TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

Treatment of Bowel Syndrome with Constipation: An Experience with The Agonist of Guanylate Cyclase Receptor in Advanced Age Patients

Valerio Massimo Magro

Department of Internal Medicine and Geriatry, University of Campania, Naples, Italy

A B S T R A C T

Background Irritable bowel syndrome is a very common condition in the elderly, and it can also be extremely disabling being able to go to undermine the patient's independence. We wanted to conduct a study on the Territory to test a recently approved molecule for treating a variant with constipation-predominant irritable bowel syndrome, testing the treatment in a cohort of elderly subjects and comparing the results with those of other existing therapies. Here we exposed the results of our experience.

Material and Methods We conducted an open-label study in the general medicine setting, enrolling patients who appeared eligible for drug treatment with the study drug during the medical examination. So we examined 20 elderly patients. Half of the patients were treated with linaclotide 290 mcg, the other 50% with macrogol 27.6 g (25%) and psyllium 2 sachets/day (25%), continuing the treatment up to 12 weeks.

Results There was a reduction of bloating in 70% of the Linaclotide group and 80% of the macrogol and psyllium group, an improvement/reduction of tenesmus in 100% of patients in the three groups, with a change in the quality of stool occurring with Bristol Stool Scale assessment. 60% of patients failed to complete therapy in 3 months.

Conclusions Linaclotide is an innovative drug increasingly gaining space in the pharmacopoeia in the possession of doctors for treating intestinal disorders on a functional basis. The limited experience has shown little tolerance of Linaclotide compared to treatments for longer in force, especially in the elderly

Turk J Int Med 2023;5(3):163-169
DOI: 10.46310/tjim.1230072

Keywords: *Irritable bowel syndrome, constipation. pharmacologic therapies. guanylate cyclase-C receptor, elderly patient.*

Received: *January 5, 2023;* ***Accepted:*** *April 10, 2023;* ***Published Online:*** *July 29, 2023*

How to cite this article: *Massimo Magro V. Treatment of Bowel Syndrome with Constipation: An Experience with The Agonist of Guanylate Cyclase Receptor in Advanced Age Patients .Turk J Int Med 2023;5(3):163-169. DOI: 10.46310/tjim.1230072*

Address for Correspondence:
Valerio Massimo Magro, M.D. University of Campania "Luigi Vanvitelli", Piazza L. Miraglia 2, 80100, Naples, Italy
E-mail: valerio_magro@hotmail.com

INTRODUCTION

One of the reasons why the elderly patient often turns to his family doctor or specialist is intestinal discomfort. Irritable bowel syndrome (IBS) is a chronic disease characterized by pain/abdominal discomfort regressing with stools/air for at least three days/month in the last three months. There is one variant with diarrhoea, one with constipation, associated with a rise of hard or caprine stools, difficulty of expulsion and often reduced evacuations number, tenesmus bloating, and one mixed variant. It is one of the most common functional gastrointestinal disorders.[1-3] The prevalence rate is 10-20%, which, according to one estimate, the shape with constipation would be represented by 5% of cases, with a higher prevalence in women. The disease, in any form, adversely affects the quality of life, and it is strongly associated with the use of health care and an increase in costs.[4] We are developing new strategies for treating IBS and have produced several innovative treatments: pharmacological therapies, lifestyle changes and diets, alternative medicine, and gut microbiota (Table 1).[5-7] Then, chronic constipation is a common gastrointestinal disorder disproportionately affecting the elderly. Immobility, polypharmacy, and physiologic changes contribute to its increased prevalence in this population. Most patients are initially treated with lifestyle modifications, such as scheduled toileting after meals, increased fluid intake, and increased dietary fibre intake, then the next step in treating constipation is the use of drugs. Linaclotide (receptor agonist for guanylate cyclase C) is a molecule suitable for treating the symptoms of moderate to severe IBS with constipation. It aimed to assess efficacy and safety in a population of aged subjects.[8]

MATERIAL AND METHODS

We conducted an open-label study in the general medicine setting, enrolling patients who appeared eligible for drug treatment with the study drug during the medical examination. So we examined 20 patients, 18 females and two males, aged 65+6 years (Figure 1-A), with the negativity of blood count, serum iron, inflammatory markers, antibodies for Celiac disease, and blood sugar for the diagnosis of diabetes. In this way, we made a differential diagnosis and eliminated all those organic secondary causes that could cause patient disorders and lead to selection bias. Then, all patients had at least one run in the last year occult blood test or a colonoscopy, and the results were negative. For the characterization of IBS, we used the Rome III criteria, Manning criteria and the Bristol Stool Scale (BSS), and the evaluation criteria recommended by the European Society for Primary Care Gastroenterology (ESPCG).[9-13] The disorders had been present for at least three months and had started more than six months before a correct diagnostic classification. Half of the patients were treated with linaclotide 290 mcg, the other 50% with macrogol 27.6 g (25%) and psyllium 2 sachets/day (25%), continuing the treatment up to 12 weeks (Figure 1-B).

One of the most frequent problems that the doctor feels to raise, especially from the patients who turn to him for solutions, is the problem of constipation,

Table 1. Current therapies and lifestyle recommendations for constipation – predominant irritable bowel syndrome and chronic constipation.

Therapy	Category
Lubipristone	Agent derived from prostoglandin E1
Linaclotide	Activator of the guanylate cyclase-C (GC-C) receptor
Chenodeoxycholic acid	Bile acid modulator
Daikenchuto, hemp seed extract	Herbal medications
Bifidobacterium infantis, Lactobacillus	Probiotics
Prunes, Kiwi	Diet
Prucalopride	Serotonin modulators
Carrying out physical activity, which helps regulate intestinal functions and is a tool for affecting stress and anxiety, eating regularly, skipping meals and taking care to chew calmly and without haste (also to avoid ingesting air, which can help increase intestinal gas and therefore bloating), drink plenty of water, which helps soften the stool	Lifestyle recommendations

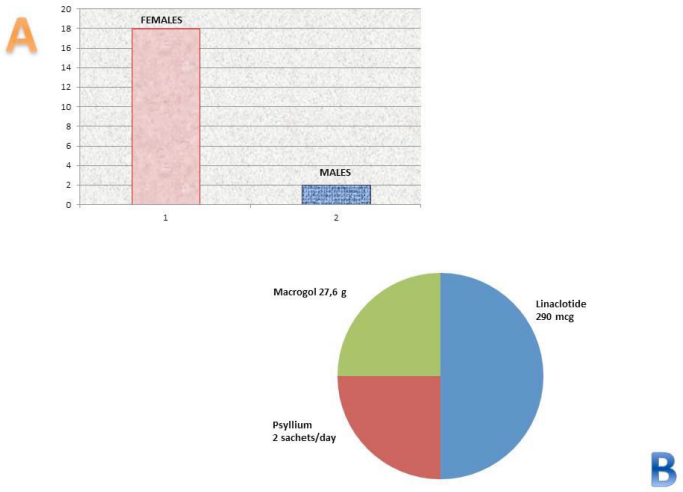

Figure 1. Cohort of patients of the study with proportions according to the gender of the patients (A) and pie chart with treatment regimens (B).

as a variety of irritable bowel syndrome, well present in patients with psychological problems. These are "fragile" subjects, mostly stressed ladies, perfect and flawless secretaries who spend their existence between the practices and the other, trying to give their best, of teachers who spend hours and hours at school, avoiding going to the toilet because this is considered "inconvenient" etc. They are women affected by internal conflicts, depressed, who were ill with their partner and family, exasperated by the psychological defence of their "look" by way of being and doing, who have had a difficult childhood, and who have not acquired the " adult objects ", which are introverted and fought by emotional states, stress, depression, who live under pressure from haste, feed poorly. Depression is also a widespread disease in the elderly population with a high prevalence.

We thus wanted to characterize this sub-population of patients using a validated scale. We assessed the point prevalence of depression and determined associations with disease activity, quality of life, and medication adherence in our elderly patients with IBS in this clinical experience. Depressive symptoms were rated with the Geriatric Depression Scale (GDS) with 15 items, which is a geriatric scale easy to administer, well understandable by the subjects, and usable in a short period in order not to increase the time of the visit, sensitive and specific as well as used also in the gastroenterological field. So, all patients were evaluated through the GDS (7+3) (Figure 2) and, in case of depressive symptoms with a positive score, treated (20%) also pharmacologically (SSRIs).

RESULTS

There was a reduction of bloating in 70% of the Linaclotide group and 80% of the macrogol and psyllium group, and an improvement/reduction of tenesmus in 100% of patients in the three groups, with a change in the quality of stool occurred with BSS assessment. 60% of patients failed to complete therapy of 3 months: there was diarrhoea in 9/10 patients in the Linaclotide group, of which (88% of cases, all aged > 65 years) the extent and the resulting discomfort were so severe as to interrupt the treatment, versus 1 case of diarrhoea (not limiting diarrhoea) in the macrogol-group and zero cases in the psyllium-group.

DISCUSSION

Chemical structure and mechanism of action of linaclotide

Linaclotide is a peptide-guanilin. The guanylin peptides are a family of peptides with a similar structure to the heat-stable enterotoxin produced by Escherichia coli and other enteric bacteria that cause secretory diarrhoea. These peptides have a structure that binds the bound receptors guanylate cyclase; this binding leads to a cascade of intracellular events leading to activation of the transmembrane conductance regulator in cystic fibrosis (CFTR) and subsequent transepithelial efflux of chloride ions (Cl-) and potassium ions (K+) by enterocytes, with a secondary passive secretion of water in the intestinal lümen.14

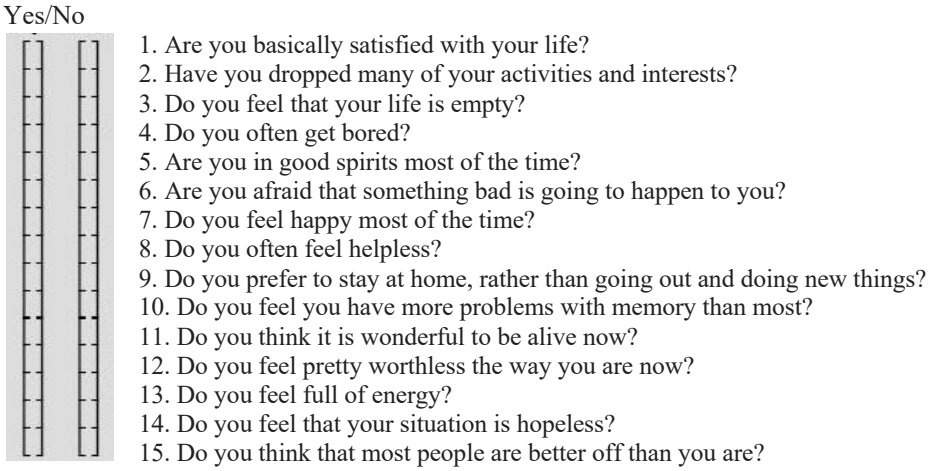

Figure 2. Geriatric Depression Scale (GDS) with 15 items for the evaluation of the presence of depression in elderly subjects. Total GDS: 0-4: normal, depending on age, education, complaints; 5-8: mild; 8-11: moderate; 12-15: severe (GDS maximum score = 15).

Mechanism of action, pharmacokinetics and effects

The molecule is not absorbed, if not in small part, for which it acts mainly locally. In the first study by Andresen *et al*.[15] of 36 women with IBS-shape with constipation, who had received Linaclotide for five days at a dose of 1 gram, there was a significantly accelerated transit through the ascending colon (p = 0.004) with an accelerated total transit time through the colon in the 48 hours (p = 0.01), in the absence of effects on gastric emptying or the transit time at the level of the small intestine. There was a reduction in stool consistency and greater ease of passage of stools.[15] The study by Rao *et al*.[16] tested the effects of the administration of Linaclotide in 395 patients receiving placebo versus 405 receiving Linaclotide: the patients who received the drug treatment in the first phase of the study were randomized to continue treatment with the active drug or stopped it, and they received the placebo. A variation of abdominal pain was observed with a deflection greater symptom pain in the Linaclotide arm.[16] Similarly, in the study of Quigley *et al*.[17], the reduction of bloating was observed; parameters were evaluated weekly. Hence, the authors considered only the group receiving the drug (-40%) compared to placebo (reduced swelling by only 20% in this group of patients) in the 26 weeks of therapy. The same study described an improved state of health (movement skills, self-care, usual activities, pain/discomfort, anxiety/depression) with Linaclotide, from baseline to 12 weeks of treatment, versus placebo.[17] The same period of therapy was adopted in the study of Chey et al.[18], but on a much higher number of patients (n: 804), bringing good results regarding the gravity and extent of symptoms (abdominal fullness, abdominal cramps, constipation) relief of patients, post-treatment satisfaction and with a low NNT for analyzed endpoints. A recent review defines the promising use.19

Side effects and poor representativeness of the elderly in the studies conducted on linaclotide

The most frequent side effect of the drug is diarrhoea, usually but not always starting within two weeks of treatment. Other side effects consist of intestinal bloating, flatulence, epigastric abdominal pain, sense of abdominal tension, headache, gastroesophageal reflux and vomiting. There is to say that patients in the study of Chey had a mean age of 44 years, as well as those in the study by Rao (mean age 43.5 years)[16,18], well away from the age of the studied patients. The elderly patient is more susceptible to fluid balance alterations with adverse events ranging from neurological symptoms to easier falls and electrolyte abnormalities. A more recent Japanese experience, with a well-designed randomized controlled trial, demonstrated the efficacy of even higher drug dosages. However, it largely excluded elderly patients.[20] Also, in this trial, as in another trial of the eastern population, always excluding the elderly population, diarrhoea represented a frequent adverse event.21 Several causes may alter these delicate balances, and diarrhoea in the elderly is undoubtedly one of them. Even drugs in this patient population are used under close monitoring by the physician, such as loop diuretics (furosemide)[22] and thiazidic agents[23],

and some antidiabetic drugs (gliflozins)[24]. The same data sheet of Linaclotide, without contraindication, recommended caution in this cluster.25 Recent experience evaluating a large sample of subjects reported satisfactory outcomes with a low percentage of diarrhoea after several weeks of treatment, using lower dosages of the molecule.[26]

Experience limitations

The clinical experience focused on a small cohort of patients, so the study sample may not represent the universe of the elderly. The study was conducted only in the open phase, so the methodology used may have unintentionally generated bias in the data, both on the subjective (a load of medical observers) that the objective (a load of subjects studied and the conditions of the study), because the condition investigated. Different scales used suffer from a certain degree of subjectivity, despite the different items. However, given the few patients, the authors were careful with the objectivity of their evaluations. Our experience, however, is quite similar to that of a Portuguese group. However, the study of those authors has not been carried out on the territory. It has been conducted with certainly more rigorous criteria, on the double of the patients seen by us.[27] Diarrhoea has also previously been reported as a potential consequence of the linaclotide-mediated increase in gastrointestinal transit and fluid secretion and, as such, was the most commonly reported adverse event during the recent Alpine study with a population that tolerated the four-week treatment well but had an average age of 50 years.[28]

CONCLUSIONS

Linaclotide is an innovative drug that is increasingly gaining space in the pharmacopoeia in the possession of doctors for the treatment of intestinal disorders on a functional basis, as demonstrated in Italy by a recent survey promoted by the Italian Association of Hospital Gastroenterologists (Associazione Italiana Gastroenterologi Ospedalieri, AIGO).[29] The limited experience has shown little tolerance of Linaclotide compared to treatments for longer in force, especially in the elderly. In particular, among the adverse events, diarrhoea, well known and described in the technical sheet, caused by increased secretory activity visceral stimulated by the guanylate cyclase C, has proved a limiting factor of the treatment, even in cases where constipation and symptoms accessories were subject to improvement. Use caution in the elderly needs, more in patients of older age and should be carefully considered in frail elderly suffering from constipation. We would need targeted blind studies eminently on elderly patients, with particular regard for those also suffering from severe, moderate depression and dementia, to understand the strengths and limitations of this type of treatment in the geriatric field.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

The author confirms that the patient consent was not required for this work. For investigations involving human participants this research was conducted in accordance with the principles embodied in the Declaration of Helsinki and in accordance with local statutory requirements. All participants of this the study are not recognizable in any way and there is no data that can be traced back to the identity of the individual.

Authors' Contribution

Study Conception: VMG; Study Design: VMG; Literature Review: VMG; Critical Review: VMG; Data Collection and/or Processing: VMG; Analysis and/or Data Interpretation: VMG; Manuscript preparing: VMG.

REFERENCES

1. Torii A, Toda G. Management of irritable bowel syndrome. Intern Med. 2004 May;43(5):353-9. doi: 10.2169/internalmedicine.43.353.
2. Rubin G, De Wit N, Meineche-Schmidt V, Seifert B, Hall N, Hungin P. The diagnosis of IBS in primary care: consensus development using nominal group technique. Fam Pract. 2006 Dec;23(6):687-92. doi: 10.1093/fampra/cml050.
3. Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther. 2003 Mar 1;17(5):643-50. doi: 10.1046/j.1365-2036.2003.01456.x.
4. Doshi JA, Cai Q, Buono JL, Spalding WM, Saro-

cco P, Tan H, Stephenson JJ, Carson RT. Economic burden of irritable bowel syndrome with constipation: a retrospective analysis of health care costs in a commercially insured population. J Manag Care Spec Pharm. 2014 Apr;20(4):382-90. doi: 10.18553/jmcp.2014.20.4.382.
5. Mayer EA. Clinical practice. Irritable bowel syndrome. N Engl J Med. 2008 Apr 17;358(16):1692-9. doi: 10.1056/NEJMcp0801447.
6. Lazaraki G, Chatzimavroudis G, Katsinelos P. Recent advances in pharmacological treatment of irritable bowel syndrome. World J Gastroenterol. 2014 Jul 21;20(27):8867-85. doi: 10.3748/wjg.v20.i27.8867.
7. Maneerattanaporn M, Chang L, Chey WD. Emerging pharmacological therapies for the irritable bowel syndrome. Gastroenterol Clin North Am. 2011 Mar;40(1):223-43. doi: 10.1016/j.gtc.2010.12.002.
8. Yu SW, Rao SS. Advances in the management of constipation-predominant irritable bowel syndrome: the role of linaclotide. Therap Adv Gastroenterol. 2014 Sep;7(5):193-205. doi: 10.1177/1756283X14537882.
9. Spiller R, Aziz Q, Creed F, Emmanuel A, Houghton L, Hungin P, Jones R, Kumar D, Rubin G, Trudgill N, Whorwell P; Clinical Services Committee of The British Society of Gastroenterology. Guidelines on the irritable bowel syndrome: mechanisms and practical management. Gut. 2007 Dec;56(12):1770-98. doi: 10.1136/gut.2007.119446.
10. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006 Apr;130(5):1480-91. doi: 10.1053/j.gastro.2005.11.061.
11. Malagelada JR. A symptom-based approach to making a positive diagnosis of irritable bowel syndrome with constipation. Int J Clin Pract. 2006 Jan;60(1):57-63. doi: 10.1111/j.1368-5031.2005.00744.x.
12. Jeong H, Lee HR, Yoo BC, Park SM. Manning criteria in irritable bowel syndrome: its diagnostic significance. Korean J Intern Med. 1993 Jan;8(1):34-9. doi: 10.3904/kjim.1993.8.1.34.
13. Brandt LJ, Prather CM, Quigley EM, Schiller LR, Schoenfeld P, Talley NJ. Systematic review on the management of chronic constipation in North America. Am J Gastroenterol. 2005;100 Suppl 1:S5-S21. doi: 10.1111/j.1572-0241.2005.50613_2.x.
14. Corsetti M, Tack J. Linaclotide: A new drug for the treatment of chronic constipation and irritable bowel syndrome with constipation. United European Gastroenterol J. 2013 Feb;1(1):7-20. doi: 10.1177/2050640612474446.
15. Andresen V, Camilleri M, Busciglio IA, Grudell A, Burton D, McKinzie S, Foxx-Orenstein A, Kurtz CB, Sharma V, Johnston JM, Currie MG, Zinsmeister AR. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. Gastroenterology. 2007 Sep;133(3):761-8. doi: 10.1053/j.gastro.2007.06.067.
16. Rao S, Lembo AJ, Shiff SJ, Lavins BJ, Currie MG, Jia XD, Shi K, MacDougall JE, Shao JZ, Eng P, Fox SM, Schneier HA, Kurtz CB, Johnston JM. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol. 2012 Nov;107(11):1714-24. doi: 10.1038/ajg.2012.255.
17. Quigley EM, Tack J, Chey WD, Rao SS, Fortea J, Falques M, Diaz C, Shiff SJ, Currie MG, Johnston JM. Randomised clinical trials: linaclotide phase 3 studies in IBS-C - a prespecified further analysis based on European Medicines Agency-specified endpoints. Aliment Pharmacol Ther. 2013 Jan;37(1):49-61. doi: 10.1111/apt.12123.
18. Chey WD, Lembo AJ, Lavins BJ, Shiff SJ, Kurtz CB, Currie MG, MacDougall JE, Jia XD, Shao JZ, Fitch DA, Baird MJ, Schneier HA, Johnston JM. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol. 2012 Nov;107(11):1702-12. doi: 10.1038/ajg.2012.254.
19. Layer P, Stanghellini V. Review article: Linaclotide for the management of irritable bowel syndrome with constipation. Aliment Pharmacol Ther. 2014 Feb;39(4):371-84. doi: 10.1111/apt.12604.
20. Fukudo S, Miwa H, Nakajima A, Haruma K, Kosako M, Nakagawa A, Akiho H, Yamaguchi Y, Johnston JM, Currie M, Kinoshita Y. A randomized controlled and long-term linaclotide study of irritable bowel syndrome with constipation patients in Japan. Neurogastroenterol Motil. 2018 Dec;30(12):e13444. doi: 10.1111/nmo.13444.
21. Yang Y, Fang J, Guo X, Dai N, Shen X, Yang Y, Sun J, Bhandari BR, Reasner DS, Cronin JA, Currie MG, Johnston JM, Zeng P, Montreewasuwat N, Chen GZ, Lim S. Linaclotide in irritable bowel syndrome with constipation: A Phase 3 randomized trial in China and other regions. J Gastroenterol Hepatol. 2018 May;33(5):980-9. doi: 10.1111/jgh.14086.
22. Rowat A, Graham C, Dennis M. Dehydration in hospital-admitted stroke patients: detection, frequen-

cy, and association. Stroke. 2012 Mar;43(3):857-9. doi: 10.1161/STROKEAHA.111.640821.
23. Chow KM, Kwan BC, Szeto CC. Clinical studies of thiazide-induced hyponatremia. J Natl Med Assoc. 2004 Oct;96(10):1305-8.
24. Cersosimo E, Solis-Herrera C, Triplitt C. Inhibition of renal glucose reabsorption as a novel treatment for diabetes patients. J Bras Nefrol. 2014 Jan-Mar;36(1):80-92. doi: 10.5935/0101-2800.20140014.
25. Allegato I. Riassunto Delle Caratteristiche Del Prodotto. Available at: https://ec.europa.eu/health/documents/community-register/2012/20121126124562/anx_124562_it.pdf. Accessed December 15, 2022.
26. Schoenfeld P, Lacy BE, Chey WD, Lembo AJ, Kurtz CB, Reasner DS, Bochenek W, Tripp K, Currie MG, Fox SM, Blakesley RE, O'Dea CR, Omniewski ND, Hall ML. Low-dose linaclotide (72 µg) for chronic ıdiopathic constipation: A 12-week, randomized, double-blind, placebo-controlled trial. Am J Gastroenterol. 2018 Jan;113(1):105-14. doi: 10.1038/ajg.2017.230.
27. Mascarenhas-Saraiva MJ, Mascarenhas-Saraiva M. Effectiveness and tolerability of linaclotide in the treatment of IBS-C in a "real-life" setting: Results from a Portuguese single-center study. Neurogastroenterol Motil. 2019 Feb;31(2):e13508. doi: 10.1111/nmo.13508.
28. Pohl D, Fried M, Lawrance D, Beck E, Hammer HF. Multicentre, non-interventional study of the efficacy and tolerability of linaclotide in the treatment of irritable bowel syndrome with constipation in primary, secondary and tertiary centres: the Alpine study. BMJ Open. 2019 Dec 30;9(12):e025627. doi: 10.1136/bmjopen-2018-025627.
29. Soncini M, Stasi C, Usai Satta P, Milazzo G, Bianco M, Leandro G, Montalbano LM, Muscatiello N, Monica F, Galeazzi F, Bellini M; AIGO. IBS clinical management in Italy: The AIGO survey. Dig Liver Dis. 2019 Jun;51(6):782-9. doi: 10.1016/j.dld.2018.10.006.