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Application of anti-Sclerostin therapy in non-osteoporosis disease models

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ABSTRACT

Sclerostin, a known inhibitor of the low density lipoprotein related protein 5 and 6 (LRP5 and LRP6) cell surface signaling receptors, is integral in the maintenance of normal bone mass and strength. Patients with loss of function mutations in *SOST* or missense mutations in *LRP5* that prevent Sclerostin from binding and inhibiting the receptor, have significantly increased bone mass. This observation leads to the development of Sclerostin neutralizing therapies to increase bone mass and strength. Anti-Sclerostin therapy has been shown to be effective at increasing bone density and strength in animal models and patients with osteoporosis. Loss of function of *Sost* or treatment with a Sclerostin neutralizing antibody improves bone properties in animal models of Osteoporosis Pseudoglioma syndrome (OPPG), likely due to action through the LRP6 receptor, which suggests patients may benefit from these therapies. Sclerostin antibody is effective at improving bone properties in mouse models of Osteogenesis Imperfecta, a genetic disorder of low bone mass and fragility due to type I collagen mutations, in as little as two weeks after initiation of therapy. However, these improvements are due to increases in bone quantity as the quality (brittleness) of bone remains unaffected. Similarly, Sclerostin antibody treatment improves bone density in animal models of other diseases. Sclerostin neutralizing therapies are likely to benefit many patients with genetic disorders of bone, as well as other forms of metabolic bone disease.

1. Introduction

The cell surface signaling receptor low density lipoprotein related protein 5 (LRP5) has emerged as a key regulator of bone mass [1–3]. Recessive loss of function mutations in *LRP5* cause Osteoporosis Pseudoglioma syndrome (OPPG), a disorder characterized by bone fragility and frequent pathologic fractures starting in childhood [1]. Dominant missense mutations in *LRP5* have the opposite effect, resulting in increased bone mass and strength by preventing inhibition of the receptor by an endogenous inhibitor, Sclerostin [2–7]. Patients with mutations in the Sclerostin gene (*SOST*) or a nearby regulatory region have a phenotype similar to patients with *LRP5* high bone mass (HBM) mutations, characterized by increased bone mass and strength [8,9]. LRP5 activates the canonical Wnt signaling pathway. [10–12] Signaling through LRP5 is known to be required for the increase in bone mass seen in response to mechanotransduction [13]. Further, osteocyte production of Sclerostin is reduced by mechanical loading and increased by hind limb unloading, suggesting Sclerostin acts on the LRP5 receptor to induce changes these changes in bone mass [14].

1.1. LRP5 high bone mass mutations are anabolic

Mouse models with mutations orthologous to the human *LRP5* HBM mutations recapitulate the phenotype of increased bone density and strength [15]. Mice with an *Lrp5* HBM mutation have increased bone formation compared to littermate controls indicating the mutation is anabolic, inducing bone formation. Furthermore, these mutations act locally to increase bone formation, consistent with the known production of Sclerostin by osteocytes [15].

1.2. Sclerostin antibody therapy

Sclerostin neutralizing antibodies have been shown to be effective in improving bone density in both animal models [16–18] and humans with postmenopausal osteoporosis [19–25]. Interestingly, a short (5-week) period of Sclerostin antibody treatment in both ovariectomized mice and adolescent cynomolgus monkeys caused an increase in bone formation and reduction in bone resorption [26]. In post-menopausal women treated with Sclerostin antibody, markers of bone formation were initially increased with treatment before returning to baseline while markers of bone turnover were decreased and remained below that of the placebo group [22,25]. These data suggest that at least in both normal bone and post-menopausal osteoporosis, Sclerostin

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inhibition is both anabolic and anti-resorptive, mirroring the effect on bone of increased loading. Similar improvements in bone density from Sclerostin antibody therapy have been seen in mouse and rat models of disuse related bone loss and spinal cord injury [27–31]. These exciting findings raised the question of whether anabolic Sclerostin antibody therapy could be equally effective at treating genetic and metabolic disorders of bone. Currently therapies for these disorders are limited, particularly in the pediatric population, as the other anabolic medical therapy, recombinant parathyroid hormone, is not used due to the risk of osteosarcoma [32].

2. Osteoporosis Pseudoglioma syndrome (OPPG)

OPPG is a rare recessive disorder characterized by bone fragility and eye findings. Bone resorptive activity in these patients is normal, but bone formation is greatly reduced, resulting in bone density scores more than 5 standard deviations below the mean [1]. The finding of reduced bone formation suggested these patients would benefit from an anabolic therapy. However, as the causative mutations result in loss of function of the LRP5 receptor, it was unclear if Sclerostin neutralizing therapy would be effective. Surprisingly, loss of the function of both alleles of the *Sost* gene resulted in large increases in bone density and strength of an OPPG mouse model with recessive loss of function mutations in *Lrp5*, fully rescuing the phenotype [33,34]. In addition, 3 weeks of therapy with Sclerostin neutralizing antibody increased bone mass and formation rates in the same model [33].

This increase in bone formation was hypothesized to result from loss of Sclerostin inhibition of the closely related signaling receptor, LRP6, even in the absence of functional LRP5. This was confirmed in further experiments which demonstrated that selectively blocking Wnt1 induced LRP6 signaling reduced bone density gains in mice with both *Sost* and *Lrp5* mutations [34]. Together these results suggest that patients with OPPG could benefit from therapies that reduce Sclerostin activity, notably Sclerostin antibody. Further, selectively blocking Wnt1 induced Lrp6 signaling may benefit patients with symptoms of skeletal overgrowth from recessive *SOST* mutations as well as dominant *LRP5* HBM mutations.

3. Osteogenesis Imperfecta

Osteogenesis Imperfecta (OI) is a genetic disorder characterized by skeletal fragility and pathologic fractures leading to bony deformities. Most patients with OI have dominant mutations in one of the type 1 collagen genes [35]. Other causes include recessive mutations in genes involved in collagen production and post-translational modification [36]. Current therapies for OI include bisphosphonates, which are anti-resorptive and prevent increased bone turnover. While bisphosphonates do not alter the underlying genetic structural disorder of collagen, these therapies have been effective in increasing bone density in both adult and pediatric patients, likely by preventing the increased bone turnover seen in patients with OI [37–39]. Data on fracture prevention is mixed, but some pediatric patients do benefit [39,40]. In adults with mild type 1 OI, recombinant parathyroid hormone (teriparatide) has been used as an anabolic therapy. In two small studies, patients had significant increases in bone mineral density. Unfortunately, both studies were underpowered to detect fracture risk [41,42]. No other anabolic therapies exist to treat these patients, raising the question of whether anabolic Sclerostin neutralizing therapies could improve bone properties in OI by increasing bone formation without altering the underlying collagen abnormalities.

3.1. An Lrp5 HBM mutation or Sclerostin antibody therapy improves bone properties in mouse models of OI

Although reducing Sclerostin activity does not affect the underlying type I collagen mutations responsible for the majority of cases of OI, studies of anti-resorptive bisphosphonates have demonstrated that increasing bone mass alone, regardless of the underlying quality of that bone, can reduce fracture rates in patients with OI [43]. This suggested that increasing bone formation through Sclerostin antibody therapy could also improve bone properties in OI. Proof-of-principle experiments demonstrated that an *Lrp5* HBM mutation that prevents Sclerostin inhibition of the receptor in combination with a dominant *Col1a2* OI mutation (G610C) results in increased femoral cortical and trabecular bone as well as increased long bone strength compared to the OI mutation alone [44]. Further studies of the effect of the *Lrp5* HBM mutation on mice with OI due to haploinsufficiency of a *Col1a1* allele (Mov13) demonstrated similar increases in cortical and trabecular bone at the femur and spine [45].

In another mouse model of dominant OI due to a *Col1a1* mutation (Brtl), 2 weeks of Sclerostin antibody therapy in juvenile mice was enough to increase both femoral cortical and trabecular bone and long-bone strength [46]. Another study found similar results with 6 weeks of therapy in juvenile mice with a *Col1a2* mutation (G610C), although the effects of the therapy were not as large as the *Lrp5* HBM allele [44]. Further work showed that 5 weeks of Sclerostin antibody therapy in both rapidly growing and adult mice (Brtl) increased femoral cortical and trabecular bone strength, although the trabecular effects were more pronounced in the adult mice [47,48]. Interestingly, the adult mice did not show improvements in bone density in the spine, suggesting there may be age dependent effects of Sclerostin antibody [48].

All of the above data is from OI mutations resulting in a mild to moderate OI phenotype. Data in more severely affected animal models are mixed. In one severe model of dominant OI due to *Col1a1* mutations (Jrt), 4 weeks of Sclerostin antibody therapy increased femoral trabecular bone in rapidly growing but not adult mice and did not increase spinal trabecular bone in either the juvenile or adult mice [49]. Further, treatment did not improve long bone strength at either age [49]. However, in another severely affected mouse model of OI due to recessive mutations in the *Crtap* gene, six weeks of Sclerostin antibody therapy given to juvenile mice resulted in increased cortical and trabecular bone at both the femur and the spine as well as increased long bone strength [50]. Rapidly growing mice treated from age 1 week to age 7 weeks showed similar results in trabecular bone at the femur and spine but did not show an increase in cortical thickness, only cortical area, and there was also no improvement in strength of the long bones [50]. This data again suggests that there may be an age dependent effect on response to Sclerostin antibody in OI and further, that the specific collagen mutation may influence the response to therapy.

3.1.1. Sclerostin antibody therapy or an Lrp5 HBM mutation do not improve bone quality in OI

While most mouse models of OI treated with Sclerostin antibody show improvements in bone mass and strength, there is little evidence of a corresponding improvement in bone quality. Mice with haploinsufficency of a *Col1a1* allele (Mov13) and an *Lrp5* HBM allele do not show an improvement in post-yield displacement (brittleness) compared to littermates with an OI allele. Further, FTIR studies of different OI mouse models with dominant OI mutations (G610C and Mov13) and *Lrp5* HBM showed no change in the abnormal mineral to matrix ratio seen in OI bone, consistent with lack of improvement in bone quality [45,51]. Similar results were seen in another mouse model (Brtl) when juvenile mice were treated for 2 or 5 weeks with Sclerostin antibody. There was no improvement in brittleness nor an effect on the estimated elastic modulus [46,48,52]. There was also no improvement in brittleness seen in the rapidly growing and juvenile recessive *Crtap* mice treated with anti-Sclerostin antibody and no improvement in increased matrix mineralization either the juvenile or adult Jrt mice treated with antibody [50,53]. Interesting, 5 weeks of Sclerostin antibody therapy in adult mice (Brtl) did increase post-yield displacement

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