World Congress on Osteoarthritis (Osteoarthritis Research Society International)

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The Osteoarthritis Research Society International (OARSI) World Congress on Osteoarthritis was held in the Hilton Hotel in Prague, Czech Republic from 7–10th December, 2006. For the congress, 784 participants from 51 countries were registered, more than for previous congresses in Chicago and Boston; the program committee received 405 abstracts, which was also an increase on previous OARSI congresses. The Congress co-chairs were Sergio Jimenez (USA) and Karel Pavelka (Czech Republic).

The program was based on four plenary and 13 concurrent sessions with introductory lectures from invited speakers related to the topics of presented abstracts. It was accompanied by six special breakfast workshops. There were also two satellite company symposia (Rottapharm and IBSA).

The scientific sessions addressed basic research topics, such as regulation of gene expression, cytokines and metalloproteinases, and biomechanics and clinical topics, including joint replacement, clinical trial design, cartilage repair, pain mechanisms in osteoarthritis (OA) and intervertebral disc degeneration, biomarkers, development of agents with potential structure-modifying effect and evidence based reviews on the Symptomatic Slow-Acting Drug for OsteoArthritis (SYSADOA) group.

OARSI initiatives

Treatment guidelines for hip & knee OA

A total of 16 experts representing rheumatology, orthopedics and primary care from six countries formed the team, with the aim of developing evidence-based international consensus recommendations for the management of knee and hip OA. They presented drafts of publications during the opening day. A systematic review of quality and contents of existing guidelines was performed using a validated Appraisal of Guidelines Research and Evaluation instrument. Out of 1462 guidelines, 23 met inclusion/exclusion criteria.

The draft consensus recommendation suggests that optimal management of patients with OA of the hip and knee requires a combination of nonpharmacological and pharmacological modalities of treatment in most patients, and surgery in some. Nonpharmacological modalities proposed for recommendation include the provision of information access, education about the objectives of treatment, importance of changes in lifestyle (exercise and weight reduction) and the appropriate use of walking aids, patellar taping, modified footwear, knee braces, and the use of acupuncture and transcutaneous electrical nerve stimulation in selected patients. Pharmacological treatments proposed for recommendation include acetaminophen (≤4 g/day) as the preferred oral analgesic for initial therapy. Alternative/additional analgesics to be considered for patients who do not respond to acetaminophen include oral nonsteroidal anti-inflammatory drugs (NSAIDs) at the lowest effective doses, topical capsicin or NSAIDs along with intra-articular injections of corticosteroids or hyaluronans. The draft recommendations suggest that the choice should be based on consideration of comorbidities, concomitant medication and relative efficacy and safety. In patients with increased gastrointestinal risk, a cyclooxygenase (COX)-2 selective agent or a nonselective NSAID with coprescription of a proton pump inhibitor or misoprostol for gastroprotection may be considered, but NSAIDs, including COX-2 selective agents, should be used with caution in patients with risk factors for cardiovascular disease. Glucosamin and/or chondroitin sulfate may provide some symptomatic benefit in patients with knee OA. It is suggested that the use of opioid analgesics should only be considered in exceptional circumstances for the treatment of severe and refractory pain where other agents have been ineffective or are contraindicated. It is proposed that patients with hip or knee OA who are not obtaining adequate pain relief and functional improvement from a combination of pharmacological and nonpharmacological treatments should be considered for joint replacement surgery. Evidence is available demonstrating that replacement arthroplasties are cost-effective interventions for patients with significant symptoms and/or functional limitation associated with a reduced health-related quality of life despite conservative therapy. Uni-compartmental knee replacements are effective in patients with knee OA where only one compartment is affected and high tibial osteotomy can delay the need for joint replacement for up to 10 years in such patients. Osteotomy and joint-preserving surgical procedures should also be considered in young adults with symptomatic hip OA, especially when this is associated with hip dysplasia or coxa varus/valgus deformity. Joint fusion can be considered as a salvage procedure when joint replacement has failed.

Radiographic atlas

Roy D Altman presented his Atlas of *Osteoarthritis of the Hand, Hip and Knee* as a supplement of *Osteoarthritis and Cartilage*. This atlas replaced the original from 1995.

Individual radiographic features (e.g., osteophytes and joint space narrowing) were recorded for hand (distal interphalangeal, proximal interphalangeal and first carpometacarpal joints), hip (acetabular and femoral) and knee (medial compartment, lateral compartment, tibial and femoral); they were also sequenced for normal, 1+, 2+ and 3+ change. Images were available in print and electronic formats.

Histopathology

OARSI created a committee for the establishment of histology criteria for animal models. This committee should suggest broadly accepted histopathological criteria for grading and staging of OA changes both in human and animal models.

OARSI/Outcome Measures in Rheumatoid Arthritis Clinical Trials initiatives

The task force has been formed to suggest criteria for total articular replacement as an outcome measure to be used in long-term studies of OA. Three groups have suggested a main pain severity scoring system, function and structure severity system. The initial data were presented by G Hawker and M Dougados.

Hip surgery

A special session was assigned to orthopedic surgeons to present *New Horizons in Surgery*' R Ganz presented the concept of femoroacetabular impingement and S Klaus the concept of osteotomies, which he recommended not only in dysplasia.

In recent years, great interest has been given to surface replacement and its use as an alternative to conventional total hip replacement (THR) with a low wear producing articulation. It has the advantage of preservation of proximal femoral bone stock at the time of surgery and avoidance of long-term stress shielding. Revision surgery, if required, should therefore be easier and more durable. In addition, the large diameter of the articulation offers increased stability and range of movement for the active individual. Further work will be required to establish the prevalence of femoral neck fractures and avascular necrosis of the remaining femoral head. Long-term observational studies and controlled trials will be required to determine if the potential advantages of hip resurfacing compared with conventional THR are realized. Whilst early results should be regarded with caution, the present generation of metal-on-metal hip resurfacing potentially offers ultimate bone preservation and restoration of function in appropriately selected young patients. Resurfacing implants demand high manufacturing standards to produce consistently low-wear bearings. Background research and better understanding of implant failure would suggest that hip resurfacing technology has now developed beyond that of an experimental procedure. Only long-term results and experience with this technology in the wider orthopedic community will give the answer as to whether the results will be durable or if hip resurfacing will simply become a bone conserving intervention prior to conventional THR.

Key lecture

Lessons from genetic forms of OA

A key note lecture was given by BR Olsen. He stressed that studies of rare forms of hereditary OA caused by mutations in genes encoding matrix molecules in cartilage are of extreme importance.

Such hereditary forms range from severe diseases in early life to mild disorders that become evident only late. The disorders can be divided into three major groups:

- Early-onset OA associated with an underlying familial chondrodysplasia
- OA associated with abnormal deposition of mineral crystals in cartilage
- Primary generalized OA with wild chondrodysplasia

The first group comprises disorders caused by mutations in genes encoding cartilage collagens II and IX. A large number of mutations associated with early-onset OA have been identified in these collagens and mouse models for studies of pathogenetic mechanisms underlying disease progression are available. Studies in the laboratory resulted in the identification of the first mutations in collagen IX and X in humans and established relevant mouse models. During the past 5 years, detailed molecular studies of the OA disease process in the knee joints of collagen IX and XI mutant mice have been conducted. The results indicate that disease progression in both mutants is associated with a time-dependent series of specific molecular changes that eventually result in loss of articular cartilage. Importantly, similar changes are observed even in wild-type mice, in which OA is initiated by surgical mobilization of the medial meniscus, and in samples of articular cartilage from OA patients undergoing joint-replacement surgery.

An update of genetic influences in OA was given by T Spector. He stated that up to 50% of variance of OA in the hands, knees and hips is accounted for by genetic factors. Reports of significant associations for candidate genes for common forms of OA of the knee and hip now include over 50 genes, and over a dozen have now been replicated independently. These include the vitamin D receptor, ets-related gene, cartilage intermediate layer protein, *Col2A1*, *AACT*, bone morphogenetic protein (*BMP*)-2, frizzled-related protein precursor, a disintegrin and metalloproteinase domain (*ADAM*)12, interleukin (*IL*)-1, IL-1-receptor antagonist, asporin, *LRCH1*, matrillin3, cartilage oligomeric matrix protein (*COMP*) and osteoprotegerin. Linkage studies using families and affected sib pairs, to date, have demonstrated a number of significant replicated loci, especially areas on chromosome 2q and 19.

J Loughlin presented both genetic and functional data that support a role for downstream *cis*-acting regulatory elements of MHP5 as OA susceptibility loci.

A Valdes presented data that indicate that, when using a multiple gene approach, a higher genetic risk prediction is achievable in women with OA.

Pathogenesis of OA

The introductory lecture *Cytokines, proteases and growth factors in pathophysiology of osteoarthritis: what are their levels of guilt?* was given by JM Pelletier. Current knowledge points to an important involvement of the metalloprotease (MMP) class in the OA process, and collagenase-3 or MMP-13 was demonstrated to play a major role in cartilage degeneration. It has been suggested that another enzyme, aggrecanase-2 or ADAMTS-5, is responsible for the proteolysis of cartilage aggrecan. Growth factors are among the factors that may be involved in cartilage regeneration. Among these, transforming growth factor-β and insulin-like growth factor-1 have been studied extensively with respect to their expression and roles in OA. Recently, others, such as the BMPs, have received more attention regarding their role in OA. BMPs are known for their role in the maintenance and repair of bone, cartilage and other tissue in adults. Interestingly, BMP activity/availability can be controlled by specific antagonists. A role for some BMP antagonists in OA has been demonstrated. Importantly, in OA cartilage, a differential topographical distribution and regulation was found between some members of the BMP antagonists in OA chondrocytes, suggesting their appearance at different stages during the OA process and/or that they play different roles. Even if cartilage destruction characterizes the OA condition, synovial inflammation is of fundamental importance in the progression of cartilage lesions in this disease. Findings point to the importance of proinflammatory cytokines in the catabolic process of OA, IL-1β being the prime cytokine involved.

Biomarkers

Many abstracts covered the still attractive field of potential biomarkers of cartilage metabolism in serum or urine. Cibere and colleagues have tested the usefulness of a battery of biomarkers (serum and urine C2C, C1, 2C, 846 epitope, carboxy propeptide II, cardiotoxin-II, COMP and hyaluronic acid [HA]) in the diagnosis of early knee OA. Addition of biomarkers to clinical and imaging findings improved prediction dramatically in early OA but not in late OA.

Biochemical markers were studied in radiographic subtypes of familial OA in multiple sites (Genetics osteoARthritis and Progression [GARP] study). Using a large well-characterized study, in which we evaluated most of the available molecular markers for bone synovial and cartilage metabolism, we were able to observe three components that may reflect different molecular mechanisms: bone turnover, inflammation and synovial degradation. The data suggest that these components may contribute differently to radiograpic OA at different joint sites, the authors suggested.

Nonsurgical therapies of OA

Several very interesting abstracts were presented. T Neogi and colleagues presented a study of the effect of alendronate on progression of spinal osteophytes. They observed a group of 200 patients from the original Fracture Intervention Trial (FIT), who were treated with alendronate (5/10 mg/day) or placebo for 3 years. Alendronate was associated with less osteophyte progression than placebo. This suggests a role for bisphonates in altering the process of osteophyte formation, which may be due to the direct effects on enchondral ossification processes or on OA.

R Raman presented results of a randomized controlled trial (RCT) comparing Hylan G-F 20 with sodium hyaluronate in knee OA. The trial included 356 consecutive patients with OA, who were followed for 12 months and standard measurements were used. Although both treatments offered significant pain reduction, it was achieved earlier and sustained for a longer period in patients treated with Synvisc®. Patients treated with Synvisc have demonstrated an early increase in activity levels, as evidenced by the Western Ontario and McMaster Osteoarthritis Index, UCLA and Tegner scores. Both treatments were well tolerated; however, a local reaction of pseudo-sepsis was observed with Synvisc in one patient. The total treatment cost, both for the patient and the hospital, is higher with Hyalgan®. From this study, it appears that clinical effectiveness and general patient satisfaction are better amongst patients who received Synvisc.

T Kvien presented data of a randomized controlled trial in hand OA. The tested drug was a novel synthetic drug candidate, CRX-102, comprising of dipyramidole and low-dose prednisolone. CRX-102 was statistically superior to placebo at 42 days for the following end points with intention-to-treat analyses: AUStralian/CANadian Osteoarthritis Hand Index (AUSCAN) pain, joint pain visual analog scale (VAS) and patient global VAS. The difference for AUSCAN stiffness was borderline significant. With the completer analyses, significant group differences were also observed for tender joint count and swollen joint count, and the AUSCAN function subscale was borderline significant ($p = 0.08$).

Symptomatic slow-acting drugs in OA

The aim of the workshop and panel discussion was to review efficacy of the SYSADOA group (glucosamin, chondroitin sulfate, diacerein and HA) from the viewpoint of evidence-based medicine.

HA was reviewed by RD Altman. He concluded that intra-articular HA therapy is a useful and safe course of therapy for OA of the knee and likely several other joints involved with OA. Not all patients respond; among those responding, many are nearly pain free. More research is needed in several aspects of this therapy, for example, spacing of injections, timing of repeat series of injections, significance of HA size and significance of the crosslinking mechanism of action. HA will continue to have a role in the therapy of OA for the foreseeable future.

Diacerein is an IL-1 inhibitor registered as a drug in several European countries. The results of a meta-analysis of 19 clinical trials provided evidence for a beneficial, statistically significant, as well as clinically relevant, efficacy of diacerein on pain and the functional status in patients suffering from hip and knee OA. The number of patients included in this meta-analysis, 1328 diacerein-treated patients and 1309 patients in the comparators groups (placebo or NSAID), gives the basis for well founded conclusions to be drawn from this investigation. It could be shown that diacerein was superior to placebo and as effective as NSAIDs with respect to pain reduction as well as to the improvement of function, which are considered to constitute major response criteria in OA during the treatment period. As functionality is highly dependent upon pain, its reduction relates directly to the improvement of functional status.

The majority of good quality randomized controlled trials have confirmed symptomatic efficacy of chondroitin sulfate in knee OA, which was also shown by a meta-analysis. The recently completed STudy on Osteoarthritis Progression Prevention (STOPP) has also confirmed previous studies, with results demonstrating a structure-modifying effect at 2 years.

Glucosamin

Glucosamin efficacy and safety was reviewed by K Pavelka. In the introduction, he mentioned some aspects which can explain different effect size and heterogeneity in clinical trials. Studies in Europe have mostly been performed with glucosamin sulfate (GS), but studies in the USA have mostly involved glucosamin hydrochloride. Bioavailability of GS is probably higher than of GS chloride, and sulfate itself may have its own antiarthrotic activity. There are, of course, big differences in study design, patients' populations and used rescue medications. In this respect, results of the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) and Glucosamine Unum In Die Efficacy (GUIDE) studies were discussed. Two large, 3-year, randomized, controlled studies have also documented structure modifying effects of GS.

There were also significantly less ($p = 0.03$) total knee replacements in the follow-up of patients treated by GS in comparison with placebo.

Conclusion

The World Congress on Osteoarthritis in Prague has clearly reflected increased interest and understanding of the pathophysiology of OA. The number of research laboratories with an interest in OA has increased and many positions are held by young investigators, which was evident in the Prague audience. OARSI is a leading force in OA research. The OARSI Congress, as a global forum for basic scientists, clinical investigators, clinicians, radiologists, orthopedics, rheumatologists, industry scientists, policy makers and patients, was a big success.

The congress venue and Prague in the Christmas advent time provided a charming setting, contributing to the success of the event and positive response of its participants.

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