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LINACLOTIDE: A NEW CURE FOR PEDIATRIC FUNCTIONAL CONSTIPATION

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Abstract : Linaclotide, a secretory agent acting on Guanylyl cyclase C in the intestinal epithelium is approved for pediatric functional constipation in the age group between 6 years and 17 years by FDA in June 2023. Linaclotide is similar in structure to human guanylin and uroguanylin which acts as an agonist for Guanylyl cyclase C (GC-C)[1]. It was previously approved for treating constipation-predominant Irritable bowel syndrome and chronic idiopathic constipation in adults. Functional constipation is idiopathic constipation that occurs most commonly in children at school entry age with a history of ≤2 defecations in the toilet per week or ≥1 episode of faecal incontinence per week[2]. So far the management included stool softeners, enema, laxatives or behavioral management in functional constipation. Recently FDA approved an oral pharmacological agent LINACLOTIDE for functional constipation in children between 6 years and 17 years. This review will briefly summarize the pharmacological properties and the use of Linaclotide in pediatric functional constipation.

IndexTerms - Functional constipation, Linaclotide, GC-C

INTRODUCTION- Functional constipation

Functional constipation in the pediatric population is very common worldwide having a prevalence of 32.2%[3]. it is Idiopathic constipation or faecal withholding that occurs in the pediatric age group without any underlying organic cause. According to Rome IV diagnostic criteria for defecatory disorders in children and adolescents, constipation occurs in children above 4 years of developmental age with a history of ≤2 defecations in the toilet per week or ≥1 episode of faecal incontinence per week with a history of painful hard bowel movements[2]. On examination a large faecal mass per rectum. Treatment included toilet training, stool-softening agents, education, laxatives, etc[4]. Pelvic physiotherapy and Neuro-stimulation are some of the non-medical management where patients have medication-refractory constipation.

LINACLOTIDE:

MECHANISM OF ACTION:

Linaclotide acts by activation of GC-C increases intracellular cGMP which in turn increases chloride and bicarbonate secretion in the gut lumen through PKG-2 dependent phosphorylation of the cystic fibrosis transmembrane conductance regulator (CFTR) channel. Increases in luminal chloride and bicarbonate ions lead to an increase in luminal water content and an increase in gut motility[5].

Guanylyl cyclase C:

Guanylyl cyclase C also known as heat-stable enterotoxin receptor (hSTAR) is an enzyme that codes for the GUCY2C gene in humans. This enzyme is abundant in the apical membrane of the intestinal epithelium and brain dopamine neurons. In the Intestine, it targets heat-stable enterotoxins from pathogenic bacteria and contains three disulfide bonds. Guanylin and Uroguanylin, endogenous peptides with two disulfide bonds compete with hSTAR in the extracellular domain. Linaclotide acts on GC-C and activates it[1].

CLINICAL STUDIES:

A Phase 3 randomized, double-blinded, multicentric, placebo-controlled clinical trials were conducted to evaluate the safety and efficacy of Linaclotide in comparison with placebo for functional constipation in pediatric age group 6- 17 years conducted by Allergan Inc., collaborated with Ironwood Pharmaceuticals. This study included 328 pediatric participants both male and female who fits in Rome diagnostic criteria for defecatory disorders in children and adolescents with < 3 spontaneous bowel movements (SBM) in a week or with 1 or more of the below said criteria in a week or 2 months before the visit. The study participants with functional constipation were given 72mcg of Linaclotide single dose orally with a matching placebo to another arm of participants with functional constipation.

The efficacy of Linaclotide 72mcg orally once daily is assessed by checking the change in spontaneous bowel movements from a baseline value and the change in stool consistency from a baseline value. The baseline SBM frequency rate is 1.2 and at the end of 12 weeks, the mean change in SBM frequency rate is 2.6 whereas in the placebo group, it is 1.3. The results have shown significant improvement compared to the placebo group both clinically and statistically[6].
Desiree F.Baaleman et al; A retrospective chart review in the use of Linaclotide in Functional constipation and IBS-C included 60 children with FC and 33 children with IBS-C concluded Linaclotide significantly improved GI motility. Above 40% of the patients benefited and improved in their constipation symptoms[7].

Pharmacokinetics and Pharmacodynamics:
Linaclotide has a local effect on the gastric lumen with the least systemic absorption on oral administration. It is not degraded by gastric acids. They get activated by oxidation in the GI tract and deactivated by reduction and excreted in the faeces. As it shows very minimal systemic absorption the parameters like plasma maximum concentration, area under the curve (AUC), and half-life cannot be calculated. No drug interactions or food interactions are noted. The most common side effect noted is diarrhoea immediately after 2 weeks of Linaclotide therapy[8].

Dosage: The dose recommended for functional constipation is 72mcg per oral once daily[9].

Adverse effects: Diarrhoea was the most common adverse effect followed by nausea, abdominal pain and severe dehydration[5,9]. Rarely hypersensitivity reactions like anaphylaxis, rashes, and angioedema[8].

Contraindication: Linaclotide causes severe dehydration so it is contraindicated in children less than 2 years of age. Absolute contraindication in Patients with any obstructive gastrointestinal problem[9].

Warning and precaution: severe dehydration is the most common adverse effect so hydration is very essential in patients taking Linaclotide[9].

Conclusion: Linaclotide is the drug approved for Functional constipation in pediatric patients in the age group between 6 years and 17 years by FDA in June 2023. In trials, it has shown good efficacy and safety in patients with Functional constipation. The most common side effects are dehydration and diarrhea. It is contraindicated in pediatrics aged less than 2 years due to deadly dehydration. No systemic side effects are seen as the drug acts locally in the gastrointestinal tract. Detailed research studies are needed for a better understanding of the efficacy, safety, and tolerability of the drug Linaclotide with different doses in pediatric and adolescent age groups.

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