Current OA Treatment and Impact of Updated OA Guidelines —New Evidence and its Implications

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This newsletter has been covering the efforts of the Osteoarthritis Research Society International (OARSI) to optimize treatment for patients with osteoarthritis (OA) worldwide. In 2008, OARSI published its expert consensus recommendations for the management of OA of the hip and knee (Part 2)[1], based on an appraisal of existing guidelines and a systematic review of evidence for relevant therapies (Part 1)[2]. To determine whether these recommendations should be modified in light of new recent research, the OARSI Treatment Guidelines Committee has updated the evidence up to January 2009 (Part 3)[3].

This year's roundtable discussion reviewed and interpreted the new OARSI guidelines as well as looking at the impact of the earlier OARSI guidelines on clinical practice in Asian countries so far. Also described were current research trends, and comments were exchanged on where scientific and clinical research is headed in future.

New OARSI guidelines (Part 3)

Kawaguchi: Since the aim of this roundtable discussion is to review the impact of the OARSI guidelines on clinical practice worldwide, today we invite one of the leaders in creating the OARSI guidelines, Dr Weiya Zhang from the University of Nottingham in the UK, and, considering that about 60% of the entire population of the world is Asians, we invite two cutting edge orthopedic clinicians from Korea and China, Dr Byoung-Hyun Min from Ajou University and Dr Quing Jiang from Nanjing University.

Dr Zhang, would you please begin the discussion by explaining briefly the differences between OARSI guidelines Parts 1, 2, and 3?

Zhang: Yes, but before I do so, I would like to reemphasize the difference between OARSI guidelines and other guidelines. The OARSI aims to develop a long-term, active global treatment guideline for OA rather than a short-term single shot national or regional guideline for the present scenario. As a result, OARSI intends not only to develop guidelines but also to monitor, update, and revise them regularly. Updating of evidence is scheduled to occur every year, and recommendations will be updated as required. That is why the various parts of the documents are issued separately—so that some clinicians who feel that they understand the evidence can apply that evidence straight away into their own clinical practice, whereas others could follow the consensus report on what to do subsequently. They are really hybrid guidelines in both the development (ie, research evidence plus clinical expertise) and application phases

(ie, evidence and recommendations). Part 1, published in 2007, is a comprehensive systematic review of research evidence for 51 treatment modalities that are currently available in the global market for the treatment of OA. Part 2 is the consensus report published in 2008, based on the research evidence and clinical expertise from the 16 OA experts from different countries. Finally, Part 3 provides a systematic review of all new evidence gleaned between 2006 and 2009, and an analysis of whether there is any change with regard to all the available evidence and whether we should change our recommendations.

In Part 3, we noted that there are a number of major changes. The first involves exercise for hip OA. By 2006 there had been no good evidence to support whether exercise is beneficial for the hip; by 2009, however, level 1a evidence had become available (**Table 1**).

Another notable change over the past 3 years is electromagnetic therapy, whose effect size fell from 0.77 to a very small and nonsignificant level, which suggests that this treatment can more or less be ruled out.

Acetaminophen now becomes questionable in OA when more evidence accumulated. The effect size for pain relief becomes almost nonsignificant. Moreover, the Quebec Study[4] conducted in a very large population of about 6 million people in Canada reported very high gastrointestinal toxicity for acetaminophen. The OARSI guideline committee has discussed whether we need to change our recommendations for this agent. The consensus will be published in Part 4 of the guidelines.

Table 1. Comparison of effect size and level of evidence for pain relief with different modalities of therapy in 2006 and 2009
Original, Table II, *Osteoarthritis and Cartilage.* 2010; 18: 476–499.

	Effect size (95% confidence interval), level of evidence	
	January 31, 2006	January 31, 2009
Self-management	0.06 (0.02, 0.10), Ia	0.06 (0.02, 0.10), Ia
Education/information	0.06 (0.02, 0.10), Ia	0.06 (0.03, 0.10), Ia
Exercise for knee OA		
Strengthening	0.32 (0.23, 0.42), Ia	0.32 (0.23, 0.42), Ia
Aerobic	0.52 (0.34, 0.70), Ia	0.52 (0.34, 0.70), Ia
Exercise for hip OA	NA	0.38 (0.08, 0.68), Ia
Exercise in water for knee and hip OA	0.25 (0.02, 0.47), Ib	0.19 (0.04, 0.35), Ia
Weight reduction	0.13 (–0.12, 0.36), Ib	0.20 (0.00, 0.39), Ia
Acupuncture	0.51 (0.23, 0.79), Ib	0.35 (0.15, 0.55), Ia
Electromagnetic therapy	0.77 (0.36, 1.17), Ia	0.16 (–0.08, 0.39), Ia
Acetaminophen	0.21 (0.02, 0.41), Ia	0.14 (0.05, 0.22), Ia
NSAIDs	0.32 (0.24, 0.39), Ia	0.29 (0.22, 0.35), Ia
Topical NSAIDs	0.41 (0.22, 0.59), Ia	0.44 (0.27, 0.62), Ia
Opioids	NA	0.78 (0.59, 0.98), Ia
IA corticosteroid	0.72 (0.42, 1.02), Ia	0.58 (0.34, 0.75), Ia
IAHA	0.32 (0.17, 0.47), Ia	0.60 (0.37, 0.83), Ia
GS	0.61 (0.28, 0.95), Ia	0.58 (0.30, 0.87), Ia
Glucosamine hydrochloride	NA	–0.02 (–0.15, 0.11), Ib
Chondroitin sulfate	0.52 (0.37, 0.67), Ia	0.75 (0.50, 1.01), Ia
Diacerein	0.22 (0.01, 0.42), Ib	0.24 (0.08, 0.39), Ib
ASUs	NA	0.38 (0.01, 0.76), Ia
Rosehip	NA	0.37 (0.13, 0.60), Ia
Lavage/debridement	0.09 (–0.27, 0.44), Ib	0.21 (–0.12, 0.54), Ib

Ia : metaanalysis of randomised controlled trials
Ib : randomised controlled trial
NA : not available

In addition, glucosamine hydrochloride has been revealed to be no better than placebo. A number of other treatment modalities can be seen differently in light of new evidence.

A further change highlighted in Part 3 is not only numbers but also the quality of studies. This has been a major concern—whether we should use all evidence, or only good-quality trials. The OARSI guideline committee recommends the use of the same quality indicators for all treatment modalities to keep the quality standards and fairness, should any quality assessment be undertaken. Table III of Part 3 gives an example that if we consider quality using the same standard—Jadad score[5] of 5—acetaminophen, avocado soybean unsaponifiables (ASUs), chondroitin sulfate, and intraarticular (IA) hyaluronic acid (HA) injections all become negative (**Table 2**).

Current OA guidelines and their impact on clinical practice in Asian countries

Kawaguchi: Now I would like to talk about the current status of OA treatment in Asian countries, because we may be doing different treatments among the countries. In Japan, most OA patients are treated by orthopedic surgeons. Very early-stage and mild OA patients are not given drugs but education on daily life and exercise. If this strategy does not work well, we usually initiate drug therapy with nonsteroidal antiinflammatory drugs (NSAIDs) including cyclooxygenase (COX)-2 inhibitors, but not acetaminophen, despite the recommendation of the OARSI guidelines. We sometimes use topical NSAIDs including loxoprofen, which is the most popular NSAID in Japan, together with oral NSAIDs. If these agents do not work, we use IA injection, and if the knee has effusion or swelling, we select a steroid injection for one or two times. And after that we use IAHA injections. In Japan, we use IAHA earlier than in the USA and Europe. Then, if IAHA injection does not work we go ahead for surgical procedures. Neither lavage nor debridement is popular, but some institutions prefer osteotomy. Finally, artificial joint replacement is performed for severe cases.

Regarding the impact of the OARSI guidelines, the Japanese Orthopaedic Association is now creating guidelines based on them. It's a modification of Part 2. But it has not yet been published.

In Japan, the biggest differences from the OARSI guidelines are: one, we do not use acetaminophen as a first-line treatment; and two, we use IAHA more frequently and in earlier stages.

Min: In Korea, we have some similarities to Japan. However, despite the good guidance from OARSI, we have difficulty in doing any nonpharmacological treatments because of our country's medical insurance, which does not cover nonpharmacological approaches for OA including education or self-management.

So, treatment in Korea starts with drugs, although not acetaminophen as is the case in Japan. We start with NSAIDs regardless of age. We also prescribe HA irrespective of the stage of OA because we expect effects of both antiinflammation and delay of disease progression from HA. One interesting point is that glucosamine (GS) and chondroitin have been very popular due to the commercial promotion of related corporations while unfortunately, in this situation, doctors can hardly intervene. In Korea, these agents are also used for prevention of OA in normal people who do not have the disease based on their

Table 2. Relation between effect size for pain relief and quality of randomized controlled trials
Original Table III, *Osteoarthritis and Cartilage.* 2010; 18: 476–499.

	Effect size (95% confidence interval)	
	All trials	High-quality trials (Jadad = 5)
Acupuncture	0.35 (0.15, 0.55)	0.22 (0.01, 0.44)
Acetaminophen	0.14 (0.05, 0.23)	0.10 (–0.03, 0.23)
NSAIDs	0.29 (0.22, 0.35)	0.39 (0.24, 0.55)
Topical NSAIDs	0.44 (0.27, 0.62)	0.42 (0.19, 0.65)
IAHA	0.60 (0.37, 0.83)	0.22 (–0.11, 0.54)
GS	0.58 (0.30, 0.87)	0.29 (0.003, 0.57)
Chondroitin sulfate	0.75 (0.50, 1.01)	0.005 (–0.11, 0.12)
ASUs	0.38 (0.01, 0.76)	0.22 (–0.06, 0.51)
Lavage/debridement	0.21 (–0.12, 0.54)	–0.11 (–0.30, 0.08)

decision.

GS is considered a nutrient, not a drug, so not covered by insurance in the setting of prevention. In Korea, both a rheumatologist and an orthopedic surgeon take care of most patients, though many fields of medicine involve treatment of OA because there are so many patients. It seems to me that the OARSI guidelines have not been well adapted by Korean doctors including orthopedic surgeons, although their amended guidelines for Korea, suitable for the situation in Korea, are now established and recommended for application.

Zhang: I cannot really understand why nonpharmacological treatments are not used in Korea. These are effective and very cheap therapies; information such as leaflets and self-management education cost practically nothing and are not related to health insurance but rather to doctor decision. To me, nonpharmacological treatment is the core of management for OA.

Min: Yes, I absolutely agree with you. However, insurance companies in Korea cannot support the expense of providing specially trained personnel with knowledge of OA and its treatment. Support for the cost of nonpharmacologic treatment such as the aforesaid education has been demanded but not approved.

Zhang: Doctors can provide educational guidance when they see the patient; they do not need any additional manpower. This should be part of good clinical practice, not something in monetary terms. Arthritis societies or charities, if there are any in Korea, would normally help to enhance the knowledge of patients about the disease and therapies. The key is whether we believe that education and exercise would work for our patients with OA. If you believe you will do it.

Jiang: The picture in China is very complicated. We have two treatment systems for OA patients: the orthopedic approach and traditional Chinese medicine. In the cities, treatment is modern and about the same as in Japan. Patients can go to an orthopedic surgeon, who will at first suggest nonpharmacological treatment. They will suggest exercise, such as swimming. If the patient has pain, the first choice is an NSAID. But in poorer or rural areas, doctors still use acetaminophen for pain relief. HA is also used. GS is used as a prescription drug in hospitals. China does not have good health insurance; most of the people have to pay for everything.

Kawaguchi: How about acupuncture? And t'ai chi, which has a very good reputation and showed beneficial effects in randomized control trials?

Jiang: Acupuncture is practiced but t'ai chi only in very few patients. Arthroscopy is popular in some major cities but may only relieve pain for a short time. In my clinic's experience, the long-term results are not so good.

As for the OARSI guidelines, many Chinese orthopedic surgeons are unaware of the organization. However, there is broad support for the development of OA guidelines for China.

Updating the OARSI guidelines and optimal treatment of OA

Kawaguchi: Let's talk about the new OARSI guidelines, Part 3. Reflecting the latest revisions, what do you think is the role of acetaminophen now?

Zhang: I think that it is okay to use acetaminophen for a short time period, for example < 3 months. However, care must be taken as acetaminophen is not as safe as we previously expected. At full dosages, 4g/day, that is, two 500-mg tablets four times daily for a long period (eg, 3 months), acetaminophen is quite dangerous for a patient aged >50 years, even if he or she does not have any gastrointestinal or liver problems. In that situation, I would perhaps try topical NSAIDs. COX-2 inhibitors are very effective and safe but more expensive.

Kawaguchi: What is your opinion about cardiovascular events associated with COX-2 inhibitors?

Zhang: Cardiovascular events due to COX-2 inhibitors are very rare. As long as you do not prescribe these drugs to someone with a history of cardiovascular problems, you should be all right. In a young patient aged <40 years who has no gastrointestinal history, I might try NSAIDs first, just to reduce cost really. In an old patient, however, I would favor topical NSAIDs.

Min: What is the best NSAID to relieve pain? Because there are no head-to-head comparisons among various NSAIDs. Besides, patients react to the same medication differently.

Zhang: We performed an indirect comparison using network metaanalysis and found no big difference between different NSAIDs for efficacy. So it is down to the individual patient's response to each particular NSAID. Some may respond well to ibuprofen, others to diclofenac. A good strategy is to start with ibuprofen since it is the safest, then if there is no response within 1–2 weeks, switch over to another NSAID.

Kawaguchi: Referring to Table III of Part 3 of the guidelines, if we take quality of trials into account, such as whether they are double blind, randomized, with intention-to-treat analysis, the effect size of IAHA decreases much from 0.6 to 0.22 (**Table 2**).

Zhang: Yes, it becomes nonsignificant, which means that it is

no better than placebo.

Kawaguchi: In Korea and Japan, IAHA is used earlier and more frequently than in Western countries. What are your opinions about IAHA?

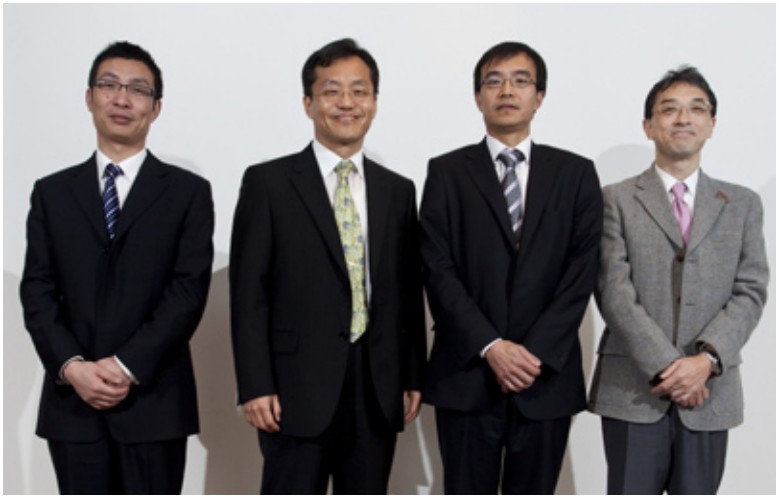
Min: Based on the article cited in the guidelines and my experience with IAHA, I do not think it helps to reduce the inflammation and retard the disease progression, even the pain. Instead, I would rather use steroids.

Kawaguchi: If the recommendations of the guidelines were to be changed right now, which modality do you personally think to be most affected?

Zhang: Personally I think that the recommendations regarding acetaminophen could be revised. Topical NSAIDs may have more of a role, particularly in older patients with gastrointestinal problems. Also, ASUs and GS have been shown no better than placebo.

Kawaguchi: So should we distinguish between GS and glucosamine hydrochloride?

Zhang: Yes.



Trends in OA research —toward improved treatment

Kawaguchi: So finally, let's talk about possible future directions of OA treatment.

Jiang: In my opinion, given enough time, OA seems fairly inevitable as you get older. So I think that we should continue to try to relieve pain and improve the function. Human genetic studies may improve our understanding of OA, but whether it will lead to identifying treatment targets is uncertain. Genetic research may have more of a role in prevention, helping identify those people who are predisposed to develop OA. We could then advise them to avoid activities that may damage the joint, and to control their weight.

Min: I have seen some compelling results suggesting that injection of adipose-originated stem cells may cover the whole defect area with new cartilage. Recently in particular, cartilage regeneration using cell treatment has achieved remarkable success. Considering the general concept of focal defect of cartilage contributing to the development of OA, early diagnosis of cartilage loss and immediate treatment may suggest a new direction of OA treatment.

Stem cell therapy could be a promising field in curing OA. In European countries, as cellular delivery systems more than thirteen biomaterials have been launched on to the market and are undergoing clinical trial.

Zhang: If you ask me what to do with OA from now on, one thing is to optimize treatments that we already have, since a revolutionary new treatment does not seem on the horizon.

Kawaguchi: So lastly would you please give any message to Asian doctors treating OA?

Zhang: I think as a first step we need to disseminate the OARSI guidelines as quickly as possible in Japan, Korea, and especially China, since that is the biggest nation. It is not necessary to copy and paste the guidelines, but more to use the evidence and ideas that we have gathered in the OARSI guidelines, and apply them to your own country according to your situation, in your own language.

Min: It would be interesting to see a new Part 4 of the OARSI guidelines next year, if it contains more about treatment algorithms Since we have been recommended acetaminophen as a first-line drug, we do not have an alternative that is more compatible with current concepts of OA. Since OA is an organ disease affecting the joint (not just a cartilage disease), we have to give more attention to the treatment of inflammation; a guideline that suggests which stage needs surgical intervention must be established. In other words, an algorithm for diagnosis and treatment based on the cartilage loss needs to be proposed.

Jiang: I think we should do more research on Asia-specific OA. In my clinic, I see patients with OA in the knee; I have very few patients with primary hip OA. And I believe that this is the usual clinical picture in Asia, unlike in the West. So, since there is some evidence that some drugs are useful for hip while others are more useful for the knee, this could be an interesting area of future research from an Asian perspective.

Kawaguchi: I think what this discussion has underlined is that to optimize treatment for Asian patients, the updated OARSI guidelines need to be tailored to suit the very different situations in each of our countries. Thank you, this has been a really fruitful discussion from which I have learned a lot.

1 Zhang W, *et al.*, *Osteoarthritis and Cartilage*. 2008; 16: 137-162
2 Zhang W, *et al.*, *Osteoarthritis and Cartilage*. 2007; 15: 981-1000
3 Zhang W, *et al.*, *Osteoarthritis and Cartilage*. 2010; 18: 476-499
4 Rahme E, *et al.*, *Am J Gastroenterol*. 2008; 103: 872-882
5 Jadad AR, *et al.*, *Control Clin Trials*. 1996; 17: 1-12