Trends-in-Medicine

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Quick Pulse

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AMERICAN SOCIETY FOR BONE AND MINERAL RESEARCH (ASBMR)

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The key topic at this meeting was Amgen's denosumab for osteoporosis, but there were also interesting data on parathyroid hormone (PTH) secretagogues – particularly Novartis's ATF-936 and GlaxoSmithKline/NPS Pharmaceuticals' ronacaleret – as well as cathepsin K inhibitors such as Merck's odanacatib.

NUCLEAR FACTOR KAPPA B LIGANDS (RANKLS)

AMGEN's denosumab – *a clear win*

➢ **Efficacy.** The denosumab FREEDOM data exceeded expectations, positioning denosumab, a monoclonal antibody injected subcutaneously twice yearly – as the best-in-class drug for treating osteoporosis. Fracture protection was arguably superior to that shown for the bisphosphonate class while safety was clearly superior.

Experts attending an Amgen analyst meeting characterized denosumab as a first-line agent for osteoporosis. Still, Amgen and denosumab face many challenges in the osteoporosis market, not the least of which is an inadequate rate of bone mineral density testing that can lead to diagnosis and treatment.

Addressing these issues, Amgen will need to increase education and awareness of osteoporosis, harnessing tools such as FRAX, the new World Health Organization (WHO) fracture risk assessment tool, and, perhaps in the future, genetics to select patients likely to benefit from denosumab. The competitive landscape will continue to change, and data were presented at ASBMR for a cathepsin K inhibitor currently in Phase III testing as well as novel PTH strategies, some of which are in late Phase II testing.

The FREEDOM trial 3-year fracture data in postmenopausal osteoporosis were presented at ASBMR, and it was about as good as it gets. Statistically significant reductions in fractures at the lumbar spine (68%), hip (40%), and non-vertebral fractures (20%) place denosumab at the top of the efficacy pyramid for osteoporosis. Without a signal for serious adverse events, serious infections, or neoplasms over placebo, denosumab may offer the best overall profile in osteoporosis.

Given the limited time for data presentation at ASBMR, few specifics on adverse events were presented, but Dr. Steve Cummings of the University of California, San Francisco (UCSF), stated that a paper will be submitted for publication in 2-3 weeks which will permit a fuller evaluation.

During a question and answer session, Dr. Ethel Siris of Columbia University and Dr. Cummings painted a compelling picture for denosumab use by both primary care and specialist physicians. Both characterized denosumab as a bona fide first-line agent. Compared to oral bisphosphonates, they claimed that denosumab is clearly more effective while lacking common side effects associated with bisphosphonates. Denosumab was described as comparable in efficacy to Novartis's Reclast (zoledronic acid), but again with a superior side effect profile, making it a more attractive product. Further, Reclast was described as an impractical drug for primary care given its Medicare Part B rating and the requirement for infusion capability.

In light of these data, it is likely that Amgen will decide to market denosumab alone in the U.S., but will offset costs for additional infrastructure by partnering in Europe.

The randomized, placebo-controlled, internationally-run FREEDOM study in 7,808 postmenopausal women compared denosumab given once every six months by subcutaneous injection for 3 years to placebo. The 5,600 patients completing FREEDOM are continuing to receive denosumab in a 3-year extension study. After three years, 82%-84% of patients completed the study, with 75% to 80% of all patients receiving all doses of drug.

The vertebral fracture benefit was observed at the end of the first year of the study with a 65% reduction. The protection benefit increased to 78% in Year 2, falling back slightly to 65% in Year 3. The absolute incidence of hip fractures observed in the denosumab arm (at 0.7% the lowest rate shown in a Phase III study) was particularly impressive. Unlike vertebral fracture data, hip fractures were not broken out by study year, but a graph of cumulative hip fracture incidence shows that the curves separated well before 12 months. By comparison, the Reclast HORIZON study showed no curve separation until 18 months. In HORIZON, Reclast reduced hip fracture rates from 2.5% to 1.4%, showing a 41% relative risk reduction. While it is difficult to compare across the FREEDOM and HORIZON studies, a 40% reduction from a base of 1.2% is impressive, given that experts opine that the base hip fracture rate for non-osteoporotic patients could be 1%-1.5%, suggesting that there is a baseline risk below which fracture rates can be reduced no further, and denosumab could have broken through this barrier.

3-Year Fracture Results in Denosumab FREEDOM Trial

Measurement	Placebo n=3,906	Denosumab n=3,902	Relative risk reduction	p-value
Vertebral fracture	7.2%	2.3%	68%	<0.0001
Clinical vertebral fracture	N/A	N/A	69%	<0.0001
Non-vertebral fracture	8%	6.5%	20%	0.011
Hip fracture	1.2%	0.7%	40%	0.036

➢ **Safety.** Despite the lack of specific detail on adverse events, many concerns were clearly addressed by the FREEDOM study. The overall adverse event profiles were no different between the two arms of the study, including new neoplasms, infections, or serious infections, and no opportunistic infections were noted. In an attempt to identify low frequency safety signals, Amgen conducted two additional analyses which looked for statistically significant differences in an event occurring at rates >2% and, following this, >0.1%. Amgen officials noted that in many cases where the causative agent for the erysipelas cases was isolated, it was shown not to be a group A beta-hemolytic streptococcus.

3-Year Safety Results in Denosumab FREEDOM Trial

Measurement	Placebo n=3,906	Denosumab n=3,902
Adverse events	**92.1%**	**92.8%**
Adverse events leading to drug discontinuation	5.2%	4.9%
Adverse events leading to study discontinuation	2.1%	2.4%
Deaths	2.3%	1.8%
Serious adverse events	**25.1%**	**25.1%**
Malignancy	2.2%	2.4%
Infection	54.4%	52.9%
Serious infection	3.4%	4.1%
Stroke	1.4%	1.4%
CHD	1.2%	1.0%
Atrial fibrillation	0.7%	0.7%
Osteonecrosis of the jaw (ONJ)	1.0%	1.2%
Delayed fracture healing	0.1%	0.1%
Neutralizing antibodies	---	0
Additional safety analyses		
Falls	6.4%	5.3%
Concussions	0.3%	0.1%
Flatulence	1.4%	2.2%
Erysipelas (a skin infection caused by group A beta-hemolytic streptococci)	0	0.2%

Diagnosing postmenopausal osteoporosis (PMOP) *– room for improvement*

Women can only be treated with denosumab if they are diagnosed, which in the U.S. relies largely on a bone mineral density (BMD) scan. As an example of the scale of this issue, a community analysis of 13 U.S. primary care practices, covering ~900 postmenopausal women, found only 56% received a BMD scan. On a more encouraging note, a high rate of anti-resorptive prescribing was observed in those patients diagnosed with osteoporosis. In addition there was a high proportion of patients receiving follow-up scans to monitor treatment effectiveness.

While the authors did not present reasons for the mediocre rate of diagnostic BMD scans, the authors of a Canadian hospice study identify a lack of education to explain their results. A potential market for denosumab

would be patients in long-term hospice care (~200,000 in the U.S.). An analysis of Canadian long-term treatment facilities showed not only a low rate of scans to diagnose osteoporosis but, even in patients with a current or prior diagnosis, low use of anti-resorptive therapy. As a result of their observations, the authors have developed materials to educate healthcare professionals at these facilities about the importance of diagnosing and treating osteoporosis.

In the context of this low rate of BMD scans in men and women over 65 years, FRAX, the WHO's fracture prediction tool, will likely not increase the diagnosis of osteoporosis, but it does become part of a multi-pronged approach to increase the overall quality of osteoporosis care. Increasing awareness and referrals for bone scans will increase the rate of diagnosis, which should become easier as new DEXA machines will come with the FRAX algorithm pre-loaded while older models can have a software upgrade to include FRAX. Further, FRAX will be continually improved, broadening its applicability to include men and non-Caucasians. Longer-term testing for target SNPs will become part of the overall risk equation.

In February, the National Osteoporosis Foundation (NOF) updated their treatment guidelines according to the WHO fracture risk prediction tool, FRAX. FRAX includes nine risk factors that can be used to predict the 10-year fracture risk for hip fracture or a major clinical fracture. Based on a pharmacoeconomic analysis, the NOF recommends that women with a 3% risk for hip fracture or a 20% risk for a clinical fracture receive anti-resorptive therapy.

Researchers from UCSF presented their analysis, applying FRAX to the Study of Osteoporotic Fractures (SOF) database of 6,096 women with clinical vertebral fractures. They concluded that 73% of women aged ≥65 and 93% of women ≥75 should receive anti-resorptive therapy, based on FRAX. Unlike the prior BMD-based treatment decisions, which recommended treatment only for women with a BMD T-score lower than -2.5, FRAX allows women to be recommended for treatment with a BMD higher than -2.5, and numerically the most osteoporotic fractures occur in this group.

Overall, FRAX is likely to shift the treatment curve toward a more aged group by including women with a T-score of >-2.5, but, and clearly somewhat controversially, can exclude treatment for younger women despite a BMD T-score of <-2.5 who, due to an absence of other risk factors, have a fracture risk below the threshold for treatment.

Genetics entering the diagnostic risk equation

FRAX takes a population-based approach to defining fracture risk, but in reality the ability to predict which patients are at the highest risk for fracture will need patient-specific genetic data. Recent reports in the ***New England Journal of Medicine*** and ***The Lancet*** have identified SNPs that correlate with both low bone density and an increased risk for fracture. Genes coding for RANK, RANKL, and OPG (osteoprotegerin) have been implicated as has the LRP5 gene, the product of which is required for wnt pathway activation and osteoblast development. One of the OPG SNPs was cloned into a cell line and resulted in a 50% reduction in OPG synthesis, which would be consistent with increased osteoclast activity, low bone mass, and increased fracture risk.

At ASBMR, a number of presentations were made evaluating additional genetic markers. These new studies also identified the RANK/OPG and LRP5 genes, providing additional validation as well as identify new genetic markers. While it is clear that no equivalent to mutated KRAS and colorectal cancer has emerged from these efforts as each mutation only adds a few percentage points of fracture risk at best, cumulatively fracture risk can be increased substantially as patients may have multiple targets.

Another interesting presentation focused on estrogen synthesis genes and, in particular, the CYP19 gene to evaluate if there was a correlation between CYP19 SNPs and sensitivity to bone loss with aromatase inhibition. Washington University researchers recruited 146 postmenopausal women with estrogen receptor positive Stage I-IIIa breast cancer with normal to low bone mass who were scheduled to receive aromatase inhibitor therapy. BMD was evaluated at baseline and at Months 6 and 12. Focusing on a SNP at the 80th amino acid, a valine, the researchers noted that patients with an A allele suffered more bone loss and had higher levels of IL-6, a cytokine linked to bone loss. They concluded that, following validation, patients with an A allele at position Valine80 could be priority candidates for anti-resorptive therapy, given greater aromatase inhibitor-associated bone loss.

Fracture costs complex

Strategies to identify the patients most at risk for fracture improve the overall pharmacoeconomic proposition for the use of anti-resorptive therapy. Key components to this equation include not only drug costs but also costs associated with the clinical event in question. Amgen set out to define the costs associated with osteoporotic fractures using a Medicare database to identify patients suffering their first osteoporosis-related fracture. Overall, they noted that two-thirds of the costs were associated with acute care following fracture, with one-third of the cost associated with increased costs for co-morbidities. Specifically for hip fracture, the incremental cost over baseline (i.e. pre-fracture healthcare costs) was estimated to be ~$30,000. However, of this, only $18,700, or 60%, was directly attributed to the fracture, with the remainder associated with non-fracture-related costs. For distal forearm fractures, only 24% of the total cost was associated with direct fracture-related costs. The researchers were unclear precisely what these non-fracture-related costs were, but changes in co-morbidities associated with a fracture could have significant quality of life implications, further emphasizing the need for fracture avoidance and use of anti-resorptive therapy.

Two areas where denosumab has a potential advantage over the bisphosphonates are convenience/compliance and osteonecrosis of the jaw (ONJ) risk, and both of these were extensively discussed at ASBMR.

1. **Compliance.** As had been widely published, compliance and persistence with bisphosphonates is low, and, despite the advent of weekly and monthly preparations, physicians remain disappointed. Illustrating this, following 24 months of either weekly Fosamax (Merck, alendronate) or Actonel (Proctor & Gamble, risedronate) only 41% of patients achieved a medication possession ratio (MPR) of 70%. That is, they took about two-thirds of their prescribed drug. The biggest drop-off occurred within the first six months, with only 62% having an MPR of 70%. Even reducing the MPR to 50% (patients who took at least half their prescribed drug) still only captured just over two-thirds of patients.

Figures were even worse for Lilly's Forteo (teriparatide). Using the DANCE cohort, Lilly showed only 23% of patients remained on drug 24 months after initiating therapy. Although this could be affected by the maximal recommended duration of dosing, which is 24 months, at 18 months only 46% of patients were still on therapy. A key factor for discontinuation of Forteo was cost. During the first 3 months of therapy, 35 of the 238 discontinuing patients (15%) withdrew due to cost reasons; and from Month 12 to Month 18, 36% (24 of 66) of patients withdrew due to drug cost. Overall, 1 in 5 patients who started Forteo in DANCE withdrew due to drug cost. This is something Amgen may need to keep in mind with denosumab.

The issue of poor compliance and stopping bisphosphonate therapy prematurely was highlighted by Dr. Jeffrey Curtis of the University of Alabama, Birmingham. Using Medicare data, Dr. Curtis identified three cohorts of patients by MPR. They compared fracture rates with compliant and non-compliant patients and found hip fracture rates were affected by prior MPR. Stopping therapy resulted in a 27%-81% increase in the fracture rate. This "more is better theme" is emphasized by restricting the analysis to patients with 3 years worth of data. Again, when the bisphosphonate was stopped after three years, the hip fracture rates increased. This suggests that even with suboptimal compliance to therapy, hip fracture rates can be reduced by increasing the duration of therapy. Overall, the data showed that even three years of being highly compliant to a bisphosphonate does not provide a long-term fracture benefit as has been shown following five years of compliant bisphosphonate therapy.

Medicare Patient Compliance with Bisphosphonate Therapy by MPR

Hip fractures per 1,000 patient years	MPR ≤50%	MPR >66%	MPR >80%
After 2 years	10.46	4.67	4.83
In patients who stopped taking a bisphosphonate after being compliant for 2 years	7.1	8.43	6.12
Patients with 3-year data			
In patients who stopped taking a bisphosphonate after 3 years	~ 5	7.1	6.4

2. **ONJ risk.** At last year's ASBMR, models of ONJ risk were under development for testing bisphosphonates, and at this year's meeting further preclinical data were presented. Yale researchers evaluated the impact of Reclast (100 mcg weekly and 250 mcg weekly vs. placebo) on bone repair in the jaw or femur of mice. At 5 weeks, mice underwent tooth extraction, a common procedure proximal to ONJ and, in parallel, received damage to a femur, which acted as a control site for bone repair. At 6 weeks the mice were sacrificed to allow an analysis of bone repair at both sites of damage. That analysis found a delay in bone repair only in a single mouse in the high dose Reclast group – and only at the site of tooth removal. Osteoclast analysis showed a more profound reduction in osteoclast number at the jaw, which was suggested by the researchers as indicating specificity of Reclast to the jaw. Amgen researchers have previously said that using a labeled bisphosphonate shows their predilection for binding to jaw.

This model was criticized at ASBMR for using a super-high dose of Reclast that bore no relation to clinical dosing, but the researcher remained adamant that, given the limitations of using a mouse model, a less intense dosing strategy mimicking clinical use was impractical. He also noted that the incidence of ONJ was similar to that observed in oncology.

PARATHYROID HORMONE (PTH) – *New Approaches*

Long-acting PTH

Researchers from the Ochsner Clinic in New Orleans presented a unique and interesting approach to PTH therapy. Using a collagen-binding domain (CBD) to target PTH to bone, they showed in animal models that a single injection of a PTH (1-33)-CBD fusion had positive effects on markers of bone turnover for 10 months in mice. The researchers are filing an IND for the use of PTH-CBD in chemotherapy-induced osteoporosis.

Using a single PTH-CBD dose of 320 mcg, which delivers the equivalent of 80 mcg PTH (1-34), PTH-CBD produced superior BMD increases to 14 days of daily PTH (1-34) 80 mcg. Further, BMD increases were maintained for 10 months in the animals receiving this single dose of PTH-CBD, but in those animals receiving 14 daily doses of PTH, BMD returned to baseline within 10 months. Supporting these observations of long-term catabolic activity, serum alkaline phosphatase, a marker of bone formation, remained elevated 10 months after a single dose of PTH-CBD, suggesting that an environment permissive for bone formation remained.

Separately a model of chemotherapy-induced osteoporosis showed that PTH-CBD is superior to PTH at protecting animals from treatment-related osteoporosis. The researchers said that no cases of hypercalcemia have been observed with PTH-CBD.

PTH secretagogues

Both GlaxoSmithKline (GSK) and Novartis presented clinical proof-of-concept data for PTH secretagogues. These orally-available small molecules trick the calcium-sensing receptor into sensing low calcium levels thereby releasing PTH. Using the PK/PD profile of Forteo, these companies have identified dosing regimens of oral PTH secretagogues that approximate Forteo.

➢ NOVARTIS's ATF-936 and AXT-914

Novartis presented data on a double-blind, placebo- and active-controlled, dose-escalation, Phase I study of ATF-936 in 14 healthy volunteers. Each volunteer received a single weekly oral dose of ATF-936 at 6 mg, 20 mg, 40 mg, 70 mg, each interweaved with a placebo, followed by Forteo at Week 6 and 140 mg ATF-936 at Week 7. The ATF-936 C_{max} appeared to be ~1 hour and the half-life was stated as 12 hours. A brisk rise in serum PTH was observed with a peak at a similar time to the ATF-936 serum peak. Achieved PTH C_{max} was related to ATF dose, and at the highest dose a 5.5-fold increase in PTH over baseline was observed. At all doses, PTH returned to the upper limit of normal 2-4 hours after dosing and was back to baseline 12-24 hours post-dosing. No serious adverse events were reported to have occurred during the study, and while a comparison between ATF-936 and Forteo was not shown – despite the data being available from the study – the PTH profiles of ATF-936 and Forteo appeared similar. Novartis has also evaluated a second oral agent, AXT-914, in a Phase II study.

➢ GSK/NPS PHARMACEUTICALS' ronacaleret (SB-751689)

A 28-day dosing study of ronacaleret (75 mg, 175 mg, or 475 mg) vs. placebo in 81 healthy postmenopausal women was presented at ASBMR. The C_{max} for ronacaleret was reached 2-3 hours post-dosing as was the C_{max} for induced PTH, which at the highest ronacaleret dose achieved a serum concentration of ~100 pg/mL. At Day 28 markers of bone formation (P1NP, osteocalcin, and bone-specific alkaline phosphatase) increased 80%, 68%, and 34%, respectively, over baseline at the highest dose.

No clear change in serum CTX, a marker of bone resorption, was noted at Day 28. However, maximal calcium concentrations were observed around Day 14, perhaps suggesting that the window for CTX increase had been missed. Data for serum calcium were presented as the daily pre-dose value. A clear dose-response between ronacaleret and serum calcium was noted. Calcium levels increased during the first 14 days before falling back and reaching a plateau for the remaining 14 days. One patient at the 475 mg dose met the protocol-defined criteria for elevated calcium, which was 2 consecutive readings >11 mg/dL, and a second patient had confirmed elevated calcium on Day 28 (the last day of the study). Of the patients treated at the 475 mg dose, 57% had at least one serum calcium >10.5 mg/dL.

The only notable adverse event was dose-related diarrhea which occurred in 17%, 24%, and 29% of the ronacaleret treated women compared to 9% in the controls. Diarrhea was described as generally self-limiting.

GSK is currently recruiting a 520-patient Phase II study testing two doses of ronacaleret in women with postmenopausal osteoporosis. The study was initiated in 2Q07, with data expected in early 1Q09.

CATHEPSIN K INHIBITORS

MERCK's odanacatib – *evidence of waning efficacy?*

Odanacatib is in Phase III testing for both osteoporosis and delay/prevention of metastatic disease in breast and prostate cancer. It is the most advanced potential denosumab competitor in development for osteoporosis, though fracture data are at least three years away.

At ASBMR, data from Year 2 of the Phase II osteoporosis study were presented, showing a continued increase in BMD between Years 1 and 2. While this is similar to other anti-resorptive agents, changes in bone turnover were distinct and at least discordant with BMD or a leading indicator of BMD loss. The double-blind, randomized, dose-ranging Phase II study enrolled 399 patients of whom 320 elected to continue from Year 1 to 2. Patients received weekly oral doses of 3 mg, 10 mg, 25 mg, or 50 mg odanacatib vs. placebo. While the sponsor was unblinded in Year 2, both patient and treating physician remained blinded to study treatment. At the highest dose, BMD at the lumbar spine increased to ~5% above baseline. Lesser BMD improvements between 12 and 24 months were also seen at the total hip and femoral neck, ranging from 3%-3.5% above baseline.

Perhaps unexpectedly, bone turnover markers did not stay depressed throughout the study. Following study initiation a rapid decrease in markers of bone loss, CTX, and NTX was observed. As anticipated, this was followed by similar changes in the markers of bone building, P1NP, and BSAP. Decreases were dose-dependent except for the lowest dose, which showed a marked increase above and beyond placebo, suggesting an activation of osteoclast activity. Between 12 and 24 months, bone turnover markers for odanacatib doses above 3 mg increased gradually and either reached baseline or were clearly trending toward baseline.

This does not appear to be an ideal profile of bone turnover marker change. Indeed, an increase in bone turnover marker levels could be a leading indicator for loss of accumulated BMD with continued odanacatib dosing. There is also a concern that the 3 mg data suggest that odanacatib increases osteoclast activity. Given that compliance and persistence with oral therapies is so poor in osteoporosis, osteoporosis-treating physicians may not embrace a drug with odanacatib's profile.

Merck has an ongoing fracture prevention study in postmenopausal osteoporosis, but with only 2,000 patients this may be woefully underpowered, indicating that perhaps it will be only

a hypothesis-generating study. The same cannot be said for recently initiated oncology trials, however. Merck has listed 2 time-to-bone-metastasis studies, one in breast (4,000 patients) and one in prostate (1,550 patients). In both studies patients are at high perceived risk for relapse. These studies are using a 5 mg/day dose, a regimen that seems poorly competitive with either annual Zometa (Novartis, zolendronic acid) or biannual denosumab. The osteoporosis study uses a 50 mg/week dose, which is more competitive with other therapies, but in four or five years time, it could look like a step backwards.

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