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Effect of Intra-Articular Steroids on Cartilage in Knee OA CME/CE

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CME Released: 11/30/2017; Valid for credit through: 11/30/2018

Target Audience
This activity is intended for neurologists, rheumatologists, orthopedists & orthopedic surgeons, and nurses.

Goal
The goal of this activity is to discuss evidence about how potential new paradigms for using steroids might treat early inflammation and alter the progression of knee osteoarthritis (OA).

Learning Objectives
Upon completion of this activity, participants will:

- Have increased knowledge regarding the impact of intra-articular (IA) steroid injections on cartilage, in patients with knee OA
- Have greater competence related to potential patient selection characteristics for the use of IA steroid injections for patients with knee OA

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Hardware/Software Requirements

To access activities, users will need:

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- Adobe Flash Player and/or an HTML5 capable browser may be required for video or audio playback.
- Occasionally other additional software may be required such as PowerPoint or Adobe Acrobat Reader.

Disclosures

Moderator

John C. Richmond, MD
Professor, Orthopaedic Surgery, Tufts University School of Medicine, Boston, Massachusetts

Disclosure: John C. Richmond, MD, has disclosed the following relevant financial relationships:
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Panelists

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Disclosure: Virginia B. Kraus, MD, PhD, has disclosed the following relevant financial relationships:
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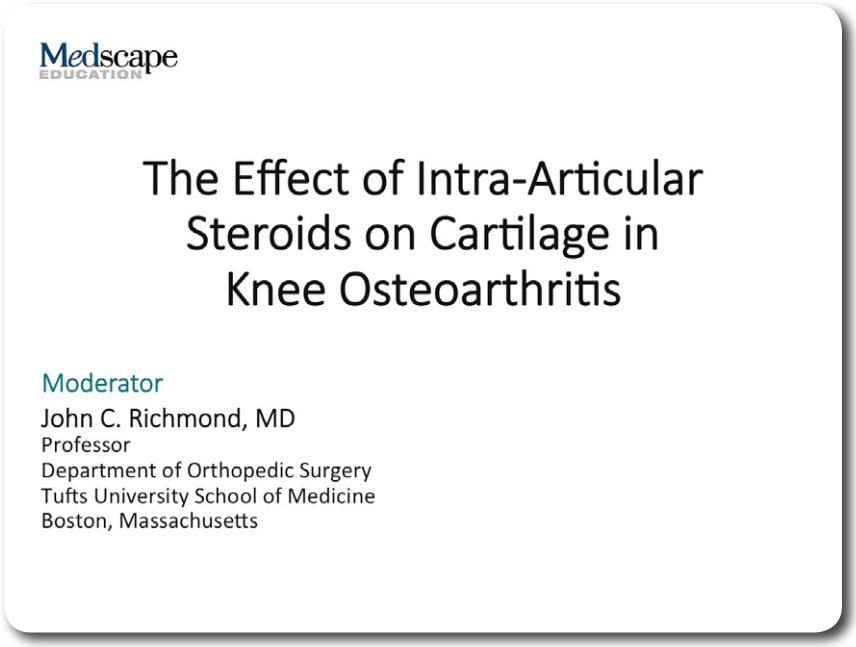
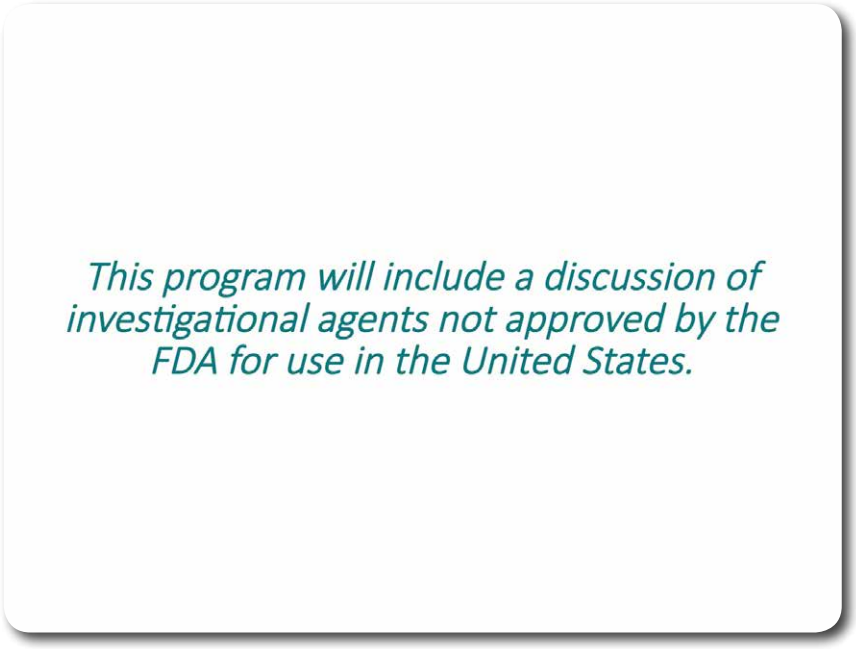


John C. Richmond, MD: Hello, I'm Dr John Richmond, professor of orthopedic surgery at Tufts University School of Medicine in Boston, Massachusetts. I welcome you to this program titled, "The Effect of Intra-Articular Steroids on Cartilage in Knee Osteoarthritis."

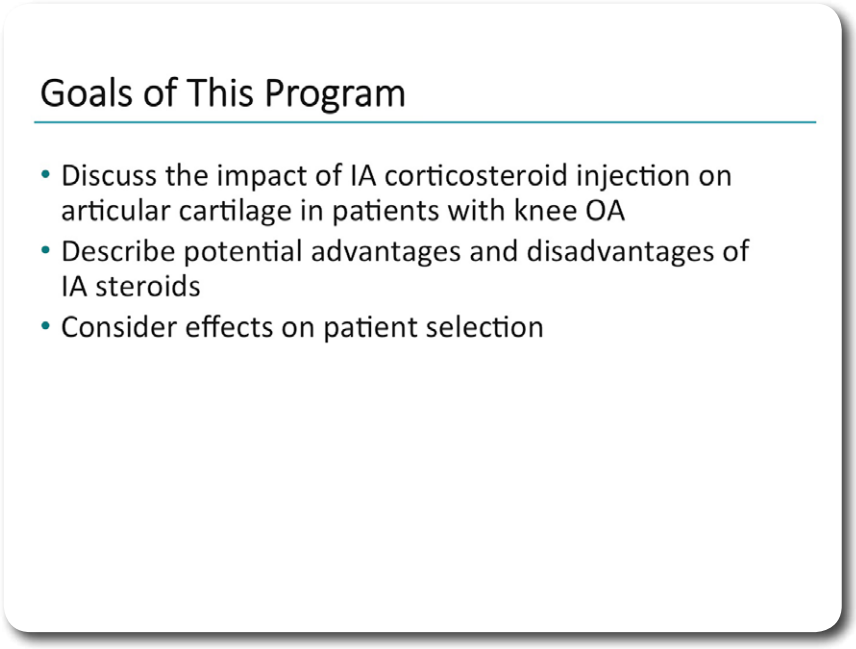
Dr Richmond: Joining me today are Dr Virginia Byers Kraus, professor in medicine, pathology, and orthopedic surgery at Duke University in Durham, North Carolina, and Dr Christian Lattermann, professor and vice chair of Clinical Research, Department of Orthopedic Surgery at the University of Kentucky in Lexington. Welcome.

Christian Lattermann, MD: Hello.

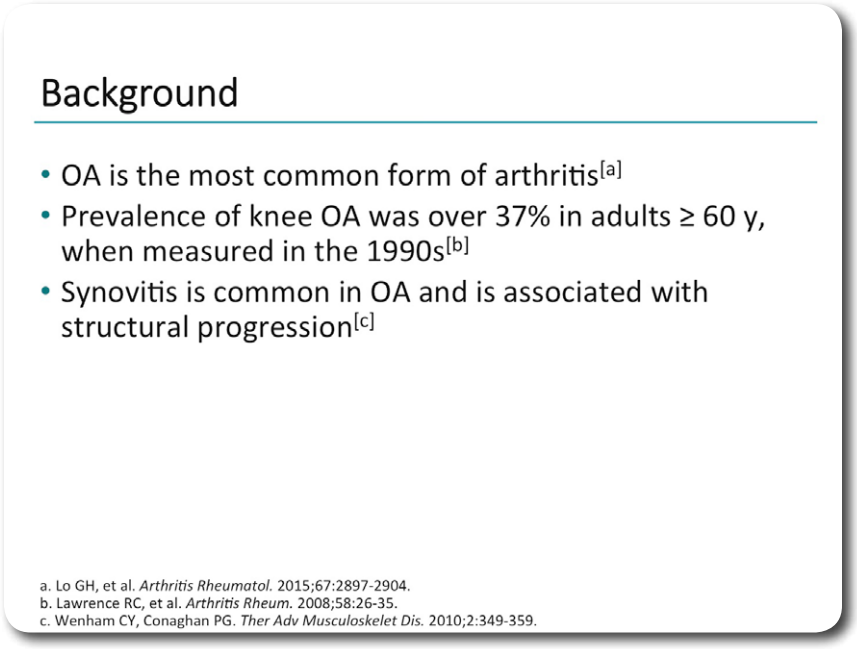
Virginia Byers Kraus, MD, PhD: Thank you.



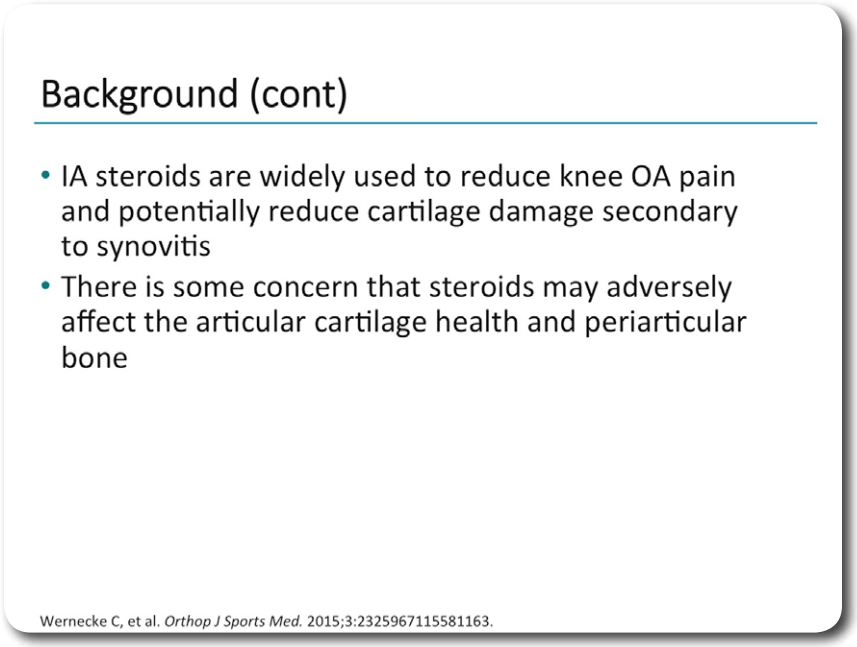
This program will include a discussion of investigational agents not approved by the FDA for use in the United States.



Dr Richmond: Today, we are going to discuss the impact of intra-articular (IA) steroid injection on articular cartilage in patients with knee osteoarthritis (OA). We will point out potential advantages and disadvantages, and how this may affect patient selection for clinical practice.



Dr Richmond: OA is the most common form of arthritis. The prevalence of knee OA was greater than 37% in adults older than 60 when measured back in the 1990s. Synovitis is a common problem in OA and is associated with structural progression. IA corticosteroids are widely used to reduce knee OA pain and potentially reduce cartilage damage secondary to synovitis.



Dr Richmond: IA corticosteroids are widely used to reduce knee OA pain and potentially reduce cartilage damage secondary to synovitis. There is some concern that corticosteroids may adversely affect articular cartilage health and periarticular bone.

Historic Perspectives: Effect of IA Steroids on Knee Cartilage

- 2-y prospective randomized, controlled trial
  - Compared 40 mg triamcinolone acetonide to saline
  - Injections repeated every 3 mo
- No difference with respect to loss of joint space width as measured on weight-bearing radiographs

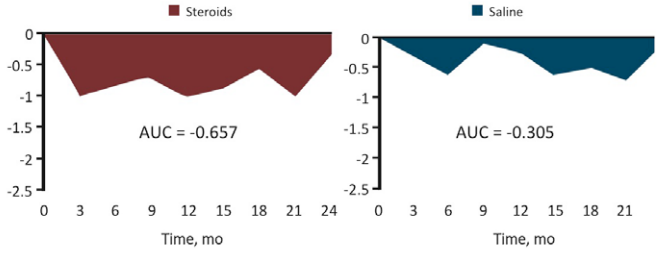
	Steroids	Saline
Baseline	4.07 (1.01)	3.93 (0.91)
1-y	4.00 (1.07)	3.86 (1.12)
2-y	4.02 (1.20)	3.86 (1.20)

Raynauld JP, et al. *Arthritis Rheum*. 2003;48:370-377. Copyright © 2003 by the American College of Rheumatology.

Dr Richmond: The historic perspectives of the impact of IA steroids on knee cartilage go back to a report by Raynauld et al almost 15 years ago. This was a 2-year prospective randomized controlled trial that compared injections of 40 mg of triamcinolone acetonide with injections of saline. The injections were repeated every 3 months. There was no difference between triamcinolone therapy and placebo with respect to loss of joint space as measured on weight-bearing radiographs.

Historic Perspectives: Effect of IA Steroids on Knee Cartilage (cont)

- Strengths of the study
  - Standardized x-rays
  - No x-ray progression (but x-rays not too sensitive)
  - Efficacy on AUC analysis, particularly for night pain



Raynauld JP, et al. *Arthritis Rheum*. 2003;48:370-377. Copyright © 2003 by the American College of Rheumatology.

Dr Richmond: To our panel, I would ask, what do you see as the strengths or weaknesses of this study?

Dr Lattermann: This is a landmark study. It was one of the very first randomized trials to address this question. One of the biggest things that I see as an orthopedic surgeon is that they used standardized radiographs, which is tremendously important if you are trying to assess progression of the disease. This study set the standard for this kind of trial back in 2003 when it was published.

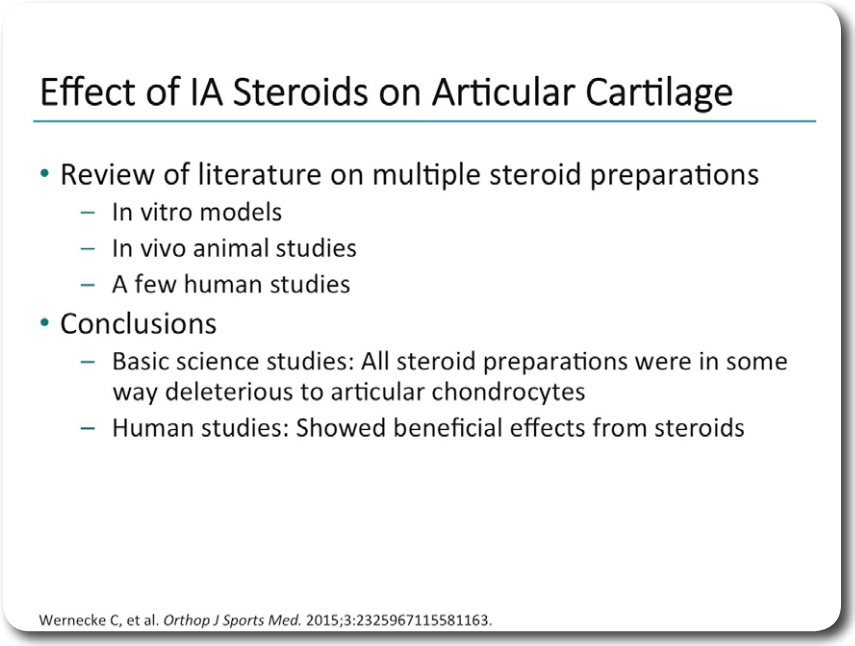
The issue is, the study did not show any radiographic progression, but you have to ask yourself, how sensitive are radiographs, even when standardized fashion? We will see examples of that a little bit later. That is probably the biggest criticism of the study.

Dr Kraus: Also, one of the unique aspects of this study was that they used an area under the curve analysis for the pain measure; in particular, they saw that night pain was improved in the triamcinolone-treated patients compared with the placebo-treated patients. When they just looked at that endpoint 2 years later and compared those groups head-to-head, they did not really see a difference. But when they accounted for the whole period of 2 years in the symptoms, there appeared to be a signal with respect to the treatment with triamcinolone.

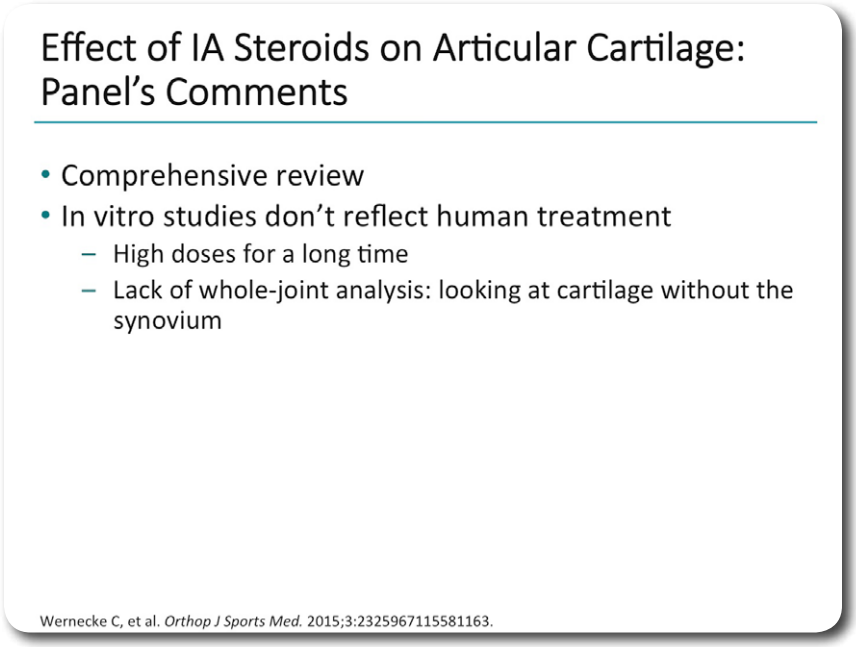
Dr Richmond: So, that was a very good study at the time.

Dr Kraus: Absolutely.

Dr Lattermann: I agree.

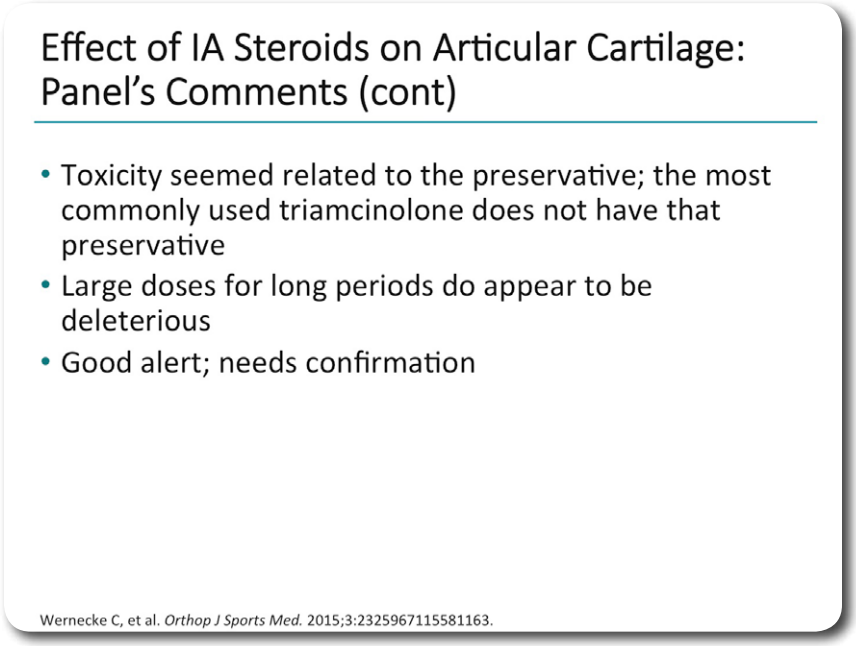


Dr Richmond: I would like to move on to results of a report by Jason Dragoo out of Stanford on the effects of IA corticosteroids on articular cartilage. He and his coauthors reviewed the literature on multiple corticosteroid preparations, both basic science using in vitro models and in vivo animal studies and a few human studies. In the basic science studies, all of the corticosteroid preparations were in some way deleterious to the articular chondrocytes. Human clinical trials did show beneficial effects from the corticosteroids.



Dr Richmond: I would ask, Dr Kraus, what would you say about this review of the use of corticosteroids?

Dr Kraus: Well, although it was very comprehensive, there are a number of cautionary notes regarding these in vitro data and translating them into in vivo effects. The primary issue is that they really don't represent physiological dosing. When you give a drug intra-articularly, you'll have a high dose at the beginning, and it wanes rather rapidly. Most of these studies used high doses for very long periods of time, which don't represent the in vivo situation. So, not only is the concentration not reflective of what we do in vivo, but also there's the lack of a whole-joint scenario. They're just looking at the cartilage without the synovium. And the synovitis is the key player in the inflammatory process that we're trying to treat with the steroids.

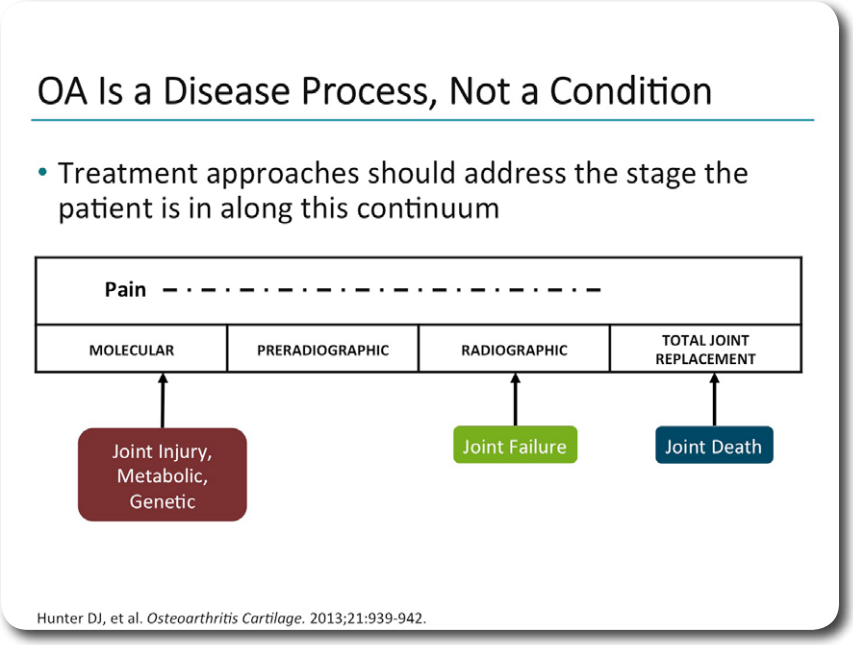


Dr Richmond: And moving on to you, Dr Lattermann.

Dr Lattermann: Again, this is a very comprehensive review, probably one of the most important ones in the past few years. What it also does show is that the toxicity of the individual preparations of cortisone product seem to be related to the preservative used in some of them. Triamcinolone, which is most commonly used, does not have these preservatives, and this is an important fact for the clinician.

The large doses for long periods appear to be deleterious to articular cartilage, and this is really a function of dosage. Small doses, particularly of hydrocortisone, are in fact used in tissue culturing of chondrocytes, so they are necessary for differentiation and proliferation of chondrocytes early on. However, in larger doses, cortisone becomes toxic. This report is a really good alert. We have to be careful how we are using cortisone, and we have to question ourselves about what the dosages need to be.

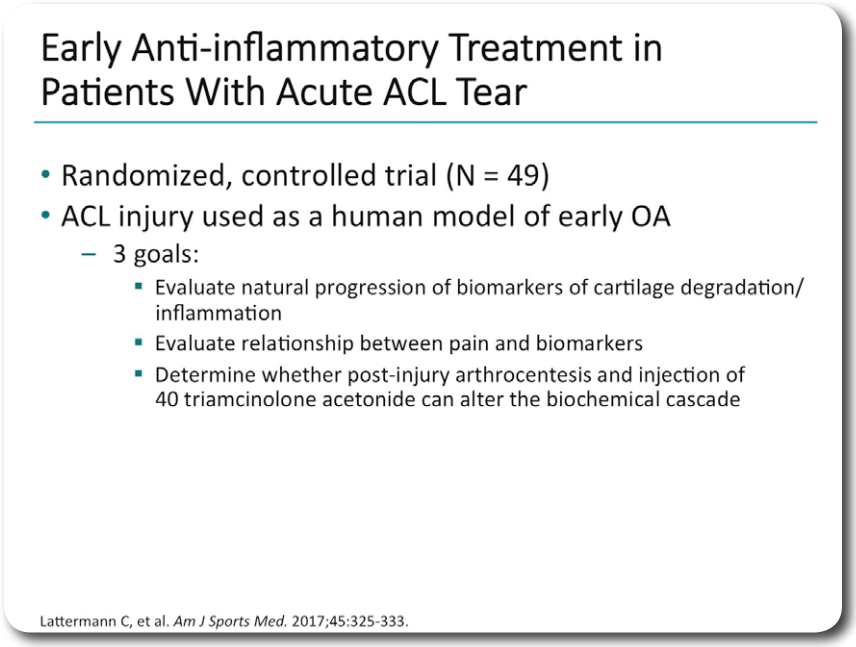
The other thing that the study pointed out, which I think is very important, is that there may be combinations that are toxic within the joint, such as local anesthetics. That is one of those things that we need to review. In combination with lidocaine, for example, a steroid may be more toxic than it is alone or with saline.



Dr Richmond: I'll step back to you, Dr Kraus. Talk to us a little bit about OA as a disease.

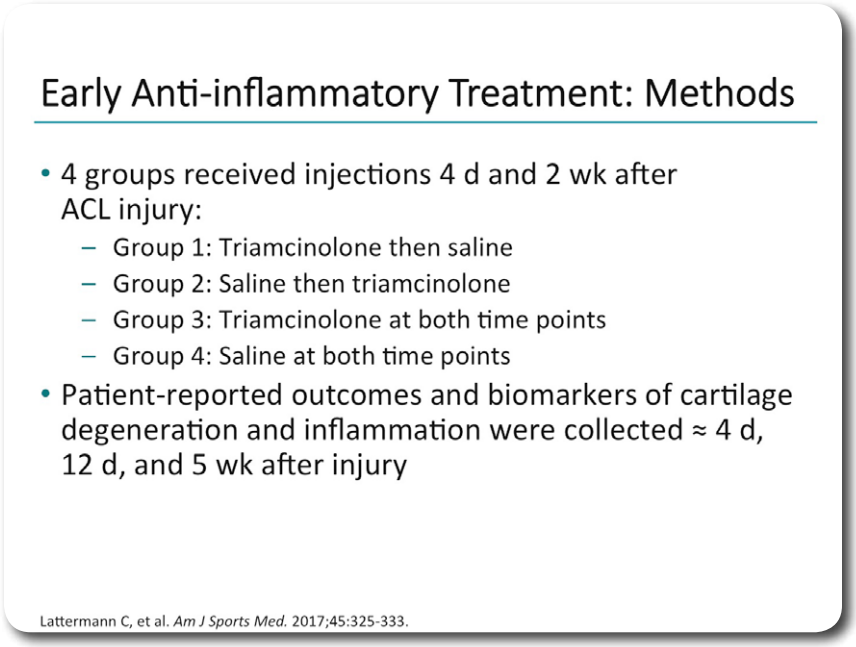
Dr Kraus: One of the things that has evolved over time is our understanding of the disease and the disease pathogenesis. We're learning that OA is not just an radiographic change; it's a biological process that occurs very early, much earlier than radiographic changes. Because OA was always traditionally thought to be a noninflammatory disease, which turns out not to be true, a radiograph was always thought to be sufficient for a diagnosis. But now we are realizing that it's a disease process.

From this graphic, which is published, we can think about the disease as starting with a histobiochemical change, a metabolic process in the tissue, in the cells, that then leads into early imaging changes that we can see on magnetic resonance imaging (MRI), and eventually in these radiographic changes. To the extent that we can intervene in the disease process and the inflammatory aspects of the disease, we might actually be able to block the progression and block the disease process.



Dr Richmond: And then I'd like to move onto Dr Lattermann's study, which was very eye opening to those of us who practice in orthopedics and deal with sports injuries.

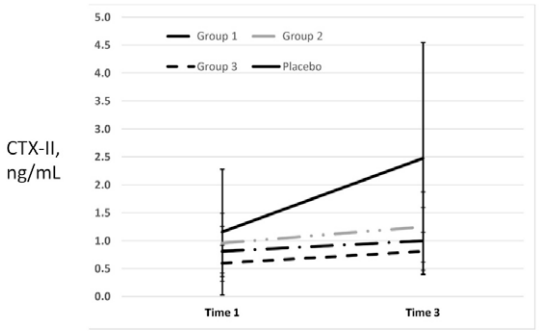
Dr Lattermann: Yes, leaning on the concept that Dr Kraus just elaborated, a few years ago we realized that there's actually a human model of early OA progression and disease, and that is the young patients who undergo anterior cruciate ligament (ACL) surgery after an ACL tear. It took us a while to realize, but 10 to 15 years after these injuries, a large percentage of those patients end up with OA, and these are young patients. And in animal models, we have used ACL tears as a model for OA for many, many years. We just haven't jumped that bridge to the human situation until fairly recently.



Dr Lattermann: Looking at that type of patients, we were able to do a randomized clinical trial that had several goals, one of which was to try to treat early inflammatory changes that may happen right after that ACL injury. We know from data out of the 1990s that there is an inflammatory cascade that starts. We also know that these patients get effusions very quickly after the injury.

Early Anti-inflammatory Treatment: Results

- Increase in CTX-II indicates collagen breakdown
- Time 1 = mean of 4 days; Time 3 = mean of 37 days



Lattermann C, et al. *Am J Sports Med*. 2017;45:325-333. Copyright © 2017. Reprinted by Permission of SAGE Publications, Inc.

Dr Lattermann: We found that the inflammatory markers, as well as markers that indicate degradation of articular cartilage within 4 weeks, are very high in these patients. They correlate very well with cartilage destruction, which is reminiscent of what we see in later stages of OA. Not to the same extent, but you can see that if you are looking at their synovial fluid, and that's what we did.

In the moment where these patients had early aspirations of the effusions, and we delivered 40 mg of triamcinolone, some of these markers, particularly collagen breakdown markers, CTX-II, were significantly reduced. And interesting enough, even at a 2-year time point, that had an effect on the clinical outcome of these patients. Now what that indicates is that OA starts within the first weeks after the injury, and it may potentially be treatable, I think this may be a shift in the paradigm of how we can treat OA. If treatment starts early, we may be able to affect a tear as well as at a later stage.

Early Anti-inflammatory Treatment: Conclusions

- Majority of biomarkers and patient-reported outcomes changed during the first 4 wk after acute ACL injury
- Changes in biomarkers were not associated with increased pain
- Post-traumatic osteoarthritis appears to be a "silent killer" of the knee joint
  - Degenerative process continues in background despite improvements in pain and function
- Change the treatment paradigm – early aspiration and intra-articular intervention?

Lattermann C, et al. Am J Sports Med. 2017;45:325-333.

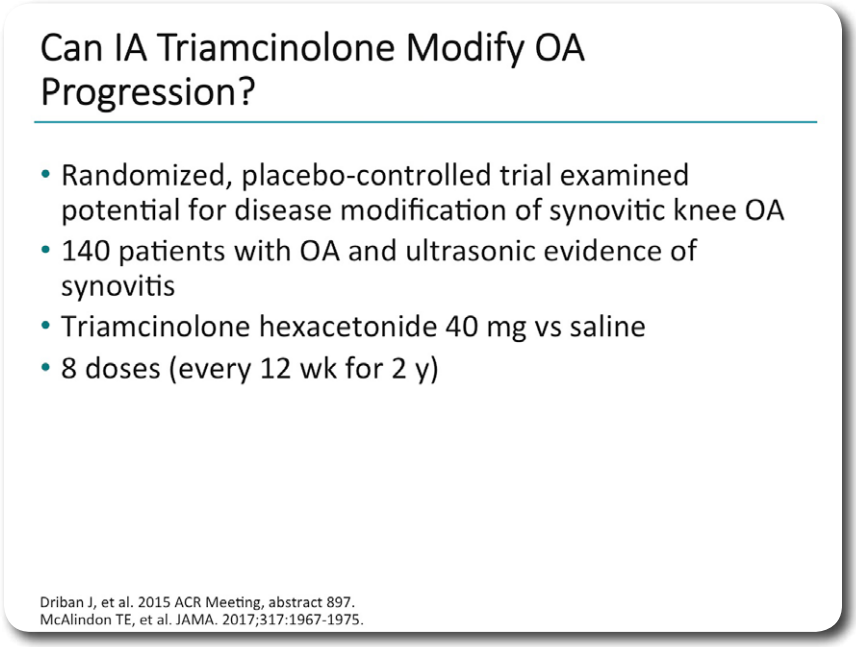
Dr Richmond: That is fascinating data. Can you just summarize this for us? Because that really is amazing information.

Dr Lattermann: Okay. The majority of biomarkers and patient-reported outcomes changed very early within the first 4 weeks after injury -- biomarkers of inflammation and cartilage degradation. The patients initially have a lot of pain after the injury, but they get better, despite the fact that these biomarkers are showing chondral wear.

From that perspective, if you think about it, the process of OA is beginning, even though the patient is getting better. You could consider that to be a silent killer, if you want to. Because the patient is starting to feel better, starting to get more active after the ACL reconstruction, despite the fact that the knee is not necessarily getting better and is starting to develop the disease, which is posttraumatic OA. I do believe that if we can affect that early on, then we have a potential way to change the current treatment paradigm with an early intervention.

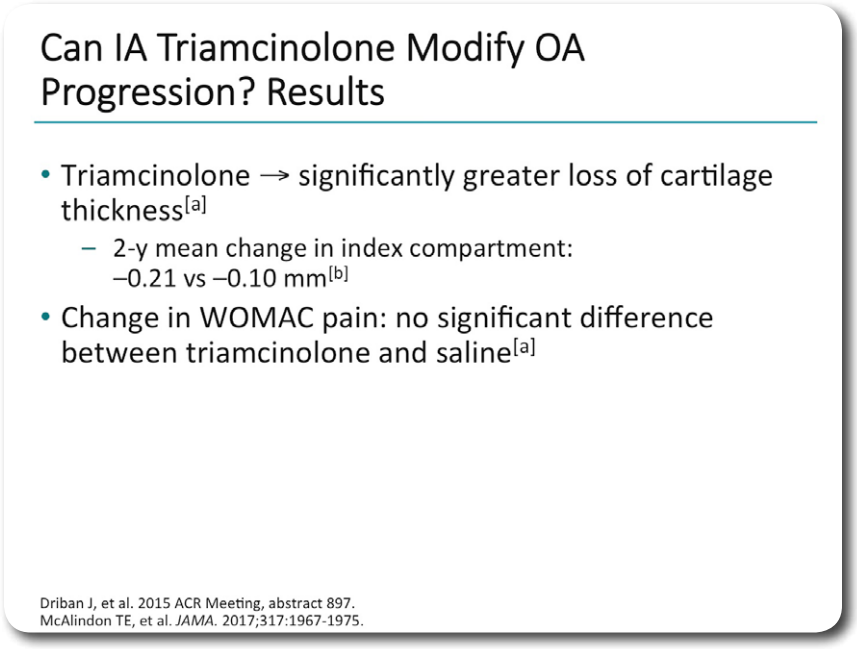
Dr Richmond: Fascinating data. All sports doctors deal with ACL injuries, yet we would worry about using cortisone on an immediate postoperative patient. So, things will have to be done in the future, we will need to either prove that this is safe or that there is some other IA intervention that will benefit these young, active athletes.
Dr Lattermann: Yes, I fully agree. And this is an experimental study; this is not the standard of care at this point.

Dr Richmond: Great, thank you.

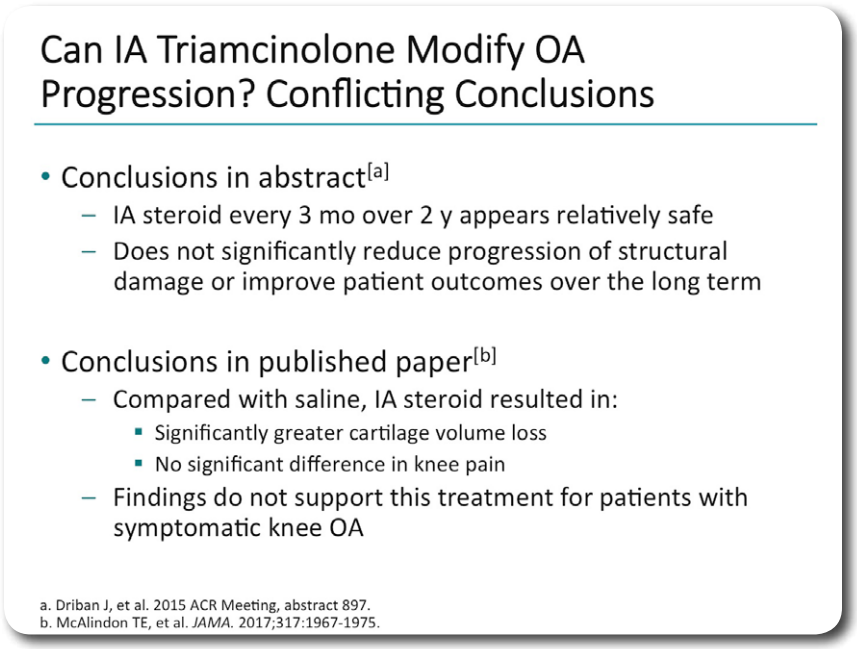


Dr Richmond: Let's discuss 2 reports that come from my home institution, Tufts, in Boston. Driban et al presented an abstract at the American College of Rheumatology in 2015, and then McAlindon et al published the data in *JAMA* in what I think is a landmark study this year.

They examined the potential for disease modification in the synovitic knee of OA with triamcinolone. They measured the effects on cartilage and subchondral bone using MRI and DXA scans. They did a randomized controlled trial of 40 mg of triamcinolone vs saline in patients with OA and ultrasonic evidence of synovitis. There were 8 doses over 2 years, so every 12 weeks. They had 140 patients.

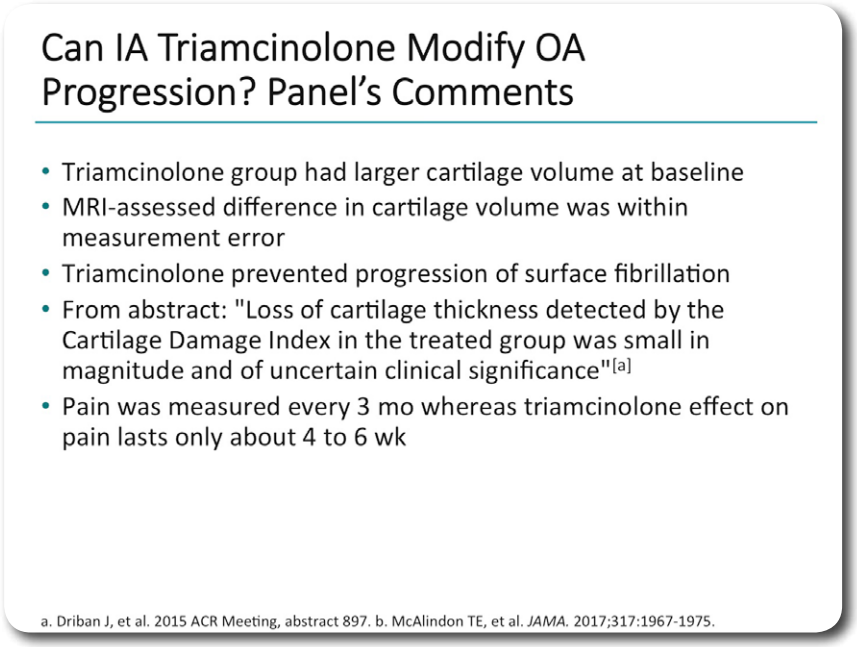


Dr Richmond: The IA injection of triamcinolone resulted in a significantly greater cartilage volume loss than did saline: 0.21 mm vs 0.1 mm was the mean change in index compartment cartilage thickness. There was no significant difference in pain.



Dr Richmond: The conclusion from the abstract was that IA corticosteroids every 3 months over 2 years was relatively safe but did not significantly reduce progression of structural damage or patient outcomes.

The conclusion from the published report was that triamcinolone vs saline resulted in significantly greater cartilage volume loss, and no significant difference of pain. So, they concluded that their findings did not support this treatment in patients with knee OA.



Dr Richmond: I would go to Dr Lattermann on this, and have him bring up his points relative to this study.

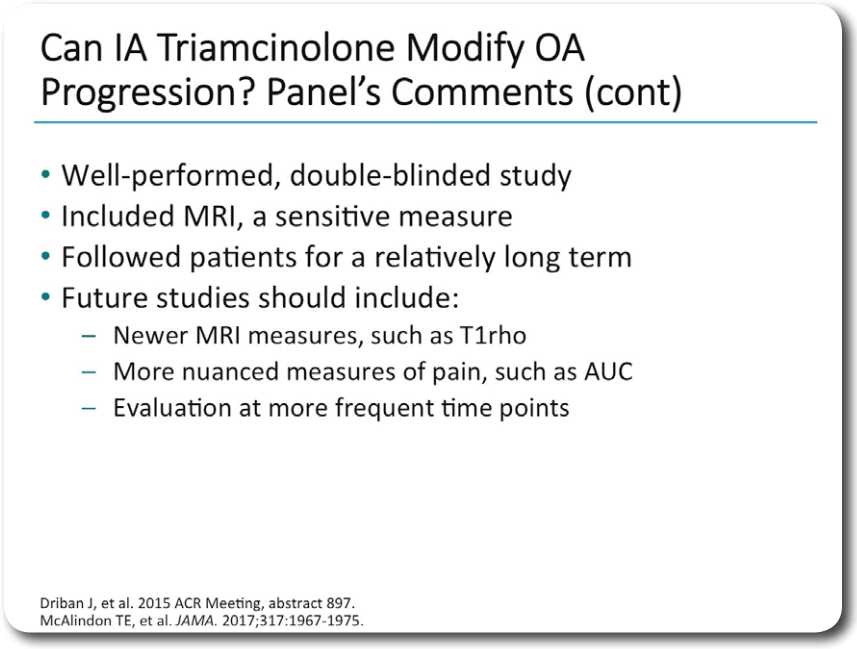
Dr Lattermann: This is obviously a very well done study with extremely well-defined inclusion criteria and long time points. However, there are some concerns with it, and I will voice these.

Starting out, their main conclusion has to do with the cartilage volume loss that they detected. What you have to point out is the group that was randomized to triamcinolone had a larger cartilage volume to start out with at the baseline, and we do know that that is a significant determinant of cartilage volume loss.

In addition to that, the MRI differences in cartilage volume were in fact within the measurement error. The 0.1-mm difference is technically not detectable. This is a statistical phenomenon that they describe. Triamcinolone prevented the progression of surface fibrillation at the same time.

So, you have 2 sets of data that stand in conflict with each other here. It's hard to support that conclusion. In the abstract they acknowledge that by saying that the loss of cartilage thickness detected by the Cartilage Damage Index in the treated group was small in magnitude and of uncertain clinical significance, which I would fully subscribe to.

The other problem is that the measurements they took were after 3 months, right before the subsequent cortisone injections, when we know that the main effect of triamcinolone lasts for only about the first 4 to 6 weeks. So that kind of stacks the deck a bit in this study.

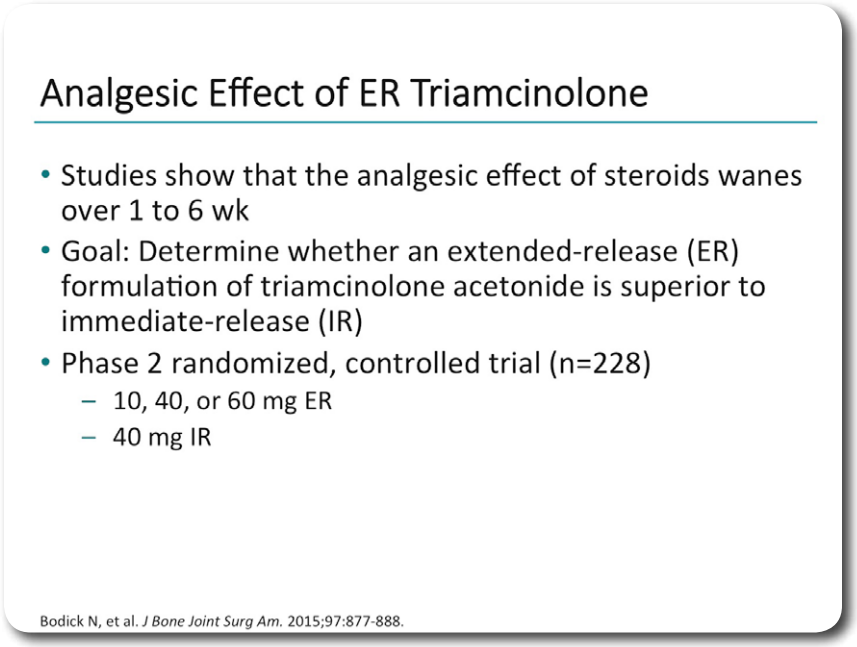


Dr Richmond: Moving on to you, Dr Kraus. I know you have some important comments on this report, too.

Dr Kraus: Well, I agree with what you said about it being a landmark study. It was very well performed. It was a double-blinded placebo-controlled trial. It included MRI, which is a very sensitive measure, much more sensitive than the prior study of a similar kind that we already talked about, which used radiography. It followed patients for a relatively long period of time, which was 2 years. It really created a paradigm for this type of work.

But some conclusions going forward with respect to a possible research agenda for studies of this kind would be to include additional, newer MRI measures such as T1rho. That might allow us to look at proteoglycan loss and give us the ability to more easily interpret some of the clinical relevance of these data.

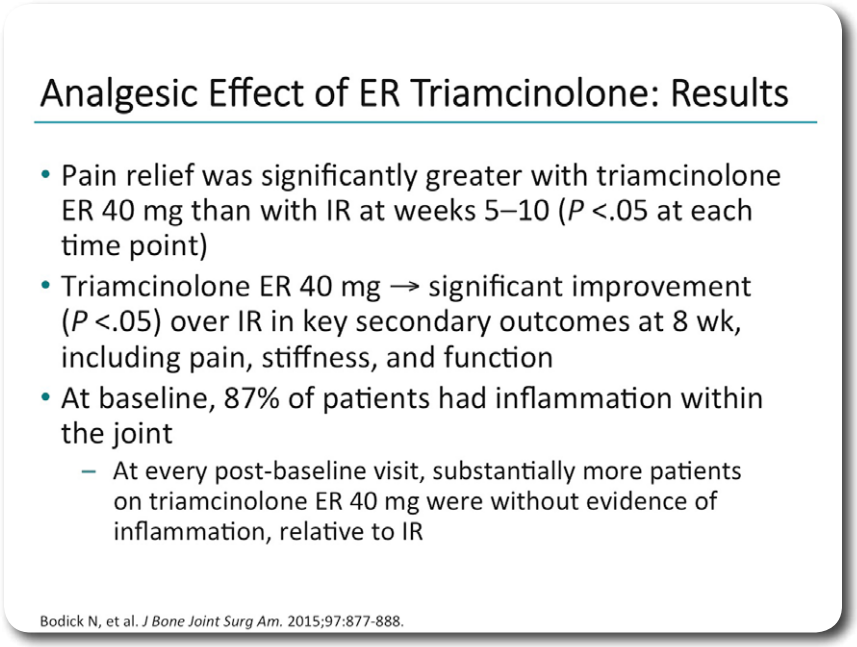
We also should look at more-nuanced measures of pain. The earlier study that we talked about, which used the x-ray endpoint, showed that the area under the curve for night pain was what seemed to be improved. Looking at area under the curve, looking at more frequent time points to try to capture the nadir of the pain effect, would potentially give us some insights into what the real effectiveness, or lack thereof, would be for this type of agent.



Dr Richmond: Let's look at some clinical practice issues. We are going to move on in a little bit different direction. I would like to reference an article by Bodick et al, which was looking at an extended-release formulation of cortisone, specifically triamcinolone.

Studies show that corticosteroids have a large analgesic effect that typically wanes relatively quickly over a week, or 2 or 3 or 6 weeks, as we have just talked about. Their goal was to determine whether an extended-release formulation of triamcinolone could provide pain relief superior to the short-term, immediate-release products that we have available to us now.

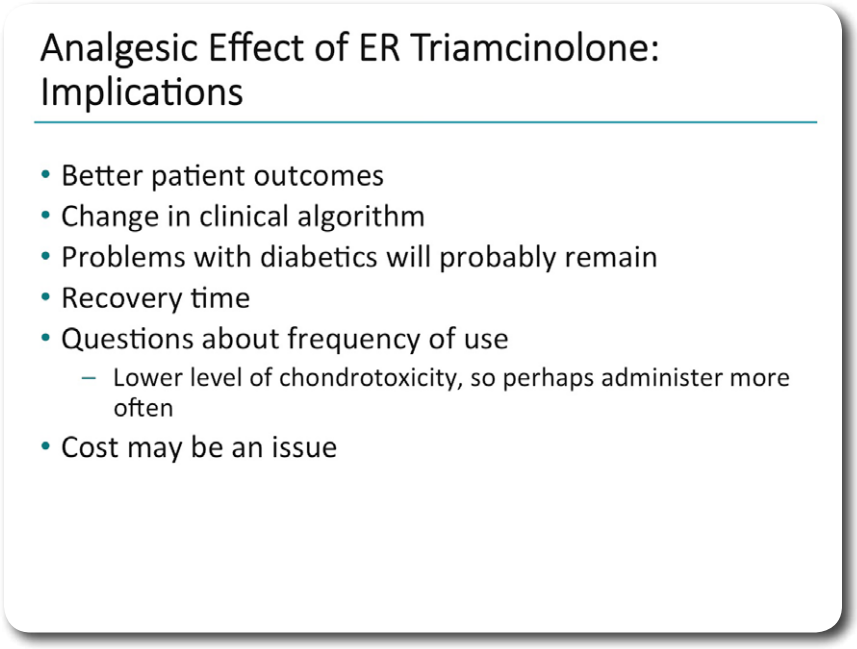
It was a phase 2 randomized controlled trial in preparation for trying to obtain FDA approval for this preparation. They randomized 228 patients into various dosages of the extended-release product and finally settled on 40 mg. Actually, only 32 mg was delivered with that. And they randomized that against 40 mg of the immediate-release standard product.



Dr Richmond: The pain relief from the extended-release product was significantly greater than with the standard product during the 5- to 10-week period, so the time after 4 weeks, when normal triamcinolone had its maximum effect.

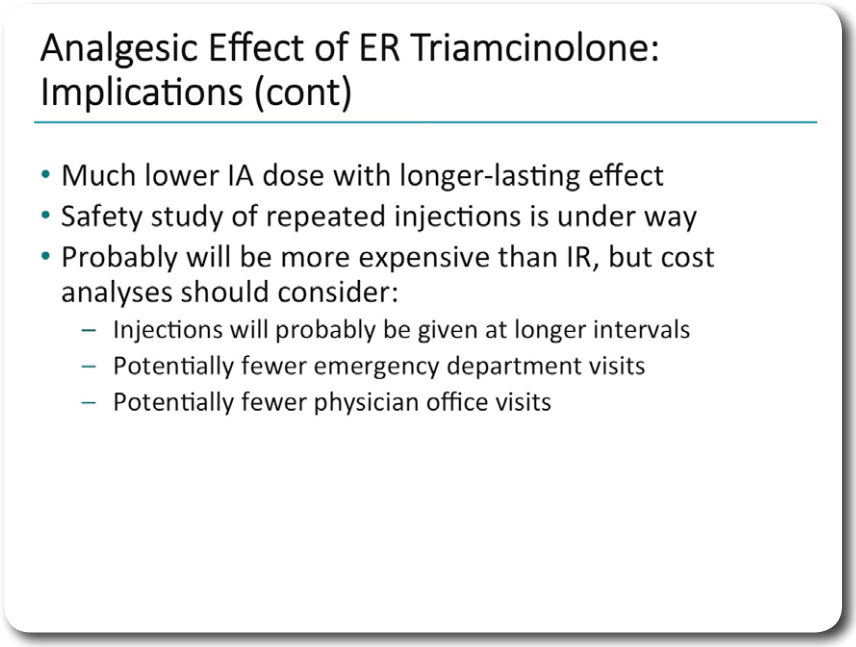
They showed a significant improvement with the extended-release product over immediate-release triamcinolone in all of the 8-week secondary outcome measures: pain, WOMAC, stiffness, all of those things that we normally look at.

And if we think of synovitis as the main problem related to progression of OA, at baseline 87% of their patients had inflammation within the joint, and the extended-release formulation substantially increased the percentage of patients with no sign of inflammation, relative to the short-term release product. So, these are all very important things.



Dr Richmond: As we move from a bolus dose to an extended-release product, this is likely going to show clinical improvement in our patients. It will also change our algorithm if we have something that lasts longer. It will likely continue to be a problem with diabetics. The average effect with corticosteroids is 3 to 6 weeks, and now with the extended-release product we have 3 months. So, that may, as we know, change the paradigm of how we treat patients.

How frequently can we use it? There are going to be questions that arise about this. Because it's a much lower dose level, the potential for toxicity may be lower, as we talked about in the basic science studies. Toxicity is related to dose, and this is going to be a very low dose, so it may be below a threshold, and we may be able to use it more often. It's new, so cost may be an issue. We have a number of things we are going to have to incorporate into our patient selection and treatment of patients going forward.



Dr Richmond: I would like both of you to comment on how it is going to change our treatment algorithm going forward.

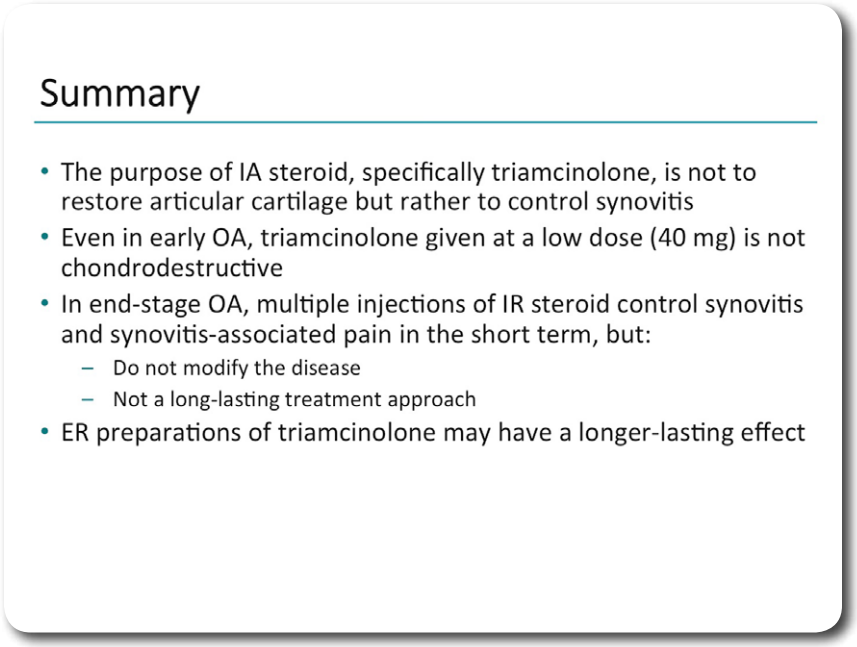
Dr Kraus: This represents a very exciting prospect and breakthrough for patients with OA. It will be a much lower dose for longer periods of time intra-articularly. The pharmacokinetic study is currently under review, so that we can compare those doses, which look to be much lower than any of the doses we talked about earlier that might have some potential chondrotoxicity.

In addition, ongoing right now is the serial injection study to look at the safety of repeat injections. If that proves to be safe, then we can have something that could be given repeatedly, and, given the longer duration of action, probably much less frequently than the current immediate-release.

Dr Richmond: That is very exciting, but this is going to be a new product. It's going to be something coming to the market and cost may be an issue. I would like to have Dr Lattermann comment a little bit on that.

Dr Lattermann: Yes, that's correct. I mean, all new technology coming onto the market usually doesn't come cheaper than the previous one. However, this is the kind of approach that will potentially have a longer-lasting effect; therefore, the actual treatments may become spaced out longer.

It is not going to abolish OA, but it will allow us to control the symptoms of these patients for longer periods of time. That may reduce things like emergency department visits; that may reduce things like physician visits. These kinds of things need to be looked at in a cost analysis in the end, and in today's day and age that will have to happen. But overall, I am very excited to see this come, because we are frankly running out of good treatment options for these patients, and I am looking forward to having this available.



Dr Richmond: Right. So, I would like to have a little moment to conclude this. I think the effect of IA steroids, specifically triamcinolone, is not to restore cartilage but to control the synovitis. We are treating the synovium and not the chondrocyte.

Even in early OA, triamcinolone given in the low dosage at 40 mg is not chondrodestructive as we look at it now. In end-stage OA, multiple injections of a short-acting steroid control the synovitis and control the synovitis-associated pain in the short term. But it neither modifies the disease nor is a long-lasting treatment approach that will solve the problem. It is a way to prolong function.

And, finally, the time-release preparations that are coming on the market now may offer us a huge opportunity for longer-lasting effect.

I would like to thank both of you, Dr Kraus and Dr Lattermann, for being here.

Dr Lattermann: Thank you.

Dr Kraus: Thank you.

Dr Richmond: And I would like to thank you, the audience, for participating in the activity. Please continue on to answer the questions that follow and complete your evaluation. Thank you.

This transcript has been edited for style and clarity.

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Abbreviations

ACL = anterior cruciate ligament
ACR = American College of Rheumatology
AUC = area under the curve
CTX = carboxyl-terminal collagen crosslinks
ER = extended-release
FDA = US Food and Drug Administration
IA = intra-articular
IR = immediate-release
MRI = magnetic resonance imaging
NSAID = nonsteroidal anti-inflammatory drug
OA = osteoarthritis
THA = triamcinolone hexacetonide
WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index