

## Structure Modification in Osteoarthritis

a report by

**Olivier Bruyère** and **Jean-Yves Reginster**

*Department of Epidemiology and Public Health, University of Liège*

For decades, the traditional pharmacological management of osteoarthritis (OA) has been mainly symptomatic, despite a lack of evidence of its influence on the duration of the disease and its progression. However, in recent years several sets of guidelines, recommendations or points to consider have been issued by regulatory authorities or scientific groups regarding requirements for the registration of drugs to be used in the treatment of OA. The ideal outcomes currently include pain and function assessment for symptom-modifying drugs, and joint-space narrowing (JSN) assessed by plain radiography for structure-modifying compounds. Taking advantage of these more precise recommendations, several chemical entities have been carefully investigated for the management of OA.

The ideal outcomes currently include pain and function assessment for symptom-modifying drugs, and joint-space narrowing assessed by plain radiography for structure-modifying compounds.

This article provides a summary of the available evidence demonstrating that some compounds can effectively interfere with the structural progression of the disease.

### Avocado/Soybean Unsaponifiables

The unsaponifiable part of avocado (A) and soybean (S) oils (ASU) mixed in a ratio of 1:2 (A1:S2) has been investigated in the treatment of connective tissues, including in OA, for several years. A pilot randomised, double-blind, placebo-controlled trial with follow-up over two years failed to demonstrate a structural effect of ASU in 163 patients with painful hip OA.<sup>1</sup> However, in a *post hoc* analysis a significant difference was detected in the subgroup with a baseline joint-space width (JSW) smaller than 2.45mm: joint space loss was halved in the treated group ( $-0.43 \pm 0.51$ mm) compared with the placebo group ( $-0.86 \pm 0.62$ mm;  $p=0.01$ ). This finding suggests that ASU may have a structure-modifying effect in patients with severe hip OA.

### Chondroitine Sulphate

Chondroitine sulphate (CS) is a major component of the extra-cellular matrix from many connective tissues, including – but not limited to – cartilage, bone, skin, ligaments and tendons. In the articular cartilage, the high content of CS in the aggrecan plays a major role in creating considerable osmotic swelling pressure, which expands the matrix and

places the collagen network under tension. In a pilot double-blind study, JSW measurement on digitalised radiographs of the extended knees was used to compare the effects of CS 800mg/day and a placebo in patients with knee OA.<sup>2</sup> There were 23 patients in each group. After one year, JSW was unchanged in the treated group but had decreased by 0.4mm in the placebo group ( $p<0.005$ ). No significant difference was found for JSW at the narrowest site. The small number of patients for whom end-point values were available (12 in the placebo group and 14 in the CS group) limits the relevance of the results.

Another study randomised a total of 120 patients with symptomatic knee OA into two groups receiving either 800mg CS or placebo per day for two periods of three months during one year.<sup>3</sup> Radiological progression was assessed as a secondary outcome by automatic measurement of medial femoro-tibial JSW on weight-bearing X-rays of both knees. Radiological progression at month 12 showed significantly decreased JSW in the placebo group, with no change in the CS group.

More recently, a randomised, double-blind, placebo-controlled trial randomly assigned 300 patients with knee OA to receive either CS 800mg or placebo once daily for two years.<sup>4</sup> The primary outcome was joint-space loss over two years as assessed by a postero-anterior radiograph of the knee in flexion. The 150 patients receiving placebo had progressive JSN, with a mean standard deviation (SD) joint-space



Olivier Bruyère is Adjunct Professor in the Department of Epidemiology and Public Health at the University of Liège. He also works in the Bone and Cartilage Metabolism Unit of the University of Liège. He is a member of the World Health Organization (WHO) Collaborating Center for Public Health Aspects of Rheumatic Disorders and the Osteoarthritis Section of the Group for the Respect of Ethics and Excellence in Science (GREETES). Professor Bruyère offers editorial expertise for *Archives of Public Health* and is the author of more than 50 scientific publications and book chapters.

E: [olivier.bruyere@ulg.ac.be](mailto:olivier.bruyere@ulg.ac.be)



Jean-Yves Reginster is Professor of Epidemiology, Public Health and Health Economics and Director of the Department of Epidemiology and Public Health at the University of Liège. He is also Head of the University Centre for Investigation in Bone and Articular Cartilage Metabolism and Director of the World Health Organization (WHO) Collaborating Center for Public Health Aspects of Rheumatic Disorders. An active member of a variety of associations, Professor Reginster is President of the Group for the

Respect of Ethics and Excellence in Science (GREETES) and General Secretary of the International Osteoporosis Foundation (IOF) and the Belgian Bone Club (BBC). He has published more than 400 original articles in a variety of reputable medical journals and has also contributed to more than 60 chapters in a variety of books.

loss of  $0.14\pm 0.61$ mm after two years ( $p=0.001$  compared with baseline). In contrast, there was no change in mean JSW for the 150 patients receiving CS ( $0.00\pm 0.53$ mm;  $p$  = insignificant compared with baseline). Similar results were found for minimum JSN. The differences in loss of joint space between the two groups were significant for mean JSW ( $0.14\pm 0.57$ mm;  $p=0.04$ ) and for minimum JSW ( $0.12\pm 0.52$ mm;  $p=0.05$ ).

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## Diacerein

In a randomised, double-blind, placebo-controlled three-year study, 507 patients with primary OA of the hip – according to American College of Rheumatology (ACR) criteria – received diacerein 50mg or placebo twice daily.<sup>5</sup> The minimal hip JSW was measured by a central reader on annual pelvic digitalised radiographs using a 0.1mm graduated magnifying glass. No significant difference in the rate of joint-space loss was found between the two groups in the intention-to-treat analysis. In the study completers, however, joint-space loss was significantly reduced in the diacerein group ( $-0.18\pm 0.25$ mm) compared with the placebo group ( $-0.23\pm 0.23$ mm;  $p=0.042$ ). In addition, the percentage of patients with definite joint-space loss ( $>0.5$ mm, which was the measurement error counted as two SDs of the intra-observer reproducibility) was smaller in the diacerein group than in the placebo group (50.7 versus 60.4%;  $p=0.036$ ). Total hip replacement of the signal hip during the study and during the three months following discontinuation of the study treatment was performed in 87 patients: 14.5% in the diacerein group and 19.8% in the placebo group. The comparison of the two groups showed a trend in favour of diacerein treatment that did not reach statistical significance ( $p=0.29$ ), but it should be emphasised that the study was not powered for this outcome measure.

## Doxycycline

The structural effect of doxycycline was recently assessed in 431 obese women aged 45–64 years with unilateral radiographic knee OA who were randomly assigned to receive 30 months of treatment with doxycycline 100mg or placebo twice daily.<sup>6</sup> The co-primary end-points were the evolution of JSN in the index knee (which exhibited radiographic evidence of established OA at baseline) and in the contralateral knee (in which radiographic evidence of tibiofemoral OA was absent at baseline). After 16 months of treatment, the mean SD loss of JSW in the index knee in the doxycycline group was 40% lower than that in the placebo group ( $0.15\pm 0.42$  versus  $0.24\pm 0.54$ mm); after 30 months, it was 33% lower ( $0.30\pm 0.60$  versus  $0.45\pm 0.70$ mm). In contrast, doxycycline did not have an effect on JSN in the contralateral knee; therefore, the two co-primary end-points were not successfully met and this study should be considered a failure. The use of a manual measurement of JSW instead of the most updated automated technologies following X-ray digitalisation, as well as the

fact that the procedure was not blinded for measurement of JSW to the sequence of the radiographs (i.e. baseline, month 16, month 30), are potential methodological issues that deserve further debate.

## Glucosamine Sulphate

Glucosamine is an aminosaccharide, acting as a preferred substrate for the biosynthesis of glycosaminoglycan chains and, subsequently, for the production of aggrecan and other proteoglycans and cartilage. To test the long-term effects of glucosamine sulphate (GS) on the progression of OA knee joint structural changes and symptoms, 212 patients with knee OA were randomly assigned in a double-blind fashion to continuous treatment with GS 1500mg or placebo once daily for three years.<sup>7</sup> Weight-bearing, anteroposterior radiographs of each knee were taken at enrolment and every year for three years. Total mean JSW of the medial compartment of the tibiofemoral joint was assessed by digital image analysis based on a validated computerised algorithm. After three years, placebo-treated patients had an average JSN of  $-0.31$ mm (range:  $-0.48$  to  $-0.13$ ), while no JSN ( $-0.06$ mm, range:  $-0.22$  to  $0.09$ ) occurred in the group treated with GS ( $p=0.043$ ). Furthermore, the percentage of patients who experienced a clinically relevant ( $>0.5$ mm) mean JSN after three years was significantly lower in the GS group (15%) than in the placebo group (30%;  $p=0.013$ ).

A five-year follow-up evaluation of patients from this trial was performed to assess long-term outcomes of disease progression after the end of the study.<sup>8</sup> The primary end-point of this follow-up study was the occurrence of OA-related joint surgery. Of the 177 patients participating in this follow-up evaluation, 26 (14.7%) underwent

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OA-related lower-limb surgery during the follow-up. Twice as many patients from the former placebo group underwent surgery, with a 48% decrease in risk with GS that was borderline statistically significant ( $p=0.06$ ). The time-to-event analysis confirmed the results of the crude primary outcome, indicating a decreased cumulative incidence of OA-related lower limb surgeries for the patients formerly on GS ( $p=0.05$ ). When only total hip and/or knee replacements were considered, the trend was similar, with over 40% reduction in risk after GS, but the level of probability was lower and showed a trend only towards the significance threshold ( $p<0.2$ ).

The structure-modifying effect of GS was later confirmed by a similar trial in a population of 202 subjects from both sexes with a slightly worse degree of knee OA.<sup>9</sup> In this trial, the sparing effect of GS 1,500mg/day on the rate of progression of the disease was statistically significant as early as the first year, and remained so until the end of the three-year follow-up. The authors also described a significant



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reduction in the proportion of patients with a worse osteophyte score at the end-point (20% in the placebo versus 6% in the GS group;  $p=0.03$ ).

## Intra-articular Hyaluronic Acid

Hyaluronate was evaluated in a one-year randomised controlled pilot study in patients with knee OA evaluated by arthroscopy.<sup>10</sup> Of the 39 included patients, 36 were evaluated after one year. Hyaluronate was injected into the joint once a week for three weeks, at intervals of three months. Lesion severity was evaluated using the score developed by the French Society for Arthroscopy. After one year, the score was significantly lower in the treated group than in the control group ( $p=0.05$ ). However, no significant difference was found for JSW measured on radiographs.

Hyaluronate has also been evaluated versus a placebo in 319 patients with knee OA. JSW was measured on conventional extended-knee radiographs. After one year, no significant difference was found between the two treatment groups. However, in the subgroup of patients whose JSW was  $>4.6$ mm at baseline, joint-space loss was reduced in the hyaluronate group compared with the placebo group ( $p=0.02$ ).<sup>11</sup>

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Another study aimed to evaluate the long-term efficacy of three iterative courses of three weekly intra-articular (IA) injections of the hyaluronic acid (HA) compound NRD101 in the treatment of symptomatic knee OA.<sup>12</sup> In this placebo-controlled study of 301 patients aged over 50 years with painful and radiological medial knee OA, patients were randomly assigned into three groups: group 1 received IA injections of HA and oral placebo; group 2 received IA injections of saline solution and diacerein 100mg/day; and group 3 received IA injections of saline solution and oral placebo. After one year of follow-up, JSW deteriorated ( $-0.09$ mm;  $n=277$ ;  $p=0.01$ ), but with no difference between the groups ( $p=0.82$ ). Percentages of

progressors (JSN  $>0.5$ mm) were 17.7, 18.9 and 20.3% ( $p=0.90$ ) in groups 1, 2 and 3, respectively.

## Risedronate

The efficacy and safety of risedronate in patients with knee OA was assessed in the British study of Risedronate In Structure and symptoms of Knee OA (BRISK).<sup>13</sup> BRISK was a one-year, prospective, double-blind, placebo-controlled study. Patients were randomised to once-daily risedronate 5 or 15mg or placebo. Radiographs were taken at baseline

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and one year for assessment of JSW using a standardised radiographic method with fluoroscopic positioning of the joint. Overall, the difference between treatment groups in terms of loss of JSW at 12 months was not statistically significant ( $p=0.275$ ). A *post hoc* analysis of the distribution of change from baseline values in JSW at one year showed a greater presence of detectable progression (i.e. loss of JSW  $\geq 25\%$  or  $\geq 0.75$ mm) in the placebo (8%) and risedronate 5mg (4%;  $p=0.36$ ) groups than in the risedronate 15mg group (1%;  $p=0.067$ ). The results of a two-year multicentre international study of risedronate in knee OA, presented in an international meeting,<sup>14</sup> found no drug effect at a dose of 5 or 15mg on JSW changes compared with placebo.

## Conclusion

Several compounds have shown small to moderate structural efficacy in OA. So far, the most compelling evidence of potential for inhibiting the progression of OA is obtained with GS, while some research also suggests that ASU, CS, diacerein or doxycycline could be used in the same indication. The structure-modifying effects of other compounds (i.e. alendronate, strontium ranelate, calcitonin, zoledronate and selective oestrogen receptor modulator) are supported by pre-clinical data and should be investigated for this specific purpose. It should be borne in mind that all conclusive results were obtained with prescription drugs containing these substances and should not be extrapolated to over-the-counter or food supplements, whose content, pharmacokinetics and pharmacodynamics are not guaranteed. ■

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