HIGHLIGHTS FROM THE UEG WEEK CONGRESS 2014: NEW EVIDENCE AND NOVEL THERAPIES FOR IRRITABLE BOWEL SYNDROME

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ABSTRACT

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder that affects up to 15% of the European and North American population, and is characterised by abdominal pain, bloating sensations, cramping, constipation, and diarrhoea. Main subtypes of IBS include constipation-predominant IBS (IBS-C), diarrhoea-predominant IBS (IBS-D), and mixed diarrhoea and constipation-associated IBS (IBS-M). The pathophysiology of IBS is still unclear, but important factors such as alterations in the brain-gut axis, bacterial overgrowth in the intestines, increased paracellular permeability, disruptions in the immune system, and accrued visceral sensitivity have been suggested. While many therapies are available to treat the symptoms associated with IBS, on a symptom-by-symptom basis, there are few effective treatments for IBS itself, including linaclotide, which was approved 2 years ago in Europe but only for IBS-C. Additional disease-modifying therapies to slow disease progression or achieve remission are needed as this represents a substantial unmet need. New emerging data on the pathophysiology of IBS are certainly promising; better knowledge of the underlying mechanisms will help refine the management of IBS, both in terms of diagnosis with the development of biomarkers, and in terms of therapeutic management with new pharmacological targets. Additional treatment options will be welcome given the variety of disease subtypes and presentations. The United European Gastroenterology (UEG) Week Congress, which was held in Vienna, Austria, 18th-22nd October 2014, was an excellent opportunity to share new findings on the pathophysiology and new clinical evidence and emerging therapies in the management of IBS. Selected abstracts received additional exposure through the "Posters in the Spotlight" session and the "Posters of Excellence" award; such abstracts will be developed in this review.

Keywords: Irritable bowel syndrome, immune system, pathophysiology, linaclotide, zonulin, permanent sacral nerve stimulation, Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (FODMAP)-restricted diet, cyclic guanosine monophosphate (cGMP), colonic tone, somatisation.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder that affects up to 15% of the European and North American population,[1-3] and that is characterised by abdominal pain, bloating sensations, cramping, constipation, and diarrhoea.[4] Main subtypes of IBS include constipation-predominant IBS (IBS-C), diarrhoea-predominant IBS (IBS-D), and mixed diarrhoea and constipation-associated IBS (IBS-M).

While the pathophysiology of IBS is still unclear, important factors such as alterations in the brain-gut axis, bacterial overgrowth in the intestines, increased paracellular permeability, disruptions in the immune system, and accrued visceral sensitivity have been suggested.[5-8] The United European Gastroenterology (UEG) Week Congress - held in Vienna, Austria, from 18th-22nd October 2014 - was an excellent opportunity to share new findings on the pathophysiology and new clinical evidence and emerging therapies in the

management of IBS. The UEG Week Congress gave additional exposure to select abstracts through the "Posters in the Spotlight" session, a new category introduced in 2014, aiming to promote hot topic research and providing in-depth scientific debates led by experts in the field; poster presenters were invited to present their work in sessions followed by an intensive discussion led by two moderators and experts in the field. The "Posters of Excellence" award honoured selected posters which were highlighted in a dedicated gallery and presented in 5-minute sessions. Such IBS-related abstracts selected by the organisation to highlight the currently most relevant topics in the field during the congress will be developed in this review.

NEW EVIDENCE ON THE PATHOPHYSIOLOGY OF IBS

The Guanylate Cyclase-C/Cyclic Guanosine Monophosphate (GMP) Pathway

Guanylate cyclase C (GC-C) is the target of linaclotide, which, as an agonist, activates its expression on intestinal epithelial cells triggering the release of cyclic GMP (cGMP) and thus accelerating the GI transit and inhibiting nociceptors in the colon.[9,10] The GC-C/cGMP pathway was further explored in 24 subjects - 10 healthy volunteers and 14 IBS patients - with the goal of comparing the expression of key components of this pathway on the colonic mucosa.[11] Seven IBS patients had IBS-M while seven others had IBS-C. Recto-sigmoid mucosal biopsies were conducted and mRNA expression of GC-C, guanylin and uroguanylin (endogenous GC-C agonists), and MRP4 and MRP5 (cGMP transporters). Immunohistochemistry was also performed to define the localisation of these components on cellular structures.

In IBS-M patients, both guanylin and uroguanylin expression were significantly reduced as compared to healthy controls ($p<0.05$ for both compounds). In IBS-C biopsies, MRP4 expression was significantly lower than in healthy controls ($p<0.001$). No statistically significant differences were observed for MRP5 or GC-C expression between all subgroups. Immunochemistry revealed that MRP4 was most present on the apical side of epithelial cells of the colon mucosa, while MRP5 was expressed on the basolateral side. These findings may help refine the pathophysiology of IBS and explain the discrepancy of symptoms among the disease subtypes, which warrant further investigation.

The Role of Intestinal Permeability and Zonulin Serum Levels

While the exact pathophysiological mechanisms of IBS are still unclear, increased intestinal permeability seems to be involved, particularly through zonulin (a pre-haptoglobin that is the human homologue of a toxin secreted by *Vibrio cholerae*), an endogenous modulator of intestinal permeability. Therefore, it would be a useful biomarker in diseases such as coeliac disease (CD), non-coeliac gluten sensitivity (NCGS), and IBS.

In a prospective study,[12] zonulin serum levels were evaluated by an enzyme-linked immunosorbent assay and spectrophotometrically in patients with NCGS (n=11) and IBS-D (n=9) and compared those of patients with CD (n=7; positive control) and healthy controls (n=7; negative control). Significant differences in zonulin serum levels were observed among the four groups. Serum zonulin levels were of 0.018±0.003 in IBS-D patients (healthy controls, 0.01±0.002; $p<0.05$). Overall, zonulin serum levels were positively correlated with serum anti-deamidated gliadin peptide and anti-transglutaminase antibodies, both involved in CD. These results indicate that zonulin, via its possible involvement in the pathophysiology of IBS, could be used as a diagnostic tool for IBS, but further clinical data are needed to clearly establish both its role and its potential as a biomarker.

The Role of the Immune System

Although IBS is considered a functional and neurological disorder, there is increased evidence of the role of an impaired immune system in IBS.[13] This impairment could manifest itself in the form a chronic low-grade immune activation impacting the visceral sensory nervous function and resulting in IBS symptoms. However, it is still unclear if these mechanisms are underlined by allergic or autoimmune pathways.

In a longitudinal, comparative study, Hughes et al.[13] investigated the immune activation in IBS in patients either presenting a flare or being symptom-free. Over 1 year, five IBS-D patients were assessed quarterly, by blood sampling, and also every single time the patient self-reported a symptom flare. Cell cultures were conducted and cytokine concentrations were reported after stimulation with lipopolysaccharides (LPS) or phorbol 12-myristate

13-acetate/ionomycin (PMA/I). At each visit, the patients completed questionnaires in the form of the IBS severity scale (IBSS).

IBSS scores were significantly higher during flare episodes, as compared with baseline values (quarterly assessments). Both innate (LPS stimulation: increased interferon gamma [IFN-γ], interleukin [IL]-2, IL-13, IL-21, granulocyte-macrophage colony-stimulating factor GM-CSF, and tumour necrosis factor alpha [TNF-α]) and adaptive (PMA/I: increased GM-CSF, IFN-γ, IL-10, IL-13, IL-17, IL-18, IL-21, IL-22, IL-23, IL-27, and TNF-α) arms of the immune response were altered in IBS-D patients during flare episodes. Further studies on wider cohorts comprising other IBS clusters are warranted to help define the role of the immune system in the pathophysiology of IBS, thus establishing potential biomarkers and new targets for novel therapies.

NEW EVIDENCE ON THE CLINICAL PRESENTATION OF IBS

Colonic Tone in IBS Patients

Bloating and visible abdominal distension are frequent manifestations of IBS, but these symptoms can be present in a variety of settings: in relation to food ingestion or not, or absent on waking and worsen during the day.[14] The colonic tone of 38 IBS patients (IBS-C 20, IBS-D 5, IBS-M 13) complaining of severe bloating and abdominal distension was evaluated in fasting and postprandial conditions.[15]

21 of the patients had a postprandial presentation and, in this subgroup, meal consumption was associated with a significant decrease of recto-sigmoid tone (mean postprandial recto-sigmoid volume modification was +26.6±4.4%). 17 patients had the symptoms regardless of food consumption and, in these, mean recto-sigmoid volume modification was -4.1±4.0%. The difference between both groups was significant (p=0.001), as also illustrated by the significant difference in abdominal girth (85.0±7.7 cm versus 83.4±7.2; p<0.01). These results highlight the possible pathophysiological involvement of decreasing intestinal tone in the postprandial period with respect to abdominal distension and bloating symptoms related to food intake.

Somatisation in IBS Patients and the General Population

While the associated prevalence of somatisation and IBS is well known, Palsson et al.[16] investigated the association between both aspects in the general population using data from a survey conducted in the US on 1,665 adults. This survey evaluated IBS and functional dyspepsia in the general population and included the Recent Physical Symptoms Inventory (RPSQ)[17] to assess somatisation, as well as the 12-Item Short Form Health Survey (SF-12) scale for quality of life (QoL), the ROME-III criteria[18] for IBS questionnaire and demographic and health history questions. Somatisation was calculated with the RPSQ answers as the number of different non-GI symptoms experienced more than once in the past month.

Among 1,277 validated forms, 7.1% of responders met Rome III criteria for IBS diagnosis while 4.5% of subjects met both IBS and functional dyspepsia criteria. Mean somatisation scores were 2-fold higher in IBS-positive subjects than in subjects not qualifying for IBS or functional dyspepsia (p<0.0001), regardless of ethnicity, gender, and age group, and even after subjects reporting physician diagnosis of any upper or lower GI disorders were removed from the analysis. Moreover, somatisation scores were consistent and significantly correlated (p<0.01) with key GI symptoms observed in IBS, such as pain anywhere in the abdomen (r=0.50), uncomfortable fullness after meals (r=0.49), pain/burning in the middle of the abdomen (r=0.41), and frequency of hard (r=0.38) and loose (r=0.38) stools.

In the IBS subpopulation, the most frequent symptoms were sleep difficulties (86%), muscle aches (82%), back pain (81%), headaches (79%), and muscle stiffness (66%), while IBS-positivity according to the Rome III criteria plus somatisation was negatively associated (p<0.01) with the SF-12 values (physical and mental composites, r=-0.51 and r=-0.35, respectively). Excess somatisation was observed in 42.9% of IBS cases. These findings highlight the link between IBS and somatisation, which is associated with impaired QoL.

NEW CLINICAL EVIDENCE ON THE MANAGEMENT OF IBS

Pharmacotherapy: Linaclotide

Linaclotide is a first-in-class, minimally absorbed, GC-C agonist that was approved by the FDA and

the EMA in 2012 for the treatment of IBS-C as it reduces abdominal pain and alleviates constipation in this subpopulation.[19] It was approved following two randomised, double-blind, placebo-controlled, multicentre Phase III studies, one of which evaluated once-daily 290 µg linaclotide for 12 weeks. After this period, patients receiving linaclotide were re-randomised to continue to receive linaclotide or placebo for 4 additional weeks.[20] Following the study completion and a randomised withdrawal period, patients could continue treatment within an open-label, long-term study.

In a post-hoc analysis, Díaz Gallo et al.[21] reported on the impact of linaclotide reintroduction on treatment satisfaction following a randomised period in which patients, after a 12-week linaclotide regimen, were reassigned either to linaclotide or placebo for 4 additional weeks. Subsequently, patients could receive linaclotide for up to 78 weeks (linaclotide-placebo-linaclotide and linaclotide-linaclotide-linaclotide arms in successive 12, 4, and 78-week periods). Patient-satisfaction was reported and used as an efficacy outcome, since patients were asked how satisfied they were with the ability of linaclotide to relieve their IBS-C symptoms on a 1-5 point scale.

During the 4-week randomised withdrawal period, patients assigned to the placebo group (who had previously received linaclotide) had significantly lower treatment satisfaction than patients who remained on active therapy (3.18 versus 3.46, respectively; $p<0.05$). In the placebo group, at the end of the withdrawal phase when linaclotide was reintroduced, treatment satisfaction returned to its initial values within a 2-week period (3.69 versus 3.70, respectively). Treatment satisfaction in both the linaclotide-placebo-linaclotide and linaclotide-linaclotide-linaclotide arms was sustained and increased through the end of the 78-week study (3.93 and 3.81, respectively). The most reported adverse event during the long-term study was diarrhoea, as reported in the Phase III trials. These results show that symptom control with linaclotide treatment can be re-established if treatment is re-introduced after a period of discontinuation.

Percutaneous Procedure: Permanent Sacral Nerve Stimulation (SNS)

SNS is a minimally invasive procedure that has been used in the last two decades to treat idiopathic faecal incontinence, but has recently been suggested as a useful procedure in diarrhoea-predominant IBS[22] or mixed-IBS.[23] Previously published results[24] suggested that SNS had no detectable effect on small intestinal transit patterns, as the median velocity of the magnetic pill through the small intestine in the fasting and the postprandial states was not significantly different between periods with and without SNS ($p=0.25$ and $p=0.14$, respectively).

At UEG Week 2014, Fassov et al.[25] presented their results on the medium-term for the same group of patients. 22 patients with severe diarrhoea-predominant or mixed IBS, who were eligible for the study, received an SNS implant. Main endpoints included change in the IBS-Symptom Severity Score (IBS-SSS) and in the IBS-specific QoL score. After a median follow-up of 42 months, the IBS-SSS was significantly lower than at baseline (26 versus 62, respectively; $p<0.0001$), regardless of the symptom cluster. The median IBS-specific QoL score was significantly improved (52 versus 134, respectively; $p=0.0001$), for all QoL domains. 82% of patients experienced persistent results, and 28% of those kept the stimulator for 5 years. While these findings warrant further investigation in larger cohorts and for longer treatment duration, in this study, the benefits of SNS therapy for selected patients with severe IBS were noteworthy and sustained at medium term.

Dietary Measures and Lifestyle Intervention: the FODMAP-Restricted Diet

At UEG Week 2014, new clinical evidence was presented on the Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols (FODMAP)-restricted diet. FODMAPs include fructose (fruits), lactose (dairy products), fructans (cereals, grains, and vegetables), galacto-oligosaccharides (vegetables), and polyols (used as sweeteners by the food industry).

The FODMAP-restricted diet was developed in Australia in the early 2000's by two researchers at Melbourne University who established the efficacy of this diet for the improvement of IBS-related symptoms.[26] The rationale behind the development of this restriction diet is that FODMAPs are fermentable carbohydrates which quickly affect the osmotic balance in the gut by increasing water resorption in the small bowel. FODMAPs processing by bacteria in the colon can also trigger intestinal lumen distension, bloating, and increased gas production, thus worsening the symptoms of functional GI disorders such as abdominal pain and

altered bowel movements. However, three previous clinical studies could not definitively establish the efficacy of the FODMAP diet in IBS, being one observational,[27] one retrospective,[28] and one with most patients unblinded.[29] In addition, many IBS patients autonomously reduce or eliminate gluten intake in their diet, reporting clinical benefit. It is not known to what extent the benefits of low-FODMAP diets are due to FODMAP per se or gluten reduction.

At UEG Week 2014, Piacentino et al.[30] presented the results of a double-blind, parallel group study to evaluate the effectiveness of a low-FODMAP diet and a low-FODMAP and gluten-free diet on abdominal bloating and pain in IBS patients; in addition, it evaluated patient compliance and satisfactory relief with the diets.

62 Rome III IBS outpatients (37 females; age range 21-67 years) were consecutively recruited. IBS patients, after registering their habitual diet for 2 weeks on a first daily diary card, followed the test or control diet for 4 weeks. During the last 2 weeks of the diet, they filled out a second daily diary card. There was comparable intensity of bloating and frequency of abdominal bloating and pain in the three groups pre-diet (p=0.217). However, a significant difference was observed in the same symptoms post-diet (p<0.001) with a greater improvement of IBS symptoms in the two test diet groups versus the control group, with a trend favouring the normal-gluten group versus the gluten-free group. Compliance was 90% in >85% of patients. IBS patients have considerable benefit by restricting FODMAPs in the diet. Gluten avoidance in addition to a FODMAP restricted diet does not offer any additional significant benefit.

At UEG Week 2014, van Megen et al.[31] presented the results from a 6-week intervention study. This study aimed to investigate the impact of this diet on patients with inflammatory bowel disease (IBD) who were in remission but with persistent IBS symptoms, as is often the case with IBD. 12 patients, of which 10 had ulcerative colitis and 2 had Crohn's disease, were included in the study. They presented C-reactive protein <5mg/L and faecal calprotectin <100 mg/kg, and fulfilled the ROME-III criteria for IBS. After determination of FODMAP intake for 4 days, a clinical dietician gave instructions to the patients on restricted intake. After 6 weeks, a second evaluation of FODMAP intake was conducted, as well as IBS symptoms, QoL, compliance, and colonic fermentation.

Mean compliance was 93%, with 73% of patients continuing the diet 1 month after study completion. Between the 0 and 6-week time points, FODMAP intake was significantly reduced (median 6.3 g to 1.5 g per day, p=0.0005). IBS symptoms, as assessed by the IBS-SSS, were significantly alleviated in the first 3 weeks to remain stable through week 6 (median scores of 265.0 and 67.6, respectively; p<0.0001), and this to the extent of achieving symptom remission (score <75) in 58% of patients. QoL, as evaluated by the 36-Item Short Form Health Survey (SF-36), was improved for the whole duration of the study, in terms of mental-related QoL (median score, 43.8 versus 53.3, respectively; p=0.039), physical-related QoL (mean score, 41.0 versus 47.1, respectively; p=0.05). The items most improved by the intervention were 'bodily pain' and 'vitality'.

The two studies indicated that FODMAP restriction diet alleviates symptoms in IBS patients and can alleviate symptoms and improve QoL in IBD patients experiencing IBS symptoms despite being in remission.

CONCLUSION

IBS-related posters, highlighted within the "Posters in the Spotlight" session and the "Posters of Excellence" award, presented new emerging and promising data on the pathophysiology of IBS, providing better knowledge of the underlying mechanisms to help refine the management of IBS, both in terms of diagnosis with the development of biomarkers and in terms of therapeutic management with new pharmacological targets. Additional treatment options will also be welcomed given the variety of disease subtypes and presentations.

Until now, therapy of IBS has been focused on the predominant symptom, either abdominal symptoms or bowel alterations, or a combination of therapies to deal with both abdominal and bowel disturbances. Many therapies are available to treat the symptoms associated with IBS on a symptom-by-symptom basis, and a FODMAP-restricted diet can be now added to the therapeutic armamentarium to deal with abdominal pain and bloating. Nevertheless, linaclotide (indicated in IBS-C, regardless of gender) and lubiprostone (only approved in the USA for treatment of IBS-C in women aged 18 years and older) are the only agents that demonstrated their efficacy for both

abdominal symptoms and constipation in IBS-C patients, and, as highlighted by the American College of Gastroenterology, are also the only two compounds which are strongly recommended for IBS-C due to high and moderate quality of evidence, respectively.[1] Additional disease-modifying therapies to slow disease progression or achieve remission are needed as this represents a substantial unmet need.

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