Mesalamine for Refractory Celiac Disease
An Old Medicine for a New Disease

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Celiac disease (CD) is an autoimmune disease affecting the small bowel, which results in malabsorption, diarrhea, and myriad extraintestinal symptoms. This autoimmune disease is triggered by the ingestion of gluten in a fraction of individuals with the human leukocyte antigen haplotypes, DQ2 and DQ8.[1] Earlier thought to be rare in the United States,[2] CD is now known to be common, with a prevalence of nearly 1%.[3] Nevertheless, CD remains underdiagnosed and is generally underrecognized, with a ratio of undiagnosed to diagnosed individuals of 20:1 in the United States,[4] a much higher ratio than that observed in European nations.[5,6] A successful case-finding initiative in the United States[7] shows that these undiagnosed CD patients are "out there," many of whom are symptomatic and treatable with a gluten-free diet.

Why is CD underrecognized in the United States? In this country, much disease awareness on the part of physicians and patients is driven by the pharmaceutical industry. The research and development of this industry pay off great dividends; the United States leads the world in the development of new pharmaceutical agents and is at the vanguard of innovation in health care. But there is a flip side. Disease awareness has become dependent on the pharmaceutical industry's awareness-raising activities. A recent analysis showed that the introduction of tegaserod was associated with an immediate rise in patient visits and new diagnoses of irritable bowel syndrome.[8] In this regard, CD has been left behind. It is a disease that is treated primarily with a diet. The diet can be difficult, expensive, and potentially unhealthy if not prescribed with close nutritional guidance, but for the majority of patients it is effective, and can result in a dramatic alleviation of the presenting signs and symptoms of CD.

Although there are many steps in the pathogenesis of CD, which could be the targets of potential drug therapies,[9] only 2 steps are currently under development.[10,11] CD remains largely a disease without a drug, and therefore keeps a low profile.

Not all patients with CD respond to the gluten-free diet. Some never respond in the first place, whereas others lose reponsiveness. The frequency of this phenomenon is unknown, and estimates of the prevalence of poorly responsive CD vary widely from 7% to 30% of all individuals with CD.[12] More recently, our understanding of refractory celiac disease (RCD) has been shaped by the crucial dichotomy between RCD types 1 and 2, the latter of which has a poor short-term prognosis and is closely associated with enteropathy-associated T-cell lymphoma.[13] These 2 types of RCD are differentiated by the T-cell make-up in the intestinal epithelium. A monoclonal T-cell receptor rearrangement and a loss of the normal CD3 surface expression and loss of CD4 and CD8 are indicative of RCD type 2, whereas a polyclonal T-cell receptor and normal expression of CD3/CD4/CD8 denote RCD type 1. As such, the use of immunohistochemistry, flow cytometry, and T-cell receptor polymerase chain reaction on intestinal biopsies has emerged as a valuable diagnostic and prognostic tool for assessing individuals with RCD.

Despite this advance and well-performed studies of the prognosis of RCD types 1 and 2 at referral centers,[14,15] we remain ignorant of the prevalence of these conditions. Much of this uncertainty stems from the fact that patients who do not respond to the gluten-free diet do not necessarily have RCD. Some may not have CD to begin with, and others may have one of several conditions associated with CD, such as small intestinal bacterial overgrowth,[16] microscopic colitis,[17] and pancreatic exocrine insufficiency.[18] Such conditions should be evaluated before the labeling of patients with RCD. Nevertheless, in 1 cohort of patients with or without symptoms undergoing follow-up biopsy, the proportion of patients with persistent abnormalities was found to be 34% in 5 years.[19] In that cohort, the lack of histologic recovery was associated with an increased risk of death, though this did not meet statistical significance.

Although that study likely overestimated the prevalence of persistent histologic abnormalities due to a selection bias, RCD type 1 may be quite common. But the issue remains understudied; the analysis of thawed serum has shown that the prevalence of CD has increased over the past 50 years,[20] but we do not have a grasp of whether RCD is increasing as well.

Once the diagnosis of RCD type 1 is established, drug therapy should be initiated, and there is currently a dearth of effective long-term options. Use of prednisone in conjunction with a gluten-free diet has been used successfully[21] but steroid use is not palatable in the long term, given the extensive side effect profile associated with chronic use. A more recent development has been the use of budesonide,[22,23] which presumably has the same mechanism of action as prednisone but has the advantage of limited systemic effects due to first-pass metabolism.

In the current issue of the *Journal*, Jamma et al[24] reported their initial experience with small intestinal release mesalamine (SIRM) for the treatment of RCD type 1. SIRM is a familiar drug to most gastroenterologists, as formulations of 5-aminosalicylic acid (5-ASA) have been used to treat inflammatory bowel disease for more than 60 years,[25] even before the discovery that it was the 5-ASA moiety, rather than the sulfa moiety, that was the active therapeutic component of sulfasalazine.[26] Sulfa-free 5-ASA compounds are commonly prescribed for the management of mild-to-moderately active Crohn's disease and ulcerative colitis,[27,28] and are generally well tolerated with an excellent safety profile. As some of the oldest drugs in our pharmacopeia, they have withstood the test of time.

The 10 patients reported by Jamma et al[24] were all considered to have RCD type 1 based on persistent symptoms in conjunction with persistent histologic abnormalities despite adhering to a gluten-free diet for at least 6 months. Careful assessment by a nutritionist (and seroconversion to a negative tissue transglutaminase level in 8 of the 10 patients) ruled out significant dietary nonadherence, and all the patients underwent immunohistochemical analysis (and a subset that underwent T-cell receptor polymerase chain reaction) to rule out RCD type 2. Assessment of other causes of persistent symptoms, such as autoimmune enteropathy and bacterial overgrowth, was made in selected patients, and all the 10 patients underwent colonoscopy so as to assess for microscopic colitis (4 of these 10 patients were diagnosed with concurrent microscopic colitis).

The patients were given open-label SIRM at a dose of 2 to 4 g/d, and the responders continued this medication for a range of 39 to 95 weeks. Overall, 5 of the 10 patients (50%) had a complete response, and an additional patient had a partial response. Subgroup analysis of this small sample showed that response did not significantly vary by concurrent budesonide use, Marsh grade, or whether the RCD type 1 was primary (ie, no initial response to the gluten-free diet) or secondary (ie, a loss of an initial response to the diet).

This pilot study is limited by its small sample size and lack of a placebo arm, and one should not interpret this study as evidence that we have an effective new (or, rather, old) drug for RCD type 1. Nevertheless, the study by Jamma et al[24] provides encouraging news on the potential use of 5-ASA compounds in the treatment of RCD type 1. Future studies, in addition to including a placebo control arm, would benefit from a more formal and validated response scale, such as the CD-related Quality of Life Survey[29] or the Celiac Symptom Index.[30] Patients with

microscopic colitis should first be treated for this coexistent condition before enrollment so as to confirm that the efficacy of mesalamine for RCD type 1 is because of its action on the small intestine, not on colonic activity.

Future studies of medical agents to treat RCD type 1 should also further elucidate the natural history of this disease. One outcome of potentially great importance is the follow-up histology after treatment with candidate drugs. Early experience with budesonide in the treatment of RCD type 1 showed that this drug provided symptomatic relief but did not result in improvement in histopathology.[23] Given the link between histologic abnormality and mortality among all individuals with CD[31] and given the recent hypothesized relationship between persistent duodenal pathology and mortality,[19] we should focus our investigative efforts on understanding and altering the natural history of CD and RCD. Just as emerging data are indicating that a "top-down" approach may favorably alter the natural history of Crohn's disease.[32] In the same vein, future research in RCD should determine whether new therapies including mesalamine result not just in symptomatic improvement, but in reversing the excess mortality associated with this condition.

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