Trends-in-Medicine

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By Lynne Peterson

SUMMARY

The PaTH study found no additive or synergistic effect of combining NPS's Preos with Merck's Fosamax, and there may even be a negative effect to the combination, but the trial did not affect the attitude of doctors toward use of either Preos or Lilly's Forteo, though they plan to stop both bisphosphenates and SERMs while giving PTH. Prior therapy with bisphosphenates -- more than with SERMs – appears to blunt the effect of PTH, but the long half-life of bisphosphenates makes it difficult to put prospective PTH patients through a wash-out period. Lilly will try to convince doctors this is a reason to start low risk patients on Evista instead of a bisphosphenate, but doctors generally consider this a marketing gimmick, and no significant market share shift due to this is expected. Doctors are not surprised at the uptake of Lilly's Forteo, and they predicted that use will continue to increase.

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Following is a look at some selected agents which were discussed at the ASBMR meeting or for which there was new data.

NPS PHARMACEUTICALS' Preos

The PaTH trial found no additive or synergistic benefit of adding Preos (rhPTH 1-84) to Merck's Fosamax (alendronate), and the combination may actually diminish the bone-building effects of Preos. The study suggests women should take Preos along – not in combination with Fosamax or any other drug which slows bone breakdown. The findings will be published September 25, 2003, in the New England Journal of Medicine.

PTH and Fosamax both increase bone mineral density (BMD) and fracture risk but by different mechanisms. PTH increases bone formation, and Fosamax decreases bone loss (resorption). The PaTH trial studied 238 post-menopausal women age 55-85 with a BMD T-score <-2.0 who had a history of minimal use of bisphosphenates. All women received calcium and 400 IU of vitamin D. Patient compliance was high: 75% with Preos and 81% with Fosamax.

An investigator concluded, "For no endpoints was the combination superior or better than alendronate or PTH alone…We saw no evidence of an additive or synergistic effect of PTH of alendronate…Concurrent use of alendronate may blunt the anabolic effect of PTH." However, he added that a case could be made that the combination of PTH and Fosamax is positive: "The strongest argument (in favor of the combination) is that alendronate decreases both bone resorption and bone formation…With the combination you are able to hold bone formation constant while decreasing resorption."

Some of the limitations of this study include:

- **Patients**. Only naïve patients were studied. Researchers did not look at the use of Preos following Fosamax or Fosamax use post-treatment with Preos.
- **PTH formulation**. It is conceivable that Preos could act differently than Forteo (Lilly's teriparatide, PTH 1-84), or that another bisphosphenate or SERM might act differently. However, sources generally dismissed this argument, assuming, for now at least, that the findings apply to all PTH formulations. A California doctor said, "I don't think there is a difference between Preos and Forteo."
- **Time period**. Perhaps the treatment period (one year) was too short. Optimal PTH treatment may be two years. PaTH patients are being followed out for at least two years.

➢ **Fracture data**. There is no fracture data on combination therapy. An expert said, "The fracture data from other trials indicates PTH is no better than alendronate; they are almost equivalent in fracture reduction, so in treating a naïve patient, I'm not sure you could choose one over the other."

➢ **Quality of bone formation**. There is no information on this yet. An expert said, "Clearly the quantity of bone is reduced (with the combination), but what is the quality of the bone made?"

12-Month PaTH Trial Results

Measurement	Preos 100 µg n=119	Preos+Fosamax n=59	Fosamax 10 mg n=60
Average age	69	70	71
Change in BMD by DXA			
Spine	+6.2%	+6.1% *	+4.6% *
Hip	+0.8%	+1.8% *	+2.0%
BMD by QCT			
Trabecular spine	+23.8%	+11.3%	+7.6%
Total hip	-2.4%	-0.%	+1.2%
Other measurements			
Formation (P1NP)	+146%	-16%	-74%
Resorption (serum CTX)	+104%	-14%	-73%
Changes in markers of bone turnover			
Formation	Up ~150% by 3 months and maintained to 1 year	Initial increase then steady decline over a year	Steady decrease over a year
Resorption	Increase	Decrease	Decrease more than combination

Doctors questioned about the study all said the PaTH results probably will affect their prescribing practices going forward. When PTH is prescribed in the future, all sources said they will make the PTH monotherapy. That is, if the patient already was on a bisphosphenate – Fosamax or any other bisphosphenate – it will be discontinued while the patient is on PTH, and naïve patients will be given only PTH during the course of treatment with PTH. One doctor said, "The bulk of evidence suggests if you are going to prescribe PTH, it would be better to use PTH alone during the period of PTH." Another commented, "Any patient getting Forteo now has to wonder about the effects of any anti-resorptive." A third said, "Just because the combination response is blunted doesn't mean there isn't still a good response." A fourth said, "I'm not sure you should stop bisphosphenates when you put a patient on PTH, but that's what I do."

However, no source plans to put patients through a "washout" period to clear the bisphosphenate from the patient's system before starting PTH. Sources explained that the half-life of bisphosphenates is too long -- a year or longer for Fosamax and Actonel (Proctor & Gamble, risedronate) – to make that feasible. A doctor said, "It is difficult for patients to have a washout when they don't take the medication, and no one knows how long the washout should be – a week, a month, six weeks, longer. It is difficult to tell someone at high risk not to take anything...and it is not clear that there is any benefit to stopping the bisphosphenate briefly…If I had a patient with a very low BMD who was on alendronate and the patient had fracture, I would stop the alendronate and use PTH, but in 18 months, when I was done with the PTH, I would then restart the alendronate." Once the course of treatment with PTH is finished, doctors all said they are comfortable starting (or re-starting) a bisphosphenate.

Other PTH trials are underway that should shed additional light on this issue. These include a small, NIH-sponsored trial of once-weekly Preos.

The injection device for Preos is different from the Forteo device. Sources familiar with the Preos device had mixed reviews. Some said it works as easily and simply as the Forteo device, but others said it is cumbersome. Most did not see this as a significant differentiating factor between the two products.

How can Preos differentiate itself from Forteo? Sources cited these possible areas:

➢ **Side effects.** A 100 µg dose of Preos was described as roughly equivalent in efficacy to the marketed dose of 20 µg of Forteo, but the side effects may be different.

➢ **Osteosarcoma**. If the Preos rat study which is due to be released in November 2003 doesn't show a problem with osteosarcoma, NPS would have a marketing advantage, doctors agreed. However, so far, sources have no indication of what the rat carcinoma data with Preos is likely to show.

➢ **Calcium metabolism**. There is a difference in calcium metabolism between Preos and Forteo but an experts said, "It is hard to say which is better, but they are different…The theory is that 1-84 (Preos) has a longer mode of action because the rise of serum calcium is slightly slower, but no one knows if that is good, bad, or indifferent."

➢ **Molecular design**. An expert said, "NPS is trying to build a story that the carboxyl end of the molecule makes a big difference, but there is no data on that."

➢ **Fractures**. If the Phase III trial currently soon to be completed shows a reduction in hip fracture with Preos or a very dramatic reduction in fractures, that would give Preos an edge, and put it at a disadvantage if it doesn't look as good on fractures as Forteo. NOTE: The Phase III trial should be finished soon, but it may be 6-12 months before the data is presented.

➢ **Data**. NPS will have data out to 24 months for PTH, and a source said this is a little longer data than is out for Forteo.

➢ **Price**. Some sources speculated that NPS may price Preos below Forteo.

There have been no leaks about either the Preos Phase III data or the rat toxicity data, both of which are expected this fall. The likelihood of the rat data showing osteosarcoma is hard to predict.

Pro: There is a mechanistic reason for worrying that Preos, like Forteo, will show an increase in osteosarcoma, in rats: Rats continually grow, throughout their life. Their bodies do not move from the modeling stage to the remodeling stage as humans do.

Con: Researchers who made a retrospective analysis of a large group of osteosarcoma patients did not find any increased incidence of hyperparathyroidism, and another study of HPT patients actually found that death by cancer is reduced in this group. Furthermore, some researchers believe that there may be something in the 35-84 segment of the molecule that lessens the risk of osteosarcoma, so Preos might not have this problem (in rats) even though Forteo does.

LILLY

Evista (raloxifene)

Lilly apparently sees the PaTH results as an opportunity to promote Evista, and a study of PTH after antiresorptive pre-treatment (see Lilly's Forteo) added fuel to this fire. Lilly is expected to make a case for using a SERM, namely its Evista, instead of a bisphosphenate for low risk patients. The rationale is that if the patient worsens, the SERM is a better precursor for PTH than a bisphosphenate. In fact, some sources said Lilly has already started using this marketing tactic. A doctor said, "Lilly is saying, 'Don't start patients on a bisphosphenate, put them all on raloxifene.' But that is a very self-serving marketing message." And other doctors indicated they are still somewhat leery of SERMs. One explained, "SERMs make everyone nervous. They cause leg cramps and hot flashes, and are not as potent as bisphosphenates. My SERM use is not going up as a result of the PaTH trial."

Forteo (teriparatide, PTH 1-34)

Doctors questioned at this meeting said they have not been surprised at the uptake of Forteo. Several sources suggested that Lilly may have deliberately underestimated the demand because they believe Lilly should have anticipated the current level of sales. They pointed out that there was a large pent-up demand for Forteo – patients who had severe osteoporosis and/or had already failed bisphosphenates. One source also commented, "There are strong pockets of PTH users around the country." Another said, "There was a lot of pent-up demand because of patients who were unable to take oral bisphosphenates or who had side effects with them. There are a lot of nursing home patients and GI-sensitive patients for which Forteo is an option."

The daily injections do not appear to be a problem. Doctors said the pen delivery system makes it easy for patients to self-administer. They generally agreed that their use of Forteo is likely to continue to increase. A rheumatologist said, "The outlook depends on the public and on the company's advertising. Consumers are more sophisticated, and patients with a fracture on a bisphosphenate will be demanding to try Forteo. But insurance will be the real determinant."

A 12-month, Merck-sponsored study found that Fosamax 70 mg weekly is more effective than raloxifene 60 mg/day. The two drugs had a comparable incidence of side effects.

% change	Fosamax	Evista
Spine	+4.8%	+2.2%
Total hip	+2.3%	+0.8%
Femoral neck	+2.2%	+1.0%

A Lilly-sponsored study found that BMD rises more in Forteo patients who had previously been on Evista (Lilly, raloxifene) than those who had previously taken Fosamax. The study looked at women who had been on one of those two drugs but agreed to stop during an 18-month course of Forteo. The researchers found that all bone turnover markers were suppressed more in women pre-treated with Fosamax than with Evista, though the differences diminished over a year. They concluded that prior Evista treatment did not alter the Forteo response, but prior Fosamax treatment resulted in an early delay in bone turnover response, unexpected early BMD changes, and much less BMD incremental gain after 18 months.

Measurement	Forteo 20 µg/day after Fosamax 10 mg/day n=33	Forteo 20 µg/day after Evista 60 mg/day n=26
Average age	71.2	68.8 *
BMI baseline	23.4	23.8 *
Months of prior therapy	29.3	29.0 *
Baseline spine BMD	-2.3	-2.5 *
Mean change in lumbar spine BMD		
At 6 months	+0.7%	+5.7%
At 18 months	+4.2%	+10.2%
Mean change in total hip BMD		
At 6 months	-1.6%	+0.5%
At 18 months	+0.3%	+1.8%

Researchers offered two explanations for this big difference between pre-treatment with Evista and Fosamax:

1. Fosamax could lessen Forteo's early anabolic effect.
2. Fosamax has produced highly mineralized bone with closed resorption space: (a) Forteo opens a larger new resorption space, and (b) in each BMU, Forteo replaced highly mineralized bone with new, less mineralized bone.

The market for PTH could expand substantially if PTH is proven to aid in the healing of fractures not related to osteoporosis. Lilly reportedly is starting a trial to see if short-term PTH use (two to three months) can speed fracture healing, especially hip fractures. A source said the trial design has not yet been approved by the FDA, but he predicted that enrollment would be quick, and the duration of the trial could be relatively short.

A 126-patient study was presented looking at PTH daily (25 µg) vs. cyclic (both combined with Fosamax) vs. Fosamax alone for osteoporosis. The Forteo cycles were three months on, followed by three months off, repeated. The women had been on Fosamax an average of three years before starting this study. Researchers found that, in the presence of Fosamax, PTH stimulated bone formation and resorption and increased spine BMD over 15 months. Cyclic PTH produced bursts of bone formation with a lesser increase in bone resorption, and BMD changes similar to those seen with daily PTH treatment. An investigator commented, "Our data imply that early stimulation of bone formation may be more important than the later activation of bone remodeling for bone density accrual in the spine…Cyclic challenges with PTH might be an efficient and economic way to use PTH for persistent osteoporosis after established Fosamax treatment."

A researcher was asked to explain the lack of blunting of the anabolic effect with daily PTH that was found in the PaTH trial. She replied, "This is a different study design. In PaTH, patients were previously untreated. Here, we are looking at patients pre-treated with alendronate for an average of three years, and the stability of our patient population in contrast to the dynamic situation of newly administered antiresorptives sets up a different outcome…We can't assess blunting in our study because there was no PTH-only arm…but the bone density change in PaTH was similar to the bone density change we saw in our study."

Another study compared the effects of daily Forteo (20 µg) vs. daily Fosamax (10 mg) on bone remodeling and bone density in 203 osteoporotic women. The study found no statistically significant reduction in back pain overall with Forteo, but Forteo was superior at reducing back pain in the women with the most severe pain. Increases in aBMD and vBMD at the lumbar spine were greater with Forteo than with Fosamax. Forteo also seemed to decrease the incidence of pain compared to Fosamax.

A poster reported that Forteo lowered the incidence of new or worsening back pain. The study was based on 1,637 women from the Fracture Prevention Trial who had prior vertebral fractures.

Measurement	Placebo	Forteo	Relative Risk Reduction
Risk of Back Pain			
Any	123	91	26%
Moderate-severe	90	62	31%
Severe	28	12	57%
Risk of Back Pain and New Vertebral Fracture			
Any	29	5	83%
1 vFracture	18	4	78%
>1 vFracture	11	1	91%
Moderate or severe vFracture	23	0	100%

AMGEN

PTH-Fc

Amgen is working on a PTH formulation that would be given weekly or less frequently, PTH(1-34)-Fc. There were several posters on this compound, which an Amgen official said is still in preclinical development, including:

1. A study which found that PTH-Fc (administered twice a week) restores bone mass in aged osteopenic ovariectomized rats.
2. A study which found PTH-Fc restores BMD and bone strength in aged osteopenic ovariectomized rats with and without estrogen supplementation.
3. A study which found that PTH-Fc increases BMD in cynomolgus monkeys.

OPG (osteoprotegrin)

The company has been working on different OPGs, and the lead agent appears to be AMG-162, and it is in Phase I. It is a humanized monoclonal antibody that would be used like PTH for osteoporosis and bone metastases by subcutaneous injection. One injection reportedly has a six-month effect.

Cinacalcet (AMG-073)

Cinacalcet (a small, oral, twice-daily pill), a joint effort of Amgen and NPS Pharmaceuticals, was filed with the FDA on September 8, 2003 for the treatment of secondary hyperparathyroidism (PHT) in renal failure patients. The Phase III data for this indication is expected at the American Society of Nephrology meeting in November 2003. Sources said Cinacalcet is likely to replace Calcigex and vitamin D analogs, but not phosphatase binders like Genzyme's Renagel. Doctors predicted that uptake would be gradual, but they do not expect reimbursement to be an issue for appropriate patients.

Cinacalcet also looks very promising for the management of primary hyperparathyroidism (PHPT). In early studies in PHPT, Cinacalcet produced a very rapid effect that also came back quickly, indicating this is a reversible chemical action. Data presented in 2002 indicated Cinacalcet normalized serum calcium, which is associated with a decrease in serum PTH levels.

New, long-term data was presented at ASBMR from the open label phase (Study B) of a trial on Cinacalcet in PHPT. In the first phase of this trial (Study A), 78-patients were randomized to either Cinacalcet or placebo and followed for 52 weeks. In the open label phase (Study B), 45 patients (24 prior placebo and 21 prior Cinacalcet) were followed for another two years. A researcher explained, "When placebo patients were put on Cinacalcet, there was a rapid return of serum calcium to the normal range and no difference between the two groups (prior placebo vs. prior Cinacalcet)…Lumbar spine BMD was maintained for three years on this drug. At the femoral neck and forearm, there was some loss with placebo over the first year and then a continued slight loss, but there was also some loss in the (prior) Cinacalcet patients…Over three years, Cinacalcet normalized serum calcium, reduced plasma iPTH, increased serum phosphorus within the normal range. BMD at the spine did not change. BMD at the hip and radius decreased somewhat. It was safe and well-tolerated. "

Adverse Events in Study B of Cinacalcet in PHTP

Adverse Event	Cinacalcet	Placebo
Myalgia	24%	25%
Headache	10%	38%
Nausea	29%	17%
Arthralgia	14%	25%

About 200,000 Americans suffer from PTHP, and an expert estimated that as many as 50% of these may benefit from Cinacalcet. He said, "The curative therapy for PTHP is surgery. If surgery is done correctly, and all goes well, it is curative, by and large. But some patients are not appropriate for surgery, refuse surgery or fail surgery. At the moment, there is no good therapy for that group, so this is a new set of agents, which will be very important in managing these patients."

Cinacalcet also may have utility in patients with parathyroid cancer who metastasize. Currently, there is no treatment available to bring down the calcium level in these patients. Cinacalcet won't cure the cancer, but it can bring the patient's serum calcium into the normal range, which is important because hypercalcemia produces confusion, drowsiness, loss of consciousness and eventually death."

NOVARTIS'S Zometa (zoledronate)

Two fracture trials are underway that should determine whether 5 mg zoledronate can be given once yearly by infusion.

➢ **HORIZON-PFT.** This is a study of 7,406 patients (age 65-89) with low BMD and/or a previous vertebral fracture. Patients were not excluded for current or previous HRT or SERM use, but PTH use was an exclusion. The last patient was recruited in June 2003, but it is a three-year trial with no planned, public, interim analyses, so the data is unlikely to be available until at least ASBMR2005. Patients were divided into two groups:

- Stratum 1 – 3,106 patients not receiving usual care osteoporosis treatment at baseline. The primary endpoint is vertebral fractures.
- Stratum 2 – patients receiving usual care medications (HRT, SERM, calcitonin, calcitriol, etc.). The primary endpoint is hip fractures.

➢ **HORIZON-RFT.** This is a multinational, double-blind, placebo-controlled, parallel group study of 1,700 patients, looking at post-hip fracture patients. Reportedly, the trial had a hard time recruiting patients because getting patient consent proved problematic. An expert explained, "Elderly hip fracture patients can be confused for days, weeks or even permanently." The primary endpoint is clinical fracture, and the secondary endpoints are serum markers of bone turnover, quality of life, ability to perform the activity of daily living, pain and cost effectiveness. The percent change in BMD of the non-fractured hip by DXA will be assessed in 600 patients. The study will complete once 303 patients have been diagnosed with a clinical fracture.

PROCTOR & GAMBLE'S Actonel (risedronate)

P&G is planning a study of risedronate plus Forteo. A doctor said, "P&G claims Actonel has a shorter half life than Fosamax – in bone and in serum, but that may be a feature of when the half-life measurement is taken." The company is emphasizing the shorter serum half-life as a reason to start new patients on Actonel (instead of another bisphosphenate)."

A cost-effectiveness study of Actonel was sponsored by P&G in Germany. Researchers found the cost for an averted hip fracture there to be 33,856 euros, and the cost per QALY gained 35,690 euros, both of which are below the generally accepted threshold of 50,000 euros.

Bisphosphenates currently are contraindicated in patients with a creatinine level <30, but a study at ASBMR challenged that assumption and could lead to a label change for risedronate if not all bisphosphenates. The study was an analysis of pooled data of 9,883 patients from eight risedronate trials. Researchers found that risedronate 5 mg results in no change in kidney function, even in patients with a creatinine <30.

ROCHE/AVENTIS' Bonviva (ibandronate)

Roche has FDA approval for a 2 mg immediate-release, once-daily tablet but has not launched it, and experts said the company will not launch that formulation, at least not in the U.S. Doctors are not surprised. They pointed out that ibandronate is slightly less effective than daily Fosamax or Actonel, and the QD formulation would be hard to market against weekly Fosamax or Actonel. An expert said, "It is not being sold because the company is looking for longer intervals. The ultimate goal is once a month or once every three months." Another expert said, "Novartis is conducting a monthly dosing study as well as a study of IV once every three months. They are hoping to bridge the lack of fracture data in the IV study with data on the daily oral formulation, but I don't know if that strategy will work." A third expert said, "Roche is testing once-every-two-months and once-every-three-months infusions, and that's what it is going for. The market is patients who can't tolerate any oral bisphosphenates, scleroderma patients, Barrett's esophagus patients, etc. It's a rather niche market."

WYETH

Rapamune (rapamycin)

A poster found that, in young rats, giving rapamycin alone or with either cyclosporine or prednisone adversely affected differentiation in growth plate cartilage. Rapamycin decreased body weight and height and lowered serum PTH. The researchers concluded that use of rapamycin as a long-term maintenance immunosuppressant agent in infants and growing children requires close monitoring.

LRP5

There was no new data on Wyeth's efforts to produce an Lrp5 blocker. Creighton, Genome Therapeutics and Wyeth were collaborating on high throughput screening to find a pharmacologic agent that will mimic this disorder by doing what the mutation does – block the Lrp5 protein receptor, and a researcher said agents have been identified and are now being evaluated at the chemistry level.

Bazedoxifene, a new SERM

This is being explored as:

- Monotherapy for treatment and prevention of osteoporosis. Two, three-year Phase III trials are underway.
- Combination therapy of bazedoxifene+estrogen (in a single pill) for treatment of the symptoms of menopause data for the prevention of osteoporosis. There will be Phase II combination data at the International Osteoporosis Federation's European Symposium on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis meeting in Nice, France, in November 14-17, 2003.

THE REGULATORY PERSPECTIVE: THE FDA

Several FDA officials participated in a session at the meeting. Among the things they explained were:

➢ The FDA is in the process of updating the guidelines in osteoporosis research. The first step was an advisory committee meeting in September 2002. That advisory committee concluded:

- Placebo is a misnomer as trials now must include background treatment with calcium and vitamin D.
- Placebo-controlled fracture trials are acceptable in patients with relatively low fracture risk but not in higher risk patients.
- There was no consensus on the use of surrogate markers for predicting fracture risk.

Within the next month the FDA will issue a request for comment on current osteoporosis guidelines, and that will be another step in changing the guidelines.

➢ The FDA is considering, as a part of the new osteoporosis guidelines, a reduction in the length of trials required from three years to two years. An official said, "We are not saying you can take a three-year study and give it to us in two years, but future guidance may make two-year studies available."

➢ There continues to be a strong emphasis on preclinical data, and that is unlikely to change. An official commented, "If we entertain shorter trials, then we may be more dependent on preclinical studies." Another official added, "If trials are shorter, there also may be more reliance on Phase IV (post-marketing) trials. That is an option. We are slightly leery of that because they don't always come to fruition as we ask."

➢ Non-inferiority trials must be in the same class of drug – for example, between two bisphosphenates.

➢ A Pfizer official asked how one trial could be used for multiple indications that fall under the jurisdiction of different divisions of the FDA" It is out of our cost range to run 10 pivotal trials. Is there a road forward on how to get a true benefit from drugs in the label without multiple studies?" An FDA official responded, "It takes some coordination with the FDA divisions involved, but it can be done in a single study. It would require separate meetings, where we look at osteoporosis and our GYN colleagues look at their areas, etc. It is possible, but it is extremely difficult."

➢ The Endocrinologic & Metabolic Drugs Advisory Committee will meet on October 7, 2003, to discuss estrogen's effect on bone.

MISCELLANEOUS

➢ Researchers at the University of Michigan have developed a method of delivering **PTH with microsphere encapsulation**. Following one injection, the microspheres deliver a burst of drug in the first week, then slowly release a lower level of drug over seven weeks, followed by another burst at week 8. So far, no companies are involved in this.

➢ **Johnson & Johnson's Remicade (infliximab).** A rheumatologist said, "Reimbursement for Remicade for rheumatoid arthritis patients is becoming more and more problematic…There is probably only one or two years left for rheumatologists on the Remicade train."

➢ **Stryker's OP-1.** A poster found that the effect of OP-1, and that of other BMPs, can be highly site-dependent.

➢ **Homocysteine.** A study of 825 men and 1,174 women from the Framingham Study cohort found that high levels of blood homocysteine may be associated with future osteoporosis and hip fracture in older persons. Investigators found the rates of hip fracture across all subgroups were abut two ties higher in women than in men, but fracture rates increased for both genders as their blood homocysteine levels rose. The question remains: Does lowering homocysteine reduce hip fracture rates?

➢ **Merck's Zocor (simvastatin).** A study of 82 women with a BMD ≤-1 found that treatment with Zocor did not impact BMD. Researchers concluded, "One year of simvastatin did not affect BMD or bone turnover."

➢ **Takeda's netoglitazone (MCC-555).** A mouse study comparing this new, investigational glitazone to GlaxoSmithKline's Avandia (rosiglitazone) found that Avandia, but not netoglitazone, decreased bone mass and altered the microarchitecture of the proximal tibia. Researchers concluded, "If our observations are confirmed in humans, they may suggest that longitudinal rosiglitazone therapy poses a significant risk to human bone" not seen with netoglitazone. ♦