Oral SMAD7 Antisense Oligonucleotide: A Novel Agent for Management of Crohn’s Disease

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Editorial

Inflammatory bowel disease (IBD) comprises two major disorders: Crohn's disease and Ulcerative colitis. They affect approximately 1.4 million Americans and several million people worldwide. The peak incidence of onset is among patients between the age groups of 15 and 30. It can affect the gastrointestinal tract anywhere from the mouth to anus but most commonly involves the ileum and colon. Transmural inflammation is the hallmark and it can be associated with strictures, granulomas, fistulas and patients are at a higher risk of colorectal malignancy. Host-microbiome interactions involving inappropriate immune response to the microbial flora in the intestines in a genetically susceptible host have been postulated as the pathogenesis of IBD. The lamina propria of the intestinal wall has a complex composition of immune cells maintaining a balance between immune tolerances and defending the body against pathogens. Infiltration of the lamina propria with innate immune cells (macrophages, neutrophils, natural killer cells and dendritic cells) and adaptive immune cells (B cells and T cells) is characteristic of IBD. Disturbance in the balance of these immune cells causes unchecked activation of these cells leading to increased levels of tumor necrosis factor α (TNF-α), interferon-γ, which along with SMAD 4 translocate to the nucleus and cause inflammation. This cytokine ultimately lead to leucocyte migration and recruitment in the microvasculature leading to inflammation in Crohn's disease. TGF-β1 serves as a negative regulator of the immune response to T-cells and acts through the SMAD (small 'mothers against' decapentaplegic) group of proteins. TGF-β1 is a cytokine with multiple functions responsible for growth, differentiation and proper functioning of the immune cells. It initiates signaling through ligand dependent activation of a Series of transmembrane kinases through type I and type II receptors which lead to phosphorylation of SMAD proteins. Most important among them are SMAD 2 and SMAD 3 which along with SMAD 4 translocate to the nucleus and cause transcription of genes [2]. In Crohn's disease, the abnormal inflammation is due to the decreased activity of TGF-β1 which leads to increased levels of SMAD7 protein. Binding of SMAD7 protein to the TGF-β receptor inhibits the normal immunosuppressive TGF-β1 signaling pathway leading to inflammation. The exact mechanism of increased production of SMAD 7 protein in IBD is not clearly understood but it has been hypothesized that increased activation of TNF-α, IL-1 and interferon-γ, which are increased in IBD mucosa can increase the levels of these proteins. Studies have shown that disruption in the SMAD 3 protein has resulted in decreased response of TGF-β1. Monteleone et al. demonstrated that there were increased levels of SMAD 7 proteins in intestinal mucosal samples of IBD patients analyzed by Western blot analysis [3]. This was associated with down regulation of phosphorylated SMAD 3 proteins. Treating the mucosal samples with SMAD 7 antisense or sense oligonucleotide demonstrated increased activity of TGF-β1 signaling and also leading to reduced activity of the pro-inflammatory cytokines like TNF-α and interferon-γ. These results of this prompted clinical trials targeting SMAD 7 proteins. Mongersen is a 21-base single-stranded phosphorothioate oligonucleotide that hybridizes with the human messenger RNA for SMAD 7 protein causing RNAse H-mediated degradation of the RNA through an antisense mechanism [4]. It is an oral medication designed to be released in the ileum and colon for local effects, by pH- dependent coating of the tablet with methacrylic acid–ethyl acrylate copolymers. In their study, Monteleone et al. demonstrated that patients taking oral Mongersen 40 mg or 160 mg daily demonstrated clinical remission with Crohn's disease activity index score (CDAI)<150 at the end of 15 days in comparison to 10 mg/day and placebo population. At the end of 28 days, patients on 160 mg/day, 40 mg/day and 10 mg/day demonstrated a 100 point clinical response (CDAI score reduction ≥ 100 points) which was significantly higher than the placebo population. These results were similar to other phase 2 trials for treatment of Crohn's disease with novel medications. Further studies to determine the right dose and regimen, duration and long term use of this medication, safety and efficacy in comparison to the currently available therapies are needed. Assessment of mucosal healing in response to the drug can also be assessed by ileocolonoscopy. Also the incidence of fibrosis due to higher dosage or long term use should be determined as TGF-β1 is known for its fibrotic potential. SMAD 7 proteins can also be degraded by deacetylation due to histone deacetylases (HDAC). But HDAC inhibitors like n-butyrate, which is produced by the fermentation of dietary fiber by the colonic bacteria has been shown to inhibit the pro-inflammatory cytokines in the colon and reducing the inflammation [5]. Studies have shown that n-butyrate acts as an inhibitor of NF-kB which prevents its nuclear translocation but the exact mechanism remains controversial. Short chain fatty acids (SCFA) which are also formed due to bacterial fermentation in the colon have been shown to have immune-modulatory effects on macrophages reducing pro-inflammatory cytokines but exact mechanism is unclear. Further studies are needed to show if combination of Mongersen which causes SMAD 7 degradation and HDAC inhibitors which have shown anti-inflammatory and anti-fibrotic properties would be beneficial, as they act through two independent mechanisms producing opposite effects on SMAD 7 protein levels.

References
