

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

Section Editor: Stephen B. Hanauer, MD

Patient Perspectives on Therapeutic Options for IBD

Corey A. Siegel, MD

Director, Inflammatory Bowel Disease Center
Department of Gastroenterology & Hepatology
Dartmouth-Hitchcock Medical Center

G&H What has your own research demonstrated regarding patient perceptions of the risk and benefit of standard inflammatory bowel disease (IBD) medications?

CS There has been concern that patients may be misperceiving the benefits and risks of IBD treatments. However, the precise ways in which risk and benefit are misunderstood had never been thoroughly examined. The point of our most recent study was to assess what patients do and do not know, as a foundation for making an attempt to better educate them. If we can understand their perceptions, we can better focus on what we need to explain to patients. What we found in our trial was that patients tend to overestimate the benefit of biologic therapies while underestimating the possible risks.

In most clinical trials of biologics for Crohn's disease (CD), remission rates at the end of 1 year are approximately 20%. In our study, the majority of patients questioned believed that remission rates were higher. Nearly 75% of subjects believed that the 1-year remission rate associated with infliximab (Remicade, Centocor) was higher than 50%. Although in actual clinical practice remission may be higher than that 20% measured in clinical trials, it is difficult to believe that these drugs put patients in long-term remission greater than 50% of the time.

We also asked patients several questions regarding the risk of biologic therapies, particularly focusing on the risk of lymphoma, as this seems to be the adverse event of most concern to both physicians and patients. Patients nonetheless underrepresented the estimated risk of lymphoma associated with these medications. According to our results, the majority of patients thought there was either no increased risk of lymphoma or perhaps a 2-fold increased risk of lymphoma, whereas some estimates in

the literature suggest that there could be a 10- to 20-fold increased risk associated with biologic therapy. There is considerable uncertainty regarding these risks but current literature maintains that they are higher, or appear to be higher, among patients taking biologic therapies versus the general population. When there is a signal of this nature in the literature, patients need to know that reports of increased risk exist, even if there is a wide range of conjecture regarding what the elevated level of risk might be.

In another part of this project, we presented patients with a hypothetical situation in which a drug might have a certain risk of death and a certain risk of lymphoma. The risks they were given were based on the risks calculated in the literature for infliximab. Then, we asked patients what level of efficacy the drug would need to show before they would be willing to take it. Over 60% of patients said that they would not take the drug at all, feeling it was too risky. Of that 60%, 30% were already taking infliximab or had taken it in the past.

G&H How do these conclusions regarding patient tolerance of risk contrast with earlier findings?

CS Earlier data counter these findings and raise other questions regarding the tolerance of risk among patients. In our earlier study, patients with moderate-to-severe CD were shown to be willing to accept heightened risk of serious adverse events if there was the potential for response to the associated medication. Hypothetical risks posited to patients in this study included progressive multifocal leukoencephalopathy (PML), serious infections, and lymphoma, which were juxtaposed with efficacy considerations such as prevention of fistulae, abscesses, and bowel obstructions, as well as lengthened time between disease flares and avoidance of steroid use. Maximum acceptable risk levels for serious adverse events associated with the various scenarios ranged from 0.69% to 0.81% in patients with severe daily symptoms and from 0.39% to 0.55% in patients with moderate disease.

PML is, without a doubt, a very serious side effect. However, the risk appears to be very small, probably less than 1 in 1,000 patients in trials of the biologic therapy natalizumab (Tysabri, Elan). When clinical trials for CD therapy with natalizumab were halted because of cases of PML, many patients called their physicians immediately

and asked how they could continue to receive it, despite the fact that they were informed about this rare risk of neurologic disease.

To make a somewhat arbitrary decision regarding what level of treatment-associated risk warrants too much risk does not make much sense when considering patients experiencing long-term, severe impairment of quality of life. These patients may be willing to take higher risks than the US Food and Drug Administration (FDA) currently allows. Regulatory committees should take this consideration into account when ruling on new medications for these conditions.

G&H What are the factors that lead patients to overestimate benefits and underestimate risks associated with biologic therapies?

CS The general perception among patients is that if drugs are approved by the FDA and their doctors are prescribing them, they must work. The marketing of these medications can at times also obscure the fact that they may not work in some patients. Further, among patients with chronic illness, there is a hope that new medications will help them, which can be attributed simply to human nature. The same can be said for patients' underappreciation of risk. Patients generally believe that the FDA is very careful in certifying drugs and that doctors would never give a medication that would harm them.

Another factor contributing to distorted patient perceptions is the fact that physicians may not be properly informed as to the actual risks and benefits, largely because they are still not fully defined. In a short office visit of 30 minutes or less, it is difficult to explain the complicated risk:benefit ratio in the face of ongoing uncertainty. Often, patients are prescribed medications with the simple explanation that "we think this medication is going to help you and though it has risks, they are outweighed by the potential benefits." Although this explanation is most likely correct, patients need more information to make individual decisions.

G&H In the current era of internet access and emphasis on patient self-education, do you feel patients are better informed or more likely misled in their efforts to understand their conditions and treatment options?

CS I think it is certainly positive when patients attempt to educate themselves and that there are a number of resources for patients to access. Based on a study conducted at the Mayo Clinic, acquisition of medical information via the internet rates second only to direct consultation with a physician in terms of how patients get information. The problem with this method is that

a simple Google search for a CD medication turns up a wide variety of Web sites, including excellent resources such as the Crohn's and Colitis Foundation of America (CCFA) and the Mayo Clinic but also those sponsored by pharmaceutical companies, law offices, and individual blogs, in which the goal of the site varies and may not always be in the interest of delivering balanced patient education. In order to make internet-based education more helpful, we might want to consider whether sites should be monitored and certified by an organization such as the American Gastroenterological Association or the CCFA and certified for proper patient education.

G&H How does all of this information help define your approach to patient education?

CS First, it should be noted that patient education is an ongoing process that should not be attempted all in one meeting. With most cases of IBD, we have the luxury of time to make decisions. Patients usually do not present in an emergency room with an immediate need for definitive therapy such as surgery. We generally have time to educate patients, let them learn more, and allow them to return in a few weeks to make a major decision in the treatment process.

Patients need to understand the natural history of disease in order to realize that risks from medications are not the only risks they face and that undertreatment of their disease may lead to the most serious adverse events. Therefore, my first priority is to explain that the disease has an unpredictable course but clinical experience allows us to predict what may happen over the next 3–5 years. Patients need to understand that IBD is a lifelong disease that needs to be approached like a chess match, where we plan well into the future, rather than only providing quick solutions for today. This strategy, at times, may entail the use of medications earlier than seems warranted in order to prevent complications, instead of treating them as they arise. With this strategy in mind, patients can be informed about treatments and assess their efficacy versus the small but serious risk of side effects.

G&H Does the decision-making process differ in patients with ulcerative colitis?

CS These decisions are very different for ulcerative colitis (UC) and CD. UC is in some ways more interesting from an academic decision-making standpoint because the possibility of colectomy as definitive treatment adds another dimension to the process. At almost any point in the UC disease course, after failing first-line medications such as 5-aminosalicylates (5-ASAs), the choice of colectomy becomes viable. Some patients may choose to try every available medication before considering colectomy,

whereas others may consider the surgical option much earlier. For patients with CD, these decisions remain complex but often there is no choice but to continue with medication. Surgery for CD, in many cases, is not an option because the disease can recur afterward.

In a recent study by Arseneau and colleagues, decision analysis was performed in patients with UC. The authors developed utility scores to reflect the effects of both disease and treatment and asked patients how efficacious medications would need to be in order to take them instead of undergoing colectomy. The study specifically examined the use of infliximab and cyclosporine. One third of patients preferred colectomy over these medications. Sensitivity analysis showed that the decisions were based in part on the efficacy of treatment and that the cut point for patient preference of biologic therapy over surgery was that biologic drugs would work 60% of the time. Looking at clinical trials of these drugs, initial response rates have been at exactly this level.

Clinicians need to remember that patients with UC might prefer colectomy to trying biologic drugs or immunomodulators or, in some cases, even steroids, so the choice of colectomy needs to come up early in discussion with patients. When UC patients are faced with the choice of treatment with biologics, they should also meet with a surgeon, so that they can make an informed decision regarding the aftereffects of colectomy versus the risk:benefit scenario of medication. In general, we as physicians need to understand and respect the fact that patients make decisions differently and that general treatment algorithms will not always hold at the individual patient level. This concept of shared decision-making defines the physician's role as educating patients. The patient's role is to see how that information plays into their personal preferences, and the decision is made in partnership with the physician.

G&H How should the heightened risk of colon cancer be presented to UC patients?

CS Alerting patients to the heightened risk from colon cancer is important. In addition to reinforcing the importance of routine colonoscopy surveillance, this information helps promote adherence to drug regimens, particularly with 5-ASAs, the regular use of which has been associated with colon cancer prevention.

However, this motivational awareness needs to be balanced against scaring patients. Patients should not live in fear of cancer all the time. Nor do they need to be informed of the heightened risk at the first visit. It can be overwhelming to patients with a new diagnosis of IBD to have to take in information on the increased risk of cancer simultaneously. However, at some point after diagnosis, patients need to understand that this disease is serious

and treatment is important for more than just keeping symptoms under control.

G&H What other research or methods are currently in development to aid patients with IBD in making treatment decisions?

CS Continued study of the risk:benefit ratios of these agents is crucial, as we still do not have definitive information regarding the likelihood of adverse events associated with biologics or immunomodulators. Current data are complicated, and we still do not know how they should be applied in clinical practice.

We also need to develop new methods of communicating odds ratios and percentages to patients. Schwartz and colleagues published a study in 1997 on numeracy and quantitative literacy in which they found that half of patients could not translate the concept of 1% to "10 in 1,000" and that patients have a very difficult time conceptualizing small numbers.

The concept of framing also plays a part. Statistics can be presented in different ways that convey the same meaning. Patients, however, make decisions based on the numbers that sound right to them. Malenka and associates offered a hypothetical medication to patients with a relative risk reduction for heart attacks of 34% or an absolute risk reduction of 1.4%. These statistics denote the same likelihood of prevention, but patients consistently said that they would take the drug with the 34% reduction but not the one with the 1.4% reduction.

The best way to help patients understand complicated statistics is to develop decision aids or tools that help them to interpret available data, understand the uncertainty behind that data, and receive clear communication of what the numbers mean. My current research focuses on trying to develop these decision aids or tools to calculate risk and benefit and properly communicate the statistics to patients and ultimately to practicing physicians as well.

Suggested Reading

Siegel CA, Levy LC, Mackenzie TA, Sands BE. Patient perceptions of the risks and benefits of infliximab for the treatment of inflammatory bowel disease. *Inflamm Bowel Dis*. 2007 Oct 9; [Epub ahead of print].

Johnson FR, Ozdemir S, Mansfield C, Hass S, Miller DW, et al. Crohn's disease patients' risk-benefit preference: serious adverse event risks versus treatment efficacy. *Gastroenterology*. 2007;133:769-779.

Siegel CA. Embracing the internet for progress in shared decision-making. *Inflamm Bowel Dis*. 2007;13:1579-1580.

Siegel CA, Bensen SP, Ely P. Should rare complications of treatment influence decision-making in ulcerative colitis? *Inflamm Bowel Dis*. 2007;13:242.

Arseneau KO, Sultan S, Provenzale DT, Onken J, Bickston SJ, et al. Do patient preferences influence decisions on treatment for patients with steroid-refractory ulcerative colitis? *Clin Gastroenterol Hepatol*. 2006;4:1135-1142.

Malenka DJ, Baron JA, Johansen S, Wahrenberger JW, Ross JM. The framing effect of relative and absolute risk. *J Gen Intern Med*. 1993;8:543-548.