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EDITORIAL

The Role of Corticosteroids in Celiac Disease

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Since Dickie first described the benefits of a gluten-free diet in the 1940s and 1950s, this diet is the standard of care for all patients with celiac disease [1, 2]. For patients with a new diagnosis, dietary compliance can be difficult to achieve, possibly resulting in a clinical course marked by delayed recovery and persistent symptoms. This is of particular concern for patients in the developing world, where gluten-free food items may be difficult to obtain or to identify. While dietary modifications are likely to remain the treatment of choice in celiac disease, the use of adjuvant corticosteroids in newly diagnosed patients is a topic that has been addressed previously. In this issue of *Digestive Diseases and Sciences*, Shalimar et al. [3] revisit the concept of corticosteroids in the management of celiac disease, focusing on their effects on cellular death and regeneration. Their objective was to identify whether adjuvant treatment with corticosteroids can help expedite clinical and histological recovery in patients with newly diagnosed celiac disease.

The use of systemic corticosteroids for severe celiac disease is not new. Dr. Jerry Trier [4, 5] described their use in severe disease in 1978 and in subsequent reviews. Currently, the most common indication for the use of corticosteroids in celiac disease is the treatment of refractory symptoms. Refractory celiac disease is defined as persistent malabsorption symptoms and villous atrophy despite strict adherence to a gluten-free diet for 6–12 months [5, 6]. There are two subtypes of refractory celiac disease: type 1 disease is characterized by normal intra-epithelial lymphocytes, whereas type 2 disease is characterized by aberrant intra-epithelial lymphocytes of clonal origin. Type 2 disease has an extremely poor prognosis as it is considered a cryptic T cell lymphoma with a high rate of progression to enteropathy-associated T cell lymphoma (EATL) [6]. Although both subtypes respond to corticosteroids, type 1 patients may need additional immunosuppression, but usually do well, whereas those with type 2 disease may respond initially but often later deteriorate [6]. Corticosteroids, however, remain the mainstay of treatment for refractory celiac disease.

A second and less common indication for the use corticosteroids in celiac disease is for the treatment of life-threatening celiac crisis. Although rare, celiac crisis is associated with high morbidity and mortality rates and necessitates immediate intervention and supportive care [7]. The goal of treatment is to promptly reverse mucosal damage and metabolic derangements. Although corticosteroids have not yet been studied prospectively, they have historically been given to individuals who are not responding rapidly enough to gluten restriction. The authors of a recent retrospective study of patients with celiac crisis reported that patients who received corticosteroids experienced rapid clinical improvement within 2 weeks of treatment initiation and were eventually able to be maintained on a gluten-free diet alone [7]. The data from this study set a precedent for the short-term use of corticosteroids when prompt reversal of symptoms is needed.

Due to the systemic side effects of systemic corticosteroids, interest in locally active corticosteroids has increased. Evidence confirming their effectiveness in celiac disease first came from in vitro studies involving samples of intestinal mucosa in tissue culture. In 1981, Bramble et al. [8] examined intestinal enzyme activity in patients

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with celiac disease following in vitro exposure to gluten. They reported that while intestinal enzyme activity was reduced in the presence of gluten, the effect was overcome when corticosteroids were added to the culture medium. Intra-epithelial lymphocyte counts also decreased in specimens treated with corticosteroids. This success was later translated into a clinical study: Bramble et al. [9] reported symptomatic improvement in patients taking locally active corticosteroids despite their continuation of a regular diet. These results were later confirmed by Mitchison et al. [10], who reported clinical and histological improvement in celiac patients consuming a regular diet while taking a locally active corticosteroid. The success of these studies was somewhat mitigated by the finding that systemic corticosteroid absorption occurred. Despite the benefits accruing from these early studies, the use of locally active corticosteroids in celiac disease has received little attention until recently.

Topically active enteric corticosteroids are frequently used in the management of immune-mediated digestive diseases. Budesonide has been formulated as an enteric-coated controlled-release capsule used primarily in the treatment of inflammatory bowel disease. It has low systemic bioavailability while delivering active glucocorticoid to the distal small intestine and colon; as such, it is appropriate for Crohn's disease patients [11–13]. Recent studies have confirmed its efficacy in patients with celiac disease. Daum et al. [14] reported a similar efficacy between systemic and enteric-coated corticosteroids by demonstrating a lack of relapse in patients who were switched from prednisolone to budesonide. A retrospective study conducted by Brar et al. [15] also demonstrated improvement in refractory disease using stool frequency and body mass index as outcome measures in patients solely treated with budesonide. The availability of this new topically active glucocorticoid has once again sparked discussion regarding the use of newer corticosteroid formulations in the management of "classical" celiac disease.

The most recent study involving budesonide, by Ciacci et al. [16], was conducted in patients with classical celiac disease and was designed as a prospective, randomized in vivo/in vitro pilot study comparing treatment with a gluten-free diet and budesonide to that with a gluten-free diet alone. The study design involved administering the capsule contents in the presence of acid suppression. A statistically significant decrease in stool frequency and 24-h stool weight was reported in the budesonide group. Clinical improvement was supported by the findings of the in vitro study, in which decreased cellular inflammatory markers were reported in celiac-positive, gliadin-exposed mucosa treated with budesonide. The results of this study supply the impetus to re-evaluate the role of short-term glucocorticoids in the treatment of classical celiac disease on both a clinical and immunohistological level. Currently, the contents of budesonide capsules is used only for poorly responsive and refractory patients. In Shalimar et al.'s paper [3], budesonide was not used, despite its availability in India (A. Puri, personal communication).

The recent focus on combined in vivo and in vitro investigations, as present in the studies by Shalimar et al. [3] and Ciacci et al. [16], demonstrates a need to further understand the mechanism underlying mucosal injury and recovery in celiac disease. Identifying the precise mechanism of injury will enable the creation of tailored therapies to expedite clinical and histological improvement. The studies by Moss et al. [17] and Di Sabatino et al. [18] focus on cellular markers of apoptosis and correlate with the leading hypothesis that mucosal injury in celiac disease is related to an increased rate of programmed cell death in the face of gliadin exposure. Corticosteroids, in systemic and local formulations, inhibit inflammation and enterocyte death through a mechanism that remains to be fully elucidated.

There is considerable interest among celiac disease subjects in the development of therapies or medications that complement the gluten-free diet [19]. Reformulation of budesonide so it is released in the upper small intestine appears to be a reasonable option, especially for celiac subjects with severe symptoms or refractory disease.

Finally, the study conducted by Shalimar et al. [3] refocuses our attention on the concept of celiac disease as an international problem. Through an increased availability of serological screening tests there is a greater awareness of celiac disease on a worldwide level [20]. This study highlights India as one such country and provides an innovative yet sensible approach to dealing with celiac disease in the developing world. While therapies involving a gluten-free diet and enteric-coated budesonide may seem reasonable to those in developed nations, therapies that are practical and economically feasible for large populations in the developing world need to be further investigated.

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