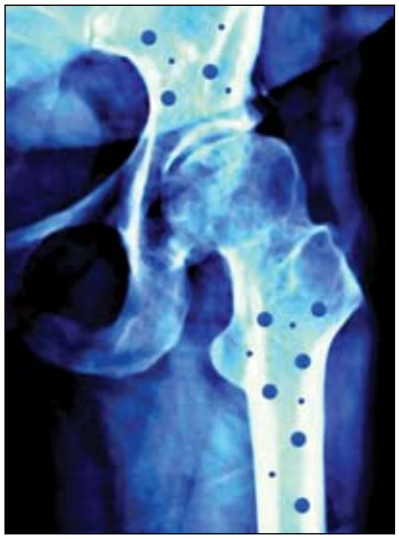
MD CONFERENCE EXPRESS

Osteoporosis in Inflammatory Rheumatic Disease



Professor Steven Goldring, Harvard Medical School, Cambridge, MA, outlined the molecular mechanism of focal bone erosions at the joint margins and in the subchondral bone of patients with osteoporosis (OP) and rheumatoid arthritis (RA). Dr. Goldring stated, "Multinucleated cells with phenotypic characteristics of osteoclasts, the cells responsible for resorbing bone during physiologic remodeling, and factors that induce osteoclast differentiation, are found in the rheumatoid synovium." These include NF-kappa beta ligand (RANKL), interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF-alpha). He cited evidence that mice unable to produce osteoclasts do not show evidence of bone resorption, despite the presence of intense inflammation; suggesting that by targeting osteoclast and proinflammatory cytokines, new pharmacological agents might prevent or reduce focal bone loss associated with OP.

Following the presentation on the mechanism of action, Professor Piet Geusens, University Hospital, Maastricht, Netherlands, presented a clinical and epidemiological overview of inflammatory diseases. It is now generally accepted that inflammation associated with RA increases the risk of hip and vertebral fractures that are independent of other risk factors such as age and gender. In RA, the risk of vertebral fractures was related to the degree of joint involvement, use of glucocorticoids (GC) and low bone mineral density (BMD). Increased levels of markers of bone resorption in patients with active RA were related to inflammation and changes in focal bone loss. Interestingly, decreased BMI was associated with a higher risk of developing fractures at an older age. Dr. Geusens concluded by saying, "the interaction between inflammation and bone, referred to as 'osteoimmunology', is a focus of major interest."

"In the RA population, there is a two-fold increase in the prevalence of osteoporosis" stated Professor Glenn Haugeberg, Sorlandet Hospital, Kristiansand, Norway, in his opening remarks on the treatment and prevention of OP. Risk factors of OP are associated with inflammation, the use of GC, and inactivity. The clinically important factor of OP in RA patients is the increased risk of fractures (1.5 – 3.0 fold increase for hip and 2.6 – 6.2 fold increase for vertebral). Potent anti-inflammatory treatment has been shown to reduce the

Highlights from the
European League Against Rheumatism 2006 Annual Meeting

rate of bone loss in inflammatory joint disorders. Patients aggressively treated with infliximab (IFX) alone, or in combination with methotrexate (MTX) show arrested bone loss in the hip. Newer agents such as the RANKL-antibody (AMG 162) are currently being tested in OP. Lastly, Dr. Haugeberg recommended that patients increase their physical activity, if possible.

Two abstracts were also presented. The study presented by M. Güler-Yüksel, Leiden University Medical Center, Leiden, Netherlands, evaluated BMD changes in early, active RA patients treated for 1 year (BeSt study) with either MTX monotherapy, step up therapy with MTX, combination therapy with high dose prednisone, sulphasalazine and MTX, or combination therapy with IFX + MTX. High BMD loss at the spine and hip were associated with high scores for joint damage at baseline and functional disability after 1 year, increasing age, and non-use of bisphosphonates. No significant differences were seen between the treatment strategies.

The second study presented by Dr. Pernille Bøyesen, Diakonhjemmet Hospital, Oslo, Norway, focused on the use of biomarkers to predict hand bone mass density (BMD) after 1 and 2 years of RA. The authors concluded that BMD loss after 1 year is best predicted by erythrocyte sedimentation rate ESR and anti-CCP; after 2 years it is best predicated by IgA RF and ESR. RANKL and osteoprotegerin (OPG) were not associated with hand bone loss.

State of the Art/ Best Practice: Osteoporosis

According to Professor Cyrus Cooper, University of South Hampton, Southampton, UK, "osteoporosis is a major health problem mainly because of its association with age related fractures." He stated that hip fractures are a particular problem since they are associated with significant morbidity and lead to an overall reduction in survival of around 15%. Reduction in bone density is an important determinant of fracture risk.

Professor Cooper pointed out that bone loss can be offset by increasing estrogen levels (in women), increasing BMI, calcium intake, activity levels, and decreasing smoking, alcohol consumption, and corticosteroid use. This strategy should be complemented with appropriate measurements of BMD and targeting of anti-resorptive and bone formation stimulating drugs.

Regardless of the preventive pharmacologic treatment, only about 50% of osteoporotic fractures can be prevented, stated Dr. Christian Kasperk, University of Heidelberg, Germany. Vertebral fractures, in particular, continue to occur and can cause pain which is not easily relieved with analgesics. Kyphoplasty and vertebroplasty (injection of bone cement) performed in OP patients with painful vertebral fractures significantly increases vertebral height, reduces pain, improves mobility, and reduces new fractures. These benefits persist up to 1 year after treatment. The key to successful outcomes is an inter-disciplinary selection of patients likely to benefit from these procedures (*J Bone Min Res* 2005;20:604-12).

Dr. William Lems, Vrije Universiteit Medical Centre, Amsterdam, Netherlands, pointed out that both anti-resorptive and anabolic drugs have been shown to be effective in the prevention of vertebral (and some non-vertebral) fractures in osteoporotic patients. He raised the question of whether combining these therapies might be more effective. Unfortunately, there are no data. Use of surrogate markers such as changes in BMD and markers of bone turnover have been studied, but the results are difficult to interpret. He concluded, "the currently available data do not support the combined use of anti-resorptives and anabolics. The data does indicate that after initiating a treatment with an anabolic agent, it may be necessary to maintain the effect with an anti-resorptive agent."

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Dr. L.A. Fitzpatrick, Amgen, Thousand Oaks, CA, reported on the efficacy of denosumab (AMG 162; a fully human monoclonal antibody that binds to and inhibits RANKL) in postmenopausal women with low BMD. Subjects treated with denosumab for 24 months had significantly greater increases in lumber spine, total hip, distal 1/3 radius, and total body BMD compared with placebo treated patients ($p<0.001$). Denosumab also caused significant sustained suppression of bone turnover markers serum C-telopeptide and urine N-telopeptide/ creatinine compared with placebo ($p<0.001$).

Dr. Wim Goettsch, PHARMO Institute, Utrecht, Netherlands, presented evidence showing that low persistent use of bishosphonates for one year resulted in a significant, 26% lower, fracture rate, whereas 2 year use resulted in a 32% lower rate in women hospitalized for previous osteoporotic fractures.

Osteoporosis is a multifaceted disease that until recently has been both under-diagnosed and under-treated. New emphasis on the disease and recent developments in the field of osteoporosis research has provided clinicians with new treatments and prevention strategies.

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Treating depression in FM often does not diminish reporting of pain and medically unexplained symptoms, but it may improve social function. Graded exercise produces improvements in functional work capacity and fatigue, while fluoxetine improves depression only (*Br J Psychiatry*. 1998;172:485-90).

Disrupted sleep appears to complicate the course of FM. For the most part, sleep complaints are either attributable to the lifestyle of FM patients, or seem inherent to the underlying condition of FM. They are generally unrelated to depression or anxiety in FM.

The correlation between tissue pathology and the perceived severity of the chronic pain experience is poor or even absent. More importantly, chronic pain seldom responds to the therapeutic measures that are successful in treating acute pain.

Dr. Morriss concluded by saying that "psychological treatments focused on the needs of the FM patients can improve clinical care, but research evidence does not support a complete shift of focus away from pain relief." Thus, for optimal management of FM, he recommends a blend of multidisciplinary group therapy and individualized clinician-based treatment.

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The endpoint of the study was the number of patients in remission defined as no swollen joints plus 2 out of 3 of the following criteria: number of tender joints ≤ 3, ESR ≤ 20 mm/hr1st, and VAS general well-being ≤20 mm fulfilled at three subsequent visits measured at three monthly intervals.

Sixty-three (41%) of the patients in the intensive strategy group achieved remission for at least 6 months versus 24% of the patients in the conventional strategy group ($p= 0.002$). Mean time until first remission was 10 months for the intensive strategy group compared with 13 months for conventional strategy group. Median (IQ 0.25-0.75 range) AUC of all clinical variables were significantly better for the intensive strategy group when compared to the conventional strategy group.

Tailoring the MTX treatment to the individual patient is significantly more beneficial than the conventional approach. Furthermore, a computer assisted approach, to make more objective decisions on dosage changes, may be beneficial.