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Review article

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THE PLACE OF TACHYKININ NK2 RECEPTOR ANTAGONISTS IN THE TREATMENT DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME

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Tachykinins act as neurotransmitters and neuromodulators in the central and peripheral nervous system. Preclinical studies and clinical trials showed that inhibition of the tachykinin receptors, mainly NK2 may constitute a novel attractive option in the treatment of irritable bowel syndrome (IBS). In this review, we focused on the role of tachykinins in physiology and pathophysiology of gastrointestinal (GI) tract. Moreover, we summed up recent data on tachykinin receptor antagonists in the therapy of IBS. Ibodutant is a novel drug with an interesting pharmacological profile, which exerted efficacy in women with diarrhea-predominant IBS (IBS-D) in phase II clinical trials. The promising results were not replicable and confirmed in phase III of clinical trials. Ibodutant is not ready to be introduced in the pharmaceutical market and further studies on alternative NK2 antagonist are needed to make NK2 antagonists useful tools in IBS-D treatment.

Key words: *irritable bowel syndrome, abdominal pain, diarrhea, tachykinins, ibodutant, NK2 receptor antagonist, transient receptor potential vanilloid 1 channel*

INTRODUCTION

Irritable bowel syndrome (IBS) belongs to the group of functional gastrointestinal (GI) disorders, characterized by chronic and relapsing abdominal pain and disrupted GI motility. The prevalence of IBS is approximated at 5 – 20% of the worldwide population with the highest prevalence in Western countries and it is still increasing (1). Based on the stool consistency (assessed with Bristol stool scale), four subtypes of IBS have been distinguished: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), IBS with mixed bowel habits (IBS-M) and IBS with no significant abnormalities in stool consistency, IBS-U (2). Notably, IBS-D affects nearly a third of all patients diagnosed with IBS. According to the Rome IV criteria IBS-D is characterized by more than 25% of stools being loose and watery and less than 25% of stools being hard or lumpy (2).

The etiology of IBS is still unknown, however it involves interactions of genetic and psychosocial factors (such as early life stress and psychological problems), dietary intolerance and allergy, disruption of the mucosal barrier, visceral hypersensitivity, dysregulation of the brain-gut axis and changes in gut microbiota (3, 4).

The multifactorial etiology and the complex course make IBS treatment difficult and long-lasting. Currently, first line therapy in IBS-D is a change of lifestyle including relaxation (*e.g.* gut directed hypnosis) and diet; if there is no improvement, pharmacological treatment is initiated. The list of available drugs in IBS-D therapy is long and includes among others: agonists of opioid receptors, antidepressants, plant derived drugs, antibiotics or serotonin 5-HT3 receptor antagonists *etc*. Most of the drugs mentioned above possess low efficacy; they rather act symptomatically (5). The novel interesting role of endocannabinoid system of the activity of the enzymes involved in the endocannabinoid degradation, may be a novel approach for development of effective anti-diarrheal strategies, *i.e*. in IBS-D patients (6).

The world economic burden exerted by IBS is still growing (7) as IBS constitutes around 12% of visits in primary care (12%) and 30 – 50% in gastroenterology practice (8). Undoubtedly, drugs acting on the novel pharmacological targets are needed. In various basic science and conceptual studies it was revealed that tachykinins and the tachykinin receptors are associated with regulation of the GI motility, secretion and visceral sensitivity (9). In this review we will also define the role tachykinin NK2 receptor antagonists in the therapy of IBS-D.

TACHYKININS AND TACHYKININ RECEPTORS

Tachykinins belong to the group of active neuropeptides expressed in the central nervous system and in the peripheral neuronal and non-neuronal tissues. Tachykinins family encompasses: substance P (SP), neurokinin A (NKA), neurokinin B (NKB), neuropeptide-K (NP-K), neuropeptide-gamma (NP-gamma), hemokinin-1 (HK-1) and neurokinin A

Table 1. Tachykinin binding affinity at respective NK receptors.

Receptor	Tachykinins binding at NK receptors
NK1	**SP** > NP-γ, NPK, NKA > NKB
NK2	NP-γ NPK, **NKA** > NKB > SP
NK3	**NKB** > NP-γ NPK NKA > SP

and neurokinin B (NKA and NKB) (10). Their structure reveals similarity at C-terminus: Phe-X-Gly-Leu-Met-NH2 (X stands for aromatic residue: Tyr or Phe) or branched aliphatic chain (Val or Ile); while it varies at N-terminal. Tachykinins origin from large protein precursors: preprotachykinin A (SP, NPK, NPA, NP-γ) and preprotachykinin B (NPB). These precursors are highly homologous (11).

The biological activity of tachykinins is mediated through three different membrane receptors, named tachykinin NK1, NK2 and NK3 receptors. Tachykinin receptors belong to the class A (rhodopsin-like) of G protein-coupled receptors; they are encoded by *TACR1*, *TACR2* and *TACR3* genes, respectively (12). Tachykinins are characterized by differential binding affinity at NK receptors: SP presents highest affinity at NK1 receptor, NKA is the most potent ligand of NK2 receptor and NKB for NK3 receptor (13). However, besides high affinity of NKA at NK2 receptors and NKB at NK3 receptors, these tachykinins exhibit also significant affinity at NK1 receptors (14). Detailed data about tachykinins binding affinity at particular NK receptor are summarized in *Table 1*.

NK1 receptors are located in the CNS (spinal cord, medulla oblongata, amygdale, striatum, hippocampus, nucleus accumbens, hypothalamus, nucleus of the tractus solitaries) and in the peripheral nervous system (enteric nervous system, urinary tract) (15). Moreover, they were found in peripheral tissues: respiratory system, cardiovascular system and GI tract (16). NK2 receptors, at first, were found in porcine spinal cord and brain, but nowadays they are mainly related to the smooth muscles in the GI tract, genitourinary, respiratory and vascular systems (17). NK3 receptors are mainly expressed in the CNS; in the periphery they were also detected in placenta and uterus (in humans and rats), skeletal muscles, lung and liver (humans), mesenteric and portal veins (rats) and in the neurons of the enteric nervous system (18).

In general, tachykinins, as distributed in a myriad of tissues within organisms, and thus they participate in a broad spectrum of biological processes. For example, according to their presence in the CNS, tachykinins are involved in neurochemical response to stress or in regulation of affective behavior. They control the production and release of several neurotransmitters, such as: acetylcholine, histamine or GABA (16). Substance P pertains important role in pain transmission (19) and neurogenic inflammation (20). Moreover, it participates in blood pressure regulation by stimulation of catecholamines secretion from chromaffin cells through the enhancement of aldosterone production (21). Tachykinins also play a role in immunomodulation: Substance P enhances IL-1 production in macrophages and sensitizes neutrophils. Moreover, it promotes prostaglandin E_2 and prostacycline release (22). Stimulation of NK1 receptor exerts inhibitory effect on hypothalamo-pituitary axis, while NK2 and NK3 related signaling stimulate this axis (16). Tachykinins participate in bronchial hypersensitivity, inflammation and cough. SP and NKA induce smooth muscles contractions in the respiratory tract and therefore they promote bronchoconstriction (23, 24). Notably, in asthmatics, bronchoconstriction is evoked by NKA (when inhaled), but not SP (25). Moreover, SP appears to interact with bronchial epithelium (as NK1 receptors are present on the epithelial cells in the respiratory tract) and it is involved in plasma extravasation with the subsequent oedema, while expression of NK2 receptors is limited to the smooth muscles (26).

TACHYKININS IN THE GASTROINTESTINAL TRACT

The major source of tachykinins in the GI tract are enteroneurones from both, myenteric and submucosal plexuses, and nerve fibers from vagal ganglia and dorsal root. Interestingly, in the stomach they are expressed only in the myenteric plexus (12). Tachykinins are also present in enterochromaffin and GI-mucosal immune cells (27). In humans concentration of SP and NKA in the mucosal and submucosal layers is almost equal or even higher than in the external muscle layers, in contrary to other mammalians (*i.e.* pigs, rats and rabbits), where their concentration is higher in external muscle layers (28).

Tachykinin NK1 receptors have been found in the enteric nervous system, on the intrinsic peripheral afferent neurons (IPANs), excitatory and inhibitory motor neurons and secretomotor neurons. Notably, NK1 receptors are localized on the effector cells, *i.e.* interstitial cells of Cajal (ICC), enterocytes, smooth muscle cells of the longitudinal and circular layers, muscularis mucosa, immune cells and blood vessels of the submucosa (29). Tachykinin NK2 receptors have been found on the smooth muscle cells of longitudinal and circular muscle layers, muscularis mucosa, enterocytes and immune cells (30). They are also expressed on the neurons of submucosal and myenteric plexuses (both excitatory and inhibitory pathways) in the colon (31). Tachykinin NK3 receptors are mainly distributed on neurons (*i.e.* IPANs, ascending and descending interneurons, excitatory and inhibitory motor neurons, vasomotor and secretomotor neurons). However, their presence has been noted on the smooth muscle cells of longitudinal and circular layers in the human colon (32).

The role of tachykinins in the gastrointestinal tract - physiology

In the GI tract, tachykinins and their receptors are involved in neuro-neuronal signal transmission, regulation of the GI motility and secretion, inflammation and visceral pain. Tachykinins, through NK1 and NK3 receptors, modulate transmission between IPANs, IPANs and interneurons, ascending interneurons and excitatory motor neurons, and secretomotor neurons (32). Tachykinins induce smooth muscle contractions of the intestines in mammalians, through activation of all types of NK receptors. Substance P promotes excitatory transmission through NK1 receptors on the interstitial cells of Cajal; it activates a non-selective ion channel (pacemaker function) and Na^+ channel (depolarization) (33, 34). Stimulation of NK2 receptors is one of the main non-cholinergic component of the ileal and colonic circular smooth muscle contractions under the electrical field stimulation (35). For example, NKA, as NK2 receptors agonist, induces contractions of the circular smooth muscles in the colon (36). Interestingly, it has been revealed that besides NKA, NKB and SP also induced concentration-dependent contractions of the isolated circular smooth muscles in the human colon. However, it was suggested that the effect of SP and NKB was mediated mainly by NK2 receptors (reversed by NK2 receptor agonist: SR 144782, while NK1 and NK3 receptors agonists (SR 140333 and SR 142801, respectively) do not reverse this contractile action (37).

Deiteren *et al*. (38) characterized the involvement of tachykinin receptors-related signaling in the modulation of colonic peristalsis *in vitro*, in mouse model of distension-induced peristalsis. The NK1 agonist, septide, increases colonic

contractility in the distal, but not in the proximal colon. The blockage of NK1 receptors with RP67580 inhibits distension-induced contractions in the proximal and distal colon (while this effect was stronger in the latter) (38). Appleyard *et al*. (39) observed the same heterogenity in the rat colon: SP through NK1 receptors induces muscularis mucosa response that increases along the intestine (it is marked in the distal colon, while remains minimal in proximal part) (39). In mouse model of distension-induced peristalsis an activation of NK2 receptors with β-A-NKA increases the amplitude of peristaltic waves in both, proximal and distal parts of the colon. Observed effect is reversed by nepadutant (NK2 antagonist). Noteworthy, similarly to NK1 related signaling, the blockage of NK2 receptors inhibits peristaltic contractions in the distal, not proximal colon (38). In contrast to NK1 and NK2 receptors, NK3 receptors do not participate in the regulation of peristalsis (or they contribute in minimal extent). SR 142801 (NK3 receptor antagonist) does not affect peristaltic activity (38). Minor involvement of NK3 activation in the regulation of peristalsis was demonstrated in the guinea pig (40) and rabbit segments of distal colon (41).

In addition, tachykinins inhibit GI motor activity *via* inhibitory neural pathways and prejunctional reduction of transmitter release (28). For instance, activation of NK1 and NK3 receptors causes the relaxation of the circular muscle of the guinea pig stomach through stimulation of inhibitory motor neurons (release of vasoactive intestinal peptide (VIP) and increases formation of nitric oxide (NO) (42). The second mechanism is a prejunctional inhibition of transmitter release. For example, SP inhibits electrically induced release of ACh in the guinea pig ileal myenteric plexus; this effect is combined with action dependent on NK1 receptor (43, 44). Moreover, it was observed that tachykinins inhibit the GI motility by stimulation of sympathetic neurons in the intestines (28).

Tachykinins have been found in the mucosal nerve endings, and thus they are involved in the regulation of water and electrolyte transport. For example, Substance P administered to the segment of the guinea pig ileum (at the concentrations ranging from 10^{-10} to 10^{-6} M; added to the submucosal side of the tissue) increased the mucosal ion transport *in vitro*. SP affected both cholinergic and non-cholinergic submucosal neurons (45). Moreover, SP had a direct impact on the epithelial cells (46).

The role of tachykinins in the gastrointestinal tract - pathophysiology

Several lines of evidence show that tachykinins could contribute to disturbances in GI homeostasis, *i.e*. abnormal GI motility or increased visceral sensitivity. Therefore numerous studies indicate the possible role of tachykininergic system dysregulation in the functional GI diseases (9). For example, Sun *et al*. (54) found that hydrogen sulfide has an excitatory effect on the gastric acid secretion, which may be mediated by activation of the transient receptor potential vanilloid 1 (TRPV1) channels in sensory nerve terminals, with the consequent release of SP, showing the importance of SP in GI homeostasis.

For example, King *et al*. (47) found that the density of SP-positive never fibers is significantly reduced in the intestines of children with constipation. On the contrary, high concentration of SP is observed in the terminal ileum and rectosigmoidal mucosa in IBS patients (48). Moreover, SP was identified in nerve fibers surrounding mast cells; the number of mast cells in terminal ileum, ileocecal junction and ascending colon is increased in IBS patients as compared to control. In the lamina propria, mast cells are localized closely to SP-ergic terminals: mast cells and SP-ergic terminals constitute a mucosal functional unit. Alterations in the intestinal mucosal mast cells and SP level are considered as related to visceral hypersensitivity (48, 49). As Jarcho *et al*. (50) assessed with positron emission tomography, lowered NK-1 receptor binding potential in cortical and subcortical regions of brain was found in patients with IBS, as compared to healthy controls.

Disturbances in NK2 receptors signaling are linked with several intestinal diseases: smooth muscles preparations from patients with chronic idiopathic constipation (CIC) are more susceptible to the contractile effect of NK2 receptor agonist ([*β*-Ala8]neurokinin A(4-10)). [*β*-Ala8]neurokinin A(4-10) evokes stronger contractile effect in CIC in comparison to healthy subjects, while NK1 and NK3 receptors selective agonists do not induce contractions in both, diseased and healthy tissue (51). However, Mitolo-Chieppa *et al*. (52) reported the opposite: the contractile potential of [*β*-Ala8]neurokinin A(4-10) was significantly lower in the colon of patients with CIC in comparison to controls. Moreover, in colonic circular muscles from CIC patients the off-contractions (observed in the presence of atropine; they follow a standard tissue response to low frequencies of electrical field stimulation) was nearly 40% reduced compared to controls; NK2 and NK3 receptors agonists increased the off-contractions, however the effect was limited to CIC specimens. This action is dose-dependently reversed by MEN-10627 (NK2 and NK3 receptors antagonist) (52). The selective impairment of tachykininergic NK2-mediated signaling was detected in the colonic circular muscles preparation from children with slow transit constipation, in these specimens the contractility to carbachol or NKA was normal, while SR48968 (NK2 antagonist) does not reduce EFS-induced contractions compared to control (53).

NK2 ANTAGONISTS AND INFLAMMATORY BOWEL SYNDROME

The clinical potency of two selective NK2 receptor antagonists: nepadutant (MEN11420) and ibodutant (MEN15596) for IBS therapy has been evaluated over the last two decades. The brief summary of NK2 antagonist on the GI functioning can be found in *Table 2*.

Nepadutant

Nepadutant is a selective, competitive and reversible antagonist of NK2 receptors. Intravenous injections of nepadutant (0.1 – 32 mg) was safe and well tolerated in healthy volunteers. Nepadutant at the dose of 8 mg intravenously (i.v.) reversed the changes in the GI motility induced by NKA administration in healthy patients, while it did not affect normal peristalsis. Moreover, in nepadutant group the occurrence of side effects related to NKA (abdominal pain, nausea, vomiting) was abolished (55). Nepadutant increased rectal compliance in glycerol-treated patients and reduced the sensitization to the defecation stimulus produced by glycerol (glycerol increases rectal sensitivity in colorectal balloon distension test and induces mild inflammation) (56). Besides good pharmacological profile of nepadunat (its influence on GI motility and IBS-like symptoms induced by NKA) its application in clinics is limited due to low oral bioavailability.

Ibodutant - preclinical studies

Ibodutant (6-methyl-benzo[b]thiophene-2-carboxylic acid [1-(2-phenyl-1R-{[1-(tetrahydropyran-4-ylmethyl)-piperidin-4-ylmethyl]-carbamoyl}-ethylcarbamoyl)-cyclopentyl]-amide), also known as MEN15596, is orally available, selective antagonist of tachykinin NK2 receptor. This novel non-peptide molecule was designed for the treatment of IBS-D by Menarini (57-59).

The pharmacological profile of Ibodutant was described by Cialdai *et al*. (60). Ibodutant exhibited subnanomolar affinity

Table 2. Brief summary of clinical trials on NK2 antagonists on gastrointestinal system functioning and irritable bowel syndrome (IBS).

Drug	**Clinical trial**	**Subjects**	**Conclusions**	Current status
Nepadutant (MEN11420)	Phase I	Healthy subjects	- Inhibition of NKA-stimulated, GI motility (but not basal motility) - Well tolerated by all participants	Completed in 2001
Ibodutant (MEN15596)	Phase II – 'IRIS'	IBS patients	- No efficacy (in comparison to healthy controls) - *Post-hoc* analysis: ibodutant was superior to placebo in IBS-D subgroup in abdominal pain alleviation	Completed in 2009
	Phase II – 'IRIS-2'	IBS-D patients	- Effective (in contrast to placebo) in induction of relief of overall symptoms and abdominal pain	Completed in 2015
	Phase III – 'IRIS-3'	IBS-D females	- No efficacy in primary and secondary endpoints (duration: 12 weeks)	Completed in 2015
	Phase III – 'IRIS 4'	IBS-D females	- No efficacy in primary and secondary endpoints (duration: 52 weeks)	Terminated in 2015
	Phase III – 'IRIS 5'	IBS-D females	- No information is presently available	withdrawn

(pK_i 10.1) at human recombinant tachykinin NK2 receptors and powerfully (pK_B 9.1) antagonized intracellular release of calcium induced by NKA. The highest antagonist potency of ibodutant was observed in the guinea pig colon, human and mini-pig urinary bladder (pK_B 9.3, 9.2 and 8.8, respectively), while in the rat and mouse urinary bladder ibodutant was less potent (pK_B 6.3 and 5.8, respectively). Low potency of ibodutant in blockage of selective NK1 or NK3 receptor agonists (SP methyl ester and senktide, respectively) was also displayed in guinea pig ileum preparations (60).

High affinity and antagonist potency, as well as persistent duration of ibodutant have been confirmed in radioligand binding and contractility assays performed by Santicioli *et al*. (59) in the human colonic circular smooth muscles. In the radioligand binding assay using iodinated NKA and smooth muscle membranes, ibodutant was compared to two other selective tachykinin NK2 receptor antagonists, nepadutant and saredutant in terms of antagonist affinity (pK_i values: 9.9 for ibodutant; 9.2 for saredutant and 8.4 for nepadutant). The antagonist potency of ibodutant was calculated as pK_B value 9.1. It was estimated by application of ibodutant (3, 10, 30 and 100 nM) towards the contractions of the human colon smooth muscle strips, which were produced by a selective tachykinin NK2 receptor agonist, [βAla^8]NKA(4-10). The inhibition induced by ibodutant remained almost constant during 3 hours even with washing cycles. No sex-related differences in tachykinin NK2 receptor pharmacology were observed in the study (59).

Ibodutant had a potent dose-dependent inhibitory effect on the colonic contractions induced by [βAla^8]NKA(4–10), a selective tachykinin NK2 receptor agonist (3 nmol/kg, i.v.), in the anaesthetized and hexamethonium-treated guinea-pigs (60). This was a long-lasting effect after i.v. (ED_{50} 0.18 µmol/kg), intraduodenal (ED_{50} 3.16 µmol/kg) or oral (10 – 30 µmol/kg) administration. Importantly, the colonic contractions elicited by the NK_1 receptor selective agonist [Sar^9]substance P sulfone (3 nmol/kg, i.v.) were not affected by ibodutant (3 µmol/kg, i.v.).

The possible role of inflammation in IBS has encouraged scientists to assess the anti-inflammatory potency of ibodutant during intestinal inflammation. Tachykinin NK2 receptor-related gender specificity of ibodutant was assessed by Bellucci *et al*. (61) in a guinea pig model of colitis. The colitis was induced by rectal instillation of 2,4,6-trinitrobenzenesulfonic acid (TNBS) in both genders. In control animals ibodutant did not affect abdominal contractions. In TNBS-treated group, ibodutant prevented the increased visceral hypersensitivity to colorectal distension (CRD); of note, the effect was observed at lower doses in females than in males (0.65 mg/kg versus 1.9 mg/kg, respectively). However, pharmacokinetics of ibodutant did not diverge between female and male individuals. Finally, higher release of tachykinins was evidenced in the smooth muscle layer than in the mucosal samples. Furthermore, a significantly lower capsaicin-stimulated release of tachykinins from the inflamed mucosal samples was observed in females than in males.

Ibodutant - clinical studies

The detailed information of ibodutant in IBS therapy is summarized in *Table 3*.

- IRIS

The tolerability, safety and efficacy of oral administration of ibodutant in IBS patients was determined in a randomized, double-blind, placebo-controlled trial named IRIS (Ibodutant for the Relief of Irritable Bowel Syndrome; NCT00761007) (62). Of note, 63.76% of the included patients were IBS-D patients. Participants were given ibodutant orally, once a day, at three different doses: 10, 30 or 60 mg. The administration of ibodutant lasted 4 weeks and it was followed by a 2-week withdrawal period.

The primary outcome was participant's response on overall IBS symptom relief for 2 of 4 weeks of treatment (50% improvement). The primary outcome was fulfilled by 56.43% (10 mg), 45.86% (30 mg) and 45.19% (60 mg) of IBS patients (as compared to 57.35% in the placebo group). Patients who reported satisfactory overall IBS symptom relief for 3 of 4 weeks constituted respectively 37.86%, 29.32% and 27.41% versus 35.29% in placebo group. Another secondary outcome, namely response of overall IBS symptom relief in IBS-D patients for 3

Table 3. The detailed results of ibodutant in the therapy of irritable bowel syndrome (IBS).

Clinical trial (NCT number)	**Subjects ibodutant doses**	**Primary endpoint**	**Primary endpoint -results**	**Secondary endpoints**	**Secondary endpoints - results**
Phase II – 'IRIS' (NCT00761007)	IBS patients 10, 30 or 60 mg	Response on overall IBS symptom relief for 2 of 4 weeks of treatment (50% improvement)	56.43% (10 mg), 45.86% (30 mg) and 45.19% (60 mg) of IBS patients (as compared to 57.35%	1) Improvement on overall IBS symptom relief for 3 of 4 weeks constituted respectively 2) Improvement response of overall IBS symptom relief in IBS-D patients for 3 of 4 weeks 3) Post-hoc outcome - the response of overall IBS symptom relief in the subgroup of IBS-D patients on abdominal pain at baseline for 3 of 4 weeks	1) 37.86% (10 mg), 29.32% (30 mg) and 27.41% (60 mg) versus 35.29% in placebo group 2) 48.53% (10 mg), 32.08% (30 mg) and 37.29% (60 mg) versus 46.27% in placebo group 3) 57.41% (10 mg), 34.88% (30 mg) and 35.42% (60 mg) of patients versus 43.18% in placebo group
Phase II – 'IRIS-2' (NCT01303224)	IBS-D patients 1, 3 or 10 mg	Relief of overall IBS symptoms and abdominal pain or discomfort (at least 6 of 8 weeks with satisfactory relief	32.14% (1 mg), 33.33% (3 mg) and 39.57% (10 mg) of patients versus 27.46% in placebo group	1) Improvement on overall IBS symptoms and of abdominal pain or discomfort at the end of 8 weeks of treatment 2) Improvement in quality of life score after 8 weeks of treatment using EuroQoL EQ-5D questionnaire	1) 51.43% (1 mg), 44.20% (3 mg) and 53.24% (10 mg) of patients versus 38.73% in placebo group 2) 71.3% (at the end of treatment) and 56.4% (baseline) – 1 mg; 72.1% and 58,2% – 3 mg; 66.7% and 57.2% – 10 mg versus 72.2% and 58.7% in placebo group
Phase III –'IRIS-3' (NCT02107196)	IBS-D females 10 mg	Improvement on weekly response for abdominal pain intensity and stool consistency over 12 weeks of treatment in at least 6 out of 12 weeks of treatment if in the same week	35.7% versus 34.7% in placebo group	1) Improvement on weekly response for abdominal pain intensity over 12 weeks of treatment in ≥ 6 out of 12 weeks of treatment with a decrease in weekly average of worst abdominal pain score in the past 24 hours of at least 30% compared with baseline 2) Improvement on weekly response for stool consistency over 12 weeks of treatment in ≥ 6 out of 12 weeks of treatment with decrease of at least 50% in the number of days per week with at least one stool that has a consistency of type 6 or 7 compared with baseline 3) Improvement on weekly response for relief of overall IBS signs and symptoms over 12 weeks of treatment in ≥ 6 out of 12 (50%) weeks of treatment	1) 48.0% versus 47.7% 2) 44.8% versus 43.1% 3) 21.3% versus 19.0%
Phase III – 'IRIS 4' (NCT02120027)	IBS-D females 10 mg	Improvement on weekly response for abdominal pain intensity and stool consistency over the first 24 weeks of treatment in at least 12 out of 24 (50%) weeks of treatment, when in the same week the patient reported a decrease in weekly average of worst abdominal pain score in the past 24 hours of ≥ 30% compared with baseline; and a decrease of at least 50% in the number of days per week with ≥ one stool that had a consistency of type 6 or 7 compared with baseline	21.6% versus 21.8%	1) Improvement on weekly response for abdominal pain intensity over the first 24 weeks of treatment in ≥ 12 out of 24 weeks (50%) of treatment with a decrease in weekly average of worst abdominal pain score in the past 24 hours of ≥ 30% compared with baseline 2) Improvement on weekly response for stool consistency over the first 24 weeks of treatment in ≥ 12 out of 24 weeks (50%) of treatment with a decrease of at least 50% in the number of days per week with ≥ one stool that had a consistency of type 6 or 7 compared with baseline 3) Improvement on weekly response for relief of overall IBS signs and symptoms over the first 24 weeks of treatment in ≥ 12 out of 24 (50%) of the weeks	1) 40.7 versus 34.9% 2) 30.5% versus 29.8% 3) 15.7% versus 12.2%
Phase III – 'IRIS 5'	IBS-D females 10 mg	withdrawn			

of 4 weeks, was reached by 48.53%, 32.08% and 37.29% of patients, respectively (compared to 46.27% in placebo group). The *post-hoc* outcome measure, namely the response of overall IBS symptom relief (in the subgroup of IBS-D patients) and abdominal pain at baseline for 3 of 4 weeks, was reached by 57.41%, 34.88% and 35.42% of patients, respectively (as compared to 43.18% in placebo group).

The most frequent adverse effect was headache, reported by 6.43% of patients receiving ibodutant 10 mg (as compared to 5.84% in placebo group). Other common adverse effects were: abnormal liver function, cerebrovascular incident, pneumonia and atrial fibrillation, with the incidence of 0.74% in ibodutant 30 mg group and 0.72% in ibodutant 60 mg group (0% in placebo-treated group).

- IRIS 2

The second Phase II clinical study, IRIS-2 (NCT01303224) (63) started in October 2010 and was performed in 8 European countries on IBS-D patients; 565 patients (59.57% women) participated in this double-blind, randomized, placebo-controlled, parallel-group trial (64). Ibodutant was given orally at three doses (1, 3 or 10 mg), once daily (under fasting conditions) for 8 weeks. A 2-week run-in period without medication use prior to the therapy and a 2-week withdrawal period were applied. The primary outcome was a response for relief of overall IBS symptoms and abdominal pain or discomfort at the end of treatment, where the response was defined as at least 6 weeks with satisfactory relief during 8 weeks of the study. The improvement in the primary endpoint was observed among 32.14%, 33.33% and 39.57% of patients treated with ibodutant at the doses of 1, 3 and 10 mg, respectively (as compared to 27.46% in placebo-group). Secondary outcomes included a response for relief of overall IBS symptoms and of abdominal pain or discomfort at the end of 8 weeks of treatment, where the response was defined as at least 4 weeks with satisfactory relief during 8 weeks of treatment. The secondary endpoint fulfilled in 51.43%, 44.20% and 53.24% patients in ibodutant-treated group (1, 3 and 10 mg, respectively), as compared to 38.73% in placebo-treated group. The improvement in quality of life after 8 weeks of treatment using EuroQoL EQ-5D questionnaire was reported as follows: 71.3% (at the end of treatment) and 56.4% (baseline); 72.1% and 58,2%; 66.7% and 57.2% in ibodutant-treated group at the doses 1, 3 and 10 mg, respectively, as compared to 72.2% and 58.7% in placebo-treated group (64).

Of note, the relief of overall IBS symptoms and abdominal pain or discomfort after 6 of 8 weeks separately in the female and male intent to treat (ITT) population was also assessed as another outcome measure. In women, the improvement in this secondary endpoint was reported by 35.96%, 40.23% and 46.84% of patients for increasing doses of ibodutant (1, 3 and 10 mg, respectively) as compared to 24.36% in placebo-treated group. In males the improvement was noted in 25.49%, 21.57% and 30.00% of patients (1, 3, 10 mg of ibodutant), as compared to 31.25% of placebo-treated patients.

The most frequently observed adverse effect was headache, reported in 4.96% and 5.76% of IBS-D patients receiving ibodutant at the doses of 1 and 10 mg, respectively (2.80% in placebo-treated group).

- IRIS 3

The first Phase III clinical trial of ibodutant, IRIS-3 (NCT02107196), started in March 2014 and was completed in June 2015 (65). This double-blind, randomized, placebo-controlled, parallel group clinical trial of 12-week duration aimed for the evaluation of efficacy and safety of ibodutant administered orally at a dose of 10 mg once daily in approximately 500 females with IBS-D in comparison to placebo. The study was preceded by up to 2 weeks of screening for patient's eligibility and a 2-week run-in period for IBS severity assessment and followed by a 4-week randomized withdrawal period and a 2-week safety follow-up. Patients in ibodutant group were re-randomized at week 13 to either ibodutant 10 mg or placebo for additional 4 weeks of treatment (in a 1:1 ratio); patients in placebo were re-randomized at week 13 to ibodutant or placebo for an additional 4 week treatment.

The primary outcome measure was a weekly response for abdominal pain intensity and stool consistency over 12 weeks of treatment in at least 6 out of 12 weeks of treatment if in the same week: there was a decrease in weekly average of worst abdominal pain score in the past 24 hours of at least 30% compared with baseline; and a decrease of at least 50% in the number of days per week with at least one stool that had a consistency of type 6 or 7 compared with baseline (Bristol stool score). The primary outcome was fulfilled by 35.7% of participants receiving 10 mg of ibodutant (versus 34.7% in placebo group).

Secondary outcome measures included a weekly response for abdominal pain intensity over 12 weeks of treatment in at least 6 out of 12 weeks (50%) of treatment with a decrease in weekly average of worst abdominal pain score in the past 24 hours of at least 30% compared with baseline; weekly response for stool consistency over 12 weeks of treatment in at least 6 out of 12 weeks of treatment (50%) with decrease of at least 50% in the number of days per week with at least one stool that has a consistency of type 6 or 7 compared with baseline; weekly response for relief of overall IBS signs and symptoms over 12 weeks of treatment in at least 6 out of 12 (50%) weeks of treatment; and evaluation of rebound effects by comparison between average abdominal pain intensity and stool consistency during the 4-week re-randomization period in patients who are re-randomized to placebo after being treated with ibodutant. Ibodutant has failed in all of the secondary outcomes. The decrease in abdominal pain intensity was reported by 48.0% (versus 47.7% in control group), the improvement in stool consistency 44.8% versus 43.1%. There was slight, but negligible improvement in IBS overall signs and symptoms score: 21.3% versus 19.0% in placebo group.

- IRIS 4

Study IRIS-4 (NCT02120027) was conducted between March 2014 and November 2015 (66). This double-blind, randomized, placebo-controlled, parallel-group clinical trial lasted 52 weeks with re-randomizations at week 25 and has been performed in approximately 500 female patients with IBS-D. The main goal of was to assess efficacy and safety of oral ibodutant 10 mg administered once daily as compared to placebo over a 24-week treatment period. *Via* mock-re-randomization at week 25, patients receiving ibodutant 10 mg continued on ibodutant 10 mg for additional 26 weeks of treatment; while patients randomized to the placebo arm were re-randomized at week 25 in a 1:1 ratio to ibodutant or placebo for additional 26 weeks of treatment.

The primary outcome measure was weekly response for abdominal pain intensity and stool consistency over the first 24 weeks of treatment in at least 12 out of 24 (50%) weeks of treatment, when in the same week the patient reported a decrease in weekly average of worst abdominal pain score in the past 24 hours of at least 30% compared with baseline; and a decrease of at least 50% in the number of days per week with at least one stool that had a consistency of type 6 or 7 compared with baseline. The primary outcome was fulfilled by 21.6% of female participants versus 21.8% in placebo group.

Four secondary outcome measures were also assessed, namely: weekly response for abdominal pain intensity over the first 24 weeks of treatment in at least 12 out of 24 weeks (50%) of treatment with a decrease in weekly average of worst abdominal pain score in the past 24 hours of at least 30% compared with baseline; weekly response for stool consistency over the first 24 weeks of treatment in at least 12 out of 24 weeks (50%) of treatment with a decrease of at least 50% in the number of days per week with at least one stool that had a consistency of type 6 or 7 compared with baseline; weekly response for relief of overall IBS signs and symptoms over the first 24 weeks of treatment in at least 12 out of 24 (50%) of the weeks; and sustained efficacy (weekly response for abdominal pain intensity and stool consistency over the first 24 weeks of treatment applying the 50% rule with at least 2 weeks of response in the last 4 weeks of treatment (week 21 to 24); the patient were considered a weekly responder as defined for the primary endpoint). The analysis of secondary endpoints showed that 40.7% of participants in ibodutant group reported and improvement in abdominal pain intensity (versus 34.9 in placebo, P = 0.193). Ibodutant induced no effect on stool consistency: the improvement was observed among 30.5% of patients receiving drug versus 29.8% in control group. The improvement of IBS overall symptoms was reported by 15.7% patients (versus 12.2%, P = 0.272).

- IRIS 5

Study IRIS 5 was aimed to assess the efficacy and safety of an oral 10 mg dose of ibodutant given once daily as compared to placebo in women (Asian) affected by IBS-D over a 12-week treatment period. IRIS 5 has been withdrawn prior to enrollment. No additional information is presently available (67).

FUTUER PERSPECTIVES

The components of tachykininergic system, as broadly expressed in the GI system, participate in modulation of the intestinal motility, water/ion transport and also immune responses. Its role is crucial in both, physiology and pathophysiology.

Recently it was proved that novel histamine H_2 receptor antagonist, Lafutidine, significantly reduced the severity of diarrhea in the rodent intestinal mucositis. This effect occurred *via* TRPV1 signalling and sensory afferent nerves, known to be a source of tachykinins, suggesting cross-talk between histamine receptors and tachykininergic system (68).

Several clinical trials have taken a deeper look on the role of NK1 antagonists in the GI functioning and IBS-related symptoms. In healthy volunteers, aprepritant does not affect the GI transit of upper and lower GI tract (69). Another NK1 antagonist, ezlopitant, reduces the emotional response in group of healthy participants to the colorectal distension (70). In women with IBS chronic treatment (3 weeks) with AV608, NK1 receptor antagonist, decreases pain scores and anxiety alleviation. Moreover, AV608 reduces the activity of brain regions related to interoception and emotional arousal in functional MRI (71). Studies on NK1 antagonist suggest that the action of these compounds is limited to diminishment of centrally mediated pain amplification not the visceral pain input in the CNS.

In rats, NK3 receptor antagonists increase the pain threshold to colorectal distension and reduce visceral hypersensitivity induced by stress (72, 73). In contrast to animal studies on NK3 receptor blockage, talnetant (selective NK3 receptor antagonist) produces no significant effect on rectal compliance or intensity and sensitivity scores in colorectal distention test in healthy volunteers (74). Moreover, in phase 2 clinical trial talnetant was ineffective and equal to placebo in alleviation of IBS-related symptoms (abdominal pain and discomfort) (75).

The preclinical studies and phase II of clinical trials present the antagonism of NK2 receptors to be promising for the therapy of IBS-D, especially in women. Ibodutant induces long lasting action, it is well tolerated and has good bioavailability, however its promising action in phase II clinical trial on IBS patients was not confirmed in further and more focused clinical trials. Two clinical trials with ibodutant have been terminated or withdrawn, suggesting that ibodutant is not ready to be introduced in the pharmaceutical market and further studies on an alternative NK2 antagonist are needed to make NK2 antagonists useful tools in IBS-D treatment.

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