ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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Anti-TNF Failures in Crohn's Disease

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G&H Why do some Crohn's disease patients fail to respond to agents that act against tumor necrosis factor?

MA Failure to respond to agents that act against tumor necrosis factor (TNF) occurs for several reasons. One group of patients who do not respond to anti-TNF agents are Crohn's disease (CD) patients who do not have inflammation; they could have diarrhea or abdominal pain for other reasons, including a stricture in the small intestine, previous surgery, or bacterial overgrowth in the small intestine. Alternatively, some patients do not respond to anti-TNF agents for mechanistic reasons. These patients have inflammation, but blocking TNF-α does not turn off their inflammatory cascade. While we do not yet fully understand why these treatment failures occur, this problem is fairly common, occurring in approximately 25% of patients.

G&H What factors are associated with anti-TNF failure?

MA Previously, clinicians thought that patients with colonic CD, who are more similar to ulcerative colitis (UC) patients, had a poorer response to anti-TNF therapy. That theory was disproven, however, as we now know that anti-TNF agents work in both UC and CD. Currently, we have no good predictors for anti-TNF failure—either genetic, virologic, or biochemical. Nonetheless, there are some factors that correlate with anti-TNF failure. We know that anti-TNF agents do not work as well in patients who smoke compared to nonsmokers, and depression and other similar factors may also correlate with anti-TNF failure.

G&H If a patient fails to respond to the first anti-TNF agent, how often do you try a second or third anti-TNF agent?

MA If I have tried 1 anti-TNF agent and the patient did not respond well, I would probably try a second agent, but I would not try a third agent if the second fails. In selecting the second agent, I aim to switch to a drug within this class that is as different from the first drug as possible, so I typically opt for an agent that is administered via a different route. For example, if I tried a subcutaneous agent first, then I would try an intravenous drug as my second agent. If I tried an intravenous drug first and it failed, then I might try a subcutaneous agent next.

G&H Does the decision to try a second agent depend on which agent was tried first?

MA I am far more enthusiastic about trying an intravenous agent as my second-choice drug if the first agent I tried was a subcutaneous agent. In part, this is because I can dose infliximab (Remicade, Centocor) in a weight-based manner, which ensures that the patient will receive

an adequate dose. In addition, randomized controlled trials have shown that infliximab works in fistulizing disease. I suspect the other anti-TNF agents also work in these patients, but not all drugs have undergone prospective studies to demonstrate this benefit.

G&H Do you prefer to start with a particular anti-TNF agent?

MA Several factors determine my initial drug choice. For induction of remission in luminal CD, however, I believe adalimumab (Humira, Abbott) and infliximab are comparable.

G&H Why might different anti-TNF agents provide different results?

MA With respect to immunogenicity, I am not sure that any of the anti-TNF agents are fundamentally different from the others; all of these drugs induce antibodies to themselves. Certolizumab pegol (Cimzia, UCB) is somewhat different from other anti-TNF agents because it is pegylated, however, which might affect how well it can penetrate into tissues and how well it is retained in tissues. Also, as I mentioned, drugs can be delivered by different routes; from a clinical standpoint, this difference is important because an agent that is dosed subcutaneously enters the circulation much more gradually than a drug that is administered intravenously. Finally, infliximab is dosed on a milligram-per-kilogram basis rather than as a fixed dose, which could make a big difference for some patients, especially heavier individuals.

G&H If several anti-TNF agents have been tried without success, what other drugs can you try?

MA Once 1 or 2 anti-TNF agents have failed, it becomes imperative that clinicians make sure that there is no other explanation for the patient's symptoms besides inflammation. In the absence of any other problems, I would then discuss with the patient the option of starting natalizumab (Tysabri, Biogen Idec/Elan). I also re-evaluate whether the patient is on an immunomodulator and check its dosing; for 6-mercaptopurine and azathioprine, efficacy is correlated with drug levels, so clinicians need to ensure that the patient is not being underdosed.

If all these steps have been completed and the patient is still not responding to immunomodulators and/or anti-TNF agents, then I try to steer the patient into a clinical trial. Many clinical trials are now enrolling patients who have failed anti-TNF agents, and these trials offer promising opportunities. Also, because patients who receive natalizumab will typically be excluded from future clinical trials, I try to enroll patients in a clinical trial before resorting to use of this drug.

G&H Have any studies examined alternative treatments for patients who have failed anti-TNF therapy?

MA Natalizumab is specifically approved for this population of patients, but the data supporting its use are based on post-hoc analyses of the clinical trials. There was also a phase II study of ustekinumab (Stelara, Centocor) in which a post-hoc analysis showed a benefit among patients who were anti-TNF failures. Post-hoc analyses can sometimes be misleading because of potential confounders, however, so prospective trials are needed to confirm these findings.

G&H Are other new drugs being tested in patients who have failed anti-TNF agents?

MA There has recently been a burgeoning of clinical trials for new agents. Vedolizumab works via a mechanism similar to that of natalizumab but is more specific to the gut, and the hope is that this new drug will provide comparable efficacy without the potential for JC virus infection of the brain that is associated with natalizumab. Vedolizumab is being tested in clinical trials for treatment of both UC and CD, and so far it shows promise. Another new agent acts against interleukin (IL)-17; IL-17 has been shown to be upregulated in inflammatory bowel disease, both in human tissues and mouse models, so I am optimistic that blocking IL-17 will be a good treatment strategy. One clinical trial of this drug did not show efficacy, but a better-designed trial is currently ongoing. Antibodies to the p40 subunit of IL-12 and IL-23 have also shown some promise in clinical trials, at least for CD, and anti–IL-6 will be tested as well. While clinicians will probably continue to use anti-TNF agents as their first anticytokine strategy in the near future, all of these newer agents have the potential for success.

G&H If a patient has failed anti-TNF agents, how often is an alternative medication successful?

MA Patients who have failed treatment with anti-TNF agents are generally a more refractory group, so the next agent often does not work well. I would estimate that alternative medications are only successful in approximately 30% of anti-TNF failures.

G&H How often must physicians resort to surgical therapy in patients who have failed anti-TNF treatment?

MA Most patients who undergo surgery have tried at least 1 anti-TNF agent, and it is not yet apparent whether anti-TNF drugs reduce the need for surgery over the long term. A short-term study that follows patients for 1 year while they are taking an anti-TNF agent will show a lower rate of surgery in the treatment group compared to the control group, but it remains to be seen whether use of these agents reduces the overall number of patients needing surgery 4 or 5 years later. We therefore need longer longitudinal studies to make the claim that our current therapies actually reduce the rate at which patients ultimately require surgery.

Suggested Reading

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