Hyaluronic Acid Improves Function in Knee OA

Number of responders increases after each treatment cycle; benefits persist at 1 year follow-up.

BY MICHELE G. SULLIVAN

FROM ANNALS OF THE RHEUMATIC DISEASES

VITALS

Major Finding: Compared with saline injections, hyaluronic injections eased pain and improved function in 22% more patients.

Data Source: A double-blinded randomized controlled trial of 306 patients with knee osteoarthritis.

Disclosures: The study was supported by Tedec Meiji Farma SA. Dr. Navarro-Sarabia and coauthors received research funds from the company as study investigators. Two coauthors are Tedec Meiji Farma SA employees.

Repeated intra-articular injections of hyaluronic acid appear to lessen pain and improve function in knee osteoarthritis between treatment cycles, and for up to a year later.

The 40-month AMELIA (Osteoarthritis Modifying Effects of Long-Term Intra-Articular Adant) project found that, compared with those getting saline as a placebo injection, patients who got the treatment were 22% more likely to experience a clinical response – a 50% or greater improvement in pain or function (80% vs. 66%; risk ratio 1.22).

However, wrote Dr. Federico Navarro-Sarabia and his colleagues, the study could not determine why the improvement persisted as long as it did after treatments stopped.

"In this regard, it is not possible to establish whether this carry-over effect reflects a true disease remission or just a modification of the natural course of the disease," the investigators wrote (Ann. Rheum. Dis. 2011 Aug. 17 [doi: 10.1136/ard.2011.152017]).

AMELIA comprised 306 patients with knee osteoarthritis. They were randomized to four cycles of five weekly injections. The treatment groups received 2.5 mL 1% sodium hyaluronate derived from *Streptococcus zooepidemicus.* The placebo group received saline injections. Patients and evaluators were both blinded to the treatments by using a blinded evaluator and an unblinded investigator to administer the injections.

Follow-up occurred during the 6 months after cycles 1 and 2; and 1 year after cycles 3 and 4. Patients were allowed to use aspirin or paracetamol, and short durations of nonsteroidal anti-inflammatories. "However, for 24 h and 1 week before efficacy evaluation, patients were required to abstain from any paracetamol or NSAID, respectively," the researchers wrote. No corticosteroid injections were allowed in the treated knee throughout the entire study.

The patients were mostly women (87%), with a mean age of 63 years. The mean body mass index was 28 (kg/m^2). The mean duration of knee osteoarthritis was 7.5 years. End-stage disease was not included and the mean joint space width of the medial tibiofemoral compartment was 3.5 mm.

Of the 306 randomized, 109 in the treatment group and 94 in the placebo group completed the entire study. In the treatment group, discontinuation was due to lack of efficacy (8), patient decision (12), adverse events (12), and investigator decision (1). The rest were lost to follow-up or left for other reasons. In the placebo group, reasons were lack of efficacy (19), patient decision (13), adverse events (16), and investigator decision (1). The rest were lost to follow-up or left for other reasons. Outcomes were assessed in an intent-to-treat analysis.

At the end of the 40-month study period, 22% more treated patients than placebo patients were judged responders according to the Osteoarthritis Research Society International 2004 criteria – a significant difference.

However, the number of responders in the treatment group progressively increased after each cycle, from 71% after the first cycle to 80% after the last cycle. Response rates in the placebo group remained stable throughout the study (68% after the first cycle and 66% after the last cycle).

The chances of response seemed to increase as the study progressed, the authors noted. Among the nonresponders in the treatment group, 54% became responders later on. Similarly, 38% of the nonresponders in the placebo group eventually became responders.

The high placebo response is not an unusual finding in osteoarthritis trials, said Dr. Navarro-Sarabi of Hospital Universitario Virgen Macarena, Seville, Spain, and coauthors.

"In AMELIA, however, the success of the study was in fact accentuated by the high placebo efficacy detected, making the results found [80% vs. 68%] even more clinically meaningful and remarkable."

Most of the patients (71% of each group) used either an NSAID or paracetamol as a rescue medication during the study. Among the 48% who took paracetamol over the study's course, the mean daily dose declined by 27% in the treatment group and 4% in the placebo group.

Twenty-nine adverse events occurred (15 in the treatment group and 14 in the placebo group), among 22 patients (11 in each group). These included allergic reaction (three in each treatment group), bleeding and pain at the injection site, arthralgia, and other events. ■

VIEW ON THE NEWS

Nonresponders Become Responders

I think this is a valuable study. It adds important information on the use of hyaluronic acid injections for osteoarthritis of the knee.

► First, under controlled conditions with a saline control parallel group, a series of four courses of repeat series of injections can provide significantly greater benefit than in the control group.

► Second, that the repeat series of injections were safe with this bacteria-derived product; there was no increase in adverse events.

► Third – which is a new finding to my knowledge – is that there is a subset of patients who don't respond to the initial series of injections but who did respond to repeat series of injections.

► Fourth – this is the first controlled study to my knowledge that has demonstrated benefit lasting for at least a year following the repeated series of injections.

Statistically, they used the OMERACT-OARSI responder criteria, a robust technique that separates responders and nonresponders.

This is the kind of study that reinforces the way I practice and may even change it. If I have someone with only a borderline response to the first injections, I now might give it a second try.

One thing I do question is the dropout rate. With a dropout rate of 27% in the treatment group and 39% in the saline group, you wonder if the significance of the findings would change if they had completed the trial.

ROY ALTMAN, M.D., *is professor of rheumatology and immunology at the University of California, Los Angeles. He reported having no financial relationship to disclose relevant to Adant. Dr. Altman said that he consults for Ferring, Fidia, Novozyme, and Smith & Nephew/Q-Med, all of which make other hyaluronic acid products.*

Manage Cardiovascular Risk in Vulnerable RA Patients

BY SHARON WORCESTER

The jury is still out on just how cardiovascular risk should be screened and managed in rheumatoid arthritis patients, but it is clear that the risk is increased and must be addressed.

Patients with RA are known to have a lower probability of survival than do controls, and a major cause of excess death is from cardiovascular disease. In one study, silent MI occurred more often in RA patients, and sudden death was more likely in these patients (Arthritis Rheum. 2005;52:402-11). In another study, survival among patients with acute cardiac syndrome was substantially reduced in RA vs. non-RA patients (Ann. Rheum. Dis. 2006;65:348-53).

Some experts say RA is now equivalent to diabetes in terms of the extent to which it confers cardiovascular risk, according to Dr. Joan Bathon, director of the division of rheumatology at Columbia University, New York.

The European League Against Rheumatism has proposed multiplying conventional cardiovascular risk models by 1.5 when risk is assessed in RA patients, said Dr. Bathon (Ann. Rheum. Dis. 2010;69:325-31).

This approach is not well validated, and may not be widely used, she said. But the proposal illustrates the importance of focusing on cardiovascular risk in RA patients. It suggests that considering RA as a risk factor equivalent to diabetes – at least for making decisions about LDL cholesterol goals – is a reasonable strategy, she said.

Consider yearly cardiovascular risk screening, she said. The benefits of imaging and biomarkers are unclear, and no guidelines are in place. As a management strategy, aspirin therapy might be useful, but should be considered in the context of the patient's other medications. Statins are a potential management tool, but questions remain about whether all RA patients should be treated regardless of LDL cholesterol level, Dr. Bathon said.

Definite treatment strategies for RA patients include weight management for overweight patients, to help reduce inflammation, as well as exercise for all RA patients, because good quality muscle building will help restore insulin sensitivity and reduce fat depots that are the most inflammatory. Tight blood pressure control and tight RA control are imperative, Dr. Bathon said.

She noted that conventional risk factors do not fully explain the excess risk in RA patients, and that inflammation probably plays a role.

Dr. Bathon said she had no disclosures. ■