[MUSIC PLAYING]

LARRY W. MORELAND: Good afternoon, and appreciate the opportunity to spend a little time talking about an area that has been of an interest of mine for many years. The real topic is about rheumatoid arthritis, but I've flown in psoriatic arthritis for a couple of reasons. One is in general, most of the biologics that we use are also interchangeable with psoriatic arthritis, as they are with RA. But we have a few additional ones, and perhaps you've learned about them by watching the TV commercials.

So we'll see what you've learned. I have a few disclosures. I have research funding from several companies, and I'm currently part of the data safety monitoring board for three pharmaceutical companies looking at biosimilars in the field of arthritis. So the major objectives, I think, first of all, is to get you acquainted with some of the names, and the targets, and hopefully a little bit about the biology.

But more importantly, to emphasize the general adverse events of each of the biological classes, and then talk about some of the monitoring that we do, I think, in conjunction with you as primary care physicians. First, I want to give you an overview of RA, and talk about, quite frankly, an area that's really revolutionized this field for some of us who are old enough to have been in training 20 to 30 years ago, and seen the patients where we could do very little for.

And now have brought some of these new therapies to market, it's been very gratifying. But the reality is, as you see here on this slide, is that the pathogenesis of RA is complex, and still yet to be defined. We now know that there's a variety of genetics that are probably occurring in the right host. And with the right exposure, patients develop auto antibodies.

And over a period of decades these auto antibodies are circulating, and then your immune system loses tolerance and starts developing in response to that. And you develop joint symptoms and joint pain. A lot of the area now is not actually in the treating. A lot of the area of interest is in the pre-RA so that we can better identify those pathogens that are causing RA and prevent this disease.

So what happens if you were in clinic 20, 25 years ago, the waiting room was full of women, 50, 55, who had the disease for 20, 25 years, who had joints to look like this. There's a reason I point this out. First of all, it's gratifying that the waiting room has less of these. But more importantly, when you see a 30-year-old woman who has a relative, or friend, this is what they think they may look like.

So it's important that you emphasize the positives that we currently have, and I think as we get into the biologic therapies, one can get overwhelmed with the potential negatives of the potential side effects. But the message you're going to hear from me today, more than once, is in general, these therapies are very, very safe. And they have revolutionized our ability to prevent this kind of damage in our patients who develop rheumatoid arthritis.

Likewise, if you have psoriatic arthritis, this is one of the forms. It looks very much like rheumatoid arthritis. So the challenge now is for many of us to keep up with the paradigm shift that's occurred with psoriasis and psoriatic arthritis. They have now caught up with us in rheumatoid arthritis, and have even more therapies to offer. So as I alluded to, some of the major breakthroughs in the field of rheumatoid arthritis over the last 20, 30 years are listed here.

Number one is the understanding and the discovery of the anti-citrullinated protein antibody, which has allowed us now to look at the antigens that may be causing this disease. Most importantly, we now know that smoking makes up anywhere from a fifth to a sixth of the cases of RA. We are understanding some of the ideologies.

And so in the middle '90s, the explosion of biological therapies, initially with a team of therapies, have now come to fruition now, where we have over 20 therapies, not counting the biosimilars, that we have to use in this field of RA. So not to be complicated, but this is a rather simple slide looking at the immune system from antigen-presenting cells to T cells, to a variety of different effector cells.

And most of the biological therapies, but not, all are listed here, that I'm going to talk about today. So one, I would imagine, if you're a general internist, as well you are in rheumatology, we're overwhelmed with the number of agents that we have. Especially how to use them. And so what I'd like to do is to walk you through the high points of these.

And again, I'm going to take the approach that in general, these therapies are very, very safe. But I'm going to hopefully hit the points that we all need to talk about, and learn about, with the potential things that we can do to prevent some of the side effects. So in 2018, here's the list of medicines that I have available to treat patients with RA. On the left, the traditional drugs, methotrexate being the cornerstone.

This drug was initially not used in the '80s. It wasn't until the early '90s that we now became safe, and felt it was a safe drug to use. And we use it as the standard therapy. The others listed on that, under the traditional, are oral drugs and many of those we no longer use. But again, as I alluded to, when I was in training you had aspirin and gold salts. And after that, you had nothing else.

So this slide has been filled up over the last 20, 25 years with this group of agents. We now have the biological therapies, which are basically genetically engineered drugs, or biologics, that target specific parts of the immune system. There are five anti-TNF therapies listed here. There are several biosimilars that have already been approved, and they're probably held up because of patent issues.

We have one IO 1 inhibitor, anakinra, which is not used much. We have one co-stimulatory blocker, abatacept, which I'll highlight in a little bit more detail later. We have one B cell inhibitor that's approved for RA. We have another one that's approved for lupus. And then we have an explosion of drugs that inhibit IL-6, six, including the two IL-6 receptor blockers listed here, tocilizumab and serilumab.

And the JAK inhibitors, the Janus kinase inhibitors, there are two on the market now, tositumomab and baricitinib inhibit a variety of different cytokines, and have similar side effect profile as the IO six drugs. So that's the RA portfolio. If you look at the psoriatic arthritis portfolio, it's the same plus it has the IL-12, IL-23 drugs, ustekinumab, ustekinumab.

And what you will see watching the TV later tonight will be the Taltz and the Cosentyx with secukinumab and ixekizumab. You would think that they could find drugs that you could spell and pronounce a little more easily than these agents. But these, I'm going to talk about just briefly at the end because those are in our armamentarium to use to treat patients with psoriatic arthritis, and ankylosing spondylitis.

The long-term effects of these clinically are not yet known, because they've only been on the market for just three or four years. But equally important, when talking about the biological therapies, we usually don't treat patients with monotherapy. These biologics are used in combination with some of our traditional drugs. So I want to spend just a couple of minutes talking about methotrexate, which again is the cornerstone.

If you develop moderate to severe rheumatoid arthritis, we're going to recommend that methotrexate is there. Leflunomide and Plaquenil, less commonly used, but then also the toxicities need to be monitored. I'm not going to highlight those today due to the time constraints. But I do want to point out, when we talk about the explosion of biological therapies, methotrexate is at the cornerstone of that therapy.

It's one of the most durable and frequently used disease modifying drugs, as well as some of the others listed here. But there's a couple reasons we don't use it as frequently, especially in younger individuals. First, you need to be very careful, and women of childbearing potential, because as you'll see, just in a couple of seconds, and later on the talk, methotrexate can be teratogenic. And so you're talking about a young woman who may be in the childbearing potential.

You need to be extremely cautious about making sure that reliable birth control measures are in place. In addition, we encourage patients not to drink much alcohol. So in some situations, the physicians will mandate that there's no alcohol, which may be an issue with some of the younger patient population, especially those of college age and a little bit beyond. But in general, if you read the package insert about methotrexate, it scares the daylights out of you.

The oncologists use big doses of it. We use as little doses of it. However, in general, it's very well tolerated, and very safe. You need to check some baseline lab, CBC, creatinine, liver, chest X-ray, and check for hepatitis B and hepatitis C. And then check labs every three or four months. And in general, it's sort of a boring task to check the labs, because most of them are not that much of a problem.

There is a small number of patients who do have some intolerancy due to de-toxicity, or feel sort of yucky the day after. And when that occurs, I will add folic acid, a milligram a day, to try to prevent some of those side effects. Some of my colleagues will go ahead and give the folic acid beforehand. I usually wait to see if there are side effects, because 90% of the patients won't have any side effects.

So if you have moderate to severe rheumatoid arthritis, and if you have moderate to severe psoriatic arthritis, methotrexate is going to be the first thing we talk about, and we're going to use it. And we'll go to high doses, perhaps up to 25 to 30 milligrams per week. Roughly a third of my patients, and other studies will show this, respond well to methotrexate, and that's all you need.

However, when failing that, we have a list of other medicines that one can use. Most often, that's dictated by what the health system, or your insurance, will allow you to use next, based on the deal that they may have made with a particular pharmaceutical company. Some patients will be asked to then take the addition of Plaquenil, sulfasalazine, because it's cheaper, less expensive.

Other patients may have leflunomide added. However, the current state of the art, I think, in most practices is to add a biologic therapy. And the anti-TNF therapies, because of their length of being on the market, and in approval, and our comfort with them, are usually ones that will be used first. However, all of these others have the FDA approval to be used in methotrexate partial responders.

So there are five anti-TNF therapies on the market. Why five? These are multi-billion dollar agents. And this is a multibillion dollar aspect that we have. Because many of these, as you'll see in a few minutes, are used for multiple indications, not just rheumatoid arthritis. What you see here is infliximab, which is like primary monoclonal antibody. Adulimumab was human, ixekizumab is the second cousin of infliximad.

Certolizumab pegol and the etanercept is a fusion protein. In general, these all have similar side effect profiles. However, the monoclonal antibodies may have more increased risk of serious infections because they bind to cells and kill cells, especially in the context of patients who may have a predisposition to opportunistic infection. But again, as I talk about the monitoring and the side effect profile, I want to make sure we understand the big picture.

These agents have revolutionized our ability to treat many inflammatory autoimmune diseases, especially kids with juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, inflammatory bowel disease. They modify the disease. They slow it down. Unfortunately, they don't put people in remission, and we're able to withdraw them in as many patients as we'd like. But we have to deal with that as we go forward.

They can dramatically neutralize acute phase reactants, and I think most importantly in the field of rheumatology, and rheumatoid arthritis, there's good evidence in multiple studies that they also affect the comorbidity conditions such as cardiovascular disease. Because the mortality in RA 20 to 30 years ago was significant. A decrease in lifespan of 10 years compared to non-RA patients.

We're making progress because of methotrexate, and anti-TNF therapies have been shown to decrease the cardiovascular side effects. So let's talk a little bit about the details, then, with the TNF inhibitors, and what you really need to know about. So when you see a patient with RA, again, I emphasize that these drugs are safe, they may markedly change your life.

And throughout the visit, then I will tease out whether they have a real contraindication. There is some evidence based on results of studies done many years ago that these TNF agents may exacerbate heart failure. So if you have monitors of your heart failure, be careful. If you have latent TB, or active TB, or an active infection, don't start them. We'll talk about them in a minute.

As I said before with methotrexate, you need to screen for hepatitis C and B. Need to do the same for anti-TNF therapy. There is some evidence that these agents have been associated with demyelinating diseases, whether it's true, true, and unrelated, or whether they increase the risk, you obviously will need to be careful about starting an anti-TNF therapy on somebody who has a demyelenating process.

The infections we worry about are bacterial, tuberculosis and other opportunistic infection. Demyelination, infusion related events rarely but can be seen drug-related vasculitis. And also talk a little bit is neutralizing antibodies to the study drugs. So what do you need to do to rule out TB? First of all, you can't get these approved by anybody unless you have a TB test.

So we have two that we use. One is the standard skin test, and the other one that we're currently using most often in our clinics is the Interferon Alfa Release Assay. The reason to do the skin test is it's relatively inexpensive. It does detect cell-mediated immunity to TB. The reading of it is quite-- needs to have a second visit.

It has to have someone who can interpret it. But more importantly, the antigens that are shared within TB are also shared with some other microbacterial, including BCG. In addition, in our patients who are on steroids and other immunosuppressive therapy, its ability may be compromised because it may not be as sensitive, and it may be a boosting phenomenon.

So what most of us have migrated to in clinical trials, and in the real world, is to use a quantiferon TB gold and in tube test, which measures the interferon gamma production upon antigen simulation. It does not detect those people who may have been exposed to BCG. The advantages is it's a single visit, and it's not affected by BCG history.

But the other important thing, again, and I take this into context is that the TV ads say that these biologics kill people, cause cancer, and cause infections. So I spend a lot of my time talking to patients as to why that's probably not the whole truth. These background of history of RA is that, as I said earlier in the introductory comments, the immune system has lost tolerance to self antigens.

So the immune system isn't working correctly. It's not destroying the appropriate antigens. We've known for several years some fundamental data from the Mayo Clinic that patients with RA in general, without any treatment, have an increased risk of infection, just because you have RA. We sprinkle a little bit of steroids on top of that.

We sprinkle a bit of methotrexate. We add anti-TNF therapy, so yes, there is a background of infections that we need to be cautious about. And the TNF inhibitors increase the risk for certain infections, and opportunistic infections is that major impact that we need to consider in educating patients, in screening for it. They're uncommon, but they shouldn't occur if you're vigilant in screening and following patients carefully.

So in summary, with infections, and again this is the big picture. There's a lot of weeds that one could go into. But I prefer to take the big picture. There is a small, absolute risk of increased bacterial infections, opportunistic viral and fungal infections, with all of the biologic therapies. The disease itself may be cause of that in many cases. And with anti-TNF, now there's an increased risk of soft tissue infection, respiratory, TB in particular.

And some of the anti-TNF in particular, the monoclonal antibodies are at increased risk. But we screen, no matter which anti-TNF therapy you're going to start. The other biologic therapies, there's probably not that much of an increased risk. However, the FDA has mandated every clinical trial that you have a prescreening TB test. So in practice, we check a TB test, even before you start these other biological therapies.

There is, I think without a question, a slight increased risk of progressive multifocal leukoencephalopathy in patients treated with rituximab. I'll come back to that later. And also, there's an increased risk of shingles with all biologics, but more common in tofacitinib, a JAK inhibitor, and we'll come back and talk about shingles in a little bit.

One of the most important studies that I continue to quote and emphasize is this study published in *JAMA* in 2011. It's old data, but old isn't necessarily bad. This was a large study done by some of my colleagues at UAB and Harvard, where they looked at multiple databases from multiple hospitalizations, and they wanted to know whether the ant-TNF therapies, this is on autopilot, I guess you want me to quit sooner.

This is a-- they looked at a lot of large databases with the hypothesis that ant-TNF therapies would be the cause of hospitalization compared to traditional biologics. The bottom line is that the initiation of TNF antagonist compared with non-biologics was not associated with an increased risk of hospitalizations. The primary risk factor for you getting in that hospital was the concomitant use of prednisone. And in fact, the more prednisone you took, the more reason you would be hospitalized.

So again, the concept you've got RA, you got a little bit of prednisone, if we give you a lot. So this was, I think, a very comforting study. There had been additional ones it that added to this in major ways. But this fundamental studies show that the anti-TNF therapies are not increasing the garden variety infections that is to what gets you in the hospital.

The other big question is malignancy. And again, coming back to the TV ads as your guide for reference, we now known for many years that patients with RA have an increased risk of cancer. Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, myeloma, and lung cancer, especially if one of your risk factors is smoking. Methotrexate has been associated with non-melanoma skin cancers.

However, there is no data that I'm aware of in any publications, in big or small studies, that show that any of the biological therapies increase your risk of malignancy. This is important, because this is the number one reason patients don't want to take the biological therapies. They saw it on TV. These drugs cause cancer. Now there has been some concern about the risk of melanoma in anti-TNF therapy.

And a recent study that was just published with a large number of European biologic registries have been reassuring that there was no increase in melanoma with the TNF inhibitors in thousands of patients treated with anti-TNF therapy. The other concern with biologic therapies is whether patients develop immunogenicity or antibodies to the drug being used. We now know that this can be seen with all the therapies.

But in particular, there's a couple that is more common. This is not something we measure routinely. But it's real important, especially if you have a patient that you're losing efficacy. Is it because the drug isn't working? Or is it because they've developed antibodies to it? And one of the most important aspects that the gastroenterologists, the dermatologist, and rheumatologists have learned, that co-administration with another agent may decrease their immunogenicity.

I think in the GI world, Imuran or azathioprine is probably the preferred drug, because they use that. We use methotrexate a lot. And one of the pivotal studies, published in 2012, showed that patients can commonly take in methotrexate adalimumab. If you had no methotrexate, you had up to 50% incidence of antibodies. Not all were neutralizing.

However, if we use methotrexate, that was decreased to about 12%. There are some recent articles, just published, that suggest methotrexate can be used in other conditions. It probably has this lack this mechanism of action by increasing Tregs. And I think more work is needed to better understand how methotrexate is decreasing this immunogenicity so that perhaps we can use other therapies other than methotrexate as the way to get around this.

This is real important in a patient that you may have of college age potential, where you want to use the treatments, and not use methotrexate, because of the childbearing potential and the alcohol use, you may use what monotherapy. However, if you've got someone, want to afflict some adalimumab, the efficacy may be lost because of the immunogenicity.

We are currently not using some of the assays. There are assays available. I think the gastroenterologists are using them more than we are. Well, they're using, that's more than I am, because I'm using none, to measure levels of antibodies. Then measure drug levels. That gets complicated and, quite frankly, expensive. I want to mention a couple other things about anti-TNF therapies.

And these are paradoxical reactions, one that we wouldn't have expected, but we've known about for several years. Many patients who were started on the anti-TNF therapy may develop rashes. And it's interesting that we use anti-TNF to treat psoriasis. But in fact, some of my RA patients treated with anti-TNF therapy developed psoriasis. We've noted that that may be the case with uveitis, sarcoid and pyoderma gangrenosum.

Likewise, some of the patients in multiple studies that received the IO six blockers develop psoriasis. And more recently in the realm of using anti-IO 17 for psoriasis, psoriatic arthritis, ankylosing spondylitis, some of them have an exacerbation or new onset of inflammatory bowel disease. I think that that underscores the significant difficulty in our immune system.

It's complicated, and when you tweak it one particular way, you may tweak it in different ways, and different individuals. So having just seen a patient a couple of days ago on an anti-TNF therapy for five years who came in with a rash, she has RA, and developed new onset RA after doing very well after a few years on anti-TNF therapy.

So rashes are not uncommon in patients who receive these. Most of them are probably self-limiting, but some of them can be serious. As you can see, some of them may develop vasculitis or more serious types of arthritis, serious types of rashes. These have been seen with all of the different biologic therapies that affect TNF. They can occur early in the disease, early in the treatment, or after several years.

It's very unpredictable. Now, I want to switch gears, and I could have had a very similar slide about TNF. But I want to then head now into IL-6 inhibition. The reason I show you IL-6 is to show you that things are a little complicated, and IL-6 is a pleiotropic cytokine that's produced by lots of your cells, and it has effects on lots of cells. So when you block it, you should see some things happen.

And as someone who's been involved in this for several years, you get a little nervous when you start blocking some of these agents since the first of man. And I want to show you that the side effect profile for the IL-6 inhibitors is a little different than the anti-TNF, and this hopefully sets the stage for why. Because it's important in the day to day home aesthetic processes that many of us go through.

Why is this important? Well, we have at least four agents on the market, and I just came from our national meeting, and we're going to have more quickly. We have two biologic therapies, tocilizumab and sarilumab, that block IL-6 receptor. The two JAK inhibitors, tofacitinib most recently baricitinib inhibit not only IL-6, but Interferon on IL-2, et cetera.

The major toxicities we see with IL-6 inhibitors are liver enzyme elevations that are mild, and reversible. But you have to monitor, so it's not like you give the drug and see them in the year. Neutropenia, mild and reversible. GI perforations, especially with tocilizumab, and an increased risk of infections. There was a lot of angst about the IL-6 inhibitors and whether they would make it to the market, because during development there were a lot of patients who developed increased lipid levels.

And in fact, there was a study that done post-marketing comparing IL-6 inhibitors to TNF inhibitors to make sure that those particular agents didn't cause more cardiovascular effects. That study's over. It's not yet been published. It's been presented international meeting. And there isn't any difference with cardiovascular outcomes in IL-6 versus TNF blockers. But the hypercholesterolemia actually slowed the progress of this agent and cause lack of enthusiasm, because we were afraid we're going to exacerbate cardiovascular disease in a disease that already had cardiovascular problems.

This is just a slide to show you the JAK inhibitors. There are lots of them, if you want to read all of them listed here. There's two, tofacitinib and baricitinib for RA. There are others approved for myelodysplastic syndrome, but they block the intracellular signaling of some of these molecules. There's some that block JAK1, JAK2, JAK3. So they block lots of different cytokines.

Any cytokine that sort of stimulates the cell receptor. So when you block a JAK, when you have a JAK inhibitor, you're blocking lots of cytokines. So not only you're blocking IL-6, you're blocking TNF, you're blocking interferon. So are you going to have therapies that may be dramatic, and you cure the disease? Or you're going to have therapies that have overwhelming side effects.

In general, the side effect profile for the JAK inhibitors is identical to blocking IL-6. The word there was in general. So IL-6 monitoring, baseline CBC, liver enzymes, hepatitis screen, you get a hepatitis no matter what. Lipid profile, when you screen for latent TB, although the IL-6 blockers really are not associated with increased risk of TB. And you need to get follow up liver enzymes and CBC. This gets a little complicated because if you're on methotrexate in IL-6, and you have a liver enzyme elevations, and neutrophils go down.

Which one's causing it? And then we get lipid profiles every six months. We do have a little discrepancy in our division as to what we do with those. I tend to ignore them, because-- and I'll show you in the why I ignore them. It's based on some of the work that we did as part of one of those clinical trials that I did. But more importantly, this is one of the side effects with IL-6 inhibitors that's probably not iffy.

And that is the association with GI perforations. There's been a large study done now in registries that show that tofacitinib and as some, but perhaps more importantly tocilizumab is associated with GI perforations. I don't have a clear understanding as to why. But when you're talking about treating elderly individuals who may have some GI issues, you need to be aware that patients may be reluctant to take these drugs.

And when they present with abdominal pain, it may be drug-related. So let me switch gears and talk about rituximab. Rituximab is a B cell inhibitor. It blocks and kills B cells. It's been on the market for a long period of time. It's probably the leading biological therapy, because it's used to treat lymphoma.

It's used to treat rheumatoid arthritis, and more recently, it's revolutionized our ability to treat ANCA associated vasculitis. We now use this instead of cytoxin for GPA and microscopic polyangiitis. CD 20 is expressed on B cells.

Rituximab causes rapid depletion of circulating B cells. There are several adverse events that can occur during the infusion. Most of these, fortunately, are with patients who have lymphoma, where a lot of patients have a reactions to a cytokine storm that can be pre-treated with IV steroids. More importantly to the rheumatology field, if you repeat treat patients with rituximab, hypogamma globulin anemia is not uncommon.

It can be severe and persistent, and so there is an increased risk of general infections. And in the vasculitis world, we tend to co-treat with bacterium and to prevent PSP. That's somewhat controversial. I don't think the infections are overwhelmingly common, but they're enough to make you nervous. Hepatitis B is really important.

If you have hepatitis B activity, and you treat with rituximab, that can be deadly. And there are clear cut cases of progressive multifocal leukoencephalopathy, usually with long term treatment. So a couple of comments about hepatitis B, because you've heard it once or twice today, so it might be important.

I rarely see anybody who has a positive test. I order the test a lot, because it's important that if we treat with high dose steroids, TNF inhibitors and rituximab, and they have active hepatitis B, you need to co-treat with an antiviral agent. And more importantly, you need to rule out hepatitis B and C with all of our therapies. And again, if you've got the need for treating with rituximab, which is not the case with rheumatoid, it may be the case with vasculitis.

And they have hepatitis B positivity, you need to treat it with the antiviral agents as well. Now let me switch gears and talk about co-stimulatory blockers. This is an important slide, in that it shows you the complexity between energy presenting cells and T cells. And I was fortunate enough several years ago to lead the first in man of cosimulatory blocker abatacept.

And when I saw that we could basically block T cell activation, I was nervous that we were going to either really cause some serious and adverse events, or we wouldn't do anything at all because this was so complex that just blocking one of these. So abatacept is basically the extracellular domain of CTLA-4 hooked to an immunoglobulin that comes in and blocks this interaction here of CD 8086.

You will hear, or you already heard, about the revolution that's undergoing now in treating cancer. We in rheumatology are trying to dampen the T cell response. The oncologist is trying to ramp it up. And this slide here illustrates the complexity of that intersection. The good news is what we're doing is not causing any infections or cancer. Abatacept is a relatively safe drug.

It's pretty-- it doesn't have any of the issues that I've talked about. As you will hear, and have already heard, is based on your syllabus, I think the oncologist are given drugs that may increase the risk of certain autoimmune and inflammatory conditions. So this is a very important concept to understand, and that's where a lot of the action is in the field of immunology now, primarily both in the rheumatology and cancer field.

Now, I know there's a talk tomorrow by somebody who's an infectious disease person, who's going to talk about vaccinations and the elderly. So my comments here are perhaps to give you my two cents worth, regarding vaccinations, because I think this is a fundamental area where we as rheumatologists and primary care doctors need to work together.

Many of our quality improvement projects in the field, in our division, have been to improve vaccination. And we've shown that quite frankly, we in rheumatology haven't been as good as this and we would like. But we've made some progress in that. But one of the fundamental questions that you're going to ask is well, do all of these drugs that dampen the immune system have anything to do with the immunogenicity of the vaccines? And the answer is yes.

And the answer is some with influenza, some. Not with pneumococcal, some yes, some not. It's complicated. And not only is it complicated, these are used in combination. But the bottom line is you still need to vaccinate with influenza. We just heard some data at our national meeting that the high-dose influenza vaccine, which should be used in elderly patients, is also more effective than a regular dose vaccine in patients younger than 65.

The pneumococcal vaccine is one that I think, obviously, should be used. There's still some room to understand whether the newer 13 valent pneumococcal conjugate is better than the other one in the setting of rheumatoid arthritis. Live vaccines has been an issue with the shingles vaccine, and I'm going to talk about that and with shingles in a couple minutes. And rituximab is probably the one where you really got to pay attention to, because rituximab decreases your immunoglobulin levels.

It does reduce the influenza and pneumococcal vaccine immunogenicity. And most likely, if you're going to use rituximab initially, you need to get your vaccines in. But rituximab, ab however, is not a drug you use once. In the field of, especially in vasculitis it's now the standard of care every six months. So this is a concern as to why rituximab then is probably higher on the list of all these agents I'm talking about that increase your risk of garden variety infections.

So, shingles is an entity that we see a lot in rheumatology, because of the immunosuppressive therapies in our underlying diseases. Whether it's in the young lady with lupus, or somebody with RA. And especially in older individuals as well. And the morbidity, the pain, and long term disability can be quite severe. Before the most recent use of a non-live vaccine, we were caught with knowing how to use this live vaccine.

Because there was some concern that giving patients who are immunocompromised, whether it's methotrexate or anti-TNF, they result in dissemination of a virus. However, despite the Zostavax being, I think, a very effective vaccine as listed here, it's recommended for healthy individuals greater than 50. Nothing for people with comorbid condition.

But there's good evidence that our literature, again, from some of my colleagues that I've worked with at Alabama, previously coming to Pittsburgh, that showed that a lot of patients who were on anti-TNF, who got vaccinated, had no dissemination and no problem. The good news is we're now moving to a non-live recombinant subunit Shingrix vaccine. It could be administered in two IM doses.

There's some recent data published in over 38,000 patients that it's 90% effective. You have to give two shots. There's really no recommendations, however, in pregnancy and in adults who are immunocompromised. But compared to a live vaccine, it's clear that this is probably where we're going to need to be so that we can give this agent, and not worry about dissemination of the virus. Now, a couple of comments about lipids.

I briefly mentioned this earlier, and I'm coming back to it. This is a conundrum as to what's going on in inflammation, and lipids. And I am reluctant to say too much about it with all the cardiovascular experts in the field here today. But 10, 15, 20 years ago, if I was talking about RA, or I talk about the increased issues of cardiovascular disease causing decreased lifespan of RA patients, I'm not sure that we've clearly shown that we have made it to where we want to go.

But one are the challenges still remains cardiovascular disease. And there there's a lot of work in this, whether it's the risk factors, hypertension, diabetes, hyperlipidemia, chronic systemic inflammation. Well we now know that if you take patients who have RA, and their cholesterol is normal, and you effectively treat them, and this is a study from the tier trial that I put together and carried out over the last 15 years, these are basically the increase in lipids in patients who received methotrexate plus etanercept, or triple therapy or methotrexate monotherapy.

So when you take a patient who has active inflammation, and you treat it effectively, whether it's with methotrexate, anti-TNF or IL-6, the lipid levels go up. And so if you measure lipid levels that in patients are doing better, than lipid levels are elevated. I think the real question is which of those lipids is the most important? Is it the HDl. And is that the inflammatory, or the non-inflammatory part of HDL?

So I'm a little concerned that we're measuring lipid levels in all of our patients, and we're chasing them with statins, and I'm not sure where we're going with, this except I think it's an area ripe for us in the field of Rheumatology. Now, I have a couple other topics that I want to cover before we close. One is perioperatively, what do we do with all these biological therapies?

If I have 10 orthopedic surgeon's work with me, I've got 10 different plans as to how they want to do it. We now have some data published by rheumatologists and orthopedic surgeons. The American College of Rheumatology, and the American Association of Hip And Knee Surgeons put together these criteria. And the bottom line is if you're undergoing surgery, you probably have an increased risk of infection, as I've already alluded.

The surgeons are a little nervous about having their hip or knee infected. So they want you to stop all the drugs for a month before, and a month after. And guess what happens if you have a flare? You give them steroids. So what's that all about? So we now have these guidelines, which surprised me a little bit because if I were talking a year ago, I would have said you should stop the methotrexate for a few weeks, and restart it.

Now we're saying it's OK to keep methotrexate going. We generally then say stop the biologics for a week, roughly, or two, depending on the half life. And then once the wound is healed, and there aren't any evidence of post-operative infections, restart them. I think these are guidelines. I defer to the surgeon. If the surgeon says they want to stop them not at all, or for a long period of time, that's the way I go.

Because the surgeon is not happy when he has a post-operative infection. The other I want to talk about, pregnancy. This is a slide that illustrates the current FDA risk if you're taking some of our drugs. Methotrexate and leflunomide have black box, which means are contraindicated in pregnancy. Mycophenolate, which we use a lot in myocitis and lupus has a D, which means there's positive risk. And everything else is C.

In other words, you can't rule it out. So what do we do? Well, keep in mind that many patients with rheumatoid arthritis, when they become pregnant, their rheumatoid arthritis would go in remissions. And so one of the treatments might be to suggest they get pregnant, and that would be the outcome you want. However, as you have hopefully illustrated, there is a time frame before they get pregnant that you have to be worried about.

And that is methotrexate, leflunomides or no. You need to counsel patients and have them off of these drugs for a period of time. Plaquenil, sulfasalazine, OK. TNF inhibitors are safe, as safe as I just illustrated in the previous slide. But we have very little data about tocilizumab, rituximab, abatacept, or tofacitinib. So I would encourage patients to take an anti-TNF.

If they become pregnant, and probably try to stop that agent. Now one last comment about recent approved drugs. And as I alluded to earlier, I put psoriatic arthritis in this because basically, we see lots of patients with our dermatology colleagues. The field of IL-17 has overwhelmed us, I think, in a positive way. This is an article in the *New England Journal,* showing that the IL-17 inhibitors are better than this one study compared to anti-TNF therapy.

So we now have four drugs in this arena, two block IL-17, Cosentyx and Taltz. One that blocks IL-12 and IL-23, Stelara, which is used for not only psoriasis, psoriatic arthritis, but inflammatory bowel disease. And the new one out, IL-23. So far, I think the side effect profile looks good. We still need to screen for TB, but there's no evidence that these drugs developed TB.

There is no increased risk of serious infections or malignancies. But these have only been on the market for three or four years, compared to 20, 25, for the anti-TNF therapy. So finally, I think it's important to emphasize that the treatment of RA is a team effort. We think, in rheumatology, that we're bringing a lot to the table based on the complexity and the number of drugs that we have to offer.

But as you can see, the toxicities need to be monitored by all of us. The risk for infections remains the number one problem, but it's manageable. It shouldn't be a showstopper. There is no evidence of malignancy. So the ads are incorrect. We need to aggressively treat the cardiovascular risk factors, because that's what is associated with a decreased lifespan.

What I haven't touched upon because of time is mental health and osteoporosis. The risk for osteopenia and osteoporosis is high, even in early RA patients, because of the ongoing auto antibodies that are probably causing the osteopenia. And mental health, I think I could have spent an hour talking about that. So I think the red light is already clicked. I'm done. Thank you very much.

[APPLAUSE]