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REVIEW

CUTTING EDGE IN OSTEOPOROSIS THERAPY: ANTISCLEROSTIN ANTIBODIES

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Summary

Introduction: Osteoporosis, especially menopause - related form, represents a condition with dramatic epidemiologic burden thus the need for clear recommendations of case finding strategies and for developing new therapies. Antisclerostin antibodies uncouple bone resorption from formation, allowing formation but not resorption. We aim to introduce a compressive approach related to antisclerostin antibodies (a PubMed- based narrative review).
General data: The inhibition of sclerostin based on human-like antibodies (like romosozumab, blosozumab) induces a consistent yet transitory bone mass elevation while the resorption is blocked. Phase two trials showed an important human skeletal effect by inducing high bone mineral density through Wnt signalling transduction. Sclerostin is presented into the body in order to control the bone formation - resorption balance. Its blood levels are increased in patients with renal failure even if it is paradoxically more excreted. This small protein is coded by SOST gene which is found in osteocytes in response to mechanical forces on the bones thus osteocytes play an essential role as key regulators of bone remodelling. Sclerostin binds to osteoblasts to inhibit them. Its production is also found in cartilages but limited data are currently known about its specific actions but, perhaps, antibodies targeting sclerostin may be beneficial for both osteoporosis and osteoarthritis.
Conclusion: The results from ongoing trials will point out the exact role of antisclerostin antibodies as anti-osteoporotic agents, and this will probably be as second line medication on a sub-set of subjects with severe forms of osteoporosis or potentially in patients with kidney failure- related bone loss.
Key words: osteoporosis, sclerostin, menopause, antibody

Résumé

Les seuil tranchant de la thérapie ostéoporotique: les anticorps antisclérostine

Introduction: L'ostéoporose, en spècial la forme liée à la ménopause, représente une condition à un fardeau épidémiologique dramatique, d'ici la nécessité de recommandations metter de trouver des stratégies de cas et de développer de nouvelles thérapies. Les anticorps antisclérostine découplent la résorption osseuse de la formation, ce qui permet la formation, mais non la résorption. Nous avons l'intetion d'introduire une approche de compression liée aux anticorps antisclérostine (une revue narrative basé sur PubMed).
Données générales: L'inhibition de la sclerostine basée sur des anticorps humains (comme romosozumale, blosozumale) induit une élévation importante de la masse osseuse, bien que transitoire, tandis que la résorption est bloquée. Les trials de la deuxième phase ont montré un effet important du squelette humain en induisant la densité minérale osseuse élevée à travers la transduction du signal Wnt. La sclérostine est présenté dans le corps afin de contrôler l'équilibre entre la formation des os et la résorption. Ses taux sanguins sont accrus chez les patients avec une insuffisance rénale, bien qu'elle soit paradoxalement plus excrétée. Cette petite protéine est codifiée par le gène SOST qui se trouve dans les ostéocytes en réponse aux forces mécaniques sur les os, ainsi que les ostéocytes jouent un rôle essentiel en tant que régulateur du remodelage osseux. La sclérostine s'attache aux ostéoblastes afin de les inhiber. Sa production est également retrouvée dans les cartilages, mais des données limitées sont actuellement connues sur ses actions spécifiques. Mais, peut-être, les anticorps ciblant la sclérostine, peuvent être bénéfiques tant pour l'ostéoporose que pour l'arthrose.
Conclusion: Les résultats des trials en cours mettront évidence le rôle exact des anticorps antisclérosine en tant qu'agents anti-ostéoporotiques, et ce sera probablement en tant que ligne seconde médicamenteuse chez un sous-ensemble de sujets atteints de formes sévères d'ostéoporose ou éventuellement chez les patients atteints d'insuffisance rénale liée à la perte osseuse.
Mots clés: ostéoporose, sclérostine, ménopause, anticorps

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Introduction – the osteoporosis medical approach

Osteoporosis, especially menopause- related type, represents a condition with dramatic epidemiologic burden thus the need for having strong recommendations of case finding strategies and developing new therapies. (1,2,3) Despite complex programs of detection and implemented tools of screening and diagnosis, many patients with osteoporosis are not recognised and neither will be adequately treated and this aspect is found worldwide. (4,5,6,7) However, progresses in the medical field of specific anti-osteoporotic drugs has been recently done, including biological medication. (8,9,10)

Underlying mechanisms of bone loss may be targeted by different drugs, including this type of treatment. (8,9,10) For instance, monoclonal antibodies target RANK-RANKL-osteoprotegerin complex (Receptor Activator of Nuclear factor κB-ligand), the key regulator of bone resorption. (11,12,13) Denosumab is a humanized monoclonal antibody which links to RANKL, and then it stimulates osteoprotegerin which blocks RANK-RANKL interaction so it stops osteoclast activation and consecutive bone resorption. (14,15,16) Denosumab acts as anti- resorptive agent when it is offered to patients through a subcutaneous injection of 60 micrograms every 6 months (FREEDOM trial). (17,18,19) Teriparatide is the analogue of human parathormone (residues 1-34) having a bone formation agent profile. (20,21, 22) It is indicated for patients with severe osteoporosis through daily subcutaneous injections of 20 micrograms once in a lifetime for 18 or 24 months depending on country protocol. (23,24,25) The subjects may be specifically treated for osteoporosis first time in life or they may be non-responders to otherwise traditional options of medication as bisphosphonates, etc. (26,27,28)

Cutting edge in treated osteoporosis is represented, among others, by antibodies against sclerostin. (29,30) While bisphosphonates and denosumab initially lower bone resorption, teriparatide primarily increases bone formation, antisclerostin antibodies uncouple resorption from formation, allowing bone formation but not consecutive bone resorption. (29,30) The uncouple mechanism is also underlined by cathepsin K inhibitors, another hot spot on anti-osteoporotic medication map. (30,31)

Aim

We aim to introduce a compressive approach related to antisclerostin antibodies.

Material and Method

This is a short commentary of narrative review type using mainly PubMed published articles.

General data – antisclerostin antibodies

As mentioned before, there is still enough space for novel therapeutically approaches in the field of osteoporosis since non-responders patients are found with different frequencies and the area of anti-osteoporosis drugs side effects is heterogeneous. (32,33,34) The inhibition of sclerostin based on human-like antibodies (like romosozumab, blosozumab) induces a consistent yet transitory bone mass elevation while the resorption is blocked. (29,30,34) Phase two trials showed an important skeletal effect by inducing high bone mineral density. (34,35,36) The pathogenic mechanisms are the action on Wnt pathway with an osteoblastic shift which is observed on patients if they are treated for a short period of time (like a year). (34,35,36) Sclerostin, as osteoprotegerin, has the ability to act as local bone regulators and key interfaces of classical hormones with skeletal action. (35,36) Wnt signalling transduction allows osteoblasts differentiation and secondary bone mass increases while suppresses osteoclasts and their associated activity of resorption. (35,36,37) Wnt pathway has natural antagonists with direct action on Wnt proteins or indirect effects on Wnt co-receptors. (37) Blocking the antagonists as antisclerostin antibodies will produce a bone mass gain. (38,39,40) Sclerostin is presented into the body in order to control the bone formation - resorption balance. (40,41) Its blood levels are increased in patients with renal failure even it is paradoxically more excreted. (40,41) This small protein is coded by SOST gene which is found in osteocytes in response to mechanical forces on the bones. (40,41,42) Even if traditionally osteocytes were considered rather not useful for bone biology modern theories recognise their essential role as regulators of bone remodelling. (40,41) Sclerostin binds to osteoblasts to inhibit them. (40,41) Sclerostin production is also found in cartilages but limited data are currently known about its specific actions here. (43,44) Thus, antibodies targeting sclerostin may be beneficial for both osteoporosis and osteoarthritis. (43,44) If the results from ongoing trials will pointed out their position will probably be as second line medication on a sub-set of subjects with severe forms of osteoporosis or potentially in patients with kidney failure-related bone loss. (45,46,47,48)

As final consideration, we should ask what about the future? We expect protocols for daily practice with clear cut indications and contraindications for antisclerostin antibodies, as well as other novel therapies like cathepsin K inhibitors or abaloparatide, a recombinant PTHrP analogue (parathyroid hormone related peptide). (34,37,39)

Conclusion

There are still many data incompletely known up to this moment in the field of antisclerostin antibodies as therapy for osteoporosis but the observations available up to this moment are encouraging.

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