ASK THE EXPERT

Viscosupplementation Relieves Knee OA Pain

Viscosupplementation with hyaluronic acid is an important option for managing osteoarthritis of the knee, particularly in patients for whom conventional analgesic drugs are ineffective or intolerable. By compensating for the characteristic decrease in native hyaluronan concentration in the synovial fluid, intra-articular hyaluronan injections modulate pain and improve the function of the joint.

ROY D. ALTMAN, M.D.

In a recently reported randomized, controlled trial, Dr. Roy D. Altman and colleagues observed significantly greater improvements in pain, joint function, treatment satisfaction, and health-related quality of life in the 293 patients with knee osteoarthritis who had been randomized to receive three weekly intra-articular injections of hyaluronate, compared with the 295 knee OA patients who received buffered saline injections. The efficacy appeared to be sustained over time, as nearly half of the treatment group subjects were pain free 6 months following the injections, according to the findings of the study, which was supported by Ferring Pharmaceuticals Inc. (Semin. Arthritis Rheum. 2009;39:1-9).

In this month's column, Dr. Altman describes intra-articular hyaluronic acid and discusses how it is best used in the clinical management of knee OA.

RHEUMATOLOGY NEWS: What is the presumed mechanism of viscosupplementation in OA?

Dr. Altman: The term viscosupplementation implies that the therapy is simply replacing synovial fluid for biomechanical purposes.

The currently commercially available intra-articular hyaluronates have a limited presence in the synovial cavity; most have a half-life of only a few days, and one for less than a week. It is not known if there is a prolonged residence time in the surrounding tissues of the joint.

There is evidence that the currently utilized hyaluronates are large enough to bind to the CD44 cell receptor, inhibiting activation of a set of inflammatory pathways that would be activated by NF-kappaB (a nuclear transcription factor), such as interleukin-1, metalloproteinases, tumor necrosis factor, and the like.

The CD44 cell receptors are present on nerve endings, synovial cells, and chondrocytes. Binding to the CD44 cell receptor appears to stimulate the synovial cells to produce more and more normal synovial hyaluronate. There is also evidence that these hyaluronates have inhibitory activity on other cell functions, such as a few Toll receptors and RHAMM (receptors for hyaluronan-mediated motility).

Thus, it appears that intra-articular hyaluronate acts as a biomaterial between joint surfaces, with more prolonged action on inhibiting the sensation of pain through synovial nerve endings, reducing inflammation and stimulating hyaluronate production from the synovium, and potentially modifying chondrocyte behavior.

Clinically, there is only one study examining structure or disease modification. This study suggested that intra-articular hyaluronate preserves radiographic joint space of the knee, unless the joint space narrowing is advanced (Int. J. Clin. Pract. 2003;57:467-74).

RN: Clinically, when and for whom is viscosupplementation a reasonable option?

Dr. Altman: At this time, intra-articular hyaluronate therapy is most appropriate in the patient with OA of the knee who has difficulty with oral medications such as analgesics and/or anti-inflammatory agents because of intolerance, adverse reactions, inefficacy, or an inability to take them. Intra-articular hyaluronates are also potentially of value in those who have failed intra-articular depot corticosteroids. At this time, it is uncertain whether there is a delay to time of joint surgery. Many of these patients are older, have many comorbidities, and take a variety of medications. For example, an elderly patient with borderline renal function would not be a good candidate for an oral anti-inflammatory agent.

RN: Who are the "ideal" candidates for intra-articular hyaluronate therapy?

Dr. Altman: Unfortunately, only about two-thirds of those with knee OA respond to intra-articular hyaluronate. It is difficult to know who will tend to respond, as demographics have not helped us identify responders or nonresponders. It does appear that the more severe radiographic changes, such as Kellgren-Lawrence grade 4, do not respond as often. The literature suggests that age does not help identify responders, so young and older patients with OA are equally likely to be candidates.

RN: What are some of the therapeutic advantages and disadvantages?

Dr. Altman: The major advantage is that intra-articular hyaluronate is a form of local therapy. Hence, there may not be a need for oral medication or the potential of adverse effects of oral medication. Also, nearly half of those responding to intra-articular hyaluronate have significant benefit, obviating the need for multimodal therapy. The disadvantages are that there may be local pain at the injection site, the injection may precipitate a flare of pseudogout, and there is a slightly elevated risk of infection. Another disadvantage is the need for the physician to be skilled in intra-articular injections. Many physicians do not do enough local injections to be comfortable or skilled at it. The local nature of the therapy is another disadvantage; pain associated with OA of other sites will not lessen.

RN: With respect to administering the injection, what are some of the critical considerations?

Dr. Altman: There are several studies suggesting that intra-articular injections in the knee are completed less than 80% of the time. Results from the inferior approaches to the bent knee are less consistent than those achieved with the lateral or medial parapatellar approaches. If there is a detectable effusion, it should be removed prior to the instillation of the hyaluronate. For those clinicians who are less skilled or uncomfortable with knee injections, ultrasound guidance may be helpful.

RN: What problems should clinicians look for?

Dr. Altman: Periarticular injections often produce some pain at the time of the injection. Additionally, an increase in pain within 24 hours may suggest a crystalline synovitis, such as pseudogout. An increase in pain in 2-3 days may suggest infection.

All patients should be advised that there is only a 66% likelihood that they will benefit from the injections. For those who respond, they may have dramatic improvement in pain. They should be advised not overuse the knee, as the benefit will be lost and cannot be recaptured.

RN: What is on the horizon for viscosupplementation in OA?

Dr. Altman: The newer intra-articular hyaluronates are no longer produced by extraction from rooster combs. Instead, they are of bacterial origin. This allows a product with minimal contamination and the production of larger molecular weight products. There is continued investigation into alternative injection programs, such as single (rather than three or five) injections per series. There is exploration into hyaluronates with longer synovial half-lives. For example, cross-linking of hyaluronate may not require chemical processing. Hyaluronates are being studied for their ability to bind to peptides for the slow release of anti-inflammatory or growth factors.

Additionally, there is continued research into intra-articular hyaluronate therapy for OA in joints other than the knee. Several publications show benefit in OA of the shoulder, ankle, first carpometacarpal joint, bunion joint, temporomandibular joint, and hip.

With increasing concern for oral agents in OA, intra-articular hyaluronate therapy will continue to be a part of our regimen for some time to come.

—Diana Mahoney

About two-thirds of patients with knee OA respond to intra-articular hyaluronate. For now, it is difficult to predict who will respond. Demographics have not been useful predictors.

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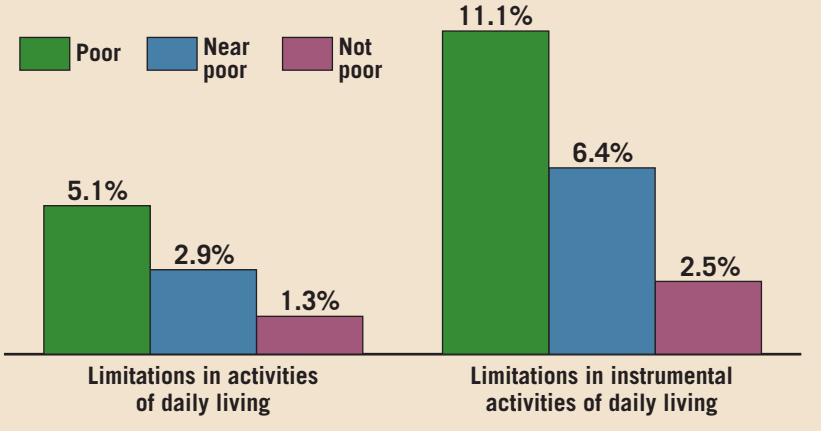
DATA WATCH

In Adults, Activity Limitations More Common Among the Poor



Notes: Based on data from the 2008 National Health Interview Survey. "Poor" persons are below poverty threshold; "near poor" have incomes 100% to less than 200% of poverty threshold; "not poor" have incomes that are 200% or more of poverty threshold.
Source: MMWR 2009;58:1357