Crohn's disease: Advise and consent

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PA: Let us begin with a new diagnosis of Crohn's disease in a 22-year-old woman, based on the typical clinical history of pain, diarrhea and terminal ileitis demonstrated on a small bowel follow-through examination. Are you comfortable initiating therapy without a histological diagnosis?

BS: This patient's symptoms are relatively non-specific. Abdominal pain and diarrhea will most often be the presenting symptoms of irritable bowel syndrome when we are talking about a 22-year-old woman. However, small bowel follow-through findings, such as a cobblestone appearance, can be relatively specific for Crohn's disease. Still, it is my strong preference to initiate a complete evaluation at the time of diagnosis, which is when the most important diagnostic information will be obtained. For example, when differentiating Crohn's colitis from ulcerative colitis, the finding of patchy inflammation in the colon after therapy has been initiated for ulcerative colitis can easily be misconstrued as providing evidence for a diagnosis of Crohn's disease. In addition, I have too often seen inaccurate diagnoses of Crohn's disease made on the basis of computed tomography findings. While I consider computed tomography enterography to be a useful study for the follow-up of well-established Crohn's disease, evidence of bowel inflammation alone is not sufficient to establish a diagnosis. Primarily, we depend on histology to confirm the chronic nature of the inflammation. Without evidence of chronicity, only a tentative diagnosis of inflammatory bowel disease (IBD) can be made (1). Also, without histological confirmation, an occasional but important alternative diagnosis, such as small bowel lymphoma, may be missed. This could have dire implications when you are considering immune-suppressing medications.

PA: How do you approach discussing the risks and benefits of steroid therapy at the outset of treatment?

BS: It is important to educate the patient about the risks and benefits of each therapy prescribed for IBD. Discussion about the expected benefits and time to onset of improvement helps set appropriate expectations for patients who might otherwise

give up on a therapy before the drug can actually work. A frank discussion about the risks and benefits of a specific therapy is

not only needed for medical-legal reasons, but is also an important part of the ethical treatment of patients, and helps them to make therapeutic decisions based on their own preferences. Perhaps most importantly, a full discussion about side effects enlists your patient as an ally in early detection of important adverse effects of medical therapy. Specifically, with regard to corticosteroids, it is important to distinguish between enteric-coated budesonide and conventional corticosteroid therapy. Enteric-coated budesonide would be an appropriate choice for this patient, who has ileal disease, provided her symptoms are in the mild to moderate range. Studies (2) show that this formulation is about as effective as conventional corticosteroids, but with a large reduction in the occurrence of troublesome cosmetic and neuropsychiatric side effects. In addition, the data are relatively reassuring with regard to preservation of bone density (3). However, some patients do not respond to enteric-coated budesonide and require treatment with prednisone. The discussion about prednisone is quite different. I typically tell patients that the majority of people who are treated with this drug will experience one or more side effects, but that the intended use is relatively short-

term, approximately eight weeks. We typically warn patients about insomnia and mood disturbance, acne and weight gain, possible effects on blood pressure and elevated blood glucose. In addition, we routinely start patients on calcium and vitamin D. It is good practice to check bone density in all patients with Crohn's disease at diagnosis, because many will present with decreased bone density, particularly in younger age groups. This provides a reference point for future bone density determinations, particularly if corticosteroids are required.

PA: The steroid therapy is partially effective, but symptoms recur as the dose of prednisone is decreased below 15 mg per day. How do you approach the risks of the next line of therapy?

BS: This, unfortunately, is the case for more than one-half of the patients who begin steroid therapy. After an initial treatment with corticosteroids, approximately 50% of patients will prove to be either steroid-dependent or steroid-refractory by the end of the year. It is very clear that the benefits of immunomodulator therapy outweigh the risks of long-term

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use of corticosteroids. Even at doses as low as 7.5 mg/day, corticosteroids can have significant side effects, including hypothalamic-pituitary-adrenal axis suppression, cataracts and decreased bone density. At doses of prednisone above 15 mg/day, there is also an increased risk of infection. Certainly, immune modulators also have risks. Azathioprine and 6-mercaptopurine require monitoring of the complete blood count, because of the risk of leukopenia. In the United States, many practitioners check thiopurine methyl transferase activity or genotype before initiating therapy with these agents. This permits dose reduction in patients with decreased thiopurine methyl transferase activity, or avoiding treatment of the approximately one in 300 individuals who are completely deficient for this enzyme. Certainly, there is also an increased risk of infection, including rare but life-threatening viral infections such as the cytomegalovirus. In addition, there is a well-recognized increased risk in squamous cell carcinoma of the skin and cervical dysplasia, both likely relating to poor immunological control of the human papilloma virus. Between 3% and 7% of patients will develop pancreatitis, usually within the first eight weeks of treatment. Most worrisome to patients and doctors is the risk of lymphoma. The best estimate for this risk comes from Kandiel et al (4). The RR is approximately 4; however, the absolute risk is still quite low. For the population aged 20 to 29 years, one lymphoma will occur among over 4000 patients treated for one year (4). This is a message that relates to the presentation of all these rare but serious risks of immune suppression. That is to say, the RRs can appear quite alarming, but for the most part, the absolute risks are quite small. Another message from the literature is that, for the most part, we do not have precise quantification of the level of risk associated with these agents. Depending on whether one looks at uncontrolled case series, large prospective cohorts, randomized controlled trials or spontaneous reports of postmarketing data, the risk estimates can be quite different. This uncertainty contributes further to the anxieties of patients and doctors surrounding medical decision-making in IBD. In the end though, it is important to recognize that IBD can have a significant impact on quality of life, and that many patients will accept a significant level of risk to achieve a better state of well-being (5).

PA: At this stage, when stronger medications are considered that have often been used in transplantation or oncology, the patient often requests surgical therapy.

BS: Of course, patients will be aware that surgery is often used in the treatment of Crohn's disease. Unfortunately, what the patient does not understand at this point is that the rate of recurrence after surgery is quite high. Approximately 80% of patients will have significant endoscopic recurrence at the end of one year after an ileal or ileocolonic resection. But after three years, one-half of patients will have recurrence of clinical symptoms. Certainly, there is a great deal of variation around these numbers. Some patients may go on for many years after a resection with no evidence of recurrence, and others will have almost immediate recurrence. Nevertheless, gastroenterologists all too often feel that surgery is a last resort in Crohn's disease, when a decision for surgery might reasonably have been made well before the point of exhausting every medical therapeutic option. The key point for this patient is that surgery is not the end of the story, that likelihood of disease recurrence is very high, and that postsurgical prophylaxis with medications such as azathioprine will be needed, anyhow.

PA: The patient took azathioprine for four months, but as the dose reached 2.5 mg/kg, she complained of a lot of nausea. She has not seen much reduction in prednisone and is complaining about the costs of her medications.

BS: This would normally be considered to be an adequate trial of azathioprine. Even if we could improve her tolerance of the medication by treating her nausea, it seems unlikely that she would respond to further treatment with this agent. Her main options at this point would be to consider trying methotrexate, beginning infliximab or undergo surgical resection. Given that she has been ill for some time now, I do not favour methotrexate, which may take an additional eight to 16 weeks to work. On the other hand, if we are considering infliximab, it might be worth considering starting methotrexate, solely for the purpose of minimizing the formation of antibodies to infliximab. There is, however, a growing sentiment that monotherapy with anti-tumour necrosis factor (TNF) antibodies may be desirable with regard to decreasing the risk of serious adverse events such as infection or lymphoma. The trade-offs between risk and benefit under these conditions are not well worked out. Ongoing studies comparing infliximab alone, azathioprine alone or a combination of the two, will greatly help to answer these questions. It is very clear, however, that patients who take biological therapies in an episodic fashion are at high risk for loss of response because of antibody formation, if they do not take concomitant immune modulators. With regard to the cost, it must be recognized that even in the era of biological therapies, surgery and hospitalization are the primary drivers of cost, and that anti-TNF antibodies have been demonstrated to be cost-effective, and significantly reduce the rate of both surgery and hospitalization in patients who have been refractory to other therapies (6). This does not speak to the patient's personal costs of treatment, but rather to societal costs, quite apart from the costs of disability, absenteeism and underemployment because of illness.

PA: The patient has heard of infliximab but is concerned about safety and is asking about the duration of therapy.

BS: The major safety concerns regarding infliximab are risks of infection and malignancy, particularly lymphoma. There is no doubt that the risk of intracellular pathogens, such as mycobacteria and fungi, are increased. We see clear signals of increased risk of tuberculosis, and in the right geographical locations, histoplasmosis, coccidiomycosis, etc. For tuberculosis, the risk can be reduced, though not completely eliminated, by careful prescreening and vigilance for atypical and extrapulmonary presentations. For lymphoma, risk estimates vary considerably depending on the data source. Randomized controlled trials, which should tend to evenly distribute potentially confounding risk exposures, such as concomitant immune suppression and disease severity, tend to show fairly small or no increases in risk. If one looks at consecutive case series from various jurisdictions, we see risks as high as one in 500 (7). In addition, pediatric gastroenterologists in particular are disturbed by recent reports of as many as 11 cases of hepatosplenic T cell lymphoma among young male patients treated with azathioprine and infliximab. This particular lymphoma is otherwise exceedingly rare, and is uniformly fatal. It is not possible at this time to know whether this occurs because of the combination of anti-TNF antibody and azathioprine, or is solely related to either individual component of combination therapy. By contrast, if one turns to the data in the very large Crohn's Therapy, Resource, Evaluation and Assessment Tool

registry (8), with over 3000 patients, infliximab does not emerge as a risk factor for either serious infection or mortality; rather, steroid use and narcotic use, as well as disease severity, turn out to be independent predictors of these outcomes. Certainly, there are other rare but serious adverse events associated with anti-TNF antibodies, including lupus-like reactions, demyelinating syndromes, liver failure and increased mortality among patients with moderate to severe congestive heart failure – which is a contraindication to treatment with these agents. Once again, the point that is missed in all this discussion of RRs is that the absolute risks remain quite small.

Finally, with regard to the question of duration of therapy with anti-TNF antibodies, this seems to depend in large part on what your route to anti-TNF was in the first place. That is to say, most patients who have run through the usual gamut of therapies leading up to anti-TNF antibodies – meaning, they have had a good attempt to get control of their disease with immune modulators – will need to continue on anti-TNF indefinitely to maintain their response. The question of whether this needs to be indefinite treatment with combination anti-TNF and immune modulator, or anti-TNF as monotherapy, is still not completely answered. The answer seems to be slightly different if the patient is relatively early in the course of their disease, and has not yet been tried on an immune modulator. In this situation, it may be useful to use anti-TNF as a bridge to an immune modulator. We know from the so-called ‘Top-Down Step-Up’ randomized controlled trial (9) that recently diagnosed patients with Crohn’s disease who have a loading regimen of infliximab followed by maintenance therapy by an immune modulator, have a durable carry-over effect with very low steroid requirements and a much higher rate of sustained mucosal healing. We all believe that these results will translate into better outcomes over longer periods of follow-up, although this remains to be proven.

PA: She eventually visits a surgeon, who tells her that she has been poisoned by the gastroenterologist and should have had surgery years ago.

BS: Just as gastroenterologists need to understand the place of surgery in the treatment of IBD, surgeons need to understand

the role of medical therapy, and be respectful of the patient’s desire to maintain the integrity of their gastrointestinal tract. Although there is surely an important role for surgery in Crohn’s disease and ulcerative colitis, there is also a price to pay for surgery – not just in the recovery time after the surgery, which is getting shorter and easier with laparoscopic methods, but with the more subtle or obvious negative effects on bowel function, such as losing the ileal break, bile salt diarrhea and so on. More than any other field in gastroenterology, I believe that the most optimal care of IBD requires a thoughtful multidisciplinary approach.

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