

## REFEREE 1

*An overview of the literature describes the modern approach to treat osteoporosis. In particular the author focuses on the potential bone anabolic therapy. While there is merit in this article, this reader found the article at times written in a disjointed style*

*1) The first part of an article describes the disadvantages of the current antiresorptive drugs. This part appears to be repetitive and not completely logical. In the beginning, the author states that bisphosphonates inhibit bone resorption mentioning the potential risk of the osteonecrosis of the jaw and of atypical subtrochanteric femoral fractures. On the same page, the author explains their mode of action referring to the decrease in the activation of frequency and again raises the same problem with osteonecrosis of the jaw and of atypical subtrochanteric femoral fractures. These complications were not definitely related to antiresorptive while treated osteoporosis, there is no reason to repeat the same. In between, strontium ranelate has been mentioned with a so called dual action which has not been proven in humans. This fact should be mentioned in addition to numerous restrictions related to the proven side effects of strontium ranelate. In general this part requires revising.*

1) The main objective of the present review was to focus on new perspective in anabolic therapy of osteoporosis, therefore the part of manuscript describing antiresorptive drugs is necessarily synthetic. However, accepting the Referee's advice we omitted to underline complications of bisphosphonates therapy and we added some detail of ranelate strontium.

*2) The part on anabolic therapy should be divided between drugs with proven anabolic activity at least in some clinical trials and only suggested to have an anabolic action without any clinical data. The data on statins is extremely vague with regard to*

*clinical practice. From the heading it appears that some statins and IGF1 are related to Antagonists of Wnt-inhibitors. Clearly, this is not the case.*

2) The Author's suggestion to underline the difference the drugs with proven anabolic activity in some clinical trials from those without appears appropriate. However, it is preferable to let the present construction underlying the presence or the absence of clinical trial data in the single section regarding drugs class. As suggested by the Referee the heading could be confounding, therefore it has been corrected making the same the main headings. In this way statins are under "Other Potential Anabolic Agents" heading that differ from "Antagonists of Wnt-inhibitors" or "Calcilytic Agents" or "PTH related peptide or Parathyroid hormone"

*3) Some figures or tables could improve the manuscript.*

3) Two figures, showing a synthesis of the main mechanisms and action site of some bone anabolic drugs, has been added as suggested by the Referee.

## REFEREE 2

It is a rather complete review about future directions in osteoporosis therapeutics. It is also well written.

## REFEREE 3

*This article don't mention deeply about the mechanisms of bone remodeling and modeling and the relationships between these anabolics and mechanisms. I don't some points in this article like "Osteoporotic fractures of the hip and spine carry a 12-month excess mortality rate of up to 20%.." in page2 line 11. In my experience, the 12-month mortality rate of osteoporotic hip fracture is up to 20%, but not of osteoporotic spine fracture. Lack of figures makes this article without attractions. There is a better review article within references (reference no.39).*

The Referee comments are important to improve the manuscript and personal experience. However, the present Referee's comment does not seem to be written with such a purpose. The Referee complains that "This article don't mention deeply about the mechanisms of bone remodeling and modeling and the relationships between these anabolics and mechanisms" but the review aims to be synthetic and not focus on bone modelling and remodelling mechanisms, which would result in an other different and long review. In addition, the Referee underline his personal experience about 12-month mortality. The present review does not report the personal Author's experience but the literature experience based on evidences, namely Center (Lancet 1999) and Cauley's experiences (Osteoprosis Int 2000).

The Referee defines as better review than the present that by Baron. I completely agree with the Referee since I know the incredible experience of such important researcher. However, the

literature is rich of several reviews that address similar issues trying to answer to specific and particular needs of the different journal's readers (the readers of JCEM should be assumed different from those of World Journal of Orthopedics). Finally, the Referee use an English form not always understandable, such as "I don't some points in this article like.....".

#### REFEREE 4

*The objective of this paper was to review bone anabolic agents in osteoporosis. The following points need to be taken into account:*

*Please describe more exhaustively all results with strontium ranelate as this product has an anabolic effect on bone through osteoblast modulation.*

More data on strontium ranelate have been added.

*Please provide more information regarding adverse events of all products.*

Some information about adverse events of all products has been added where lacking (see: raloxifene, denosumab, strontium ranelate, calcylitic agents, sclerostin antibodies).

*Please provide more data regarding health economics data on all products.*

Addressing the issue on health economic aspects relative to all new osteoporosis therapies is beyond the aim of this review, considering the fact that the most recent and innovative therapies lack of such data.

*Regarding other potential anabolic agents, it would be interesting to have information regarding clinical trials currently planned or performed.*

I agree with the Referee that could be interesting to complete the review with some information about the future clinical trials and perspectives. However, I think that the most promising clinical data about the new bone anabolic therapies have been already reported in the manuscript and that other data available in [www.clinicaltrials.gov](http://www.clinicaltrials.gov) are not useful to improve the clarity and simplicity of the present manuscript