application of direct measurements of change in cartilage on MRI. The design of MRI-based efficacy studies includes decisions on sample size, based on estimations of statistical power derived from prior data or expectations concerning progression. The sample size depends on (a) the expected rate of progression in participants treated with placebo, (b) the minimum size of drug effect judged to be clinically relevant, or rate of progression expected in the active treatment arm(s), (c) the variation in progression rate that occurs between participants, and (d) the precision of the assay and potential technique. Despite the infirmity of older studies in persons with knee OA suggesting rates of change for cartilage volume loss in the range of 5–7% per year, more recent studies including from the OAI have produced more conservative estimates in the range of 1–3% per year with substantive variability. To date despite major advances in measurement methods, structure-modifying efficacy has not been convincingly demonstrated for any of the existing pharmacologic agents. Current trials have wanted for more responsive outcome measures both for symptoms and structure in order to identify change.

Methods: Thus conservative study designs based on large x-ray and MRI progression series currently in the public domain require large sample sizes. If we could confidently design studies based on smaller sample sizes and/or shorter study durations, this would reduce the resource implications for MRI based interventional studies.

Results: An increase in the study power could be gained by selecting participants that have features that predict rapid progression in future studies. Several studies have suggested that baseline clinical, biomarker and radiographic features are predictive of more rapid progression of cartilage loss in the medial compartment of the knee. These include increased body mass index (BMI), an increased level of type II collagen C-terminal degradation products detected in the urine, the presence of varus malalignment at the tibiofemoral joint, the presence on MRI of subchondral bone marrow lesions or meniscal abnormalities. Such non-specific benefits could result from a patient’s response to placebo effects by use of a placebo control. However, some investigators have questioned whether the placebo effect exists at all, preferring to explain most practitioners’ satisfaction with knee OA (0.54, 95% CI 0.49, 0.6) and lowest for hip OA (0.37, 95% CI 0.21, 0.53) perhaps implying that hip OA is more severe disease and less amenable to non-specific effects.

Conclusions: Although regarded largely as a “nuisance” in RCTs, it is apparent that non-specific effects of treatment in OA confer greater benefit in terms of symptom improvement than the effect derived from the more specific effect of any one treatment. This has clear implications for design of RCTs. More importantly, it emphasises the potential major role for non-treatment effects in the medical care of people with OA and should encourage us to investigate ways of optimising such benefits.

I-7 PLACEBO RESPONSE IN OA TRIALS

M. Doherty. University of Nottingham, Nottingham, UNITED KINGDOM

Purpose: Clinical evidence of non-specific treatment effects, often termed “placebo effect”, has been documented in a wide range of conditions. Such non-specific benefits could result from a patient’s response to observation and assessment (Hawthorne effect), the administration of a therapeutic treatment or ritual (placebo treatment), or the patient-practitioner interaction. Randomised controlled trials (RCTs) to investigate the benefits of a treatment attempt to take into account such non-specific effects by use of a placebo control. However, some investigators have questioned whether the placebo effect exists at all, preferring to explain improvements from baseline on placebo in terms of natural disease remission or chance regression to the mean. Recently we undertook a systematic review and meta-analysis of RCTs in OA to determine whether there is evidence for placebo effects in OA and to examine potential determinants of the size of such effects.

Methods: A systematic literature search was undertaken using Medline, EMBASE, Scientific Citation Index, CINAHL and Cochrane Library. Randomised placebo controlled trials in OA were included. The placebo effect was estimated as the effect size (ES) – the standard mean difference between baseline and endpoint. This was compared with the ES obtained from untreated (observation) controls. ES for pain was the primary outcome. Statistical pooling was undertaken as appropriate and 95% confidence intervals (CI) was used for comparison. Quality of trials was assessed and potential determinants of placebo effect were examined using multiple regression analysis. Partial regression coefficient (β) was used to present the adjusted size of the association.

Results: We identified 198 trials with 193 placebo groups (16,364 patients) and 14 untreated control groups (1,167 patients) that met our inclusion criteria. These included a range of therapies (non-pharmacological, pharmacological and surgical treatments). The following results were obtained:

1. Placebo was effective at relieving pain (ES = 0.51, 95% CI 0.46, 0.55). This effect was superior to untreated control (ES = 0.03, 95% CI –0.13, 0.18), supporting placebo as a real entity.
2. Placebo also improved function (ES = 0.49, 95% CI 0.44, 0.54) and stiffness (ES = 0.43, 95% CI 0.38, 0.49), but the highest ES was for physician global assessment (ES = 0.66, 95% CI 0.53, 0.78). No improvements were seen for more objective measures such as quadriceps strength, knee circumference or range of movement.
3. Placebo ES for pain relief was higher with treatments that had a larger effect, perhaps reflecting greater expectancy of efficacy from the patient.
4. Placebo ES increased as baseline pain and sample size increased.
5. Route of delivery affected placebo ES for pain, with highest effects seen when given by injection (higher with multiple than single injections), needing, and topical application.
6. Placebo ES for pain was highest for hand OA (0.80, 95% CI 0.65, 0.96), intermediate for knee OA (0.54, 95% CI 0.49, 0.6) and lowest for hip OA (0.37, 95% CI 0.21, 0.53) perhaps implying that hip OA is more severe disease and less amenable to non-specific effects.

I-8 OARSI-OMERACT SET OF CRITERIA IN KNEE/HIP OSTEOARTHRITIS TO BE USED AS A HARD ENDPOINT IN CLINICAL TRIALS EVALUATING POTENTIAL DISEASE-MODIFYING DRUGS

L. Gossec. Cochin Hospital, Paris Descartes University, Paris, FRANCE

Purpose: Little is known about the natural course of deterioration of pain, physical function or joint structure as a result of hip or knee osteoarthritis. An international OARSI/OMERACT working group was created; the objectives are to develop pain, physical function and structure states that represent the progression from early to late disease for individuals with OA of the hip and knee. These states are planned to be used as a “hard endpoint” in potential disease-modifying drug trials, with some states defining “theoretical need for total joint replacement”.

Methods: New questionnaires were created to assess pain and functional impairment. Structural assessments have been compared and structural severity was defined as joint space width loss on radiographs. A large multicenter study is ongoing to assess these criteria.

Results: Work is ongoing. Current results will be presented at the OARSI meeting.

Conclusions: The final objective will be to combine the 3 domains (pain, function and structure) and to create a composite index to define states of severity and “theoretical need for total joint replacement” in hip/knee osteoarthritis.

I-9 TRADEOFFS BETWEEN PAIN RELIEF AND THE RISK OF SIDE EFFECTS IN THE TREATMENT OF OA: THE PATIENT’S PERSPECTIVE

J. Kopeć1, C.G. Richardson1, H. Llewellyn-Thomas2, A. Klinkhoff1, A. Carwell3, A. Chalmers1, 1University of British Columbia, Vancouver, BC, CANADA, 2 Dartmouth Medical School, Hanover, NH, USA, 3 Dalhousie University, Halifax, NS, CANADA

Purpose: Therapeutic decisions in osteoarthritis (OA) often involve trade-offs between accepting risks of side effects and gaining pain relief. Previous studies suggested that the risk of side effects affected treatment preferences but data on patients’ preferences for specific trade-offs between pain relief and each side effect of treatment in OA are scarce. Our objectives were (1) to determine patients’ maximum acceptable risk increments (MARI) for different adverse effects from OA medication and (2) to identify predictors of these preferences.

Methods: Participants were individuals diagnosed with OA of the hip or knee according to standard ACR criteria, age 45–74, able to understand English and mentally competent. They were stratified into three categories of disease severity — mild, moderate, and severe. MARI were measured with a probabilistic threshold technique (TT). Risk and pain levels in the TT scenarios were controlled for in a 2 × 2 randomized factorial design. Clinical, sociodemographic, and psychological characteristics (decisional conflict and locus of control) of the participants were assessed using a self-administered questionnaire.

Results: 196 subjects participated in the study. For most side effects, higher initial-risk levels in the TT tasks were associated with subjects’ reports that they would be willing to accept higher additional risks. Depending on the initial level of risk and pain relief, mean MARI ranged from 3% to 5% for heart attack/stroke, 5% to 8% for stomach bleed, 13% to 21% for hypertension, 22% to 33% for fluid retention, and 23% to 35%
for dyspepsia. Age, gender, education, physical and mental health, pain, disability, and locus of control were not associated with MARI.

Conclusions: This study quantified osteoarthritis patients' preferences toward trade-offs between the risk of specific side effects of treatment and pain relief. As expected, the average additional risk that would be acceptable to subjects varied by side effect and increased in conjunction with the amount of potential pain relief. For all side effects, the acceptable level of risk for a given level of pain relief varied substantially among the subjects. Demographic, clinical, and psychological factors did not explain the variation in trade-off preferences. The study demonstrated the usefulness of the probabilistic threshold technique in eliciting preferences for trade-offs between the risk of side effects and pain relief. These observations are important for the development of practice guidelines for physicians and patients' decision aids that can foster individualized, evidence-based yet preference-sensitive care for patients with OA.

---

**[I-10] INTRA-ARTICULAR THERAPIES FOR OA: TARGETS OF INTEREST FOR INTRA-ARTICULAR THERAPY AND STRATEGY TO PROMOTE INCREASED EFFICACY**

X. Chevalier Sr. Hôpital Henri Mondor, Creteil, FRANCE

**Purpose:** No treatments capable of slowing the osteoarthritic process have been so far. Intra-articular treatment is a promising new approach that targets locally released cytokines and proinflammatory mediators in the synovial fluid. Furthermore, intra-articular treatment may be the best way to access the cartilage and synovial membrane and offers a better risk-benefit ratio than systemic treatment.

**Methods:** Large review of the literature concerning i.a therapies was performed excluding current intra-articular treatments which are available, namely, glucocorticoid injection, hyaluronic acid injection, and joint lavage.

**Results:** Targeted treatments designed to restore the balance between prodegradative cytokines and anabolic factors must be developed. IL-1 and TNFα are the most powerful cytokines in OA. Cytokine blockers can be injected intra-articularly, either directly or via gene therapy. Intra-articular injection of IL-1 receptor antagonist (IL-1ra) produced promising results in animal models of OA. IL-1ra injection is well tolerated in humans. However, in the only randomized controlled trial, a single IL-1ra (50 or 150 mg) injection for knee osteoarthritis had little effect, possibly because of the short half-life of this cytokine antagonist. Intra-articular TNFα antagonist therapy has not been evaluated in clinical trials in humans. Downstream from IL-1 and TNFα, caspases can be blocked by direct injection of caspase inhibitors. Synovitis is thought to be involved in OA progression and therefore constitutes a major target. Depletion of synovial-membrane macrophages is associated with decreased metalloproteinase expression. Injection of an agent that blocks bone remodeling is an original and appealing approach. In mice, intra-articular injection of osteoprotegerin decreased the severity of OA lesions. Injection of anabolic factors might promote cartilage repair, thereby stabilizing the intra-articular process. Intracellular injection of encapsulated bFGF microspheres holds some promise. TGFα is an extremely powerful stimulant of cartilage repair but also induces synovial membrane fibrosis and osteophyte growth. To avoid these adverse effects, gene therapy using both TGFβ and Smad 7 has been used in experimental models of OA. The short half-lives of growth factors and cytokine antagonists indicate a need for developing new delivery strategies, such as liposomes, microspheres, and gene therapy, all of which exhibit limitations.

**Conclusions:** Intra-articular therapy holds promise for the treatment of OA, although many issues await resolution.

---

**[II-12] VALUE OF AUTOLOGOUS CELL TRANSPLANTATION IN THE TREATMENT OF OSTEOSTEOARTHRITIS**

A. Facchini 1, B. Griggolo 2, G. Lisignoli 2, C. Cavallino 1, G. Desando 1, G. Grasso 1, M. Fini 2, R. Giardino 1.

1Istituto Ortopedico Rizzoli/University of Bologna, Bologna, ITALY, 2Istituto Ortopedico Rizzoli, Bologna, ITALY

**Purpose:** Chondrocyte transplantation (ACT) has been a widely used clinical strategy in the repair of damaged cartilage from lesions resulting from traumatic injuries. In the last decade, good clinical results have been obtained together with the formation of a new tissue with many hyaline features. More recently, suitable scaffolds loaded with chondrocytes have been used to hold the cells in the defect site, thus, permitting their proliferation, differentiation and maintenance of the chondrocyte phenotype. We explored the ATAP approach to treat osteoarthritis (OA) lesions by using an experimental animal model of OA into which autologous marrow-derived mesenchymal stem cells (MSCs) were seeded onto a hyaluronan-based scaffold (Hyaff®-11, Fidia Advanced Biopolymers, Abano Terme, PD, Italy) that was surgically positioned on the cartilages lesions of the knee.

**Methods:** Rabbit knee joints were bilaterally subjected to anterior cruciate ligament transection (ACL T) to surgically induce OA. Autologous rabbit MSCs have been isolated from the bone marrow, expanded in vitro and loaded on a hyaluronan polymeric scaffold (Hyaff®-11). After 8 weeks, necessary to the development of cartilage surface damage, animals were treated with MSCs seeded onto Hyaff®-11 scaffold in the left condyle and with Hyaff®-11 scaffold in the right condyle (sham operated). In the left knee (ACL T operated), rabbits with ACL T were used as control. All the animals were sacrificed at 3 and 6 months after surgery. Morphological, histological, histomorphometric and immunohistological evaluations were performed.

**Results:** OA changes developed in all animals subjected to ACL T. The predominant macroscopically observed OA changes were mild (lateral femoral condyle) or moderate (medial femoral condyle) ulcerations. Articular cartilages harvested after 8 weeks from ACL T and stained with Safranin-O clearly showed a superficial fibrillation with microscopic cracks and proteoglycan depletion in the cartilage matrix particularly in the medial condyle. At 3 and 6 months the untreated cartilage presented the progression of OA process with evident signs of matrix loss extended to deep zones of cartilage and particular evident in the medial condyle. The animals treated with MSCs-HA scaffolds showed a better matrix organization, a higher presence of proteoglycan component and normal distribution of the cells together with an increase in collagen II expression in comparison with rabbits treated with HA scaffold alone or the untreated groups. In the animals treated with MSCs-HA scaffolds histomorphometric parameters showed a decrease of modified Mankin score after 3 and 6 months after the treatment.

**Conclusions:** The present study demonstrates that the use of MSCs loaded on a HA scaffold can contribute to the regeneration of a new cartilage tissue in a rabbit model of OA. It is possible to speculate that the beneficial effects of MSCs might reflect, in part, some trophic and protective activities they exert on injured cells and tissue, together with their property to differentiate into chondrocytic lineage.