Closing Fistulas in Crohn’s Disease — Should the Accent Be on Maintenance or Safety?
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Among the many complications of Crohn’s disease, the development of fistulas is one of the most distressing to patients because it decreases their quality of life and one of the most frustrating to physicians because of the dishearteningly high rate of management failure. Review articles offer complex clinical algorithms and long lists of therapeutic options for fistulizing Crohn’s disease, ranging from antibiotics, immunomodulators, and biologic and miscellaneous agents to complementary, but seldom definitive, surgical interventions. Long experience has shown that the more diversified the therapeutic options are, the less likely it is that any one of them will work well, and this is certainly the case for fistulas in patients with Crohn’s disease. Like the primary disease, the fistulas are eminently chronic, and the goal of therapy should be not simply closure, but permanent closure. How to accomplish this is a challenge, because although remission of acute flare-ups can be achieved with a reasonably good degree of success, preventing recurrences and managing the complications of Crohn’s disease are still major challenges. The investment made in more than 20 years of research on the mechanisms of intestinal inflammation is finally paying off, with the development of new approaches based on biologic agents that can block molecules or stop the signals that inflammation relies on for its initiation and perpetuation. Among a number of new biologic agents, infliximab, a chimeric monoclonal antibody against the broadly active inflammatory molecule tumor necrosis factor α (TNF-α), was originally shown to be effective for the short-term treatment of patients with moderate-to-severe, treatment-resistant Crohn’s disease. Its efficacy has been confirmed by the true acid test — real-world clinical practice — with obvious benefits consistently seen in a reasonably large percentage of patients.

If a major problem in Crohn’s disease is its unrelenting nature, could the beneficial effects of infliximab be extended through the use of maintenance therapy in patients with active disease that has responded to a short initial course of treatment? The answer is yes, according to the results of the ACCENT I study (A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen), a year-long randomized, placebo-controlled trial showing that treatment with infliximab every eight weeks resulted in increased rates of sustained remission and a decreased need for corticosteroids. The ACCENT I study excluded patients with fistulas, leaving open the question of whether prolonged therapy with infliximab would be equally effective in keeping the fistulas closed. A hint that this might be so could be inferred by the observation that almost 70 percent of the patients who received three infusions of infliximab over a 6-week period had at least a 50 percent reduction in the number of draining fistulas, with an average duration of response of 12 weeks.

Now, the question about the ability of infliximab to keep fistulas closed has been answered by the results of the ACCENT II study (A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulizing Crohn’s Disease), reported in this issue of the Journal. Sands et al. analyzed a number of clinical and immunologic outcomes in this large, thorough study of fistulizing Crohn’s disease. They found that at the end of one year, maintenance therapy with 5 mg of infliximab per kilogram of body
weight, as compared with placebo maintenance therapy, resulted in a significantly longer time to the loss of response, as defined by the recrudescence of fistulas; a higher rate of complete closure of fistulas; a decline in clinical activity; and an improvement in the quality of life. In addition, maintenance therapy with infliximab had an acceptable safety profile — a finding similar to that in the ACCENT I study.6

No study can be perfect, not even major, multicenter studies that are reasonably well controlled and properly analyzed, such as ACCENT II. Thus, rather than praise its strengths or criticize its weaknesses, depending on individual biases, which certainly abound in the field of inflammatory bowel disease,7 it seems more productive to focus on the numerous outstanding questions about efficacy, cost, and safety. As far as efficacy is concerned, how much healing of the mucosae and fistulous tract truly occurs with the cessation of external drainage? Is the absence of draining fistulas at one year in 36 percent of patients who were treated with infliximab as maintenance therapy better than what antibiotics or immunosuppressive agents (azathioprine, mercaptopurine, or tacrolimus), surgery, or even spontaneous healing can offer? If so, how much better? Antibiotics and immunosuppressive agents have their own verifiable effect, and the use of combined approaches should be considered, particularly if concomitant immunosuppressive therapy reduces the risk that antibodies against infliximab will develop and improves the response to treatment.8

Are there factors that predict fistula closure, such as smoking status, the NOD2 genotype, or C-reactive protein levels, and if so, when should infliximab maintenance therapy begin and how long should it be given? Perhaps a period of 8 or 6 or even fewer months of repeated infusions is just as good as a 12-month infusion period, and perhaps this treatment should be followed by maintenance therapy with standard immunosuppressive agents. Such a hypothetical but reasonable regimen has obvious cost savings.

In regard to costs, more than the duration of treatment, the interval between infusions can have a major financial impact, and the most appropriate, cost-effective interval needs to be determined. There are no data showing that an infusion every 8 weeks is the ideal approach, and perhaps an interval of 12 or 16 weeks is just as good.

More pressing than efficacy and cost is the issue of safety. Despite the fact that infliximab therapy has entered routine clinical use — and perhaps overuse — the rate of adverse events is high.4-6,9 Fortunately, the vast majority of them are acute, such as infusion reactions or hypersensitivity reactions that can be quickly recognized and managed at the bedside, but the serious events are clearly the late ones. Reactivation of latent tuberculosis and the development of lymphomas have been reported after infliximab therapy, but their incidence is low.10,11 In the ACCENT II study, the finding of rectal carcinoma in two men, one with chronic colonic Crohn’s disease and one with ileal Crohn’s disease, approximately two years after the completion of infliximab maintenance therapy is as disturbing as it is puzzling. Are these two cancers related to the immunosuppressive effects of anti–TNF-α therapy? This possibility cannot be excluded, considering the young age of both patients and the fact that only one had perianal disease. Reports of a possible temporal association between infliximab therapy and the development of lung cancer or non-Hodgkin’s lymphoma, along with a reported 1 percent rate of death from any cause,9 keep the threat of infliximab-induced cancer in the minds of clinicians.

However, it is the immunogenicity of the murine component of the infliximab molecule that probably poses the most serious long-term threat, particularly given that prolonged treatment regimens are advocated by the ACCENT I and II studies. The development of antibodies against infliximab is associated not only with an increased risk of infusion reactions and a reduced clinical response,8 but also with the development of antinuclear antibodies (against histone and double-stranded DNA) in approximately 60 percent of patients.12 The incidence of an overt lupus-like syndrome is reportedly low in the infliximab-treated population, but in patients with systemic lupus erythematosus, autoantibodies may be present for several years before the disease becomes clinically apparent.13 One can only hope that such a pattern occurs in the spontaneous rather than the drug-induced form of this autoimmune disease.

By oath, physicians must abide to the primum non nocere principle. Hence, they will inevitably face the dilemma of deciding what is best for a patient with Crohn’s disease who has had lifelong disabling fistulas and is considering infliximab therapy. In practice, if traditional approaches have failed, the decision comes down to a matter of how much risk the physician and the patient are willing to ac-
cept, given the often remarkable healing effects of infliximab and the possibility, currently remote, that malignant or autoimmune disease will develop. For now, most will opt for infliximab and take their chances as long as the drug continues to provide tangible clinical benefits. Meanwhile, new knowledge should emerge on the fistula-healing power of other biologic agents with less immunosuppressive activity or none, combination therapies, thalidomide, probiotics, or even a trip to the Dead Sea for a good dose of hyperbaric oxygen.\(^{15}\)

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