Mongersen, an Oral *SMAD7* Antisense Oligonucleotide, and Crohn's Disease

TO THE EDITOR: Monteleone and colleagues (March 19 issue)[1] show encouraging results regarding the use of mongersen, an oral antisense *SMAD7* oligonucleotide, for the treatment of Crohn's disease. SMAD7 protein binds the transforming growth factor (TGF) β1 receptor, with concomitant inhibition of antiinflammatory TGF-β signaling. Mongersen-mediated reduction of SMAD7 protein through the degradation of its messenger RNA is therefore an attractive strategy for restoring TGF-β signaling. After translation, SMAD7 is also regulated by acetylation of its lysine residues.[2,3] Deacetylation of SMAD7 by histone deacetylases (HDACs) increases the degradation of SMAD7, with derepression of TGF-β signaling. However, HDAC inhibitors, such as *n*-butyrate (produced within the colon by its normal microbiome), have been implicated in the reduction of immune-mediated inflammation within the bowel.[4] Indeed, the depletion of *n*-butyrate–forming bacteria may be deleterious in patients with inflammatory bowel disease. HDAC inhibitors are also antifibrotic.[5] Decreases in SMAD7 translation that are caused by mongersen may potentiate HDAC inhibition therapy in patients with inflammatory bowel disease. As SMAD7 production is decreased by mongersen, its deacetylation-mediated breakdown pathway becomes redundant. The antiinflammatory and antifibrotic effects of HDAC inhibition could therefore be exploited without a resulting increase in deleterious SMAD7 activity.

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THE AUTHORS REPLY: We agree with Kennedy that HDAC inhibitors, such as short-chain fatty acids, have the potential to be used as treatment for inflammatory bowel diseases. However, it is difficult to foresee whether combination therapy with mongersen would be more advantageous than treatment with single compounds for the control of inflammatory responses in the gut. In theory, HDAC inhibitors should increase, rather than inhibit, SMAD7 expression, since SMAD7 acetylation on lysine residues prevents ubiquitination-driven proteosomal degradation. Thus, if a combined therapy were adopted, the beneficial effects of mongersen could be partly hampered by HDAC inhibitor–induced stabilization of SMAD7 protein. SMAD7 is overexpressed in T cells and epithelial cells in inflammatory bowel disease, and it remains unknown whether short-chain fatty acids act as HDAC inhibitors in these cells as well as in macrophages. It is also unknown whether short-chain fatty acids and other HDAC inhibitors promote deacetylation of SMAD7 in the presence of elevated levels of the acetyltransferase p300, which is overexpressed in inflammatory bowel disease and promotes SMAD7 acetylation and stabilization. We believe that further experimentation is needed to explore this proposed mechanistic interaction.

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