There are many other pathological similarities between degeneration of the IVD and osteoarthritis and is perhaps not surprising that as we obtain an increased understanding of the disease processes many similarities (as well as differences) are exposed in the cell and molecular processes underlying OA and degeneration of the IVD.
This talk will describe some of these mechanisms and link them to the origins of CLBP. It will also describe data from experimental regenerative medicine to explain some aspects of the differences in the behaviour of IVD cells in normal versus abnormal environments and explain how these influence thinking about applying regenerative medicine to IVD repair and reconstruction.

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HYALURONATE FOR OSTEOARTHRITIS

Roy D. Altman

Hyaluronate (Hyaluronan, Hyaluronic acid, HA), a straight chain polymer of the disaccharide D-glucuronic acid and β1, 3-N-acetyl-D-glucosamine was purified in 1934. The use of HA for intraarticular (IA) injections in osteoarthritis (OA) has been in practice for over 10 years.
There are several HA formulations available, varying in size of the polymer, some with crosslinking to increase their size and viscosity. Although most are derived from rooster combs, a few are derived from a bacterial source. Most of the clinical trials have been in patients with OA of the knee. However, more recent trials have examined the use in other joints with OA, such as shoulder, hip, 1st CMC and ankle. The number of injections in any series varies from one to five, depending on the product. However, defining the number of injections in a series, the spacing between the series and the amount of HA injected have been empiric.
The mechanism of action of HA in OA is not known. HA of low molecular weight has been shown to induce inflammation in many organ systems through binding to several receptors; eg CD44, RHAMM, Toll. HA of high molecular weight (eg >300 kDa) have been shown to interfere with the activation of these receptors—suspected by the way the high molecular weight HA binds to the receptors. Hence, in one proposed mechanism of action, high molecular weight HA retards the activation of the NFκB promoter system and the resultant multitude of inflammatory mediators by the synovial cell or the chondrocyte.
There has been reluctance in accepting HA therapy for OA based on the negative results of several clinical trials. IA therapy presents several chalanges that accentuate the problems of OA clinical trials, not the least of which is a large placebo effect that reduces the effect size.
Bellamy has performed the most complete analysis of the clinical trial results of HA in OA through the Cochrane mechanism. He has determined that all the HAs have demonstrable benefit with an effect size that is clinically relevant. Re-injection and prolonged benefit have been demonstrated. Although there are few trials that compare different HA products, no single HA product has appeared superior to another.
There are a few clinical trials suggesting the IA HA may have structure modifying properties.
Adverse events of IA HA are mostly limited to injection site reactions, although pseudogout, pseudoseptic reactions and granuloma formation with repeated injections have been reported.
There are incomplete guidelines on when HA injections are to be used. Clinical trials usually exclude patients with severe radiographic changes, so that any delay to surgery is hypothetical. At present, HAs are often used when other therapies have failed, when the patient is a poor candidate for oral agents, when the patient is intolerant of oral agents, when the patient is not a candidate for or declines surgery, and to delay surgical intervention.
There is minimal information on additive therapy of oral agents and IA HA.
IA HA therapy is a useful and safe course of therapy for OA of the knee and probably several other joints involved with OA. Not all patients respond. Among those responding, many are nearly pain free. More research is needed in several aspects of this therapy, eg spacing of injections, timing of repeat series of injections, significance of HA size, significance of crosslinking, mechanism of action, HAs will continue to have a role in the therapy of OA for the foreseeable future.

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SYMPTOMATIC SLOW ACTING DRUGS IN OSTEOARTHRITIS: WORKSHOP AND PANEL DISCUSSION: WHAT IS THE EVIDENCE? DIACEREIN IN OSTEOARTHRITIS

Burkhard F. Leeb

Diacerein, a slow acting symptomatic drug in osteoarthritis (SYSADOA) with interleukin-1 (IL-1β) inhibitory properties, is widely used for for the treatment of osteoarthritis (OA). Like other products of this group, diacerein has a slow onset of efficacy, which becomes evident after 2–4 weeks of treatment and significantly different versus placebo at 4 weeks in knee OA and 6 weeks in hip OA. It also has a long carry over effect once treatment has stopped.
The compound was rated as a therapeutic option in OA with evidence level 1b within the EULAR recommendations 2003, and was highly recommended class A according to the experts opinion [1].
An explanation for a slow onset of activity and long carry-over effects once treatment is stopped may be due to the fact that it has effects on underlying causes of OA. In vitro studies in cultures of chondrocytes, synovial tissue and inflammatory cells, have shown that therapeutic doses of both diacerein and its active metabolite rhein inhibit the production and activity of the pro-inflammatory and pro-catabolic cytokine IL-1β [2,3] both in the superficial and deep layers of the cartilage [4] and in the synovial membrane [5] from OA patients while stimulating the production of growth factors such as TGF-β [6] and extracellular cartilage matrix components such as proteoglycans [2,7] aggrecans [8], HA [9], and collagen type II [9,10] even in the presence of IL-1β. Both agents also reduced IL-1β-induced MMP levels and nitric oxide by chondrocytes [2,4,5,11] and reduced the synthetic activities of OA osteoblasts which could be responsible for abnormal subchondral bone remodelling occurring during the course of OA [12].
The effects on pro-inflammatory, pro-catabolic cytokines seen in the in vitro studies mentioned above have been confirmed in vivo in an animal model [13] i.e. the granuloma-induced cartilage breakdown model in the mouse. Diacerein was also shown to down-regulate IL-1 levels in the synovial fluid of patients with knee OA [14]. Studies in different animal models of OA [15–17] showed that diacerein consistently reduced cartilage loss in OA compared to untreated OA controls. In addition, a long-term study in the ovine model of OA [18] showed that diacerein treatment caused a significant increase in bone mineral density measurements, in the density of the internal zone of the external condyles and a decrease in the thickness of the subchondral bone plate of the median zone of the tibial plateaux.
These postulated modes of action make the drug an interesting option not only for symptom relief, but also for structure modification in OA
Indeed, the ECHODIAH-trial, dealing with structure modification in hip OA, came up with a reduction of the progression of hip OA in Diacerein treated patients compared to the placebo group, however, without symptomatic efficacy over three years [18].

The results of a meta-analysis of 19 clinical trials provide evidence for a beneficial, statistically significant as well as clinically relevant efficacy of diacerein on pain and the functional status in patients suffering from hip and knee OA [19]. The number of patients inluded in this meta-analysis, namley, 1328 diacerein-treated patients and 1309 patients in the comparator groups (placebo or NSAID) gives the basis for well founded conclusions to be drawn from this investigation.

It could be shown that diacerein was superior to placebo and as effective as NSAIDs with respect to the reduction of pain as well as to the improvement of function which are considered to constitute major response criteria in OA during the treatment period. As functionality is highly dependent upon pain its reduction relates directly to the improvement of the functional status.

Considering the pain relief results, one has to keep in mind that no complete withdrawal of analgesic medication was possible during the investigations analyzed within this meta-analysis. In most of the trials, acetaminophen, which can be also seen as an appropriate treatment of moderate OA, was allowed as additional medication.

In addition the results of this meta-analysis give a proof for the carry over effect, SYSADOA are postulated to exert, concerning pain assessed by VAS.

The most common side effects of diacerein are related to the gastrointestinal tract like abdominal pain or diarrhoe. Moreover, change of the urine colouration, pruritus and skin rash occurred within the clinical trials. All these adverse events were reversible and not life threatening. In France, over a period of 11 years (from September 1994 to November 2005) and with more than 14 million prescriptions of DIA, only 9 cases of cardiovascular adverse events with DIA were spontaneously reported. Patient tolerability assessments revealed the superiority of placebo over diacerein with no differences between diacerein and NSAIDs. Given the meta-analytic results obtained here, a trial powered to ultimately prove the usefulness of diacerein as a symptom-modifying or even disease-modifying drug in osteoarthritis can be expected to give similar results.

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GLUCOSAMINE

Karel Pavelka

Despite several new studies [1,2] several meta-analysis and new Cochrane analysis, discussion on efficacy of glucosamine in both symptomatic and structural modification of OA continues.

Why? Firstly, there are general problems with evaluation of drugs in OA. There is high placebo response, problem with rescue medication and other therapies. We definitively need better study designs and outcome measures.

Secondly there is a problem with the drug. Is glucosamine sulfate equally effective as glucosamine hydrochloride? New studies