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Exploring a Subgroup Analysis of TNFi-IR Patients With Moderate to Severe RA

Announcer:
You're listening to ReachMD. This medical industry feature, entitled "Exploring a Subgroup Analysis of the TNFi-IR Patients With Moderate to Severe RA," is sponsored by AbbVie. This program is intended for healthcare professionals. Your host is Dr. Jennifer Caudle.

Dr. Caudle:
This is ReachMD, and I'm your host, Dr. Jennifer Caudle and joining me to discuss the results of the SELECT-COMPARE Prespecified Subgroup Analysis, and to dive into long-term safety data for RINVOQ, is Dr. Ara Dikranian. Dr. Dikranian is a rheumatologist at the Cabrillo Center for Rheumatic Disease in San Diego, California. Dr. Dikranian, thanks so much for being here today!

Dr. Dikranian:
It's a pleasure to be with you. Thank you for having me, Dr. Caudle.

Dr. Caudle:
Of course, and before we begin, let's take a moment to review both the indication and some safety considerations for RINVOQ.

Announcer:
INDICATION

RINVOQ® (upadacitinib) is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blockers.

Limitations of Use: RINVOQ is not recommended for use in combination with other Janus kinase (JAK) inhibitors, biologic disease-modifying antirheumatic drugs (bDMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

RINVOQ is contraindicated in patients with known hypersensitivity to upadacitinib or any of its excipients.

BOXED WARNING, including Serious Infections, Mortality, Malignancies, Major Adverse Cardiovascular Events, and Thrombosis, with additional Warnings and Precautions, including Hypersensitivity Reactions, Gastrointestinal Perforations, Laboratory Abnormalities, Embryo-Fetal Toxicity, and Vaccinations, will be covered in the safety section of this video.

Dr. Caudle:
Now, Dr. Dikranian, to start us off, can you tell us about the RA clinical program that evaluated RINVOQ?

Dr. Dikranian:
Of course. So the clinical development program spanned six phase 3 clinical studies, from moderate rheumatoid arthritis to severe RA, in different patient populations.

These trials include SELECT-BEYOND, SELECT-EARLY, SELECT-MONOTHERAPY, SELECT-NEXT, SELECT-COMPARE, and SELECT-CHOICE. And they were developed so that patients could either advance or switch to 15 milligrams of RINVOQ from the placebo, or be rescued to RINVOQ from an active comparator or placebo, as early as week 12, depending on the study design of the trial.

A total of 3,833 patients with moderate to severe RA received at least one dose of RINVOQ 15 milligrams a day, and of these, 2,806 patients were exposed for at least one year.

The data from the SELECT-COMPARE Prespecified Subgroup Analysis of TNF inhibitor partial responder and nonresponder patients are similar to the results from SELECT-BEYOND, a 12-week, double-blind, placebo-controlled study of 499 adult patients with moderate to severe RA who had an inadequate response or intolerance to biologic DMARDs. 164 patients on background conventional synthetic DMARDs were randomized to receive RINVOQ 15 milligrams once daily, while 169 patients on background conventional synthetic DMARDs were randomized to receive placebo once daily.

The primary endpoint of ACR20 in SELECT-BEYOND was achieved at week 12 by 65 percent of RINVOQ patients versus 28 percent of placebo patients.

Dr. Caudle:
Now, if we focus on the SELECT-COMPARE study for a moment, what can you tell us about the study design and patient population?

Dr. Dikranian:
Yeah, so just to give some background, the SELECT-COMPARE study was a 48-week, randomized, double-blind, active comparator–controlled study of RINVOQ versus a TNF inhibitor or placebo in patients with moderate to severe RA.

For this study, 1,629 adult patients who had an inadequate response to methotrexate were randomized to receive either RINVOQ, placebo, or adalimumab. Once patients were randomized, 651 of them received 15 milligrams of RINVOQ daily, 651 received placebo, and 327 of these patients received adalimumab 40 milligrams every other week, all in combination with their background methotrexate.

Then, in a prespecified, blinded, rescue protocol, patients who had an inadequate response to adalimumab were categorized into two groups: non-responders and partial responders.

Nonresponders were those who did not achieve 20 percent or greater improvement in both tender and swollen joint count from baseline at Week 14, 18, or 22, while partial responders were those who did not achieve a CDAI low disease activity with a score of less than or equal to 10 at Week 26. The rescue therapy was immediate and did not have a washout period.

Dr. Caudle:
So now let's take a look at some of these clinical trial endpoints. Dr. Dikranian, can you tell me about the primary and secondary endpoints for this study?

Dr. Dikranian:
So, the primary endpoint was the ACR20 response of RINVOQ versus placebo at Week 12.

The results of the study showed that 71 percent of patients exposed to RINVOQ with methotrexate achieved an ACR20 response versus 36 percent of patients who were exposed to placebo with methotrexate.

As for secondary endpoints, select ranked secondary endpoints at Week 12 of RINVOQ versus placebo with methotrexate were a proportion of patients achieving DAS28-CRP less than 2.6 and DAS28-CRP less than or equal to 3.2.

Dr. Caudle:
And now let’s dive into remission data for a moment. What can you tell us about these data from patients taking adalimumab plus methotrexate who were rescued to RINVOQ plus methotrexate?

Dr. Dikranian:
Well, we know that remission data are very important and clinically relevant to both ourselves and our patients.

Now, looking at the nonresponder remission data following rescue, 26 percent of patients who were rescued to RINVOQ plus methotrexate achieved the DAS28-CRP less than 2.6 at 12 weeks post-rescue, and 31 percent of these patients achieved a DAS28-CRP less than 2.6 at 24 weeks post-rescue. On top of that, 42 percent of the nonresponder patients achieved low disease activity at 12 weeks post-rescue, while 54 percent achieved low disease activity at 24 weeks post-rescue.

Now if we look at the partial responders, the post-rescue remission data showed that 34 percent of patients who were rescued to RINVOQ plus methotrexate achieved a DAS28-CRP less than 2.6 at 12 weeks post-rescue, and 38 percent achieved DAS28-CRP less than 2.6 at 24 weeks post-rescue. And when we look at low disease activity, 61 percent of partial responders met the criteria at 12 weeks post-rescue, while 57 percent met the criteria at 24 weeks post-rescue.

Announcer:
SAFETY CONSIDERATIONS

Serious Infections: RINVOQ-treated patients are at increased risk of serious bacterial (including tuberculosis [TB]), fungal, viral, and opportunistic infections leading to hospitalization or death. Most patients who developed these infections were taking concomitant

immunosuppressants, such as methotrexate or corticosteroids.

Mortality: A higher rate of all-cause mortality, including sudden cardiovascular (CV) death, was observed with a Janus kinase inhibitor (JAKi) in a study comparing another JAKi with tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients ≥50 years with ≥1 CV risk factor.

Malignancies: Malignancies have occurred in RINVOQ-treated patients. A higher rate of lymphomas and lung cancer (in current or past smokers) was observed with another JAKi when compared with TNF blockers in RA patients.

Major Adverse Cardiovascular Events: A higher rate of CV death, myocardial infarction, and stroke was observed with a JAKi in a study comparing another JAKi with TNF blockers in RA patients ≥50 years with ≥1 CV risk factor. History of smoking increases risk.

Thrombosis: Deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions. A higher rate of thrombosis was observed with another JAKi when compared with TNF blockers in RA patients.

Hypersensitivity: RINVOQ is contraindicated in patients with hypersensitivity to RINVOQ or its excipients.

Other Serious Adverse Reactions: Hypersensitivity Reactions, Gastrointestinal Perforations, Laboratory Abnormalities, and Embryo-Fetal Toxicity.

Dr. Caudle:
Dr. Dikranian, now that we have some data on these clinical trials, let's turn our attention to the RINVOQ RA safety profile. What can you tell us about the scope of this profile to date?

Dr. Dikranian:
So, the latest RA safety profile data that were presented recently at the European Alliance of Associations for Rheumatology (EULAR) 2022 Congress have helped us expand how we understand this type of data.

So for us, when we talk about the RA safety profile, we're looking at more than 4,400 patients evaluated on RINVOQ 15 milligrams and upadacitinib 30 milligrams in those six phase 3 studies.

And we've gone from greater than 7,000 patient-years of exposure, with the previous data across six clinical trials, to now more than 9,000 patient-years of exposure to RINVOQ at the approved 15-milligram dose.

In these studies, the maximum length of exposure has grown from about 4.5 years to now 5.5 years, and the median exposure has gone from 2.6 years to now 3.5 years.

Now it's really important, because we now have several years of data to consider when evaluating RINVOQ.

So the 12-week safety data give us an opportunity to take a look at the exposure-adjusted incidence rates.

In the short term, we need to define any tolerability issues that may or may not limit a patient's ability to continue on therapy.

However, some adverse events may not be noticeable in the initial three-month period, which is why we need the long-term safety data.

Dr. Caudle:
Thank you. And before we close, Dr. Dikranian, do you have any key takeaways that you'd like to share with our audience?

Dr. Dikranian:
Yes, Dr. Caudle. I think there are two key takeaways. The first is that the data that we presented here reaffirm the use of RINVOQ for those patients who have not responded adequately or tolerated a TNF inhibitor. And the second is that this is all done with the background of a well-studied safety profile.

Dr. Caudle:
Well, with those takeaways in mind, I'd like to thank my guest, Dr. Ara Dikranian, for helping us better understand the efficacy and safety of RINVOQ.

Dr. Dikranian, it was great speaking with you today.

Dr. Dikranian:
Thank you so much for having me.

Dr. Caudle:
I'm your host Dr. Jennifer Caudle.

And before we close, let's take a moment to review additional important safety information.

Announcer:
IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids. If a serious infection develops, interrupt RINVOQ until the infection is controlled.

Reported infections include:

- **Active tuberculosis (TB), which may present with pulmonary or extrapulmonary disease. Test patients for latent TB before RINVOQ use and during therapy. Consider treatment for latent TB infection prior to RINVOQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

Carefully consider the risks and benefits of treatment with RINVOQ prior to initiating therapy in patients with chronic or recurrent infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with RINVOQ, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

MORTALITY

In a large, randomized, postmarketing safety study comparing another Janus kinase (JAK) inhibitor with tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients ≥50 years old with at least one cardiovascular (CV) risk factor, a higher rate of all-cause mortality, including sudden CV death, was observed with the JAK inhibitor. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with RINVOQ.

In a large, randomized, postmarketing safety study comparing another JAK inhibitor with TNF blockers in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer [NMSC]), lymphomas, and lung cancer (in current or past smokers) was observed with the JAK inhibitor. Patients who are current or past smokers are at additional increased risk.

With RINVOQ, consider the benefits and risks for the individual patient prior to initiating or continuing therapy, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy when on treatment, and patients who are current or past smokers. NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. Advise patients to limit sunlight exposure by wearing protective clothing and using sunscreen.

MAJOR ADVERSE CARDIOVASCULAR EVENTS

In a large, randomized, postmarketing study comparing another JAK inhibitor with TNF blockers in RA patients ≥50 years old with at least one CV risk factor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke) was observed with the JAK inhibitor. Patients who are current or past smokers are at additional increased risk. Discontinue RINVOQ in patients that have experienced a myocardial infarction or stroke.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ, particularly in patients who are current or past smokers and patients with other CV risk factors. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions. Many of these adverse events were serious and some resulted in death.

In a large, randomized, postmarketing study comparing another JAK inhibitor to TNF blockers in RA patients ≥50 years old with at least one CV risk factor, a higher rate of thrombosis was observed with the JAK inhibitor. Avoid RINVOQ in patients at risk. Patients with symptoms of thrombosis should discontinue RINVOQ and be promptly evaluated.

HYPERSENSITIVITY

RINVOQ is **contraindicated** in patients with known hypersensitivity to upadacitinib or any of its excipients. Serious hypersensitivity reactions, such as anaphylaxis and angioedema, were reported in patients receiving RINVOQ in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue RINVOQ and institute appropriate therapy.

GASTROINTESTINAL PERFORATIONS

Gastrointestinal (GI) perforations have been reported in clinical trials with RINVOQ. Monitor RINVOQ-treated patients who may be at risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs). Promptly evaluate patients presenting with new onset abdominal pain for early identification of GI perforation.

LABORATORY ABNORMALITIES

Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (absolute neutrophil count [ANC] <1000 cells/mm^3). Treatment with RINVOQ is not recommended in patients with an ANC <1000 cells/mm^3. Evaluate neutrophil counts at baseline and thereafter according to routine patient management.

Lymphopenia

Absolute lymphocyte counts (ALC) <500 cells/mm^3 were reported in RINVOQ-treated patients. Treatment with RINVOQ is not recommended in patients with an ALC <500 cells/mm^3. Evaluate at baseline and thereafter according to routine patient management.

Anemia

Decreases in hemoglobin levels to <8 g/dL were reported in RINVOQ-treated patients. Treatment should not be initiated or should be interrupted in patients with hemoglobin levels <8 g/dL. Evaluate at baseline and thereafter according to routine patient management.

Lipids

Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Manage patients according to clinical guidelines for the management of hyperlipidemia. Evaluate patients 12 weeks after initiation of treatment and thereafter according to the clinical guidelines for hyperlipidemia.

Liver enzyme elevations

Treatment with RINVOQ was associated with increased incidence of liver enzyme elevation compared to placebo. Evaluate at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. If increases in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ should be interrupted until this diagnosis is excluded.

EMBRYO-FETAL TOXICITY

Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks after the final dose. Verify pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ.

VACCINATION

Avoid use of live vaccines during, or immediately prior to, RINVOQ therapy. Prior to initiating RINVOQ, patients should be brought up to date on all immunizations, including varicella zoster or prophylactic herpes zoster vaccinations, in agreement with current immunization guidelines.

LACTATION

There are no data on the presence of RINVOQ in human milk, the effects on the breastfed infant, or the effects on milk production. Available data in animals have shown the excretion of RINVOQ in milk. Advise patients that breastfeeding is not recommended during treatment with RINVOQ and for 6 days after the last dose.

HEPATIC IMPAIRMENT

RINVOQ is not recommended for use in patients with severe hepatic impairment.

ADVERSE REACTIONS

The most common adverse reactions in RINVOQ clinical trials were upper respiratory tract infections, herpes zoster, herpes simplex, bronchitis, nausea, cough, pyrexia, acne, headache, increased blood creatine phosphokinase, hypersensitivity, folliculitis, abdominal

pain, increased weight, influenza, fatigue, neutropenia, myalgia, influenza-like illness, elevated liver enzymes, and rash.

Inform patients that retinal detachment has been reported in clinical trials with RINVOQ. Advise patients to immediately inform their healthcare provider if they develop any sudden changes in vision while receiving RINVOQ.

Dosage Forms and Strengths: RINVOQ is available in 15 mg, 30 mg, and 45 mg extended-release tablets.

Announcer:
This program was sponsored by AbbVie. If you missed any part of this discussion, visit ReachMD.com/IndustryFeature. This is ReachMD. Be part of the knowledge.

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