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MINIREVIEWS

Inhibition of ileal bile acid transporter: An emerging therapeutic strategy for chronic idiopathic constipation

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Abstract

Chronic idiopathic constipation is a common disorder of the gastrointestinal tract that encompasses a wide profile of symptoms. Current treatment options for chronic idiopathic constipation are of limited value; therefore, a novel strategy is necessary with an increased effectiveness and safety. Recently, the inhibition of the ileal bile acid transporter has become a promising target for constipation-associated diseases. Enhanced delivery of bile acids into the colon achieves an accelerated colonic transit, increased stool frequency, and relief of constipation-related symptoms. This article provides insight into the mechanism of action of ileal bile acid transporter inhibitors and discusses their potential clinical use for pharmacotherapy of constipation in chronic idiopathic constipation.

Key words: Bile acids; Chronic idiopathic constipation; Ileal bile acid transporter

Core tip: Increasing the delivery of bile acids to the colon is considered one of the most promising treatment approaches for patients with constipation. This review discusses recent advances in the field of inhibitors of bile acid transporters and future perspectives in their clinical use.

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INTRODUCTION

Chronic idiopathic constipation (CIC) and constipation-predominant irritable bowel syndrome (IBS-C) are common motility disorders of the lower gastrointestinal tract. CIC occurs in 2%-28% of the population worldwide[1], whereas the overall prevalence of IBS is estimated at approximately 12%-20%[2,3]. CIC and IBS are more commonly reported in women rather than men; however, functional constipation appears to become more frequent with age, and is primarily found in patients over 65 years, while IBS mostly affects people younger than 50 years of age.

The symptoms of CIC and IBS-C are diverse; however, a wide range of gastrointestinal symptoms in CIC overlap with those reported by IBS-C patients and include bloating, infrequent bowel movements, and abdominal pain and/or discomfort[4-6]. Additionally, recent studies demonstrate that incomplete emptying, painful defecation, straining, and hard and lumpy stools are the chief complaints among CIC patients[1,7]. Of note, the major factors distinguishing between CIC and IBS-C are the severity and nature of the abdominal pain[5]. Although the symptoms of CIC and IBS-C are not life threatening, their chronic nature may cause considerable morbidity and can deteriorate the patient's quality of life.

Currently available pharmacologic treatments for CIC and IBS-C are directed mainly towards increasing fecal residue and stimulating colon activity, and include laxatives, prokinetics, secretagogues,and bile acid (BA) modulators (Table 1). Consequently, reduced visceral sensitivity/pain and improved peristalsis in the upper and lower gastrointestinal tract are observed[2,26,29-31]. Unfortunately, these treatment options are often of limited efficacy, and according to Johanson *et al*[32], approximately 50% of patients are not satisfied with their constipation therapies. Thus, a novel therapeutic strategy is urgently needed. Increasing the delivery of BAs to the colon is considered one of the most promising treatment approaches for patients with constipation[33].

ILEAL BA TRANSPORTER AS PHARMACOLOGIC TARGET IN CONSTIPATION

BAs are synthesized in the liver through hydroxylation and conjugation of cholesterol to chenodeoxycholic acid (CDCA) and cholic acid. Their biosynthetic pathway includes a series of enzymatic conversions initiated by cholesterol-7α-hydroxylase, which simultaneously constitutes a rate-limiting factor (Figure 1). The rate of hepatic BA synthesis in humans is reflected by the measurement of serum concentrations of the nonspecific marker 7α-hydroxy-4-cholesten-3-one (C4)[11].

Enterohepatic circulation (EHC) is an important mechanism responsible for the movement of BA molecules from the liver to the small intestine and back to the liver. EHC of BAs depends on absorption of BA in the terminal ileum and colon. Once synthesized, BAs are secreted from the hepatocytes into the canalicular tube and traverse through the biliary tract into the intestine, where they play a crucial role in absorption and solubilization of cholesterol, dietary lipids, and fat-soluble vitamins[36]. Some BAs are reabsorbed *via* a passive mechanism, mostly in the upper intestine. However, almost 95% are reclaimed by the ileal BA transporter (IBAT), also known as apical sodium-dependent BA transporter, abundantly expressed in the terminal ileum[8,10,33,36]. This sodium- and potential-driven transporter reabsorbs BAs from the lumen of the intestine through the apical brush border membrane[12]. This mechanism is considered a major determinant of BA pool size in the human body and is an essential regulator of lipid and cholesterol homeostasis. BAs are then recycled back into the liver *via* the portal vein for their resecretion into bile, which constitutes the final step of the EHC.

The equilibrium between BA synthesis, secretion, and intestinal reabsorption is vital for the maintenance of important physiologic processes, especially in the case of colonic secretion and motility. Wong *et al*[11] found a correlation between BA synthesis and constipation, which results from the reduction of hepatic BA synthesis and lower stool BA excretion. Furthermore, mutations in the IBAT gene (*SLC10A2*) contribute to the disruption of EHC caused by BA malabsorption, in which congenital diarrhea, steatorrhea, and low level of plasma cholesterol are present[12,13]. The same effect of malabsorption was also observed in IBAT-knockout mice[12]. Hence, a number of studies targeted impaired IBAT reabsorption due to its role in colonic transit and its considerable contribution to the effectiveness of the treatment of constipation[11].

Inhibition of IBAT results in a reduction of ileal BA reabsorption, therefore, the concentration of BAs in the proximal colon is increased, similar to the infusion of both conjugated and non-conjugated BAs into the colon. This promotes intracolonic secretion *via* several mechanisms, including intracellular activation of secretory mechanisms, *e.g.,* adenylate cyclase, enhancement of mucosal permeability[14], and inhibition of apical Cl^-/OH^- exchange[15]. A study by Bampton *et al*[16] revealed a twofold increase in proximal colonic propagating sequence frequency in healthy volunteers after administration of 1 mmol of CDCA. Moreover, administration of CDCA in patients with chronic constipation, at dosages of 750-1000 mg/day, resulted in an increase of bowel movements, decrease in stool consistency, and shortened period of fecal excretion[18,20]. Treatment with sodium chenodeoxycholate at a low dosage of 0.5-1.0 g/d also ameliorated colonic transit, and enabled frequent defecation in healthy volunteers

Table 1 Most common types of drugs used for the treatment of chronic idiopathic constipation and constipation-predominant irritable bowel syndrome

Drug class	Generic name	Phase of clinical trial/approval status	Proposed mechanism of action	Therapeutic effect	Most frequent adverse effect	Ref.
Secretagogue	Linaclotide	Ⅲ/FDA approval (2012)	GC-C agonist	Antinociceptive and antihyperalgesic. Increases intestinal fluid, accelerates GI transit, reduces abdominal pain	Mild or moderate diarrhea	[4,8-11]
	Lubiprostone	Ⅲ-Ⅳ/FDA approval (2008)	CIC-2 activator	Promotes intestinal fluid secretion, increases SBM frequency, reduces abdominal bloating and discomfort	Nausea, diarrhea, abdominal distention, headache	[8,12-14]
	Plecanatide	Ⅱ, Ⅲ for CIC and Ⅰ for IBS-C	GC-C agonist	Facilitates bowl movements, stimulates water secretion, improves stool consistency and frequency	Diarrhea (mild or moderate), nausea, abdominal discomfort, abdominal pain, vomiting (at the highest doses)	[12,15,16]
Prokinetic	Tegaserod	Withdrawn by the FDA in 2007 due to risk of adverse cardiovascular effects	Selective partial 5-HT$_4$ agonist	Stimulates motility in the upper and lower GI tract, reduces visceral sensitivity and pain, improves stool consistency	Diarrhea, cardiovascular effects (angina, myocardial infarction, and cerebrovascular events)	[12,17-19]
	Renzapride	Ⅱ and Ⅲ for IBS-C; remains under evaluation	Full 5-HT$_4$ agonist and 5-HT$_3$ receptor antagonist	Administered twice daily increases gastric emptying rate Smooth muscle relaxant, reduces colonic pseudo-obstruction and constipation Prokinetic and stimulatory effect on GI transit, improves stool consistency	Diarrhea, abdominal pain, constipation, nausea	[8,20-22]
	Prucalopride	Ⅲ, undergoing clinical trials	5-HT$_4$ agonist	Improves the frequency of SBM, reduces abdominal discomfort	Headache, nausea, abdominal pain, diarrhea	[12,14,20]
	Velusetrag, naronapride	Completed Phase Ⅱ	5-HT$_4$ receptor agonist	Accelerates colonic and orocecal transit, increases SBM, normalizes stool consistency	Diarrhea, headache, nausea	[23-25]
Laxatives	Lactulose, sorbitol, polyethylene glycol, magnesium citrate	Approved	Osmotic water retention, stimulant	Increases fecal volume and peristalsis	Bloating, cramping, and flatulence	[17,26-28]
Bile acid modulators	Chenodeoxycholate	Ⅱ, remains under evaluation	Intracellular activation of adenylate cyclase, inhibition of apical Cl-/OH - exchange	Accelerates colonic transit, improves stool consistency	Lower abdominal cramping, diarrhea	[18,27]

CIC: Chronic idiopathic constipation; FDA: Food and Drug Administration; GC-C: Guanylate cyclase C; GI: Gastrointestinal; IBS-C: Constipation-predominant irritable bowel syndrome; SBM: Spontaneous bowel movement.

and patients with ailments related to constipation[18,20]. Finally, it has been suggested that high luminal accumulation of selected BAs may produce a laxative effect, generally by the stimulation of its prosecretory and promotility actions[8,11,33,38].

CURRENTLY AVAILABLE IBAT INHIBITORS

Elobixibat (former name: A3309) is a novel and promising approach in the treatment of constipation. Elobixibat inhibits ileal BA reuptake *via* the inhibition of IBAT; during this process, the hepatic synthesis of BA is upregulated on account of the maintenance of EHC homeostasis. Interestingly, the abundant synthesis of cholesterol derivatives leads to the depletion of cholesterol stores in the liver, which simultaneously stimulates the expression of low-density lipoprotein (LDL) receptors on hepatocytes and reduces the level of serum LDL[37].

A recent phase Ⅰ randomized trial showed acceleration of colonic transit, reductions of total plasma cholesterol and LDL by 11% and 16%, respectively, and an increase in the plasma C4 levels in CIC patients after 14 d of treatment with 10 mg of elobixibat. Moreover, a double-blind, placebo-controlled, single-center clinical trial conducted by Simrén *et al*[39] reported that there were no side effects after its administration. It was suggested that a higher dose of elobixibat may be incorporated into the treatment; however, an overdose of elobixibat may lead to excessive colonic motility, resulting in diarrhea.

Similar favorable therapeutic effects of elobixibat,

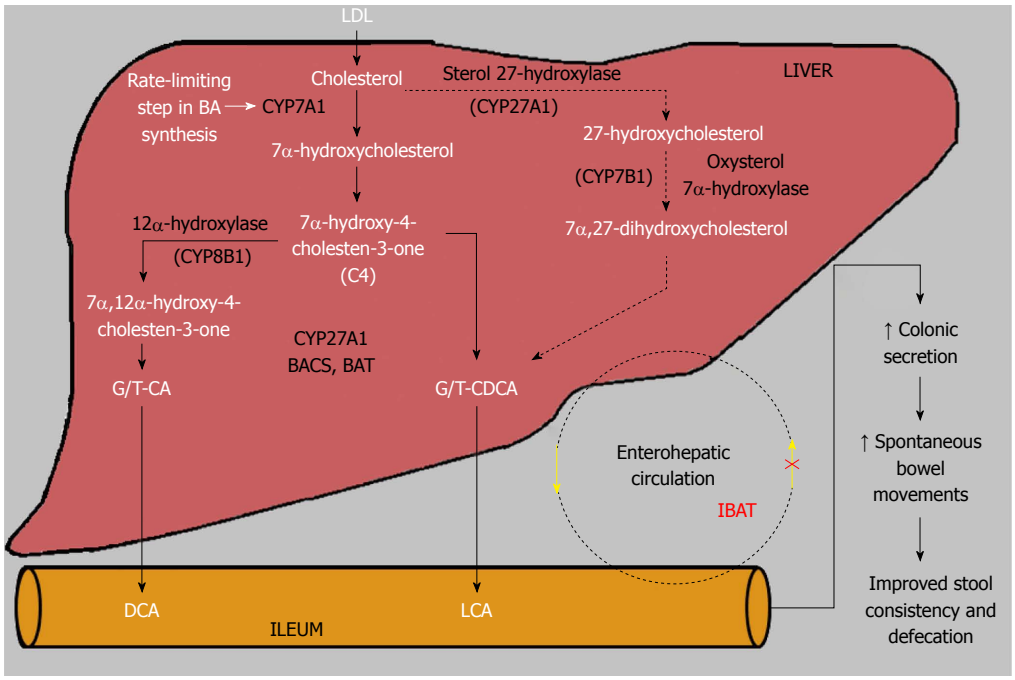

Figure 1 Effect of ileal bile acid transporter in the proximal ileum. BA synthesis is a major metabolic pathway for catabolism of cholesterol. Primary BAs, CA and CDCA, are obtained via the alternative (acidic) pathway, initiated by mitochondrial CYP27A1, or by the classical (neutral) biosynthetic pathway, catalyzed by microsomal CYP7A1. CYP7A1 is a rate-limiting enzyme that regulates the overall rate of BA synthesis in the liver. The activity of CYP7A1 depends upon the quantity of BAs absorbed in the intestine. Inhibition of IBAT contributes to upregulation of BA synthesis and therefore promotes the maintenance of BA pool size. Simultaneously, a decrease in the concentration of serum LDL and an increase of C4 level, which is a surrogate for CYP7A1 activity, may occur. BACS and BAT are two key enzymes involved in the conjugation of BA to amino acids (G or T). In the intestine, conjugated G/T-CDCA and G/T-CA are dehydroxylated to the secondary BAs, DCA and LCA. The action of a selective IBAT inhibitor increases the concentration of BAs entering the proximal colon, which in turn stimulates colonic motility and secretion resulting in enhanced laxative properties. BA: Bile acid; BACS: Bile acid CoA synthase; BAT: Bile acid amino acid transferase; CA: Cholic acid; CDCA: Chenodeoxycholic acids; CYP27A1: Sterol 27 hydroxylase; CYP7B1: Nonspecific 7α-hydroxylase; DCA: Deoxycholic acid; G: Glycine; IBAT: Ileal bile acid transporter; LCA: Lithocholic acid; LDL: Low-density lipoprotein; T: Taurine. Modified from[34-37].

administered orally for 14 d, were shown by Wong *et al*[37] in a phase Ⅱa, single-center, randomized, double-blind, placebo-controlled trial. Overall colonic transit in CIC patients was significantly accelerated at 24 h and 48 h in comparison with the placebo group. Both doses tested, 15 mg and 20 mg, were well tolerated and produced alteration in stool consistency, ease of passage and straining, and an increase in the frequency of spontaneous bowel movements, but no increase in stool frequency. No significant ameliorations were detected regarding abdominal bloating and discomfort. After the treatment with elobixibat, only 4/11 patients in the 15 mg group, and 6/12 patients in the 20 mg group experienced mild to moderate abdominal cramps and pain.

A recent placebo-controlled, phase Ⅱb clinical trial in 190 CIC patients evaluated the efficacy and safety of elobixibat at three doses[38]. The IBAT inhibitor significantly increased bowel movements at 10 mg and 15 mg, but not 5 mg, and led to an alleviation of constipation-associated symptoms, such as straining, bloating, and increased stool consistency. The majority of patients in the 10 mg and 15 mg groups manifested an increase in bowel movements within 24 h of the initial treatment. Moreover, the effect of elobixibat was maintained up to 8 wk after administration. As expected, an increased C4 value, which is an intermediate plasma marker in BA synthesis, was documented. Furthermore, consistent with increased BA synthesis, the total plasma and LDL cholesterol levels were diminished[38]. It was also revealed that the most common side effects, such as abdominal pain/discomfort and diarrhea, were associated most commonly with the 15 mg group. Moreover, the 10 mg dose of elobixibat offered the best efficacy-to-safety ratio, which may be suited for individual treatment in functional constipation. Interestingly, three large, randomized, multicenter phase Ⅲ trials, ECHO1 (ClinicalTrials.gov identifier: NCT01827592), ECHO2 (ClinicalTrials.gov identifier: NCT01833065) and ECHO3 (ClinicalTrials.gov identifier: NCT01895543), are anticipated to assess the safety and efficacy of elobixibat within a period of 26 wk, 12 wk, and 52 wk, respectively, with the outcomes expected to appear by the end of 2014. Overall, long-term beneficial effects in patients with CIC need to be evaluated, and further studies designed to address the potential of elobixibat are warranted.

CONCLUSION AND FURTHER PERSPECTIVES

Inhibition of IBAT constitutes a promising novel approach in the treatment of constipation. The only IBAT inhibitor currently available, elobixibat, exerts prokinetic and prosecretory effects in the colon by enhanced BA synthesis and has been shown effective in CIC patients[40]. The applicability of elobixibat in IBS-C remains questionable, and its effects on sensory symptoms still require additional investigation.

Of note, a large body of data indicate that fecal levels of secondary BAs are significantly greater among patients with colorectal adenomata and colorectal cancer[40-42]. Moreover, it was shown that deoxycholic acid (DCA) and lithocholic acid may indirectly promote carcinogenesis by modulating intracellular signaling, *e.g.*, *via* induction of cyclooxygenase-2, secretion of matrix metalloproteinase-2, or activation of plasma membrane muscarinic and epidermal growth factor receptors that lead to alterations in gene expression and stimulate colon cancer proliferation[43,44]. Exposure of rodent colonic mucosa cells or human adenocarcinoma cell lines, such as HCT-116 and CaCo-2, to BAs stimulates the production of reactive oxygen species, which consequently can result in gene mutation and constitutive activation of prosurvival stress-response pathways[45]. In line with this, DCA administration in a rat model of colonic carcinogenesis enhances the incidence of K-ras point mutation and proliferation in colon tumors[46]. Additionally, Qiao *et al*[47] showed the correlation between tumor-promoting BA DCA and the tumor suppressor gene p53, resulting in the inhibition of p53 response to genotoxic compounds in the colon, which ultimately enhances mutagenesis and can increase the risk of cancer. An investigation by Little *et al*[48], which was based on subjects with asymptomatic cancer and adenomatous polyps, found a relationship between an increased concentration of major BAs and villus adenomas; nonetheless, the risk of large adenomas or colorectal cancer did not correlate with elevated fecal BA concentration. Similar outcomes were obtained in a cohort study by Haines *et al*[49], where there were no significant differences between the left-sided bowel cancer and control groups for any of the concentrations of individual BAs, total BA concentrations, fecal-neutral steroids, percentage bacterial conversion, or the ratio of lithocholic acid to DCA concentrations. A weak correlation between CDCA in feces and the risk of right-sided bowel cancer were reported; however, it was postulated that other factors such as genetic predisposition were also involved in the development of large bowel cancer.

Elobixibat is a relatively new drug and only a limited number of studies are available. Thus, in order to comprehensively evaluate the risk and benefit profiles of this IBAT inhibitor, a meta-analysis is desirable, especially in terms of cancer related-issues and possibility of treatment of IBS-C. On the other hand, development of novel IBAT inhibitors with a modified pharmacologic profile and bioavailability could provide drug candidates with a favorable endpoint and no adverse effects. Yet another possibility is to encourage research on other signaling pathways that involve a distinct BA transporter that is not involved in tumor progression.

To conclude, further meticulous studies are needed to facilitate the development of optimal chemoprotective strategies for the treatment of constipation.

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