Cathepsin K inhibitor enters clinical trials for the treatment of osteoporosis

Medivir begins trial of new osteoporosis drug in humans

In the USA, osteoporosis is a public health risk for an estimated 44 million people, which equates to 55% of people over 50 years of age. Of these 44 million, 10 million have been diagnosed with the disease and 34 million have a low bone mass, which predisposes towards osteoporosis. Sex differences exist, with osteoporosis being more common in women than men; in fact, it is estimated that 80% of those affected by osteoporosis are women.

A total of 1.5 million fractures occur as a result of osteoporosis every year, and in Europe an osteoporosis-related fracture occurs every 30 seconds. Not only does osteoporosis have a significant impact on the patient's quality of life, it also has a significant financial burden. In 2002, the annual national care expenditure was approximately US$18 billion and these costs are increasing.

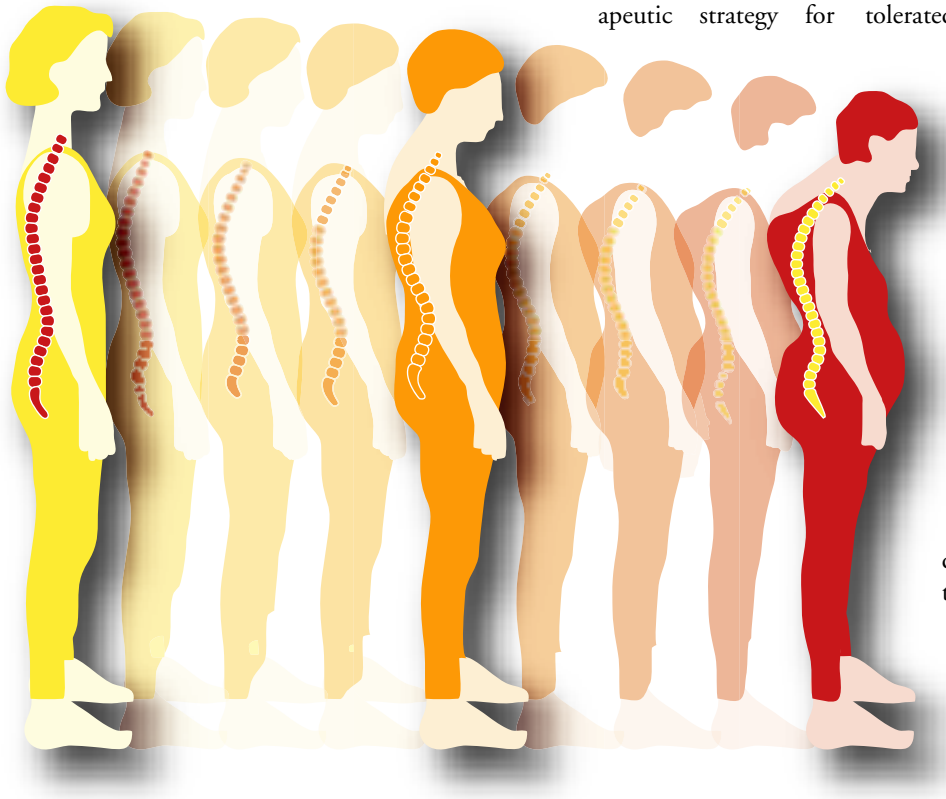
Currently, osteoporosis is treated with bisphosphonates, such as calcitonin, hormone therapy and selective estrogen receptor modulators, such as raloxifene. However, owing to the prevalence of the disease, and the serious side effects associated with current therapeutics, there is an increasing need for new drugs to treat the condition. One such drug, currently in development, is MIV-701.

MIV-701 has been developed over the last 5 years by Medivir, a Swedish pharmaceutical company. MIV-701 has a novel mechanism of action; it acts as a cathepsin K inhibitor. Cathepsin K is a protease that plays a role in the degradation of gelatin, collagen and elastin, all of which are major components of collagen and bone. Thus, inhibition of cathepsin K is an attractive therapeutic strategy for osteoporosis. Although several large pharmaceutical companies are pursuing research into the development of drugs to treat osteoporosis, there are currently no drugs with the same mechanism of action as MIV-701.

During the development of MIV-701, preclinical studies have shown promising results and it has demonstrated efficacy in reducing bone degradation. "It feels extremely exciting to participate in the development of a new Swedish drug directed to such an important, widespread disease as osteoporosis," says Lars Adlersson, Medivir's CEO. The drug now needs to meet Medivir's expectations in terms of safety and efficacy.

MIV-701 has now entered clinical trials in humans. These trials aim to determine the uptake of an oral dose of the drug and also to investigate how well tolerated it is. In addition, the efficacy of the drug in treating osteoporosis, as well as arthritis and bone metastases, will be assessed using biomarkers. Initially, trial subjects will be administered single, increasing doses. As the trial progresses, multiple doses of MIV-701 will be administered to subjects over an extended period.

Medivir "…intend to present data from the newly begun trials during 2007," states Adlersson, after which point they will continue the development, and hope to begin the marketing, of this new drug.



Source: Medivir http://www.medivir.com/v3/enir_media/press_releases.aspx?id=123

Priority Paper Alerts

Genetic variations of Toll-like receptor 9 predispose to systemic lupus erythematosus in Japanese patients.

Tao K, Fujii M, Tsukumo SI et al.: Ann. Rheum. Dis. DOI:10.1136/ard.2006.065961 (2007) (Epub ahead of print).

This study aimed to determine the effect of polymorphisms in Toll-like receptor (TLR) 9 on the risk of developing systemic lupus erythematosus (SLE). DNA samples were collected from Japanese patients with SLE and control subjects. PCR, DNA sequencing, a reporter gene assay and an enzyme-linked immunosorbent assay were carried out. The G allele at position +1174 and the C allele at position -1486 were both associated with an increased risk of SLE. The reporter gene assay showed that both alleles downregulated TLR9 expression. Furthermore, anti-double stranded DNA antibody titers were higher in the serum of TLR9-null mice compared with control mice. The authors conclude that genetic variations in the TLR9 gene are associated with the risk of SLE.

Is rheumatoid arthritis a disease that starts in the intestine? A pilot study comparing an elemental diet with oral prednisolone.

Podas T, Nightingale JM, Oldham R, Roy S, Sheehan NJ, Mayberry JF: Postgrad. Med. J. 83(976), 128–131 (2007).

Describes a study aiming to assess the efficacy of an elemental diet in treating rheumatoid arthritis compared with oral prednisolone. The study involved 30 rheumatoid arthritis patients who were randomly assigned to receive either an elemental diet or a single, daily oral dose (15 mg) of prednisolone. Assessments were made at 0, 2, 4 and 6 weeks. Of all the chosen parameters, only the swollen joint score in the elemental diet group did not show an improvement. Duration of early morning stiffness, pain on a 10 cm visual analog scale and the Ritchie articular index showed more than a 20% improvement in both groups. The study demonstrated that a 2 week elemental diet was as affective as oral prednisolone in treating rheumatoid arthritis. This supports the hypothesis that rheumatoid arthritis begins in the intestine as a reaction to food antigens.

Obese women more at risk of infection, septic loosening and dislocation of artificial hips following total hip arthroplasty

Researchers report increased risk of complications in obese women undergoing total hip arthroplasty

Researchers at Geneva University Hospital, Switzerland, have been studying the effects of obesity on the outcome of total hip arthroplasty (also known as total hip replacement) procedures. This study, which is published in *Arthritis and Rheumatism*, also examines the sex differences in the effect of obesity on complications, such as infection, dislocation and loosening of the joint, following the procedure. The authors state "…to the best of our knowledge, this is the first study analyzing sex differences as related to outcomes in obese total hip replacement patients".

'In the USA, it is estimated that 150,000 hip joints are implanted annually and the success rate is greater than 90%.'

Total hip replacement has become a common procedure in patients with rheumatoid arthritis, osteoarthritis and various hip related problems. It has been shown to be of benefit in alleviating the pain and debilitation caused by these conditions. In the USA, it is estimated that 150,000 hip joints are implanted annually and the success rate is greater than 90%. However, there are risks of complications, including infection, joint loosening and dislocations.

The researchers studied all the patients who underwent a total hip replacement procedure between March 1996 and July 2005 at Geneva University Hospital. A total of 589 out of 2495 total hip arthroplasties were carried out in obese patients, with the definition of obese being a body mass index score greater than 30. A greater number of procedures were carried out in obese men than women.

The study demonstrated that obese women were more prone to infection and, thus, were more at risk of septic loosening. Obesity was also associated with an increased risk of dislocation, particularly in women. A total of 183 obese and 635 nonobese hip replacement patients were followed up after 5 years. Researchers found that obese women were more likely to experience lower functional outcomes and report less satisfaction compared with men. In most cases, this was a result of a higher incidence of complications following surgery in obese women.

"…total hip arthroplasty is a successful intervention in obese patients…"

The results of this study are of particular importance owing to the fact that obese patients are at an increase risk of developing osteoarthritis and requiring hip replacements. This should also be put into the context of increasing obesity rates in developing countries. The authors conclude that "…total hip arthroplasty is a successful intervention in obese patients…" but recommend "…participating in a weight-loss program prior to surgery…" and counseling obese women on the risk of complications.

Source: Lubbeke A, Stern R, Garavaglia G, Zurcher L, Hoffmeyer P: Differences in outcomes of obese women and men undergoing primary total hip arthroplasty. *Arthritis Rheum.* 57(2), 327–334 (2007).

Bone-marrow stem cells suggested as a possible tool for bone-tissue regeneration and restoration of function to diseased or damaged bone

Current status of bone-tissue engineering

In Public Library of Science Medicine, Gert Meijer (University Medical Centre Utrecht, The Netherlands) and colleagues review the available clinical data on bone-tissue engineering (BTE) in human studies, together with their own clinical research findings.

Until recently, the use of bone grafts from a different part of the patient's own body has been the number one choice for attempting to restore function to diseased or damaged bone. However, there are major problems with such grafts, such as post-operative pain, infection, abnormal sensations and morbidity at the removal site. Moreover, there is a limit to the amount of bone that can be collected. An alternative, say the authors, is to use bone from donors, but these are less successful and bring with them the risk of transmitting infections from donor to recipient.

Owing to the number of problems associated with bone grafts, BTE using bone-marrow stem cells has been suggested as a possible tool to mend bone defects. Indeed, various animal studies have demonstrated the capacity of BTE to produce bone, thus, "bone-tissue engineering using bone-marrow stem cells has been suggested as a promising technique for reconstructing bone defects", say Meijer and colleagues. However, until recently, no convincing successes have been achieved in humans. Meijer and colleagues reviewed human studies published in international English language peer-reviewed literature regarding the treatment of osseous defects with tissue engineered constructs. They searched for studies in the Cochrane Central Register of Controlled Trials (Cochrane Library 2006, issue 2) and Medline (from 1966 up to March 2006). The search terms included culturing cells, mesenchymal, clinical, human study, orthotopic, ectopic and bone formation.

Meijer and colleagues discuss possible new directions that need to be exploited to enable the restoration of the function of diseased or damaged bone by bone-tissue regeneration, which "could well revolutionize the future of regenerative medicine."

Source: Meijer GJ, de Bruijn JD, Koole R, van Blitterswijk CA: Cell-based bone tissue engineering. *PLoS Med.* 2, E9 DOI: 10.1371/journal.pmed.0040009 (2007) (Epub ahead of print) .

Increased risk of fragile bones in children with cancer

The combination of sedentary behavior and the inhibition of bone growth as a side effect of treatment regimes have been shown to put children with cancer at an increased risk of bone fragility and osteoporosis, as revealed in the April issue of *Cancer*. Physicians have been advised to look-out for signs of bone fragility that result from cancer directly, or following treatment, as this risk can be reduced with exercise and the use of bisphosphonates.

Normal bone development is maintained in an equilibrium between bone formation and bone resorption. This system is regulated by a complex hormonal signaling network, which can be drastically changed by altering any one pathway. For example, in postmenopausal women who have reduced levels of estrogen (a stimulator of bone formation), osteoporosis is a common occurrence. External factors, such as drugs, diet and exercise, can also affect these pathways. Previous studies have shown that children with cancer have multiple risk factors for osteoporosis and fractures. This review focuses on the relationship between pediatric cancer, bone loss and its management.

Alessandra Sala (McMaster Univeristy, Ontario, Canada and Universita di Milano Bicocca, Milan, Italy) and Ronald D Barr (McMaster University) report that there are two factors that negatively affect bone turnover in children with cancer. First, patients are likely to be less active as a result of chronic illness and, second, treatments such as radiotherapy and chemotherapy are linked to decreased bone formation and low bone mineral density (BMD). The authors note that "loss of bone mineral is clearly a common consequence of the treatment of cancer in children and adolescents, fitting the paradigm of chronic disease often attended by therapy".

The authors report, however, that several treatments are available that can stimulate mineralization and minimize the loss of bone during the critical bone development years. These include physical exercise, dietary modification and the use of bisphosphonates, which are used in the treatment of osteoporosis in postmenopausal women.

The authors state that "osteopenia in children with cancer is of multifactorial origin requiring comprehensive strategies for amelioration and prevention", leading to the new advice for physicians to take more time to look for symptoms of bone fragility in children with cancer.

Source: Sala A, Barr RD: Osteopenia and cancer in children and adolescents – the fragility of success. *Cancer* DOI: 10.1002/cncr.22546 (2007).

Link between rheumatoid arthritis and cancer

A team from the University of Manchester, UK, have produced evidence that inflammatory arthritis may increase the risk of dying from cancer, but not the risk of developing it. The team, led by Dr A Silman, investigated, for the first time, whether the incidence of cancer is increased and whether the rate of cancer survival is reduced in patients following the onset of inflammatory polyarthritis (IP).

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease, making patients at least twice as susceptible to death from disease as the general population. Whether or not RA patients are at increased risk from cancer is still in doubt. "This is the first investigation of overall cancer survival in patients with IP' Silman commented; results were published in the March 2007 issue of *Arthritis & Rheumatism*.

Between 1990 and 1999, a total of 2105 patients with new-onset polyarthritis were recruited and subsequent cancers and deaths recorded. Over time, a large proportion of new-onset IP cases evolve into RA, meeting the diagnostic criteria of the American College of Rheumatology. The incidence of cancer was compared with regional rates, adjusting for age, sex and calendar year. Cancer survival was also recorded and compared with regional data using Kaplan–Meier curves and Cox regression.

Overall, the incidence of cancer was not increased in IP subjects compared with the general population. However, there were striking differences in the survival rates of cancer patients with IP compared with cancer patients without a history of IP. There was a 40% increase in mortality in cancer patients who also had IP or RA.

Silman observed that "the results of this study demonstrated that 5-year cancer survival in patients with RA is substantially reduced in comparison with that in the general population, even after adjusting for differences in age, sex, and cancer site, whereas the overall cancer incidence does not seem to be increased." In the future, targeted cancer therapies could help to improve the survival rate for RA patients.

Source: Lunt FJ, Bunn M, Symmons D, Silman AD: Influence of inflammatory polyarthritis on cancer incidence and survival: results from a community-based prospective study. *Arthritis Rheum.* 56(3), 790–798 (2007).

CD40L protein appears to regulate bone mass loss

Osteoporosis affects approximately 10 million Americans, and 34 million Americans are at risk for developing the disease. Osteoporosis is caused by an imbalance between bone mineral formation and loss, resulting in severe loss of bone mineral density, fragile bones and an increased risk of fractures. However, the biological processes leading to this imbalance are not completely understood.

Researchers at the National Institute of Allergy and Infectious Diseases (NIAID) have been studying people with X-linked hyper immunoglobulin (Ig)M syndrome, a rare genetic disorder caused by a deficiency of CD40 ligand (CD40L). CD40L is an essential protein for the development and maturation of immune cells, without which people are susceptible to a range of opportunistic infections.

A study by Lopez-Granados and colleagues reports an unexpected connection between X-linked hyper IgM syndrome and the loss of BMD. This connection was discovered by a doctor at NIAID who noticed that children with this disease often also sustained unexplained rib fractures. He hypothesized that these could be caused by a loss of BMD, as with osteoporosis.

CD40L appears to regulate cells secreting chemicals that inhibit bone metabolism, therefore, in people with X-linked hyper IgM syndrome, the loss of CD40L appears to accelerate bone loss. Lopez-Granados and colleagues report that CD40L can influence receptor activator of NF-κb-ligand signaling through T-cell priming and, thus, they demonstrate a regulatory role for CD40L in bone mineralization that is absent in patients with X-linked hyper IgM syndrome.

These results demonstrate a clear relationship between CD40L and osteoclastogenesis, and further experiments will determine whether treatments to correct the immune deficiency of X-linked hyper IgM syndrome can also reverse the bone loss. This knowledge could be applied to the development of treatments to help people at high risk of developing osteoporosis.

Source: Lopez-Granados E, Temmerman ST, Lynne Wu *et al.*: Osteopenia in X-linked hyper-IgM syndrome reveals a regulatory role for CD40 ligand in osteoclastogenesis. *Proc. Natl Acad. Sci. USA* DOI: 10.1073/pnas.0605715104 (2007) (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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