Reply

ALEXANDER C. FORD
Leeds Gastroenterology Institute
St. James's University Hospital *and*
Leeds Institute of Biomedical and Clinical Sciences
University of Leeds
Leeds, UK

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Conflicts of interest
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Reply. We thank Black et al for their interest in our recent publication describing the results of the largest randomized controlled trial with peppermint oil in irritable bowel syndrome (IBS) to date.[1]

Black et al have updated their previous meta-analysis adding our data for global relief of IBS symptoms, which did not result in an overall change in efficacy numbers for peppermint oil. When pooling results for purposes of meta-analyses, the different outcome measures used across studies have to be considered. In this sense, the results of our current study might not necessarily be "at odds" with previous meta-analyses, as Black et al suggest, but merely a consequence of our study being the first and only to use the rigorous and rather stringent US Food and Drug Administration/European Medicines Agency (FDA/EMA) responder criteria. The widening of the uncertainty around the estimate of efficacy, as demonstrated by the updated meta-analysis, is therefore likely related to the broad array of different outcome measures used in the included studies. This is in itself not unique to peppermint oil trials, but to all trials in patients with functional gastrointestinal disorders in which assessment of efficacy relies on patient-reported outcomes owing to the relative lack of adequate biomarkers.

Our study underscores the large impact of clinical outcome definition in IBS as this has important repercussions in terms of trial data interpretation. Since the introduction of the FDA/EMA end points, novel drugs for IBS that have been assessed for efficacy according to these new guidelines, all have had fairly modest therapeutic gains between 8.3% and 14.4%. Accordingly, all studies investigating linaclotide,[2,3] plecanatide,[4] eluxadoline,[5] rifaximine,[6] and more recently tenapanor[7] have used rather large sample sizes (between 606 and 1135 patients) to demonstrate statistically significant differences versus placebo. Trials of such magnitude necessitate considerable effort and financial support, the latter not readily available via sources of public funding. It is reasonable, however, that such a high threshold is maintained for market authorization of novel drugs, allowing proper comparison even in the absence of head-to-head trials. Nevertheless, such rigorous efficacy assessment has not been done for other traditional forms of pharmacotherapy generally used in IBS, such as tricyclic antidepressants or selective serotonin reuptake inhibitors.

It is also important to realize the context in which such efficacy assessment is performed, that is, whether it is related to potential market authorization (regulatory purposes) or to ascertain a clinically relevant effect. In this regard, it has previously been suggested that other outcome measures that might be less robust than the FDA/EMA end points, such as the "moderate symptom relief response rate" (which adopts a different threshold to the degree of relief and embodies the smallest difference in score regarded as beneficial), might be of superior or at least equal importance when guiding clinical decision making.[8]

When using this moderate relief end point, that is, a symptom relief score of $\geq$5 (moderate relief) on a 0–7 scale, we found a significant difference of 18.4% in response rate between small intestinal release peppermint oil and placebo (38.7% vs 20.3%; odds ratio, 2.47; 95% confidence interval, 1.09–5.56; $P = .030$). Although this did not reach the prespecified level of statistical significance for exploratory secondary outcomes (alfa = 0.025), these results and results from other secondary efficacy analyses, such as the significant effect on the IBS Severity Scoring System, underscore the beneficial clinical effects of therapeutic agents potentially missed when not taking into account other outcome definitions. This finding is of particular importance in a multidimensional disorder such as IBS, when a single outcome measure might not capture the entirety of the disorder.

Although harmonization of trial design in IBS is definitely warranted and the introduction of the (provisional) FDA/EMA end points represent an excellent step in the right direction, we advocate for a broader assessment of overall drug efficacy to provide additional valuable information to make treatment decisions specific to the individual patient.

We therefore agree with Black et al that our trial adds to the knowledge on peppermint oil in IBS, covering for the first time both strict end points according to regulatory guidelines and other clinically relevant but less robust end points. In addition, we fully agree with Black et al, who mention the need for corroborating results in a primary care population. We would like to point out that our study population included 109 patients (57.7% of the overall population) recruited from primary care and by this in itself

represents the largest of such population examined with regards to peppermint oil efficacy.

ZSA ZSA R.M. WEERTS
AD A.M. MASCLEE
DAISY M.A.E. JONKERS
DANIEL KESZTHELYI
Division of Gastroenterology and Hepatology
Department of Internal Medicine
NUTRIM School for Nutrition and
Translational Research in Metabolism
Maastricht University Medical Center
Maastricht, the Netherlands

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Conflicts of interest
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Two Sides of the Same Coin: The Roles of Transforming Growth Factor-β in Colorectal Carcinogenesis

Dear Editors,

We read with great interest the article by Gu et al,[1] which investigated impaired transforming growth factor (TGF) beta signaling and its link with carcinoembryonic antigen-related cell adhesion molecule family and microbiome in colorectal carcinogenesis (CRC). The authors found that TGF-β signaling-deficient mice spontaneously developed adenomas and CRC with altered health microbiome in the gut. Moreover, the authors found that overexpression of carcinoembryonic antigen-related cell adhesion molecule promoted cell proliferation and colony formation via inhibition of TGF-β pathway activity. Intriguingly, the authors showed that the stemness of CRC was inversely correlated with the TGF-β pathway activity, which is different with the scenarios in breast cancer, liver cancer, gastric cancer, skin cancer, glioblastoma, and leukemia, showing that TGF-β is a positive regulator for cancer stem cell identity.[2] This finding further supports the notion that TGF-β can either work as tumor suppressor or inducer depending on different contexts (eg, TGF-β is a tumor suppressor in normal tissue and early cancer cells, whereas TGF-β frequently plays a protumorigenic role in advanced stages of cancer).[3] For example, TGF-β can promote epithelial-to-mesenchymal transition, cell proliferation, and metastasis, and suppress the immune response, which are critical for cancer progression. Furthermore, TGF-β maintains the self-renewal and pluripotency of human embryonic stem cells, and has been similarly implicated in promoting the stem cell-like characteristics of cancer stem cell by promoting their self-renewal and expression of stem cell factors. In other cell types, TGF-β signaling can induce cell cycle arrest by upregulating cyclin-dependent kinase inhibitors, induce apoptosis, regulate autophagy and suppress inflammation.[3] Considering this dual function of the pathway, cellular heterogeneity and dynamics of colorectal cancer stem cells,[4] it will be interesting to compare the activity and functionality of TGF-β signaling pathway in the cancer stem cells from primary and metastatic CRC.

The multitude, contrasting, and context-dependent function of TGF-β signaling pathway makes it also challenging to use as a target for therapeutic applications. Currently, monoclonal antibodies and inhibitors targeting TGF-β have been used in clinical trial (ClinicalTrials.gov Identifier: NCT01291784, NCT00043706, NCT02452008, NCT02581787) to treat myofibrosis, systemic sclerosis, metastatic prostate, and non-small cell lung cancer, respectively. Considering the difficulty of predicting the effects of all TGF-β blocking from the current strategies, especially the potential CRC risk inferred from the study by Gu et al, it might be important to monitor the gut microbiome and incidence of CRC in the patients during long-term follow-up. Moreover, because TGF-β is a critical regulator in the balancing of tolerance and response of the gut immune system,[5] the impact of anti-TGF-β therapy on the immune homeostasis of the gut should not be overlooked.

Mechanistically, the pleiotropic nature of TGF-β signaling pathway may largely rely on the interaction partners of Smad2/3 transcription factors and the functionality of Smad4 in the TGF-β pathway. For example, FoxH1, ID1, or other cofactors that can facilitate the activation of specific transcriptional programs to enhance the protumorigenic arm of TGF-β signaling (eg, up-regulation of stem cell factors and developmental plasticity of cancer stem cells, stimulation of epithelial-to-mesenchymal transition, cell migration, angiogenesis, chemoresistance, immune-suppressive functions etc) while removing its antitumorigenic arm (eg, induction of cell cycle arrest, apoptosis, autophagy, tissue inflammation, etc).[6] Thus, in the future, it will be vital to specifically manipulate the downstream signaling interaction partners/cofactors of