Growing understanding of the complex pathophysiological pathways that underpin inflammatory bowel disease (IBD) has led to the introduction of many biological agents and small molecules that target different pathways, T cell function and one or more cytokines – for example tumour necrosis factor (TNF), Janus kinases and various interleukins, notably IL-17 and IL-23. Such agents are effective in the treatment of severe active IBD when other options have failed but they maintain mucosal healing in only one-third to one-half of people with Crohn’s disease or ulcerative colitis.\(^1,2\)

The search therefore continues for new therapeutic targets, with mixed success. SMAD7 antisense oligonucleotides

Transforming growth factor beta (TGF-\(\beta\)) is a cytokine that downregulates inflammation in the intestinal tract. Levels are raised in intestinal tissue in IBD but they are not sufficient to suppress chronic inflammation, in part due to raised levels of SMAD7, a protein that inhibits TGF-\(\beta\). The mucosal expression of SMAD7 can be reduced by an antisense oligonucleotide – a synthetic single-stranded portion of DNA matching the region of human DNA responsible for SMAD7 synthesis that, after oral administration, is taken up by epithelial and lamina propria cells.\(^3\)

In 2015, a phase 2 trial in 166 patients with active moderate to severe Crohn’s disease (median Crohn’s disease Activity Index [CDAI] score 240–264), of whom about one-quarter were treated with immunosuppressants, showed that treatment with the oral SMAD7 antisense oligonucleotide mongersen (40mg or 160mg) daily achieved remission (CDAI score <150 at day 15, maintained for two weeks) in 55–65% of patients vs 10% with placebo.\(^4\) At day 28, clinical response rates (reduction in CDAI score \(\geq\)100) were 58–72% (vs 17% with placebo).

A recent uncontrolled phase 2 trial reported endoscopic results after treatment with mongersen 160mg daily in patients with active Crohn’s disease.\(^5\)
Of 52 patients with evaluable endoscopy after 12 weeks, an endoscopic response (≥25% reduction in endoscopic score) occurred in 37% and two patients were in endoscopic remission. Although these results seem promising, manufacturer Celgene announced in October 2017 that it was terminating trials of mongersen for the treatment of Crohn’s disease following disappointing efficacy data from a phase 3 trial. Celgene also stated it would review its role in treating ulcerative colitis after evaluating the results of a phase 2 trial.ª

**Sphingosine-1-phosphate receptor modulators**

Sphingosine-1-phosphate receptors (S1PRs), of which there are five subtypes, are cell surface proteins with multiple functions. S1PR subtype 1 is the main mediator of lymphocyte trafficking from lymph nodes. Fingolimod, introduced in 2011 for the treatment of multiple sclerosis, is a non-selective S1PR modulator. Several S1PR modulators are now undergoing clinical trials in patients with IBD (and multiple sclerosis), of which ozanimod, an oral selective S1PR1/S1PR5 modulator, is now being evaluated in a phase 3 trial as induction and maintenance therapy in patients with Crohn’s disease and ulcerative colitis (see www.clinicaltrialsregister.eu).

Phase 2 data have been published from the TOUCHSTONE trial in patients with ulcerative colitis.ª TOUCHSTONE randomised 197 adults with moderate to severe ulcerative colitis to receive placebo or treatment with ozanimod 0.5mg or 1.0mg daily. The primary endpoint was clinical remission at week eight (defined as Mayo Clinic score ≤2 with no subscore >1; the maximum possible score on this scale is 12). About one-third had previously been treated with an immunosuppressant and one-quarter with a TNF inhibitor; one third were using a steroid and 80% were using an aminosalicylate during the trial.

After eight weeks, the proportions of patients in clinical remission were 6% with placebo, 14% with ozanimod 0.5mg daily (p=0.14 vs placebo) and 16% with ozanimod 1mg daily (p=0.048 vs placebo). Other analyses were considered exploratory: clinical response rates were 37% with placebo, 54% with 0.5mg ozanimod and 57% with 1mg ozanimod, and mucosal healing rates were 12%, 28% and 34% respectively.

After 32 weeks, remission rates were 6% with placebo and 26% and 21% with ozanimod 0.5mg and 1mg daily. Clinical response rates were 20%, 35% and 51% respectively and mucosal healing rates changed little compared with week eight (12%, 32% and 33% respectively). There were no important differences in adverse effects. Most patients in TOUCHSTONE entered an open-label extension study (so far unpublished).ª Outcomes were available for 100 patients after 92 weeks: physician global assessment found little or no active disease in 91% of patients and 97% had little or no blood in their stools. There were no new safety signals.

Data from the so-far unpublished open-label phase 2 STEPSTONE trial provide endoscopic outcomes in patients with moderately to severely active Crohn’s disease after 12 weeks’ treatment with ozanimod 1mg daily.ª Reductions in endoscopic score of ≥50% and ≥25% occurred in 27% and 43% of patients respectively.

**Summary**

SMAD7 and S1PR are new therapeutic targets in the treatment of moderate to severe active IBD. So far, results have been disappointing for SMAD7 inhibition and, for S1PR modulators, possibly no more effective than current options with limited but encouraging evidence of safety. Phase 3 trials will provide more definitive evidence of the benefits of ozanimod, after which further research will be needed to compare it with biological agents.

**References**


**Declaration of interests**

None to declare.

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