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Measurement of structure (disease) modification in osteoarthritis

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Summary

Osteoarthritis (OA) research is beginning to focus on developing structure (disease) modifying treatments that will stabilize or reverse morphological changes, thereby altering the underlying pathologic process. The ability of anti-arthritic agents to modify the course of disease has been investigated in a limited number of clinical trials. Agents studied in published clinical trials include glycosaminoglycan-peptide complex (GP-C), glycosaminoglycan polysulfate (GAGPS), diacerein, and glucosamine sulphate. These clinical trials have been difficult to interpret and compare because the patients studied are often inadequately characterized or are not comparable across studies. Studies also vary with respect to the outcome measures analyzed and the methodology applied to measurement and data analysis. Further, in general, the rate of radiographic progression of OA is slow and is not consistent across populations and patients with varying disease severity. In man, the radiograph has been the gold standard for evaluating treatments. Further longitudinal validation of the radiograph is needed. As techniques improve, variation in the system and the number of patients needed in studies are decreasing. It may be that the radiograph will not achieve the needed degree of validation and will be supplanted by magnetic resonance imaging as the surrogate marker of joint status.

Key words: Osteoarthritis, X-ray progression, Structure-modifying drugs, Criteria.

Structure modifying treatments for osteoarthritis

Currently available treatments for osteoarthritis (OA) combine nonpharmacologic and pharmacologic regimens directed toward relief of symptoms. At present, no drugs or devices have been consistently shown to modify joint structure or reverse joint pathology. Nevertheless, considerable research is now being focused on structure modification. The objective of structure modifying therapies is to prevent, stabilize or reverse the morphological changes of the cartilage in OA, thereby altering the underlying pathologic process. These treatments may or may not have an independent effect on symptoms. Disease-modifying therapies include anti-inflammatory drugs, anti-osteoclastic agents, cytokines/growth factors, enzyme inhibitors, gene therapy, non-sulfated glycosaminoglycans, a variety of sulfated sugars, and stem cell/transplantation. Demonstration of the benefits of treatment will depend upon the trial design and outcome parameters selected.

Disease classification

Clinical trials of OA therapies are difficult to interpret and compare because the patients studied are from different populations, are often inadequately characterized or are not comparable across studies. Some years ago, a check list for classification of OA of the knee based on the results of clinical examination, laboratory tests, and radiographs was proposed (Table I)[1]. According to this system, patients are classified as having OA if they have knee pain and radiographic osteophytes. Knee pain cannot be referred and has to be present for most days of the prior month. In the absence of osteophytes, patients are classified as having OA if they have knee pain, a synovial fluid examination consistent with OA, morning stiffness of 30 min or less, and crepitus on active motion. In patients for whom synovial fluid has not been examined, age of 40 years or older can be used as a surrogate for the synovial fluid criterion. This check list has been shown to have a sensitivity of 94% and a specificity of 88%. Although, these criteria are useful for classification of disease and may not be specific enough for use in selecting patients for trials of structure-modifying agents. Selection of a well-characterized subset of patients makes possible detection of differences between treatment groups that may not be apparent in studies of less well-defined populations.

Most commonly, patients with OA are classified into 2 subgroups: patients with primary or idiopathic OA, in whom no known prior event or disease is related to the OA, and patients with secondary OA, in whom no known event or disease is related to OA. The subclassification criteria proposed by the American College of Rheumatology are presented in Table II[1,2]. Primary or idiopathic OA is subdivided according to whether it is localized or generalized.

Table I

Checklist for classification of osteoarthritis of the knee (adapted from Reference[1] with permission from W.B. Saunders Company.)

Knee pain (most days of prior month)
• Major
Radiographic osteophyte
• Minor criteria
Synovial fluid (SF) findings consistent with osteoarthritis (age ≥40 years can be used as surrogate for SF if SF is not examined)
Morning stiffness (<30 min)
Crepitus (active motion)
Sensitivity 94% Specificity 88%

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Table II
The American College of Rheumatology Classification for Subsets of Osteoarthritis (Reprinted from Reference[1] with permission from W.B. Saunders Company.)

I. Idiopathic
A. Localized
   1. Hands: Heberden's and Bouchard's nodes (nodal), erosive interphalangeal arthritis (nonnodal), scaphometacarpal joint, scaphotrapezial
   2. Feet: hallux valgus, hallux rigidus, contracted toes (hammer/cockup toes), talonavicular
   3. Knee
      a. Medial compartment
      b. Lateral compartment
      c. Patellofemoral compartment (chrondromalacia)
   4. Hip
      a. Eccentric (superior)
      b. Concentric (axial, medial)
      c. Diffuse (coxae senilis)
   5. Spine (particularly cervical and lumbar)
      a. Apophyseal
      b. Intervertebral (disc)
      c. Spondylosis (osteophytes)
      d. Ligamentous (hyperostosis [Forestier's disease or diffuse idiopathic skeletal hyperostosis])
   6. Other single sites: shoulder, temporomandibular, sacroiliac, ankle, wrist, acromioclavicular
B. Generalized: includes 3 or more areas listed above (Kellgren-Moore)
   1. Small (peripheral) and spine
   2. Large (central) and spine
   3. Mixed (peripheral and central) and spine

II. Secondary
A. Posttraumatic
B. Congenital or developmental diseases
   1. Localized
      a. Hip diseases: Legg-Calve-Perthes, congenital hip dislocation, slipped capital femoral epiphysis, shallow acetabulum
      b. Mechanical and local factors: obesity (?), unequal lower extremity length, extreme valgus/varus deformity, hypermobility syndromes, scoliosis
   2. Generalized
      a. Bone dysplasias: Epiphyseal dysplasia, spondyloapophyseal dysplasia
      b. Metabolic diseases: hemachromatosis, ochronosis. Gaucher's disease, hemoglobinopahty, Ehlers-Danlos
C. Calcium deposition disease
   1. Calcium pyrophosphate deposition disease
   2. Apatite arthropathy
   3. Destructive arthropathy (shoulder, knee)
D. Other bone and joint disorders: avascular necrosis, rheumatoid arthritis, gouty arthritis, septic arthritis, Paget's disease, osteopetrosis, osteochondritis
E. Other diseases
   1. Endrocrine diseases: diabetes mellitus, acromegaly, hypothyroidism, hyperthyroidism
   2. Neuropathic arthropathy (Charcot joints)
   3. Miscellaneous: e.g., frostbite, Kashin-Beck disease, Caisson disease

Disease may be localized to the hands, feet, knees, hips, spine, or virtually any other articulation. Generalized disease may involve small joints, large joints, or a mix of the two with spinal involvement. Secondary OA is subdivided by etiology or associated condition or disease. OA may be secondary to trauma, congenital/developmental abnormalities, calcium deposition, bone and joint disorders, or other conditions, such as endocrine or neurogenic abnormalities. Although many trials are designed to enroll patients with primary or idiopathic OA, these trials often include patients with OA secondary to one or more factors. In such cases, it is difficult to determine the influence of such factors on the study population and the response to treatment. Although studies of broadly defined patient populations allow study conclusions to be generally applied, wide variability across the patients studied increases the sample size of the study population needed to show statistically significant differences between treatment groups and may prevent the recognition of subsets of patients who may benefit from treatment unless extensive stratification is performed.

Outcome measures in arthritis clinical trials

Advances in the diagnosis and treatment of OA have led to re-evaluation of the outcome measures and measurement procedures used in clinical studies of OA. Guidelines for clinical studies of the effects of OA therapies have been published by a number of individuals and groups in the last decade[3–5]. The Outcome Measures in Arthritis Clinical Trials (OMERACT) group recommended a core set of outcome measures for future phase III clinical trials of knee, hip, and hand OA[6]. It was determined that 4 core domains should be evaluated: pain, physical function, patient global assessment, and joint imaging (for studies of ≥1 year). Secondary outcome measures (strongly recommended) included health-related quality of life measures and physician global assessment. Tertiary outcome measures (optional) included measures of stiffness, biologic markers, measures of inflammation, performance-based measures, flares, time to surgery, and analgesic consumption.

The Osteoarthritis Research Society (now the Osteoarthritis Research Society International) also established a Task Force to address the issue of clinical trial guidelines for OA, and in 1996, this group published a set of recommendations for the design and conduct of clinical trials in patients with OA[7]. These recommendations addressed trials of both symptom-modifying drugs and structure-modifying drugs. The guidelines recommend that for studies of potential structure modifying drugs the primary outcome variable should be a measure of joint morphology obtained through imaging techniques or direct visualization (i.e., arthroscopy). Currently, time to joint replacement surgery is not recommended as a primary outcome variable because it appears, at least in part, on factors that are unrelated to disease progression. Patients participating in trials of structure modifying drugs should be evaluated at intervals of about 3 months. Imaging modalities may consist of radiography or magnetic resonance imaging. Computed tomography, ultrasonography, and scintigraphy are other available imaging modalities, but these have not been adequately validated and are not therefore recommended for use in long-term studies. Molecular markers continue to be an area of intense research but have not yet been validated as outcome measures in clinical trials of OA. Arthroscopy measures surface changes of cartilage. Although standardization techniques have been proposed, they have not been uniformly accepted[8].

Problems related to imaging studies

There are multiple problems related to imaging studies. Obtaining reproducible images at successive visits is critical to reliably assess progression of OA. There are numerous sources of variability associated with measurement of joint space width on radiographs, including differences in patient positioning, radiographic procedures, measurement processes, and reading techniques, as well as inter-reader and intra-reader variability. Even digitized computer techniques may present problems in terms of how landmarks are identified, where the narrowest point is measured, what is meant by volume, etc. There are also problems associated with magnetic resonance imaging, including variability in patient positioning, precision of measurement, coefficient of variability, and validation of ability to demonstrate change. Long-term studies present a challenge in that the methodology specified in the protocol at the start of the study must be used throughout the trial, even though technological advances lead to dramatic improvements in state-of-the-art methodology as the study progresses[9,10]. Studies that adhere to the protocol throughout their duration are usually criticized for not using the most current imaging methods – even though the most current imaging technique was not the standard at the time the study was initiated.

Radiographic progression of knee osteoarthritis in patients receiving only physical therapy and nonsteroidal anti-inflammatory drugs

Pavelka *et al.*[10] conducted a study to determine the 5-year radiographic progression of OA of the knee in a cohort of 139 patients with idiopathic OA who received only physical therapy and nonsteroidal anti-inflammatory drugs (NSAIDs) as needed. This cohort was the control group for a trial described later. Radiographs were taken at baseline and at the final assessment and evaluated according to the Kellgren-Lawrence (K-L) scale[11], and joint space width was measured according to the Lequesne technique[12]. After 5 years, the overall mean change in joint space width was 0.39±0.95 mm, representing a mean change of 0.078± 0.19 mm per year. The progression in joint space reduction was not linear, being most rapid in the first year. The smallest reductions in joint space width were noted in patients in K-L class 0 or 1, while the greatest reductions in joint space width were noted among patients in K-L class 0 or I, while the greatest reductions in joint space width were noted among patients in K-L class III. Overall, 25% patients had progression of disease, with the highest percentages of patients with progression in K-L classes II (25%) or III (26.8%). Hence, changes in joint space width were small and occurred in only a quarter of the patients over a 5-year period. This slow progression raises the issue of the value of examining progression of joint space narrowing in a general OA population by this technique.

Studies of structure (disease) modifying agents

The ability of anti-arthritis agents to modify the course of disease in man has been investigated by a limited number of trials. Agents studied include glycosaminoglycan-peptide complex (GP-C, Rumalon®; Robapharm, Ltd, Basel, Switzerland) and glycosaminoglycan polysulfate (GAGPS; Arteparon®, Luitpold-Werk, Munich)[9,13,14]; diacerein[15]; and glucosamine sulphate[16].

GP-C AND GAGPS

In the early 1960s, Rejholec and colleagues[14] performed a 10-year, randomized, placebo-controlled study to evaluate the long-term therapeutic effect of GP-C in patients with OA of the hip. The population evaluated consisted of 112 pairs of patients with OA of the hip matched for age, sex, weight, physical stress, joint involvement, and radiologic stage of the disease according to the K-L classification[11]. One member of each pair received GP-C 1 mL injected twice weekly; these patients received 2 series of 25 injections yearly. The second member of each pair (control) received vitamin B_{12} 0.1 mg twice a year.

At the start of treatment, 52 patients in the control group and 52 in the GP-C group had K-L X-ray grades I or II (Fig. 1). At the 10-year follow-up, K-L grades of I or II persisted in 29% of the patients in the control group and in 60% of those in the GP-C group. Sixty patients in the control group and 60 in the GP-C group had K-L X-ray grades III and IV at the start of treatment. At the 10 year follow-up, the number of patients with K-L grades III and IV had increased to 68 (113%) in the control group and had decreased to 52 (87%) in the GP-C group. The severity grade of OA in the GP-C group was significantly lower than in the control group (P<0.005). Joint space width, measured in the standing position, could be compared in 35 pairs of patients after 16 years of treatment. There was significantly less narrowing in the GP-C group (–47%) than in the control group (–75%) (P<0.05). Total hip replacement was needed in 17 patients in the control group, compared with only 6 in the GP-C group (P<0.05). The investigators concluded that the study showed the therapeutic value of treatment with GP-C in OA of the hip.

Nevertheless, the study was criticized on the basis of reproducibility, the applicability of its findings to other types of OA (such as in hands and feet), and the possibility that

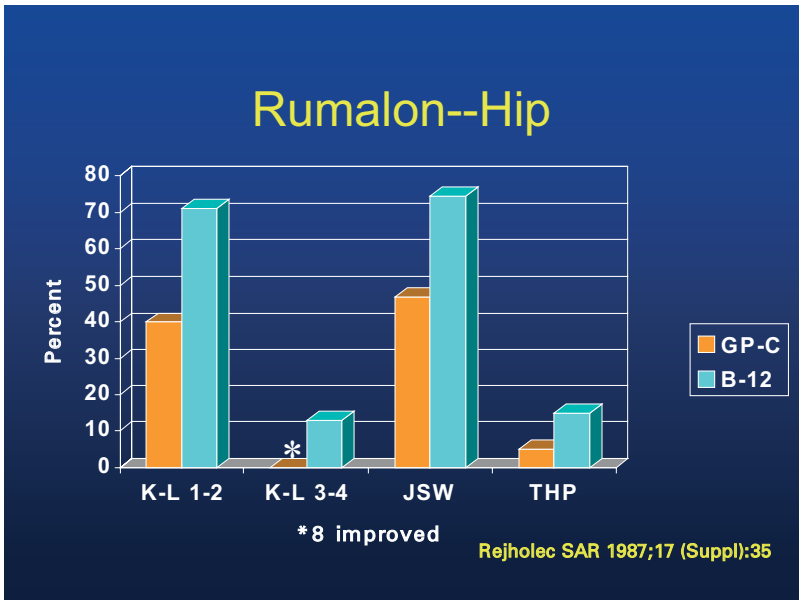

Fig. 1. Results of long-term study of GP-C in 112 pairs of patients treated with GP-C and or vitamin B_{12} (control). K-L 1-2: JSW: Bars represent percentage decrease from baseline in joint space width (JSW) after 16 years of treatment with GP-C (*N*=35) or vitamin B_{12} (control; *N*=35). The change from baseline was significantly greater in the control group than in the GP-C group ($P<0.05$). THP: Bars represent the number of patients in the GP-C group (*N*=112) and vitamin B_{12} (*N*=112) group who required total hip replacement (THP) over the course of the 16-year study.

different results could be found using more current measurement techniques. As a consequence, Rejholec *et al*. performed a study comparing GP-C and GAGPS with standard therapy[14].

The second study was a placebo-controlled trial in 147 patients ≥55 years of age, with K-L grades II and III. Patients received symptomatic treatment (control group), GP-C 1 ml injected twice weekly for 12.5 weeks of each 6-month interval over a 5-year period plus symptomatic treatment (GP-C group), or GAGPS 50 mg injected twice weekly for 7.5 weeks of each 6-month interval over a 5-year period plus symptomatic treatment (GAGPS group). Subjective and objective parameters were measured at baseline, monthly for 4 months, and then every second month until completion of the study at 60 months (or until discontinuation). Patients had assessment of arthritic pain, nocturnal pain, pain on maximum passive movement, NSAID use, working days, knee circumference, maximum flexion, walking time, sit/stand time, and time required for climbing stairs, and physician's global assessment. Radiographs were assessed before entry into the trial and at the end of the trial or after at least 36 months. The roentgenologic criteria evaluated included joint space width, tibial intercondylar eminences, osteophytes, subchondral sclerosis and bone cysts, and marginal defects and bone necroses. The number of surgical interventions was also recorded, as were all side effects.

After 2 years of study, NSAID use increased in the control group but decreased in the GP-C and GAGPS groups. Improvements in symptoms and measures of joint function and status were significantly greater in the two active treatment groups than in the control group. Also, quality of life and ability to work were markedly improved in the two active treatment groups, and in some cases, were better than at baseline. The frequency of surgical interventions was also reduced in these two groups. Both GP-C and GAGPS favorably affected radiographic findings. The percentages of patients in the GP-C and GAGPS groups with no progression of OA were seven and nine times higher, respectively, than in the control group. At the end of therapy, medial joint space widths were significantly less in the active treatment groups than in the control group (Fig. 2).

Pavelka *et al*.[9] initiated further study of GP-C in OA in response to questions concerning methodological issues raised regarding the previous studies. This group conducted a 5-year, randomized, placebo-controlled, double-blind study of GP-C to determine the structure (disease) modifying effect of long-term therapy with GP-C in patients with knee and hip OA[9]. In this study, 277 patients with knee OA and 117 with hip OA received 15 intramuscular injections of GP-C or placebo twice weekly every 6 months for 5 years. NSAIDs and analgesics were permitted at the discretion of the investigator. The outcome measures used in this study were selected on the basis recommendations of an external advisory group set up by the sponsor. The primary outcome measure was changed in radiographic joint space width from baseline to the final visit at 5 years. Joint space width was measured by the method of Lequesne[17], with a ×10 magnifying lens marked with a 20-mm scale at 0.1 mm intervals. This technique was reliable and easy to use. Secondary outcome measures included pain, pain on passive motion, patient global, investigator global, and NSAID consumption.

The drop out rate of this study was low; over 90% of patients completed the study. The results of this trial showed no difference in the progression of joint space narrowing between the GP-C and control groups at the hip or knee (Figs. 3 and 4). At the hip, the mean change in joint space width was –0.22 mm in the placebo group, compared with –0.21 mm in the GP-C group (difference not significant). At the knee, the mean change in joint space width was –0.42 mm in the placebo group, compared with –0.37 mm in the GP-C group (difference not significant).

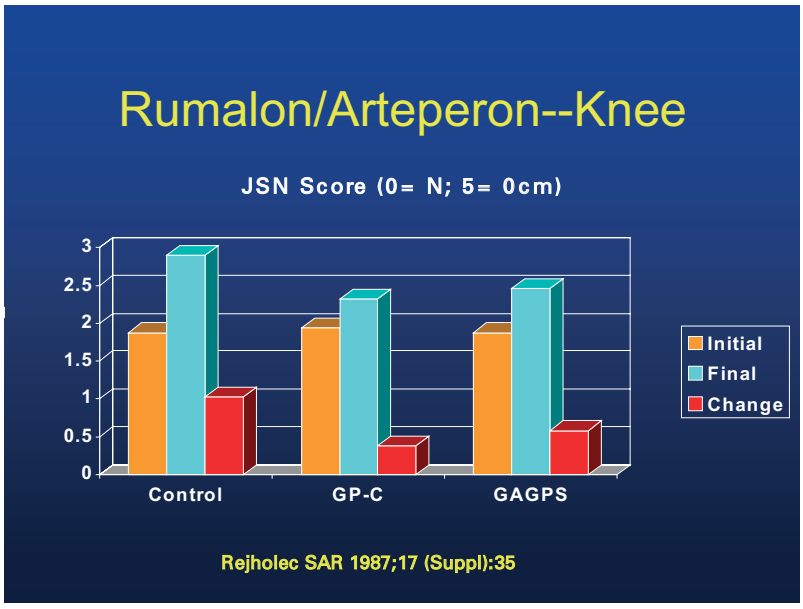

Fig. 2. Degree of narrowing of medial joint space width in patients with knee OA who received symptomatic treatment only (control, *N*=42); GP-C (*N*=47); or GAGPS (*N*=41). Mean values are expressed as scores: 0=normal to 5=joint cavity absent (based on data presented in Rejholec, 1987).

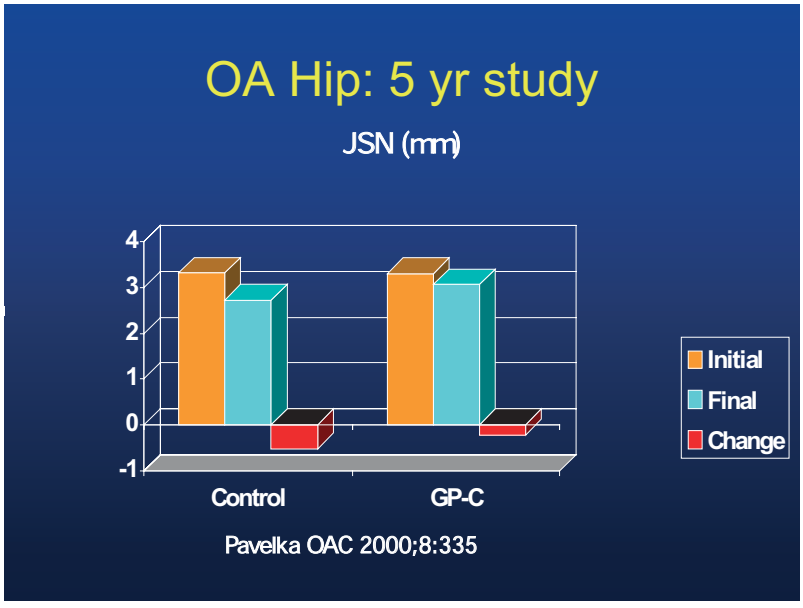

Fig. 3. Mean hip joint space width (mm) at baseline and at the end of treatment with placebo (*N*=59) or GP-C (*N*=58) and change (mm) from baseline in hip joint space width at the end of treatment.

Similarly, there was no difference between the groups in the secondary outcome measures. Unfortunately, the study population was too small to allow for adequate evaluation of subsets of patients. However, in an examination of patients with OA of the hip with joint space width ≥1 mm baseline; noprogression occurred in the 25 patients on GP-C, whereas progression occur in 4/21 (19%) patients in the control group, and the difference approached significance. There are no adequate explanations for the differences between these findings and those reported earlier by Rejholec. The findings may have differed because the effects of GP-C were small, the measurements selected for the study were not adequately sensitive to reveal differences between treatments, or the patient selection criteria used in this study may have influenced the trial results.

DIACEREIN

Dougados *et al.*[15] conducted a randomized, double-blind, placebo-controlled, 3-year study to evaluate the ability of diacerein, a possible interleukin-1 beta inhibitor, to slow the progressive decrease in joint space width observed in patients with hip OA. In this study, 507 patients with primary OA of the hip received oral diacerein 50 mg

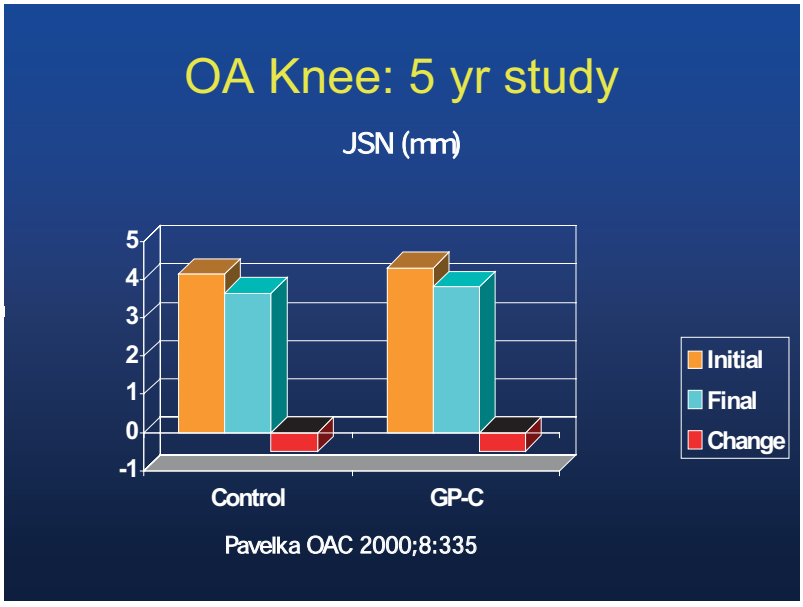

Fig. 4. Mean knee joint space width (mm) at baseline and at the end of treatment with placebo (*N*=139) or GP-C (*N*=138) and change (mm) from baseline in knee joint space width at the end of treatment.

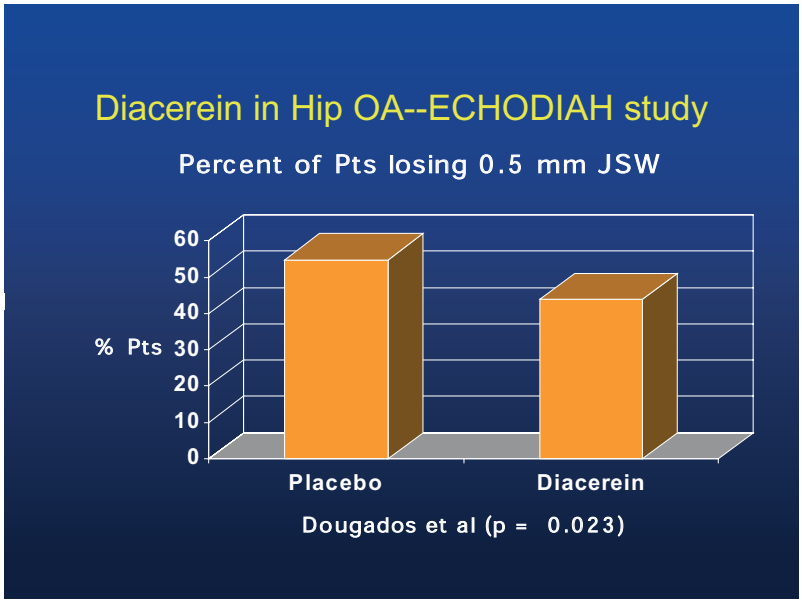

Fig. 5. Percentage of patients treated with placebo (*N*=225) or diacerein (*N*=221) for 5-years who had radiographic progression (decrease from baseline in joint space width of at least 0.5 mm).

twice daily or placebo. The primary end-point of the study was the radiographic progression of OA as determined by the change in joint space width from baseline to the final evaluation.

The percentage of patients with radiographic progression, defined by a joint space narrowing of at least 0.5 mm, was significantly lower in patients receiving diacerein than in patients receiving placebo (51% in diacerein group versus 60% in the placebo group; *P*=0.036). In those patients who completed 3 years of treatment, the annual rate of joint space narrowing was significantly lower in the diacerein group (mean±SD 0.18±0.25 mm/year) than in the placebo group (0.23±0.23 mm/year) (*P*=0.042) (Fig. 5). Diacerein had no apparent effect on the symptoms of OA in this study. The authors concluded that diacerein has a significant structure-modifying effect in hip OA and can retard the progressive decrease in joint space width in affected patients.

GLUCOSAMINE SULPHATE

In a recent study, Reginster *et al.*[16] assessed the effects of glucosamine sulphate on the progression of OA joint

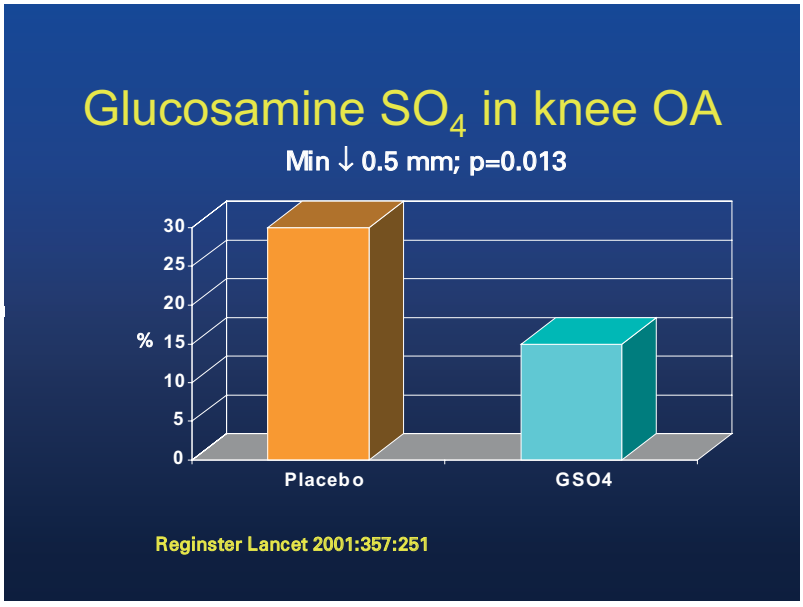

Fig. 6. Percentages of patients treated with placebo (*N*=106) or glucosamine sulphate (GSO_4) (*N*=106) for 3 years who had joint space narrowing of more than 0.5 mm.

structure changes and symptoms in a randomized, double-blind, placebo-controlled trial. In this study, 212 patients with knee OA were assigned to receive glucosamine sulphate 1500 mg or placebo once daily for 3 years. Radiographs were taken of each knee at enrolment and after 1 and 3 years. The primary outcome measure was mean joint-space width of the medial compartment of the tibiofemoral joint. Anteroposterior radiographs were taken with the patient standing with the knee weightbearing and fully extended. The patella was centralized over the lower end of the femur by rotating the lower extremity. The feet were placed a short distance apart, and foot maps were used to re-position the patient. The X-ray beam was parallel to the tibial plateau and fluoroscopically centered on the joint space and parallel to the tibial plateau. Mean joint space width was assessed automatically from digitized images. In addition, changes in joint space width were confirmed by the Lequesne visual method of inspection using a 0.1-mm graduated magnifying glass[18]. Symptoms of OA were assessed according to Western Ontario and McMaster Universities (WOMAC) OA index.

In the intention-to-treat worst scenario analysis of all randomized patients, after 3 years, a mean joint space loss of –0.31 mm was observed in the placebo group, compared with no significant joint space loss (–0.06 mm) in the glucosamine sulfate group (placebo vs glucosamine sulfate, *P*=0.043). After 3 years, 32 (30%) of 106 patients in the placebo group had a mean joint space narrowing of more than 0.5 mm, compared with only 16 (15%) of 106 in the glucosamine sulphate group (*P*=0.013) (Fig. 6). Comparisons of the changes from baseline in the primary WOMAC scores showed that symptoms worsened slightly in placebo-treated patients, whereas they improved in the glucosamine sulfate group. The differences between the mean changes from baseline in the placebo and glucosamine sulphate groups were significant. The authors concluded that administration of glucosamine sulphate over 3 years can prevent structural changes in the joints of patients with OA of the knee with a significant improvement in symptoms. A possible limitation of this study is the use of the radiographic views of the leg fully extended and weight-bearing for assessment of structural changes. It has been suggested that other views may avoid changes in patient positioning that could result from changes in symptom severity during the study. Patients whose symptoms diminish may achieve better knee extension and, as a result, lower apparent joint space narrowing[19]. The findings from this study appear to have been duplicated in a study by Pavelka[20].

Technical aspects of radiographic imaging

Posterior knee cartilage is thicker on the posterior lateral aspect of the condyle, where most of the weight is distributed, and not on the inferior aspect of the condyle, which is reflected in straight leg weight bearing views. This finding in cartilage is consistent with Wolff's Law, which holds that change in the form and function of bones is followed by alterations in their conformation. Hence, an X-ray of a partially flexed, weight-bearing knee is more likely to reflect clinically relevant cartilage thickness.

During assessment joint space width, it should be noted that in the tibial configuration in the medial compartment there is a dip, causing the anterior and posterior lips of the tibial plateau to have a double density on the X-ray. There may be three levels seen: anterior lip, posterior lip and trough of the dip. A fourth level of density often appears from posterior tibial osteophytes. A superimposed anterior and posterior lip is needed with an X-ray beam that runs parallel to the tibial plateau. Fluoroscopic positioning, use of a metal ball to adjust for magnification, and foot maps for repositioning are some of the methods proposed for improving consistency among X-rays that are obtained months apart. Many studies are being conducted to standardize the radiographic techniques. However, it may be that newly developed techniques of magnetic resonance imaging will replace the radiograph as the primary efficacy variable in future structure modifying trials.

Concluding comments

Very few trials have been completed to date that examine the ability for an agent to alter the course of OA. All trials to date have had difficulty because the primary end-point has been hard to define and measure. In man, the radiograph has been the gold standard, since examination of tissue is not practical or ethical. Further longitudinal validation of the X-ray is needed. As radiographic techniques are improved, there is less variation in the system and fewer patients are needed in studies. It may be that the radiograph will not achieve the needed degree of validation and that magnetic resonance imaging will supplant it as the surrogate marker of joint status.

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