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Treatment Considerations in Ulcerative Colitis: Shared Decision-Making

Narrator

At the intersection of science and clinical experience in IBD, this is *Gut Reactions*. Settle in, as our host, Dr. David Rubin, brings leading gastroenterologists together for one-on-one conversations. This podcast is brought to you by AbbVie.

Dr. David Rubin

Welcome to the *Gut Reactions* podcast. I'm your host, Dr. David Rubin, Chief of the section of Gastroenterology, Hepatology, and Nutrition, and Director of the Inflammatory Bowel Disease Center at the University of Chicago. Today, I'll be joined again by Dr. Josh Steinberg to discuss how we identify appropriate patients with moderate to severe ulcerative colitis for their specific treatment options. We'll explore two different treatment options currently available, what factors to consider when assessing these treatments, and when to prescribe them for the best possible treatment outcomes.

Dr. Steinberg is a board-certified gastroenterologist and the Director of Inflammatory Bowel Disease at Gastroenterology of the Rockies, where he serves patients in the Denver and Boulder, Colorado, metropolitan areas. He completed his advanced IBD fellowship with us here at the University of Chicago and his GI fellowship at Georgetown in Washington, DC.

Josh, I'm very happy to have you back with us on *Gut Reactions*.

Dr. Josh Steinberg

David, thanks so much for having me back. It's a pleasure to come back to *Gut Reactions*. I really can't wait to start our conversation today.

Dr. David Rubin

Well, we have been trying to schedule this since your first podcast because we had such a good time. So, I'm really glad we all landed on a date today to start having this conversation. So why don't we start with something that I think would be really helpful for our colleagues, a discussion about the objective measures of disease activity. Why are the objective measures so critical in the treatment of ulcerative colitis? Why don't we just ask patients how they're feeling?

Dr. Josh Steinberg

Yeah, this is a really important concept and first we should try and dive into the distinction between what we describe as subjective and objective measures of inflammation. Right? So subjective measures are based on the patient's personal experiences, what they're actually feeling and experiencing from day to day based on self-reported symptoms of what they're going through, like describing the severity of their abdominal pain or how frequent they're having bowel movements, or if they're having rectal bleeding or not.

These reports are valuable and they're important to help us guide treatment decisions, but they can be quite varied and influenced by patient perspectives. When you contrast this to objective measures of disease activity, which typically involve concrete data and assessment of inflammatory burden as reflected by diagnostic tools, we're thinking about colonoscopy, biopsies with histopathology, or laboratory results like blood and stool-based testing.

So, these provide a much more standardized and reproducible assessment of disease activity and inflammation. And of course, subjective feedback helps us understand how the patient feels and the symptoms they're experiencing, but it's really the objective measures that provide this concrete data that we really need to help guide our treatment decisions effectively. As you know, there can be this discordance between what the patient is experiencing clinically in terms of their symptoms and what the inflammatory burden as

reflected by these objective measures is actually doing.

Dr. David Rubin

How do these objective measures help in managing these challenges?

Dr. Josh Steinberg

So objective measures, including endoscopic assessments and laboratory tests, play a vital role here. For instance, using a colonoscopy or flex sig allows us to visually assess the colonic mucosa and grade the inflammation using various scoring systems, such as the Mayo endoscopic subscore for UC. This helps us determine the severity of the disease and monitor challenges over time. To objectively assess disease activity, we typically use the modified Mayo score or mMS.

Dr. David Rubin

I wanna dive in a little bit and ask you, what are your targets in ulcerative colitis and how do you do it in your practice?

Dr. Josh Steinberg

Yeah, this is important. And we often talk about STRIDE-II that help us kind of frame our treatment paradigm and treatment management for patients. So first we want to talk about short-term goals or short-term targets. And that's typically the clinical targets, right? So, in the setting of UC, we're talking about reduction of rectal bleeding and improvement in stool frequency and urgency and some of the other clinical symptomatic factors.

We talk about intermediate targets. So that's looking at biomarkers, in particular, blood and stool-based tests, right? So, looking at CRP, fecal calprotectin as surrogate markers of inflammation as we start a particular therapy. And then ultimately long-term, what we're really striving towards is objective assessment as based on colonoscopy, right?

So endoscopic outcomes. Trying to achieve endoscopic improvement as demonstrated on a colonoscopy when we're reassessing patients after starting or changing their therapy. So not just the subjective approach, including their improvement in clinical symptoms, obtaining that clinical remission, but really that remission that includes biomarker remission and histologic or endoscopic remission. These are some of the targets that we try to achieve in all of our patients with UC.

Dr. David Rubin

Super helpful. I often say to patients that symptomatic remission is critical, but objective confirmation of disease control is how we make sure it lasts. And when I talked about symptoms, as you've seen, because we work together and I've learned from you as much as I hope you've learned from me, it's about formed stool and the absence of bleeding. But really one of the most important symptoms is also urgency and resolving that particular symptom.

And the astonishing thing, whether it's because patients may normalize their symptoms or whether in fact there really is a disconnect between symptoms and objective findings, is the reality that people who say that they're not having symptoms will still be inflamed if we were to look with a scope or a biomarker. And the implication of that, of course, is that they're more likely then to relapse over time. So that's part of the important messaging regarding combining symptoms and those objective measures.

So, you've made a really good point that really every patient is a bit different and requires this personalized approach, whether we call it treat-to-target or the way you've outlined it. Tell us a little bit more about how you think about the one-size-fits-all or the personal approach to your individual patients with UC.

Dr. Josh Steinberg

Yeah, you know, unfortunately there's really not a one-size-fits-all approach to ulcerative colitis management. Sometimes we try to fit patients in particular boxes when we're thinking about what particular therapy might work best for them. But we really want to take an individualized, patient-centered, patient-first approach for all of our patients. And it's really important that we use all of the tools in our disposal, both from a diagnostic perspective and of course, a disease monitoring perspective.

And then including our medical armamentarium to help determine what treatment is going to work best for them individually. And there's obviously patient characteristics, perhaps contraindications or relative contraindications, underlying risk factors. So, everyone's different.

There's a lot of things that we take into consideration and just really that shared decision-making with the patient at the forefront that we want to take into account when making these decisions together.

Dr. David Rubin

All right, terrific. Now, before we talk about the treatments that are available, we want to distinguish what we've just covered, which is really the pragmatic and clinical practice approach to management with some of the definitions that are used in clinical trials and when we look at data for therapies.

So, Josh, let's set the stage and outline a treatment path for an adult patient who's been recently diagnosed with moderately to severely active ulcerative colitis.

We want people to feel better right away. That makes complete sense, of course. But what are the symptoms you're looking for when you start a patient on a new therapy? And how do you explain it to the patient? What does that first step look like?

Dr. Josh Steinberg

It's an important question, David. So, it's critical, right? That we consider what the patient treatment goals are and that me, as their clinician, and the patient are aligned in their goals and kind of where they're at overall in their journey. So, an important part of this decision-making process involves taking the time to really get to know the patient sitting in front of you, right? And ensuring that we are both equally involved in the decision-making process. As I mentioned before, the shared decision-making is really critical in optimizing a successful outcome.

Dr. Josh Steinberg

So, when we understand where the patient's really at in their treatment journey or in their disease journey, we might be able to better understand the individual patient in front of us and what prior treatments might have been effective or ineffective and if they had any potential adverse reactions or side effects from prior treatments that they had previously been on.

We also want to consider the severity of their disease. And we consider severity as this kind of wide-lens, big-picture, longitudinal assessment of the patient's disease burden, as well as the patient's disease activity, right? And then when we have these things in place, we try to weigh the balance of the benefit-risk profile to any particular therapy when we're discussing with the patient. And when we start treatment, we initially focus on addressing symptoms that are really debilitating the patient from day to day.

So, we're talking about rectal bleeding and urgency and frequency. In the short term, we really want these symptoms to start to improve. And once the patients start to feel better, we know that their symptoms can become under better control, which of course is our immediate priority. And we'll get next to our more long-term outcomes as assessed by biomarkers and endoscopic outcomes.

Dr. David Rubin

So as ulcerative colitis is a chronic condition, the treatment plan obviously needs to be assessed over time and monitoring of the disease in terms of early response as well as maintenance of response is part of our management. This obviously depends on how our patients are doing and any changes that occur in their condition or in their age or their body or other physiological changes that occur as well as our new research and treatments that are becoming available.

For example, we've been thinking more about biologics as early or first-line options for patients when they're getting started. On the other hand, JAK inhibitors are often considered for adults with moderate to severe UC, who have not responded adequately to anti-TNF therapies. So, Josh, let's outline standard treatment protocols for a patient diagnosed with ulcerative colitis. What are the typical first steps for treatment and how are you doing this?

Dr. Josh Steinberg

Great question, David. So, there is somewhat an order to things. I would typically start them off with a 5-ASA and if necessary, start them on a short course of a corticosteroid. And if we are not able to achieve this response with 5-ASAs alone or with steroids in combination with 5-ASAs, really the next step is gonna be incorporating one of our advanced therapies.

Narrator

Advanced therapies in ulcerative colitis include biologics, S1Ps and JAKs.

Dr. David Rubin

So, depending on how the patient's responding and what their previous medical history tells us, this would involve drugs such as tumor necrosis factor inhibitors or anti-TNFs, integrin receptor antagonists, interleukin inhibitors like the IL-23 inhibitors, or the S1P receptor modulators, and JAK inhibitors. So, let's talk a little bit about anti-TNFs. What can you share with us about that class of therapies, Josh?

Dr. Josh Steinberg

Yeah, of course. So anti-TNF were our first biologic therapies that became available for ulcerative colitis. And while these anti-TNF agents can be effective for many patients with UC, it's important to note that they really don't necessarily work for every single patient. So, patients might experience this primary nonresponse, right? They might never respond at all to that initial anti-TNF agent. And additionally, patients might develop the secondary loss of response over time, which as I mentioned, the patient might do well and then lose that response over time. And this could be due to the development of anti-drug antibodies to the agent that they're on, or sometimes the patient might be underdosed and have subtherapeutic drug levels based on the drug level for the individual agent that they're on.

So, it's really important to consider that patients who did have this primary nonresponse to an anti-TNF probably won't respond very well

to another anti-TNF agent if they didn't originally respond favorably initially. So instead, we probably want to consider another class, another mechanism of action of biologic agent or a small molecule agent that the patient previously has not been on that might give them a fair chance of having a beneficial effect in endoscopic improvement long-term.

Dr. David Rubin

I usually divide the primary nonresponders into a couple categories, and I think that you do the same, which is, is this truly a mechanism failure or is this a dose or exposure failure? So, when somebody isn't responding to an anti-TNF, of course, we can consider other biologic agents like the integrin receptor antagonist, or the IL-23 inhibitors. They can, in fact, be used in people who are TNF-naïve or TNF-experienced, but some patients may not respond to those or have a delayed response, and we have to think carefully about where's the drug going when this is occurring.

So, Josh, thinking more broadly, why don't you share an example of a patient profile that would be ideally suited for an advanced therapy in treating their UC?

Dr. Josh Steinberg

Of course. So, I have this patient in mind who does have moderate to severely active ulcerative colitis, and he was diagnosed with left-sided UC about three and half years ago. And when we first met, he was initially treated with steroids and 5-ASAs, but I performed a colonoscopy and he presented with a Mayo score of 2, which just for reference is defined by marked erythema, absent vascular pattern, friability, and the presence of erosions. And this patient, he's a young engineer, he's an active father of two, and he enjoys outdoor activities.

So, there's luckily a lot of therapies that we can start discussing that are advanced treatments in nature that are inclusive of biologics and small molecules that hopefully can get him the chance to get into a remission.

Dr. David Rubin

That's a really great example, Josh, so thanks for sharing that. Could I ask you, do you ever skip 5-ASA and go directly to an advanced therapy, and if so, who might that patient be?

Dr. Josh Steinberg

It's a great question. And the short answer is yes. In patients that really do present with a high or severe inflammatory burden—so, I'm talking about patients who are presenting with extensive colitis with Mayo 3 disease, deep ulcers on colonoscopy, perhaps elevated CRP, perhaps they're anemic, have high platelets, just all signs and symptoms, so to speak, of a high inflammatory burden, where we know that in the broader sense or longer term that the patient has higher risk of a more complicated disease course—in these patients, I would probably bypass a oral 5-ASA and go directly to an advanced therapy for sure. Great question.

Dr. David Rubin

So, what treatment did you land on for your patient with moderate to severe UC?

Dr. Josh Steinberg

So, we have many more treatment options that are available now. And one of them is an interleukin-23 inhibitor, IL-23 agent, from AbbVie that was approved for adult patients with moderate to severely active ulcerative colitis. And that is called SKYRIZI, risankizumab.

Narrator

Indications

Ulcerative Colitis: SKYRIZI is indicated for the treatment of moderately to severely active ulcerative colitis in adults.

Crohn's Disease: SKYRIZI is indicated for the treatment of moderately to severely active Crohn's disease in adults.

SAFETY CONSIDERATIONS

SKYRIZI is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of its excipients. Serious hypersensitivity reactions, including anaphylaxis, have been reported with use of SKYRIZI. If a serious hypersensitivity reaction occurs, discontinue SKYRIZI and initiate appropriate therapy immediately. SKYRIZI may increase the risk of infection. Instruct patients to report signs or symptoms of clinically important infection during treatment. Should such an infection occur, discontinue SKYRIZI until infection resolves. Evaluate patients for tuberculosis infection prior to initiating treatment with SKYRIZI. Drug-induced liver injury was reported in a patient with Crohn's disease during induction dosing of SKYRIZI. For the treatment of Crohn's disease and ulcerative colitis, evaluate liver enzymes and bilirubin at baseline and during induction (12 weeks). Interrupt treatment with SKYRIZI if drug-induced liver injury is suspected, until this diagnosis is excluded. Avoid use of live vaccines in SKYRIZI patients.

Please continue listening and stay tuned for additional Important Safety Information for SKYRIZI within this podcast.

Dr. David Rubin

It's really exciting that we have so many treatment options for our patients with ulcerative colitis and I am really happy that we're able to talk about it and share this with our colleagues.

Dr. Josh Steinberg

It really is exciting and the results from these two pivotal clinical trials are promising and we'll dive into those.

Dr. Josh Steinberg

So, this INSPIRE Induction study was a Phase 3, randomized, double-blinded, placebo-controlled study to evaluate the efficacy and safety of SKYRIZI 1200 milligrams IV at Weeks 0, 4, and 8 versus placebo over 12 weeks in adult patients with moderate to severely active ulcerative colitis. The primary endpoint was clinical remission at Week 12.

The COMMAND maintenance study was a Phase 3, randomized, double-blinded, placebo controlled study to evaluate the efficacy and safety of SKYRIZI 180 milligrams or 360 milligrams subcutaneously versus placebo, up to 52 weeks in adult patients who were clinical responders to one of the three SKYRIZI induction regimens consisting of 600 milligrams, 1200 milligrams, or 1800 milligrams IV in both the Phase 2b study and the Phase 3 INSPIRE study.

Please note though that the 600 milligram and 1800 milligram IV doses are not the FDA-approved induction regimens. The primary endpoint was clinical remission at Week 52.

Narrator

The all-subjects maintenance population includes patients who responded per modified Mayo Score to 1800 mg, 1200 mg, or 600 mg in Phase 2b/3 induction study.

Clinical remission at Week 12 and 52 in UC is defined as stool frequency subscore ≤ 1 and not greater than baseline, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1 without friability.

Dr. Josh Steinberg

At Week 12, 24% of patients on the SKYRIZI 1200 milligram intravenous infusion achieved clinical remission, compared to 8% of patients on placebo, which is a three-fold delta.

Narrator

At Week 52, in the All Subjects Maintenance Population, 45% of patients receiving SKYRIZI 180 mg subcutaneously achieved clinical remission, based on 179 patients. Additionally, 41% of patients receiving SKYRIZI 360 mg subcutaneously achieved clinical remission, based on 186 patients. In comparison, 26% of patients on placebo achieved clinical remission, based on 182 patients.

Dr. Josh Steinberg

COMMAND also included a pre-specified subgroup analysis inclusive only of patients who responded to the FDA-approved induction dosing of SKYRIZI 1200 milligrams IV. At Week 52, 45% of patients on the subcutaneous injection of SKYRIZI 180 milligram and 50% of patients on the subcutaneous injection of SKYRIZI 360 milligram observed clinical remission compared to 29% of patients on placebo.

Narrator

Patients in the pre-specified subgroup analysis include 90 patients on 180 mg, 92 patients on 360 mg, and 89 patients on placebo.

Advanced therapy-naïve population consisted of 42 patients on 180 mg, 44 patients on 360 mg, and 41 patients on placebo. Advanced therapy-naïve patients include some patients who were exposed to an advanced therapy (biologics, JAK inhibitors, and/or S1P receptor modulators) but did not experience treatment failure.

Dr. Josh Steinberg

Continuing with the findings for advanced therapy-naïve patients at Week 52, the data show promising results for SKYRIZI. Clinical remission was observed in 59% of patients taking the 180 milligram dose and 70% of those on 360 milligram dose compared to the 32% remission rate observed in the placebo group.

Narrator

Limitations of prespecified subgroup analysis: Overall and Advanced Therapy-Naïve patient results discussed are only among patients who responded to the FDA-approved 1200 mg IV induction dose. Excluded are those who received unapproved induction doses (600 mg or 1800 mg). Data were not controlled for multiplicity. No conclusions or statistical inferences can be made.

Dr. David Rubin

Alright Josh, that was a really nice summary and thanks for helping us understand those data. So, when we put this all together to understand it, we have a therapy that has an IV induction that is quite effective, and then we have maintenance dosing of two different subcutaneous doses delivered over time that are both better than placebo.

So, remember, this is also emphasizing what happens when you use this drug as your first advanced therapy.

SKYRIZI also provides patients with the opportunity for endoscopic improvement, which as we've highlighted is a key long-term treatment target in our patients with ulcerative colitis. Endoscopic improvement is defined in pivotal trials for SKYRIZI as the Mayo endoscopic subscore of 0 or 1 without friability. Friability is defined as bleeding with gentle bumping of the scope or the forceps into the mucosa. Endoscopic results are based on a full colonoscopy or flexible sigmoidoscopy that was performed at the discretion of the investigator.

At Week 52, 51% of patients on SKYRIZI 180 milligrams sub-q and 48% of patients on SKYRIZI 360 milligrams sub-q achieved this endoscopic improvement endpoint compared to 31% of patients receiving placebo.

Narrator

In the all subjects maintenance population at Week 52, 51% of 179 patients on SKYRIZI 180 milligrams sub-q and 48% of 186 patients on SKYRIZI 360 milligrams sub-q achieved this endoscopic improvement endpoint compared to 31% of 182 patients receiving placebo. In the 1200 mg prespecified subgroup analysis, 58% of patients who received SKYRIZI 360 mg subcutaneously, and 52% of patients who received 180 mg subcutaneously, observed endoscopic improvement at Week 52, based on 92 patients and 90 patients, respectively. In comparison 36% of patients on placebo observed endoscopic improvement at Week 52, based on 89 patients.

Dr. David Rubin

So, for those patients who responded well to the FDA approved 1200 milligram IV induction doses, about 77% of advanced therapy-naïve, which included some patients who were exposed to an advanced therapy but did not experience treatment failure, continued with the 360 milligram subcutaneous dose and observed endoscopic improvement at Week 52. Even at the lower 180 milligram subcutaneous dose, 62% of these patients observed endoscopic improvement.

Narrator

In the advanced therapy-naïve population, 44 patients on 360 mg and 42 patients on 180 mg observed endoscopic improvement, compared to 34% with 41 patients on placebo.

Limitations of prespecified subgroup analysis: Overall and Advanced Therapy-Naïve patient results discussed are only among patients who responded to the FDA-approved 1200 mg IV induction dose. Excluded are those who received unapproved induction doses (600 mg or 1800 mg). Data were not controlled for multiplicity. No conclusions or statistical inferences can be made.

Dr. Josh Steinberg

I should remind our audience that there are two maintenance dosing options for SKYRIZI, the 180 milligram and the 360 milligram, both of which are given subcutaneously via an on-body injector every eight weeks.

Narrator

Use the lowest effective dose.

Dr. David Rubin

SKYRIZI's endoscopic outcomes coupled with the clinical remission data demonstrate its efficacy, making it a viable first line advanced therapy treatment option for our patients with moderately to severely active UC.

Dr. David Rubin

So, Josh, can you elaborate on the treatment regimen for SKYRIZI? We've gone through this now in the clinical trial data, but how do you actually use this in practice?

Dr. Josh Steinberg

Of course, so we're talking about ulcerative colitis specifically. So, we're talking about starting SKYRIZI. First, we start with the induction dosing, which is three IV doses at 1200 milligrams over the course of eight weeks, which basically is one dose IV every four weeks at Week 0, 4, and 8. And then four weeks after that last induction or infusion therapy, the patients would then be transitioned to the on-body injector, which the patient injects subcutaneously at home once every eight weeks.

Narrator

Administration Considerations: SKYRIZI is intended for use under the guidance and supervision of a healthcare professional (HCP). SKYRIZI vial for intravenous administration is intended for administration by an HCP. Prior to starting therapy, please refer to the

Dosage and Administration section of the Prescribing Information for complete information on how to prepare and administer SKYRIZI. Patients may self-inject SKYRIZI using the on-body injector with prefilled cartridge after training in subcutaneous injection technique. Provide proper training to patients and/or caregivers on the subcutaneous injection technique of SKYRIZI according to the Instructions for Use.

Dr. David Rubin

So, Josh, can you tell me what specifically made your patient with ulcerative colitis, whom you had spoken about earlier, an ideal candidate for SKYRIZI?

Dr. Josh Steinberg

Of course, so for one thing, he's bio-naïve, right? He's naïve to any advanced treatments. And he initially started, as we talked about, on mesalamine about six months prior, but because he didn't have any meaningful response, we added rectal mesalamine, right? So topical therapy, sometimes on top of oral mesalamine therapy can help improve outcomes. And we also started this patient on the course of oral corticosteroids. And despite all these efforts, he unfortunately continued to struggle.

He still had disease activity with elevated frequency, about five bowel movements or so a day, as well as quite significant rectal bleeding. He overall was defined as having moderate disease as reflected during his endoscopic evaluation, which showed an endoscopic Mayo subscore of 2.

Dr. David Rubin

Thanks so much, Josh. So, it's really exciting to know that SKYRIZI is available for our adult patients with moderate to severe ulcerative colitis.

As we discussed earlier, anti-TNF therapies play a significant role in managing moderate to severe cases of UC. However, some people are primary non-responders. So, it's important to consider alternate options. As I mentioned, oral small molecules offer a different mechanism of action for patients.

One class of small molecules we use in these scenarios are the JAK inhibitors, such as upadacitinib, which has the brand name RINVOQ.

Narrator

INDICATION

RINVOQ is indicated for the treatment of adults with moderately to severely active ulcerative colitis (UC) who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blockers. If TNF blockers are clinically inadvisable, patients should have received at least one approved systemic therapy prior to use of RINVOQ.

Limitations of Use: RINVOQ is not recommended for use in combination with other Janus kinase (JAK) inhibitors, biological therapies for UC, or with potent immunosuppressants such as azathioprine and cyclosporine.

Narrator

SAFETY CONSIDERATIONS for RINVOQ (upadacitinib)

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.

Thromboses: Deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. 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; hypoglycemia in patients with diabetes; laboratory abnormalities; and embryo-fetal toxicity.

Please continue listening and stay tuned for additional important safety information for RINVOQ within this podcast.

Dr. David Rubin

I have a patient in mind who I think would be a suitable candidate for RINVOQ. I think that this is an ideal patient for a JAK inhibitor. Similar to your patient, Josh, treatment with 5-ASAs and oral steroids didn't work. She's 22 and has moderately to severely active UC. She was able to control her disease for 12 months with an anti-TNF agent before experiencing breakthrough symptoms, highlighting the challenge you mentioned earlier, Josh. She was experiencing elevated stool frequency, rectal bleeding, and a colonoscopy revealed a Mayo endoscopic subscore of 2 with marked erythema, friability, and erosions, and the lab work confirmed all of this with an elevated fecal calprotectin. Given her prior treatment history and the increased disease activity she was experiencing, it made sense to consider an oral small molecule and specifically, upadacitinib. Knowing that she lost response with an anti-TNF, transitioning her to a treatment option other than a biologic, it made sense. So, she was prescribed RINVOQ once daily and this is a patient who's also of childbearing age, but she's not actively trying to get pregnant, is on contraception, and we had a conversation about that, and that is absolutely appropriate.

It is important to note that RINVOQ is not contraindicated in women of childbearing age, but it's contraindicated in women who are planning imminent pregnancy or who are pregnant or breastfeeding. RINVOQ was approved for ulcerative colitis in 2022. After two 8-week multi-center double-blind placebo-controlled UC induction trials, participants on RINVOQ who achieved clinical response at Week 8 per modified Mayo Score with 45 milligrams of RINVOQ were moved into the U-ACHIEVE maintenance trial where they were randomized to 15 milligrams daily, 30 milligrams daily, or placebo.

Narrator

RECOMMENDED MAINTENANCE DOSING

The recommended maintenance dosage of RINVOQ is 15 mg once daily. A dose of 30 mg once daily may be considered for patients with refractory, severe, or extensive disease. Discontinue RINVOQ if an adequate therapeutic response is not achieved with the 30 mg dose.

Dr. David Rubin

The clinical trials had a primary endpoint of clinical remission defined as no rectal bleeding, reduced stool frequency, and an endoscopic subscore less than or equal to 1 without friability and a variety of ranked secondary endpoints which included clinical response per the adapted Mayo score, endoscopic improvement, and histo-endoscopic mucosal improvement. So, Josh, tell us how RINVOQ did in meeting its endpoints in these clinical trials.

Dr. Josh Steinberg

Of course. And in fact, RINVOQ achieved all primary and secondary endpoints. Firstly, RINVOQ met its primary endpoint of clinical remission at Week 8 in the induction trials. And then in the 52-week maintenance trial, RINVOQ met its primary endpoint, demonstrating remission at Week 52. 42% of the 148 patients on RINVOQ 15 milligrams and 52% of the 154 patients on RINVOQ 30 milligrams achieved clinical remission, compared to just the 12% of the 149 patients on placebo.

When we look at the secondary endpoints, such as endoscopic improvement, we see that in the U-ACHIEVE maintenance trial, 49% of the 148 patients on RINVOQ 15 milligrams and 62% of the 154 patients on RINVOQ 30 milligrams achieve endoscopic improvement, compared with 14% of the 149 patients receiving placebo. Endoscopic improvement was defined as Mayo endoscopy subscore of 0 or 1 without friability. Endoscopic results were based on a full colonoscopy or flexible sigmoidoscopy depending on the extent of disease at study entry.

Dr. David Rubin

What's important to consider is where the patients started at the entrance of the induction studies—approximately 70% of patients began as Mayo endoscopic subscore of 3 or severe disease, and 30% as Mayo endoscopic subscore of 2.

In addition to endoscopic improvement, the RINVOQ trials also measured endoscopic remission, defined by a Mayo endoscopic subscore of 0, or normal appearance of the colon. I want to emphasize that, a Mayo endoscopic subscore of 0. At Week 52, approximately a quarter of patients achieved an endoscopic remission on RINVOQ, compared with 6% on placebo.

This is important to our long-term treat-to-target goals and a metric that I aim for with my patients or at least acknowledge to them after I scope them what the positive predictive value is after finding this.

Narrator

24% of 148 patients on RINVOQ 15 mg, 26% of 154 patients on RINVOQ 30 mg, and 6% of 149 patients on placebo achieved endoscopic remission at Week 52.

Dr. David Rubin

Data are also available for RINVOQ's open-label extension, the U-ACTIVATE study. The long-term extension study evaluates as-observed data over an extended period. We're combining the results of the initial 52-week Maintenance trial with the long-term extension findings.

Narrator

These patients in OLE were those that completed the U-ACHIEVE maintenance trial and achieved clinical remission per modified Mayo Score at Week 52.

Dr. David Rubin

The long-term extension study evaluates as-observed data over an extended period.

The results are promising, especially when we look at the key endpoints we discussed earlier. Endoscopic improvement, clinical remission, and now endoscopic remission.

So, Josh, to get back to our discussion about the Week 52 data, in my practice, as I'm sure is the case in yours, the data suggest that RINVOQ is a proven treatment option for our moderate to severe UC patients who have had intolerance or an inadequate response to anti-TNF. To bring back our patient example, she's an ideal candidate for RINVOQ. She had a history of being treated with an anti-TNF agent and needed relief due to her significant symptoms.

Additionally, she's a young adult. She's not actively trying to get pregnant. She's taking contraception and she does not have any risk factors. So really a perfect person for this. So, Josh, back to you.

Dr. Josh Steinberg

It's a really great point you make, David, and I completely agree. And it's really important that we consider individual patient risk factors when we're trying to determine what might be the most appropriate treatment option in our patients with ulcerative colitis. And like we mentioned before, you always want to try to really individualize this benefit-and-risk discussion to the patient's unique situation based on their disease characteristics, other risk factors and the like. So, for instance, if the patient is elderly and has two or three cardiovascular risk factors, that might warrant perhaps a more cautious approach and might lead me or other providers to reconsider prescribing RINVOQ and maybe consider an alternative option. But that being said, sometimes the most effective treatment is going to be the one that we feel like is going to work best, but we obviously have to take safety into consideration. In our particular patient's case, after carefully weighing the potential benefits and risks, it really became clear that RINVOQ made sense as an option for managing her ulcerative colitis.

Dr. David Rubin

So, Josh, have you found RINVOQ to work well with some of your patients?

Dr. Josh Steinberg

Overall, yes, I really have. It's been the case in my practice that RINVOQ has worked very well for many of my patients with ulcerative colitis. And in particular, my adult patients with moderate to severe UC, I typically transition them to RINVOQ after they've failed just one anti-TNF. I don't really wait and try and cycle them if they had a primary non-response to the first anti-TNF to try to go to another anti-TNF.

Dr. David Rubin

Terrific. Let's talk a little bit more about safety. We want to see patients improve on all levels and we want them to remain safe. And of course, we think about long-term safety when we're using therapies for maintenance. SKYRIZI, as you already covered, is an effective therapy. It has a safety profile established across four indications with approximately nine years of clinical trial experience and has undergone extensive research and follow-up with 34 clinical trials across all those indications.

It's been evaluated in over 8,700 patients globally across all dose levels, providing us with data for more than 26,800 patient-years of clinical trial exposure.

Narrator

Common adverse events for UC patients taking SKYRIZI can include arthralgia, pyrexia, injection site reactions, and rash. Serious adverse events for patients taking SKYRIZI can include infections and hepatic events.

The most common side effects of SKYRIZI in people treated for Crohn's disease and ulcerative colitis include upper respiratory infections, headache, joint pain, stomach (abdominal) pain, injection site reactions, low red blood cells (anemia), fever, back pain, urinary tract infection, and rash.

Adverse drug reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Please continue listening and stay tuned for additional important safety information for SKYRIZI within this podcast.

Dr. David Rubin

RINVOQ has a well-studied safety profile as well. That being said, discussing the safety of RINVOQ with patients is essential to ensure they are fully informed. During our consultation, I explained, RINVOQ may have side effects.

Narrator

The most common adverse reactions in RINVOQ clinical trials were upper respiratory tract infections, herpes zoster, herpes simplex, bronchitis, nausea, cough, pyrexia, acne, headache, peripheral edema, increased blood creatine phosphokinase, increased blood cholesterol, hypersensitivity, folliculitis, abdominal pain, increased weight, influenza, fatigue, neutropenia, myalgia, influenza-like illness, elevated liver enzymes, rash, and anemia.

Please continue listening and stay tuned for additional important safety information for RINVOQ within this podcast.

Dr. David Rubin

I consistently engage in comprehensive discussions with my patients regarding the potential risks associated with their treatment, and I put it in the context of the risk of inadequately treated disease. It's important for me that they understand that while my primary goal is to effectively manage their UC, I am equally committed to prioritizing their safety. The benefit versus risk conversation between the patient and doctor should be applied to each patient and assessed individually. Not everyone will have the same experience, underscoring the value in this type of discussion with the patient. The patient needs to feel comfortable with what we're recommending. So, we must consider the risk of not treating or under treating the patient and what the other options might be.

We also can decide after we have someone on therapy how they're feeling and reevaluate that risk to benefit by the individual patient. That conversation is dynamic and should occur at different time points during their management. I've had many adult patients with moderate to severe UC achieve clinical remission and after they do so they want to stay on the therapy and we continue to discuss and consider the potential for any side effects.

Dr. Josh Steinberg

That's generally been my patients' experience as well, David. And I really have to say that as a practicing gastroenterologist treating patients with inflammatory bowel disease every single day, it really is so exciting to know that there are more treatment options now than ever for our patients, particularly with moderately to severely active ulcerative colitis.

Dr. David Rubin

So, Josh, we've talked about two different therapies today, SKYRIZI, an IL-23 inhibitor, and RINVOQ, which is a selective JAK-1 inhibitor. Just to summarize, in your practice, how do you decide between those two therapies when you see a new patient with ulcerative colitis?

Dr. Josh Steinberg

I think there's a lot of things that go into consideration when trying to make this decision. But one framework to kind of keep in mind is whether or not this patient in front of you is bio-experienced, particularly anti-TNF experienced or bio-naïve. So, in our patients with UC who are biologic-naïve, an interleukin 23 inhibitor such as SKYRIZI might be a very viable option because we know that we can use it as a first line advanced therapy in this bio-naïve patient.

Now in our bio-experienced patients, right, the more refractory patient that perhaps has previously failed an anti-TNF and we want or need these patients to get better as soon as possible, a small molecule such as RINVOQ, a Janus kinase inhibitor, might be a more favorable approach to take just because we know that we can start therapy and they can have a quite immediate response as we know that the onset of action for a small molecule like RINVOQ is quite rapid.

Dr. David Rubin

So, there's lots of different places where it makes complete sense to use these therapies. And we're hopeful that this conversation is giving some of the folks listening ideas about how to use these drugs more effectively.

Dr. David Rubin

Josh, I'm glad we finally found a date to have this conversation and to continue our dialogue about managing IBD. Thank you for joining us and talking about SKYRIZI as a first-line option and RINVOQ as an option after patients have been on anti-TNF.

Dr. Josh Steinberg

Thank you for having me back. It's been an absolute pleasure as per usual. So, David, I'm really looking forward to hearing more from you and learning more from you and your future guests. And thanks again for having me. I hope you have me back for a third time.

Dr. David Rubin

Yeah, we'll see how people evaluate this session and then decide. No, in all seriousness, Josh, it's great having this conversation. So, if you've enjoyed this episode of *Gut Reactions* and found it educational, you can share it via the share button, email, LinkedIn, or on any of your preferred platforms. Until next time, thank you for joining us on *Gut Reactions*.

Narrator

Please continue listening for additional important safety information for RINVOQ & SKYRIZI.

INDICATION for RINVOQ (upadacitinib)

RINVOQ is indicated for the treatment of adults with moderately to severely active ulcerative colitis (UC) who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blockers. If TNF blockers are clinically inadvisable, patients should have received at least one approved systemic therapy prior to use of RINVOQ.

Limitations of Use: RINVOQ is not recommended for use in combination with other Janus kinase (JAK) inhibitors, biological therapies for UC, or with potent immunosuppressants such as azathioprine and cyclosporine.

IMPORTANT SAFETY INFORMATION for RINVOQ (upadacitinib)

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 (MACE)

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 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

Thromboses, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. 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 GI perforation (e.g., patients with a history of diverticulitis and patients taking NSAIDs or corticosteroids). Promptly evaluate patients presenting with new onset abdominal pain for early identification of GI perforation.

HYPOGLYCEMIA IN PATIENTS WITH DIABETES

Hypoglycemia, including severe hypoglycemia, has been reported following initiation of RINVOQ and other JAK inhibitors in patients with diabetes. During treatment with RINVOQ, consider increased monitoring of blood glucose as clinically indicated in patients with diabetes. Advise patients with diabetes to notify their healthcare provider if they develop signs or symptoms of hypoglycemia.

LABORATORY ABNORMALITIES

Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (absolute neutrophil count [ANC] < 1000 cells/mm³). Treatment with RINVOQ is not recommended in patients with an ANC < 1000 cells/mm³. Evaluate neutrophil counts at baseline and thereafter according to routine patient management.

Lymphopenia

Absolute lymphocyte counts (ALC) < 500 cells/mm³ were reported in RINVOQ-treated patients. Treatment with RINVOQ is not recommended in patients with an ALC < 500 cells/mm³. 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 prophylactic varicella zoster or herpes zoster vaccinations, in agreement with current immunization guidelines.

MEDICATION RESIDUE IN STOOL

Reports of medication residue in stool or ostomy output have occurred in patients taking RINVOQ. Most reports described anatomic or functional GI conditions with shortened GI transit times. Instruct patients to contact their healthcare provider if medication residue is observed repeatedly. Monitor patients clinically and consider alternative treatment if there is an inadequate therapeutic response.

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, peripheral edema, increased blood creatine phosphokinase, hypersensitivity, folliculitis, abdominal pain, increased weight, influenza, fatigue, neutropenia, myalgia, influenza-like illness, elevated liver enzymes, rash, and anemia.

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.

Visit rxabbvie.com/pdf/rinvoq_pi.pdf for Prescribing Information, including **BOXED WARNING**, for RINVOQ.

IMPORTANT SAFETY INFORMATION & INDICATIONS for SKYRIZI (risankizumab-rzaa)

INDICATIONS for SKYRIZI (risankizumab-rzaa)

Crohn's Disease: SKYRIZI is indicated for the treatment of moderately to severely active Crohn's disease in adults.

Ulcerative Colitis: SKYRIZI is indicated for the treatment of moderately to severely active ulcerative colitis in adults.

IMPORTANT SAFETY INFORMATION for SKYRIZI (risankizumab-rzaa)

Hypersensitivity Reactions

SKYRIZI® (risankizumab-rzaa) is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients. Serious hypersensitivity reactions, including anaphylaxis, have been reported with the use of SKYRIZI. If a serious hypersensitivity reaction occurs, discontinue SKYRIZI and initiate appropriate therapy immediately.

Infection

SKYRIZI may increase the risk of infection. Do not initiate treatment with SKYRIZI in patients with a clinically important active infection until it resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, closely monitor and discontinue SKYRIZI until the infection resolves.

Tuberculosis (TB)

Prior to initiating treatment with SKYRIZI, evaluate for TB infection and consider treatment in patients with latent or active TB for whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

Hepatotoxicity

Drug-induced liver injury was reported in a patient with Crohn's disease who was hospitalized for a rash during induction dosing of SKYRIZI. For the treatment of Crohn's disease and ulcerative colitis, evaluate liver enzymes and bilirubin at baseline and during induction (12 weeks); monitor thereafter according to routine patient management. Consider an alternate treatment for patients with evidence of liver cirrhosis. Interrupt treatment if drug-induced liver injury is suspected, until this diagnosis is excluded. Instruct your patient to seek immediate medical attention if they experience symptoms suggestive of hepatic dysfunction.

Immunizations

Avoid use of live vaccines in patients treated with SKYRIZI. Drugs that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating SKYRIZI, complete all age-appropriate vaccinations according to current immunization guidelines.

Adverse Reactions

Most common (>3%) adverse reactions associated with SKYRIZI in Crohn's disease are upper respiratory infections, headache, and arthralgia in induction, and arthralgia, abdominal pain, injection site reactions, anemia, pyrexia, back pain, arthropathy, and urinary tract infection in maintenance.

Most common (≥3%) adverse reactions associated with SKYRIZI in ulcerative colitis are arthralgia in induction, and arthralgia, pyrexia, injection site reactions, and rash in maintenance.

Lipid Elevations: Increases from baseline and increases relative to placebo were observed at Week 4 and remained stable to Week 12 in patients treated with SKYRIZI in Crohn's disease. Lipid elevations observed in patients with ulcerative colitis were similar to those in Crohn's disease.

Dosage Forms and Strengths: SKYRIZI (risankizumab-rzaa) is available in a 600 mg/10 mL single-dose vial for intravenous infusion and a 180 mg/1.2 mL or 360 mg/2.4 mL single-dose prefilled cartridge with on-body injector.

Visit rxabbvie.com/pdf/skyrizi_pi.pdf for Prescribing Information for SKYRIZI.

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