ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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De-escalation of Therapy for Patients With Inflammatory Bowel Disease

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G&H What are the most common reasons for de-escalating therapy for inflammatory bowel disease?

RU There are a number of reasons that doctors discuss therapy de-escalation or withdrawal with patients who have inflammatory bowel disease (IBD). One reason is that the medication may not be working. Another reason is to prevent or minimize the risk of side effects of a drug, such as infection and neoplasia, especially over the long term. This scenario involves a shared decision-making approach, typically from the patient's perspective but also from the doctor's.

In addition, there may be practical reasons for therapy de-escalation. Patients may want to be on a simpler, easier-to-follow regimen; for example, they may prefer to take 1 medication instead of 2, or 2 medications instead of 3. Cost may also be an issue, whether referring to out-of-pocket costs to the patient or general health care system costs.

In my opinion, one of the best times to have a discussion about therapy de-escalation is when patients start therapy. At that time, patients often want to know how long treatment will be needed. Another time this issue frequently arises is when patients are doing well on therapy.

G&H What are the main risks of IBD therapy de-escalation?

RU The main risk is that patients will have a severe flare, lose control of their disease, and develop complications related to IBD. Flares of IBD can lead to longer-term complications such as bowel damage and poor quality of life. Therefore, it is important to tell patients that if there is any inkling of active disease returning, therapy will need to be restarted in a timely fashion to avoid the risk of progression of their underlying IBD.

G&H What factors should be considered when identifying candidates for successful de-escalation of IBD therapy?

RU Patient selection is key for treatment de-escalation. Doctors should not stop therapy at random; it is important to select the patients who are most likely to have success. When patients stop immunomodulator treatment or biologic monotherapy, various studies have shown that the rate of relapse over 1 to 2 years can be quite high (up to 50%). This should be kept in mind when counseling patients. When de-escalating from an immunomodulator plus a biologic to biologic monotherapy, studies have suggested that the risk of a flare is relatively low; thus, stopping the immunomodulator tends to be a preferred de-escalation strategy for patients on combination therapy. When a patient on combination therapy instead stops the biologic, the risk of relapse over 1 to 2 years is between 30% and 50%. Thus, when selecting patients for therapy de-escalation, it is important to discuss the possibility of relapse with them.

Patients can be de-escalated more easily if they are in remission and have a history of disease that is not very aggressive. In general, there are several risk factors for having an unsuccessful de-escalation (ie, having a quick or significant relapse) in ulcerative colitis. Young men

appear to have a slightly elevated risk for relapse, as do patients with extensive colitis or those who have a history of relapsing while on therapy. In addition, de-escalating patients after they have been taking a therapy for only, say, 3 to 6 months may be too soon. Ideally, patients with ulcerative colitis should have endoscopic evidence of remission and should be doing well on their current therapy for at least a year.

In Crohn's disease, the risk factors for relapse are similar and include young age and male sex. In this disease setting, there is particular concern about patients who have a history of very aggressive disease, including those with perianal disease, fistulas, penetrating complications, extensive small bowel disease, history of surgery, and need for corticosteroids because of flares while on their current therapy. Doctors are often more hesitant to de-escalate these patients.

Therefore, it is important to select patients who have few to none of these risk factors and then confirm that these patients are in remission when de-escalation is being considered. Doctors should use a combination of noninvasive markers (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], and fecal calprotectin), colonoscopy, and/or imaging to make sure that the disease is truly inactive. If a patient has disease activity even though he or she is feeling well, that patient is more likely to flare if therapy is de-escalated.

G&H What has recent research found regarding therapy de-escalation in patients who have IBD?

RU The SPARE trial is an interesting study that was recently presented at this year's annual congress of the European Crohn's and Colitis Organisation. This was a randomized study performed in Europe that looked at Crohn's disease patients who were doing well on combination therapy (an immunomodulator plus an anti–tumor necrosis factor [TNF] drug). Patients were randomized to 1 of 3 strategies: continuing combination therapy, stopping the immunomodulator, or stopping the anti-TNF drug. The researchers found the lowest rates of relapse over the next year-plus in the groups that continued on combination therapy or stopped the immunomodulator. The patients who stopped the anti-TNF drug had the highest rate of relapse, which is consistent with prior data. However, this was the first time that these 3 general strategies were evaluated in a prospective randomized study in such detail.

Thus, the takeaway message is that it is preferable to de-escalate an immunomodulator over an anti-TNF drug in patients taking combination therapy. Reassuringly in this study, the vast majority of patients who were re-treated with anti-TNF therapy because of a relapse of disease were able to recapture response. This shows that reintroduction of therapy can be successful the majority of the time if patients have a flare when they are selected well for de-escalation.

G&H How should other therapies, such as mesalamines, be de-escalated?

RU Mesalamines are not discussed as frequently in terms of de-escalation because of their good side-effect profiles. However, mesalamines have a high pill burden and can be quite costly, with high out-of-pocket expenses for patients. Data have suggested that if a patient with ulcerative colitis or Crohn's disease is doing well on a biologic and a mesalamine, the mesalamine can be stopped with a low risk for relapse. Post hoc data of clinical trials, as well as real-world cohorts, have suggested that this strategy is likely safe.

G&H Could you expand on the ideal timing for de-escalation?

RU The ideal time for considering de-escalation is after a patient has been doing well for at least a year, paired with assessments of both clinical disease activity and objective disease activity (endoscopy, colonoscopy, and imaging as appropriate) showing inactive disease. If a patient is taking biologic therapy, particularly anti-TNF therapy, the strategy of de-escalation should incorporate assessment of the patient's biologic drug level. If a patient on combination therapy has a low anti-TNF drug level and then stops using an immunomodulator, his or her anti-TNF drug level will likely drop and thus may be less effective; in addition, the patient may be at risk for immunogenicity. Thus, in such a patient, the anti-TNF drug should be dose-optimized to increase its level before de-escalation so that when the immunomodulator is stopped, the anti-TNF drug will maintain a therapeutic level.

G&H How should patients be monitored following de-escalation of IBD therapy?

RU It is important not to lose touch with patients and to explain that even though they are doing well, they need to be monitored to make sure that they continue to do well. Regular follow-up is key. No patient undergoing therapy de-escalation should be told to merely return in a year. Patients should be assessed at least every 3 to 6 months with the noninvasive markers of CRP, ESR, and fecal calprotectin. Often, increases in these noninvasive markers can precede the occurrence of a clinical flare. If inflammatory markers that were normal at the time of de-escalation

are starting to increase, a colonoscopy or another assessment of disease activity should be considered. Therapy should be reinstated or adjusted if inflammation is found.

In addition, as mentioned, when de-escalating a patient from combination therapy, it is important to monitor the patient's anti-TNF drug level in particular to make sure that he or she is maintaining a good level after the immunomodulator is stopped.

G&H When does therapy need to be restarted after de-escalation?

RU Therapy should be restarted in the setting of a clinical relapse that has been confirmed to have an objective inflammatory component. In other words, the patient is having active inflammation that has been confirmed with symptoms, biomarkers, and/or colonoscopy. Timely reintroduction of therapy is important.

G&H How should therapy be reinitiated?

RU If patients are experiencing a flare, it is important to keep in mind when reinitiating therapy, in particular anti-TNF therapy, that they are at risk for developing antidrug antibodies, which can result in adverse events. There is no set consensus on how to handle such situations. However, studies have suggested that week 2 levels of drug and antidrug antibody levels after restarting anti-TNF therapy can be predictive of later success. One common strategy when patients have a flare after stopping biologic therapy is to restart anti-TNF therapy and then check drug and antidrug antibody levels. It is important to note that a patient needs to be rechallenged with the drug to see if his or her body will develop antidrug antibodies, so checking levels before restarting therapy has limited utility.

Accordingly, drug and antidrug antibody levels should be checked 1 to 2 weeks after the first dose of the drug is given but before administering the second dose. If the patient has no antibodies but has detectable drug levels, reinduction can be continued. However, if antidrug antibodies are present with little to no drug, then the patient is immunized and should be started on an alternative therapy. Very little data are available on de-escalation with non–anti-TNF drugs. Further research is needed.

G&H How effective is retreatment with the same IBD drug?

RU Studies have shown that reinitiating the same drug is successful in 75% to 90% of patients with IBD. Thus, retreatment is not successful in every patient, but it is in the majority of patients. This is a reassuring piece of data that has emerged from the literature.

G&H What are the priorities of research in this area?

RU We need to understand better, perhaps with risk prediction calculators or clinical decision support tools, how to select the patients who are at the lowest risk for relapse if therapy is de-escalated. The individual risk factors are well known, but it would be helpful to have a composite score or a type of metric (whether it is a clinical metric and/or incorporates novel biomarkers) that shows which patients will do well in the long term if therapy is stopped.

Research is also needed with the newer IBD drugs, including novel biologic agents, anti-integrins, anti–interleukin-12/23 inhibitors, and small molecules such as Janus kinase (JAK) inhibitors. It is important to determine whether these therapies will act similarly to anti-TNF drugs when stopped or whether the novel therapies can be stopped more easily. Some doctors have suggested that it may be possible to cycle JAK inhibitors on and off, as is done with corticosteroids; however, that is not completely clear at this point. It is also not clear what the risk of relapse is with the new classes of biologics.

Disclosures

Dr Ungaro has served as an advisory board member or consultant for AbbVie, Bristol Myers Squibb, Janssen, Pfizer, and Takeda. In addition, he has received research support from AbbVie, Boehringer Ingelheim, Eli Lilly, and Pfizer.

Suggested Reading

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