OVERVIEW

Leonard Calabrese, DO, Professor of Medicine at the Cleveland Clinic Lerner College of Medicine and Director, RJ Fasenmyer Center for Clinical Immunology at the Cleveland Clinic, provides his perspectives on key posters presented at the 2018 European League Against Rheumatism Annual European Congress of Rheumatology, on the treatment of patients with psoriatic arthritis.

CONTENT AREAS

Efficacy of apremilast • Long-term efficacy and safety of ixekizumab • Long-term safety of secukinumab Impact of background therapy on tofacitinib efficacy • Utility of cardiovascular risk tools

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Learning Objectives
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- Summarize the latest research developments in the treatment of psoriatic arthritis
- Incorporate evidence-based research into clinical practice

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Editor's Note

This is a transcript of Dr. Leonard Calabrese's analysis for 'Psoriatic Arthritis Posters and Abstracts from Amsterdam.'

Secukinumab Demonstrates a Consistent Safety Profile With Up to Five Years Treatment in Patients With Psoriatic Arthritis and Moderate to Severe Plaque Psoriasis: Updated Pooled Safety Analysis

Phillip Mease, MD and colleagues

Dr. Calabrese: The summary of this is that secukinumab may have demonstrated a favorable safety profile during treatment for up to 5 years in patients with moderate to severe psoriatic arthritis, as well as psoriasis alone. The safety profile is largely comparable across patients with psoriatic arthritis and psoriasis.

Before we get to the data, I'll tell you the importance of this is 5-year safety data is what we want to see. The patient years are now getting up and I believe that the data that I'll briefly describe supports the long-term use in patients with psoriasis and psoriatic arthritis.

How did they do this? As you know, secukinumab is approved for psoriasis and psoriatic arthritis. There were 3 large phase 3 studies that were pooled. These contained patients with moderate to severe psoriatic arthritis. There were different doses of secukinumab utilized in these studies, and that's important because we are not largely using intravenous, so this contained the IV ramp-up dose as well as loading doses with the 75 and the 300 mg that we're most familiar with. The loading dose was followed by maintenance of either 300, 150, or 75 mg administered subcutaneously. Patients were initially randomized to placebo or active drug, and at weeks 12 and 24 could be switched for reasons of dose response. Analyses included all patients who received at least 1 dose of secukinumab.

Key findings of this is that a total of 1380 patients with psoriatic arthritis, representing 3867 patients-years, were included in the study. It also included 5000 patients with psoriasis, representing 10,417 patient-years. And that is what I always look at as a benchmark of a safety study. We're getting up into 5 figures.

A serious event in this study occurred at an exposure-adjusted incident rate of 7.9 per 100 patient-years in patients with psoriatic arthritis. In patients with psoriasis, the exposure-adjusted incident rate was about 6.9 per 100 patient-years.

The most frequently reported adverse events were mild viral upper respiratory infections occurring at an adjusted incident rate of 12.1 per 100 patient-years with psoriatic arthritis and 21 for patients with psoriasis. Exposure-adjusted incident rates for serious infections, candida infections, inflammatory bowel disease—those are both events of special interest—and major adverse cardiac events, were low and similar in patients treated with psoriasis and psoriatic

arthritis. There were no examples of tuberculosis in the study.

What's the bottom line? How do we interpret this? Secukinumab is one of the IL-17 inhibitors that we now have. It is . . . for a class, there is a remarkably low incidence rate of what we would call serious opportunistic infections. This has added to the attractiveness of drugs in this class. What about the events of special interest? Candidiasis, particularly mucocutaneous candidiasis, is a complication of interest because we know from preclinical animal models that if you inhibit or knock out IL-17, patients develop overwhelming candida of mucosal and cutaneous surfaces. Also, primary immunodeficiency diseases develop the same type of candida.

The experience to date is that while these complications are seen in few percentages of patients who are exposed to IL-17 inhibitors, and verified in this study, these are not serious infections. They're certainly not disseminated candidiasis, something that is really not seen within the scope of these trials. The serious infection rate overall is in the realm of other biologic agents, so there's no surprises there. And there were no new signals in this Study. So, to me, this furthers the safety signature of the IL-17 class. There are certain things that we look for. I might also mention the inflammatory bowel disease concern because this has been a consideration since the earliest phase trials. There were very few cases identified in this integrated safety database. This, to me, reaffirms the safety of this agent and has not changed my practice at all.

Efficacy and Safety of Ixekizumab in Patients With Active Psoriatic Arthritis: Three Year Results From a Phase 3 Study the SPIRIT-P1 Trial

Dr. Chandran and colleagues

Dr. Calabrese: The bottom line of this study is that in patients who are biologically naive with psoriatic arthritis, treatment with the IL-17 inhibitor ixekizumab for up to 3 years resulted in sustained improvements in signs and symptoms of the disease. Importantly, there were no unexpected safety signals. The safety profile was consistent with previous studies.

The importance of this is, with all of these studies of this relatively new agent, we want long-term follow-up and this demonstrates, to some degree, a 3-year follow-up of persistent efficacy and safety.

Let's take a dive into the methods. This was a poster and it reported on the extension phase of the 24-week SPIRIT-P1 study. In this study, 417 biologically-naive patients were randomized to ixekizumab every 2 or 4 weeks, or placebo. At 24 weeks, ixekizumab was superior to placebo in improving the signs and symptoms of psoriatic arthritis. The primary endpoint of this study was the ACR 20 at week 24 which was observed in 58% or 62% of patients treated with ixekizumab either at the 200 or 400 mg dose, respectively, vs only 30% of patients treated with placebo. Three hundred eighty-one patients entered into that extension phase and patients failing to demonstrate 20% improvement in tender and swollen joints at week 32 were discontinued from the study.

The key findings of this study were that 125 of the 210 patients, that's 60%, initially randomized to ixekizumab at week 0, completed 156 weeks of treatment. At 156 weeks, the following were observed in the 2-week and 4-week intention-to-treat groups, respectively; you saw a 62% and 69% improvement in ACR 20, which is more than respectable; 44% and 33% improvement in the ACR 70, extreme endpoint. Importantly, the PASI 75, the robust marker of skin improvement, was improved in 69% and 63%. The PASI 100, which we, in previous eras of drugs we didn't even look at, was improved in 61% and 44%. Very importantly, enthesitis and dactylitis were both improved, and they used 2 indices; the Leeds Enthesitis Index and the Leeds Dactylitis Index. And you can see that it was knocked down to 0 in 40% and 47% of these groups. And the dactylitis index was knocked down to 0 in 69% and 62%.

The mean change for baseline in the HAC Quality of Life measure was -0.5 in the 2-week group and -0.4 in the 4-week group. And that's a significant and meaningful improvement.

In the extension phase, treatment emergent adverse event was observed in 76% of patients in the 2- and 4-week groups. The majority of these, however, were mild or moderate in severity. A serious adverse event occurred in 10% to 15% of patients treated with the active drug at 2-week and 4-week dosing intervals,

respectively. The most common adverse effect was infection. But these were mostly mild, observed in 49% and 48% of these 2- and 4-week dosing groups. The other adverse events, far less in the way of serious adverse events, and small numbers of patients with adverse events of special interest, such as inflammatory bowel disease-like presentations.

What are my thoughts on this drug? Ixekizumab is also a drug in the IL-17 inhibitor family. We now have 3 drugs available across the spectrum of psoriasis-attended complications. This is approved for psoriatic arthritis and psoriasis. Three-year data shows that it is persistently active and effective at a clinically meaningful rate. There were no surprises in the safety database. And the thing that I found most important in this is that there were impressive reductions in both enthesitis and dactylitis. And I will tell you that enthesitis, which is seen in the majority of patients with psoriatic arthritis, is something that patients are interested in. Tender joints might go down, but persistent enthesitis at the Achilles, at the knee or the shoulder or elbow, can be debilitating. Across all domains this drug was effective.

This adds to the long-term use of this, I look forward to the 5-year cuts of these data. This adds to reassurance of my use of this drug and does not change my practice pattern.

Underestimation of Cardiovascular Events by Cardiovascular Risk Score in Psoriatic Arthritis Patients by Dr. Lam and colleagues

Dr. Calabrese: The bottom line of this is that similar to other forms of inflammatory arthritis, this study showed that a variety of cardiovascular disease risk scores significantly underestimate cardiovascular risk in patients with psoriatic arthritis. In addition, adaptation of the EULAR recommendations only partially accommodated that to a moderate level.

Let's dig into this. I found the study quite interesting. The reason is that in terms of importance, the accurate estimation of cardiovascular risk is important in patients with psoriatic arthritis since they do have an elevated risk of cardiovascular events. In our practice, we want to give accurate modeling and predictors to our patients. As I will show you, current risk scores, no matter which one you're picking, is likely to underestimate these risks.

How did they do this? First of all, these investigators collected data from 2 Hong Kong cohorts of patients with psoriatic arthritis. The discriminatory ability to predict cardiovascular risk was estimated by the area under the receiver-operated characteristics curve. This plots sensitivity vs 1 minus specificity. The perfect point is at the zero x-axis and the top of the y-axis, where it would be a perfect test.

Four different cardiovascular risk scores were utilized. They were the Framingham Risk Score that we have had for many years. The QRISK, the HEART score—these are European variants. One from the UK, the other from European cardiovascular groups. And finally, the more recent American College of Cardiology/American Heart Association 10-year atherosclerotic cardiovascular disease risk score. In previous iterations of EULAR recommendations, there has been a suggestion to take the existing cardiovascular risk score and multiply it by 1.5, which was proposed for patients with rheumatoid arthritis. The hypothesis was, let's take that recommendation, which basically upped the ante and increases the risk by a factor of 0.5, and apply it to psoriatic arthritis.

The primary outcome was first cardiovascular events. This, actually, is very important because it's a little nontraditional. They included a wide variety of events, including MI, angina, stroke, heart failure, bypass, also implantation of a pacemaker, defibrillator, peripheral vascular disease, and a number of others. It's a little more broad, and a little more sensitive index of cardiovascular disease.

What about the key findings? It's a small study, 228 patients were recruited over a decade; from 2006 to 2016. Mean age of almost 49 years, 54% male. Over a mean period of follow-up of 6.7 years, 30 patients experienced a cardiovascular event. Then they got baseline data available to calculate all these risk scores; Framingham, QRISK, HEART score, ACC/AHA, in groups of patients where all of these data were available. As you can see, the majority of patients had data available for all of these calculations.

At baseline, those who went on to experience cardiovascular events were significantly older, had a higher prevalence of diabetes, high blood pressure, and elevated triglycerides. That was statistically significant. As expected, their risk scores were significantly higher at baseline. However, many were not identified in the highest risk categories. So, if you look at the identified risks at baseline, you could see that 63% of the patients in Framingham fell into high risk groups, where QRISK was 20%, HEART score only 13%, and the more recent ACC/AHA 46%. So now, applying the EULAR recommendations, this hypothesis-driven fudge factor, if you will, that increased Framingham to 80%, QRISK only to 36%, HEART score 27%, and ACC/AHA to 57%. These findings demonstrated that 4 risk scores utilized in this study, even after adjustment, underestimated the cardiovascular risk among patients with psoriatic arthritis.

So how do I interpret this? First of all, I think it's an interesting attempt, and if you actually go back and read the original EULAR recommendations, it's not all patients with rheumatoid arthritis, particularly those with longer disease and higher risk of prognostic factors of their rheumatoid are the ones where we recommend adjusting this. I wonder, maybe if they just focused on patients with psoriatic arthritis that were moderate or severe, you may have come out with another answer.

Secondly, while this is intriguing, and I actually believe in the conclusions, this is a very small study. Very small number of events and they cast their nets so broad; they used so many cardiovascular endpoints I would like to have seen it be done more traditionally with just MACE events. Lastly, you should ask yourself, "Why is this? Why do all these risk scores underestimate cardiovascular risk of patients with rheumatic disease?" I think the answer is this is classical risk partitioning. Those scores are driven by the risk factors in the general population, which are generated largely by [the fact that] we live in a lipid-rich world. Lipid-driven high blood pressure. We live in an inflammatory world and not all these incorporate as many inflammatory markers.

I will continue to look at cardiovascular risk predictors of all sources underestimating, and I will continue with my practice. Every single patient that comes to the Cleveland Clinic with inflammatory rheumatic disease our electronic medical record says, "Has this patient been evaluated for cardiovascular disease? Have they been referred to preventive cardiology?" I think we need systems to make sure that each and every patient is followed for this.

Efficacy of Tofacitinib by Background Methotrexate Dose in Patients With Psoriatic Arthritis: A Post-Hoc Analysis of Pooled Data From Two Phase Three Trials

Dr. Kivitz and colleagues

Dr. Calabrese: Let me summarize for you. First, I'll tell you that in patients with psoriatic arthritis, the efficacy of tofacitinib was greater than placebo. It really didn't differ when evaluated by background methotrexate dose. And the dose here, we'll come back to this several times, less than 15 or greater than 15 mg per week. That's the pivot point, you can question how it was derived, but that is the pivot point of this study. These findings are consistent with results of similar analysis of tofacitinib in patients with RA.

The importance of this is that several treatments are available for the treatment of patients with psoriatic arthritis. In some cases, it's unclear if the sequence of treatment affects patients' outcomes. This study demonstrates, as best as possible, that the initial treatment with methotrexate does not affect the patient's response to tofacitinib.

Let's take a deep dive into the methods of this. This study is a post-hoc analysis of pooled data from 2 phase 3, randomized, doubled-blinded, placebo-controlled studies of tofacitinib in patients with active psoriatic arthritis. To get in, you had to have greater than 3 tender and/or swollen joints. In one study, patients were TNF inhibitor-naive and had inadequate response to one or [more] conventional synthetic DMARDs. In the other study, patients had to be an inadequate responder to one or more TNF inhibitors. So different substrates going into the study.

All patients were randomized tofacitinib 5 or 10 mg twice daily or placebo and there was an adalimumab comparator arm, 40 mg every 2 weeks. All patients received stable doses of 1 conventional synthetic DMARD as background therapy. The maximum dose of methotrexate was 20 mg a week, which is of note, as well.

The key finding of this study is that a total of 556 patients who had received tofacitinib plus methotrexate only, or placebo plus methotrexate only, were included in the study. Two thirds of the patients were treated with background methotrexate as less than 15 mg, mean dose about 12.6. Low by rheumatology standards. The other one-third were on higher dose; mean methotrexate dose of 19.8.

At month 3, both tofacitinib doses, 5 mg and 10 mg twice daily, were associated with numerically greater improvements in ACR and Health Assessment Questionnaire-Disability Index (HAQ-DI) scores, as well as change in the HAQ-DI score from baseline, compared with placebo.

The magnitude of tofacitinib effects on efficacy outcomes was broadly similar to patients with background methotrexate doses below 15 mg compared to those in the 15 to 20 mg per week. In patients treated with tofacitinib 5 mg daily, an ACR 20 response was observed in 47% treated with methotrexate at doses less than 15, compared with 51% treated with methotrexate

greater than 15. For patients in the 10 mg limb, ACR responses observed in 55% vs 52% of these 2 dosing limbs of methotrexate.

In patients with tofacitinib 5 mg twice daily, a decrease of greater than 0.35 in the HAQ-DI response was observed in 48% of patients on methotrexate less than 15, compared with 56% of patients treated with methotrexate above 15. For patients treated with tofacitinib 10 mg twice daily, a decrease of greater than 0.35 in the HAQ-DI response rate was observed in 52 vs 43%, respectively, of these 2 methotrexate arms.

Let me break this down, at least the way I think about this study. We have patients with psoriatic arthritis who are candidates for advanced therapy. Small molecules are now a viable option. We can triage patients in our mind as to those that are poor prognosis, better prognosis, who have low disease activity, who have high disease activity. We have a lot of bio markers. One of the things we consider is background methotrexate dose. Are the patients on greater than 15 mg, are they not going to be as robust responders as those on less methotrexate? It's a valid question. This study shows quite clearly that, at least within the confines of this dosing range and this breakdown, less than 15 and greater than 15, this is not a variable that warrants clinical concern. This encourages me to use this drug in patients on methotrexate regardless of the dose and does not change my practice at the present time.

Probability and Impact of Achieving Low Disease Activity or Remission in Patients With Psoriatic Arthritis Treated With Apremilast: Pooled Analysis of the PALACE-1 Through -3 Phase Three Trials

Dr. Ian McInnes and colleagues

Dr. Calabrese: Let me summarize this for you first. I think the study shows us that chances for achieving low disease activity or remission with apremilast were greater for patients with psoriatic arthritis in the cDAPSA, that is a responder index that we are increasingly familiar with, in the moderate disease activity category; 13 to 27 at baseline or week 16 compared to patients in the higher disease activity category. Also achieving low disease activity or remission at week 52 with apremilast was associated with good outcomes across core domains of psoriatic arthritis.

Let's get into how we did this, because the importance of this is that this suggests that patients with psoriatic arthritis who have baseline moderate cDAPSA disease activity may be particularly suitable for apremilast therapy.

Let's dive into the methods a little bit. The PALACE-1 through -3 studies, [with which] most of us are familiar. These are large, robust trials that form the basis for the approval of apremilast. This is a pooled analysis of patients treated with apremilast 30 mg twice daily. To be eligible, patients had to complete 52 weeks of this therapy and have components of the clinical Disease Activity index for Psoriatic Arthritis, so-called cDAPSA, score available. Results were grouped according to cDAPSA categories at week 52. You had low, moderate, or high disease activity. So in this study, the key element is classification according to the cDAPSA categories at week 52. If you're like me, you don't remember these scores off the top of your head. Remission is 4 or less on this scale, whereas low disease activity is 4 to 13. Moderate disease activity is 13 to 27 and high disease activity is 27 and greater.

Key findings are, first of all, 374 patients were included. The means of the baseline cDAPSA scores were 41 or less, associated with achieving a moderate or low disease activity and remission at week 52. So we'll come back to that number. Patients in the high disease activity group at baseline had a 42% chance of achieving moderate disease activity, a 24% chance of achieving low disease activity, and a 5% chance of achieving remission. While patients in the moderate disease category had a 41% chance of achieving low disease activity and 12% chance of achieving remission. So we have to go back and look at the comparator limb. This is 41% vs 24%, and 12% vs 5% favoring those starting in the moderate disease category. Patients in the low disease activity group at baseline had a 20% chance of achieving remission. Similar trends were observed upon response at 16 weeks. So it gives you a little chronopharmacology here. For example, patients with moderate disease activity at week 16 had a 38% chance of achieving low disease activity and a 2% chance of achieving remission at week 52. Achieving cDAPSA low disease or remission at week 52 was associated with residual disease activity. For example, you could have swollen joints, 1.2 vs 0.24 in these

comparator groups vs tender joints at 2.6 vs 0.5, and dactylitis score of 0.47 vs low. So better to be in remission than to be in low disease activity. Removing patients with high disease activity at baseline suggests that cDAPSA of 21 was associated with achieving low disease activity or remission at week 52 corresponding to a mean 5.5 swollen joint count and 9 tender joint counts at baseline.

I've given you a lot of numbers. What does this mean? When I approach patients with psoriatic arthritis and I'm trying to pick from this wealth of drugs we have available to us, I divide patients into 4 plots; bad joints, bad skin. Bad joint, mild skin. Bad skin and mild joints. And mild skin and mild joints. As so we have this matrix. Here we have TNF inhibitors, we have IL-17 inhibitors. We have drugs down the pike. We have conventional synthetic DMARDs. I like apremilast in particular for patients with more modest skin and more modest joint disease. The drug is an oral drug which requires very little therapeutic monitoring. If patients can get through the initial phase of tolerability, it has a very low dropout rate.

And here we provide data that perhaps people on the milder end of the spectrum are going to be the most robust responders. It's consistent with the way that I have practiced with this since the drug was introduced, based on relatively limited data. So this is very reassuring to me. I might add, this does not mean that patients with more severe forms of the diseases don't respond, but if I had to pick the sweet spot, this is what it has done for me. I think this added considerable to the literature on it and I thought this was a very nice way to project the data.