Concise Commentary: Budesonide—When Going Gluten-Free Is Not Good Enough

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In this issue of *Digestive Diseases and Sciences*, Therrien et al. in a well-written, retrospective, observational study describe their experience with enteric-release budesonide in 42 patients with non-responsive celiac disease (NRCD) at two referral centers [1]. NRCD was defined as symptoms or signs suggestive of CD after at least 12 months of a gluten-free diet (GFD). They reported that 57% of the cohort had a clinical response to budesonide (i.e., patient-reported clinical improvement) and 66% of the responders had a complete clinical response (i.e., complete resolution of symptoms).

Budesonide has been shown previously to be effective in refractory celiac disease (RCD) which refers to persistent villous atrophy, with signs and symptoms of malabsorption after at least 12 months of GFD and for which other causes of NRCD were excluded. The current study provides evidence that its use can be extended to patients with CD who have persistent clinical symptoms despite their adherence to a GFD [1, 2]. Of note, they observed a superior clinical response to budesonide in patients with RCD (70%) compared with those who were eventually diagnosed with irritable bowel syndrome (11%) or gluten contamination (50%). Thus, the overall efficacy of budesonide in the NRCD population could be driven by the RCD group. It is imperative to eliminate the source of gluten contamination once it is identified in a patient with NRCD. Nevertheless, as the study shows, this can be difficult despite consultation with an expert dietitian.

The authors found that NRCD patients with diarrhea had a sixfold increased odds of responding to budesonide compared with those who did not, likely due to the anti-inflammatory effects of budesonide on the small intestinal mucosa, reducing the severity of diarrhea. The presence of fatigue

was inversely associated with response to budesonide possibly due to either high first-pass metabolism of budesonide or a lack of association of fatigue with gastrointestinal/systemic inflammation. Nevertheless, the effect of budesonide is not long-lasting, with symptomatic recurrence fairly common. (About 80% of responders had symptomatic relapse.)

Since only 38% of patients with a clinical response had mucosal healing, the short-term clinical efficacy of budesonide does not appear to be related to mucosal healing. Of note, the mucosal recovery in patients with type 1 RCD was significantly lower in this study (25%) compared with 67% observed by Mukewar et al. [1, 2], likely due to a significantly shorter mean duration of treatment with budesonide in the current study (16 weeks vs. 15 months) [1, 2]. Nevertheless, persistent villous atrophy was associated with clinical recurrence after stopping budesonide in responders. Thus, the long-term use of budesonide in patients with RCD could reduce mucosal inflammation, promote histological recovery, and achieve clinical remission.

In summary, budesonide may provide symptomatic relief in NRCD patients with diarrhea who are compliant with a GFD. Long-term budesonide with a slow taper might be necessary in the majority of patients with RCD as relapse is common.

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Compliance with Ethical Standards

Conflict of interest The author declares that there is no conflict of interest.

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