Drug-Induced Osteoporosis

Corticosteroids - A Balanced View

Willem Lems, MD, University Medical Centre, Amsterdam, The Netherlands, discussed the pathogenesis of glucocorticoid-induced osteoporosis.

Glucocorticoids have been shown to stimulate apoptosis of osteoblasts and osteocytes, interfere with the Wnt-signaling pathway (a pivotal pathway for modulating osteoblastic activity, bone formation, and bone strength), and increase the lifespan of osteoclasts [Shoback D. *J Clin Endocrinol Metab* 2007]. They also reduce the intestinal absorption of calcium and augment calcium excretion in the urine [van Staa T. *Calcif Tissue Int* 2006].

The increased fracture risk in patients who receive glucocorticoid therapy may be offset by alendronate [Saag KG et al. *N Engl J Med* 1998], risedronate [Reid DM et al. *J Bone Miner Res* 2000], active vitamin D3, and bisphosphonates [de Nijs RN et al. *Osteoporos Int* 2004]. Teriparatide, the first anabolic agent, appears to significantly ($p<0.001$) increase bone mineral density (BMD) and decrease fracture incidence more than alendronate [Saag KG et al. *N Engl J Med* 2007].

Despite increases in the frequency of screening for and treatment of glucocorticoid-induced osteoporosis, adequate prophylaxis is only prescribed in roughly 50% of glucocorticoid-treated patients [Saag K et al. *J Rheumatology* 2006].

Cancer Treatment-Induced Bone Loss

Jean-Jacques Body, MD, PhD, CHU Brugmann, Universite Libre de Bruxelles, Brussels, Belgium, discussed recent data that concern osteoporosis that is induced by adjuvant antineoplastic treatment in pre- and postmenopausal women with early breast cancer and by androgen deprivation therapy (ADT) in men who are being treated for prostate cancer.

Chemotherapy, GnRH analogs, tamoxifen in premenopausal women, ADT, and aromatase inhibitors (anastrozole, letrozole, and exemestane) can increase bone turnover, reduce bone mass (up to 4% to 5% per year), and increase fracture rates as much as 35% to 50%. Risedronate and to a greater extent zoledronic acid as adjunctive therapy, however, have been shown to significantly ($p<0.01$) prevent bone loss and reduce bone turnover in women with breast cancer and chemotherapy-induced menopause or those who are treated with aromatase inhibitors (anastrozole/letrozole) [Greenspan SL et al. *J Clin Endocrinol Metab* 2007; Gnant MF et al. *J Clin Oncol* 2007; Brufsky A et al. *J Clin Oncol* 2007]. In men who are being treated with leuprolide, a gonadotropin-releasing hormone agonist, pamidronate significantly ($p<0.02$) prevents bone loss [Smith MR et al. *N Engl J Med* 2001]. Zoledronic acid and alendronate even can increase BMD in such patients [Greenspan SL et al. *Ann Intern Med* 2007]. Prof. Body stated that "the initiation of therapy should begin early, prior to the occurrence of severe osteoporosis."

Which Other Dugs Cause Problems?

Besides the glucocorticoids, Peter Vestergaard, MD, PhD, The Osteoporosis Clinic, Aarhus Amtssygehus, Aarhus, Denmark, summarized studies on other drugs that are used to treat rheumatologic diseases, such as immunosuppressives (methotrexate, cyclosporine, azathioprine) and the older disease-modifying antirheumatic drugs (DMARDs; gold, penicillamine, chloroquine, sulphasalazine). Methotrexate, most DMARDs, and the newer biological agents seem safe in terms of the risk of osteoporosis and fractures, although the number of studies is limited. Some of the newer biological agents may even have positive effects on bone density. For pain medication, nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates also have been associated with an increased risk of fractures, which, in the case of opiates, may be linked to an increased risk of falls. An important confounder is "confounding by indication," which means that the effects of the underlying disease may be confounded with the effects of the drugs that are given to control the disease in question. For example, many patients with advanced disease have a higher risk of decreased bone density and fractures due to the effects of the disease per se. However, these patients also may be more likely to receive drugs in high doses for their disease, and the drug treatment may thus be confounded with the effect of the disease. The increase in fracture risk that is shown in some studies may be due to the underlying disease, not the treatment, concluded Prof. Vestergaard.

A Victory in the War on Osteoporosis?

In contrast to the negative news about osteoporosis, Ms. Amrita Sehgal, a student at Menlo-Atherton High School, Atherton, CA, presented data that showed that in the United States, inpatient days that were attributed to hip fractures dropped by almost 73% between 1988 and 2005 ($p<0.0001$), despite an 11.4% increase in all-cause

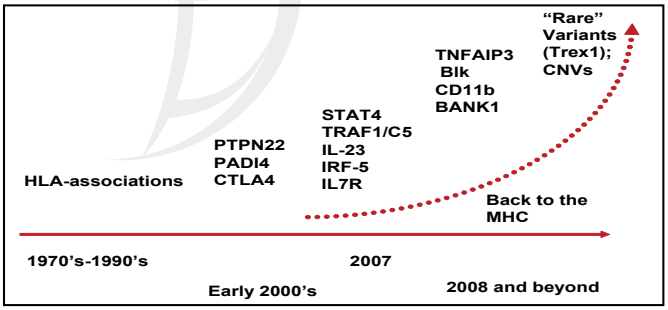
hospitalizations. However, the total cost of care for such hospitalizations (in 2005 US dollars, assuming 3% inflation rate) increased from $4.04 billion to $5.9 billion (p<0.05), suggesting that hip fractures continue to be associated with significant costs of care.

What Clinicians Should Know About Genetics

New Genes in Rheumatoid Arthritis (RA)

In the last year, there has been an explosion in the discovery of new genes that are related to autoimmunity (Figure 1). The sudden increase began with the discovery of a single nucleotide polymorphism (SNP) in the gene PTPN22 that holds a 2-fold increased risk for a number of autoimmune disorders, including RA. Peter Gregersen, MD, Feinstein Institute for Medical Research, Manhasset, NY, discussed the significant variations in risk alleles, sometimes based on ethnic groups, and how these variations confer significant differences in risk for RA diseases.

Figure 1. Accelerating Discovery of Genes for Autoimmunity.



Two new gene areas of interest are the TRAF1 (Figure 1) and STAT4 loci. Genetic variants at the TRAF1-C5 locus on chromosome 9 are associated with an increased risk of anti-CCP-positive RA and chronic inflammation [Plenge RM et al. *N Engl J Med* 2007], and significantly (p=0.008) increased radiographic progression [Kurreeman FAS et al. *PLoS Med* 2007]. A SNP haplotype in the third intron of STAT4 is associated with susceptibility to both RA and systemic lupus erythematosus (SLE), suggesting a shared pathway for these illnesses. The odds ratio for having the risk allele in chromosomes of RA patients versus controls was 1.32 [Remmers EF et al. *N Engl J Med* 2007]. Beyond these new discoveries, Dr. Gregersen added, there are multiple independent genetic risk factors in the large genomic region that is known as the major histocompatibility complex (MHC) that impact RA.

New Genes in Ankylosing Spondylitis (AS)

Matthew Brown, MD, University of Queensland, Brisbane, Australia, discussed the of progress that has been made in identifying genes that are involved in the risk of developing AS with the advent of high-density linkage disequilibrium mapping. The technique has identified 2 genes so far, IL23R and ARTS1, which have a combined population attributable risk >30% [Brown MA. *Rheumatology* 2007]. Along with the previously identified HLA-B27 gene, these genes can predict the risk of AS in 70% of cases. The IL23R gene encodes a cytokine receptor on a subset of effector T-cells. Variants of IL23R have been identified in patients with Crohn disease and those with inflammatory bowel disease, as well as AS, suggesting a commonality for these pathologies. The ARTS1 gene encodes a protein that is involved both in immune regulation and in the processing of cell surface receptors for proinflammatory cytokines. "The successful identification of ARTS1 and IL23R should give those who are involved in AS genetics research great encouragement of the potential of this research," Prof. Brown concluded.

New Genes in Systemic Lupus Erythematosus (SLE)

Timothy J. Vyse, MD, PhD, Imperial College of London, London, UK, reviewed recent data from genome-wide association studies (GWAS) that identified genes that are associated with an increased risk for SLE. There is overwhelming evidence that the MHC is the primary locus for these genes. Within the MHC, he identified the ITGAM, BANK1, LYN, BLK and ATG5, MECP2, UBE2LS, and SCUBE1 genes as being significant risk factors for SLE. Despite the number of new SLE associated genes that already has been identified, Prof. Vyse believes there are more to be discovered.

Quantitative Heritability of ACPA-Positive and ACPA-Negative Rheumatoid Arthritis

Diane van der Woude, MD, Leiden University Medical Center, Leiden, The Netherlands, presented the results of a study that investigated the quantitative contribution of genetic factors to disease development: the heritability. In a cohort of subjects that consisted of 148 twins in which at least one twin had RA, the overall heritability of RA was 66% (95% CI, 44-75). For anti-citrullinated protein antibody (ACPA)-positive RA, heritability was 68% (95% CI, 55-79), compared with 66% (95% CI, 38-83) for ACPA-negative RA. She concluded that these 2 subsets of RA have comparable heritability. This indicates that there may be many genetic risk factors for ACPA-negative RA that remain to be discovered.