The role of AST-120 and protein-bound uremic toxins in irritable bowel syndrome: a therapeutic perspective

Ther Adv Gastroenterol
2015, Vol. 8(5) 278–284
DOI: 10.1177/1756283X15587866

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***Abstract*:** AST-120 (kremezin) exhibits its favourable effects in reducing the levels of renal toxins by selective adsorption of low molecular weight substances from the intestinal lumen. So far, a vast majority of studies were focused on the role of AST-120 in the treatment of chronic kidney diseases and cardiovascular disorders, and positive therapeutic effects of the agent have already been confirmed in clinical conditions. Up to the present, there are only a few studies regarding the role of AST-120 in irritable bowel syndrome (IBS). Compelling data suggest the ability of the compound to adsorb protein-bound uremic toxins and mast cell derived mediators and to modulate the farnesoid X receptor, which is a bile acid sensor indispensable for maintaining homeostasis in the intestine.
In this review we focus on the actions of AST-120 on intestinal permeability, reduction of visceral sensitivity and alteration of gut motility. We also discuss whether AST-120 can mitigate common IBS symptoms, such as abdominal pain, bloating and malfunction of the colonic transit and thus improve the quality of life of patients with IBS.

Keywords: AST-120, cardiovascular disease, chronic kidney disease, irritable bowel syndrome, kremezin

Introduction

AST-120, also known as kremezin, is an orally administered intestinal sorbent which has been reported to slow chronic kidney disease (CKD) progression and delay the initiation of dialysis by reducing the levels of renal toxins or their precursors in the gastrointestinal (GI) tract [Konishi *et al.* 2008]. AST-120 takes the form of spherical particles, 0.2–0.4 mm in diameter, composed predominantly of porous carbon material with a high surface area, exceeding over 1600 m^2/g [Marier *et al.* 2006]. The abundant porosity and its wide distribution provide an extensive and efficient binding surface, which enables selective adsorption and removal of low molecular weight substances from the intestinal lumen. Noteworthy, the unique composition of AST-120 particles and inaptitude to dissolve in water and organic solvents provide lower adsorption capability for amylase, pepsin, lipase, and chymotrypsin in comparison with activated charcoal [Marier *et al.* 2006; Schulman *et al.* 2014].

AST-120 has been used as a renoprotective agent in Japan since 1991; it has also been made available in Korea (since 2005) and the Philippines (since 2010). Its therapeutic indication is to prolong the time to initiation of dialysis therapy and to improve uremic symptoms in patients with CKD stage 4–5 [Schulman *et al.* 2014]. Moreover, studies confirm a positive role of AST-120 in preventing cell senescence and vascular calcification, and consequently delaying progression of cardiovascular diseases (CVDs). More recently, the possibility of using AST-120 in the treatment of several other diseases, such as irritable bowel syndrome (IBS), has been suggested. IBS is a chronic, relapsing functional bowel disorder, associated with altered GI motility, secretion and sensitivity. It is the most commonly diagnosed GI condition in the population worldwide, which considerably reduces patients' quality of life. Although a fair number of pharmacological targets have been proposed for alleviating IBS symptoms, only a small number of therapeutics have been implemented,

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implying that there is still need for a more plausible way of IBS prevention and treatment. Here, we discuss both advantages and disadvantages of AST-120 as a potential anti-IBS drug.

Molecular mechanisms of action of AST-120

One of the mechanisms by which AST-120 exhibits its favourable effects in CKD is by decreasing the levels of nephrotoxic metabolites in serum, including advanced glycation end products (AGEs), indoxyl sulfate (IS) and *p*-cresol. Both IS and *p*-cresol are protein-bound uremic toxins that originate from protein fermentation by intestinal bacteria. Dietary tryptophan is metabolized to indole, absorbed into the peripheral blood and further converted to IS in the liver. In comparison, *p*-cresol emanates from the catabolism of the amino acids tyrosine and phenylalanine, and if synthesized by bacteria, undergoes conjugation *via* sulfotransferases in the submucosal tissue of the gut [Bohlender *et al.* 2005; Dou *et al.* 2004]. Therefore, in the plasma *p*-cresol occurs notably in the form of *p*-cresyl sulfate (PCS) [Watanabe *et al.* 2013]. The excretion of IS and other uremic toxins is of limited efficacy in patients with renal dysfunction. Consequently, accumulation of uremic toxins impairs renal function and leads to further buildup of circulating toxins, which in turn intensifies the state of disease and enhances renal failure and mortality of patients with CKD. Several studies confirmed that AST-120 can hamper this vicious circle by adsorbing uremic toxins in the intestines, what stimulates their excretion into faeces and consequently retard the functional and histological aggravation in patients with CKD and animal models [Shoji *et al.* 2007; Maeda *et al.* 2009; Miyazaki *et al.* 2000].

Intracellular accumulation of IS through organic anion transporters (OAT1 and OAT3) and enhanced production of reactive oxygen species (ROS) by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, particularly Nox4, result in greater toxicity of IS and thus mediate further progression of CKD [Ito *et al.* 2010; Motojima *et al.* 2003]. Several studies reported a positive linear correlation between IS and oxidative biomarker levels, acrolein and 8-hydroxyl-2′-deoxyguanosine, which accelerate progression of uraemia [Nakagawa *et al.* 2006; Fujii *et al.* 2009]. However, one needs to mention that recent literature suggests antioxidant activity of IS against hydroxyl radicals under physiological conditions [Miyamoto *et al.* 2010].

In parallel with renal damage progression, elevated accumulation of toxins in circulating blood may also contribute to vascular alterations, including atherosclerotic lesions, which enhance the probability for cardiovascular event occurrence. A number of studies have indicated that IS induces endothelial dysfunction and plays a dominant role in monocyte adhesion during inflammation by releasing endothelial microparticles, such as tumour necrosis factor (TNF)-α and interleukin 1β [Ito *et al.* 2010]. *In vitro*, uremic toxins reduce the endothelial response to inflammatory cytokines, increase vascular permeability and promote elastolytic metalloproteinase release. Moreover, some clinical relevance has also been attributed to the action of PCS, which causes upregulation of the inflammatory cytokines, such as transforming growth factor (TGF)-β, tissue inhibitor of metalloproteinase-1 (TIMP-1), and pro-α1 collagen in the human kidney-2 (HK-2) cell line [Watanabe *et al.* 2013]. In addition, PCS displays pro-oxidant properties through activation of NADPH oxidase and increase in TGF-β1 and ROS production, which result in augmentation of cytoskeleton changes in vascular endothelial cells [Watanabe *et al.* 2013; Martin-Garrido *et al.* 2011]. Furthermore, Dou and colleagues speculated that *p*-cresol has an inhibitory effect on endothelial proliferation and exhibits self-healing ability, and therefore can be associated with the effects on the endothelial actin cytoskeleton [Dou *et al.* 2004]. Eventually, the accumulation of PCS alters endothelial function and is attributable to enhanced mortality rate among patients on haemodialysis [Meijers *et al.* 2009; Schepers *et al.* 2007].

Recent reports suggest that AST-120 significantly reduced gene expression of TGF-β1, TIMP-1 and pro-α1 (I) collagen in the renal cortex of uremic rats [Miyazaki *et al.* 2000; Inami *et al.* 2014]. Furthermore, Nakagawa and colleagues [Nakagawa *et al.* 2006] reported that AST-120 decreased serum creatinine and urinary protein levels, and attenuated histological changes, such as glomerular sclerosis and interstitial fibrosis [Lee *et al.* 2010]. Reduction in serum IL-6, serum creatinine (sCr), estimated glomerular filtration rate and suppressed urinary excretion levels of 8-OHdG and L-fatty acid binding protein, markers of oxidative stress and tubular injury, have also been connected with the administration of AST-120 to patients with uraemia [Nakagawa *et al.* 2006; Nakamura *et al.* 2011].

AST-120 alleviates progression of CKD

The usefulness of AST-120 in the treatment of CKD is supported by retrospective studies, including those conducted by Ueda and colleagues [Ueda *et al.* 2008] and Inami and colleagues [Inami *et al* 2014]. Similarly, long-term effects of AST-120 in patients with chronic renal failure in the predialysis stage were also reported [Maeda *et al.* 2009]. In contrast, some recent randomized control trials revealed no significant evidence in the effectiveness of the orally administered AST-120 in preventing or delaying the progression of CKD after 1 year of treatment [Akizawa *et al.* 2009; Wu *et al.* 2014]. However, it has to be mentioned that no serious adverse events were identified. Recently, large phase III clinical trials on 2000 subjects have been initiated in North/Latin America and Europe; the data are still being analyzed [Schulman *et al.* 2014].

AST-120 in CVDs

CVDs are a hallmark of patients with uraemia. It has been reported that the probability of cardiac mortality in patients receiving dialysis is 10–20 fold higher in comparison to those without CKD [Johnson *et al.* 2007]. Moreover, a relation between CVD and renal failure was found even in patients with minor renal dysfunction [Go *et al.* 2004]. Many studies proved that IS is a key factor, which triggers injury to endothelial and vascular smooth muscle cells in patients with CVD, mainly because of aortic calcification and wall thickening [Adijianfg *et al.* 2008]. Moreover, certain proinflammatory cytokines, AGEs and monocytes/macrophages, which are present in the calcified vascular wall, may favour vascular or valvular calcifications [Massy *et al.* 2005].

Studies have shown that AST-120 can be effective in delaying the progression of arteriosclerosis, wall thickening and consequently improve CVD [Muteliefu *et al.* 2012; Nakai *et al.* 2011; Shibahara and Shibahara, 2010]. Interestingly, a study by Adijiang and Niwa demonstrated that administration of AST-120 preserves renal expression of Klotho and prevents tubular cell senescence in the kidneys of chronic renal failure (CRF) rats [Adijiang and Niwa, 2010]. A decreased expression of Klotho, a protein predominantly expressed in mouse, rat and human kidneys, may play an important role in vascular calcification, arteriosclerosis and osteoporosis development.

AST-120 in IBS

A fair number of factors, such as colonic motor disturbances, visceral hypersensitivity or augmentation in mucosal permeability impair the function of the intestines and may lead to IBS development. AST-120 has affinity for several molecules implicated in the etiopathology of IBS, including neuroactive agents (serotonin, histamine, tyramine, tryptamine and caffeine), toll-like receptor ligands, bacterial exotoxins (*Escherichia coli* heat stable enterotoxin, *Shigella dysenteriae* type 1 Shiga toxin, and *Vibrio cholera* cholera toxin) and bile acids (BAs), and could thus be regarded as a potential anti-IBS drug [Araki *et al.* 2000; Soares, 2014; Furuhashi and Hotamisligil, 2008]. Noteworthy, a nonmetabolized AST-120 displays minimal, if any, interference with digestive enzymes and exerts no significant effect on the adsorption of fat-soluble vitamins, allowing patients with IBS to maintain a nutritional diet during the long-term therapy [Schulman *et al.* 2014; Soares, 2014; Tack *et al.* 2011].

AST-120 and its role in intestinal permeability and epithelial barrier

It has been suggested that low-grade mucosal inflammation underlies the development of IBS, and mucosal mast cells (MCs) are thought to play a particular role in the process. MCs, which can be found throughout the GI tract, including the duodenum, ileum, jejunum, caecum, colon and rectum, are implicated in the pathophysiology of IBS due to their ability to regulate intestinal permeability and the integrity of the epithelial barrier [Vivinus-Nebot *et al.* 2012; Park *et al.* 2006]. The correlation between MCs' presence and the severity of abdominal pain, bloating and altered bowel habit, which are common features in patients with IBS, were confirmed in several studies [Park *et al.* 2006; Barbara *et al.* 2004]. In accordance, O'Sullivan reported an increase in MCs in the caecal mucosa of patients with IBS compared with normal controls [O'Sullivan *et al.* 2000].

Degranulation of MCs contributes to mucosal inflammation by releasing potent inflammatory and immune modulators. Of all, tryptase has recently attracted most attention as it may release protease-activated receptor 2 (PAR-2) located at the basolateral site of enterocytes, which affects paracellular permeability and alters gut motility and thus generates IBS symptoms (Lee *et al.* 2010). PAR-2 causes a rearrangement in the cytoskeletal organization of tight junction proteins, which allows

passage of macromolecules and bacteria across the intestinal epithelial barrier resulting in intensified inflammation and infection [Eutamene *et al.* 2003]. It has not been examined yet whether AST-120 has any affinity to tryptase and whether it can suppress an enhanced mucosal permeability. However, it can easily be hypothesized that the coadministration of AST-120 and tryptase inhibitors may further diminish intestinal mucosal permeability and downregulate the immune-mediator response.

AST-120 and intestinal hypersensitivity

Animal studies showed that an increased level of mediators released upon MC activation may alter the enteric nervous system (ENS) activity and is prone to increase visceral sensitivity [Eutamene *et al.* 2003]. Due to close proximity to mucosal innervations, MC-derived mediators provide neuroimmune interaction, provoke hyperexcitability of nociceptive visceral sensory nerves, and disturb smooth muscle function [Matricon *et al.* 2012]. The major chemical mediators derived from MCs are histamine, serotonin (5-HT), platelet-activating factor, tryptase, chymase, prostaglandins, cytokines and leukotrienes [Matricon *et al.* 2012]. It is important to note that an increased level of MCs is observed in a subgroup of patients with IBS [Barbara *et al.* 2004]; it can thus be suggested that the capability of AST-120 to adsorb MC-derived mediators would prevent sensitization of nociceptors in the intestinal mucosa and therefore reduce abdominal pain and discomfort common among patients with IBS.

There is a large body of evidence for a decreased activity of the rectal serotonin reuptake transporter (SERT) in patients with IBS [El-Salhy *et al.* 2013]. An impaired SERT function leads to an extensive increase in the number of 5-HT molecules within the gut mucosa, which simultaneously influence ENS and the central nervous system (CNS), impact lymphocyte proliferation, promote T-cell recruitment and inhibit immune cell apoptosis [Khan and Ghia, 2010]. An increased availability of 5-HT modulates the afferent mechanohypersensitivity and accelerates segmental contractile colonic motor activity *via* the H_1 and H_2 receptors [Barbara *et al.* 2004]. Studies revealed that an elevated level of 5-HT is observed in diarrhoea-predominant IBS (IBS-D), and concurrently its decrease is associated with constipation-predominant IBS (IBS-C). Taken together, the administration of AST-120 may prolong intestinal passage in IBS-D by indirectly targeting 5-HT and thereby reduce the levels of proinflammatory mediators, such as IL-1, IL-2, IL-6, IL-8, IL-12, TNF-α and interferon (IFN)-γ, which are responsible for escalation of IBS symptoms and deterioration of the quality of life of patients with IBS [Ueda *et al.* 2008].

AST-120 and other mechanisms of enteroprotection

Farnesoid X receptor. Farnesoid X receptor (FXR), which is abundantly expressed in the liver, gut, kidneys, reproductive tissue, adrenal gland and pancreas, modulates transcription of genes involved in BA synthesis, transport and absorption. FXR acts as a BA sensor, which prevents intracellular BA overload and toxicity. Notably, activated FXR is involved in the negative feedback regulation of BA in the liver, predominantly by the modulation of fibroblast growth factor (FGF) 15/19. Accordingly, the BA-FXR-FGF15/19 signalling pathway is an important mechanism which maintains the BA homeostasis in the gut. Gene knockout of any part of this pathway results in an increased cholesterol 7-α hydroxylase (CYP7A1) mRNA expression and enhanced BA pool size, leading to exacerbated BA excretion. FXR-deficient mice experience aberration in BA and lipid homeostasis, with elevated cholesterol levels in the liver, as well as serum [Sinal *et al.* 2000]. An impaired FXR-19, which normally binds to FGF–R4/Klotho-β on the basolateral surface of hepatocytes, blocks the cascade that represses the gene encoding CYP7A1 causing diarrhoea [Camilleri and Di Lorenzo, 2012]. Considering the capability of AST-120 to adsorb BAs in the intestinal lumen, we hypothesize that it could diminish gut peristalsis and therefore alleviate IBS-D symptoms through FXR-dependent pathways.

Of note, FXR activation involves an indirect influence on the modulation of epithelial permeability and proinflammatory mediators in the murine intestinal mucosa. In $FXR^{-/-}$ mice, an uncontrolled immune reaction occurred and the level of several proinflammatory mediators, including IFN-γ, TNF-α, IL-6, IL-18, suggesting an additional role of FXR in immunoregulation [Vavassori *et al.* 2009]. The study by Inagaki and colleagues provided strong evidence that $FXR^{-/-}$ mice experienced bacterial overgrowth, particularly in mesenteric lymph nodes and developed

inflammation of the gut wall [Inagaki *et al.* 2006]. Consistently, elimination of intestinal BA by AST-120 may upregulate FXR activation and restrain the accumulation of proinflammatory mediators by promoting the expression of genes involved in enteroprotection.

It needs to be underlined that a long-lasting elimination of BAs from the colon may result in a counter-regulatory increase in hepatic BA synthesis, which will sustain the expression of FXR in the ileal epithelium [McGuckin *et al.* 2009]. Exacerbated secretion of BAs can result in deterioration of symptoms in patients with IBS-D; however, it may be beneficial in IBS-C. This aspect still needs to be investigated further.

Intestinal bacteria. It is well known that the carbohydrate to nitrogen ratio is one of the crucial regulators of bacterial metabolism [Evenepoel *et al.* 2009]. Consistently, dietary restrictions implemented in patients with IBS can easily impair this balance and enlarge the generation of potentially toxic protein fermentation metabolites, such as phenols. Higher endotoxin levels can exacerbate the levels of several cytokines and acute phase reactants, and lead to changes in the intestinal barrier, dysregulate its function and finally contribute to microscopic inflammation of enteric mucosa. AST-120, which has the ability to reduce the levels of microbial metabolites through adsorption onto a high-affinity surface may thus prevent the accumulation of toxins in the gut and preserve the intestine from any damage. Consequently, AST-120 could decrease intestinal permeability and therefore reduce monocyte-derived cytokine level mediators in the gut.

Effectiveness and safety of AST-120 in IBS

Due to a very small number of clinical trials available, the influence of AST-120 cannot be unambiguously determined. A placebo-controlled, double-blind treatment study conducted by Tack and colleagues indicated at least 50% reduction in days with pain and bloating [Tack *et al.* 2011], rising from week 4 to week 8, in nonconstipating IBS after AST-120 treatment compared with the placebo group. Furthermore, amelioration of watery and loose stools was observed in patients with IBS-D. Noteworthy, no significant adverse effects were recorded, which justifies the potential of AST-120 in subsequent treatment of patients with nonconstipating IBS. Interestingly, the dose of 2 g was employed in the trial, which is similar to the regimen used in the treatment of CKD. Nevertheless, additional dose-ranging studies should be explored both in IBS-C and IBS-D.

Conclusion

Oral adsorbent AST-120 is believed to exert its action by removing uremic toxins, predominantly IS, within the intestine. Data show that AST-120 can slow the deterioration in renal function and can prevent CVD progression; however, the precise mechanism by which AST-120 can influence IBS symptoms remains to be determined. Here we demonstrated several possibilities that may support the usefulness of AST-120 in IBS treatment and expect that further investigations will provide novel insights into the complex mechanism of its action. It needs to be underlined that the conclusions drawn in this paper rely predominantly on theoretical mechanisms and sequences of events that can occur after administration of AST-120 and thus its role in IBS still remains questionable.

Funding

Supported by the Medical University of Lodz (Project 'UMED Grants' 63/2014-2015 to PM and 503/1-156-04/503-01 to JF); National Science Center (UMO-2013/11/B/NZ7/01301 and UMO-2014/13/B/NZ4/01179 to JF), and the Iuventus Plus program of the Polish Ministry of Science and Higher Education (0107/IP1/2013/72 to JF).

Conflict of interest statement

The authors declare that there is no conflict of interest.

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