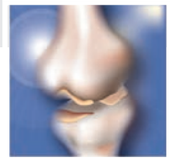
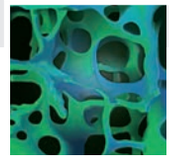




Bulletin Board

Novel osteoporosis drug safe and well tolerated after 4 years

A Phase II study of the investigational osteoporosis drug odanacatib has shown it to be safe and well tolerated after 4 years of treatment. Results also demonstrated that the cathepsin K inhibitor provided continual increases in bone mineral density and that when patients stopped taking odanacatib there was a prompt decline in bone mineral density.

The study initially randomized patients to either placebo or one of four possible odanacatib dosing groups for 2 years. Patients were then rerandomized in the third year to either placebo or odanacatib 50 mg/week. Those patients who received placebo or the lowest dose of odanacatib (3 mg/week) during the trial were then given odanacatib 50 mg/week for the fourth year, while the remaining patients stayed on their year 3 dosing group.

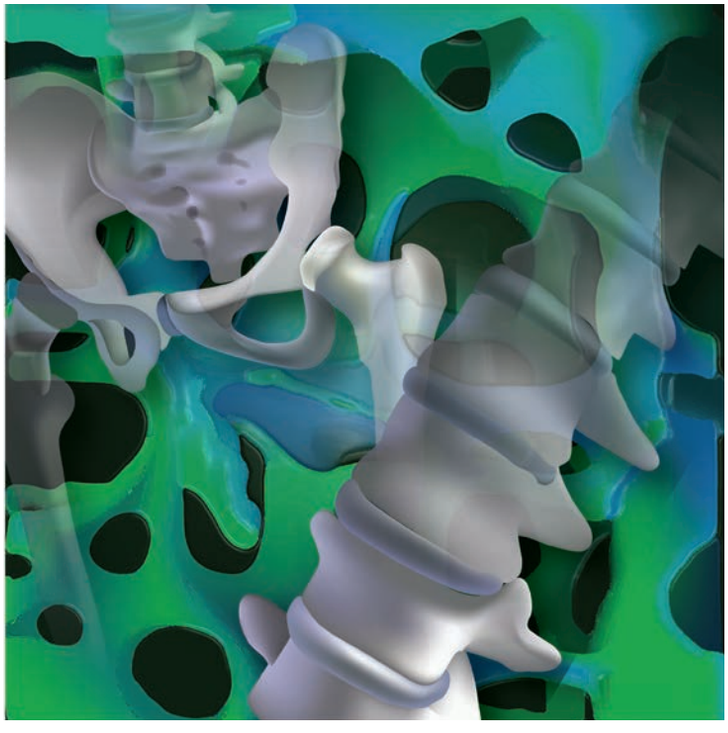
A total of 133 patients completed the fourth-year extension study, with 39 patients receiving placebo. Adverse events occurred in 79% of the odanacatib arm and 70.1% in the placebo arm, with serious adverse events in 9 and 14.6% of patients, respectively.

The primary end point was bone mineral density in the lumbar spine and a 10.7% increase was observed in patients treated with odanacatib for the full 4 years. Spinal bone mineral density was observed to rise continually, with a 2.8% average increase in the fourth year. However, a rapid decline was observed in patients originally treated with odanacatib who then switched to placebo, with patients finishing, on average, only 0.4% above baseline.

One of the key findings of the study was that the drug appears to have little or no effect on the skin, with no cases of scleroderma or morphea-like lesions reported, although higher adverse events of the skin were reported in the odanacatib arm.

Dr Lorenz Hofbauer, Dresden Technical University Medical Center, Dresden, Germany, who moderated the session where the results were presented, is encouraged by the results, but believes that results from the large Phase III trial that is currently ongoing are necessary to provide definitive results on the safety and efficacy of odanacatib.

The prompt decrease in effect observed after cessation of treatment has both positive and negative implications, in that it enables an easily reversible therapy, but requires strict monitoring of adherence during treatment, as its beneficial effects appear to cease rapidly after discontinuation of treatment. "You will have to have some sort of recall system and ensure that women either continue or that they switch to something else. Otherwise, they will lose the effect of treatment. Obviously, we will have to wait for the Phase III trial and fracture data," concluded Hofbauer.



Source: Binkley N *et al.*: Effect of odanacatib on bone density and bone turnover markers in postmenopausal women with low bone mineral density: Year 4 results. Presented at: *American Society of Bone and Mineral Research (ASBMR) 2010 Annual Meeting.* Toronto, ON, USA, 15–19 October 2010 (Abstract 1247).

in the news...

Lubricin molecule helps reduce wear in bone cartilage

Researchers at Duke University have discovered that the synovial fluid glycoprotein lubricin helps reduce wear in bone cartilage.

Articular cartilage is the load-bearing surface of mammalian joints and while it is able to sustain millions of load-bearing cycles, it has limited regenerative capacity. Osteoarthritis, which is the most common form of arthritis, causes cartilage to be broken down, and it is widely believed that mechanical wear contributes to the degenerative disease.

While many studies have investigated cartilage friction and lubrication, with the aim of understanding methods for prevention, this new research focused on measuring wear directly and the role played by synovial fluid constituents.

The investigators induced cartilage wear *in vitro* via colloidal probe microscopy and observed that the level of wear was significantly less in the presence of lubricin, compared with in the control solution.

Professor Stefan Zauscher, Duke University, NC, USA, comments, "Our measurements were performed at the surface level using an atomic force microscope with pressures and sliding speeds comparable to those seen in joints. The measurements show a direct link between lubricin in solution and reduction of cartilage wear."

The new finding suggests that lubricin plays an important physiological role in preserving cartilage and may provide new approaches to treatment of joint diseases such as osteoarthritis in the future.

Source: Coles JM, Chang DP, Zhang L, Jay GD, Guilak F, Zauscher S: Lubricin reduces microscale cartilage wear. Presented at: *AVS 57th International Symposium and Exhibition.* Albuquerque, NM, USA, 17–22 October 2010 (Abstract).

Fibromyalgia patients 11-times more likely to suffer restless legs syndrome

Researchers from Loyola University Medical Center, IL, USA, have demonstrated that adult patients with fibromyalgia have a significantly higher incidence of restless legs syndrome.

The study examined 172 patients with fibromyalgia who met the American College of Rheumatology diagnostic criteria, along with 63 control patients for comparison. It was designed to investigate the prevalence of restless legs syndrome in fibromyalgia patients, the strength of association between the two conditions and whether sleep disruption attributable to restless legs syndrome is greater than that of fibromyalgia.

Restless legs syndrome was self-reported in patients via a validated diagnostic telephone interview. The results showed that the prevalence on restless legs syndrome was 33% greater among fibromyalgia patients, with the odds of fibromyalgia patients suffering from restless legs syndrome 11.7-times higher compared with the control group, after adjustment for age and sex.

"Sleep disruption is common in fibromyalgia, and often difficult to treat,"

in brief...

Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and TNF inhibitors. Observations from the EIRA cohort and the Swedish Rheumatology Register. Saevarsdottir S, Wedrén S, Seddighzadeh M *et al. Arthritis Rheum.* (2010) (Epub ahead of print).

Smokers suffering from early rheumatoid arthritis (RA) are less likely than nonsmokers to respond to methotrexate treatment a Swedish study has reported. Dr Saedis Saevarsdottir and colleagues, from the Karolinska Institute and Karolinska University Hospital in Stockholm, Sweden, compared methotrexate and TNF inhibitor treatment in 1430 early RA patients, of which 305 were current smokers, 340 were past smokers and 349 had never smoked. Of the patients who have never smoked 35% had a good response (based on EULAR criteria) after 3 months of treatment, compared with 32 and 26% in the past smokers and current smokers, respectively. The risk of remission after 3 months was also significantly lower for current smokers. "We intend to explore further how and what it is in the cigarette smoke that mediates the negative effect," comments Saevarsdottir. "Previous studies suggested it is the cigarette smoke, and not the nicotine (as in moist snuff), which is associated with the risk of getting RA, and we have reason to believe that the same could apply to the negative influence of smoking on disease course."

Inhibition of follicular T-helper cells by $CD8^+$ regulatory T cells is essential for self tolerance. Kim HJ, Verbinnen B, Tang X, Lu L, Cantor H. *Nature* 467(7313), 328–332 (2010).

Researchers at the Dana-Farber Institute (Boston, USA) have discovered a new cell in mice that suppresses the immune system to protect healthy organs and tissues from mistakenly being targeted for attack. Previous attempts to identify cells involved in quietening the immune system focused on $CD4^+$ T cells, but this new breakthrough reports a subset of $CD8^+$ T cells involved in suppressing antibody production to healthy cells. The new discovery was borne out of an investigation into the role of osteopontin in autoimmunity. "We were testing osteopontin's activity against a population of cells known as follicular T helper cells. We noted that the cells were responsive to osteopontin but also that they expressed what we knew to be the target of suppressor $CD8^+$ T cells," explained Harvey Cantor, whose team made the discovery. The next steps are to investigate whether defective $CD8^+$ T suppressor cells could be a cause of lupus and therefore a potential autoimmunity target for future therapies.

comments Dr Nathaniel F Watson, one of the study investigators. "It is apparent from our study that a substantial portion of sleep disruption in fibromyalgia is due to restless legs syndrome."

However, there are a number of limitations regarding the study in that patients self-reported restless legs syndrome, and any medications being taken or other sleep disorders that might result in restless legs syndrome were not taken into account. The control patients were also free of fatigue and so may have skewed the results by having generally healthier sleeping patterns.

Fibromyalgia affects over 5 million adults in the USA, approximately 90% of them women. These new findings, despite their limitations, suggest that combating restless legs syndrome may provide significant improvements in sleep and quality of life in fibromyalgia patients.

Source: Viola-Saltzman M, Watson NF, Bogart A, Goldberg J, Buchwald D: High prevalence of restless legs syndrome among patients with fibromyalgia: a controlled cross-sectional study. *J. Clin. Sleep Med*. 6(5), 423–427 (2010).

Synthetic bone material developed to allow flexible approach in bone transplant recovery

Researchers from the University of Massachusetts (UMass) Medical School, MA, USA, have recently published details of a new synthetic bone grafting material, named FlexBone, for use in orthopedic surgery. The new material is intended to address the problems associated with bone grafts. Bone grafts can be used in the treatment of significant bone voids caused by trauma or tumor removal. Complications that are associated with bone grafts include infection and poor tissue integration.

The FlexBone material combines nanocrystalline hydroxyapatite, a mineral found in bone, with a crosslinked hydrogel that is similar to those used in contact lenses, and is designed to provided stability and elasticity. In an article published in *Tissue Engineering Part A,* the UMass team discuss the results of a trial conducted in rats to asses the suitability of FlexBone as a synthetic bone graft material.

Commenting on the FlexBone material, David Ayers, Professor of Orthopedics and Physical Rehabilitation at UMass, said, "FlexBone has a bone mineral content approaching that of human bone, enabling the elastic FlexBone material to be cut and shaped prior to surgery or intraoperatively and then pressed into a bone gap. When used in conjunction with traditional fixation techniques, the FlexBone material provides ideal scaffolding for new bone growth." Jie Song, Assistant Professor of Orthopedics and Physical Rehabilitation and Cell Biology, and corresponding author of the *Tissue Engineering Part A* article, highlighted the potential benefits of using FlexBone in bone grafting, "What makes FlexBone so ideal for healing large bone gaps is that it absorbs and retains the proteins associated with the natural healing process from the surrounding tissue once implanted … This helps accelerate healing."

Following on from the study conducted in rats, Song and Ayers are hoping to test FlexBone in larger animals, taking the first steps on the way to human clinical trials.

Sources: University of Massachusetts Medical School: www.umassmed.edu/news; Filion T, Li X, Mason-Savas A *et al.*: Elastomeric osteoconductive synthetic scaffolds with acquired osteoinductivity expedite the repair of critical femoral defects in rats. *Tissue Eng. Part A* DOI: 10.1089/ten.tea.2010.0274 (2010) (Epub ahead of print).

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of rheumatology. If you have newsworthy information, please contact:

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Canakinumab exceeds expectations in gout trial

A Phase II study of the anti-IL-1-β monoclonal antibody, canakinumab has shown it to be effective in relieving pain and preventing recurrent flares in gouty arthritis.

A total of 200 patients were involved in the 8-week, single-blind, double-dummy, Phase II dose-ranging study, and were randomly assigned to receive either a single subcutaneous dose of canakinumab (10, 25, 50, 90 or 150 mg; n = 143) or an intramuscular dose of triamcinolone acetonide (40 mg; n = 57).

A statistically significant dose response was observed 72 h after canakinumab treatment and all doses were associated with numerically less pain than triamcinolone acetonide, which therefore prevented an equivalent dose to triamcinolone acetonide after 72 h being determined. Significant reductions in the risk of recurrent flares was also observed in all canakinumab groups, compared with triamcinolone acetonide, while the incidence of adverse events was comparable in both groups (41% of canakinumab-treated vs 42% of triamcinolone acetonide-treated patients).

The researchers, led by Dr Alexander So, from the University Hospital of Lausanne, Switzerland report, "Our findings indicate that canakinumab 150 mg provides rapid and sustained pain relief in patients with acute gouty arthritis, and significantly reduces the risk of recurrent flares compared with triamcinolone acetonide."

A limitation, however, is that triamcinolone acetonide is often administered as a 60-mg dose, but the researchers commented that it is produced as 40-mg vials across nearly all of Europe and they were reluctant to use two 40-mg vials as a comparator dose, which may go some way in explaining the favorable results of canakinumab.

Dr Dennis McGonagle, Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds, UK, an expert in gout, saw promise in the results, but took a more cautious approach in his analysis. "This is a solid study and adds further support for the idea that gout is a disease driven by innate immune system dysregulation via [interleukin 1] and that this cytokine can be usefully blocked in practice. However, in [the] real-world setting of acute gout, we use much higher doses of steroid than reported in this study. A clinical setting steroid dose may have shown comparable efficacy."

Source: So A, De Meulemeester M, Pikhlak A *et al.*: Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: Results of a multicenter, Phase II, dose-ranging study. *Arthritis Rheum.* 62(10), 3064–3076 (2010).

Bone density in children with Gaucher disease improved by early treatment

A study presented at the American Society of Bone and Mineral Research (ASBMR) 2010 Annual Meeting has found that early treatment of Gaucher disease appears to enhance bone density.

Skeletal involvement is a major source of complications in patients with type 1 Gaucher disease and patients do fracture bones. The study set out to see what effect the treatment was having on disease progression and bone mineral density.

The treatment was imiglucerase infusion therapy, to replace the enzyme glucocerebrosidase, which is deficient in patients with Gaucher disease. The investigators categorized patients into various groups and used dual-energy x-ray absorptiometry to asses the z scores in each child. They demonstrated that z scores were below -1 in 44% of children aged 5–12 years, in 76% of adolescents aged 12–20 years, in 54% of young adults aged 20–30 years and in 52% of adults aged 30–50 years.

The results after administering imiglucerase showed an improved z score. Of the 19 children who had low z scores, the median dual-energy x-ray absorptiometry z score improved from a baseline of -1.38 to -0.73 over 6 years of the therapy. Similar improvements were observed in 30 young adults with low baseline z score following 10 years of treatment.

The investigators concluded that, "It looks like when you administer [imiglucerase] early in life, the children can profit more [in terms of bone mass] than if you wait to administer it," said Dr TN Hangartner, lead investigator, "If you want to have a positive effect on bone, do not wait to give treatment."

Source: Hangartner TN *et al.*: Osteopenia in Gaucher disease develops early in life: response to imiglucerase enzyme therapy in children, adolescents and adults. Presented at: *American Society of Bone and Mineral Research (ASBMR) 2010 Annual Meeting.* Toronto, ON, USA, 15–19 October 2010 (Abstract SA0444).

Statins are not the solution for the pediatric lupus population

The largest study of pediatric patients to date, involving 221 participants, has suggested that routine use of statins to treat pediatric lupus patients at higher risk of coronary artery disease does not provide sufficient benefit for regular use in children and adolescents.

Children with lupus often show early signs of atherosclerosis and research has shown that postmenopausal women with lupus are 50-times more likely to suffer a heart attack or stroke.

Laura Schanberg, Professor of Pediatrics at Duke University Medical Center, NC, USA, who presented the findings at the American College of Rheumatology meeting in Atlanta, GA, USA, commented, "As treatments for lupus improve and kids live longer, they are more likely to develop significant heart disease. We wanted to find a way to lower their risk." The investigators turned to statins as a solution, having proven success in reducing rates of heart disease in adult populations. The 221 patients aged between 10 and 21 years were randomized to receive either atorvastatin or placebo for 36 months, and ultrasound techniques were used to detect the thickening of arterial walls of carotid arteries. Blood lipid levels, inflammation markers and lupus disease activity measures were also recorded to determine if there was a significant benefit to using statins that outweighed the potential risks.

The results, however, suggested that the risks involved with statin use in the pediatric population did not significantly outweigh the associated risks. "The statins had positive effects on CRP and lipid levels, and they appear to be safe and well tolerated, but their effect on atherosclerosis was not significant enough to warrant routine use," reported Schanberg.

The researchers stated that the use of statins should not be abandoned in the pediatric lupus population, but that, at present, they are not the solution for routine treatment of lupus in children and further research is necessary to draw definitive conclusions. "There are rare long-term risks associated with statins that outweigh the risks of using them routinely without proof of clinically significant benefit," concluded Schanberg.

Source: Schanberg LE, Sandborg CI, Barnhart HX *et al.*: Does atorvastatin reduce carotid atherosclerosis in pediatric SLE? Results from the Atherosclerosis Prevention in Pediatric Lupus Trial: the largest multicenter, randomized, double-blind, placebo-controlled study in pediatric SLE. Presented at: *American College of Rheumatology (ACR) Annual Meeting.* Atlanta, GA, USA, 10 November 2010 (Abstract).