EDITORIAL

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Seeking to understand non-responders to ablative therapy for dysplastic Barrett's esophagus

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See "Bile acid sequestrants in poor healing after endoscopic therapy of Barrett's esophagus" by Lukas Welsch, Andrea May, Tobias Blasberg, et al., Clin Endosc 2023;56:194–202.

The ablation of dysplastic Barrett's esophagus (BE) has been a mainstay of endoscopic therapy for BE since the landmark publication by Shaheen et al.[1] demonstrated the effectiveness of radiofrequency ablation (RFA). In that study, complete eradication of BE was observed in 77.4% of patients in the RFA group. More importantly, this study reported a lower rate of disease progression in the ablation versus control group. In a bivariate analysis of the ablation group, individuals who were younger and had shorter BE segments, a lower body mass index, and a shorter history of dysplasia were more likely to experience complete eradication of intestinal metaplasia (CE-IM), although none of these factors were significant in the multivariate analysis.[1] Subsequent studies demonstrated that patients with an incomplete response to ablation are more likely to have longer BE segments, more reflux, and a larger hiatal hernia.[2,3] Furthermore, incomplete healing between ablation sessions results in a lower likelihood of achieving CE-IM.[4]

However, little is known about patients who do not experience CE-IM and those with poor healing between ablative sessions. In a meta-analysis, CE-IM was achieved in 78% of patients undergoing ablation therapy.[5] Given that up to 20% to 25% of individuals undergoing ablative therapy for BE with dysplasia will not attain complete eradication, further study of this cohort is essential. We also know from the landmark trial for ablation in BE[1] that the patients underwent a mean 3.5 ablations; therefore, it is less likely that patients will achieve complete eradication after 1 to 2 episodes, especially in cases of longer segments. This occurred despite the application of ablative therapy to the entire BE segment. Therefore, it is important to clearly understand the group of non-responders who may be a subset of those with poor healing or response, ultimately resulting in a lack of complete eradication.

In this issue of *Clinical Endoscopy*, Welsch et al.[6] reported the role of bile acid sequestrants in cases of poor healing after endoscopic ablation therapy for BE with dysplasia. The authors ought to be commended for investigating the subset of patients with a less than desirable outcome after ablation. In this study, 12% of patients (76/627 patients) experienced insufficient healing at 8 to 12 weeks with insufficient healing defined as (1) ulceration or (2) >30% of the ablated area with persistent BE on follow-up endoscopy. It is important to note that the majority of individuals respond to ablative therapy, while non-responders represented only 12% of the total population. Regardless, with the large cohort of individuals undergoing ablation therapy for BE worldwide, there is a large population of non-responders; thus, understanding this group is important to enable more effective therapy.

In the population of non-responders (n=76), healing was

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accomplished in 13 patients after intensifying proton pump inhibitor (PPI) therapy, suggesting a lack of adequate acid control. Forty-eight patients were started on bile-acid sequestration (most commonly cholestyramine 4.5 g three times daily) and resulted in complete healing in 29 patients (60%), partial healing in five (10%), and no response in 11 (23%). These data suggest that, in a subset of patients with poor healing and a lack of response to more intensive PPI therapy for an additional period, bile acid sequestrants may be beneficial. In the multivariate analysis, longer BE segments and larger hiatal hernias were associated with inadequate healing, a phenomenon supported by prior publications.[2,3]

The authors' trial of bile acid sequestration is interesting and compelling in a subset of non-responders to ablation despite intensive post-ablation PPI use. However, these data should be analyzed with caution. First, the study was retrospective and could not control for unmeasured or unknown variables, including those mentioned by the authors such as body mass index and smoking status. Additionally, most patients were treated with argon plasma coagulation (67.5%) or hybrid argon plasma coagulation (4.8%), whereas only 5.4% were treated with RFA. As most of the literature on ablation for BE involves RFA or cryotherapy, it is difficult to determine whether these results would be similar in a population treated with these ablative therapies. RFA is a more uniform ablative therapy in terms of both extent and likely depth of ablation. Finally, we do not know the exact number of individuals with insufficient healing due to ulcerations versus a lack of >30% response to ablation. In particular, the assessment of a response >30% can be subjective and may be due in part to the ablative technique or depth. In essence, the group of non-responders may comprise two different cohorts: (1) those with poor healing of the ablated mucosa as demonstrated by persistent ulceration; and (2) those with poor response to ablative therapy without adequate neosquamous mucosa on follow-up endoscopy.

Regardless of these limitations, the data from this study suggested that the use of bile acid sequestrant therapy resulted in healing among a significant proportion of non-responders. Previous *in vivo* and *in vitro* studies demonstrated that bile acids may play a role in the carcinogenesis of BE.[7-9] Conceptually, treatment with bile acid sequestration, as in this study, could improve outcomes, particularly in non-responders to PPI therapy. Even based on limited data, the use of bile acid sequesters is low risk, particularly in the population of individuals with dysplastic BE who do not respond well to ablation.

In summary, Welsch et al.[6] should be commended for their work aiming to better understand non-responders to ablative therapies for BE. In this subset of non-responders with inadequate healing despite a longer duration of PPI therapy, bile acid sequestration remains a clinical consideration, particularly given the safety profiles of these medications. However, further data are needed to support the widespread use of bile acid sequestration medications before we can wholeheartedly recommend this therapy.

Conflicts of Interest

The author has no potential conflicts of interest.

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