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Survey Says: Aligning Early Advanced IBD Therapy with Patient Priorities

Announcer:
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Dr. Axelrad:
We are now going to move on to talking about treatment advances in Crohn's disease. We are going to spend some time on this section, and then Russ, Jess, and I will talk about some things that are important to you. You will be able to select what we should be chatting about and discussing as far as management of our patients.

Patient Pulse Survey Showdown

All right, so before we do that, we will take a patient pulse survey showdown.

Which of the following did patients rank as the most important treatment outcome they want to achieve?

A. Convenience of treatment;
B. Improved quality of life;
C. Long-term disease control;
D. Safety or adverse effects; or
E. Symptom control.

Patient Pulse Survey Showdown Results!

All right, so it sounds like patients really ranked as most important treatment outcome they want to achieve, improved quality of life. So that is where all of us agree on. But symptom control is also up there. Okay.

What Do Patients Have to Say?

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All right, so now we are going to turn to a patient who is going to let us know what their goals of therapy are.

Emily:
I think my goal was just that I wanted my life back. I had gotten stuck in this really terrible carousel of hospital visits, and it was just preventing me from going to college, meeting friends, and I just wanted to be able to have a normal life like a normal teenager.

Carole:
My goal was to prevent flare-ups and urgencies. It is the riskiest move when you are traveling or just going to work when you are in the car. And so until you find a medication that can give you that relief, you are just on the hunt for the right medication or injections or infusions or anything. And for me, two years ago, my medicine wore out. It just stopped working. I had it for 12 years, and it completely stopped.

And because of a great GI, he really advocated for me, which is very important, and helped me find a medication that would set me back to not having flare-ups, and knock on wood, get me into remission. And so as of right now, that is where I am at, but I do not like to say it too much because I do not want to mess with it.

Dr. Axelrad:
All right, so hopefully those patient perspectives will maybe frame how we will discuss some of the treatment options we have available, and of course, some of our novel agents so we can help patients achieve those goals.

Advanced Treatment Options for CD: Biologic Therapies

So this is a list of all of the advanced treatment options in Crohn's disease, which include anti-TNF, anti-integrins, IL-12/23s, and of course, our most novel class, which are selective IL-23 inhibitors, the P19 inhibitors, and of course, JAK inhibitors. So we are going to review all of these advanced treatment options in Crohn's disease.

Recent Drug Approvals for Patients With CD

So let us start with the most recent drug approvals.

Select Immunology Targets in IBD

This just represents the landscape of IBD therapies. This actually lists our currently approved therapies in addition to a couple of pipeline agents, which will become critically important in our treatment paradigm.

So here all the way on the right, ozanimod, etrasimod, those are for ulcerative colitis. Jess will touch on those in a bit. That is actually a lymph node.

But you can see highlighted here is the IL-12/23 and IL-23 class in the red box. And these act on an inflammatory cytokine, IL-23, which reduces a variety of downstream inflammatory responses. And of course, we will touch on some other agents, including JAK inhibitors, which act on the intracellular part of inflammatory cells to reduce inflammatory signaling. So a little bit of a different mechanism. But this slide just sort of nicely shows you an overview of all of our currently available FDA-approved therapeutics and a couple of pipeline agents as well.

Selective IL-23 Inhibitors for moderate-to-severe CD

All right, so turning to IL-23 inhibitors, we have three ,that are currently FDA-approved for inflammatory bowel disease.

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I am going to focus on Crohn's disease because the dosing for some of these is a bit different. And then Jess will review ulcerative colitis.

Risankizumab is approved in both Crohn's and colitis. It is a humanized IgG1, selectively binds the P19 subunit of IL-23. This in Crohn's disease is dosed as 600 mg IV on weeks zero, four, and eight, followed by maintenance of a subcutaneous on-body injector at either 180 or 360 mg subcutaneous every eight weeks. I will say there is submitted to the FDA from our AbbVie is the on-body injector for subcutaneous injection for induction, so that hopefully may be available for us soon.

We also have mirikizumab, also approved in both Crohn's and colitis. It is a humanized IgG4, also binds to the P19 subunit of IL-23. This is dosed as 900 mg IV induction at zero, four, and eight weeks, followed by a 300 mg sub-Q maintenance every eight weeks.

And then guselkumab, which is most recently approved in both Crohn's and ulcerative colitis. This binds human IgG1. It binds not only the P19 subunit, but also binds CD64 on macrophages and monocytes, so may work in a slightly different mechanism. It is dosed both IV infusion induction and as a subcutaneous induction as well, which currently is unique in the IL-23 agents at zero, four, and eight weeks, followed by two possible maintenance regimens, 100 mg every eight weeks, or 200 mg every four weeks. So a little flexibility there on maintenance as well.

So these are all of our currently FDA-approved IL-23 agents.

GRAVITI: Guselkumab in moderate-to-severe CD – Primary Efficacy

All right, so what are the data? First, I just want to show you GRAVITI, which was a study of guselkumab in moderate-to-severe Crohn's disease.

This was a double-blind placebo-controlled Phase III on the subcutaneous induction. Here you could see on the right, I am showing you the primary efficacy at week 12, both clinical remission and endoscopic response. Important to note, most of us really focus, particularly in Crohn's, on the endoscopic outcomes because our clinical outcomes with CDAI is really rather subjective.

But here on an endoscopic response, you could see guselkumab at 400 mg during induction, subcutaneous at zero, four, and eight, significantly better than placebo.

GRAVITI: Guselkumab in moderate-to-severe CD – Response by Previous Treatment at Wk 48

Turning to outcomes to week 48, again, you can see that guselkumab was more effective than placebo, and this was a treat-through design for both clinical remission and endoscopic response. Uniquely here, we are showing you the data, who are also stratified by prior inadequate response or intolerance to advanced therapies, and you could see that when you look at the endoscopic response graphs here on the right, that that higher dose in maintenance 200 mg Q4, that seemed to have a relatively better benefit for endoscopic response in patients who had prior advanced therapy failures.

So here is where maybe that maintenance dose is distinguished for guselkumab.

GRAVITI: Guselkumab in moderate-to-severe CD – Corticosteroid-Free Remission and Safety

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Continuing out, specifically looking at corticosteroid-free remission and also safety events, of course, guselkumab was better than placebo for maintaining clinical remission at week 48 that was corticosteroid-free, and then when we look on the right, we could see that adverse events were more common in placebo-exposed patients, which is quite common when you have drugs that work, and discontinuation was low, and discontinuation of drug was particularly lowest in those who were on the 200 mg Q4 maintenance.

So many of us, when we utilize guselkumab in practice, are actually reaching for that 200 mg Q4 maintenance dose.

VIVID-1: Mirikizumab in moderate-to-severe CD – Composite Endpoint Primary Efficacy

Turning to VIVID, this was the study of mirikizumab in moderate-to-severe Crohn's disease. This was a double-blind Phase III RCT with active and placebo controls.

This, too, was more of a treat-through design, and we are seeing here on the right, this is a little bit of a different endpoint that we just discussed. This is slightly more stringent, looking at PRO, patient-reported outcome, remission at week 12, who then had remission or response at week 52. So a bit of a more stringent co-primary endpoints to look at, and you can see here that, again, mirikizumab, obviously far superior to placebo in achieving those co-primary endpoints.

VIVID-1: Mirikizumab in Moderate to Severe CD – Response by Failure to Biologic Therapies at Wk 52

Okay, what about response by failure to prior biologic therapies? So I showed you this data stratified with guselkumab. Here, you are now seeing with mirikizumab.

It is important that these data are a little different. You can see that mirikizumab actually works in both patients with and without prior failure to biologic therapies, and in VIVID-1, there was also an active comparator to ustekinumab. Here in these studies, mirikizumab was non-inferior to ustekinumab, and that differs from some of our other IL-23s, but again, showing you here that mirikizumab for clinical remission at week 52 and endoscopic response at week 52, superior to placebo for achieving our outcomes, regardless of prior advanced therapy exposure.

And I will just point out that maybe there were numerically better outcomes with mirikizumab in endoscopic response at week 52 in patients who had prior failures, but not statistically significant compared to ustekinumab.

VIVID-1: Mirikizumab in Moderate to Severe CD – Corticosteroid-Free Remission and Safety

Okay, what about corticosteroid-free remission and safety events? So again, on that stringent outcome, PRO2 remission at week 12, now tied to corticosteroid-free clinical remission at week 52, mirikizumab significantly better than placebo as expected.

For safety events, similar to guselkumab, we see that there were fewer adverse events with patients who were given drug compared to placebo. Again, that is how you know your drug works when there are fewer adverse events with that. And treatment discontinuations were significantly lower in the treatment groups, Miri and ustekinumab compared to placebo.

ADVANCE, MOTIVATE, and FORTIFY: Risankizumab in

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Moderate to Severe CD

All right, turning to the last IL-23 inhibitor for Crohn's disease. These are data from ADVANCE and MOTIVATE, and then I am going to show you in a bit data from FORTIFY. Those were the clinical trials in Crohn's disease.

ADVANCE and MOTIVATE were induction trials. ADVANCE was a mixed population of ADVANCE therapy-naive and exposed patients, whereas MOTIVATE was isolated to those with prior AT failures. FORTIFY was the re-randomization maintenance trial.

So just to rephrase, guselkumab and mirikizumab were treat-through designs. Risankizumab with FORTIFY was a re-randomization trial. So responders to induction were then re-randomized in maintenance.

But here I am showing you clinical remission at week 12 and endoscopic response at week 12. As expected, risankizumab was more effective than placebo across endpoints. And in particular, looking at some of our more important endpoints like endoscopic response at week 12 in a prior ADVANCE therapy exposed failure population all the way here on the right.

So again, showing nice differentiation within Crohn's disease that prior ADVANCE therapy failures in induction data across the IL-23 class that there is utility in some of our more important outcomes, like endoscopic response, for these agents.

FORTIFY: Risankizumab in Moderate to Severe CD

Turning to FORTIFY. So this was the maintenance data for risankizumab in moderate-to-severe Crohn's disease.

I just want to call out again that this was re-randomization. So there were patients who were exposed to risankizumab in induction who then got placebo in maintenance. And that is why you are seeing relatively higher placebo rates in this trial.

So that is important to contextualize. There is a very long tail on risankizumab. You may notice that with your patients that if they have an interruption in therapy that they maybe are not flaring immediately for a little while. So there is that long half-life on risankizumab.

And here you can see across are the endpoints of clinical remission and endoscopic response of week 52. Risankizumab at both FDA-approved doses, 360 and 180, significantly better than placebo for achieving these outcomes.

FORTIFY: Risankizumab in Moderate to Severe CD Long-term Efficacy

What about more longer-term efficacy data? So here we are looking at patient-reported outcomes like stool frequency and abdominal pain, clinical remission, endoscopic endpoints. In particular, I will point you to look at endoscopic remission, one of our most stringent outcomes that we really pay quite a bit of attention to that across the board and across the doses, risankizumab was superior to placebo, but in particular, superior to placebo and at the highest dose numerically for things like endoscopic remission.

So again, many of us in practice for maintenance are using that higher dose.

Select Immunology Targets in IBD

So turning now to JAK inhibitors in Crohn's disease.

JAK Inhibitors for Moderate to Severe CD

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So tofacitinib, all the way on the right, not approved in Crohn's disease, and Jess will review that for ulcerative colitis, but upadacitinib, which is a JAK1 selective inhibitor, is approved in Crohn's disease. It is, of course, also approved in ulcerative colitis. This is dosed in Crohn's disease as 45 mg daily for 12 weeks, followed by maintenance at either 15 mg or 30 mg daily. Most of us in clinical practice are really reaching for that higher dose, and we could chat about that.

U-EXCEL/EXCEED: Upadacitinib in Moderate-to-Severe CD

Here, these are the data from U-EXCEL and EXCEED, which were the trials of upadacitinib in Crohn's disease. These were 12-week induction trials, and then patients were then re-randomized to maintenance. Here you could see on the right, this is being isolated to patients with prior biologic failure, which per the FDA label is where upadacitinib is utilized.

There has recently actually been a label change, which we can chat about, that this potentially could be used in first-line patients. But here, we are isolating it to our more refractory population who failed prior advanced therapies, clinical remission, and endoscopic response, very low placebo rates, so you know your population was sick. And of course, upadacitinib at 45 mg during induction, significantly better than placebo at these endpoints.

U-ENDURE LTE: Upadacitinib in Moderate to Severe CD – Long-term Outcomes

U-ENDURE, which were the long-term extension data, or the maintenance data, rather. You can see here both clinical remission in patients with prior biologic failure and endoscopic response at week 52 across doses was superior to placebo. And just again of note, we are getting numerically better data with that higher upadacitinib dose, which again, is what most of us tend to use in clinical practice, unless indication to drop the dose for a couple of reasons, and we could chat about that.

Experts in the Hot Seat

All right, so now we have a couple of minutes, and you guys can choose what we will chat about. You could choose that we will talk about:

A. Sequencing after TNF failure;
B. Updated labeling for upadacitinib, as just mentioned, and how that works practically;
C. Updated safety and positioning on JAK inhibitors;
D. Speed of symptom resolution with novel advanced therapies; and
E. Managing partial responders when to declare treatment failure.

Dr. Cohen:
Okay, so sequencing after TNF failure. So this is Crohn's disease. Okay. So, it will allow Jessica to speak.

Dr. Allegretti:
Oh, wonderful.

Dr. Cohen:
Hello, everyone. So patients who has Crohn's, let us say the patient does not have fistulas Crohn's disease. Where do you look?

Dr. Allegretti:
Yes, you know, it is interesting. I think my first question is like, would I have even started with the TNF? You know, I think in my mind when I am initiating new therapy, I always ask myself, has this patient earned an anti-TNF or not? And I am actually trying to reserve my anti-TNFs for later in line. So unless they have a severe disease phenotype, perianal disease, fistulizing disease, bad structuring

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disease, I am probably not starting with the TNF first if it is up to me.

Dr. Cohen:
But if I am. But this is not about starting. This is TNF failures. Stay on topic.

Dr. Allegretti:
Okay. I just wanted to give that perspective. If I am starting with an anti-TNF and the patient is failing, again, and this patient does not have fistulizing disease as Russ just said, I am probably moving on to an IL-23.

We know these agents work really great in TNF failures, as you just saw Jordan just presented. And so, I think JAKs remain an option as well. But again, that is probably more of a patient with a more severe phenotype.

Dr. Cohen:
Jordan, how would you decide whether to do an IL-23, a JAK inhibitor, vedolizumab?

Dr. Axelrad:
Yes, it is a good question. I think, and you specifically qualified about the fistula. So I will try to stay on topic that there is no fistula.

Dr. Cohen:
No fistula. Stay on topic.

Dr. Axelrad:
Yes. So after TNF failure, I think it is a very reasonable, and I just showed you the data about folks who have failed prior advanced therapies, that IL-23s are a very good option. I think JAK inhibitors could be considered. We also have, which we have not talked about and I did not show the data, but there are very interesting retrospective data showing that IL-23 inhibitors also work particularly well for folks with ileal Crohn's disease as compared to our other drugs when specifically looking at patients with ileal disease distribution. So again, another sort of option that there is good data for IL-23 inhibitors in ileal Crohn's disease, where upadacitinib and other agents in this segment maybe are not going to have as much good utility for ileal Crohn's disease.

So that is something I think about as well.

Dr. Cohen:
What about vedolizumab and TNF failures for Crohn's disease? Yes or no?

Dr. Axelrad:
For me, no.

Dr. Cohen:
Yes or no?

Dr. Allegretti:
No.

Dr. Cohen:
Okay, Jordan, patient does have fistulas Crohn's disease. He failed therapy, He has had an MRI, seen a colorectal or Crohn's surgeon. They are on board, does not need a CTON. They say, okay. What medical therapy would you move to now?

Dr. Axelrad:
I still think the answer is probably IL-23s. We actually have some data being presented at this conference that IL-23 inhibitors are actually pretty good for healing perianal fistula. The upadacitinib data is also demonstrated; it is useful in healing some fistula.

I would say in clinical practice, I find IL-23 inhibitors to sometimes be better for treating fistula's disease. Upa, I would definitely consider it. I think it really depends on the patient. Again, I am thinking about, is there ileal disease as well in addition to the fistula. I think it is our natural feeling that a fistula, we should use Upa because it is a drug that has more data for advanced therapy experience to "sicker" patients. I think we are finally getting a lot of data that fistula may be healed with IL-23, so I would consider both.

Dr. Cohen:
Jess?

Dr. Allegretti:
Yes, I agree. I think if this is the patient's first fistula, it does not need a CTON, seems otherwise fairly uncomplicated, I think IL-23 is a great choice, and again, we are seeing that data at this meeting. But if this is a patient with complicated perianal disease, and I would

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say a more severe luminal phenotype as well, like there is still ongoing severe rectal disease, I would use Upa.

Dr. Cohen:
Agreed, agreed. Would you use vedolizumab for TNF failure for perianal disease?

Dr. Allegretti:
No.

Dr. Axelrad:
No.

Dr. Cohen:
All right. So we give you guys answers, right? Not this wishy-washy stuff. Okay, so I think we are going to move forward now with Jessica's discussion about ulcerative colitis.

Round 2: Treatment Advances in Ulcerative Colitis
Jessica Allegretti, MD, MPH

Dr. Allegretti:
All right, so Jordan really set the scene well for me, so it is going to be smooth sailing through the ulcerative colitis data.

Patient Pulse Survey Showdown

But first, let us see what you guys think the patients care about. So how long does the average patient with IBD wait to change treatment after symptoms get worse?

Patient Pulse Survey Showdown Results!

All right. So it looks like most people are leaning 3-6 months is what is coming out in the lead.

What Do Patients Have to Say?

All right. So let us hear what the patients say.

Emily:
For me, I really wanted convenience with my treatment. I did not want to have to drive all the way out of my way to go to a clinic to get an injection. I wanted to do something in my home that would not interrupt the rest of my day-to-day life.

Carole:
The correct, right treatment for me was to find a pill instead of infusion or injections, which is totally fine for a lot of people. But I am kind of a type A, and I am very organized, and I like to have a pill to put into my other pill box with all my other vitamins and stuff. And so if I could have that, it was beneficial. If I could not, then we will work with the program. But that was the number one. And also, it is much easier when you do travel. And I also travel a lot.

And I would add on the second part of this answer is to have insurance cover it, which my insurance did not cover it for 2.5 years. And it just started covering it this January. And thankfully, I was on a patient program that I got it for free, again, because of an awesome GI, and he advocated to put me into that program. Having insurance cover it is so big because these medicines cost so much money.

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Advanced Treatment Options for UC: Therapies

Dr. Allegretti:
All right, so that was not the answer to the question that we asked you guys. But what we were just hearing is about what is really important to patients with regards to how they think about therapy selection. And I feel like Carole, that last patient, really wants us to guess what therapy she is on, but she is not going to tell us.

Dr. Cohen:
But she really likes her provider.

Dr. Allegretti:
She really likes her provider, which is great.

Dr. Cohen:
It must be Dave Rubin, then.

Dr. Allegretti:
All right, so as I mentioned, Jordan just really set the scene with the Crohn's presentation. And so you are going to hear a lot of similarities, but we will go through what differences there are with regards to the ulcerative colitis data. Here are the lists of advanced treatment options that we have for ulcerative colitis.

We have got the TNF inhibitors, the anti-integrin receptor antagonists, the IL-12/23s, the selective IL-23s, the JAK inhibitors. And unique to ulcerative colitis, we have got the S1P receptor agonists, which we do not have approved for Crohn's disease.

Recent Drug Approvals for Patients With UC

So let us go through the recent drug approvals within this disease state.

Select Immunology Targets in IBD

Jordan just walked us through this nicely.

QUASAR: Guselkumab in Moderate to Severe UC

And so, let us go through each of these different classes and walk through the data. So here is the QUASAR program. This is guselkumab for the treatment of moderate-to-severe ulcerative colitis. I will sort of orient you to all the data that you are seeing up here.

In the upper left, we have the primary endpoint, which is clinical remission measured at week 12. And you can see here that 23% of the patients treated with guselkumab achieved that endpoint compared to 8% in the placebo arm. Moving over, we have the maintenance data out to week 44. And again, looking at clinical remission, and you can see here that there were two maintenance doses assessed compared to placebo, and we see maybe some dose response here with the higher dose having a slightly numerical benefit.

But again, we see good response rates across both maintenance doses compared to placebo. Something we often ask with many of our agents is, how fast do they work? And you can see at the bottom, symptomatic response at week 12. And we start to see separation of those curves as early as one week. But you can see a significant separation by week 4.

And then the last graph we see here is endoscopic remission, again at week 44. This is out in the maintenance program. And again, we do not see any major dose differences between the two maintenance doses tested.

And you can see, again, slightly higher response rates in the bio-naive population. But we still see very good efficacy among those who

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are experienced with regards to both clinical and endoscopic remission out at week 44.

LUCENT-1/2: Mirikizumab in Moderate to Severe UC

All right, so here is mirikizumab. This is LUCENT-1 and 2. And again, looking at the primary efficacy endpoint measured at week 12. Here I am showing you clinical remission, endoscopic remission, and endoscopic healing, or HEMI as we call it.

And so, you can see here that with regards to the primary endpoint, 24% of patients treated with Miri achieve that endpoint compared to 13% in placebo. We see higher endoscopic remission rates, 36% who receive Miri compared to 21% in placebo. And again, as we move down the graph, that sort of deeper endpoint of HEMI, 27% of those who were treated with Miri achieve that.

These are, of course, all statistically significant. As we move out into maintenance, looking at just one maintenance dose compared to placebo, we see that all of these endpoints are met. And so, I think what is nice to see is that you see those endpoints are sustained through week 44. So we are seeing good durability with this agent.

INSPIRE and COMMAND: Risankizumab in Moderate to Severe UC

All right, our last IL-23 in the bunch, risankizumab. So this is data from the INSPIRE and COMMAND programs.

And so, looking again at the primary induction study, INSPIRE, this is clinical remission measured at week 12. You are noticing some trends. These studies have a lot of similarities.

But you can see in the overall population, 20.3% of patients achieved clinical remission at week 12 compared to placebo, 6.2%. And then this data is split up by those who have been exposed to prior advanced therapies versus not. And not surprisingly, we see higher rates of clinical remission among those who are bio-naive, as we see with most of our agents. But we still see statistically significant efficacy among those who are advanced therapy experienced.

And then looking out at maintenance in week 52, again, two maintenance doses were studied as well as placebo. And we do not see any major dose differences between the two maintenance doses studied. But we do see that they both performed better than placebo across clinical remission, clinical response, and endoscopic improvement.

Notably, in this program, AEs were similar across treatment groups, with no new safety risks reported. This class overall looks very safe and very well tolerated.

U-ACHIEVE/ACCOMPLISH: Upadacitinib in Moderate to Severe UC

All right, so moving on to our JAK inhibitors.

So this is upadacitinib. Here is data from two Phase III trials covering eight-week induction. Patients were randomized to receive upadacitinib 45 mg or placebo.

And then we also have the U-ACHIEVE study, which is the maintenance study where induction responders received either Upa 15 mg or 30 mg or placebo. So you can see here data measuring out to week eight for induction. And again, looking at sort of stratification by how many prior advanced therapies patients have been exposed to, you can see 19% of patients who are bio-naive achieved clinical remission out at week eight. And we see lower rates but still efficacy among those who have experienced one or two or more prior advanced therapies.

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Looking at endoscopic remission at week eight, we see 28.8% of those who are bio-naive achieved endoscopic remission at week eight. And again, we see slightly lower rates of endoscopic remission the more experienced the patient is. But we are still seeing sizable deltas compared to placebo.

U-ACHIEVE Substudy 3: Upadacitinib in Moderate to Severe UC – Long-term Outcomes

All right, what about in maintenance with this agent? Here is the data out at week 52. Again, two maintenance doses were studied. And we see here that there are some numerical differences between the two doses. But both doses performed better than placebo.

And again, what I think is notable out at maintenance, you see less difference between those who are bio-naive and those who are bio-experienced. We saw some differences in induction. But as you get further out, this drug, especially the higher dose, the 30 mg, performs very well among those who have been previously experienced, including those who have had two or more prior advanced therapies. That is for clinical remission. And then we see similar trends for endoscopic remission. And you can see here, again, stratified by previous exposure.

ELEVATE UC 12/52: Etrasimod in Moderate to Severe UC

All right, so what about the S1Ps? We have not seen any S1P data yet. Here is the data from ELEVATE UC 12 and 15.

This is the etrasimod data. So at 12 weeks, the primary endpoint, again, of clinical remission was measured. We see 26% of those who were treated with etrasimod. And the dose is 2 mg once daily. Achieved that endpoint compared to 15% in the placebo arm. Looking at some of the other key secondary endpoints, endoscopic remission and endohistologic mucosal healing, we see that patients who received etrasimod 2 mg did perform better than placebo across all those key secondary endpoints.

If we look out at week 52, again, this is one dose. There is no dose titration with this agent. So patients continued to receive 2 mg compared to placebo. Again, we see statistically significant higher rates of clinical remission, endoscopic remission, and endohistologic mucosal healing across all of those key endpoints compared to placebo.

Experts in the Hot Seat

All right, so now we are going to vote again. What do you want us to talk about next?

A. Clinical nuances of selecting IL-23 inhibitors. How might we select between the three that we have just shown data on?
B. Speed and safety: discussing JAK inhibitor therapy with patients; or
C. Managing the multifailure patient in 2026.

Let us know.

Dr. Cohen:
It is pretty close. Yes, I think we can probably do the top two. You have multifailure patients and selecting IL-23 inhibitors is about the same.

Dr. Allegretti:
Yes.

Dr. Cohen:
Okay. So, Jordan, guess what? Your patients come in to you with ulcerative colitis, moderate-to-severe, and they have seen TV commercials for all three of the IL-23 medications, right, mirikizumab, risankizumab, and guselkumab. I usually ask them, well, which

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commercial did you like the best, because we will go with that one. No takers on that one. But what perhaps nuances are there in choosing for induction and for the maintenance with these medicines?

Dr. Axelrad:
Yes. So, I think in ulcerative colitis, there is maybe a little bit of data, if you really, really, really, focus in on the data on the sub, sub, sub groups of patients, particularly in guselkumab, who received 400 mg Q4, that maybe those who were the sickest actually did a little better at that higher dose compared to potentially a similar group who were in the risankizumab Phase III program. So, risankizumab program.

I think those things, you know, everything else being equal, it is a very difficult decision, because as you have probably heard from most of us, we tend to position IL-23s as more of that first-line drug for more of the moderate-to-severe patients. And so, looking at that population, they are going to do well, actually, with kind of whatever you give them. I think, actually, there is very little that differentiates it. But when you look in at the data very closely, there is potentially some benefit to that guselkumab 200 mg Q4 in a sicker population. It is not necessarily most of the patients we are talking about.

I think the other major differentiator is that currently, guselkumab is fully subcutaneous for induction and maintenance. And I think that makes a big difference, where we do not have to do two authorizations. There is not an authorization for an infusion, not an authorization for maintenance for an injectable.

It is just one authorization, and that tends to give patients a lot more flexibility. And I think that being said, as we know, recently, the affirmed data for, and this, again, is not an ulcerative colitis and Crohn's disease, that there is going to be subcutaneous injection likely coming, at least for Crohn's disease. But I do think that subcutaneous induction, that is infusion versus injection, is something that patients care about.

Dr. Cohen:
So for induction, while all three initially were week 0, 4, and 8 IV once a month, currently, the guselkumab option, you can get subcutaneous 0, 4, 8. And then what are your maintenance options for the IL-23s?

Dr. Allegretti:
Yes, so, well, I mean, the maintenance options all look very similar. They are all sub-Q. But there are some important differences, and I think this does come into my decision-making. Again, when you are talking about what is going to work best for the patient, I think from an efficacy and safety standpoint, these drugs look very similar. I think they all work. All three work well. They all, I say both, because I only have two on formula in my hospital, but they work, right? So I think any of them would be good choices.

I think when you are getting down to the nitty-gritty with patients, the induction question, I think, comes up, but then for maintenance, with guselkumab, you have a bit more dosing flexibility because there is a 100 mg Q8 week dose and a 200 mg Q4 week dose. So if you have a bit of a sicker patient, as Jordan just pointed out, you may want to just automatically go to that four-week dosing, which is what I tend to do because of the population I see. But you have two FDA-approved doses that you can move through.

Risankizumab also has two doses, the 180 mg Q8 and 360 mg Q8, although I have never prescribed the 180 mg. I think I use 360 mg exclusively. And so, if you do need to escalate to, say, Q4 week dosing, which would be off-label dosing, you often have to sort of fight insurance and appeal.

Dr. Cohen:
But what about the injector?

Dr. Allegretti:
Oh, sure. Yes. So the guselkumab is an auto-injector, and risankizumab comes in an OBI. So if you are not familiar with OBI technology, it looks like, I would say it looks like a cassette tape. Risankizumab, it is a little device that you actually stick to yourself so the patient does not actually have to push the button and feel the needle or see the needle going through. If you have any patients who are really needle-phobic or have had bad previous experiences with injectables, I think this is actually a really nice option. It takes a lot of that injection anxiety out. And so I think for patients who are hesitant or trepidatious around injections, the OBI that risankizumab offers is a really nice option.

Dr. Cohen:
So Jordan, so you are sitting there at NYU, and you get someone who comes stomping into your office saying, well, I failed everything. So what do you do? I mean, and I do not want surgery. And let us presume that you do not think the patient actually needs surgery for this part of the discussion. So how do you assess this patient?

Dr. Axelrad:

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Yes. Well, I actually think what you said was really important because I was going to say, push back and say, well, does the patient actually need surgery? So I think you actually hit a really important point, which is that you should not be avoiding surgery if that is actually what the patient needs and would actually benefit the patient most. And so I just want to make a plug for surgery.

The multifailure patient, it depends what they failed, right? It depends what they have been through and how they have been through it, right? So for me, for example, an adalimumab failure is not the same as a dose-optimized infliximab failure. Those are very different failures in my mind. The Entyvio failure is not the same, again, as a dose-optimized infliximab failure. And of course, the upadacitinib failure is also very different than all the others as well.

So it really depends on where they are at when they are walking through the office, I think, as far as therapy exposures. The other is, what is their disease activity, right? Is this someone that is super on fire, lots of disease activity in Crohn's, lots of complications maybe? Again, I am going to be managing that patient very differently. And I use the data that we have both from our clinical experiences and so far observational data but also from our trials to help us understand which drugs may work best in people who have failed other drugs.

So for example, our S1P receptor modulators, not great options for people who have failed other drugs and just sort of alluded to that data. And that is important, and it comes into play. I think it really depends where they are in the moment.

Dr. Cohen:
I think it is important also to remember, we are gastroenterologists, prove that your patient is really failing a therapy. How many of you have done a scope on someone who is failing and the scope is so normal that even the pathologist tells you, I do not even see evidence of the disease? It is pretty shocking.

Do not send us patients who, in the past six months, they have done five different therapies. Treat to target is you want to show that they are getting better but also prove that their ulcerative colitis is still there and they do not just have three cm of proctitis now giving them the miserable symptoms. Also in ulcerative colitis, remember there is a role for topical therapies, enemas, suppositories, foams, giving rectally that helps with the urgency, the frequency and sometimes help tides them over.

I think that is one of the biggest mistakes I see. Yes, I guess we should define failure, right?

Dr. Allegretti:
I mean, and I would say to that point, right? Often I ask my patients who come in this scenario, well, let us go through each agent and define what actually happened on them, right? Did you actually really fail them, or did you just get cycled through too quickly? Were they dose optimized? What happened on each of these? Because you actually might be able to go back to something that actually maybe was going to work.

But I think if you have done your due diligence and the patient really has truly failed, I think often in my practice, I am doing more combination approaches. We are seeing data presented, I think tomorrow, on sort of the first randomized controlled trial of a combination biologic approach. And so, I often do end up doing that in my practice for these truly refractory patients.

Dr. Cohen:
Right. Right. You know, one of the things is take a patient history. It is really nice when your patient also has psoriasis, okay? Because guess what? Then you can have their dermatologist prescribe the FDA-approved therapy for their psoriasis that also is used for Crohn's or colitis. It is really nice when your patient has rheumatoid arthritis or one of the other indications for perhaps an anti-TNF or a JAK inhibitor.

So you can try doing it yourself. You always get refused, denied. You always get denied. I will say though, but you will resubmit and often it comes through. But try to get people on combo biologics if possible because you will pick up probably about 20-25%.

Dr. Allegretti:
Because we used to have to game the system a lot and like partner with a dermatologist or rheumatologist. I find lately, especially if I sort of explain, I need to do this for six months to really try to achieve a set endpoints. I think insurance companies are much more on board with that.

Dr. Cohen:
Right. So kind of think out of the box.

Dr. Allegretti:
Yes.

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Round 3: What Is New in the IBD Guidelines

Dr. Cohen:
Okay. So we are going to go on to our next round, if you will. So what is new in the IBD guidelines?

So there are many different organizations that put out guidelines. And then once you do a guideline, a new drug comes out, and you have to read your guidelines.

Patient Pulse Survey Showdown

Patient pulse survey showdown. What information did patients say is missing from their treatment conversations?

A. The real-world likelihood of adverse effects;
B. Clear comparison of available options;
C. What to do if treatment fails; or
D. Timeline for symptom improvement.

Patient Pulse Survey Showdown

So it looks like we are pretty close with a clear comparison of available options and the real world likelihood of adverse effects.

2025 AGA Guidelines: Recommendations for Managing CD

So there are multiple societies that do guidelines. And guess what? We also go to European meetings. So they have their guidelines too. And there are Australian meetings. But it is worth the trip.

In 2025, the AGA updated its recommendations for managing Crohn's disease. And these analyses were done. It is hard because there, we will show you some examples of head-to-head trials. But almost all the data is the own drug against placebo. And some of the studies with infliximab, you know, were done in the 1990s. And some of them were done within the past few years.

So keep that in mind. There are analyses that have been done that have tried to control for these differences, these network meta-analyses. So some of the recommendations are ones that you should consider. Although, I think many of us feel that selecting the right medicine for your patient depends on what the patient is, who the patient is walking in the door.

There does seem in the studies to have higher efficiencies. You see in the green box for adalimumab, for Crohn's, risankizumab, guselkumab, upadacitinib. They probably should have listed infliximab, too.

You know, the data for ustekinumab, I think that you have to realize that the ustekinumab data kind of got a little downgraded because in some of the direct comparisons with the newer IL-23s, it did not seem to do as well. Mirikizumab actually does work in Crohn's, it just dd not give this clear efficacy. Lower efficacy, vedolizumab, you know, vedolizumab is effective in Crohn's disease. But we generally do not go to that if the patients have failed the TNF. And certolizumab pegol, it clearly has been not as effective for an anti-TNF. The FDA indications actually for induction were just for response, not for remission.

And then, you know, one of the things, too, is that unlike in the past, we generally do not any longer start patients on azathioprine, 6-MP, or methotrexate to induce them to get better as monotherapies. There is data that they maintain therapies, but that data was all based on patients who were induced with steroids. So this is data from the 1990s.

Nowadays, with all these modern therapies, most of us reserve the immune suppressants, azathioprine, 6-MP, and methotrexate for patients, perhaps, who need combination therapy for perianal Crohn's disease, maybe for antibody issues with the anti-TNFs. But it is

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hard to look a patient in the eye these days and say, well, I am going to start you first-line therapy for moderate-to-severe Crohn's disease with azathioprine, 6-MP, or methotrexate. There are clearly better and safer options.

2025 ACG Guidelines: Recommendations for Managing CD

So this is the American College of Gastroenterology's (ACG) guidelines. It talked about trying to determine practical fecal calprotectin thresholds. Now, you have to realize that fecal calpro is very sensitive to when the patient collected it, when they brought it into the lab, and things, too.

Unfortunately, in the United States, we do not have approved home testing of fecal calprotectin. Hopefully, that will change, and we will get more reliable numbers. Also, for Crohn's disease, intestinal ultrasound has emerged as a non-invasive adjunct, and you are going to be seeing more and more.

Many of the doctors and nurse practitioners who are being trained in the United States to use intestinal ultrasound are being trained in New York or at the University of Chicago, as they go through.

And now, post-operative monitoring, typically, we suggest that 6-12 months after your patient's had their Crohn's resection, scope them and see if whatever your plan is working, whether it was no medicines or continue their previous medicine or newer medicines.

And then actually, there was a very good diet lecture just before this session. Mediterranean diets seem to have some more support rather than a specific carbohydrate diet, but I would be very patient-selective and would not advocate diet versus medications.

2025 ACG Guidelines: Recommendations for Managing CD

As I mentioned, we do not use the thiopurines and methotrexate before advanced therapies. We generally only use mesalamine for mild-to-moderate ulcerative colitis, and if they really are using mesalamine, which works in mild-to-moderate, proves that they are better, proves they do not have inflammation, and if they do, move on to better therapies. And then some of the newer therapies have been actually incorporated into the update.

The other part is steroids. You know, really, you should challenge yourself to see how many months can you go without prescribing steroids, or if you are, try to do the steroid courses by weeks rather than months, because we are trying to use them less and less.

PROFILE: Top-down vs Accelerated Step-up Therapy in Newly Diagnosed CD

Now it is very interesting. One of the group's investigators, they decided to do a study to see if they could predict, based on a certain genetic profile, whether patients would respond to infliximab. So this was a modern, top-down versus step-up study.

And it was modern, too, because these are newly-diagnosed Crohn's patients. So the top-down versus step-up, what we talked about for decades now, actually were patients who had been on therapies before, but these are newly-diagnosed Crohn's. And while the intent was to see if this novel marker predicted remission, which it did not, we actually got some really good data.

PROFILE: Should All Patients With IBD Be Treated Early With Advanced Therapy?

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And look at this here. This is patients' early-advanced therapy. They present with moderate-to-severe Crohn's disease. They are thrown on infliximab and azathioprine in this case. And you can see the patients treated that way in orange. Their corticosteroid and surgery-free remission rates on the far left, 79% versus 15%.

These numbers are outstanding. And they are reminiscent of the pediatric Crohn's studies with infliximab, where they have like 88% response rates. It is pretty remarkable that it is taken us this long to again prove that if you start people on effective therapy early, you have outstanding results.

And look on the right-hand side, endoscopic remission, just the first set of data. You can see the 67 % versus 44%. The step-up, people had to go through the usual steroids, azathioprine, then adding the infliximab.

Head-to-Head Trials Used to Formulate IBD Guidelines

Now, we are seeing more and more head-to-head trials, because would not you love to know which medicine you should choose? You hear the expert panel, and you know, sometimes you go to the next talk, and someone tells you differently. Up to now, there have only been a few head-to-head trials, but that is going to be changing.

So, the SEAVUE trial for Crohn's disease actually compared ustekinumab to adalimumab. And actually, they were pretty similar for the outcomes that were studied. In the SEQUENCE study, risankizumab, an IL-23, was superior for an endoscopic response and not inferior for clinical remission versus ustekinumab. This is one of the IL-23 studies that kind of showed it is better than ustekinumab. And then, in the Johnson & Johnson's GALAXY-2/3 studies, their IL-23 guselkumab actually had an arm where patients got ustekinumab, because they owned both drugs, so they can do the trial. And actually, there was benefit of the IL-23 agent, guselkumab, in endoscopic clinical remissions, responses, and deep remission, too.

This is one of the reasons why many of us have ratcheted down our use of ustekinumab anymore and moved to the IL-23s, because there is head-to-head data showing, in Crohn's disease in this case, that they are probably better.

Now, many of you will probably remember when Takeda reps were running into your office with their varsity trial, where they did a head-to-head of adalimumab versus their vedolizumab. The vedolizumab was superior, at least unless you looked at steroid use for clinical remission and endoscopic improvement. And that has actually ratcheted adalimumab pretty far down on the ulcerative colitis treatment protocol. I do not think you would find many organizations or providers using adalimumab first-line in ulcerative colitis or even at all.

2024 AGA Guidelines: Recommendations for Managing UC

Last year, 2024, the AGA actually had UC guidelines.

I showed you the Crohn's ones before, and you can see on the green box, the tofacitinib, upadacitinib, those were the highest efficacy ones, and they actually had ustekinumab in there. The intermediate efficacy, this is likely going to change, because, again, this was already two years ago, were the IL-23s. Filgotinib, we actually do not have filgotinib in this country. And the lower efficacy was vedolizumab, adalimumab, and the S1P modulators. You know, again, I would just caution that these were not head-to-head trials, so the data in them is sometimes difficult to compare head-to-head directly against each other.

Now, one of the key things is that, especially in ulcerative colitis, the data with infliximab plus azathioprine in the clinical trials that were done was far better than either agent alone. It is supported that giving in ulcerative colitis, and I, personally, do this in my practice, if I am giving infliximab or adalimumab, which I do not really do very much, I give it with azathioprine because of the data from the UC SUCCESS trial.

2025 ACG Guidelines: Recommendations for Managing UC

The American College of Gastroenterology (ACG) last year, management of ulcerative colitis, and these guys, you will be able to get

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these slides, actually. They were more explicit, integrating monitoring strategies, checked their fecal calprotectin, checked their C-reactive protein, and eventually scoped the patients, especially with ulcerative colitis. Guess what? You can do a flex sig and find out if the patient's getting better. Do not cycle a patient for three to four different therapies for ulcerative colitis if you have not looked with a flex sig to prove that they are really inflamed, okay? They actually expanded the landscape with the S1Ps, the JAKs, and IL-23s.

With hospitalized acute severe UC, I think that in the guidelines, they reinforce the basics. Many of us now, though, are using JAK inhibitors, either tofacitinib or upadacitinib, as an option in patients who have acute severe ulcerative colitis. Being from the University of Chicago, we are a big cyclosporine center, and infliximab also has had data for years, too.

Partnering With Patients to Determine Treatment Priorities

One of the things that is important is we have all these therapies now, right? It was not like the patient came in and you said, okay, well, guess what? There is one FDA-approved therapy for your treatment, so why do not we use that one? End of story. It was a much shorter visit, right?

Part of it, too, is partnering with the patient. This way, we can determine what are their treatment priorities. Because sometimes what providers think, well, the patient wants this, is completely different than what the patient wants.

Challenges of Treat to Target in IBD

Now, we already saw a video where one of the patients mentioned the insurance challenges. That is something that is pretty much isolated to the United States, although if you are in other countries, sometimes your access to the medicine at all may be limited. The providers in the office all know about the increased administrative burden due to prior authorization, and there has been legislation to try to help this. Some of this is usually state-based because of the way that pharmacy rules work. Increased need for clinical monitoring and patient follow-up and also personal constraints.

Financial Toxicity in IBD

Again, the patient interview, she really talked a lot about the financial toxicity, if you will. There is toxicity on the patient as well as on the providers. Sometimes also, as you will find out, that their patients may not be that well-educated about their condition. They may have the income issues, food insecurity.

Well, at University of Chicago, we are on the south side of Chicago. We are in the inner city of Chicago. The cars in the physician's parking lot are the only cars, because no one else has cars. They take the bus. It is a big difference when you are treating those patients. Basically, patients who have the highest cost, actually, are the ones that have the worst quality of life.

IBD Treatment Delays: Associated Challenges

Then there are also associated challenges, too. Healthcare providers, say 50% of the healthcare providers, report that prior authorizations are universally required for initiating biological therapies, and about half of them require further healthcare provider involvement. There is a lot of burnout.

Some of them have to actually hire additional people just to do their prior authorizations, not just for their medicines, but for their CAT scans and things, too. About half of patients, or more, said they actually had problems accessing their medicine simply because of insurance.

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What Contributes to Treatment Delay?

Treatment delays, this is probably one of the most frustrating things, as you guys know. You are prescribing a medicine, and then suddenly a patient cannot get it for a time because of these delays, usually from insurance. The median delay of initiating biological therapies is about 20 days, and it is disproportionate for patients of color and lower socioeconomic class. The type of payer and route of administration may also influence delays.

The group up here, all three of us commented that one of the, perhaps, benefits in the IL-23 world is that currently, guselkumab has subcutaneous induction. That actually has translated in our practice to a big benefit in the patients getting the medicine sooner because we do not have to wait for the IV dose to get approved and the sub-Q dose to get approved and for the IV to be scheduled, too.

Improving Collaboration Across Stakeholders: Reducing Financial Toxicity for Patients

I think it is important to talk to your patients. I want to point out that all of these companies will have patient assistance programs. Many of them have co-pay programs that patients are eligible if they have commercial insurance, and many of them also have programs for financial hardship. So please interact with the representatives from, and this is not just in GI, anything, representatives from the companies so that way they can get the patients on the programs, or just tell the patient to go to the name of the program, the name of the drug.com, or they will find it there, too. Please make sure all of your patients sign up for the programs.

Believe it or not, Chicago, I have had patients who have told me they had to sell their farm because they had to pay so much money for their subcutaneous TNF when they could have gotten it for $5, but no one told them. So part of your responsibility, your office responsibility is make sure they sign up for these programs or get them signed up.

Resources for Patients With IBD

There are great resources online, Crohn's and Colitis Foundation, and other IBD communities.

Shared Decision-making in IBD

So I think we already talked about that.

The SHARE Approach: Shared Decision-making in IBD Care

And there is a whole acronym called SHARE Approach.

(S)eek their participation. So you may have patients who may have multiple options. Let us say you talk to them, we gave the examples of the IL-23s. Well, some patients like the idea of the auto-injector. Some people like the idea that they are getting IVs for inductions because this way it is being done in a controlled setting.

So if you do have options, let your patient choose which one they want, okay? For example, you may say, well, do you want it, you have, let us say, moderate-to-severe ulcerative colitis, let us say you have already failed a therapy. Well, your options are a pill therapy, a JAK inhibitor, right? An IV therapy, vedolizumab or infliximab. Subcutaneous therapy, every two weeks, every four weeks. Therapy

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where you can start with a few shots or IVs, and then you can do an auto-injector.

If you provide the patient with the options, let them choose because then when they leave your office, you have not told them what to take, they have decided what they want to take based on their priorities. And I think you can really help them out with that too.

Addressing Corticosteroid Dependence in IBD

Really want to point out that we are trying to remove corticosteroids from our practices, short-term use, limited. Obviously, during DDW, I am getting a lot of calls from my nurse what to do, so perhaps my corticosteroid use might be a little higher than before. Nevertheless, the idea should never be an endless prescription or a constant dose of 40 mg. Always give them a taper and try to use short one- or two-week courses as well, too.

Experts in the Hot Seat

Okay, now for you guys to pick what you want to talk about.

A. Does top-down treatment always apply;
B. Practical implications of head-to-head trials; or
C. Contemporary treatment targets in IBD.

We can talk about practical implications of head-to-head trials and contemporary treatment targets in IBD.

Okay, so, Jessica, what do you think? Head-to-head trials, good, bad, evil, do you believe them?

Dr. Allegretti:
Yes, I mean, I think they are important and really helpful. I mean, I think there was a long period of time where all of our guidelines just said these drugs work better than placebo, and so, you know, I think it has been really great to see that we are now getting more data, head-to-head studies, and I think, you know, I commend our industry colleagues for actually taking on these trials to help us really start to understand the differences, the different phenotypes of patients who are more likely to respond to one therapy over the other, and I think we are going to continue to get more.

We will never be able to compare every therapy to every therapy, but I think helping us think through, you know, certain cohorts of patients and who may be appropriate for what, I think head-to-head trials are really important.

Dr. Axelrad:
I think, you know, non-inferiority, too, is also important for us, right? So, if we think something's better than the other and in a head-to-head trial where patients are well-matched, there is non-inferiority, right, that they are actually equivalent, that also helps us so you know you are not sacrificing by choosing one over another, especially if a payer gets in the way, for example.

Dr. Allegretti:
So, you would certainly rather a trial than a network meta-analysis.

Dr. Axelrad:
Right, you are certainly right, right, right. So, unfortunately, as Russ just went through, a lot of our guidelines, especially the AGA guidelines, are based in network meta-analysis, which is not the same as head-to-head, as Russ said, so that is important.

Dr. Cohen:
Head-to-head's a real thing, and there are additional trials where the patients are blinded. Some of them, they actually may have three or four different options. Some of them are therapies that might be available, and some of them may be novel therapies, and some of them now, they are multiple novel therapies.

This way, there is a placebo group, but then you can run each therapy against the placebo, but also against each other. It is kind of neat. We are really entering a new world.

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So, Jessica, what would you consider to be a contemporary treatment target?

Dr. Allegretti:
Yes, so I think, you know, we have alluded to and Russ has talked about treat-to-target and the STRIDE guidelines and how we are actually doing this in practice right now. So, the most important thing is to benchmark your patient with the available, you know, monitoring tools that you have to know what is going to be appropriate for that patient. So, we still have the mainstays, CRP and fecal calprotectin are our main biomarkers, but we also have things like intestinal ultrasound, as you heard about today, as targets that we can start to follow, and of course, imaging, if the patient has, you know, upper small bowel Crohn's, you may need things like MRE or CTE, and then patient-reported outcomes, you know, stool frequency, abdominal pain, rectal bleeding scores, etc.

And so, making sure that you are getting all of that information on your patient before you start your new therapy so that you can know how to follow them going forward, because not every patient's going to mount to CRP, not everyone's going to mount to fecal calprotectin. You have to know where you are starting so that you can understand if you have actually achieved a delta or not.

Dr. Axelrad:
I think also in some of these more difficult-to-achieve outcomes, it is important to keep in mind what our currently available therapies actually achieve, right? So, when we think about things like histologic healing in ulcerative colitis or transmural healing in Crohn's disease, as assessing by radiography, either MRI or intestinal ultrasound increasingly, you know, these are difficult-to-achieve outcomes without currently available therapies, and you want to make sure you are meeting reasonable targets, and if you are not achieving some of these aspirational, difficult-to-achieve ones, it does not mean you should just give up and start cycling through drugs.

Dr. Allegretti:
But to be fair, histology and transmural healing are not current targets on the STRIDE guidance, but I hear next year STRIDE-III is coming out, so we will see if there is a movement there, and if what we are hearing is that we should be moving towards treating towards those targets.

Dr. Cohen:
However, that is the least of our worries. If every patient came into our office with one of these or two of these therapies, and everything was healed up, but there was still some activity under the microscope, but everything else was healed up, then I would say we are doing pretty darn good.

So the key is to treat the target. What you target is your patient has to not only feel better, inflammatory markers improve, and you prove that they are healed, or nearly healed at least, endoscopically, cross-sectional imaging, if that is more appropriate for Crohn's, and now some more intestinal ultrasound, as that becomes more available to you. But do not just let them linger with symptoms. I mean, the timeline for feeling better is a few weeks for the inflammatory markers in the first couple of months, and then eventually endoscopy.

I scope everyone at six months. Every time, new therapy, change in therapy, oh, I am feeling great. Look in six months. And that way you actually can show that that is happening.

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