ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Approach to Treatment Failure in Inflammatory Bowel Disease

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G&H What are the current options for conventional therapy for inflammatory bowel disease, and what are the typical response rates?

AM Multiple options have been approved by the US Food and Drug Administration for inflammatory bowel disease (IBD). Conventional therapies for ulcerative colitis include mesalamine, azathioprine or 6-mercaptopurine, anti–tumor necrosis factor (TNF) agents, anti-integrin agents, and, most recently, Janus kinase (JAK) inhibitors. Except for mesalamine, the same classes also apply for Crohn's disease. Conventional agents also include corticosteroids, which are typically used for induction but not for maintenance.

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Response rates vary across classes. In general, between 50% and 60% of patients initially respond to therapies in terms of improvement in symptoms or inflammation markers. Of those patients, approximately 20% to 30% go into remission, and of those in remission, at least half remain in remission over time based on clinical trial data.

G&H When a patient with IBD appears to be losing response, when is it appropriate to escalate therapy?

AM It is appropriate to escalate therapy when patients have evidence of active disease, by objective measures, despite their existing therapy. In the past, clinicians had very few treatment options, so they would often empirically escalate doses, particularly for anti-TNF agents. Over the past decade, clinicians have become more informed about the importance of measuring drug levels and antidrug antibody levels for monoclonal antibodies. Therefore, if a patient is losing response and has objective evidence of increased inflammation, clinicians can now measure drug trough levels and antibodies when using biologic drugs. On the basis of that data, clinicians can decide whether there is room to increase the dose, or whether increasing the dose would be futile and it is time to move onto a drug with a different mechanism of action. As an example, in a patient losing response to infliximab who has adequate drug trough levels and no antibodies to infliximab, there is limited benefit from increasing the dose of infliximab. A more successful approach would be to switch to another mechanism of action in this scenario.

G&H How should treatment failure be determined?

AM It is important to first ensure that the patient has had an adequate exposure to the drug at the correct dose.

For most IBD drugs, that means at least 2 weeks during the induction phase. Exceptions are anti-integrin agents, which may take a little longer, perhaps 10 to 12 weeks, for full induction. At the end of that time point, clinicians should assess the patient's symptoms and biomarkers such as fecal calprotectin or C-reactive protein (CRP) level. In some circumstances, clinicians may need to use endoscopy to determine whether the patient has experienced mucosal healing in addition to an improvement of symptoms.

G&H Why may patients with IBD fail to respond to therapy?

AM The reasons that patients fail to respond to therapy can be grouped into 2 types: noninflammatory reasons and inflammatory reasons. In the first group, the symptoms of patients are not driven by active inflammation. These patients may have developed complications such as strictures or fistulas, or they may have developed overlapping conditions such as irritable bowel syndrome or small intestinal bacterial overgrowth. In these scenarios, patients will not respond to their anti-inflammatory therapy. In the second group, patients have active inflammation that is not responding to the current therapy. In these patients, clinicians look at drug levels and metabolites, and use dose optimization to try to regain response; if response cannot be achieved, clinicians should consider changing the mechanism of action of the treatment.

G&H Is it possible to predict which patients are likely to fail to respond to therapy?

AM Several markers are available, particularly for anti-TNF agents. Patients who have deep ulcers, patients who have high CRP or low serum albumin levels, and patients with a high inflammatory burden are less likely to respond to anti-TNF therapy than patients who do not have those factors at baseline.

However, there is no single biomarker that can show what is causing inflammation in a given patient. Clinicians often have to empirically try different mechanisms of action to achieve remission. Hopefully, with additional research and biomarkers, it will be possible to determine, based on a blood sample or biopsy, whether a patient is more likely to respond to, for example, a JAK inhibitor or an anti–interleukin (IL) 23 agent than just empirically guess which one to choose, which is what clinicians do now.

G&H Should clinicians keep anything else in mind when deciding to move onto a new treatment approach or agent?

AM Clinicians focused too much on symptoms in the past and have realized now that the correlation between symptoms and inflammation is often weak. Thus, I encourage clinicians to look at symptoms as well as an objective measure of inflammation, and then, depending on the drug that the patient is taking, to check drug levels and antidrug antibodies. The objective measurement could be a simple noninvasive test such as fecal calprotectin or CRP level or an invasive procedure such as a sigmoidoscopy or colonoscopy.

G&H What factors should be considered when deciding which IBD therapy to try next?

AM In general, I consider several factors with patients. The first is the reason(s) they failed to respond to the initial therapy. I also look at the mechanism of action of the drug that they just failed. A good example is someone who failed to respond to anti-TNF therapy despite adequate dosing and good drug levels. For such a patient, there is no point trying another anti-TNF agent. I would consider a different mechanism of action. There are now many choices, such as small molecules, which are oral agents, or other monoclonal antibodies, which can be administered as either infusions or injections. Sometimes, the administration mode also comes into play, as some patients prefer oral agents instead of injections, whereas other patients would rather receive a once-every-8-week injection from a convenience perspective rather than take 2 pills every day, for example. All of these factors are considered when deciding on the next agent.

G&H Are there any special considerations when the failed therapy is a biologic?

AM After failing a biologic, response and remission rates for a second and third biologic are not as high. Patients who develop antibodies to 1 biologic are more likely to develop antibodies to the next biologic, so clinicians should consider switching these patients to a small molecule. Another factor involves pharmacokinetics and how rapidly patients clear monoclonal antibodies. Patients who have high clearance rates of biologics should also be considered for a small molecule for the next agent and not another biologic.

G&H How can therapy, especially with biologics, be optimized?

AM Clinicians can optimize biologics by using therapeutic drug monitoring. In this scenario, the clinician can determine the patient's drug trough level and adjust the dose or change the interval to get the patient to an

ideal trough level, which varies depending on the agent being used.

Several recent studies have looked at dose optimization to see whether increasing the dose or changing the interval is better. For patients who have low trough levels, it appears that shortening the interval between infusions with infliximab, for example, is more likely to produce response and remission than giving a higher dose at the same interval. Another example involves maintenance dosing. Clinicians initially thought that giving patients higher doses of maintenance therapy would be better than standard doses, but that does not appear to be the case. In addition, increasing the dose during maintenance empirically does not appear to improve the probability of remission.

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G&H How successful is response to second- or third-line therapies?

AM Research has recently shown that over 2 years, less than 40% of patients who are on their second or third agent remain on that agent, either because they lose response or they never obtained response in the first place. This has taught clinicians to determine more quickly when a patient is not responding or is losing response. Clinicians should measure parameters such as inflammatory markers and drug levels, and should decide in a shorter time frame to move onto a different mechanism of action or class of drug. In the past, fewer options were available, so clinicians would often take a long time to make this decision. Now, clinicians have realized that it is better to make the decision sooner to allow the patient to try to achieve remission rather than use the same agent for a long period of time.

G&H What have studies found regarding response or remission rates with a different mechanism of action following therapeutic failure?

AM Several groups have reported their experiences with different mechanisms of action. Certainly, if patients fail anti-TNF therapy, for example, they can still achieve reasonable remission rates with anti–IL-12/23 therapy, JAK inhibitor therapy, and anti-integrin therapy. There does not appear to be any one mechanism of action that is better than the others for second-line therapy. All of the approved therapies appear to have similar efficacy, which is important real-world knowledge to have when deciding among agents. Then it comes down to questions about safety, patient preferences, and mode of administration.

G&H How often must clinicians resort to surgical therapy after failure of conventional therapy?

AM Thankfully, over time, there has been a small incremental decline in the proportion of patients who need surgery, particularly in ulcerative colitis and less so in Crohn's disease. That is likely because of earlier and expanded use of biologics over the past 20 years. However, approximately 15% of patients will still require surgery early in the course of their disease, often because of complications or refractory disease.

G&H When starting a new medical therapy after therapeutic failure, how should patients be monitored?

AM There are 2 parts to monitoring. The first involves safety and monitoring for side effects. That may involve monitoring, for example, lipids, white blood cell counts, and liver function as well as screening for infections such as latent tuberculosis. The second part involves monitoring for response, which is why it is important to check a measure such as fecal calprotectin or CRP early after induction. With biologics, it is also important to check drug levels and antibodies at least before the maintenance phase to determine whether the patient is on the right dose and is likely to go into long-term remission.

G&H Do you have any advice for managing patients with IBD whose therapy is failing?

AM It is important to have good communication with patients to flag early whose therapy is failing and why, as well as to use objective measures to try to tease out patients who have complications in whom more drug may not be

the best solution vs patients who have inadequate drug levels vs patients who just have a refractory inflammatory pathway. It is also helpful to obtain a patient's input on his or her priorities. A clinician may think that a patient may have a better chance of remission with a different agent, but the safety concerns from that agent may not be attractive to the patient, so having him or her involved in the discussion on safety vs efficacy is an important piece of the puzzle.

G&H Are there any other recent studies on this topic that you would like to mention?

AM There have been several recent studies looking at measuring, for example, fecal calprotectin early on to determine who should receive a dose change, even if the patient feels well. This approach is known as proactive monitoring. Clinicians can monitor pharmacodynamics serially and then adjust treatment accordingly, regardless of the patient's symptoms.

Some of the other research currently underway is focusing on biomarkers. As mentioned, no single biomarker yet can identify which patients are likely to respond before therapy is started.

G&H Are there any common misconceptions about this topic?

AM The most common one in recent years has been that every biologic failure is because of inadequate drug levels. It is now known that only 20% to 30% of patients who fail a biologic do so because of inadequate dosing or drug levels. The majority of patients fail either because of complications they have developed or because their inflammatory pathways are not responsive to the therapy's mechanism of action. Thus, drug levels are a factor but are not the complete story in terms of explaining loss of response.

Disclosures

Dr Moss has served as a consultant for Janssen and Pfizer.

Suggested Reading

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