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## Use of Glucagon-like peptide 2 (GLP-2) analogs in inflammatory bowel disease

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**Abstract:****Introduction:**

Inflammatory bowel disease (IBD) is a chronic condition that involves long-term treatment and chronic idiopathic inflammation within the gastrointestinal tract. The predominant forms of IBD are: Crohn's disease and ulcerative colitis. These diseases cause significant physical as well as psychological dysfunction - patients with this condition are thought to have an increased risk of depression as well as anxiety. Standard treatment for IBD most commonly includes aminosalicylates, corticosteroids, immunomodulatory drugs, and biologic therapy. In some cases, particularly when it comes to Crohn's disease, it is necessary to remove a portion of the inflamed bowel. Multiple segmental bowel resections can result in the rare but serious complication of short bowel syndrome, which leads to intestinal failure and necessitates parenteral nutrition.

Glucagon-like peptide-2 exhibits intestinotropic properties and also acts as a growth factor in the gastrointestinal tract, thereby increasing intestinal perfusion, causing increased absorption of nutrients, and enhancing proliferative mechanisms while inhibiting apoptotic processes.

**Methods:**

We carefully reviewed the medical literature on inflammatory bowel disease, short bowel syndrome and the potential treatment of this condition with GLP-2 and its analogs. The materials for the analysis we presented came from the PubMed database.

**Conclusions:**

Glucagon-like peptide 2 (GLP-2) analogs may prove to be new treatments for short bowel syndrome (SBS). They exhibit growth-stimulating effects on the intestinal membrane and promote normal function.

**Key words:**

GLP-2; inflammatory bowel disease; Crohn's disease, ulcerative colitis, short bowel syndrome

## **Glucagon-like peptide-2 (GLP-2)**

Glucagon-like peptide-2 is a 33-amino-acid peptide derived from proglucagon, the expression of which takes place in the gastrointestinal tract, mainly in the small intestine, and primarily in the terminal part of the ileum[2]. Expression of the aforementioned peptide also occurs to a lesser extent in the colon (least in the proximal part, through the distal part, reaching the highest level in the rectum, where there is a maximum concentration of GLP-2-positive cells[1]).

GLP-2 (1-33) is the active form of glucagon-like peptide-2, which is released when stimulated by neural, nutritional and hormonal routes. It is believed that substances such as lipids, carbohydrates, short-chain fatty acids and fiber can strongly stimulate the digestive system to produce the aforementioned peptide[1].

GLP-2 (3-33) is an inactive form of GLP-2 that is formed as a product of the destruction of the N-terminus of GLP-2 (1-33) by the integral type II(DPP-IV) trans-membrane glycoprotein, can act as a weak, incomplete GLP-2 receptor agonist by negative feedback[1].

Glucagon-like peptide-2 acts through the GLP-2 receptor (GLP-2R), which exhibits coupling to the G protein. Based on current studies, stimulation by GLP-2/GLP-2R signaling is thought to include: activation of adenylyl cyclase, increased accumulation of cAMP and PKA, and stimulation of the ELK-1/c-fos/c-jun gene[1].

Impaired GLP-2R signaling results in increased intestinal vulnerability and impaired mucosal adaptations to food reabsorption[8].

GLP-2 is a growth factor for the gastrointestinal tract, increases mesenteric blood perfusion, reduces intestinal secretion, and increases nutrient absorption, among other things, which can be used to treat people with short bowel syndrome[7].

## **Types of GLP-2 analogues**

According to studies, GLP-2 preparations, as well as their analogs, exhibit an enterotropic effect. They induce proliferation of cells of the crypts of the small intestine and, also to a lesser extent, of the large intestine[10]. They also reduce apoptosis of enterocytes, resulting in an increase in epithelial area and morphological adaptation. In addition, they stimulate intestinal blood perfusion, strengthen the intestinal barrier, and increase fluid and nutrient absorption[53]. Nutrient ingestion results in GLP-2 secretion through L-cells located primarily in the ileum[9]. Circulating native GLP-2, however, has a short half-life of only 5-7 minutes. This is due to the rapid action of the enzyme dipeptidylpeptidase-IV. GLP-2 analogs have a longer half-life, making them more effective for therapy[9].

A degradation-resistant GLP-2 analogue that has received approval for treating patients with short bowel syndrome is tedeglutide. Other long-acting GLP-2 analogs include glepaglutide and apraglutide, which are currently in phase III clinical trials[11].

## **Tedeglutide (TED)**

This is an analog of GLP-2, for which alanine has been converted to glycine in the natural peptide. In this way, the degradation point of dipeptidyl peptidase IV is eliminated. After subcutaneous administration, its half-life is about 3 to 5.5 hours. TED has similar specificity toward the GLP-2 receptor compared to the natural peptide[13]. It is approved for the treatment of short bowel syndrome dependent on the use of intravenous supplementation (IVS) in patients  $\geq 1$  year of age in the US, Europe and Japan[23]. According to national guidelines, as well as those of the European Society of Clinical Nutrition and Metabolism (ESPEN), tedeglutide should become a first-line drug in patients with SBS carefully selected as candidates for growth factor therapy[23].

## **Glepaglutide:**

In the case of this analogue, compared to the native form of GLP-2, amino acid substitutions of nine were added and a probe tail was attached, boosting the C-terminal structure, which consists of six lysines. This resulted in a

linear peptide that contains L- natural amino acids thirty-nine in number with a longer half-life of about 2 hours. This peptide is stable in aqueous solution, which allows the gluteptide to be dosed with an auto-injector[9].

In addition, studies have shown that a single subcutaneous dose of glepaglutide, which is 10 mg, has safety and good tolerability in both patients with normal renal function and those with renal failure[12].

### **Apraglutide**

Apraglutide is a synthetic analog of GLP-2 that was developed to provide long-term sustained exposure to GLP-2. It is distinguished from natural GLP-2 by four amino acid substitutions. It has a long half-life of up to 72 hours, a time that is longer than both the half-life of natural GLP-2 and tedeglutide. This is due to its low excretion, which is due to the fact that it is DPP-IV resistant and highly bound to plasma proteins. As a result, the drug can potentially be given in fewer injections than tedeglutide and could be administered only once a week[61].

### **GLP-2-2G-XTEN**

GLP-2-2G-XTEN is a fusion protein that was created by genetic fusion of GLP-2-2G with XTEN, a unique hydrophilic amino acid sequence. This compound has a long half-life which is in mice, rats and monkeys respectively: 34,38 and 120 hours. According to the study, the predicted half-life of this compound in humans could be up to 240 hours[43].

### **Elisiglutide**

Elisiglutide is a GLP-2 analogue that, in rat models, caused a reduction in diarrhea caused by lapatinib(a tyrosine kinase inhibitor used to treat breast cancer). The reduction in diarrhea was probably not due to a decrease in inflammation or a decrease in intestinal barrier permeability, but more to a thickening of the intestinal mucosa, leading to an increase in the area of fluid absorption in the distal part of the small intestine. The substance is currently in the preclinical phase of research in terms of its effects on the human body[54].

### **Dapiglutide**

Dapiglutide is a dual agonist of the GLP-1 and GLP-2 receptors. Studies in mice with SBS show that dapiglutide promotes intestinal growth, as evidenced by increased villi height and an increase in intestinal length and body weight, despite a continuous liquid diet. Therefore, dapiglutide may find future applications in humans[55].

### **Crohn's disease (CD)**

Crohn's disease is a gastrointestinal disease of a chronic nature. Its hallmark is chronic inflammation of any part of the gastrointestinal tract[26].

CD most often has an onset in young people between the ages of 20 and 40[28], but it can also occur as early as in the pediatric population. It is then often characterized by a more aggressive, severe and dynamic course, and usually requires a greater need for immunosuppressive therapy[29].

The causes of Crohn's Disease are not well elucidated, but they are potentially an interplay of factors such as genetic predisposition, environmental factors and the intestinal microflora, leading to an abnormal immune response within the mucosa and may also impair the epithelial barrier[28].

In this disease, there is inflammation of the tissue in the intestinal lumen, caused by an uncontrolled immune reaction against bacterial antigens. Immune cells are involved in this process: B lymphocytes, NK cells, CD14 monocytes, CD4 T cells, and CD8 T cells. These cells infiltrate the intestine in CD patients[27].

The symptoms of this condition are nonspecific and can often resemble other diseases, such as irritable bowel syndrome, which often causes a delay in diagnosis[32]. The most common symptoms include abdominal pain, fatigue, weight loss, lack of appetite and associated malnutrition, diarrhea, and the presence of blood in the stool[31].

Diagnosis of the disease can be difficult and requires evaluation of the clinical history, physical examination of the patient, and complementary diagnostic tests such as serologic tests or fecal biomarkers. Imaging studies, such as endoscopic and cross-sectional imaging, and histologic evaluation of biopsy specimens are also used[26]. Blood tests should include a biochemistry panel, complete blood count, iron and vitamin B12 levels (iron deficiency anemia, vitamin B12 deficiency or chronic disease anemia are common) C reactive protein(CRP),and erythrocyte sedimentation rate (ESR). Both CRP and ESR are highly sensitive laboratory indicators used to monitor treatment response and predict disease course[31].

Serological markers such as anti-neutrophil cytoplasmic antibodies (p.ANCA), antibodies to *Saccharomyces cerevisiae* (ASCA) (this is the most well-known serological marker used in CD diagnosis), antibodies to outer membrane protein C, antibodies to CBir1,and antibodies to the I2 sequence associated with *Pseudomonas fluorescens* are also used for diagnostic purposes[26].

The treatment of CD patients depends on: the severity of the course of the disease, the patient's preference, and various clinical factors, such as the age at which complications developed or penetrating complications, among others. Patient risk stratification should also be taken into account when choosing the appropriate therapy[30].

Two types of therapy are used; non-biological and biological. In non-biological therapy, induction therapy is most commonly used. Drugs such as corticosteroids (budesonide and prednisone), mesalazine and in the case of perianal complications such as an abscess- antibiotic therapy are used here. Maintenance therapy is also used in which immunosuppressive agents and biologic treatment are mainly used[26].

Biological treatments include tumor necrosis factor (TNF) antagonists such as infliximab, certolizumab pegol, adalimumab as well as golimumab, and anti-adhesion drugs such as natalizumab and vedolizumab[31].

#### **Use of GLP-2 in Crohn's Disease:**

The biological functions of GLP-2 are regulated by the expression of GLP-2R receptors. Expression of these receptors occurs virtually exclusively in the gastrointestinal tract, making the most prominent function of GLP-2 the stimulation of the intestinal mucosa to grow and promote its function. Because of this, GLP-2,as well as its analogs, are used in the treatment of inflammatory bowel diseases, including Crohn's disease[39]. In addition, studies show that patients with CD have abnormal levels of GLP both fasting and after a meal[40].

The efficacy of GLP-2 in CD is also evidenced by a study involving 100 patients with moderate-to-severe CD[41]. They were randomly assigned to groups taking placebo or tedeglutide at one of three doses(0.05; 0.10 or 0.20 mg/kg/day). The drug was administered daily by subcutaneous injection for eight weeks. After this period, higher remission and response rates were noted for patients who received tedeglutide, compared to those receiving placebo[41]. In addition, a reduction in the need for parenteral nutrition was observed in patients with CD and short bowel syndrome, as shown, for example, in a study involving 13 patients with CD and SBS[42]. All of them received parenteral nutrition prior to the start of tedeglutide; the average administration was 9,000 ml/week. The requirement for parenteral nutrition decreased by an average of 3100 ml/week, and six patients (46%) discontinued parenteral nutrition altogether[42]. Studies are also currently being conducted on the efficacy of GLP-2-2G-XTEN, which is a new, long-acting form of tedeglutide (GLP-2-2G)[43]. A study has been conducted on rats, in which administration of GLP-2-2G-XTEN produced an apparent enterotropic effect - there was a marked increase in weight and length of the small intestine. A comparison of the efficacy of GLP-2-2G-XTEN with that of GLP-2-2G in a rat model of Crohn's disease was also made. Prophylactic administration of GLP-2-2G XTEN resulted in a significant increase in intestinal length, reduced the number of adhesions and ulcers, and caused a decrease in TNF $\alpha$  within the small intestine. There was also histological improvement, which confirmed the effects of the treatment. This may have therapeutic benefits in humans as well[43].

#### **Short Bowel Syndrome (SBS):**

SBS is a relatively rare pathology in which there is impaired absorption of food, most often as a result of surgical resection of a significant portion of the small intestine[14]. The hallmarks of this disorder are diarrhea, fatty stools, malnutrition and dehydration[15]. In short bowel syndrome in adults, the length of the ileum is shortened to less than 200 cm compared to the normal length of this section of the gastrointestinal tract, which is approximately 275-850cm. In children, the definition is not clear-cut, as the length of the intestine depends on the child's stage of growth; most commonly, however, in this age range, it is defined as the need for intravenous nutrient supplementation or a remaining ileal length of less than 25% adequate for gestational age[17].

Short bowel syndrome can lead to in adults: Crohn's disease, mesenteric ischemia, radiation enteropathy or postoperative adhesions. In children, the most common causes are: congenital intestinal malformations, intestinal torsion and necrotizing enterocolitis.

SBS is the main pathophysiological basis for chronic intestinal failure (CIF)[15]. In CIF, the intestines are incapable of absorbing sufficient amounts of water, electrolytes, micronutrients and nutrients for life. It is a chronic and irreversible condition, and its main treatment is home parenteral nutrition[16].

In addition, according to studies, patients suffering from SBS are more likely to have such ailments as compared to the general population: Kidney stones (especially in patients on home parenteral nutrition)[19], Osteoporosis (mainly due to impaired absorption of micro and macronutrients that affect bone metabolism)[20], Gallstones (with a particular prevalence of cholesterol gallstones)[21], or even intestinal failure-associated liver disease (IFALD), which is diagnosed on the basis of abnormal liver function tests and radiological evidence and/or histopathological exclusion of other liver disease[22].

Treatment of SBS depends on the predominant symptoms of the disease. In the case of diarrhea, which is the most common symptom, drugs that inhibit motility (PPI, H2RA) and antisecretory drugs (loperamide, diphenoxylate - atropine) are used. In case of water-electrolyte imbalance, oral rehydration solutions (ORS) and supplementation of deficiencies are used[18]. Reduced reabsorption of bile acids is also often observed in patients. This disorder can be alleviated by cholestyramine therapy. Proton pump inhibitors are used for excessive gastric secretion. Bacterial overgrowth can also occur, in which case antibiotic therapy in particular rifaximin is applicable[52].

Although the above treatment modalities initially improve and enhance quality of life, they do not result in an improved prognosis for these patients. The mainstay of treatment in this case becomes home parenteral nutrition (HPN), which is a life-saving treatment for these patients[52]. HPN should be administered regularly, preferably during the night, via an implanted port or central venous line. The amount of HPN administered depends on energy requirements, fluid and electrolyte requirements, and the absorption value of nutrients from the oral diet. It is also important to add micronutrients (trace elements and vitamins). The initiation of home parenteral nutrition is possible only after proper optimization in the hospital setting, with a properly adjusted fluid-electrolyte balance[56]. Although HPN is the mainstay of treatment for patients with SBS, it is associated with a number of complications. These include catheter-related complications, such as: catheter-associated infections; catheter obstruction or venous thrombosis[57]. Another possible complication is: Liver disease associated with liver failure (IFALD). Its main cause is possible overfeeding of HPN or soy-based lipid emulsion[58]. Therefore, to prevent the above complication, lipid intake should be limited in these patients to one gram per kilogram of body weight per day[56].

#### **The use of GLP-2 in short bowel syndrome:**

Since enterohormones such as, for example, GLP-2 and its analogs, which are responsible for, among other things, maintaining normal intestinal transit and producing bile acids in healthy people, are produced mainly in the distal part of the ileum and the proximal part of the colon (which are the parts of the gastrointestinal tract most often resected in people with SBS), glucagon-like peptide 2 is also used to treat the disorder[18]. GLP-2 analogs reduce the dependence of SBS patients on HPN and also improve their quality of life[56].

The most effective and approved GLP-2 analogue for the treatment of short bowel syndrome is tedeglutide[11].

The first study to confirm the efficacy of this molecule and patients with SBS was conducted in 2005[59]. The study included 16 patients with either an jejunostomy or colonic continuity. The subjects were administered TED for a period of 21 days. After this period, there was increased diuresis, increased urinary sodium excretion, and increased nutrient absorption. In patients with a terminal jejunostomy, it was observed that the height of the intestinal villi increased significantly. The most commonly observed complications of therapy were increased size of the stoma papilla and edema of the lower extremity area[52,59].

Another study on the efficacy of tedeglutide treatment was a study showing that tedeglutide reduces the need for parenteral nutrition in patients with SBS[24]. In this study, after a 24-week follow-up of patients who received subcutaneous TED at a dose of 0.05 mg/kg/d or placebo, there appeared to be a reduction in the volume and number of days of parenteral supplementation use at the end of the study in the TED group. tedeglutide also increased plasma levels of citrulline, a biomarker of mucosal mass[24].

In addition, similar studies have also been conducted in the pediatric population where, in 14 studies, 248 patients participated 223 of them were treated with tedeglutide. The duration of treatment averaged about 45 weeks. At the end of the study, a reduction in the need for parenteral nutrition was also observed[25]. In the pediatric population, studies have been conducted that have shown an improvement in stool consistency after tedeglutide treatment in patients with SBS[46].

Other GLP-2 analogs that appear to be attractive for the treatment of SBS, but are still in the research phase, are apraglutide and glepaglutide[11]. In a study in a mouse model, apraglutide administered at a dose of 3mg/kg for 3 weeks was shown to significantly increase the weight and length of the small intestine and colon. In addition, an increase in the height of villi and an increase in the depth of intestinal crypts were also observed after this period. Therefore, it can be speculated that this effect may also be applicable to patients with SBS or IBD[52,60].

A placebo-controlled, double-blind, randomized phase II crossover study evaluating safety and changes in urine output volume in patients taking apraglutide was conducted in 2021[61]. The study found that adverse events resulting from therapy were most often mild to moderate and included polyuria, decreased stoma capacity, decreased thirst and edema. Treatment with apraglutide also increased the volume of urine excreted compared to placebo, which is evidence of increased intestinal fluid absorption[52,61].

An animal model study was conducted in which rats with indomethacin-induced small bowel inflammation were administered glepaglutide at various stages of the disease[62]. At the end of the study, a reduction in inflammation and an increase in small intestinal mass were observed. Thus, glepaglutide is characterized by intestinotropic and anti-inflammatory effects, which could potentially be used in patients with IBD[62].

There was also a single-center, double-blind, randomized Phase II study evaluating the therapeutic potential of glepaglutide in increasing intestinal absorption and reducing fecal excretion in SBS patients[63]. This study showed that glepaglutide therapy has good tolerability and improved intestinal absorption in SBS patients. Phase III studies have also been initiated to fully evaluate the safety and efficacy of this molecule[63].

## **Ulcerative colitis (CU)**

Ulcerative colitis is a lifelong inflammatory disease. The inflammatory lesions involve the colon and rectum to varying degrees. The estimated prevalence of the disease worldwide in 2023 was about 5 million cases[33]. The incidence of CU in men and women is similar. The disease can occur at any age however there are two peaks of incidence: the first, higher between the ages of 20 and 40, and the second, lower between the ages of 60 and 70[34].

The causes of the disease are not fully understood, but the sum effect of many factors such as genetics, environmental factors, intestinal microbiota, epithelial dysfunction or abnormal immune response has been suggested[35].

The most common symptoms of CU are: diarrhea with blood, which often co-occurs with pain located mostly in the lower left quadrant of the abdomen, and painful stool pushing. If a patient presents with severe colitis along with fever, abdominal tenderness and peritoneal symptoms, this is a warning sign that may indicate a worse prognosis with the risk of fulminant inflammation up to the development of toxic colonic distension"[37].

The diagnosis of CU is based on symptoms that are presented by the patient, sigmoidoscopy or colonoscopy, in which in this case continuous colitis originating in the rectum will be seen. Colonic biopsies are considered confirmatory when the specimens show changes that are consistent with chronic inflammatory changes[37]. Various biomarkers, such as fecal calprotectin or lactoferrin, and intestinal ultrasound are also increasingly used in diagnosis.[38] Blood laboratory tests should include a complete blood count, ferritin, vitamin D and inflammatory markers, such as CRP and sedimentation rate, for example. However, it should be taken into account that inflammatory markers may not be above normal in exacerbation situations, so they do not have adequate diagnostic value against CU[37].

Mesalazine is most commonly used in the treatment of uncomplicated CU. Steroid drugs are also highly effective in the acute treatment of this disease, but due to the high number of side effects, they can only be used short-term. For patients with a more complicated course of the disease, drugs such as calcineurin inhibitors, azathioprine, JAK inhibitors (included here are ustekinumab, tofacitinib, vedolizumab, anti-TNF antibodies and

biosimilar antibodies, among others) and biological treatment are applicable. In refractory cases or when high-grade epithelial dysplasia is present, proctocolectomy should be considered[36].

#### **Use of GLP-2 in CU:**

Studies have shown that in patients with CU, GLP-2 levels are reduced and its levels correlate positively with the abundance of microflora in the gut[45]. Thus, GLP-2 improves bacterial colonization of the gut and reduces the severity of CU by increasing the diversity and number of cells in the intestinal mucosa[44]. Also, another study, conducted in mouse models, shows that GLP-2 has a protective effect on the gut by regulating the diversity of bacterial flora in the gut and increasing the dominant strain. In addition, this study also shows that GLP-2 can inhibit the pro-inflammatory cycle by blocking the NF- $\kappa$ B pathway and the JAK/STAT3 inflammatory pathway, and by regulating glucose metabolism[45].

#### **Safety of therapy:**

The most common dose-dependent adverse effects with tedeglutide treatment were complaints such as vomiting, fever, upper respiratory tract infections, abdominal pain and diarrhea[49]. Another adverse effect is an increase in pancreatic enzymes (amylase and lipase). Although the increase in the activity of these enzymes in the study was not pathological and did not cause clinical symptoms associated with acute pancreatitis or imaging abnormalities in patients, it does require monitoring of these parameters in patients taking tedeglutide[47]. As treatment with GLP-2 analogs is a proliferative treatment, there is a potential risk of proliferative lesions such as polyps, as has been observed in adult patients, especially with prolonged use when tedeglutide was marketed, but the observation period was too short to conclusively determine this[48]. In pediatric patients, exposure to the drug was too short to confirm the risk of the aforementioned lesions. Currently, registries are being conducted to investigate the above-mentioned phenomena in patients using tedeglutide[48]. However, due to the possibility of the formation of proliferative lesions, screening for this, such as colonoscopy, is recommended in adult patients, and in children, a fecal occult blood test is recommended before starting treatment; if the result is positive, colonoscopy is recommended. Colonoscopy is also recommended after one year of treatment and for continuous treatment every five years[48].

In addition, it has been shown that with a high dose of GLP-2 compared to a lower dose and to placebo, there can be a delay in gastric emptying, an increase in plasma CCK levels, an increase in total cholesterol levels, an increase in glucagon levels, and an increase in heart rate with no effect on blood pressure[50]. GLP-2 also affects gallbladder emptying-at a lower dose there may be a delay in post-meal gallbladder emptying, and at a high dose even abolition of the gallbladder[50]. Tedeglutide can also cause cardiovascular events associated with fluid overload, central line-associated (CLABSI) bloodstream infections, and neuropsychiatric disorders manifested by an increased incidence of cognitive and attention disorders, as well as sleep disorders and depression. In children, the most common side effects were vomiting, fever, cough and upper respiratory tract infections. More serious side effects observed infrequently were intestinal obstruction, D-lactic acidosis and hard stools[51]. Other side effects included peristomal complications, such as enlargement of the stoma papilla[59].

#### **Summary:**

GLP-2 preparations, like their analogs, exhibit an enterotropic effect. They induce proliferation of cells of the crypts of the small intestine and, also to a lesser extent, of the large intestine[10].

The biological functions of GLP-2 are regulated by the expression of its GLP-2R receptors. Expression of these receptors occurs virtually exclusively in the gastrointestinal tract, making the most prominent function of GLP-2 the stimulation of the intestinal mucosa to grow and promote its function. Because of this, GLP-2, as well as its analogs, are used in the treatment of inflammatory bowel diseases[39].

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A degradation-resistant GLP-2 analog that has received approval for treating patients with short bowel syndrome is Tedeglutide. Other long-acting GLP-2 analogs include glepaglutide and apraglutide, which are currently in phase III clinical trials[11].



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