risk equivalence. Logically, it has been suggested to take into account the usual risk factors, but it has not been specified how to do so (whether risk scales should be used, which ones in particular, what values should be taken into consideration...). However, we will not dwell on this aspect now.

We do however, wish to emphasize the interest that discrepancy seen between the efficacy results in fracture prevention from the aforementioned ARCH trial and those from a previously published trial, the FRAME trial, (2) may have. In the first 12 months of the ARCH trial, romosozumab reduced non-vertebral fractures compared to alendronate approaching statistical significance ($p = 0.06$). In contrast, in the first 12 months of FRAME trial, romosozumab did not significantly reduce the incidence rate of this same type of fracture compared to placebo ($p = 0.10$). The explanation for this paradoxical difference (greater efficacy vs active comparator than vs placebo) is that the fracture risk of the patients included in the ARCH trial was considerably higher than that of those included in the FRAME trial. Information about this is provided by the comparison of the incidence rate of fractures in patients treated with romosozumab in the two studies; in the FRAME trial, the incidence rate of non-vertebral fractures in patients treated with romosozumab within the first year was 1.6 % while in the ARCH trial, it was 3.4 %. Hence, romosozumab demonstrates greater efficacy when the risk of fracture is higher. The overall results of the FRAME trial point out the same thing. At 24 months, there was no significant difference in the incidence rate of vertebral fractures or clinical fractures between the two study arms. However, the difference became statistically significant when patients recruited from Latin America (43 % of the overall study population), mainly from Colombia and Brazil (2,3), were excluded from the analysis. In these countries the risk of osteoporotic fracture is lower compared to the remaining countries that had included patients in the study. Once again, it is observed that the efficacy of romosozumab in the prevention of non-vertebral fractures varies with the risk level of the patient, showing greater efficacy when the risk is higher. All in all, these findings lead to the conclusion that the drug will be particularly useful in individuals with a higher risk, which should be taken into account when establishing its indications.

A third factor that has contributed to the confusion mentioned at the beginning —perhaps the main one in practice— is the price of the drug. Although it is of a similar order compared to the other anabolic drug marketed in Europe, teriparatide, it is notably higher compared to antiresorptive drugs. This has led health authorities in different countries to consider imposing conditions for its prescription and dispensation. These conditions often are not consistent with the indications proposed by the experts who have investigated the drug, which logically leaves the prescribing physician in a situation of uncertainty and confusion. Therefore, it is worth analyzing the underlying factors in this situation. We consider the following 3 factors to be the most relevant ones: a) confusion in the terminology describing the severity of the risk of fracture for which the drug may be indicated (sometimes referred to as "severe" osteoporosis, other times as "very high" risk of fracture or simply as "high" risk of fracture...); b) the addition of the notion that the risk of fracture in the period immediately following a previous fracture is "very high" (and use of the term "imminent" to refer to it, which is semantically questionable in this context and, therefore, misleading); and c) introduction of the idea that anabolic drugs are more effective when administered to patients who have not previously received an antiresorptive drug.

AMBIGUITY REGARDING TERMINOLOGY: HIGH RISK OF FRACTURE, VERY HIGH RISK OF FRACTURE, AND SEVERE OSTEOPOROSIS

Recently (April 2022), the National Institute for Health and Care Excellence (NICE), after a previous period of opposition, gave its approval regarding the use of romosozumab to treat postmenopausal osteoporosis (4). The corresponding document literally says that: romosozumab is recommended as an option for treating severe osteoporosis in peopleafter menopause who are at high risk of fracture only if they have a major osteoporotic fracture (MOF) within 24 months. It adds that the pharmaceutical company proposes that romosozumab should be used only in cases of imminent risk of fracture, defined as the risk associated with a person with severe osteoporosis who has had a MOF over the last 24 months (interestingly, NICE also states that its recommendation is broader than that of the pharmaceutical company, although in reality the difference is not as easy to see). In these comments, several terms need clarification: a) what does NICE mean by "high" risk of fracture; b) what do NICE and the pharmaceutical company mean by "severe" osteoporosis. Regarding the latter, we should mention that the World Health Organization (WHO) calls severe (or established) osteoporosis as having a T-score of ≤ -2.5 plus 1 or more fragility fractures (5). However, we should remember that the WHO's sole intention

when using this term was to distinguish densitometric osteoporosis with fractures from osteoporosis without fractures without trying to establish a specific therapeutic indication (it is well-known that the WHO classification was primarily formulated with epidemiological purposes in mind). We should also mention, regarding the scope of these concepts, that when the WHO speaks of severe osteoporosis, it does not specify the location of the fracture or the time elapsed since it happened unlike what NICE and the pharmaceutical company do when they limit the use of romosozumab to MOFs occurred over the past 24 months. In other words, they limit the indication of the drug to a narrower field compared to what the WHO understands as severe osteoporosis.

After the position of NICE regarding the use of romosozumab, the National Osteoporosis Guideline Group (NOGG) and the Royal Osteoporosis Society (ROS) in the United Kingdom, that had pressured NICE to modify its initial opposition to accepting the drug, drafted a consensus document in May 2022 (6). In it, they literally say that "treatment with romosozumab, is prioritised in postmenopausal women who have had a MOF within 24 months, with any one of the following: a) a BMD T-Score ≤ -3.5 (at the hip or spine), or b) a BMD T-score ≤ -2.5 (at the hip or spine) and either i/ vertebral fractures (either a vertebral fracture within 24 months or a history of ≥ 2 osteoporotic vertebral fractures), or ii/ very high fracture risk (e.g., as quantified by FRAX". The proposal, which is somewhat unclear and presents some differences with respect to what NICE suggests (e.g., T-score ≤ -3.5) introduces a new term: "very high risk." The document does not define it, but we know that the NOGG, in a previous publication, gives an accurate definition: it is the risk that corresponds, in the British version of FRAX, to the value resulting from multiplying the therapeutic threshold by 1.6 once BMD has been taken into account. A clear limitation of this definition is that it is associated with the use of that version of FRAX.

Unlike NOGG's approach, the term "very high risk" has been used in several American guidelines without a precise definition. For example, the American Association of Clinical Endocrinologists (AACE) (7) refers to "very high risk" patients as those with any of the following characteristics: "a recent fracture (e.g., within the past 12 months), fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (e.g., less than -3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (fracture risk assessment tool) (e.g., major osteoporosis fracture > 30 %, hip fracture > 4.5 %) or other validated fracture risk algorithm)." Aside from the high number of situations considered, we should mention the inaccuracy and questionable reliability and relevance of several of them: how many doctors actually believe that a T-score < -3.0 should be considered as "very low" risk?; what should we understand by "high risk of falls"? (patients with Parkinson's disease or stroke tend to fall: should they be treated with romosozumab only because they have these conditions?). In response to a letter asking the authors of these guidelines why they chose fracture probabilities of 30 % and 4.5 % (8), they answered (9) that they are "simple examples" and "not based on published evidence."

Other American endocrine guidelines like those from the Endocrine Society (10) define "extremely high risk" in a much easier and concise way though perhaps not sufficiently precise. Regarding the type of patient for whom they recommend the use of romosozumab, they state that they do so "in postmenopausal women with osteoporosis at very high risk of fracture, such as those with severe osteoporosis (*ie,* low T-score < -2.5 and fractures) or multiple vertebral fractures". As observed, they don't seem to establish restrictions regarding the type of fracture when the patient also has a T-score < -2.5. However, in another section of the document —in the footnote of the algorithm where they explain it— they literally say: "In postmenopausal women with osteoporosis at very high risk of fracture, such as those with severe osteoporosis *(ie,* low T-score < –2.5 and fractures) or multiple vertebral fractures". Since in this second case only vertebral fractures are mentioned, after reading these guidelines there is a feeling of inaccuracy left.

The guidelines from the Bone Health and Osteoporosis Foundation (BHOF, former National Osteoporosis Foundation, NOF) (11), although recognized based on the guidelines published by the Endocrine Society, introduce a few changes. They define "very high risk" as that patients with multiple vertebral or hip fractures and a T-score ≤ -2.5 in the lumbar spine or hip have. This is a very accurate definition. However, they, then, add that anabolic drugs are also advised in patients with recent fractures and/or a T-score < -3.0, situations that, precisely because anabolic drugs are recommended for them, can be included in the concept of extremely high risk. This time, the type of fracture is not specified, it is not said what is considered a recent fracture, and most importantly, the term "and/or" is introduced adding ambiguity to the profiles of the risk that should be taken into considered. It is not the same to require the coexistence of 2 different phenomena (recent fractures plus a T-score ≤ -3.0, as indicated by the "and" of the "and/or") as to accept the presence of either one of them (as indicated by the "or").

To conclude with the American proposals, we should note that the American College of Physicians (ACP) recently published its guidelines (12) also recommending the use of romosozumab in patients at "extremely high risk," but once again without precisely defining the boundaries of this concept. It simply states that it is "based on" "on older age, a recent fracture (for example, within the past 12 months), history of multiple

clinical osteoporotic fractures, multiple risk factors for fracture, or failure of other available osteoporosis therapy."

In conclusion, although what has been discussed so far indicates agreement that romosozumab is indicated for patients with a particularly high risk of fracture, in the definition of this degree of risk terms are used whose specific meaning is not specified, and whose scope is conceived differently by different authors. This complicates having a clear understanding of the problem, and also hinders reaching consensus.

CONSIDERATION THAT THE RISK OF FRACTURE IMMEDIATELY AFTER THE OCCURRENCE OF A PREVIOUS FRACTURE "IS EXTREMELY HIGH", AND ADDITION OF THE TERM "IMMINENT RISK" TO REFER TO IT

Various epidemiological studies conducted over the past few decades have indicated that the risk of fracture within the first few years following a previous fracture is greater than in subsequent years (13-15). Based on this, but without demonstrating that the initial risk is necessarily very high in absolute terms (although in relative terms it may be greater than the subsequent risk), it was decided to classify this risk of the early years as "very high." It is evident that accepting this approach implies that all women diagnosed with a fracture when it happens (in practice, all patients who suffer a fracture, except for those who are asymptomatic —morphometric vertebral fractures—) should be treated with romosozumab (or alternatively, with teriparatide).

To reinforce this idea, its advocates have gone further and agreed to label this initial risk with an pressing term: "imminent" (16-18). From a semantic point of view, its suitability is questionable so it is worth making a linguistic comment about it. In the world of communication, it is a common thing to apply a term to a specific concept that does not truly correspond to it, at least not fully, to persuade a certain audience and shape their way of thinking. This creates a distortion of the concept, creating what some describe as a "new reality," which leads to a change in the way the issue at stake is actually perceived (these inappropriately used terms act as "thought-creating elements" and are known as "linguistic framing"). The term "imminent" behaves this way when applied to the risk that follows the occurrence of a fracture initially. "Imminent" means "something that is about to happen" (according to the Royal Spanish Academy-DRAE). However, here this word is being used to describe something that may or may not happen and, in any case, even if it does happen, it does not have to happen immediately (that is, it is not "about to" happen). By using it in this particular circumstance a "new reality" is created with connotations of immediacy that do not correspond to the actual reality. This term is, therefore, misleading.

Semantics aside, it is important to know to what extent risk within the first few years after a fracture is truly higher compared to the following years. Two studies (19,20) —conducted with the goal of adding this aspect to FRAX— have quantified this difference. They are too complex to go into detail here, but the conclusion has been that the difference varies depending on the circumstances at stake (age, sex, type of fracture) that may not even be present, and that generally is not large. The authors themselves indicate that current knowledge is not enough to reach a definitive conclusión, and that further studies are needed to better understand the phenomenon. Accordingly, inferring that a recent fracture, simply because of being recent (without considering the absolute risk it represents based on its characteristics) should be treated with an anabolic drug is an unjustified generalization. As a matter of fact, a study published by Kanis et al. (21) that evaluates intervention thresholds for very high risk of fracture applied to NOGG guidelines explicitly states that "recent fracture alone did not invariably give rise to very high risk and depended in part on the site of the sentinel fracture." Similarly, in a recent editorial published in *Lancet Rheumatology*, Dr. R. Eastell is quoted in response to a question posed by the author of the editorial saying that "many patients with a major fracture in the previous 2 years will not have a high risk of subsequent fracture" (22).

In conclusion, the risk of fracture in the immediate period that follows a previous fracture does not have to be "very high" *per se*. Therefore, it does not necessarily require treatment with anabolic drugs. We should mention that this does not mean that patients should not be treated early. They should be. There is no sense in delaying the treatment of a patient who has had an osteoporotic fracture. However, it is crucial to understand the distinction between these 2 concepts: one thing is that early treatment should be initiated immediately after a fracture, and a totally different thing is that it must necessarily be done with an anabolic drug.

Regarding the confusion surrounding the use of romosozumab (or anabolic drugs in general) in the period following a fracture, we should mention that there is not agreement either on the duration of this period. For example, the NICE technology assessment document and the previously mentioned NOGG-ROS consensus document refer to a period of 24 months. However, the AACE and ACP guidelines mention a period of 12 months. In a recent conference (Budapest, Hungary, March 2023), Dr. B. Langdahl commented that Danish guidelines —seemingly still unpublished— mention a 3-year period.

There are also discrepancies regarding the type of fracture to which different authors believe that the idea of increased risk after the occurrence of a previous fracture is aplicable. As mentioned before, the AACE and ACP guidelines do not specify any particular type of fracture, therefore suggesting that they consider it applicable to any fragility fracture. In contrast, the NICE document and the NOGG-ROS consensus document limit it to major osteoporotic fractures (FOM). Other authors focus on vertebral and hip fractures (23). Some even propose more complex scenarios. For example, in the aforementioned Danish guidelines, romosozumab is considered for the management of both FOM and pelvic fractures while teriparatide is considered for vertebral fractures alone.

RECOMMENDATION FOR USING ANABOLIC DRUGS TO START TREATMENT IN ANY OSTEOPOROTIC PATIENT

Several studies (24,25) conducted with bone mineral density as the efficacy variable seem to indicate that the effect of anabolic drugs is lower when administered to patients who have previously received an antiresorptive drug compared to those who have not. Based on this, some authors argue (26,27) that osteoporotic patients should generally be initially treated with anabolic drugs because, should the patient not respond well, starting with an antiresorptive drug and then changing to a bone-forming drug, would reduce its efficacy. This approach seems to disregard the degree of the risk of fracture. As a matter of fact, if we were to apply this approach, the concepts of very high risk and increased risk in the initial post-fracture period would lose their meaning, since both define specific subpopulations of patients with osteoporosis obviously included in the overall osteoporotic population. The approach of treating all osteoporotic women in general is incompatible with treating only a portion of them.

Not only does this proposal disregard the degree of risk of fracture, but it also fails to consider the associated cost. Even if it were truly beneficial —which we'll discuss shortly— one must consider to what extent the increased benefit exceeds the higher cost involved. It is known that in any curve that relates the resources used to achieve a certain benefit with the actual benefit obtained, there's an "optimal zone" beyond which further benefit (including the "maximum" benefit) does not justify any additional expenses. This search for the optimal therapeutic zone is also applicable to the treatment of fractures with anabolic drugs, so it is of paramount importance to try to identify it.

But, above all, this approach ignores the fact that the only evidence we have regarding the efficacy of anabolic drugs on the management of fracture outcomes when administered after an antiresorptive drug is not indicative of a loss of efficacy. The VERO study [28], that compared the efficacy of teriparatide to risedronate in patients who had previously received an antiresorptive drug in approximately two-thirds of the cases, demonstrated that the anabolic drug retained its full anti-fracture efficacy in these patients.

We must remain attentive to studies conducted with romosozumab and how they vary from what we just mentioned regarding teriparatide. Because if the former does not behave similarly to the latter and loses efficacy when administered after an antiresorptive drug, it would clearly be a point where teriparatide would come out as the preferred option in the comparison.

CONCLUSIONS

The introduction of romosozumab to the market has led to a review of the drug selection criteria for the treatment of osteoporosis. Previously, there was a general agreement that the anabolic drug available in Europe, teriparatide, should be spared for cases of osteoporosis with a higher risk of fracture. While this condition was never precisely defined, its use did not pose significant problems because prescribing physicians often used it appropriately. Romosozumab, however, sought to have its indications clearly defined from the beginning. It immediately claimed a therapeutic niche defined as "very high risk" osteoporosis, and this expression appeared in the updates that various societies quickly made of their clinical practice guidelines to accommodate it. Due to its nature as an anabolic drug, this way of thinking was also applied to teriparatide (and abaloparatide), and we started talking, generically, about the indications of bone-forming treatment. However, the definition of "very high risk" remained unclear. The initial clinical practice guidelines that addressed this issue (AACE [7], Endocrine Society [10], IOF [29]) were far from offering a uniform criteria. As a result, clinicians did not have concrete and consensus-based rules on how to use these drugs. Things have not improved since then, quite the opposite. The introduction of debatable concepts (imminent risk, generalized initial anabolic treatment —"anabolics for everyone—") has generated more confusion. There are currently no signs that the problem will be solved in the short term. It is not surprising that health authorities from different countries are issuing restrictive regulations on this situation. How should we approach the problem? First, I believe we should ask experts to provide recommendations based on solid scientific evidence, free from conjecture, wishful thinking (in the sense of thinking guided by desire) or commercial interests. Second, we should remind prescribing

physicians that in medicine, when there is confusion, it is often preferable to exercise moderation regarding decision-making. And that, furthemore, it is desirable to adhere to indications that are formulated in a precise way, so as to leave no room for doubt.

ADDENDUM

Across this manuscript, we deliberately did not mention the clinical guidelines from the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM) (30). The reason is that we wanted to make sure that the reasoning developed therein was not influenced by any desire to defend our guidelines. However, upon reading it after completion, we were under the impression that not referring to them could be interpreted as a lack of interest or even dismissal of the guidelines. Therefore, we believe it is necessary to make this final comment, placing them in relation to the issues raised above.

First, our guidelines do not mention the advisability of administering anabolic drugs as the initial drug. The reasons why we disagree with the "anabolics for everyone" strategy have been explained in the aforementioned discussion. We remain committed to classifying patients based on their level of risk, and starting with anabolics in "very high risk" patients only. We will not dwell on this point.

Secondly, our guidelines do not refer either to treating patients who have sustained a fracture over the past 2 years with anabolic drugs. As a matter of fact, there are no problems in adding this aspect to the guidelines. However, we don't believe it is beneficial for all patients, as we will discuss later on. Let's consider, for example, the proposal from NICE, a well-accredited organization. They suggest treating with romosozumab women who have had a MOF over the past 2 years. This idea can be easily added to our algorithm regarding the 2 most important fractures, vertebral and hip fractures, simply by modifying the wording of the second criterion we mentioned to identify very high risk patients. Instead of saying "patients with vertebral or hip fracture and a T-score < -3.0," we can say "patients with vertebral or hip fracture sustained over the past 24 months and a T-score < -3.0." Obviously, this excludes the other 2 major osteoporotic fractures. However, we should say on this regard that we share the opinion of those who do not attribute the same importance to wrist fractures as to vertebral and hip fractures. Wrist fractures do not exhibit a significantly higher risk within the 2 years following the fracture compared to later periods (as a matter of fact, it may be lower depending on age [19,20]), and the morbidity and mortality rates associated with wrist fractures are not comparable to those of vertebral and hip fractures. Therefore, the same therapeutic approach would not be justified. Humeral fractures are also quite different from vertebral and hip fractures. It is understandable that they are not considered eligible for anabolic treatment unless they are associated with other factors.

In conclusion, our clinical practice guidelines can add the temporal concept by simply redefining the second criterion of "very high risk" as mentioned earlier. Personally, we would not introduce such a modification because it essentially represents a restrictive change (we would no longer be treating patients who had a vertebral or hip fracture prior to the 24-month timeframe). Finally, regarding this temporal issue (the much talked about "imminent" risk), we should mention that when the last iteration of the guidelines was drafted, a survey was submitted to members of the committee responsible for drafting them. They were asked whether they supported or opposed the administration of an anabolic drug to patients who had had a fracture in the previous year based only on the fact that it had occurred within this timeframe. A total of 70 % of the responses were contrary to this.

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