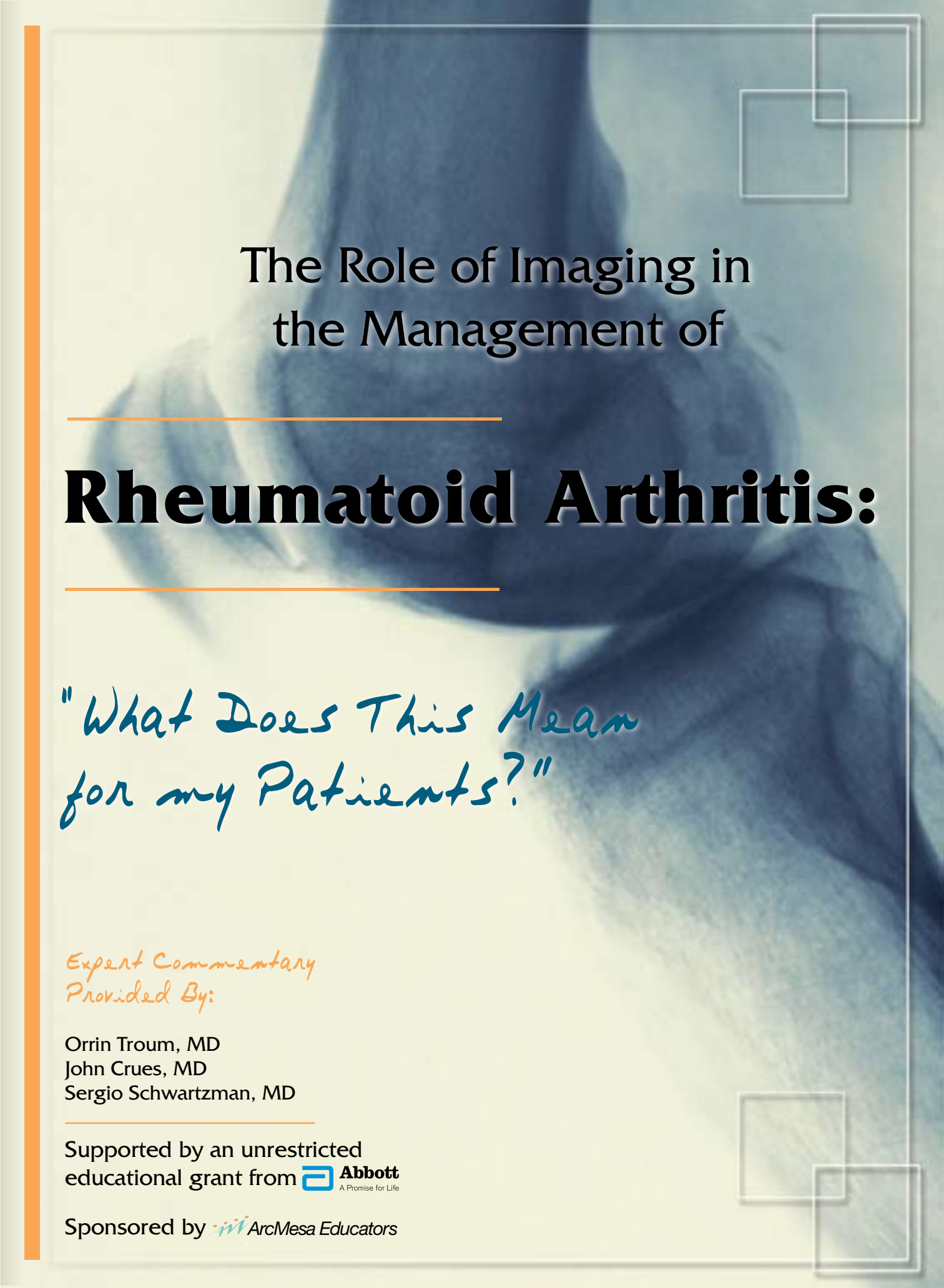

The Role of Imaging in the Management of

Rheumatoid Arthritis:

"What Does This Mean for my Patients?"

Expert Commentary Provided By:

Orrin Troum, MD
John Crues, MD
Sergio Schwartzman, MD

Supported by an unrestricted educational grant from Abbott
A Promise for Life

Sponsored by ArcMesa Educators

Rheumatoid Arthritis:

NARRATOR: The following 1-hour educational activity is sponsored by ArcMesa Educators for Physicians. ArcMesa Educators is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. ArcMesa Educators designates this educational activity for a maximum of one AMA PRA Category one credit. Physicians should only claim credit commensurate with the extent of their participation in the activity. And now, I would like to turn the program over to Dr. Orrin Troum.

DR. ORRIN TROUM: Welcome to today's CME activity entitled, *The Role of Imaging in the Management of Rheumatoid Arthritis Patients. "What does this mean for my patient?"* I would like to introduce our expert faculty who will be leading today's discussion. Dr. Sergio Schwartzman; Franchellie M. Cadwell Associate Professor of Medicine in the Division of Rheumatology Weill Medical College, Cornell University and the Hospital for Special Surgery, New York Presbyterian Hospital; and Dr. John Crues, MRI fellowship Director and Vice President of RADNET, and visiting clinical professor of radiology, University of California San Diego School of Medicine. I would also like to recognize Dr. Richard Wakefield, senior lecturer in rheumatology of the Academic Unit of Musculoskeletal Disease, Chapel Allerton Hospital, who kindly provided the section on ultrasound for this program.

Patients with active rheumatoid arthritis are most likely to experience irreversible joint deterioration within the first two years following diagnosis. Joint deterioration is associated with poor physical function, poor response to treatment, and increased health costs.

Therefore, early detection and treatment of RA is critical to prevent further erosion of the joints. Ultrasound and magnetic resonance imaging are both able to detect early changes in joint structure that would not be observed with radiography. Thus, advances in imaging in RA may lead to earlier detection of joint deterioration and allow the clinician to identify more accurately those patients in need of biologic versus traditional disease-modifying therapy.

And now I would like to turn over the program to Dr. Schwartzman.

DR. SERGIO SCHWARTZMAN: Thank you, Dr. Troum. As we all well know, the use of biological therapies, both in the United States and in the world, has dramatically expanded over the last decade. Over 1.5 million patients have been treated with the three anti-TNF agents with close to a million of those treated with infliximab.

The actual approved indications for anti-TNF therapies vary, which implies that there is a difference between the three anti-TNF agents. If we look at this next slide on the worldwide approved indications for anti-TNF agents, you can see that all three anti-TNF agents: etanercept, infliximab, and adalimumab are approved for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Two of the anti-TNF agents, etanercept and infliximab, have been approved for the treatment of psoriasis and adalimumab has been submitted for approval to the FDA in the United States.

Juvenile rheumatoid arthritis has only one anti-TNF agent that has been approved, and that has been etanercept. Adalimumab has been submitted to the FDA, but has not yet been approved, and infliximab will probably not be submitted to the FDA.

Inflammatory bowel disease is a group of diseases where we do see a clear-cut difference between these agents. Infliximab and adalimumab have been approved for the treatment of Crohn's disease, whereas for ulcerative colitis, only infliximab is approved. Adalimumab is being studied for this indication, but has not yet been submitted to the FDA.

Finally, we look at worldwide indications. There has been one anti-TNF agent that has been approved for uveoretinitis in Japan, and that is infliximab.

If we look at the frequency with which these anti-TNF agents are utilized, this has also been rapidly expanding. This next slide looks at rheumatoid arthritis and the use of therapies over the last six years. If we look at this slide, you can see that the use of biological agents has expanded dramatically, and through 2005, 41.8% of patients with RA will have had some exposure to a biological agent. This data is two years old, so if we extrapolate this further, clearly, there has been a much more dramatic increase in the use of these medications. Interestingly, corticosteroid use is slowly going down, and these two may be connected in some manner.

The topic for this discussion is the radiographic changes, radiographic progression, and the importance of imaging in the treatment of patients with rheumatoid arthritis. One of the issues that has been raised has been the importance of is radiographic change. Does it truly have any impact on ultimate disability? This paper, published three years ago by Maillefert, looked at patients who had rheumatoid arthritis and found several things.

Number one, it was clear that radiographic progression could be noted very early, within two years of the disease if we are using plain x-rays, and clearly, within the first five years of the disease, this is relatively obvious. The other issue is that it occurs in most patients with rheumatoid arthritis. One study looked at patients with very short duration of disease, that is less than one year but with followup of five years or more, the and asked whether the patients who had radiographic change had a higher HAQ (Health Assessment Questionnaire) or disability index. And that clearly was found as well.

Rheumatoid Arthritis:

As we think about the current commonly utilized strategy for the treatment of early rheumatoid arthritis, clearly the first issue is to establish the diagnosis. Once that is done, most rheumatologists in the United States will very aggressively treat with a remitive medication, commonly methotrexate. The question of followup of these patients is still open. In Europe, very frequently the DOS 28 is utilized, whereas the process of objective outcome measurements in the United States is one that is currently evolving. Most rheumatologists will obtain baseline x-rays and repeat these yearly. If a response is achieved, the therapy is maintained; however, if that is not the case, depending on how that is defined, most rheumatologists will then move to a biological agent.

As we think about radiographic progression, the anti-TNF agents have all been studied in patients with early RA, here defined as having had the disease for less than three years. I am going to review the three trials looking at the individual ant-TNF agents with a particular emphasis on radiographic progression. This next slide delineates the three anti-TNF agents, etanercept, in which the ERA trial looked at 632 patients who were methotrexate naïve and actually dosed them with either 10 or 25 mg etanercept. The Aspire trial had slightly over 1,000 patients. Again, patients treated had a disease of less than three years duration and were given either 3 mg or 6 mg of infliximab with methotrexate versus a methotrexate control. Finally, the Premier trial looked at close to 800 patients that were treated with one of three arms, adalimumab every other week by itself, adalimumab plus methotrexate, or methotrexate alone.

So I am just going to briefly go over the study designs, and this next slide delineates the ERA study design. You can see that these patients have now been followed for more than five years, and that the group that was the placebo group for the first two years was crossed over into the etanercept group. This next slide follows the change in total SHARP score through two years. You can see that when you compare the etanercept treated group through two years to the methotrexate control at a reasonable dose of methotrexate, there is a statistically significant difference between the two. This data has now been available for more than four years.

Next we look at the infliximab study in the next slide. This is the Aspire study where they looked at over 1,000 patients and looked at three arms, all of which contained methotrexate. The first arm was methotrexate plus placebo. The second arm was methotrexate plus infliximab at a dose of 3 mg/kg, and the third arm was a higher dose of infliximab; that is 6 mg/kg with methotrexate. And if we look at radiographic results from this trial over a one year period of time, you can see that in this early RA trial whether you use 3 mg/kg or 6 mg/kg of infliximab, these were super-imposable curves; the methotrexate arm showed clear-cut progression. The infliximab arms were almost completely flat.

The last trial set is the Premier Trial, which is interesting because it differentiated between an anti-TNF agent alone or an anti-TNF agent plus methotrexate versus a methotrexate alone control arm. So, there were three arms in this study, and this next slide looking at the Premier trial shows the change in total Sharp score. You can see that the methotrexate alone in blue has a progression that is much greater than the adalimumab arm or than the adalimumab plus methotrexate arm. And it was the adalimumab plus methotrexate arm that had the greatest benefit.

So, I think that this introductory piece does demonstrate that anti-TNF therapy, particularly in combination with methotrexate, is superior to methotrexate alone in preventing straight radiographic progression. We know that radiographic progression does have importance. It does correlate with HAQ and disability. The issue that will be raised further is the question of how good x-rays are to follow the patients with rheumatoid arthritis.

Finally, I think that as we move forward, we need to come to some sort of consensus as to what type of objective visual and radiographic changes we need to follow over time. I will now introduce Dr. John Crues, who will contrast and bring information regarding methods of imaging, x-rays and MRIs.

DR. JOHN CRUES: Well, thank you very much, Dr. Schwartzman, for setting the stage and so nicely showing the role of the different new therapeutic modalities in the treatment of rheumatoid arthritis. What I'd like to do is try to put imaging into a proper perspective. In order to do that, I think we need to determine what critical information is in inflammatory arthropathy that imaging may be able to help us determine to manage patients. And I think this can be divided into four overall groups. One is to quantify and evaluate synovial inflammation. Another is to detect early bone injury while at a reversible stage, and this would be at a stage probably before it is detectable by x-ray techniques. Yet another is to detect stage and quantify total bone injury and much of this will be at an x-ray detectable stage. The last is to evaluate cartilage and other soft tissue injury, which may be important in managing the patient with rheumatoid arthritis.

In the next slide, projection radiography or standard x-rays has been the standard way of using imaging evaluation for patients with rheumatoid arthritis in the past. X-ray is very effective at detecting cortical bone detail, but it shows very poor contrast for soft tissues and for trabecular bone. It displays the images in very high resolution in two planes, but the problem with projection radiography or standard x-rays is that you have very poor depth resolution. Therefore, the sensitivity for trabecular bone pathology and for anywhere where you have overlapping cortical bone is poor.

The next slide shows a standard AP projection radiograph and a low-field MRI next to it; this is a patient who has a

large bone erosion in the third metatarsal head. And you can see it's really not detectable by x-rays but is detectable by using an MR technique.

The next slide shows a high-quality AP projection x-ray and a high-field MRI, which shows a small erosion of the lunate, which was also not detectable on x-rays. There have been many studies, at this point probably in the neighborhood of 50 to 60 studies that have been published in the rheumatology literature which have looked at the difference in sensitivity between x-rays and erosions. Some of them are listed in this next slide, and all of them have shown that MR is more sensitive than x-rays, anywhere between twice to 9.5 times more sensitive for MR versus x-rays.

Now, though x-rays are probably not as sensitive as MR, there has been an important role for radiography in the past. Because of its poor sensitivity for detecting bones and soft tissues, it has had relatively limited use in the management of individual patients, though a number of people, as Dr. Schwartzman has stated earlier, have recommended that it be used yearly to evaluate patients because some patients may progress with their bone injury even though clinically they may be in remission. The bone injury, as he stated, is really what's most important in the long-term prognosis of these patients' functionality.

Projection radiography has been used most in conjunction with scoring systems as a primary outcome measure in clinical trials. This was the kind of data that Dr. Schwartzman presented to us earlier, where the Sharp score was used as the primary outcome for bone injury. These scoring systems, reviewed a little bit in the next slide, are the Sharp Larsen and Genent scoring systems, and there are many variations of each of these that have been published in the literature. They are very advantageous because they do three things. They increase the overall sensitivity for projection radiography for detecting bone injury because they sum up large areas.

They use uniform interpretive criteria, which are important for clinical trials, and simplify the reporting to a single number. They do this by assigning numerical values to the amount of erosion at each individual joint, which are scored. They also assign a numerical value to joint space narrowing and some other findings. They add these to come up with the overall score, and that's what is used to follow patients in clinical trials.

Now, MRI shows different information than x-rays, and the next slide summarizes some of these differences. MRI can quantify synovial thickness, volume, and vascularity. As we'll see, this may be important for evaluating synovitis. MRI is the most sensitive technique for detecting early osteitis, which may be the early erosive lesion at a stage where there is very limited destruction of trabecular and cortical bone. Therefore, it cannot be detected by x-ray techniques, which are most sensitive to the density of the calcium in the calcified mineralized bone.

MRI and CT are both very good for looking at standard erosions where the cortex has been violated, and there is a cortical defect. But MRI is really better for looking at articular cartilage disease and other soft tissue inflammatory diseases, which are a component of rheumatoid arthritis, and also may be important in properly managing patients.

The next slide shows a marked synovial thickening. This is really the hallmark of synovitis with MRI or any imaging technique. Typically, the synovium is a very thin structure that is only a millimeter or two in thickness, and here we can see that the synovium in this ankle is well over a couple of centimeters. That's very abnormal.

The next slide talks about early enhancement. People who have acute inflammation of the synovium also have synovial thickening, as well as acute inflammation. Histologically, you get increased vascularity as well as inflammatory cells. Those acute inflamed synovium will enhance very early, within a minute of injecting the IV contrast. Chronic synovial inflammation, however, tends to lose the abundance of vascularity and tends to have later enhancements. This may be very important because with standard x-rays and using a Sharp score, it takes somewhere between two and six years to see detectable changes in erosions. With MR, there have been several papers to show that you can see significant erosions and their change within a six to eight month time frame. There are some suggestions now that if you have a drug that is effective in treating inflammation, you can see changes in the rate of enhancement within weeks of introducing that patient to the new drug.

So, the early synovial enhancement may be a very rapid indicator of drug efficacy, and this still has to be further studied. Nonetheless, it is a very promising area for both evaluating drug efficacy as well as very rapidly evaluating patient's response to anti-inflammatory medication.

The next area I'd like to talk about is erosions by MRI. In this particular patient on this high-field MR scan, we can see several different stages of erosive disease. The red area shows an irregularly marginated area that is low in signal on the T1-weighted image on the left but very bright on the water sensitive proton density fat suppressed image on the right. This is the typical appearance of osteitis, and the paper listed below in *Arthritis and Rheumatism in 2007* by Jimenez-Boj has shown with biopsies that this is early osteitis. It's not really interstitial edema. These are actual inflammatory lesions in rheumatoid arthritis.

The yellow arrow shows an area that's not very bright on the proton density fat suppressed image. This is characteristic

of more chronic erosions. The one in the lunate in between is very characteristic of middle stage erosions where you have sharp margins. It doesn't look like the acute osteitis, but it still doesn't have enough fibrous tissue in it to be low in signal intensity on the PD fat image. So these are, kind of, three stages of erosions.

Multiple papers have also shown that we actually can see changes in erosions with MRI. This particular paper by Chen et al, published last year in *Journal of Rheumatology*, shows an erosion in a patient in the distal ulna, which on 12-21-05 was first visualized by MR. The patient was placed on TNF alpha agent, and you can see a significant decrease in just a little over a year in the size of the erosion. So this is improvement in erosive disease. More frequently, we'll see progression in erosive disease and as Orrin may talk about later in this program that may be an indicator to potentially change treatment.

Next, I'd like to talk a little bit about the soft tissue changes, which MR can show. One of the end stage changes in rheumatoid arthritis is degenerative joint disease and osteoarthritis, which typically occurs because of destruction of articular cartilage. This next slide shows a full thickness defect in the articular cartilage of the knee, which can be seen by MRI. So MRI is a technique which we're using frequently now to evaluate the status of articular cartilage, and that may be important in patients with rheumatoid arthritis.

Other areas of importance include soft tissues, and can be seen in the next slide, which is an axial image through the wrist in a patient with rheumatoid arthritis. The red arrow shows the extensor carpi ulnaris tendon, which is dislocated away from the normal little recess that is the distal ulna. We can also see that it's enlarged and has increased signal intensity within it, as well as fluid surrounding it. These are all indications of severe tinosynovitis of the extensor carpi ulnaris, which we see in almost 50% of the rheumatoid patients we evaluate. We can also see fluid around the flexor tendons, more to the left of the image and also synovial thickening and effusion within the distal radioulnar joint. All of these are manifestations of the inflammatory process, which is active in this particular patient.

Finally, MRI can be used similarly to plain films in quantifying progression of disease in longitudinal studies. The EULAR has created a group called OMERCT, Outcome Measures in Rheumatology Clinical Trials, and that group has put together a scoring system similar to the Sharp score but for MRI, and it's called RAMRIS or RA MRI Scoring System. As with the Sharp score, it assigns numerical values for the amount of erosions at different joints, but it also evaluates the amount of synovial thickening and marrow changes within the bone or the osteitis changes. It assigns these numbers for every joint, and then these are summed to a single numerical score.

And I think the next slide just summarizes; this can be very helpful for clinical trials. It is somewhat cumbersome to use in management of individual patients because it is time consuming, which would increase the expense of regular MRI, but it also has some limitations in individual patients. We found that up to 15% of patients on biologics show both progression and regression in the same interval, which might decrease the sensitivity of a single scoring system for evaluating active disease. Also, small definitive changes in the size of erosions may not cause changes in the RAMRIS score. So it may be a little bit insensitive for significant changes in individual patients, and there's a lot of information on MRI studies in individual patients, which are not included in the RAMRIS score.

The next slide talks about management of individual patients. MRI detects osteitis, what we believe is a reversible stage before erosions can be seen by x-ray techniques, and these have now been biopsy proven to be inflammatory lesions. Unlike projection radiography, MRI detects changes in erosion size in months rather than years, and this is of individual erosions. And MRI can see soft tissue changes that may be important for patient management.

Now, there are several different types of MR systems. They are generally classified as whole body scanners, which can be of multiple field strength and extremity scanners. Extremity scanners typically come in either 0.2 Tesla with a low field, or 1 Tesla, which would be a high field scanner.

The next slide shows two common ones at 0.2 Tesla. One on the left is a very open arrangement, and you can evaluate the shoulder as well as the distal extremities. The one on the right is a little bit more closed, allowing just the distal extremities to be scanned. The next slide shows a high field extremity scanner, just allowing the extremities to be scanned. And the next slide shows a small portable MRI scanner that is also 0.2 Tesla, which just evaluates a small field of view in the hand or feet.

The next slide contrasts imaging at high field, 1.5 Tesla on the top, with low field, 0.2 Tesla on the bottom. For classic bone erosions, the two give very similar information. Where there is a difference, however, is in the ability to evaluate synovial enhancement. The early enhancement that we're talking about we believe can only be done accurately, right now, using a high field scanner. Several studies have shown that early osteitis can be picked up more sensitively at high field than at low field, but the overall volume of the synovium and the erosions are seen well with both fields.

The next study was a study that looked at dedicated low field MRI, and showed that if you use a scoring system, low field MRI is similar to conventional MRI in diagnosing and scoring synovitis in patients with rheumatoid arthritis. The next slide summarizes a study by Lindegaard, showing that

low field MRI and portable MRI can be very effective at assessing patients who are at risk for more rapidly progressing disease. Again, we can see in the next slide that even the low field portable MRIs are much more sensitive for detecting erosions than standard plane radiograph. We also published a study in the *Journal of Rheumatology* in 2004, which showed that portable MRI was much more sensitive than x-rays.

In summary, I think there are some advantages of small MRI systems; though at low field the image quality may be a little bit worse than at high field. Outside of looking for a time intensity curve analysis of synovial enhancement or maximum sensitivity for early osteitis, I think high field and low field systems are very similar in their overall accuracy in evaluating rheumatoid arthritis. The smaller systems lower the cost of providing the services. They can be more convenient because they can be placed within the clinic. Patients don't have to go to special imaging centers to have the studies done. The positioning of the patients is much easier, and it's safer for some people who may have risk factors for a standard whole body MRI scanner. There may be some technical differences in what information one gets between high field versus low field scanners, but we've found that the low field extremity scanners can be very effective in helping the rheumatologist get the information he or she needs in managing their patients.

DR. ORRIN TROUM: John, that was a very nice overview, and we appreciate that input. It really added to what Sergio had said earlier in regard to the next step in imaging and how we're utilizing that. It's very promising, at least from our work using advanced imaging, both ultrasound and the extremity scanners that seem to facilitate the availability and usefulness of MR. Patients don't have the fear of getting into the larger machines, and so we're actually getting this information.

Sergio and I and others were actually going to do studies to help in standardizing this so that we are able to utilize advanced imaging. At this point, we're utilizing it as though it's a day to day event, at least for those of us using MR and several now are using ultrasound to really replace x-rays. Do you think that there will ultimately be a place for plane radiography in evaluating new medications for rheumatoid arthritis or inflammatory arthritis, or will there still be use for an x-ray?

DR. JOHN CRUES: None in the areas of musculoskeletal disease. In areas like oncology and in sports medicine, x-rays are still used, but their use is very limited as a secondary tool to evaluate unusual findings on an MR. They are really not the primary tool anymore because of their lack of sensitivity.

DR. SERGIO SCHWARTZMAN: John, I have a couple of questions, and I'm not sure if they are all going to have definitive answers. Can you give me a sense as to the natural history of erosions as viewed through the MRI? What happens from start to finish?

DR. JOHN CRUES: I think we'd have to put this under the idea of theory, and I think some people would agree with it. Some people feel now that parts of it may not be correct. I think the initial event is synovitis. You can see it as synovial thickening and especially in the early acute stages as a really early enhancement pattern on MR. Then where the capsule and the synovium are attached to the bone, on the periphery where the bone is not protected by the articular cartilage, that the inflammation can extend through the cortex of the bone on the margin of the joint. The inflammation extends into the medullary bone where it replaces the normal medullary fat with inflammatory cell, and I think that's the lesion that's often called bone marrow edema. But I think, as what we've been shown recently by the group out of Vienna, that that's actually true inflammatory cells, not extravascular edema. It's really inflammation, and I think that is the initial erosion lesion. And at that time, the trabecular bone is still intact. It's probably in the matter of weeks and months before that inflammation then destroys the trabecular bone.

DR. SERGIO SCHWARTZMAN: And that causes the erosion. Now, where would you put osteitis as you've described it so far is synovitis, bone marrow edema, erosion? Define osteitis and tell me where you would put it.

DR. JOHN CRUES: I think it goes synovitis, osteitis, and erosion.

DR. SERGIO SCHWARTZMAN: What about bone marrow edema, or do you equate osteitis with bone marrow edema?

DR. JOHN CRUES: I personally don't think bone marrow edema should be used. I think it was used because when we see increased water in the bone, in the subchondral bone like that, in sports medicine it's due to fractures and edema. In rheumatology, I think this is osteitis.

DR. SERGIO SCHWARTZMAN: Do you think that bone marrow edema is part of osteitis? It's basically inflammatory cells that are permeating the bone and the bone marrow?

DR. JOHN CRUES: Yes and I think that's the initial erosive lesion, but at that point, it's x-ray negative.

DR. SERGIO SCHWARTZMAN: Got it.

DR. JOHN CRUES: It has not destroyed enough of the mineralized bone yet, but if a specific study was directed at it, it would probably show that if you treated the patient with effective anti-inflammatories at that time, you would completely reverse the lesion.

DR. SERGIO SCHWARTZMAN: Okay, so then synovitis, osteitis, erosive disease is the way that you would go?

DR. JOHN CRUES: Yes, and I would also like to emphasize that the body can rebuild cortical bone because it has a periosteal scaffolding to rebuild the bone on. It cannot rebuild trabecular bone effectively because it's a three dimensional structure, and it has no substrate to rebuild the trabecular bone. So the irreversible event is probably the destruction of the trabecular bone, which occurs in the osteitis phase.

DR. SERGIO SCHWARTZMAN: So it occurs pretty early?

DR. JOHN CRUES: Yes.

DR. SERGIO SCHWARTZMAN: You demonstrated very nicely if you look at an MRI image of a patient who is successfully treated, at times there is "improvement." What areyour views were regarding what exactly that represents when we see it?

DR. JOHN CRUES: I don't have any histologic proof of what's happening. My guess is that in the earlier stage, you still have intact trabecular bone in the periphery of the lesion.

DR. SERGIO SCHWARTZMAN: Although it's not an erosion, right?

DR. JOHN CRUES: It's an erosion. Again, my feeling is that the early erosion is the osteitis, but if it is x-ray positive, it has to be an erosion. I think that's a late stage erosion, but that's all semantics. But when you see the erosion at the early stage when it's developing, the trabecular bone in the periphery of that erosion is still not destroyed. So if you stop the inflammatory process, that area of the erosion can heal itself. Often, the center of the erosion where the trabecular bone is completely destroyed is irreversible, and you'll be left with a central little geode even if you have effective treatment.

DR. SERGIO SCHWARTZMAN: You know that they are doing these arthroscopy studies on "patients who have not healed" but had improvement. I think Artie Cavanaugh is doing one such study.

DR. JOHN CRUES: Oh, good.

DR. SERGIO SCHWARTZMAN: Sometimes what looks like a tremendous erosion on an MRI, doesn't look like anything on the plane film. I understand the difference between two dimensional and three dimensional, but at times the erosions are so large on the MR and you see nothing on the x-ray that I have trouble reconciling that. How definitive are we about what we're describing as erosive disease on MR?

DR. JOHN CRUES: I think it's a little bit supported by the pathologic study that came out of Vienna that was in *Arthritis and Rheumatism*. I think what's happening is that the erosion that we see on an MR in the early stages is the replacement of the normal fat by inflammatory cells which don't have fat in them; they're water-based cells. MR is very sensitive to that.

DR. SERGIO SCHWARTZMAN: So it's not a cortical defect necessarily?

DR. JOHN CRUES: Right, it's what you're doing. We're seeing the bone marrow replacement. If the trabecular bone is still intact and most of the cortical bone is still intact, you're not going to see that on an x-ray.

DR. SERGIO SCHWARTZMAN: So we're not looking at destruction of the cortical and all of the trabecular bone, we're looking more at the osteitis or the bone marrow edema? I know you're not comfortable with that term, at that phase when we are seeing that on MR and not seeing it on an x-ray.

DR. JOHN CRUES: Yes, and I think those are very important lesions.

DR. SERGIO SCHWARTZMAN: I agree.

DR. JOHN CRUES: Because those are the reversible lesions?

DR. SERGIO SCHWARTZMAN: Correct.

DR. ORRIN TROUM: Sergio, you really asked the most pertinent questions, and John you clarify that for me every time I hear you talk about it. If you go back to the 2002 American College of Rheumatology Guidelines, one of the goals of treatment for rheumatoid arthritis is preventing structural damage. The point here is if we have better technology and outcome studies that suggest things like synovitis and osteitis ultimately lead to erosive disease and structural damage. The whole point here is that the utility of these imaging techniques is really to get to the patients earlier. Do you agree?

DR. JOHN CRUES: I think it is something that we are beginning to look at not only from the radiographic perspective but from the clinical perspective as well. So I think that there has been a movement along the specialty, and I think that this is the objectivity that we need.

DR. ORRIN TROUM: John, what do you think would be needed to make this a well accepted technique to move rheumatology forward with other subspecialties in utilization of, in particular, MR?

DR. JOHN CRUES: We were at this level in orthopedics

Rheumatoid Arthritis:

about 10 to 12 years ago, where we thought we were seeing a lot of things with MR, but we didn't have any papers to actually show that if you used MR information in the management of people in orthopedics that you could actually change the outcome. When those studies came about, MR became the dominant imaging technique in sports medicine and orthopedics. I think what would be necessary in rheumatology would be to find studies based upon the theory that we think may well be correct. If you define studies where they use MR information to change the management of the patient and show that patients treated with the MR information have better outcomes, what we showed with orthopedics was that it also decreased the cost of overall care by using MRI. That's when MRI became the dominant imaging modality in sports medicine. I think we need those same studies in rheumatology. By treating early osteitis, we can have our maximum impact upon the long term prognosis of the patient and potentially create treatment mechanisms where you stop the disease process. We can then use less costly maintenance programs using MR to more sensitively define progression of the disease. Then I think we can come up with ways to improve patient outcomes and decrease the cost of the medication by using MR to very accurately define the progression of the disease.

DR. ORRIN TROUM: I think you said it all. With that I wanted talk about the methods of imaging, in particular ultrasound, and to give credit to Dr. Rick Wakefield, who is a senior lecturer in Rheumatology of The Academic Unit of Musculoskeletal Disease, Chapel Allerton Hospital. In Europe, this has been a way to image patients with rheumatic diseases for a lot longer than it has been utilized in the United States, although it is certainly gaining popularity here.

The advantages of ultrasound are that it's inexpensive relative to MR, and John, you pointed out nicely the four FDA approved extremity MR imaging machines that are available. There's a shorter scanning time and potentially, immediate interpretation in the clinical for the person actually performing the ultrasound study. There's relatively good access, especially in Europe and now more so in the United States. It's well tolerated, which is especially important for multiple examinations in the office. It's relatively quick to perform, although that depends on the technician or the physician doing the study. Many joints can be assessed, with simultaneous visualization of soft tissue and bone.

The next slide talks about the disadvantages, and one of them in particular is this operator dependency. Standardization is required, currently underway by OMERACT, which is the Outcome Measures in Rheumatology Clinical Trials group. It requires an acoustic window, avoiding blind spots, and the specificity decreases with osteoarthritis.

In regards to cortical bone erosion, the OMERACT definition is an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes. It has high sensitivity compared to x-ray but is lower compared to MR. There's high specificity. Interpretation may be difficult in context of osteoarthritis, and the requirement of an acoustic window may miss erosions, especially in the wrist where you can't visualize or see around the complete carpal bone. There is little data on responsiveness to change, although there are recent papers that have been presented to that effect, in particular at Barcelona at EULAR this year. Also there are potential problems with scoring, and John, you mentioned scoring earlier in regard to MR.

The next slide gives you an example on the left of the bone, and you can see that yellow arrow is pointing to the metacarpal head bone in the phalanx as you see to the right. And then on the right-hand slide, you have the red arrows pointing to a defect, and obviously, this is not as clear as MR images, but with practice and by visualization of course, this is operator dependent again. You can see what's an outline of an erosion.

In regards to synovitis, the next slide describes it in clinical practice. This is usually taken as a composite of synovial hypertrophy and/or synovial fluid because although in some joints it's easy to differentiate between fluid and tissue, in many it is not. Synovial tissue may or may not exhibit Doppler flow. I'll describe that in a moment. Increased Doppler flow may suggest active disease, but joints with no obvious Doppler flow still erode, and not all joints in early RA with significant amounts of what's called gray-scale synovitis exhibit Doppler signal. The OMERCT definition of synovial hypertrophy is an abnormal hypoechoic that's relative to subdermal fat, it sometimes may be isoechoic, the same as, or hyperechoic intra-articular tissue that is non-displaceable and poorly compressible and may exhibit Doppler signal. There's no agreed scoring system, although most currently rely on a 0 to 3 semi-quantitative score. However, it's not often scored separately to fluid.

Ultrasound is more sensitive than clinical examination but less than MRI. Again, there's that limitation by the acoustic window. Gray scale has reasonable specificity in the metacarpophalangeal joints, which is increased by power Doppler at the expense of sensitivity.

The next slide discusses the different types of Doppler and methods of measurement. There's power Doppler, traditionally the most sensitive, but recent developments demonstrate less difference with color Doppler. Then there is color Doppler, and then the spectral Doppler with calculation of resistive index, allowing quantification of the signal. When talking specifically about synovial effusions, this is an abnormal hypoechoic or anechoic, again, relative to the subdermal fat also could be isoechoic or hypoechoic. Intra-articular material is displaceable and compressible but does not exhibit Doppler signal. Again, there is no agreed scoring

system and ultrasound is better for detecting fluid than clinical examination even in the knee.

The next slide actually shows gray-scale synovitis. There are four images here. On the top, you see the metacarpophalangeal area. You see the extensor tendon on the left upper, and on the right upper you see the proximal interphalangeal. The flexor tendon is outlined there, and then when you look below on the left, you see synovitis with the asterisks there, and you see that darker area. This takes some time to become familiar with this, but with a lot of experience, it becomes relatively easy to see. The advantage is you're able to manipulate the probe to pick this up, and you can do it right in the office.

The next slide shows power Doppler of the metacarpophalangeal joint region, with the white area just being the bone. Just above that, you see synovitis, and with the power Doppler, you see this activity. In regard to joint space narrowing, there is little data available. It's not reproducible unless assessing complete loss of joint space, and defining bony landmarks is problematic. It depends on where you take the measurements, which we do when using ultrasound.

In regards to the predictive value of ultrasound, the next slide describes early studies that suggest that the magnitude of the gray scale and power Doppler studies may predict outcome. The first study from Peter Taylor was published in *Arthritis and Rheumatism* three years ago and a more recent study by Naredo in *Arthritis and Rheumatism* was published this year.

In regards to the diagnostic value of ultrasound, it detects synovitis and erosions earlier than standard means, specifically x-ray. Therefore, it is likely to quicken the diagnosis and allow early disease suppression. There is little formal data, but studies of oligoarthritis suggest that ultrasound allows earlier fulfillment of ACR rheumatoid arthritis criteria. Karim et al highlighted a change in site-specific diagnosis and overall diagnosis in patients with musculoskeletal problems.

In regards to disease monitoring, ultrasound is able to demonstrate changes in erosions and synovitis over time. Several papers have demonstrated changes post-treatment, specifically after corticosteroids and anti-TNF therapy. Ultrasound detected synovitis correlates with changes in the disease activity score, DAS 28. There are some other references that are available as you see in the next slide. We will now discuss the clinical relevance of imaging in rheumatoid arthritis.

The previous demand for joint imaging was modest. Prior to effective structure- modifying therapy, detailed information about joint structure really wasn't needed to monitor patients. Plane radiography was sufficient. Why would you pay more for an MRI or even for ultrasound? With effective structure-modifying therapy, specifically biologic therapy, imaging, I believe, becomes an essential component of therapy and managing patients. We must now consider the pros and cons of various imaging techniques, which would include plane radiography x-ray, CT scan, MRI, and ultrasound.

The next slide again brings up the point regarding structure-modifying therapy, raising the bar and shifting in therapeutic strategy from controlling pain and limiting toxicity to really minimizing joint destruction. Early intensive treatment before irreversible damage occurs is essential. Thus, the demand for better methods of identifying patients who actually need intensive therapy ultimately controls costs and limits risks. In private practice and those in clinical practice monitoring patients, can monitor treatment effectiveness by seeing whether or not structural damage is arrested, either adjusting the dose of medication if there is an adjustable dose for the medication I'm using, or potentially changing therapy.

The next slide discusses a paper by Fiona McQueen published several years ago in *Annals of Rheumatic Diseases* on MR predicting the erosive phenotype and particularly rheumatoid arthritis. They found that the MR erosion score was predictive of two-year x-ray erosion score. Only 18% without MR erosions at baseline showed x-ray erosions at two years. Sixty-one percent with MR erosions at baseline showed x-ray erosions at two years. But what I think is very important here, was that multi-feature MRI was more predictive than MR erosion alone. John alluded to this earlier and Sergio also brought up the question regarding osteitis, synovitis, but erosion marrow edema or osteitis, synovitis, and tendonitis, the sensitivity was 80%, specificity 76%, and the negative predictive value was 86%.

This next slide shows MR of tendonitis and tinosynovitis. The three images here show in white, areas that really would not be picked up by x-ray except possibly for soft tissue swelling. The next slide from Chuck Peterfy shows pre-erosive, what was termed then marrow edema or inflammation, and John helped to clarify it as being termed osteitis, which really does and can progress to erosion. You look at the baseline on the top and then 17 months later on the bottom. Here's T1 images before it breaks through the cortical bone and then below that an obvious erosion. Then as you go through the T2 fat suppressed and the Gadolinium enhanced images on the top and then on the bottom, erosion is clear 17 months later.

The next slide shows that osteitis can progress rapidly. On the top you see in the metacarpal head, the darkened area to the right of the metacarpal bone, and then ultimately at six months, erosion and then similar findings below. Baseline osteitis can predict functional disability at six years. Benton and Fiona McQueen's group in New Zealand published this in 2004 in *Annals of Rheumatic Diseases* showing that baseline osteitis score was more predictive of erosions and disability

at six years than other MRI features, clinical features or CRP alone or in combination. Erosion score correlated with disability at six years, but not at baseline. Osteitis correlated with disability at baseline but not at six years.

The next slide shows that erosions can resolve also. The top shows x-ray and the bottom MRI findings. It's hard for me to discern on the x-ray over the baseline 3, 6, and 24 months any significant change in the carpal bones there, but below you see the obvious darkened area within the carpal bones, and it shows that it actually has resolved with the use of anti-TNF therapy. In a paper published in the *Journal of Rheumatology* last year, Chen et al looked at the detection of change in size of erosions on MRI. This was actually a group of patients from my office; they were followed to evaluate changes in erosion over time among patients with inflammatory arthritis on aggressive therapy. Over 95% of these patients had rheumatoid arthritis. The baseline MRI was using the portable unit that John showed earlier, obtained in 406 patients. Almost all of the patients were on TNF inhibitors, 156 patients had 276 followup exams, ranging between 1 and 19 months, averaging 8 months. The change in erosion or erosion diameter of 20% was considered significant; 184 patients had x-rays for comparison. For overall MRI findings, 50% of the patients had not detectable change, but 30% had an increase in erosion size of at least one erosion, 178 individual locations initially with no erosions. Eighty-four percent showed no change, but in 26 of 178 patients, 15% showed new erosions, and in fact, those are the patients that ultimately had a switch in therapy. In 184 patients with followup x-rays, only one exam showed a new erosion, and 1 showed an increase in previous erosion, showing the lack of sensitivity with plane radiography.

The conclusion of that study was that MR was better than x-ray in showing the change in damage. In an average followup of eight months, 30% of patients on aggressive DMARD therapy and biologic therapy had an increase in the size of at least one erosion. To summarize what we've talked about, imaging data can help predict when a patient may need a biologic therapy versus standard DMARD therapy. Early detection of radiographic progression is key to minimizing structural damage. The use of imaging can help improve the cost efficacy of treating patients with rheumatoid arthritis. I believe that ends this discussion. Sergio or John, do you have other comments?

DR. SERGIO SCHWARTZMAN: Actually, I have two questions that I can pose to both of you. In terms of x-rays or radiographic followup of patients with rheumatoid arthritis in the clinic in both non-studies and studies is it standardized to some extent in that we do x-rays of the hands and feet? Depending on where you are, do some places just do an AP of the hands and wrists and of the feet as well once a year? If we look at ultrasound and/or MRI how would you follow patients over time? Is there a standardized MR or ultrasound that you would do that was not necessarily directed to the joints that were inflamed?

DR. ORRIN TROUM: I can answer that question from what I actually do in clinical practice. But just to maybe better understand what you're asking me. If I was to look at one area.

DR. SERGIO SCHWARTZMAN: Right.

DR. ORRIN TROUM: What area would I look at?

DR. SERGIO SCHWARTZMAN: Right.

DR. ORRIN TROUM: What I've done is to try to look at the hand and wrist. In the early studies the data was not available. John and I had collaborated on this, and we have looked at both the hands and the wrists bilaterally. Over time, we have limited that to the dominant hand and wrist and in clinical practice, which would be different than any studies that were done. It is also then limited by payors and insurance and that's a whole separate issue. From a scientific standpoint, I would think you would go where you would expect to see the changes happening the fastest and that would be the hand and the wrist, although previous studies have looked at the foot. David Yocum and Ewa Olech looked at that in the past, but how I've utilized this is looking at the metacarpal joints, depending on the machine that you're using in the extremity MR. If you are using the portable machine, you're basically limited to two joints in the hand and most of the rest. If you are using one of the larger machines, you can look at the entire hand and wrist, and that's how I would utilize this in my practice.

DR. SERGIO SCHWARTZMAN: Orrin, how long does it take to do the entire hand and the wrist in your practice?

DR. ORRIN TROUM: A hand and the wrist would take about an hour and 15 minutes. If you are looking at one study, it's about 45 minutes. We'd go through all of the sequences; we'd look at all the same regulations and the protocols that they would for a standard MR. John, you might add to that.

DR. JOHN CRUES: Sergio, are you talking about people who are in clinical remission?

DR. SERGIO SCHWARTZMAN: I mean people who may or may not be clinically active; your garden-variety patient in a clinical rheumatology practice.

DR. JOHN CRUES: But they don't have a new hot joint?

DR. SERGIO SCHWARTZMAN: They don't have a new hot joint. Yes, they are somebody who has been on an anti-TNF, for a year, and they've had low-grade of disease

but nothing dramatic. You are wondering should I standardize the way I follow this patient. It's not at a time when the patient is completely failing and you're thinking about switching medications. I think that this is a more common type of patient, although obviously we see both types. I guess my question is really two fold. First, is there standardization for what joints we should image in a given patient who may or may not be very active? The other part of that question, which I think is the more difficult one, is who should we be doing these imaging procedures on? From what we've presented, we can almost argue that every patient with rheumatoid arthritis should have either an MRI or an ultrasound. But is that something that we should be considering? Should every patient who's had rheumatoid arthritis have a baseline imaging procedure and then be followed in a standardized manner over time?

DR. JOHN CRUES: We've discussed that a lot with the rheumatologists I've worked with, and I feel we should. You have to realize, a lot of people are concerned about the costs. But if you actually look at the cost of the TNF alpha inhibitor, the drug costs are far greater than any MRI costs. If we can show that MRI is effective and if we can actually develop treatment protocols, which can limit the cost of the drugs based upon being confident that there is not progressive bone damage, MR may actually be able to save a lot of costs and improve outcomes. I like to use a little bit of a model that's used in oncology because rheumatoid arthritis is an erosive disease. It destroys bone and can affect many parts of the body not dissimilar from what happens with malignancies.

I think it makes most sense to get a baseline imaging on every patient who's diagnosed with rheumatoid arthritis. And I think, you know, the diagnosis is based upon your criteria. The MR shouldn't be used so much in the diagnosis, but MRI should really be the staging. I think it's best to know the extent of the disease at time zero, especially the extent of bone erosion and osteitis as a baseline. Typically the hands and wrists, both sides are used for a baseline study. If they have symptoms in the feet, then include the feet, but most of the time, without foot symptoms it's just the hands and wrists bilaterally.

Ostergaard showed last year in a paper that was published in *Arthritis and Rheumatism* that if you follow people over time and just image the dominant hand and wrist, very little information is lost. After that, if there isn't a hot joint that you really need to look at, following the dominant hand and wrist will probably get most of the information you need to follow patients over time.

DR. SERGIO SCHWARTZMAN: Orrin, any difference in terms of that?

DR. ORRIN TROUM: No, John stated it better than I attempted to, but that's basically what I've done. The question then would be how frequently to image? That obviously would need protocols and would have to be proven and studied, but in essence, it is not at one year. If I have a patient who has new onset rheumatoid arthritis and I was to image their hands and wrists and see osteitis, this would be the deciding point to start anti-TNF therapy or biologic therapy with methotrexate. I'm likely to rescan that patient in six months. I might rescan them six months later if everything is now stable. I would feel as though I've done the best I can to get the most information regarding stopping progression of structural damage.

Ultimately, the question is when you can potentially stop therapy and still be able to follow patients over time with the usual clinical measures, DAS scores, HAQ scores, and whatever clinical parameters you're following in the office along with imaging. Then potentially the cost savings that John was talking about might take place by withdrawing therapy. That's yet to be determined. Are there any other questions or comments?

DR. JOHN CRUES: I had a question for Sergio. Sergio, the imaging information that we've talked about and the differences between ultrasound, MR and regular x-rays, will this have an impact upon the way clinical trials are going to be designed in the future, since we get different kinds of information from MR and CT than with a standard x-ray?

DR. SERGIO SCHWARTZMAN: John, I think really across many rheumatic diseases, that is something that we're already seeing. Orrin and I were just at EULAR, and it is amazing how many trials now include an MR or an ultrasound component. These are both investigator-initiated trials as well as pharmaceutically-sponsored trials. So I think that from the trial perspective, the information is much more useful when it can demonstrate earlier disease, and perhaps more objective about whether there's halting or progression of the disease. So I think this is already happening.

The question is, is it going to become standard? I think in rheumatology in that regard things go slowly. We're still using the ACR 20 as a primary outcome for many trials. And I think that is an antiquated outcome measure. It doesn't necessarily reflect what it was intended to, which is efficacy. So I think that, yes, MR and ultrasound are going to replace radiographic outcome measures.

DR. JOHN CRUES: Sergio, I appreciate your enthusiasm, and I also appreciate you retracting that quickly, because things do take time in our rheumatology community. I may mention that ISEMR, the International Society for Extremity MR in Rheumatology, has been formed and is also looking to promote research, publish papers, and be a forum for those of us that are utilizing this technology in the United States and internationally. There are also ultrasound societies that

are available and continuing to gain support. I know in university centers, such as at University of Southern California, they now have an ultrasound-teaching course for the fellows as they rotate through their fellowship.

So it's an exciting time. I think that we're looking to do the right thing, to get to our patients earlier, to utilize better technology, to confirm that what we're doing is correct, and that we're really looking to halt the progression of disease. This is a way that we can prove it to ourselves and to our patients earlier than with plane radiography. Are there any other comments? If not, I'd like to thank you, Sergio and John, and also to thank Rick Wakefield for his slides that I presented for him, and I appreciate everybody's enthusiasm and interest, and thank you very much.

DR. ORRIN TROUM: This concludes our activity. We would like to thank our faculty for imparting their expertise in the use of imaging in rheumatoid arthritis. Thank you for joining us. It is our hope that your participation in this activity has been not only thought provoking but will assist you in your clinical practice.

NARRATOR: Thank you for your participation in this activity. Please remember, to receive your credits you must complete the on-line post examination and evaluation forms. Your certificate of completion will be provided immediately upon successful completion.