Medical Case Reports Journal

Available Online: https://mcrj.edwiserinternational.com

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 "Luigi Vanvitelli", Piazza L. Miraglia 2, 80100, Naples, Italy

Article info

Received 20 January 2022
Revised 20 November 2022
Available Online 12 Dec 2022

*Corresponding author:
Dr. Valerio Massimo Magro, M.D; Department of Internal Medicine and Geriatry, University of Campania "Luigi Vanvitelli", Piazza L. Miraglia 2, 80100, Naples, Italy.

Abstract

The irritating 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, wanting to test a molecule recently approved for the treatment of 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 expose the results of our experience.

***Keywords**: Irritable bowel syndrome; Constipation; Pharmacologic therapies; Guanylate cyclase-C receptor; Elderly patient*

Abbreviations

IBS: Irritable Bowel Syndrome; BSS: Bristol Stool Scale; ESPCG: European Society for Primary Care Gastroenterology; GDS: Geriatric Depression Scale; SSRIs: Selective Serotonin Reuptake Inhibitors; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator; AIGO: Associazione Italiana Gastroenterologi Ospedalieri.

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 3 days/month in the last 3 months. There is one variant with diarrhea, one with constipation, associated with a rise of hard or caprine stools, difficult of expulsion and often reduced evacuations number, with tenesmus bloating, and one mixed variant. It is one of the most common functional gastrointestinal disorders1-3. The prevalence rate is 10-20%, which, according to one estimate, the shape with constipation would be represented by the 5% of cases, with 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 increase of costs4. We are developing new strategies for the treatment of IBS and have been produced several innovative treatments: pharmacological therapies, lifestyle changes and diets, alternative medicine, gut microbiota5-7 (Table 1). 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 fiber intake, then the next step in the treatment of constipation is the use of drugs. Linaclotide (receptor agonist for the guanylate cyclase C) is a molecule suitable for the treatment of the symptoms of moderate to severe IBS with constipation. It aimed to assess efficacy and safety in a population of aged subjects8.

Methods

We conducted an open-label study in the general medicine setting, enrolling patients who during the medical examination appeared eligible for drug treatment with the study drug. So, we examined 20 patients, 18 females and 2 males, aged 65+6 years (Figure 1-A), with negativity of blood count, serum iron, inflammatory markers, antibodies for celiac disease, 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 they resulted were negative. For the characterization of IBS we used the Rome III criteria, Manning criteria and the Bristol Stool Scale (BSS), as well as 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. One of the most frequent problems that the doctor feels to raise, especially from the patients who turn to him for solution is the problem of constipation, 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 are ill with their partner and family, exasperated by the psychological defense of their "look", by the way of being and doing, who have had a difficult childhood, and 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, usable in a short period of time 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). Half of the patients was 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).

Table 1: Current Therapies and Lifestyle recommendations for Constipation-Predominant Irritable Bowel Syndrome.

Therapy	Category	Therapy	Category
Lubipristone	Agent derived from prostaglandin E1	Bifidobacterium infantis, Lactobacillus	Probiotics
Linaclotide	Activator of the guanylate cyclase-C (GC-C) receptor	Prunes, Kiwi	Diet
Chenodeoxycholic Acid	Bile Acid Modulator	Prucalopride	Serotonin modulators
Daikenchuto, hemp seed extract	Herbal Medications	Carrying out physical activity, which helps regulate intestinal functions and, moreover, is a tool for affecting stress and anxietyeating 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

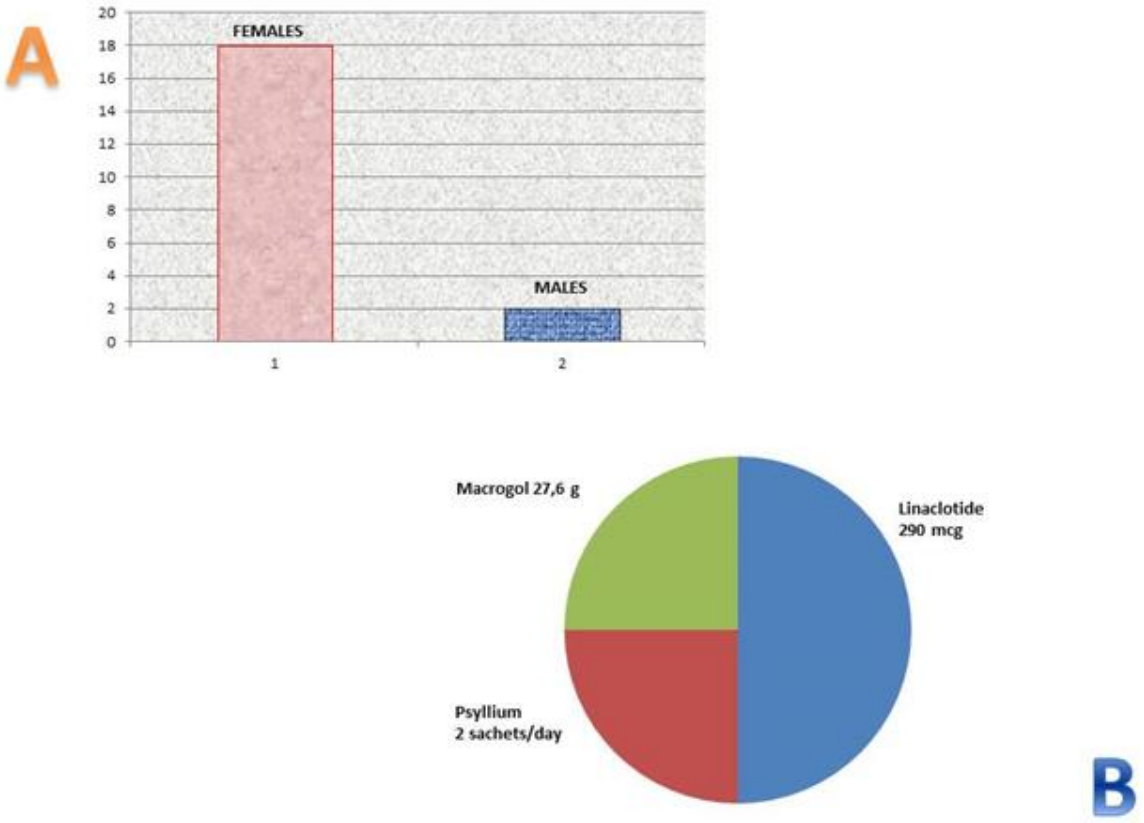

Figure 1 (A-B): Cohort of patients of the study with proportions according to the gender of the patients (A) and pie chart with treatment regimens (B).

Yes / No

- [] [] 1. Are you basically satisfied with your life?
  [] [] 2. Have you dropped many of your activities and interests?
  [] [] 3. Do you feel that your life is empty?
  [] [] 4. Do you often get bored?
  [] [] 5. Are you in good spirits most of the time?
  [] [] 6. Are you afraid that something bad is going to happen to you?
  [] [] 7. Do you feel happy most of the time?
  [] [] 8. Do you often feel helpless?
  [] [] 9. Do you prefer to stay at home, rather than going out and doing new things?
  [] [] 10. Do you feel you have more problems with memory than most?
  [] [] 11. Do you think it is wonderful to be alive now
  [] [] 12. Do you feel pretty worthless the way you are now
  [] [] 13. Do you feel full of energy?
  [] [] 14. Do you feel that your situation is hopeless?
  [] [] 15. Do you think that most people are better off than you are?

TOTAL GDS:
(GDS maximum score = 15)
0 - 4 normal, depending on age, education, complaints
5 - 8 mild
8 - 11 moderate
12 - 15 severe

Figure 2: Geriatric Depression Scale (GDS) with 15 items for the evaluation of the presence of depression in elderly subjects.

Results

There was a reduction of bloating in 70% of Linaclotide-group and in 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 occurred with BSS assessment. The 60% of patients failed to complete therapy of 3 months: there was diarrhea in 9/10 patients in 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 diarrhea (not limiting diarrhea) in the macrogol-group and zero case in the psyllium-group.

Discussion

Chemical structure and mechanism of action of linaclotide. Linaclotide is a peptide-guanilin. The guanilin peptides are a family of peptides with similar structure to the heat-stable enterotoxin produced by Escherichia coli and other enteric bacteria that cause secretory diarrhea. 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 lumen14.

Mechanism of action, pharmacokinetics and effects. The molecule is not absorbed if not in small part for which it acts mainly at the local level. In a first study of Andresen et al. of 36 women with IBS-shape with constipation, who had received Linaclotide for 5 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 reduction of stool consistency and greater ease of passage of stools15. In the study by Rao et al. were tested the effects of 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 they stopped it and they received the placebo. It was observed a variation of abdominal pain with a deflection greater symptom pain in the Linaclotide arm16. Similarly, in the study of Quigley et al. it was observed the reduction of bloating, paramether evaluated weekly, so the authors considered only the group receiving the drug (-40%) compared to placebo (reduction of 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 placebo17. The same period of therapy was adopted in the study of Chey WD et al., but on a much higher number of patients (804), bringing good results in regard to the gravity and extent of symptoms (abdominal fullness, abdominal cramps, constipation) relief of patients, post-treatment satisfaction and with a low NNT for analyzed endpoints18. A recent review defines the promising use19.

Side effects and poor representativeness of the elderly in the studies conducted on linaclotide. The most frequent side effect of the drug is diarrhea, usually but not always starting within 2 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 of the study by Rao (mean age 43.5 years), well away from the age of the studied patients. The elderly patient is more susceptible to alterations of your fluid balance with adverse events ranging from neurological symptoms and the easier falls and electrolyte abnormalities. There is to say that patients in the study of Chey had a mean age of 44 years, as well as those of the study by Rao (mean age 43.5 years), well away from the age of the studied patients. A more recent Japanese experience, with a well-designed randomized controlled trial, which demonstrated an efficacy of even higher dosages of the drug, however, largely excluded in elderly patients20. Also in this trial, as in another trial of the eastern population, always excluding the elderly population, diarrhea represented a very frequent adverse event21. The elderly patient is more susceptible to alterations of your fluid balance with adverse events ranging from neurological symptoms and the easier falls and electrolyte abnormalities. There are several causes that may alter these delicate balances and diarrhea in the elderly it is undoubtedly one of them. Even drugs in this patient population are in fact used under close monitoring by the physician, such as loop diuretics (furosemide)22 and thiazidic agents23, and some antidiabetic drugs (glifozines)24. The same data sheet of Linaclotide, without controindicate its, recommended caution in this cluster25. Recent experience evaluating a large sample of subjects reported satisfactory outcomes with a low percentage of

diarrhea after several weeks of treatment, using lower dosages of the molecule26.

Experience limitations. The clinical experience focused on a small cohort of patients, so that the study sample may not be representative of the universe of the elderly. The study was conducted only in open phase, so the methodology used may have unintentionally generated bias on the data, both on the subjective (a load of medical observers) that the objective of (a load of subjects studied and the conditions of the study), because the condition investigated and different scales used suffer from a certain degree of subjectivity, despite the different items. However, given the not significant number of patients, the authors were careful to objectivity of its evaluations. Our experience, however, is quite similar to that of a Portuguese group, although the study of those authors has not been carried out on the territory and has been conducted with certainly more rigorous criteria, on the double of the patients seen by us27. Diarrhoea has also previously been reported as a potential consequence of 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 years28.

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 population. In particular, among the adverse events, diarrhea, well known and described in the technical sheet, caused by increased secretory activity visceral stimulated by the guanylate cyclase C, it has proved 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, as well as suffering from dementia, to understand well the strengths and limitations of this type of treatment in the geriatric field.

Author Contribution

Magro VM was the primary researchers and wrote the manuscript. Magro VM provided research and editing assistance to the manuscript; he provided research and editing assistance to the manuscript. Magro VM contributed to overall article design, data collection as well as revising and approving the manuscript. All authors are meeting the criteria of authorship.

Conflicts of interest and Financial Disclosures

None.

Previous Presentation

This case was presented at the Oral Communications and Posters of the 116th National Congress of the Italian Society of Internal Medicine Rome, 10-12 October 2015 which was published in the Internal and Emergency Medicine Volume 10 - Supplement - February 2016.

References

1. Torii A, Toda G. Management of irritable bowel syndrome. Intern Med. 2004 May;43(5):353-9.
2. Rubin G, De Wit N, Meineche-Schmidt V, et al. The diagnosis of IBS in primary care: consensus development using nominal group technique. Fam Pract. 2006 Dec;23(6):687-92.
3. Hungin AP, Whorwell PJ, Tack J et. Al. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40000 subjects. Aliment Pharmacol Ther. 2003;17(5):643-650.
4. Doshi JA, Cai Q, Buono JL, et al. 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.
5. Mayer EA. Clinical practice: Irritable bowel syndrome. New Engl J Med 2008; 358: 1692–1699.
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.
7. Maneerattanaporn M, Chang L, Chey WD. Emerging pharmacological therapies for the irritable bowel syndrome. Gastroenterol Clin North Am 2011; 40: 223-243.
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.

9. Spiller R, Aziz Q, Creed F, et al. Guidelines on the irritable bowel syndrome:mechanisms and practical management. Gut. 2007; 56(12):1770-1798.
10. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disoders. Gastroenterology. 2006; 130(5): 1480-1491.
11. Malagelada JR. A symptom-based approach to making a positive diagnosis of irritabile bowel syndrome with costipation. Int Clin Pract. 2006;60 (1):57-63
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.
13. Brandt LJ, Prather CM, Quigley EM, et al. Systematic review on the management of chronic costipation in North America. Am J Gastroenterol. 2005; 100 Suppl 1: S5-S21
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.
15. Andresen V, Camilleri M, Busciglio IA, et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. Gastroenterology 2007; 133: 761-768
16. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomizzed, controlled trial with a 4-week, randomizzed withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with costipation. Am J Gatroenterol. 2012; 107: 1714-1724.
17. Quigley EM, Tack J, Chey WD, et al. Randomised clinical trials: linaclotide phase 3 studies in IBC-C – a specified further analysis based on European Medicines Agency-specified endpoints. Aliment Pharmacol Ther. 2013; 37(1): 49-61
18. Chey WD, Lembo AJ, Lavins BJ, et al. 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; 107: 1702–1712.
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.
20. Fukudo S, Miwa H, Nakajima A, et al. A randomized controlled and long-term linaclotide study of irritable bowel syndrome with constipation patients in Japan. Neurogastroenterol Motil. 2018 Dec;30(12):e13444.
21. Yang Y, Fang J, Guo X, et al. Linaclotide in irritable bowel syndrome with constipation: A Phase 3 randomized trial in China and other regions. J Gastroenterol Hepatol. 2018 May;33(5):980-989.
22. Rowat A, Graham C, Dennis M. Dehydration in hospital-admitted stroke patients: detection, frequency, and association. Stroke. 2012 Mar;43(3):857-9.
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.
25. http://ec.europa.eu/health/documents/community-register/2012/20121126124562/anx_124562_it.pdf
26. Yang Y, Fang J, Guo X, et al. Low-Dose Linaclotide (72 µg) for Chronic Idiopathic Constipation: A 12-Week, Randomized, Double-Blind, Placebo-Controlled Trial. Am J Gastroenterol. 2018 Jan;113(1):105-114.
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.
28. Pohl D, Fried M, Lawrance D, et al. 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.
29. Soncini M, Stasi C, Usai Satta P, et al. IBS clinical management in Italy: The AIGO survey. Dig Liver Dis. 2019 Jun;51(6):782-789.