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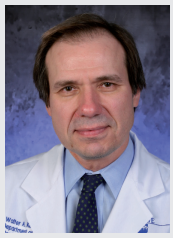

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"…it is quite concerning that ulcerative colitis patients who already have a predisposition toward malignant degeneration in their colon might now be treated with a biologic drug that appears to compromise tumor surveillance."

The article by Doherty and Cheifetz in this issue of *Expert Review of Gastroenterology and Hepatology* is a review designed to advise the clinician on the medical management of the patient presenting with acute severe ulcerative colitis (UC) and, specifically, how to assess the relative roles of various forms of medical 'rescue therapy' for those who fail the standard institution of high-dose steroids [1]. Approximately 15–25% of UC patients will have a severe flare of their disease requiring hospital admission and approximately a third of these will fail high-dose intravenous steroids. There are really only two medical options for such patients, ciclosporin A or infliximab, although there are relatively less data supporting the latter in such severely ill patients. However, the article is generally an excellent summary from a medical perspective in choosing between these two drugs. Especially appropriate is their time-constrained flow diagram describing a protocol for management, since often these patients languish on ineffective steroids and hyperalimentation for too long before being reconsidered for more aggressive therapy.

However, the authors do the surgical option for these patients a relative injustice. They correctly describe the standard total abdominal colectomy/Hartmann/ileostomy procedure that is the surgical maneuver of choice in such critically ill patients with interval reconstruction after regaining their health using the ileal pouch–anal anastomosis (IPAA). Although their flow diagram comments on counseling the patient regarding risks and benefits of surgery, infliximab and ciclosporin, they only provide details regarding the 20-year long-term outcomes of the surgical option (in Table 2) [1]. Admittedly, these are imperfect or as the authors state, "most patients do not return to what they would consider normal bowel function". However, there is no similar long-term outcomes table provided describing the consequences of 20 years of ciclosporin A or infliximab therapy in the setting of ongoing UC. Could this be, perhaps, because there are no such long-term data, since in fact, such patients infrequently last 20, 10 or even 5 years? With both ciclosporin and infliximab, even when initially successful (which is only approximately 60–80% of the time), longer term colectomy rates are such that the majority of these patients will deteriorate and require colectomy, certainly within 5 years and usually much sooner. If a table describing the long-term consequences of such medical management of UC were to be theoretically constructed, it would have to include all the negatives of having the disease, including the number of bowel movements, cancer risk (approximately 10–20% at 20–30 years), compromised quality of living (e.g., worse sexual function and time lost from work) in addition to the significant risks associated with long-term immunosuppression and the use of infliximab. Thus, the comparison is not IPAA versus 'normal bowel function' but rather IPAA versus medically managed UC, a distinction that is frequently blurred by proponents of these drugs.

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Besides the near inevitable need for eventual colectomy in the majority of such critically ill patients, those who are initially successfully managed with ciclosporin A or infliximab need to then deal with the very real complications of long-term immunosuppression and infliximab use. Such complications are many but are largely two in type: cancer and infectious. As the authors point out, ciclosporin A is usually transitioned to azathioprine/mercaptopurine and in these patients, the long-term risk of lymphoma or other malignancy is quite equivocal. In the case of infliximab, however, there are increasing reports of hepatosplenic T-cell lymphoma – a particularly lethal form of lymphoma found in these patients [2]. This happens nearly always in concert with simultaneous azathioprine/mercaptopurine treatment. Even the Crohn's Therapy Resource, Evaluation and Assessment Tool (TREAT) registry showed a small increase in lymphoma risk (62 vs 57 cases per 1000 person-years in infliximab versus no infliximab) while a study using Surveillance Epidemiology and End-Results (SEER) data showed a relative risk of 2.88 versus 1.5 in Crohn's disease patients treated with infliximab versus immunosuppression alone [3,4]. Thus, it is quite concerning that UC patients who already have a predisposition toward malignant degeneration in their colon might now be treated with a biologic drug that appears to compromise tumor surveillance. The uncertainty of malignant risk with such long-term treatment must be part of the educational process that needs to be balanced by the patient when presented with the option of medical versus surgical management.

The infectious risk is similarly real, especially in infliximab-treated patients and those receiving multiple immunosuppressive drugs. Infectious complications, especially opportunistic infections of the lung (e.g., pneumocystis, histoplasmosis and TB) are the most common complications associated with infliximab (approximately 35%) and can be lethal if treatment is delayed [5]. All of the pneumonias, including the one death in the Active Colitis Trial (ACT) 1 and ACT 2 were in infliximab-treated patients, for example [6]. The recognition of this infectious pulmonary risk has resulted in a 'black box' warning by the US FDA. Toruner *et al.*, in a case–control retrospective study, have also shown a 3.1 odds ratio of infectious risk associated with azathioprine/mercaptopurine use, which rose to 4.4 for infliximab use [7]. If two or more such drugs were administered simultaneously, the odds ratio sky-rocketed to 12.9! The longer term infectious risk of such medical management of the UC patient is, therefore, significant.

There are very little data directly comparing the longer term care of medically managed severe UC patients versus those managed surgically. The article by Cohen referenced by the authors suggesting that quality of life (QoL) is better in ciclosporin A-treated versus surgically managed UC patients in fact showed no difference in two of the three questionnaire tools used, and in the one tool (which had not been validated) where a difference was seen, there were only three patients in the ciclosporin A arm after 24 months [8]. In addition, such studies are highly selected since the surgical arm effectively contains all of the medical failures, while the medical arm only contains the successes. Conversely, there are a profusion of data in the surgical literature showing excellent QoL in IPAA patients. The summary by Lichtenstein acknowledges that eight out of ten studies showed an improved QoL after IPAA [9].

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However, there are some very relevant longer term data on surgical versus medical management of all UC patients (not just those severely affected) out of the UK. Roberts *et al.* looked at relative 3-year survival rates of over 28,000 patients admitted to the hospital with colitis based on whether the patient had an elective colectomy, an emergent colectomy or medical management during the hospitalization [10]. The lowest 3-year mortality rate was seen in the elective colectomy group (3.7%), while the highest were seen in the medically managed (13.6%) and urgent colectomy (13.2%) groups. This study reviewed data over two time periods (1968–1999 and 1998–2003) with infliximab and ciclosporin A certainly being available during the second period. Although specific details of medical management were not documented, the results were virtually identical in both time periods and were very highly statistically significant. This study casts serious doubt on the medical management of severe UC, since its results suggest that all medically treated UC patients requiring hospitalization (no matter the severity of their disease) have the worst outcome, which is comparable to that of a much smaller group of severely affected UC patients requiring emergent colectomy. As the authors stated [1]:

"*As the patients who underwent emergency colectomy were, in general, more severely ill than those who had no colectomy, this suggests that the decision not to operate may be the more dangerous option for severe cases.*"

So, how should infliximab and ciclosporin A be viewed and utilized in the severe UC patient failing steroids? Simply put, these drugs should be seen as a 'bridge to surgery' and used accordingly. Their value is in converting a patient from an emergent colectomy done under adverse circumstances to a colectomy performed under more elective circumstances and hopefully will change a three-stage IPAA operation into a two-stage one. Their use is appropriate when instituted in a timely fashion in the patient who does not have any of the contraindications described in the paper, and especially in those who may have a specific, but temporary prohibitive risk for surgery (e.g., recent myocardial infarction). However, the patient accepting the risks of such medical management should similarly acknowledge the near certainty of eventual colectomy. Thus, I fully agree with the authors in their recommendation of a multidisciplinary educational process to assist the patient in choosing their therapy. In my own experience, however, after describing the imperfect response rate to these drugs and all their associated complications, the patient's response is usually something similar to "…and then I still have my disease after this 'success'? I still need treatment, maybe steroids, probably long-term

immunosuppression or I might have another flare and then maybe even get cancer…?" The patient usually chooses surgery, looking forward to the admittedly imperfect surgical cure of their UC.

So, overall, I feel the authors do an excellent job of describing rescue therapy from a medical perspective. Their flow diagram expediting the care of these patients is especially good and will facilitate timely intervention in patients failing high-dose steroids. Their recommendation to educate the patient regarding all of the options, including surgery, is quite correct. However, such education needs to stress the long-term complications of medical management with these significantly dangerous drugs, including the very uncertain consequences of compromised tumor surveillance in a disease that has an increased risk of colorectal cancer. When such rescue therapy is implemented, it should be with a plan to medically optimize the patient for eventual, curative colectomy.

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