A Multi-Centre, Parallel Group, Randomised Placebo Controlled Trial of Mesalazine for Treatment of Diarrhoea-Predominant Irritable Bowel Syndrome (IBS-D)

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Introduction: Irritable bowel syndrome with diarrhoea is a common outcome after inflammation due to bacterial gastroenteritis. Several studies have shown on going immune activation in the mucosa of IBS-D patients and a number of studies have suggested that Mesalazine(M) may provide benefit including a reduction in stool frequency. Our aim was to compare the effect of M versus placebo on stool frequency, powered at 90% using 1% significance level. Secondary aims were to assess effect of M on abdominal pain, stool consistency, satisfactory and relief of IBS symptoms. Methods: Eligibility was based on a 2-week baseline stool diary with a daily stool frequency of ^{3}3 for more than 2 days/week and stool consistency of ^{3}25% type 5-7 and ^{2}25% type 1-2 according to the Bristol Stool Form Scale. Baseline colonoscopy/ sigmoidoscopy was performed to exclude microscopic or inflammatory colitis. Medications that may affect the gut motility and anti-inflammatory drugs were excluded from the study. Participants were randomised using a concealed web-based system to take either 2g M/ placebo (P) for a week, increasing to 2g twice a day for the remaining 11 weeks if tolerated. All participants completed a 12-week stool diary, and Hospital and Anxiety (HADS), Patient- Health (PHQ15) and EQ-5D questionnaires at baseline and end of study. At the end of each week in the stool diary, participants were required to answer ‘yes' or ‘no' to the question "Have you had satisfactory relief of your IBS symptoms this week?". The primary outcome of stool frequency and other clinical outcomes were based on a stool diary completed during weeks 11-12. A satisfactory relief of IBS symptoms was defined as answering ‘yes' to weeks 11 and 12 of the stool diary. Compliance with treatment was defined as taking ^{3}75% of medication during the study. Participants and outcome assessors were all blinded to allocation. Results: 68 patients with IBS-D, meeting the Rome III criteria, were randomised to each

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group. 20 patients withdrew from the study and 1 patient had incomplete stool diary. Mean (SD) age was 47.1(13.5) years in P and 42.6(15.2) in M, F: M ratio was similar at 40:28 in P and 42:26 in M. Treatment compliance for P and M were 59% and 58%. Analysis by intention to treat showed M did not improve bowel frequency, abdominal pain and stool consistency compared to P during the last 2 weeks. Treatment did not affect satisfactory relief of IBS symptoms, HADS, PHQ15 and EQ5D VAS scores compared to P. See Table 1 for results. Conclusion: This large study rules out any clinically meaningful benefit or harm of M compared with P. Better understanding of the underlying disease mechanisms are needed to allow more effective targeting of treatment in these patients.

Table 1

Mean(SD)	Baseline placebo (n=58)	Final 2 weeks placebo (n=58)	Baseline Mesalazine (n=57)	Final 2 weeks Mesalazine (n=57)	Between group difference at week 11-12*(95% CI)	P value
Daily mean stool frequency	3.6 (1.8)	2.7 (1.9)	3.6 (1.6)	2.8 (1.2)	0.1 (-0.33,0.53)	0.658
Daily mean abdominal pain (0-10)	3.6 (2.0)	2.2 (2.1)	4.1 (2.2)	2.8 (2.1)	0.07 (-0.54,0.68)	0.828
Mean stool consistency	5.6 (1.0)	4.7 (1.1)	5.4 (0.7)	4.7 (1.0)	0.13 (-0.21,0.48)	0.452
No. of patient had satisfactory relief of IBS symptoms	0	24	0	25	1.13** (0.51,2.47)	0.762
HADS score	8.6 (4.3)	6.9 (3.6)	9.0 (4.5)	7.5 (5.0)	0.67 (-0.38,1.72)	0.21
PHQ15 score	13.1 (5.6)	9.4 (5.0)	12.6 (5.2)	10.0 (5.2)	0.63 (-0.93,2.20)	0.428
EQ-5D VAS score	64.3 (20.2)	69.7 (18.3)	64.2 (20.6)	72.6 (19.2)	2.39 (-3.24,8.02)	0.406