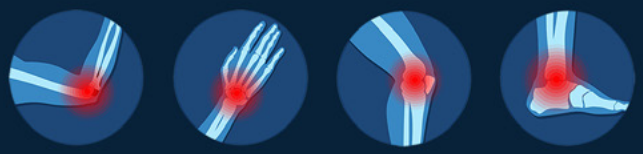
NAVIGATING THE RECENT RHEUMATOID ARTHRITIS GUIDELINES TO ACHIEVE DISEASE REMISSION AND REDUCE PATIENT BURDEN



OVERVIEW

Roy M. Fleischmann, MD, discusses the latest evidence for the management of patients with moderate-to-severe rheumatoid arthritis who do not achieve treatment goals with initial disease-modifying antirheumatic drug therapy. A key treatment principle emphasized by Dr. Fleischmann is using a treat-to-target approach guided by validated tools for assessing disease activity and patient-reported outcomes. Among the treatment options, Dr. Fleischmann highlights the pharmacology of the latest approved treatments for rheumatoid arthritis. Using case scenarios, he illustrates how they might be integrated with other therapies.

TARGET AUDIENCE

This activity was developed for a national audience of rheumatologists, primary care physicians, nurse practitioners, physician assistants and other healthcare providers who manage patients with rheumatoid arthritis.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Describe the clinical pharmacology, safety and efficacy of the latest approved treatments for rheumatoid arthritis (RA)
- Incorporate bDMARDs and tsDMARDs into management of patients with moderate-to-severe RA based on their individual needs, best evidence, and treatment guidelines
- Use a treat-to-target approach guided by validated tools for assessing disease activity and patient-reported outcomes
- Select evidence-based therapy options including combination therapy when RA treatment goals are not achieved with initial DMARD therapy
- Identify extra-articular manifestations in a patient with RA through collaboration with the primary care provider

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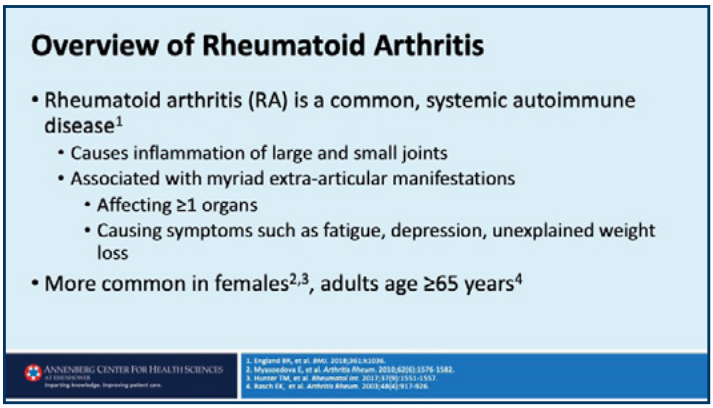
Editor's Note: This is a transcript of the activity. It has been edited for clarity.

Hello. I'm Dr. Roy Fleischmann. I'm a clinical professor of medicine at the University of Texas Southwestern Medical Center in Dallas and the co-medical director of the Metroplex Clinical Research Center in Dallas. And I'm going to speak to you about navigating the recent rheumatoid arthritis guidelines to achieve disease remission and reduce patient burden.

EPIDEMIOLOGY

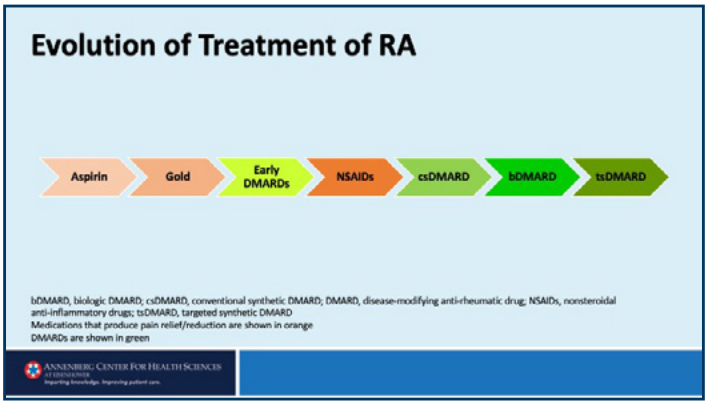
Rheumatoid arthritis is a systemic autoimmune disease that produces inflammatory arthritis involving both large and small joints. More importantly, it can affect other organs. It's a systemic disease. The prevalence in the United States is estimated to be between 1.3 and 1.5 million people, about 0.5% of adults. There is a sex variation with predominance of females of about 75%. And although it can occur at any age, it does vary by age, with the highest ratio in adults greater than age 65 years, with 2% of adults over the age of 60 years suffering from rheumatoid arthritis. The reason for this is that rheumatoid arthritis doesn't disappear in virtually anyone. As patients age, they continue to have rheumatoid arthritis. We have noticed that there is a lower ratio of male-to-female in declining 10-year age groups.



This is a multisystem disease. It can affect the eyes. It can affect the lungs. It can affect the heart. It can affect the gastrointestinal (GI) tract. It can affect the hematologic system, the skin, nerves, and the kidney, amongst other organs. The controlling of the disease is not just control of the symptoms in the joints. It really is controlling inflammation so that the systemic manifestations of rheumatoid arthritis are brought under control. And as a systemic disease, it is associated with patient features such as fatigue and generalized weakness, depression, malaise. Patients can have low-grade fever and they can have a weight loss, which is explained by the systemic nature of the disease.

PHARMACOLOGIC OPTIONS

The first drug for rheumatoid arthritis was aspirin, which was discovered in the late 1890s. And not until the 1930s was there a second drug, which was gold injections. Gold injections came about because it was felt that the disease could be infectious. And it was noted that in patients who had tuberculosis (TB) and were treated with gold for the tuberculosis, the patients with



rheumatoid arthritis actually got better. And that became the gold standard for rheumatoid arthritis for the next 50 years. In the 1950s, hydroxychloroquine was used with some success. And more importantly, steroids were first introduced with dramatic success, although with significant side effects. In the 1960s, we saw other disease-modifying antirheumatic drugs approved, including D-penicillamine and sulfasalazine, which had various effects and various side effects.

It was only in the 1970s that other nonsteroidals, other than aspirin, were introduced. And a plethora of NSAIDs were introduced in the 1970s and 1980s, which did help the patient with respect to pain, but did not stop the systemic complications of the disease or the progression of the disease in the joints.

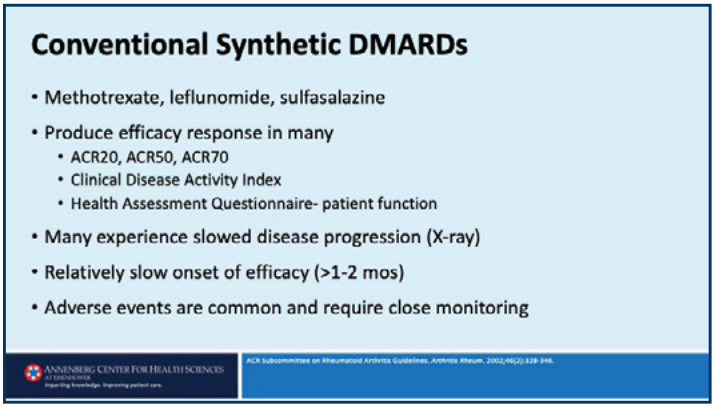
Dramatically, in the 1980s, methotrexate was introduced. Oral gold was used for a short period of time. It had toxicity issues. It wasn't that effective. And azathioprine was used, but methotrexate turned out to be the new gold standard as about a third of patients treated with methotrexate went into a true remission and many patients felt better. It's truly a disease-modifying drug. In the 1990s, we saw the introduction of cyclosporine, which does have an effect, and leflunomide, which has an effect perhaps as good as methotrexate.

But then the next dramatic change after methotrexate was the introduction of biologic DMARDs. And this included both etanercept in 1998 and infliximab in 1999. And in the 2000s, we had other tumor necrosis factor (TNF) inhibitors introduced such as adalimumab, certolizumab, golimumab, but also other mechanism of action of biologics. An IL-1 inhibitor, anakinra, a B cell depletor rituximab and a costimulatory molecule inhibitor, abatacept. And in the past 10 years, we've had even more. We've had IL-1 effective agents approved such as tocilizumab, sarilumab. And then even more recently, we've had the introduction of Janus kinase (JAK) inhibitors, which are oral DMARDs. They're called targeted synthetic DMARDs, as opposed to the biologics, which have to be injected. There's been dramatic evolution in the treatment of rheumatoid arthritis.

The pathobiology of rheumatoid arthritis is very, very complex. As you can see on this slide, there are multiple cells that are involved. Antigen-presenting cells, T cells, monocytes, B cells, plasma cells. All of which have effects systemically, but also on the joints—particularly on the osteoclasts, synoviocytes, and chondrocytes—they do joint destruction. And as you can also see on the slide, there are multiple immunoactive molecules, interleukin (IL) -6, other cytokines, TNF, IL-17 amongst them,

that are involved in the interplay between the cells and the immunopathology of rheumatoid arthritis. This presents multiple targets for the treatment of rheumatoid arthritis.

To go back to the conventional synthetic DMARDs, what we did find in clinical trials in the 1980s, 1990s, was that methotrexate, leflunomide, and sulfasalazine were effective in controlled clinical trials. They do achieve an ACR20 response vs placebo or an active comparator. And the ACR20 response is the best metric to determine whether the drug is active or not. As you can see that all 3 of these were able to achieve ACR20 responses vs their comparators. But they also achieved ACR50 responses and even, to some extent, ACR70 responses.



There were some patients who did achieve true remission, such as a Clinical Disease Activity Index (CDAI) of less than 2.8, and this is more so for methotrexate and perhaps leflunomide and sulfasalazine. All 3 also did help patient function, with a decrease of the Health Assessment Questionnaire (HAQ), which is a measure of patient function. And they also all inhibit X-ray progression to some extent.

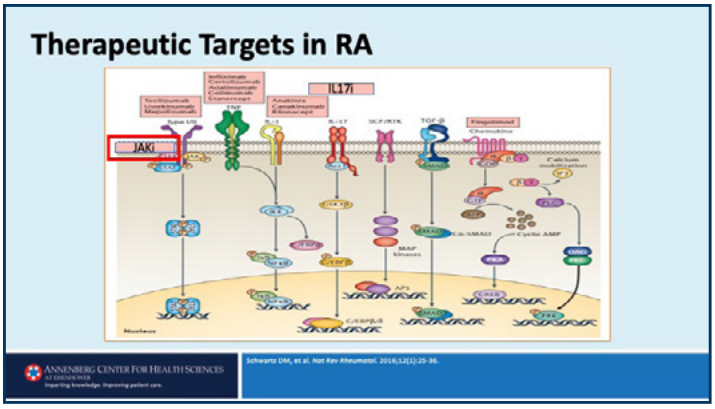
As we've seen in clinical trials over the years, about 70% of patients treated with methotrexate or leflunomide, perhaps sulfasalazine, will not have X-ray progression if treated with a drug, no matter what the clinical response is.

While all of these drugs are effective, they do have toxicities. Methotrexate can cause myelosuppression. It can affect the liver, causing hepatic fibrosis and cirrhosis. There can be allergic reactions, pulmonary infiltrates, certainly serious infections are increased. Patients can develop stomatitis, mouth ulcers, alopecia, fatigue, and malaise. Much of this can be controlled if you use folic acid daily, which is the standard of care.

Leflunomide can produce hepatotoxicity, also diarrhea, which is a significant problem to patients. It can also produce alopecia, skin rash, headache, pulmonary infiltrates, which are different than methotrexate and increase the risk of serious infection. Sulfasalazine is more benign, but can produce myelosuppression and infection.

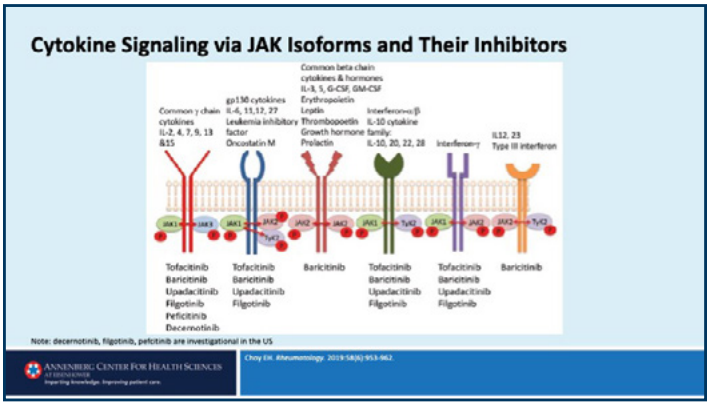
Importantly, the time to benefit for these drugs is rather slow. They're disease modifying, but they're not rapid. Usually you can see an effect within 1-2 months, but you don't really begin to see effects for about 3 months, and you don't see depth of effect until you reach about 6-9 months.

On this slide, what you see is the intracellular and extracellular schema in this cartoon. You can see, for instance, TNF, which



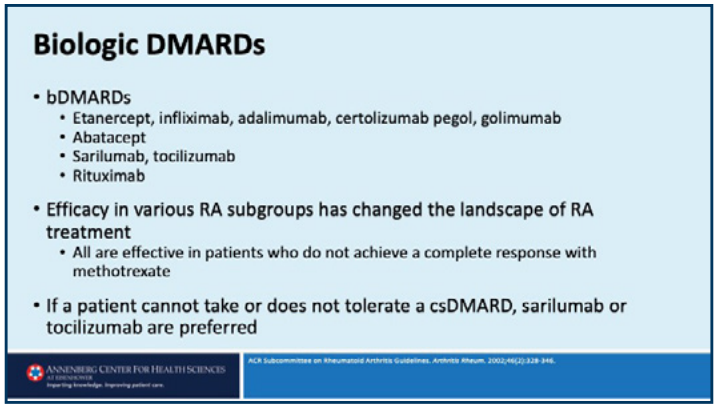
is up in the green, which is an extracellular component, which is why the biologics do work extracellularly. And you can see there you have infliximab, certolizumab, adalimumab, golimumab, and etanercept. Also, for IL-1, anakinra is approved. That's also extracellular. IL-17, which is not really that effective, or the anti-IL-17 agents are not that effective in rheumatoid arthritis, is extracellular as well. But what you can also see is the type 1 and type 2 receptors for the JAK inhibitors. The JAK inhibitors work intracellularly.

Here you can see that there are many isoforms of JAKs. There are 4 JAKs, JAK1, 2, 3, and tyrosine kinase 2 (TYK2). They generally work in dimers, occasionally in trimers, and they are found in multiple cells as you can see, including T cells, B cells, natural killer (NK) cells, mast cells, dendritic cells, eosinophils, basophils, and epithelial cells. And you can see that the function of the JAKs are multiple, but as you can see at the top it's inflammation. Then you can see the different pairs of the JAKs, such as JAK1 and JAK3, in the bottom left, affects the common gamma chain cytokines, IL-2, -4, -7, -9, -13 and -15.



And because tofacitinib is a JAK3/1, baricitinib is a 1/2, upadacitinib is a 1, filgotinib (investigational) is a 1, peficitinib (investigational) is a 3, decernotinib (investigational) is a 3, they all work on the JAK1/3 pathways. You can then see in the trimer of JAK1, JAK2, and TYK2, you get 4 of the JAKs that are effective. Baricitinib is more of a JAK2 than the others and it does work on the JAK2 dimer. You can see that the different JAKs will work in different pairs, producing their effects.

Biologic DMARDs are efficacious and they have certainly changed the landscape of the treatment of rheumatoid arthritis. Here, I've listed all the biologic DMARDs and their efficacy in patient populations, whether it's methotrexate-naive, early RA



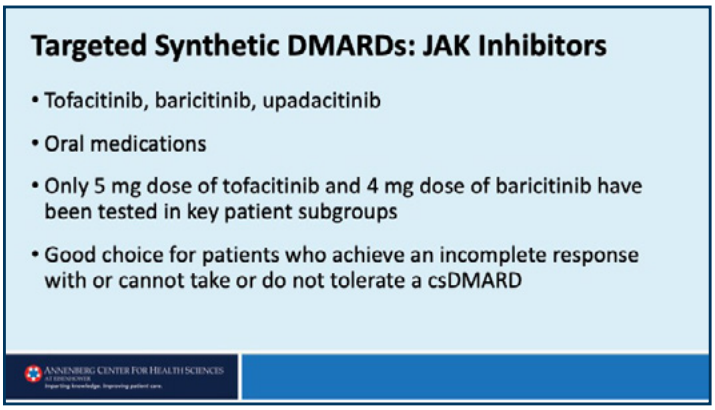
as monotherapy, methotrexate incomplete responder, or TNF incomplete responder.

You can know that many of them actually work in TNF incomplete responders. It has been shown that certolizumab, golimumab, abatacept, sarilumab, tocilizumab, rituximab all work in TNF incomplete responders. There've been no trials of etanercept, infliximab, or adalimumab in this group. They all work on methotrexate incomplete responders. They can work as monotherapy, except for golimumab, which does not work that well, nor does rituximab work that well.

And they do work in early rheumatoid arthritis, but there have not been trials of the IL-6 inhibitors or the B-cell inhibitor rituximab in this group. And in methotrexate-naive patients, neither sarilumab or rituximab has been tested.

What I would say about the monotherapy, though with this is the biologics all work better in combination with methotrexate. But if a patient cannot or will not take methotrexate, then the American College of Rheumatology (ACR) and EULAR, the European League Against Rheumatism, both recommend either sarilumab or tocilizumab, the IL-6 inhibitors, as being more effective than the other biologics.

When we take a look at the target synthetics, the JAK inhibitors, you can see that tofacitinib has 2 dosage forms, 5 mg and 11 mg. The 5 mg has been shown to be effective in methotrexate-naive patients, early RA, monotherapy, methotrexate incomplete responders, and TNF failures. The 11 mg, although it's approved, has only been tested in methotrexate-incomplete responders. Although it's probably effective in these other populations, it has not been tested.



Baricitinib is approved as 2 mg in the United States, 4 mg in much of the rest of the world. And the 2 mg has not been tested in methotrexate-naive, early RA, or as a monotherapy, but the 4 mg baricitinib has been effective in each of these populations. The upadacitinib 15 mg has been tested in all 5 of these populations and is effective. If a patient cannot take or tolerate a conventional synthetic DMARD, any JAK inhibitor is preferred, as is the IL-6.

When we take a look at the TNF inhibitors, their time to benefit is 1-3 months. They do work relatively early. I have the dose of each of these drugs on this slide and the toxicities are all fairly similar. They can all produce serious infectious episodes (SIE), they can produce opportunistic infections (OI), such as herpes zoster. They can produce demyelinating disease, cytopenias, a systemic lupus erythematosus (SLE) -like disease, hepatotoxicity defined by elevated liver function tests (LFTs). I have a question for lymphoma, but we don't really think the lymphoma is related to these drugs, but actually it's the activity of the disease itself that produces the lymphoma. They have been associated with congestive heart failure (CHF) and with venous thrombotic episodes (VTEs).

Abatacept also works as a TNF inhibitor, easy to dose. Its safety profile is different than TNF inhibitors. You can see serious infections, opportunistic infections, and autoimmune effects.

Rituximab is slower, you can see its dose. But it has been associated with serious infectious episodes and immunoglobulin depletion. And when you have significant immunoglobulin depletion, the SIEs can increase.

The IL-6 inhibitors also work relatively rapidly, within 1-3 months. You can see the 2 drugs and their doses, but they've also been associated with serious infection, opportunistic infection, LFT elevation, hyperlipidemia, although the ratio of HDL to LDL does not change, as well as neutropenia, which may be margination of the white blood cells (WBCs).

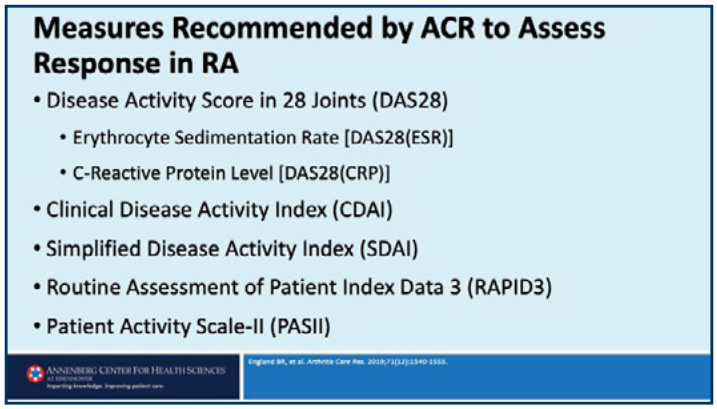
The JAK inhibitors work the quickest. If they don't work by 12 weeks, they won't work. They can work within a week, they can work within just a few weeks, and you can see the doses that are approved in the United States for the 3 of them. Their side effect profile is very similar to the TNF inhibitors; they are associated with an increased risk of herpes zoster. They also increase serum creatinine, but they don't produce renal damage. They also raise creatine phosphokinase (CPK) levels, but they do not produce myositis. They may be associated with gastrointestinal (GI) perforations, as are the IL-6 inhibitors, which I did not list on this slide, but I should have. There is certainly discussion about the relationship with venous thrombotic episodes.

MANAGEMENT PRINCIPLES

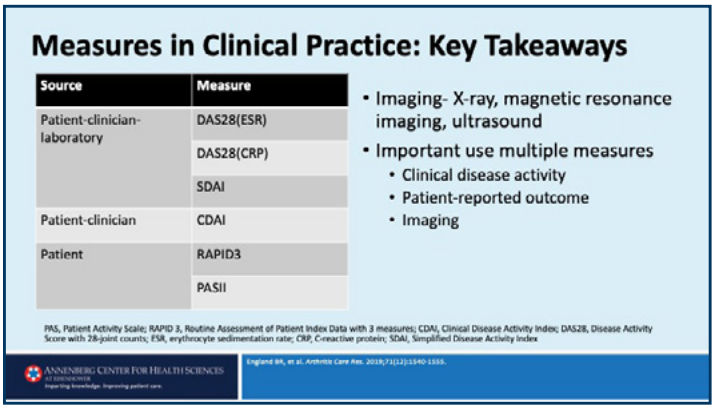
We are going to begin talking about management principles of rheumatoid arthritis. This is really multiple parts. One is assessing treatment response using validated tools and patient reported outcomes, and then I'm going to talk about treat-to-target. This philosophy has certainly taken hold in much of the world. Rheumatologists I think all agree with it. We don't quite follow it, we should. We'll talk somewhat about the overarching principles and the recommendations. And then I will briefly describe the American College of Rheumatology (ACR) guidelines and the European recommendations for treatment of RA.

The ACR recently published recommended metrics to assess responses in RA, and what they talked about was the Disease Activity Score in 28 joints, either by the erythrocyte sedimentation

rate (ESR) or by the C-reactive protein (CRP), the Clinical Disease Activity Index or the CDAI, the Simplified Disease Activity Index or the SDAI, the Routine Assessment of Patient Index Data 3, RAPID3, and the Patient Activity Scale-II, or the PASII.



In clinical practice, the DAS28, either ESR, which I prefer, or the CRP, which other people prefer, is widely used, particularly in Europe. The CDAI is more used in the US, but it is gaining popularity in the rest of the world. And the SDAI actually is a part of the ACR/EULAR remission criteria, along with Boolean remission. And the RAPID3 is a patient-reported outcome that's very easy to do and it is one of the recommended metrics that you can use, especially for patient-reported outcomes in patients.



For the Clinical Disease Activity Index, the CDAI, is the easiest to do in practice. I will show you a little bit later what the components are, but you can also use the SDAI and the DAS28. The cut points that you need to know for disease activity are lower for the DAS28 CRP than they are for the ESR, and that's really important if you're treating towards remission.

In the patient-reported outcomes, one that we can use is the RAPID3, which is the easiest to use in practice. You can use the Health Assessment Questionnaire (HAQ), which is also relatively easy to use, but the RAPID3 changes more rapidly and I think that you can see a better depth of response with the RAPID3 than the HAQ. The Short Form-36 (SF-36) is a very good instrument for health-related quality of life, but we never use it in practice. It's too difficult to do. You can use metrics for fatigue, such as the FACIT-F, which is not that difficult to do. And then there is a metric for sleep, but we generally do those in clinical trials rather than in the office.

Certainly, for imaging, most of us do radiographs, you can use ultrasound or you can use magnetic resonance imaging (MRI). But you do need to assess not one of these, but multiple ones. You need to assess clinical disease activity. You need to assess patient-reported outcome and imaging. So, in my practice, I will use a CDAI, I might also use a DAS28(ESR). I would use a RAPID3 or a HAQ, and usually a RAPID3. And for imaging, I use X-ray, although there are many people who use ultrasound, and you can use MRI, which is quite expensive, as you know.

You can see the scale for the DAS, the CDAI, the SDAI, the RAPID3, and the PASII and you can see the components of them, but I'll show them more graphically in just a moment. Now, these are disease activity. You can look at disease activity in terms of remission or low disease activity or moderate disease activity or high disease activity, using each of these.

The RAPID3, for instance, is scaled 0-10. If the patient is less than or equal to 3-4, that's thought to be remission. There's obviously still some disease activity, but it's called remission. Low disease activity would be 4-6, MDA would be 7-12, and high disease activity would be greater than 13.

For the CDAI, it's less than or equal to 2.8, and low disease activity would be 2.8-10, and then there's another metric for moderate disease or high disease activity.

Then I want to point out the DAS28(ESR) and DAS28(CRP). The metric for remission for the DAS28(ESR) is less than 2.6, but for CRP it's 2.3. And for low disease activity it's 2.6-3.2 for the ESR, but it's 2.3-2.9 for the CRP. It's important to know these differences. And then you can also see the SDAI, which as I said, is part of the ACR and EULAR definition of remission being less than or equal to 3.3.

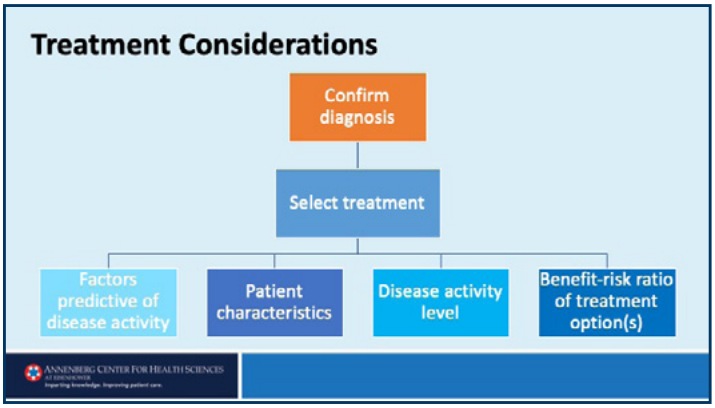
And when we take a look at these measures, you need to understand that they overlap, but there are major differences. If you see this slide, which looks at this, it's abatacept plus methotrexate in the clinical study that I did, where we looked at the DAS28. Patients who were in remission, there were 127 in this group, but when we looked at Boolean remission, there were only 52. The Boolean base is more restrictive.

If we take a look at DAS28 vs the SDAI, the SDAI is a little bit less restrictive than the Boolean, but still much more restrictive than the DAS28. Then if you take a look and see on the top, you see the RAPID3 and the DAS28 have a correlation of about 50%. And that's why you have to do both metrics. You need to look at a clinical as well as a patient-reported outcome. And if you look at D, the CDAI remission, it's 80 patients, RAPID3 is 76, but again this is about a 50% correlation. This is not only true for abatacept in this trial, but also for adalimumab.

Here is an example of imaging results. This is from the ACR slide collection, and it shows an early erosion that you might or might not pick up by a standard X-ray, but it's very obvious on the MRI. And that's one of the reasons why we think about using ultrasound as being more sensitive than X-ray and MRI being even a little bit more sensitive.

When we take a look at the therapeutic strategy in the real world, however, and we think about therapeutic choices, we start off with a diagnosis which we confirm, and then we take a look at disease severity, predictive factors of severity. We would look at

rheumatoid factor, we would look at the level of the CRP or the ESR. We look for erosion. These are all predictive of more disease severity.

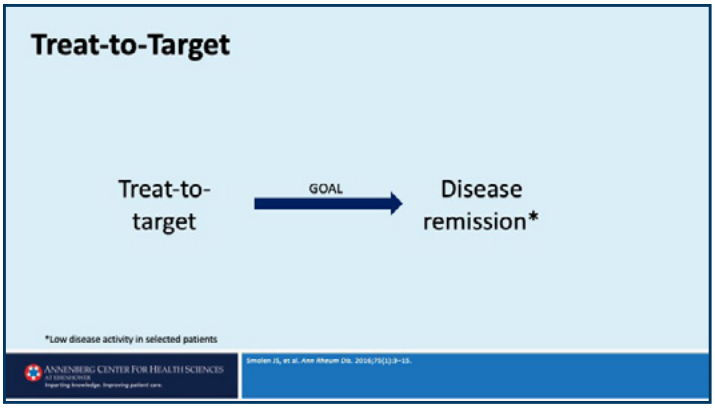


But then we also have to look at patient characteristics. What's the age of the patient? If the patient's older, the patient's more likely to have comorbidities and more likely to have serious infections. You have to think about that before we select a drug. And we have to think about patient's wishes. Do they want a pill? Do they want an injection? Do they want a drug that's new to the market? Do they want a drug that's been on the market for 30 years? And it's a shared decision with the patient where you can give the patient what your thoughts are, the patient should give you their thoughts, and you come to a meeting of the minds to pick out which medication you think is most appropriate.

You also have to think about disease activity. If a patient has high disease activity, even at the beginning, you would think about getting very aggressive with therapy. If the disease activity is where you're looking at low disease activity, and it's really very stable and really pretty/fairly low, you might think about tapering some medications, not discontinuing, but tapering. And then when you think about the drugs, you have to think about the benefit/risk ratio in each individual patient. Although the TNFs are very, very beneficial and very effective, if I have a patient with congestive heart failure, I'm not going to use a TNF. I'm going to use another mechanism of action.

Let's move to treat-to-target. The key takeaway from treat-to-target is the treatment aim is remission. And when we talk about remission, I am talking about Boolean remission or an SDAI remission or a CDAI remission. I'm talking about very, very little disease activity. In a Boolean remission, a patient can only have 1 tender or 1 swollen joint. They cannot have 2 and be in remission. But if I'm looking at DAS28(ESR) of 2.5, the patient can actually have 2 or 3 swollen joints, 6 or 7 tender joints. It's not the same. I use a strict metric that's harder to achieve, it is, but it's what you really want to go to. If a patient has long-standing disease or has significant comorbidities, treatment to remission may not be possible because you may have to use drugs that are too powerful, and you may accept low disease activity in those patients.

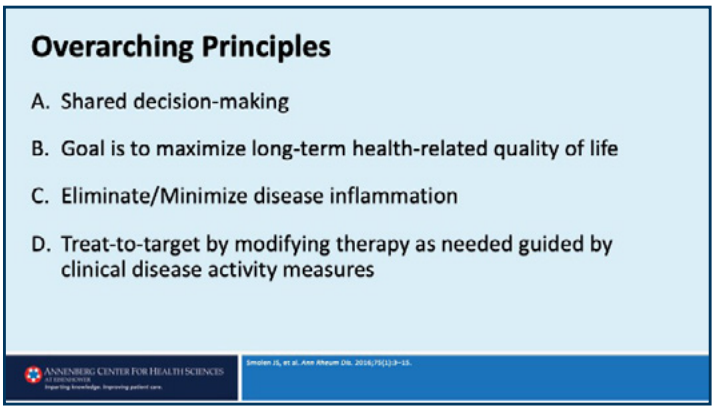
There are other patients in which you might accept moderate disease activity. You want to treat the patient to the lowest disease activity that you can, considering safety. The key takeaways from treat-to-target is when you're first seeing the patient, the follow-up has to be regular. I don't care how busy your schedule is.



You do have to see the patient probably every month until the patient achieves the goal of therapy. You shouldn't wait more than 3 months before you see the patient. You need to think about adoption of new therapies to reach the desired state within 3 to a maximum of 6 months. If you don't achieve what you're trying to achieve in 6 months, it's really time to change. One of the key components of treat-to-target is employing a composite measure of disease activity including joint counts. This does say you have to examine joints. You can't just do a RAPID3.

The other key takeaway, it's a shared decision of the patient and physician. I may know exactly what the patient needs, but if the patient doesn't agree with me, the patient's not going to do what I think they need to do. We have to come to a shared opinion as to what we're going to do.

Here are the overarching principles. It has to be shared decision and the primary goal is to maximize long-term health-related quality of life. This is controlling the symptoms, prevention of structural damage. You want to try and achieve normal function in the patient, or as normal as you can, their being able to participate in social- and work-related activities. And from the rheumatologist's perspective, the abrogation of inflammation is the most important way to achieve these goals, which is the use of medication.

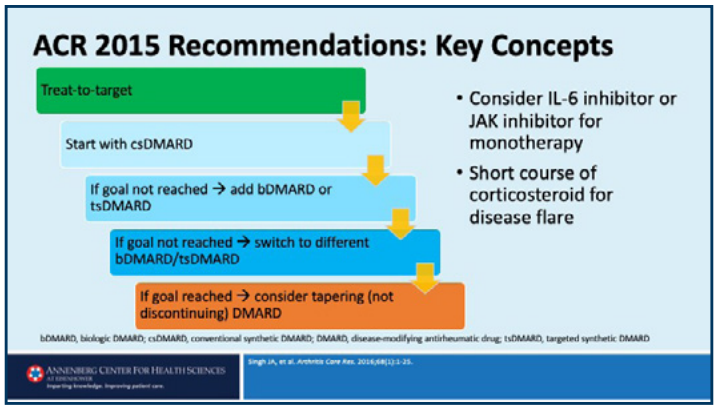


Again, D is important, treat-to-target by measuring disease activity, and adjusting therapy accordingly, optimizes the outcomes in RA.

Here are the 10 recommendations, and I'm going to go through these briefly. The primary target is remission, it's clinical remission with a strict metric. Low disease activity could be acceptable in patients with longstanding disease or a patient with comorbidities. Use validated composite measures which include joint counts.

You have to use those measures regularly, and as frequently as monthly for patients with high and moderate disease activity, but less frequently once there is sustained low disease activity or remission. And until the desired treatment targets are reached, drug therapy should be adjusted at least every 3 months. Doesn't mean you have to change drugs, but you have to change mechanism, but you have to adjust it. If you start off with methotrexate 15 mg a week, I start off with 20 mg a week, but if you start off with 15 mg a week and you give that for 3 months, the patient's better, but they're not really at target, adjustment of therapy could be raising it to 20 mg. I would raise it to 25. And, the desired treatment target should be maintained throughout the remaining course of disease, and this is very important. You have to maintain medication to maintain the patient under control. Very few patients are able to discontinue medication and remain in remission or very low disease activity.

I'm next going to talk about the ACR 2015 guideline for the treatment of RA, and I'm not going to go through it in depth. I'm going to show it to you, but here are the key takeaways. You treat-to-target, as we've discussed. You start with the conventional synthetic DMARD, usually methotrexate. If you don't reach your goal, you add a biologic or a targeted synthetic DMARD, and if you have an unsatisfactory response to that, you switch to a different biologic or targeted synthetic DMARD. Once the goal is reached, consider tapering, but not discontinuing, DMARDs. Tapering, not discontinuing, particularly if the patient's only in low disease activity.



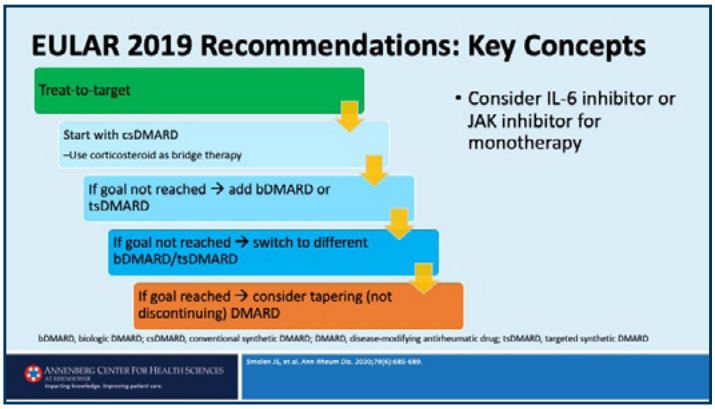
If monotherapy is used, consider using an IL-6 inhibitor or a JAK inhibitor. Every study has shown that the majority of patients require methotrexate. There are some who don't, but it's better with an IL-6 inhibitor or JAK inhibitor as monotherapy. This is different than the EULAR recommendation. You can use a short course of glucocorticoids for disease flares. The ACR, at least by the 2015 guideline, doesn't recommend starting off with glucocorticoids, although many of us do.

Here is the guideline. You see they start to have low disease activity or moderate or high disease activity. This is early RA with less than 6 months of disease and a conventional synthetic DMARD as monotherapy. They still have disease activity, then you either combine conventional synthetics, or you add a TNF inhibitor, or you add a non-TNF inhibitor. They still have disease activity; you go on to the next box. Then you can see treat-to-target is on the left, and then they have strong and conditional recommendations. This is not really based on evidence, as a matter of fact, it's based on opinion. Some of the strong recommendations are based on very weak evidence, some of the conditional on very strong evidence.

This is the second phase. They still have disease activity, and then you just keep switching. It's a very complicated schema, but that's basically what you do. You don't achieve your target, you switch.

And this is established RA. In established RA, there are other parts of this algorithm where if you had a single TNF inhibitor failure, you switch to a non-TNF inhibitor. You go to single non-TNF inhibitor, you go to another non-TNF inhibitor, but a lot of this doesn't make sense. I think the new guideline, which will be coming out later in 2020, will be clearer.

Here are the EULAR recommendations. These are relatively new, 2019, and the key takeaways are very similar. Treat-to-target, start with conventional synthetic, and use glucocorticoids as bridge therapy initially. They took about 3 months of 10 mg or less of a prednisone equivalent. If the goal isn't reached, you add a biologic or targeted synthetic, and they don't differentiate between those. The ACR, and the old guideline says, "A biologic before a target synthetic." EULAR says, "No, it doesn't make any difference." I think the new ACR guideline will say it doesn't make any difference either, and if you have an unsatisfactory response, you switch. If the goal is reached, consider tapering, but not discontinuing the DMARD.



Then I wrote DMARD. I didn't say biologic or conventional synthetic because you may be able to discontinue conventional synthetic and continue with targeted synthetic or a biologic, or you may be able to continue conventional synthetic and discontinue the biologic or the targeted synthetic. But usually when you get the patient under control and you need to add, when you begin tapering, many patients do begin to flare. Also, EULAR suggests that if monotherapy is used, consider using an IL-6 or a JAK inhibitor.

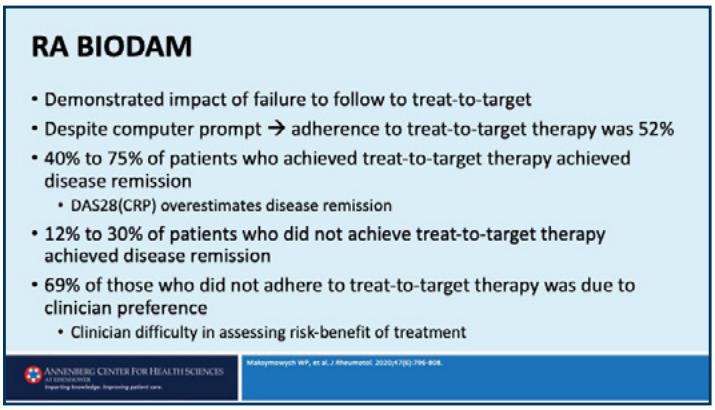
Here are their recommendations, and they're really much easier. If there's no contraindication, use methotrexate. You start methotrexate plus short-term glucocorticoids. If you can't start methotrexate, use leflunomide or sulfasalazine. If they're improved and they're on target, you're good, you don't have to go any further. You can have a dose reduction and sustained remission. They don't say stop, they say dose reduction.

But if you don't achieve your target, then you switch. Then they have poor prognostic factors present or absent. If it is present, immediately go to a biologic or a JAK inhibitor. But if the patient doesn't have poor prognostic factors, I'm going to say you can try

a second conventional synthetic, but the studies have shown that these don't work as well as adding a biologic or a JAK. Then if the patient's improved in 3 months, you're good. If not, then you need to modify what you're doing.

MODIFYING THERAPY

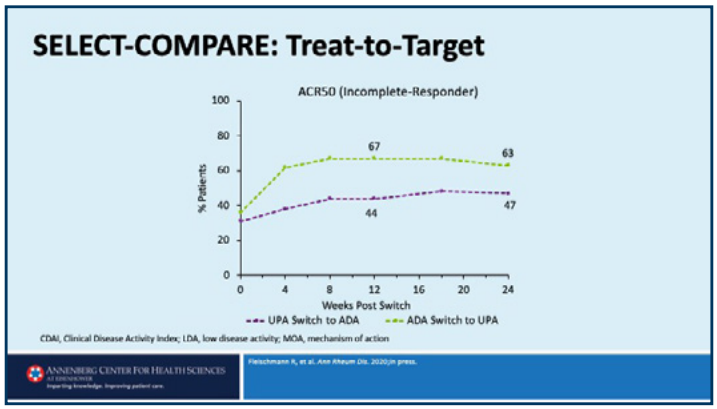
We've talked about treat-to-target. What's the impact of failure of treat-to-target? This is an interesting study. It's the RA BIODAM study. It's 172 patients with established rheumatoid arthritis with 15 months of follow-up. And the intent of this study was to develop a soluble biomarker, which they didn't find, incidentally. There was a computer prompt for treat-to-target. The patient came in, put in one of the metrics you're going to put in, joint count, patient global, physician global, sedimentation rate, and the computer would tell you whether you're at target or not. If you're not at target, it would say, "You've got to change." And what they found in this, even with a computer modeling and a computer prompt, was there was only 52% adherence and 42% nonadherence of treat-to-target.



But if we take a look at the graph at the bottom left, and whether you looked at DAS28, this was a CRP incidentally, or CDAI, or SDAI, or ACR Boolean remission, you hit treat-to-target, then those are the new numbers of patients who achieved the remission. If they didn't treat-to-target, you can see in the purple, very few patients actually achieved it. This slide also makes a point that I made in a previous section. I prefer the CDAI, SDAI, or ACR Boolean remission. They're harder to achieve. You can see 75% of patients achieved a DAS28(CRP) remission, but only 40% CDAI, SDAI, or ACR Boolean. You're fooling yourself if you think the patient's in remission with the DAS28(CRP), with the non-remission with the CDAI.

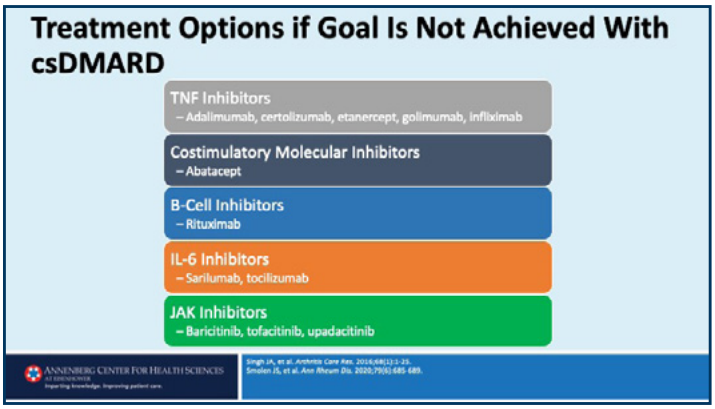
Then on the right side of the slide, you can see the reasons that the patient preferred not to change. They had adverse events (AEs), they couldn't take a medication, and the other, but 70% of noncompliance was MD preferred. The reason for this was actually because of the comorbidities that we talked about before, that the physician didn't feel comfortable looking at risk/benefit, and they would take a situation where they had more disease activity, not perfect control, but to mitigate the risk.

But this is a very interesting slide. This is a slide from SELECT-COMPARE, which is now in press in the *Annals of Rheumatic Diseases*, and SELECT-COMPARE was a head-to-head study of upadacitinib 15 mg a day to adalimumab 40 mg every 2 weeks, both with background methotrexate. At month 6, patients who didn't achieve the CDAI low disease activity (LDA) less than 10, despite significant improvement in their CDAI from baseline, were



switched to the alternative mechanism of action.

What I have in the slide is that the baseline for these patients was all around 40 or 45, whether they were on adalimumab or upadacitinib. Now, in month 6, their mean CDAI was about 15, 16. Their CDAI had decreased 66%, but there was still not low disease activity. They weren't less than 10, and if they were on upadacitinib and hadn't achieved it, they were switched to adalimumab, and if they were on adalimumab, they were switched to upadacitinib. If you take a look at the graph you can see the green is adalimumab switching to upadacitinib, purple switching to adalimumab. Two-thirds of the patients who switched from adalimumab to upadacitinib had an ACR of 50 when they switched, and half were switched from upadacitinib to adalimumab. So, although they had a good response before—they had a reasonable response—they had a much better response with switching. This is the proof, the treat-to-target, that if you don't reach your goal in 6 months, you should consider switching mechanisms.



What about a biologic or targeted synthetic DMARD option after negative response to initial conventional synthetic, such as methotrexate? You can use any of these. If a patient does not reach goal with a conventional synthetic, every one of these drugs can be effective in that patient population. It's all the TNF inhibitors, the costimulatory molecule inhibitors, B cell inhibitors, the IL-6 inhibitors, and all the JAK inhibitors.

Let me show you examples of JAK inhibitors in conventional synthetic DMARD incomplete responders. What I have here is tofacitinib, baricitinib, and upadacitinib. You can see in tofacitinib, on the left, wherever you use 5 mg, which is the approved dose, many patients responded compared to placebo in terms of an ACR20 response. The middle is baricitinib, which has the same thing with both 2 and 4 mg. This is 2 and 4 mg, which did not separate. Two mg is an effective dose. On the right,

you can see upadacitinib. They use 15 or 30 mg of upadacitinib. There was no difference between 15 and 30, which is why the approved dose is 15 mg, but in each of these drugs, you had benefit with conventional synthetic DMARD adequate responders in combination.

What about combination with the conventional synthetic DMARD vs monotherapy? The ACR guidelines and the EULAR recommendations both advocate the addition of a biologic or targeted synthetic to conventional synthetic if the patient can tolerate a conventional synthetic. They both advocate addition, not switching, as long as the patient can take a conventional synthetic DMARD. All biologics and all targeted synthetic exhibit better efficacy in combination with a conventional synthetic in a group of patients. We've shown this with every biologic and I've shown this with every targeted synthetic. The combination works better in a group of patients than the monotherapy. But if a patient cannot tolerate conventional synthetic, there are patients who do well with monotherapy biologics and targeted synthetic, but not quite as many. But if you're going to use monotherapy, again, the best results will be seen with a JAK inhibitor or an IL-6 inhibitor. These are based on studies of IL-6 inhibitors vs TNF inhibitor as monotherapy, and targeted synthetics as monotherapy.

You want to use combination if you possibly can. If you can't, then you can use the others, but you'd probably, in a group of patients, do better with an IL-6 inhibitor or a JAK inhibitor.

Here is the evidence for tocilizumab, an IL-6 inhibitor, monotherapy vs methotrexate, vs tocilizumab plus methotrexate. The green and the blue of the ACR20 is tocilizumab plus methotrexate vs methotrexate. The purple is monotherapy. Monotherapy works, it just doesn't work quite as well. Eight mg works as well or better than the 4 mg. You can see this through the ACR20, the ACR50, and the ACR70. There's no study of sarilumab to show this, but I'm fairly convinced that sarilumab would do the same.

Let's take a look at tofacitinib monotherapy vs methotrexate with tofacitinib and adalimumab. In this study, it was tofacitinib monotherapy vs tofacitinib plus methotrexate and adalimumab plus methotrexate. It was a non-inferiority trial. You can see on this slide in the green, the tofacitinib monotherapy was very effective in terms of the ACR20, 50, and 70, but it was not as effective as tofacitinib or adalimumab plus methotrexate in the blue and the pinkish color. You can see this to some extent in the ACR20, but certainly in the ACR50, and to some extent, in the ACR70. What this trial showed was that tofacitinib monotherapy is not non-inferior to tofacitinib plus methotrexate or adalimumab plus methotrexate, but tofacitinib plus methotrexate is non-inferior to adalimumab plus methotrexate. Monotherapy works, but it's not quite as good.

As we go to the next slide, what we can see is an IL-6 monotherapy vs the tofacitinib monotherapy. This is sarilumab 200 mg every 2 weeks, monotherapy, compared to adalimumab 40 mg every 2 weeks, monotherapy. Not the best way to use adalimumab, but there are patients who cannot take methotrexate. You can see here, there's a dramatic difference between the ACR20, 50, and 70 favoring sarilumab vs adalimumab. This is the reason why both ACR and EULAR talk about use of an IL-6 inhibitor or a targeted synthetic as monotherapy over other biologics.

What about TNF inhibitor cycling vs a switch to a biologic DMARD or targeted synthetic DMARD? There is a feeling in the community that if you fail TNF inhibitor, you won't respond to a second TNF inhibitor, but that's not true. That's actually not true. If you fail a TNF inhibitor, you could respond to a second TNF inhibitor, or you could respond to any other biologic, or to a JAK inhibitor, as shown in this slide. Patients with an incomplete response to a JAK inhibitor, as I've shown you before, may respond to a TNF inhibitor. As I showed you, the patients who didn't have a good outcome with upadacitinib, 50% did with adalimumab. There are no randomized trials of a patient failing abatacept, or tocilizumab, sarilumab, or rituximab responding to another biologic or a JAK inhibitor. We haven't seen that. My guess is that's true though, that it could be shown.

This is the proof of a response to a second TNF inhibitor after primary non-response. This trial, which is ACCELERATE, what we did was we took patients, we put them on certolizumab 200 mg every 2 weeks plus methotrexate, or adalimumab 40 mg every 2 weeks plus methotrexate. We looked at DAS28(ESR) LDA, or DAS28(ESR) change from week 12 for a reduction of at least 1.2. And if patients did not achieve LDA at week 12, they were switched from certolizumab to adalimumab and adalimumab to certolizumab. And you can see on this slide that there was no difference between the 2. Patients who didn't respond to certolizumab couldn't respond to adalimumab and vice versa.

And this is sarilumab in TNF incomplete responders. This is the TARGET study with sarilumab where we looked at patients who had failed the TNF inhibitor, and we placed them on sarilumab, and you can see that with the 200 mg every 2 weeks had a quite good ACR20 response and decrease in the HAQ-DI that was clinically very significant, statistically significant. And better than the 150 mg every 2 weeks, which was also effective, but not quite as effective. This is an IL-6 inhibitor and a TNF inhibitor incomplete responder.

And this is upadacitinib, another JAK inhibitor, in a biologic incomplete responder. And what this shows is, if you take a look at the purple, which is upadacitinib 15 mg a week, compared to a placebo, that there was a good ACR 20/50/70 response to upadacitinib compared to placebo plus methotrexate in biologic DMARD- IR.

What about a TNF inhibitor in a JAK inhibitor incomplete responder? I said that that could occur, and this is again from COMPARE. This is actually a little bit better slide showing the treat-to-target. These are the CDAI low disease activity non-responder. These are patients who didn't even achieve a decrease of 20% in tender and swollen joint count with the initial drug. And then when they're switched, the green is add or switch to upadacitinib. The purple is upadacitinib switching to adalimumab. A third to 50% who had no response initially, have a response with a switch in terms of a CDAI low disease activity response.

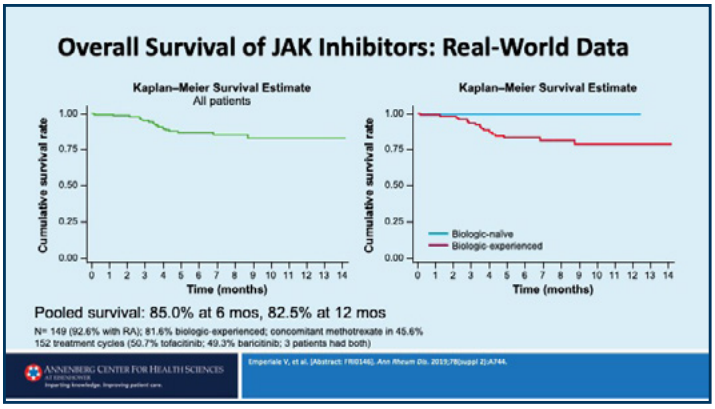
And this is the CDAI LDA and the incomplete responder. These are the patients who had achieved a significant decrease in the CDAI prior to the switch but did not achieve low disease activity. And here you can see about 50% of the patients, a little bit more with one than the other because this is small groups, but about 50% were able to achieve CDAI LDA. And the TNF inhibitor switched to a JAK inhibitor, the upadacitinib going to adalimumab.

And the goal of therapy here is persistent remission. And the important part of this slide is the desired treatment target should be maintained throughout the remaining course of the disease.

There are studies which show that a patient achieves remission and even a Boolean remission achieves it, and then loses it after 3 months, goes to low disease activity, and then comes back to remission 3 months later, and then loses it and goes to low disease activity, and then loses and goes back. Doesn't fare as well as a patient who maintains Boolean remission or CDAI remission or SDAI remission continuously. The goal should be maintenance of the remission or the lowest disease activity possible throughout the treatment targeting course. And when you taper medication or certainly stop medication, many patients will flare, and that's not good enough. If they go from remission to low disease activity, they're not going to do as well as maintaining remission.

And here you can see that persistent remission is not achieved in most patients. Here we're looking at patients who are on therapy. And again, you can look at the difference between the DAS28(CRP) and the SDAI, CDAI, and Boolean remission, the percentage of patients. And this is upadacitinib, these are the best results I've seen in clinical trials in terms of the percentage of patients achieving rigid metrics for a remission with the SDAI, CDAI, and Boolean. But again, you can see it's 20% to 25% of patients, the DAS28(CRP) series 40%, but we know that that's bogus. It really is at 25% of patients. It's really hard to achieve remission with a strict metric, but it is the goal. And once you reach it, you don't want to lose it.

This next slide talks about real world data. And this is from Spain. It's the overall survival of a JAK inhibitor for biologic-naive and biologic-experienced patients. On the left, you can see the cumulative survival. This is over a year, and you can see the cumulative survival for the JAK inhibitor is actually... this is tofacitinib actually, is fairly good. It's about 80%, 85% of patients.



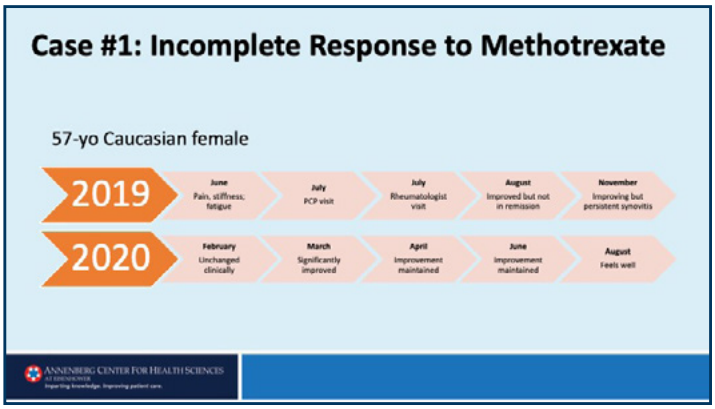
And if you take a look at biologic-naive vs biologic-experienced, biologic-naive, almost everybody stayed on the tofacitinib vs the biologic-experienced.

And this is another key point. When you have a patient who's failed methotrexate, no matter what the first drug you go to, whether it's biologic or targeted synthetic, the patient has the best chance of responding to that first drug. And most patients do respond to that first drug, probably 80% of patients. And if they do respond, the chances of their maintaining response are actually pretty good. You don't see a 50% drop off in 2 years. You see that in registries, but there are lots of reasons for that. In clinical practice, you see maintenance most of the time, but if the patient's already failed a drug, now this is the biologic-experienced, the chances are still good that they'll respond and maintain response, but not quite as good.

CASE SCENARIOS

Now we're going to talk about 2 case scenarios. We're going to talk about a patient with established rheumatoid arthritis with moderate disease, symptom improvement but not in remission with methotrexate monotherapy, and what do we do? And the second case is going to be established rheumatoid arthritis managed by the rheumatologist, both communication regarding management of our extraarticular manifestations and comorbidity, by the PCP.

In the first case, it's going to be a methotrexate incomplete responder. It's a 57-year-old Caucasian female, she's a teacher. Last June, she developed pain, stiffness and swelling in her feet. She had fatigue. She used over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), felt a little bit better, but not much. By July, she had synovitis, which she recognizes as swelling in her



elbows, wrists, hands, and feet. She saw her family doctor PCP, who noted the synovitis and obtained a C-reactive protein (CRP), an anti-nuclear antibody (ANA), a rheumatoid factor (RF) and X-rays of the hands and feet. This is not unusual.

And the PCP noted the CRP was elevated, was 20 mg per liter. The ANA was negative. The rheumatoid factor was positive in high titer, however, and the X-ray showed erosions of the hand joints. And what the PCP did was the PCP started prednisone 10 mg a day, really as bridge therapy, and arranged for a rheumatology consultation that week. Was able to call a rheumatologist and get the patient in that week.

And the patient did see the rheumatologist, who agreed with the diagnosis of rheumatoid arthritis with the high positive rheumatoid factor and the erosions. The rheumatologist did a joint exam. Did the CDAI, the CDAI was 45 which is high disease activity. Also did a DAS28(ESR) which was 6.2, which confirmed the high disease activity and did a HAQ, and the HAQ was 1.75, which shows moderate-to-severe decrease in function.

And on the complete blood count (CBC), the patient had mild anemia. It was anemia of chronic disease. The comprehensive metabolic panel (CMP) was normal, normal creatinine, normal LFTs. Chest X-ray was normal. The patient was going to be started on methotrexate. Had negative hepatitis panel and HIV screen, which we normally do before we start any of our advanced therapeutics. And the rheumatologist continued the prednisone 10 mg a day, started hydroxychloroquine 200 mg twice a day, and methotrexate 20 mg once weekly plus folic acid once a day.

Checked that her vaccinations were up to date which they were. And in August, the patient was significantly improved, with less joint pain and swelling, better function, had much less fatigue. And her CDAI was half of what it was, it was 22, but still high disease activity.

The DAS was better, but still moderate disease activity. And the HAQ was better, still showing moderate interference with function. And the CBC and CMP were normal. And because the patient had a response, even within a month had a response, it was a good response. Medications are continued. Methotrexate doesn't work overnight.

And when the rheumatologist saw the patient a few months later, in November, she continued to feel improved, but she still had synovitis. CDAI was 12, the DAS28(ESR) was 3.4, the HAQ was 1. It was still better, but not great. CBC, CMP were normal. The ESR was down to 32. And now we're at a time point where you should adjust therapy, and the rheumatologist increased the methotrexate to 25 mg a week, but tapered the prednisone to 5 mg a day because prednisone was on for months at this point. And in February, the patient was unchanged. CDAI, the DAS, the HAQ were still about the same as was the ESR, and patient had plateaued with moderate disease activity despite full-dose methotrexate.

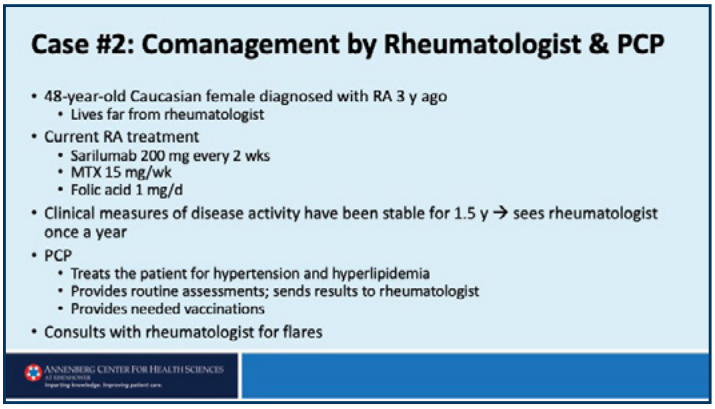
The rheumatologist discussed with the patient what the change in therapy could be, including the addition of other conventional synthetics, biologics, or a targeted synthetic. She had erosive disease. And in this case, if you look at the EULAR recommendation, but even the ACR guidelines, the best option would be the addition of a biologic or a targeted synthetic. And after a full discussion of rationale, side effects, and alternatives, which was full of all of these drugs, the patient preferred an oral option and was interested in a JAK inhibitor. That's the decision the patient and the physician made.

The insurance company made another decision. The insurance company said she had to try a TNF inhibitor as her first option. As I said before, it doesn't actually make much of a difference in terms of the long-range outcome what the first drug is. It will probably work. The rheumatologist was not too concerned, spoke to the patient, patient understood that the difference in cost was $5 a month vs $2,000 a month and agreed to do the TNF inhibitor. And she had access to adalimumab which she started every other week with a combination of current medications. QuantiFERON was negative because you screen for latent tuberculosis (TB). And in March, she felt significantly improved. CDAI was low disease activity as were the DAS20 and the ESR. The HAQ was just mildly abnormal. CBC and CMP were normal, and all meds were continued except for tapering of the prednisone because the patient was doing better.

And in April, the patient maintained improvement. CDAI was now 4, which is very low disease activity. The DAS is remission, but the CDAI is 4 and I go by the CDAI a bit more. The HAQ is down to normal, almost normal. Normal is less than 0.5. CBC, CMP were normal and all meds were continued. And in June, she had maintained improvement, CDAI changed just by 1, the DAS was still the same, HAQ was still the same. Methotrexate was reduced because she was doing well. And in August of this year, just a few weeks ago, the patient felt well, and her metrics were unchanged, and all meds were continued.

And the reason for this is following the ACR recommendation, the ACR guideline actually. And what it says is if a patient has low disease activity, you maintain medication. And that's what was done here. Were the patient to go into sustained remission, say they were to drop to 2, and this was sustained for a period of 6 months or a year, then you might think about further reduction of therapy and you might think about further reduction in the methotrexate. This is a patient who has had a very good response initially to methotrexate, but not good enough, who responds to the addition of a TNF inhibitor.

This is established RA managed by the rheumatologist, but with input from the PCP. This is a 48-year-old Caucasian female with rheumatoid arthritis for 3 years, and she lives 150 miles from the rheumatologist. And as I stated before, you've got to do laboratory frequently, particularly for patients on methotrexate or targeted synthetic. A patient needs to have somebody close by. The patient was treated with sarilumab 200 mg every 2 weeks by this point in life, and she was on methotrexate 15 mg a week with folic acid. Her CDAI was 2, her DAS was 2.3, her HAQ was normal function, been stable for one and a half years, and she sees her rheumatologist once a year as she's now in a stable remission. She's been stable for a year and a half on this treatment. And the only reason to see the rheumatologist would be if she had a side effect from the medication or she flares, she'd require a change in therapy.



Her PCP treats the patient for hypertension and hyperlipidemia. With sarilumab, there is an incidence of hyperlipidemia which can be controlled quite easily by the use of lipid-lowering medications. This is an IL-6 effect. This is an anti-IL-6 as you know, sarilumab. And the PCP performs the following assessments and sends the results to the rheumatologist. Even with sarilumab you're supposed to do a TB screening annually. The PCP does that. You should be looking at the CBC, the blood urea nitrogen (BUN), the serum creatinine. The patient's on methotrexate, and a liver function test every 8 weeks. This is a conservative rheumatologist, which is what I would do because I'm still concerned about methotrexate. I don't check every 12 weeks, which many rheumatologists do, certainly don't check every 6 months or once a year, but because she lives so far away, the PCP can certainly do this and can do this quite well.

And because she's on a biologic, and she has rheumatoid arthritis, she's on methotrexate, she should have an annual flu vaccination. The PCP does that. And the PCP monitors that are all vaccinations are up to date. And if the patient flares, the PCP will consult with the rheumatologist to decide on therapy, and whether this can be

treated locally, or the patient needs to see the rheumatologists earlier. And this is the best way for the PCP and the rheumatologist to comanage this patient. And when I do this with patients, patients feel very, very comfortable because now they know they have 2 people that are following them, and they can see the rheumatologist whenever they really need to, but if they don't need to, it's more convenient and quite accessible to see the PCP.

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