Current Status of and Prospects for Osteoarthritis Treatment

Development of Japanese OA guidelines based on OARSI Part 2

Timothy E. McAlindon, MD, MPH
Tufts Medical Center
USA
Current Chair of the OARSI Treatment Guidelines Committee

Francis Berenbaum, MD, PhD
Pierre and Marie Curie University
Saint-Antoine Hospital, AP-HP
France
Former President of OARSI

[Chair]
Hiroshi Kawaguchi, MD, PhD
University of Tokyo
Japan
Member of the OARSI Board of Directors

This newsletter, first published in 2007, covers the efforts of the Osteoarthritis Research Society International (OARSI) to improve the treatment of patients with osteoarthritis (OA). Previous newsletters have covered roundtable discussions by experts on current treatments for OA, the introduction of new recommendations for treating OA, and the future of orthopedic research. This year, the Japanese Orthopaedic Association (JOA) developed Japanese knee OA guidelines based on the OARSI treatment guidelines to provide a 'bible' for Japanese clinicians. The new guidelines offer a unique clinical perspective on treating knee OA in Japan.

Current status of and prospects for the OARSI treatment guidelines

Kawaguchi: This roundtable discussion, held alongside the annual OARSI congress, is now in its fifth year. This year, we have two main aims: first, to review the impact of the OARSI treatment guidelines on clinical practice worldwide, including the development of Japanese knee OA guidelines by JOA (Dr. Naoki Ishiguro, Chair of the knee OA guideline committee), which was adapted from the OARSI treatment guidelines; and second, to provide clinicians with an update on the prospects for OA treatment. To achieve these aims, we invited two leading experts, Dr Francis Berenbaum from the Pierre and Marie Curie University and Dr Timothy E. McAlindon from Tufts Medical Center, to share their thoughts on these topics.

First, I would like to ask both experts to go over the current status of and prospects for the OARSI treatment guidelines. Dr Berenbaum, would you please describe the history and present status of the three parts of the current recommendations?

Berenbaum: At the time OARSI started this process, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) had published recommendations, but there were no international guidelines. Therefore, OARSI established a taskforce to develop recommendations for the treatment of knee and hip OA. These recommendations were based on the available evidence and on consensus between experts.

McAlindon: The first step was to survey all the existing recommendations for OA and to appraise their quality, comprehensiveness, and applicability. The OARSI Treatment Guidelines Committee built a database of all existing evidence and ranked research according to its quality, with metaanalyses at the top of the hierarchy, followed by clinical trials and other studies. They also compiled a database that allowed us to pool data and run metaanalyses. These data formed the basis for Part 1: recommendations for the management of hip and knee OA.[1]

The second step was to present the evidence to an expert committee, obtain their insights, and develop a set of propositions reflecting each of the treatment modalities. The experts first voted to either accept or reject each proposition and then voted on a quantitative score for each accepted proposition to indicate the strength of recommendation (SOR). Of 100 initial propositions, the experts accepted 25, based on evidence published up to January 2006. These propositions formed the basis for Part 2 of the recommendations.[2] Part 3 included an updated review of the evidence published up to January 2009.[3]

Berenbaum: The SOR is unique to the OARSI recommendations and is not featured in the recommendations developed by the EULAR or ACR. This is very important.

Kawaguchi: Dr McAlindon, as you are the new chair of the Treatment Guidelines Committee, can you comment on the future direction of the recommendations?

McAlindon: Our next goal is to update the propositions and obtain expert consensus based on new evidence published up to January 2011. This will provide the basis for Part 4 of the recommendations. We may add some propositions or rephrase

existing propositions, and we are considering ranking propositions as either core treatments or adjunctive treatments. Our goal is to publish Part 4 by April 2012. So far, there seem to be very minor changes in the evidence since Part 3, although there are some new publications on chondroitin, which focus on tissue structure modification, and acetaminophen, which focus on its toxicity.

Comparison of treatment regimens used in Europe, the USA, and Japan

Kawaguchi: I would like to compare the treatments currently used in Europe, the USA, and Japan, because clinicians may be using different treatment strategies in different countries. In Japan, most people with OA are treated by orthopedic surgeons rather than rheumatologists or general physicians. People with very early or mild OA are usually given advice on lifestyle and exercise rather than being prescribed drugs. If this is unsuccessful, we usually start oral and/or topical nonsteroidal antiinflammatory drugs (NSAIDs), including cyclooxygenase (COX)-2 inhibitors. We rarely use acetaminophen as an initial drug therapy, despite the OARSI recommendations.

If this approach is unsuccessful, we use intraarticular (IA) injections. If the knee joint has an effusion or other signs of inflammation, we inject IA corticosteroid once or twice; after that, we use intraarticular hyaluronic acid (IAHA) injections. In Japan, we use IAHA earlier than in the USA or Europe. If these injections are unsuccessful, we consider surgery. Osteotomy is sometimes considered, but lavage and debridement are rarely performed in Japan. Artificial joint replacement is generally limited to severe cases.

There are two major differences between treatment practices in Japan and the OARSI recommendations. First, we do not use acetaminophen as first-line therapy. Second, we use IAHA more frequently in the early stages of OA.

Dr Berenbaum, could you talk about the current status of OA treatment and the impact of the OARSI recommendations in Europe?

Berenbaum: The situation in France is not that different from the situation in Japan. One difference is that, in France, general practitioners usually refer people with OA to a rheumatologist for treatment, rather than to an orthopedic surgeon. Another difference is that the costs of nutritional products, such as glucosamine, chondroitin, and avocado–soybean unsaponifiables, are reimbursed because they are currently considered as drugs. Therefore, doctors will commonly prescribe these products and patients are willing to use them. However, national agencies are currently reassessing how these products are approved and reimbursed.

General practitioners will usually start treatment with acetaminophen, followed quickly by NSAIDs. Rheumatologists are more likely to start with NSAIDs because they usually see patients with more severe OA. Subsequent treatments are similar to those in Japan, particularly the use of IA corticosteroids for inflammation. Injections are performed by the rheumatologist after the patient is referred.

McAlindon: In the US, there are some differences in clinical practice. Nutritional products and acetaminophen are usually purchased over the counter by patients for self-medication. Glucosamine and other nutritional products are not considered to be pharmaceuticals in the US, and the medical profession is somewhat ambivalent about their use.

I think that there has been a decline in acetaminophen use, because it is perceived to be less effective than NSAIDs. There is also greater concern over potential acetaminophen toxicity, which means physicians are more likely to prescribe NSAIDs instead.

Another issue is that patients copay for every medication, and that preauthorization for more expensive drugs may be needed from the insurance company, who may deny funding. Therefore, some newer drugs may not be prescribed because not all insurance companies will pay for them, a situation that hampers clinical practice.

Introduction to the Japanese knee osteoarthritis treatment guidelines

Kawaguchi: The JOA knee OA committee, consisting of 12 orthopedic surgeons chaired by Dr. Naoki Ishiguro, developed recommendations for the treatment of knee OA by translating and modifying Part 2 of the OARSI treatment guidelines to provide a 'bible' for clinicians in Japan. The JOA committee made two major modifications to the OARSI recommendations. First, they added their own SORs for treating knee OA, some of which differ from those used in Western countries. Second, they removed three treatments (acetaminophen, acupuncture, and opioids) because these are not covered by Japanese public health insurance. This reduced the number of propositions from 25 to 22 (**Table**).

The SORs for most propositions are generally similar between Western countries and Japan. The main differences in the Japanese SORs apply to propositions 15 and 16, which relate to the use of IAHA and of glucosamine and chondroitin sulfate. Therefore, I would like us to focus on these treatments.

Intraarticular hyaluronic acid

Kawaguchi: The SOR for proposition 15 (IAHA) is much higher in the JOA recommendations (87%) than in the OARSI recommendations (64%). This might be because we use IAHA much earlier and for milder OA in Japan than in the USA and Europe. I think that Dr McAlindon's recent metaanalysis comparing IAHA with corticosteroids or placebo probably influenced the use of IAHA in Japan.[4] Dr McAlindon, what do you think about these differences in the SORs, and could you give us some new information on IAHA?

McAlindon: I believe that when you make evaluations by combining expertise with data, and you change the expertise of the panel, it is not surprising that there could be some perceptual differences. It is also important to consider that new data have been published since the original SORs, which were based on data published before 2006. The JOA committee had access to more recent data, including our metaanalysis, which showed an important improvement with IAHA. Our metaanalysis also showed that the effects peaked at about 8 weeks and then decreased. Integrating this information provides a broader pic-

Table. Comparison of OARSI and JOA strengths of recommendation as percentages (95% confidence intervals)

OARSI recommendations for the management of hip and knee OA, Part II: OARSI evidence-based, expert consensus guidelines adapted for Japanese patients by the JOA Committee on Clinical Practice Guidelines on the Management of OA of the Knee

		SOR: % (95% CI)	
		OARSI	JOA
General recommendations			
1	Optimal management of OA requires a combination of non-pharmacological and pharmacological modalities.	96 (93-99)	94 (87-99)
Non-pharmacological modalities of treatment			
2	All patients with knee OA should be given information access and education about the objectives of treatment and the importance of changes in lifestyle, exercise, pacing of activities, weight reduction, and other measures to unload the damaged joint(s). The initial focus should be on self-help and patient-driven treatments rather than on passive therapies delivered by health professionals. Subsequently emphasis should be placed on encouraging adherence to the regimen of non-pharmacological therapy.	97 (95-99)	97 (94-99)
3	The clinical status of patients with knee OA can be improved if patients are contacted regularly by phone.	66 (57-75)	58 (52-64)
4	Patients with symptomatic knee OA may benefit from referral to a physical therapist for evaluation and instruction in appropriate exercises to reduce pain and improve functional capacity. This evaluation may result in provision of assistive devices such as canes and walkers, as appropriate.	89 (82-96)	86 (82-90)
5	Patients with knee OA should be encouraged to undertake, and continue to undertake, regular aerobic, muscle-strengthening and range of motion exercises.	96 (93-99)	94 (88-100)
6	Patients with knee OA, who are overweight, should be encouraged to lose weight and maintain their weight at a lower level.	96 (92-100)	96 (93-98)
7	Walking aids can reduce pain in patients with knee OA. Patients should be given instruction in the optimal use of a cane or crutch in the contralateral hand. Frames or wheeled walkers are often preferable for those with bilateral disease.	90 (84-96)	94 (91-97)
8	In patients with knee OA and mild/moderate varus or valgus instability, a knee brace can reduce pain, improve stability, and diminish the risk of falling.	76 (69-83)	76 (72-79)
9	Every patient with knee OA should receive advice concerning appropriate footwear. In patients with knee OA, insoles can reduce pain and improve ambulation. Lateral wedged insoles can be of symptomatic benefit for some patients with medial tibio-femoral compartment OA.	77 (66-88)	81 (76-85)
10	Some thermal modalities may be effective for relieving symptoms in knee OA.	64 (60-68)	63 (54-71)
11	Transcutaneous electrical nerve stimulation (TENS) can help with short-term pain control in some patients with knee OA.	58 (45-72)	46 (37-55)
Pharmacological modalities of treatment			
12	In patients with symptomatic knee OA, non-steroidal anti-inflammatory drugs (NSAIDs) should be used at the lowest effective dose, but their long-term use should be avoided if possible. In patients with increased gastrointestinal (GI) risk, either a COX-2 selective agent or a non-selective NSAID with coprescription of a proton pump inhibitor or misoprostol for gastroprotection may be considered, but NSAIDs, including both non-selective and COX-2 selective agents, should be used with caution in patients with cardiovascular (CV) risk factors.	93 (88-99)	92 (90-95)
13	Topical NSAIDs and capsaicin can be effective as adjunctives and alternatives to oral analgesic antiinflammatory agents in knee OA.	85 (75-95)	82 (78-87)
14	IA injections with corticosteroids can be used in the treatment of knee OA, and should be considered particularly when patients have moderate to severe pain not responding satisfactorily to oral analgesic or antiinflammatory agents and in patients with symptomatic knee OA with effusions or other physical signs of local inflammation.	78 (61-95)	67 (55-79)
15	Injections of IA hyaluronate may be useful in patients with knee or hip OA. They are characterized by delayed onset, but prolonged duration, of symptomatic benefit when compared with IA injections of corticosteroids.	64 (43-85)	87 (81-92)
16	Treatment with glucosamine and/or chondroitin sulfate may provide symptomatic benefit in patients with knee OA. If no response is apparent within 6 months, treatment should be discontinued.	63 (44-82)	41 (32-49)
17	In patients with symptomatic knee OA, glucosamine sulfate and chondroitin sulfate may have structure-modifying effects.	41 (20-62)	31 (23-40)
Surgical modalities of treatment			
18	Patients with knee OA who are not obtaining adequate pain relief and functional improvement from a combination of non-pharmacological and pharmacological treatment should be considered for joint replacement surgery. Replacement arthroplasties are effective, and cost-effective interventions for patients with significant symptoms, and/or functional limitations associated with a reduced health-related quality of life, despite conservative therapy.	96 (94-98)	94 (92-98)
19	Unicompartmental knee replacement is effective in patients with knee OA restricted to a single compartment.	76 (64-88)	77 (69-85)
20	For the young and physically active patient with significant symptoms from unicompartmental knee OA, high tibial osteotomy may offer an alternative intervention that delays the need for joint replacement some 10 years.	75 (64-86)	83 (77-88)
21	The roles of joint lavage and arthroscopic debridement in knee OA are controversial. Although some studies have demonstrated short-term symptom relief, others suggest that improvement in symptoms could be attributable to a placebo effect.	60 (47-82)	75 (66-84)
22	In patients with OA of the knee, joint fusion can be considered as a salvage procedure when joint replacement has failed.	69 (57-82)	55 (43-68)

ture of the efficacy of hyaluronic acid, and it is possible that this swayed the opinion of the JOA committee. It remains to be seen whether we will see a similar effect when we repeat this exercise with the OARSI panel.

Berenbaum: I agree that the composition of the expert panel is very important. If you have doctors and surgeons sitting on the panel, the surgeons will generally consider more hands-on approaches. Of course, evidence from recent trials is very important for developing SORs.

In France, we now have 10 different brands of IAHA to choose from, some natural and some synthetic, with different molecular weights. Although studies have shown differences in outcomes between products, limitations in trial size and design mean that it is difficult to confirm whether these differences are clinically relevant.

Glucosamine and chondroitin sulfate

Kawaguchi: Moving on to glucosamine and chondroitin sulfate, the SOR published by the JOA committee (41%) for proposition 16 is much lower than that published by OARSI (63%). Dr Berenbaum, you recently published a comprehensive review on these pharmacologic therapies.[5] Therefore, could you give us a summary or discuss new evidence on this treatment?

Berenbaum: Actually, I think that French experts are likely to give an SOR higher than 63% for using glucosamine and chondroitin sulfate. These treatments are very popular in France because they are reimbursed, as are avocado–soybean unsaponifiables. In general, however, the use of these products varies between countries within Europe, depending on the local health insurance systems.

Although the manufacturers of these products have conducted clinical trials, which showed statistically significant effects, I question whether these effects are clinically relevant, particularly because the effect size in the newer trials with larger patient numbers is smaller than that in earlier studies. I am also unaware of any independent trials showing positive results for these products.

Considering these results, my opinion is that, even though these products show only a statistically greater effect than placebo, they are likely to show limited clinical efficacy.

Kawaguchi: Dr McAlindon, I believe you were one of the first researchers to perform a high-quality clinical trial on these treatments in 2000. Could you talk about this study?

McAlindon: Yes, this was actually an online trial that examined the effectiveness of glucosamine for knee OA.[6] We also did the first metaanalysis evaluating the use of glucosamine and chondroitin for treating OA.[7] I think almost all the studies included in the metaanalysis were conducted by the manufacturers, and they were pre-CONSORT (Consolidated Standards of Reporting Trials) recommendations. Although the pooled effect size was positive, a stratified analysis gave strong evidence of bias in relation to trial size and study quality. Overall, the effect size for glucosamine is now close to zero, whereas the effect size for chondroitin is still above zero, indicating uncertainty over the clinical effects of these drugs.

Topical NSAIDs

Kawaguchi: Now I would like to discuss the use of NSAIDs, particularly topical NSAIDs, which are recommended in the UK's National Institute for Health and Clinical Excellence (NICE) treatment recommendations (**Figure**).[8]

A recent Japanese study compared a topical (patch) NSAID

Figure. The NICE treatment algorithm for knee OA

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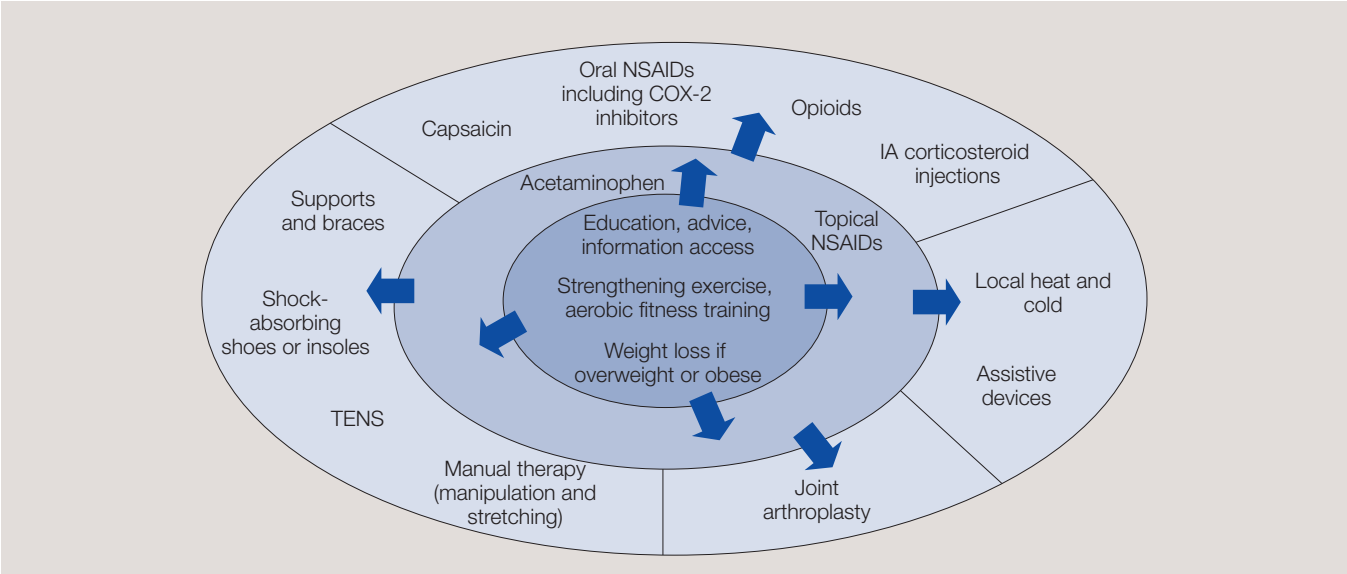
Osteoarthritis: the care and management of osteoarthritis in adults. London: NICE, 2008.



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with an oral NSAID and showed no differences between the two groups in terms of efficacy or incidence of adverse effects.[9] Therefore, topical or patch NSAIDs may offer an alternative to oral NSAIDs.

Berenbaum: I think topical NSAIDs are less popular in France than in the UK. Several very high-quality clinical trials have been conducted in the UK, and doctors in the UK frequently recommend topical NSAIDs for knee OA. The study you mention is interesting and seems to suggest a better benefit–risk ratio for topical NSAIDs compared with oral NSAIDs, because of the similar clinical effects of the two treatments but fewer adverse events with the topical NSAID.

McAlindon: The situation in the US is slightly different. We only have one topical NSAID, which is quite expensive and needs insurance company preauthorization. Another problem is that we do not have patch formulations, only a cream, which is more difficult to administer.

Update on other conventional therapies

Kawaguchi: Earlier, we focused on IAHA, glucosamine, and chondroitin sulfate. However, there are many other conventional treatments, including NSAIDs, COX-2 inhibitors, opioids, IA corticosteroids, diacerein, bisphosphonates, and antidepressants.

Dr Berenbaum, can you please provide an update on these conventional treatments?

Berenbaum: I think that doctors, particularly rheumatologists, are becoming more aware of the CV risks of NSAIDs. We need to provide more information to general practitioners to help them understand this risk.

I think that over the next few years, the focus will be on the effects of NSAIDs on the lower GI tract. Coprescription of acetaminophen with an NSAID seems to lower the hemoglobin level and increase the GI risk. Patients using NSAIDs may require proton pump inhibitors to reduce the risk of gastric ulceration or bleeding.

Kawaguchi: Do you think that the risk of CV events is higher for COX-2 inhibitors compared with conventional NSAIDs, or do you think this is a class effect of all NSAIDs?

Berenbaum: Unfortunately, I do not think we have an answer to this question. Several long-term randomized controlled trials have compared a coxib with placebo for preventing colon cancer, but they showed an increased risk of CV events with coxibs. However, we do not yet have comparable data for classic NSAIDs, as some NSAID studies involved very few patients. These days, we cannot expect a trial involving 16,000–20,000 patients treated with a classic NSAID or placebo for 18 months. We must compare drugs as best we can with the available information.

McAlindon: In the US, the Food and Drug Administration (FDA) has taken the stance that this is an across-the-board effect and has placed a black box warning on all NSAIDs, including topical NSAIDs.

Berenbaum: The situation is slightly different in Europe. The European Medicines Agency has placed a black box warning only on coxibs because of their increased CV risk and because they are contraindicated for patients with history of myocardial infarction, stroke or peripheral arteritis.

Kawaguchi: Other than NSAIDs, do you have any updates on other drugs, such as corticosteroids and antidepressants?

McAlindon: One area of interest is the use of serotonin norepinephrine reuptake inhibitors (SNRIs). One view is that OA is a chronic pain syndrome in some people. SNRIs are often used to treat chronic pain, and the FDA has approved duloxetine for chronic musculoskeletal pain.

Kawaguchi: That is interesting, and this is a topic that may be included in future propositions for OA treatment.

Biotherapy for osteoarthritis

Kawaguchi: Now I would like to discuss biotherapies for OA. At the moment, I am only aware of tanezumab, an antibody against nerve growth factor (NGF). Although a phase 2 study showed strong evidence supporting this drug, subsequent trials were halted by the FDA because of an unexpected increase in the incidence of joint replacement in the tanezumab group compared with the placebo group.

Berenbaum: Actually, it is not only trials for tanezumab that have been halted. All anti-NGF drugs under development are being reviewed by the FDA. One reason for this was an increase in joint replacements seen in patients treated with anti-NGF compared with those treated with placebo in some studies. It is now being discussed whether this represents osteonecrosis or accelerated OA, although I believe it is accelerated OA. It is possible that this is more evident in patients treated with an NSAID in combination with an anti-NGF drug. The mechanism is unknown, and more data are clearly needed.

McAlindon: Other biotherapies that have been tested in people with OA, including those with inflammation, are adalimumab (an anti–tumor necrosis factor antibody) and abatacept. In addition, there has been a phase 1 study, and a phase 2 study is now underway, of recombinant osteogenic protein-1 (bone morphogenetic protein-7) administered by IA injection into the knee joint.

Berenbaum: Another biotherapy in phase 2a development is recombinant fibroblast growth factor-18. One study showed that this drug reduced cartilage destruction.[10] However, there was an increase in pain compared with the placebo group, which could be a limitation. Nevertheless, it is possible that the long-term suppression of cartilage destruction may ultimately lead to less pain.

Another biotherapy that has been considered is interleukin-1 receptor antagonist. However, the results of studies of this drug to date have been negative.

Promising future therapies

Kawaguchi: Do you have any information on future promising treatments with either symptom-modifying or disease-modifying effects? Dr McAlindon, if you could start.

McAlindon: I think the trend now is to consider IA and targeted therapies with direct delivery to the affected joint. I think a number of biotherapies and growth factors will be evaluated, and it will be an exciting time.

Berenbaum: It is interesting that companies are targeting

bone with many different types of drugs, including oral calcitonin (albeit with unconvincing results) as well as strontium ranelate and zoledronic acid, a bisphosphonate. For example, intravenous injection of zoledronic acid after 6 months showed promising results for treating knee OA.[11] We should expect further results for these drugs over the coming year.

Currently, the most advanced trials are for drugs used for postmenopausal osteoporosis, but we do not know what the future will bring. Although some of our current targets may not prove to be useful, this is a very exciting time as we wait for these and other targets, including local drug delivery, to be evaluated.

Kawaguchi: What do you think are the ideal treatment targets for OA in the future?

Berenbaum: This is a very difficult question. There has been some discussion on what could be the best target for disease-modifying OA drugs. Of course, our efforts have been disappointing, because there is still no magic bullet, unlike the case for rheumatoid arthritis, probably because of the impact of biomechanical factors.

McAlindon: Yes, the consensus seems to be that cartilage and bone should both be treatment targets for OA, but the biomechanical factors can be overriding. This was illustrated in two studies published earlier this year. One study was a long-term follow-up of patients with meniscal damage who received collagen meniscal implants.[12] That study showed less pain and less cartilage loss after 10 years. The other study showed that joint distraction for 2 months was associated with cartilage regrowth, with benefits lasting for 1 year.[13]

Although these studies both involved surgical procedures, I think such results are informative and indicate that we must also address the biomechanical issues.

Messages to Japanese clinicians treating people with osteoarthritis

Kawaguchi: Finally, could you both send a message to Japanese doctors treating people with OA?

Berenbaum: My first message is to emphasize the importance of starting with non-pharmacologic approaches, although you say that is already common in Japan. I am very surprised when I encounter patients who are given a list of drugs, even though nobody has suggested weight loss, because the majority of people with knee OA are overweight. I think this message is very important.

My second message is that it is important to provide positive messages, and emphasize that the problem is not just because of age. It is disappointing for a person to be told by their doctor that their pain is age-related and is normal. We often encounter people with OA in their 40s, indicating that OA and joint pain are not simply due to age. I think it is very important to tell the patient that they have a disease and that, even though we may not have the right drugs available to treat it, there are things we can do right now to improve symptoms.

McAlindon: I think we have reached a very interesting and encouraging time, because our conceptualization of OA is maturing. We understand the joint-specific nature of the disease and the need for joint-specific treatments. Many of these treatments are non-pharmacologic, and we are getting better at applying them.

I think that more studies are needed to examine exactly what type of exercise or what type of muscle strengthening is appropriate. We may also establish physical medicine approaches to avoiding the development of hip OA.

I strongly believe that this area of personalized medicine is the future, and that developments in pharmacologic treatments, conceptualization of the disease, and understanding of pain mechanisms will ultimately produce helpful therapies.

Kawaguchi: I wish to thank you both for your informative insights into the current status of and prospects for OA treatment. The next few years will be very exciting, and I believe that significant breakthroughs will be made for the treatment of OA. I believe the information presented here will be of great value for clinicians in Japan, including general practitioners, who are involved in treating people with OA.

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