ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Restarting Biologic Agents After a Drug Holiday

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G&H What are the most common reasons that patients with inflammatory bowel disease have a drug holiday from biologic therapy?

DR The most common reasons are delays related to insurance re-authorizations and elective discontinuations due to infections or surgeries. One of the other reasons that patients stop biologic therapy is that they are doing well, and they (and/or their physician) think they may not need it or think that they are in stable remission and, therefore, can be off treatment for a while.

G&H Are there any predictors for how long a drug holiday in the last scenario may last (ie, when relapse might occur)?

DR One of the most common questions that patients ask is how long they need to stay on their medicine (or when can they stop their medicine). However, our current understanding of inflammatory bowel disease (IBD) is that, in most patients, it is considered a chronic condition that is not medically curable, so some form of maintenance therapy is necessary. We have learned that safe drug holidays and de-escalation of treatment are based on the stability of the remission and the risk factors the patient has for aggressive disease.

For example, the STORI study, which was conducted by Dr Edouard Louis and colleagues and published in *Gastroenterology* in 2012, has shown that discontinuing infliximab (Remicade, Janssen) resulted in an approximately 50% clinical relapse in patients with Crohn's disease by the end of 1 year. A major predictor of relapse was elevated inflammatory markers at the time that the patients came off the drug. This makes sense because if the patients had inflammation and stopped the therapy that might have been helping, they would be more likely to relapse. In addition, men were more likely to relapse than women, and patients who had measurable drug levels at the time they stopped infliximab were more likely to have recurrence. That may initially seem a bit counterintuitive, but if patients had undetectable drug levels and came off infliximab, it would be expected that the patients would do fine because they already were not receiving enough of the drug to feel its effect and they were already fine by definition in the trial.

Another predictor of relapse is recent surgery. Sometimes patients with Crohn's disease discontinue therapy after they undergo resection because doctors may escalate treatment prior to surgery. In addition, it appears that patients who quit smoking might be more stable if they de-escalate therapy.

G&H When should biologic therapy be restarted?

DR The traditional teaching was that if a patient's biologic therapy was interrupted and his or her drug level dropped too low, restarting the therapy carried a high risk of developing antidrug antibodies and, therefore, losing response to the therapy. Thus, the dogma was that once the patient started the therapy, he or she needed to stay on it and be adherent to the maintenance regimen. The current thinking is that when a patient has a drug holiday, whether it is intentional or unintentional, and

the drug level drops to zero in between dosing, the need to restart therapy is based on 2 factors: clinical recurrence of the disease (ie, the patient has a relapse and needs to be treated actively) or, in the modern era, subclinical recurrence (ie, a doctor is monitoring the patient and detects inflammation before symptoms develop). Those are the times when treatment needs to be restarted, whether that means going back to a therapy the patient has already been on (and from which the patient is currently on a drug holiday) or moving to a new therapy (possibly with a novel mechanism of action). This decision should be discussed very carefully.

G&H Why is restarting biologic therapy now being considered as a viable treatment strategy?

DR The reason that doctors can now have discussions with patients about cycling back to a treatment that was tried previously is because of the theoretical concept that the inflammatory pathways in an active IBD patient may change based on the treatment and time. For example, if a doctor treats a patient with an anti–tumor necrosis factor (TNF) drug such as infliximab, and the patient responds and does well initially but then loses response, the presumption is that his or her inflammation may have been driven by TNF, and, therefore, the anti-TNF drug treats it. However, if the loss of response is not due to antidrug antibodies, it may be due to a change in mechanism, or what some doctors call mechanistic escape. That principle, in theory, means that the patient had a different inflammatory pathway become activated. This may occur because the human body has many collateral and backup systems. If one inflammatory pathway is blocked, and whatever is driving the patient's Crohn's disease or ulcerative colitis has not been addressed, the body will try to find a new pathway to keep driving the disease forward. When a new pathway becomes dominant, the patient loses response to the current treatment and the doctor tries a different therapy, and perhaps that works for a while, but at some point, the patient may lose response to the new therapy.

What we have started to see is that doctors can cycle back to the drug that the patient lost response to in the first place. Researchers have now demonstrated that this can be done safely in many patients as long as the loss of response was not due to antidrug antibodies. That is the one exception where it is not possible to go back to the original drug.

G&H How should biologic therapy be restarted? For example, is standard dosage sufficient, and is premedication needed?

DR Before restarting treatment, the doctor needs to make sure that the patient is inflamed and needs to understand the current status of the patient's disease. If the patient is on a different therapy and the question is whether or not the patient should go back to a treatment that previously worked, the doctor needs to understand why the current therapy is not working. It is also important to have a good understanding of why the patient came off the previous therapy, again making sure that it was not due to an immunologic antidrug antibody response, because that will recur.

If the patient electively stopped the therapy, had surgery and stopped the therapy, or lost response, several retreatment strategies have been described by colleagues around the world that my coworkers at the University of Chicago and I have modified (Figure). Premedication can help prevent an immunologic reaction to the drug. In our practice, we provide premedications for each of the loading doses, and, depending on the patient's risk factors, we may do so in combination with an immunomodulator. We use the standard loading dose of the drug. For example, we use an intravenous loading dose of 5 mg/kg for infliximab and a subcutaneous loading dose of 160 mg for adalimumab (Humira, AbbVie). After 7 to 14 days, we check the drug level and make sure that there is detectable drug and no antidrug antibodies. If the body has developed an anamnestic response to exposure of the drug and there are antidrug antibodies and a low or undetectable drug level, then the patient should not proceed with their second loading dose. If, on the other hand, the patient has detectable drug and no antidrug antibodies, those are signs that the patient is tolerating the drug and the patient can move forward with the second loading dose. Whether the drug will actually work or not is a separate issue, but short- and long-term response are likely.

G&H Once patients restart biologic therapy, how should they be monitored?

DR When patients restart therapy, if they respond early and do not have an immunologic response against the drug, then they should be monitored the same way they are with other new therapies. Regular follow-up is needed to make sure that patients achieve not only symptomatic improvement but also disease control through improvement in inflammatory markers. Once the patient moves beyond the initial loading phase, if he or she is responding, the likelihood of doing well and being able to continue the treatment is high.

If restarting a prior biologic therapy does not work, one of the challenges is not leaving patients on the ineffective treatment too long. It is important for the doctor to

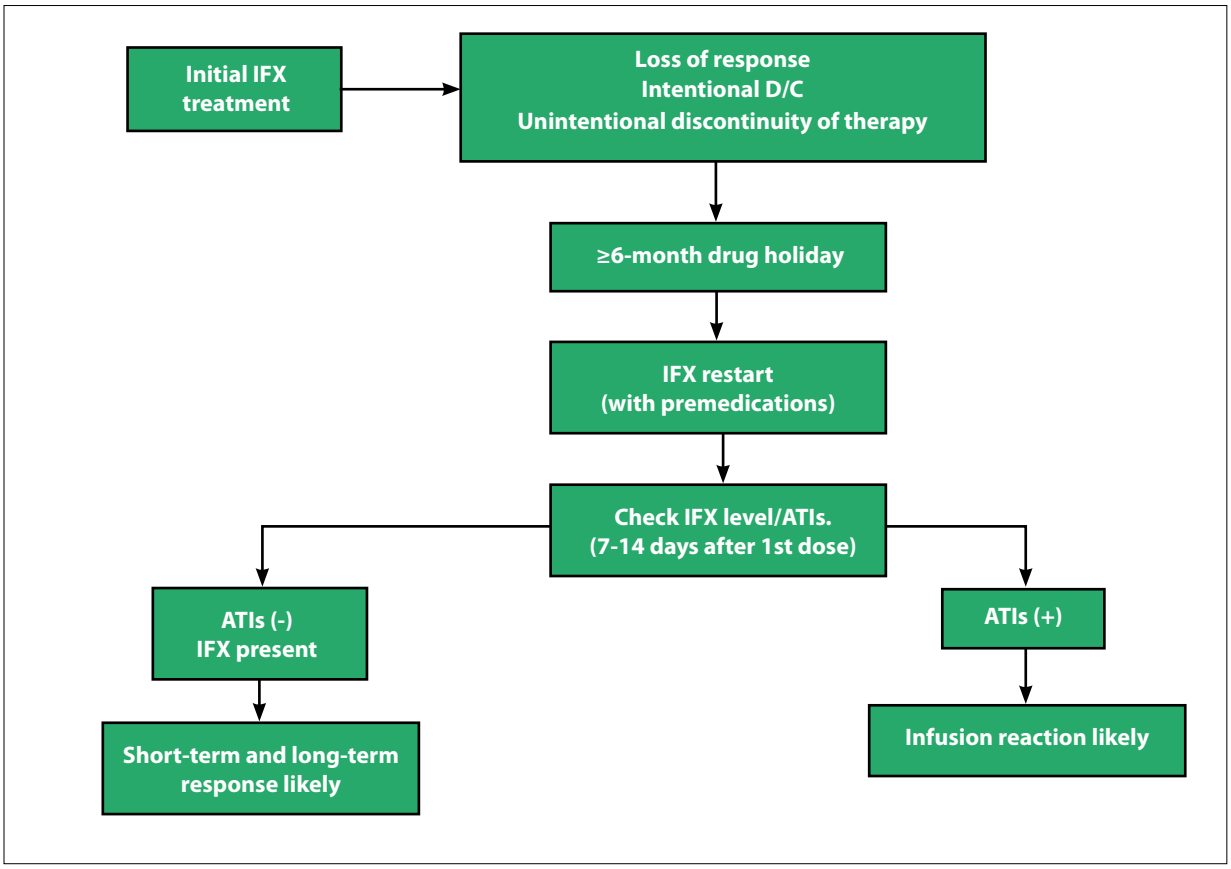

Figure. Algorithm used by the University of Chicago for restarting infliximab (IFX).

ATIs, antibodies to infliximab; D/C, discontinuation.

Reproduced from Normatov I, Wang JD, Gulotta GE, Patel S, Rubin DT. Using therapeutic drug monitoring to predict success of restarting infliximab therapy after a drug holiday in inflammatory bowel disease [DDW abstract Mo1890]. *Gastroenterology*. 2019;156(suppl 1).

know early that the patient is not doing as well as would be liked and, thus, decide early whether the patient should be switched to a different treatment or should consider a surgical approach.

G&H Can all biologic agents now be restarted after a drug holiday (when appropriate)?

DR It has been demonstrated that up to 60% of patients may be able to benefit from this treatment strategy. Most of the research currently available has been conducted on restarting infliximab, although that might be just because that agent has been around the longest. Research has also been conducted on restarting adalimumab.

There is not much research yet involving the restarting of the newer therapies of vedolizumab (Entyvio, Takeda) and ustekinumab (Stelara, Janssen), but these agents have fairly low immunogenic potential and restarting them does not appear to have a high risk of stimulating antidrug antibodies. My colleagues and I have had some patients who had drug holidays from those therapies and then went back to them without experiencing any difficulty.

G&H What research has been conducted on the short-term response rates associated with restarting biologic therapy following a drug holiday?

DR At this year's Digestive Disease Week (DDW) meeting, 3 different groups—one that I led at the University of Chicago, one led by Dr Maria T. Abreu at the University of Miami, and one led by Dr Laurent Peyrin-Biroulet at several centers in France—described restarting infliximab or adalimumab after drug holidays from those agents. The findings were similar in that restarting did not work in all patients. However, having a monitoring strategy, such as using therapeutic drug monitoring

and looking for antidrug antibodies, is predictive and can guide doctors as to whether the patient will do well with the therapy, or whether the restarted treatment should be discontinued and a different therapy should be tried.

G&H Has there been any research looking at long-term response with this treatment strategy?

DR Right now, prospective research in this area is still in the early stages, but one of the key efforts was published in 2014 by Dr Filip Baert and colleagues. This retrospective study describes one of the most thorough approaches to restarting biologic therapy and was the inspiration for some of our current efforts. The researchers followed patients after restarting for between 1 and 4 years. Once patients were out of the loading phase, if they were tolerating therapy and were having an early response, their likelihood of continuing to respond was similar to that of treatment-naive patients.

G&H What are the main challenges and concerns with restarting biologic therapy after a drug holiday?

DR We need to be cautious and understand the risk of having an immune or hypersensitivity reaction. If a patient has been off a drug for more than 3 to 6 months, there is a real chance that he or she may have an immune response to it when it is given, just as happens with a vaccine. Therefore, appropriate monitoring is needed.

G&H What are the next steps in research in this area?

DR Better markers of mechanisms are needed. It would be ideal if doctors could have a serologic marker or panel of inflammatory pathways so that they could use the dominant one to know which treatment to choose in which patients. In addition, serial measurements of the panel could be used to predict loss of response (which would allow us to be proactive) or to help determine the reason for loss of response based on the mechanism, rather than just on the drug level.

More research is also needed on the newer biologic drugs and in larger groups of patients. My colleagues and I are collaborating with Dr Abreu's group to combine our research from DDW so that we can have a larger group of patients to examine, and those findings will be interesting to see.

Dr Rubin is a consultant to AbbVie, Janssen, Takeda, Pfizer, Merck, Samsung Bioepis, and Prometheus.

Suggested Reading

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