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Review

A short update on new approaches to celiac disease

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Abstract. Celiac disease is an autoimmune enteropathy of the small intestine, related to gluten intolerance occurring in genetically predisposed patients. Currently, the only available treatment is a lifelong gluten-free diet. However, the total avoidance of gluten is difficult and poses a challenge to patients, nutritionists and treating physicians. For this reason, scientists have developed in recent years new therapeutic approaches complementary to dietary treatment, such as modification of gluten to make gliadin non-toxic, reduction of the inflammatory response with elafin and Lactococcus Lactis, degradation of gluten by endoproteolytic enzymes, and correction of nutritional deficiencies by adding pseudo-cereals to the diet of celiac patients. This literature review focuses on the different treatment strategies for celiac disease previously studied and summarizes the latest advances in this field. (www.actabiomedica.it)

Key words: Celiac Disease, Gluten-free diet, Elafin, Endoproteolytic enzyme, Pseudocereals

Introduction

Food intolerance is characterized by a delayed reaction after consumption of a food, beverage or food additive that may produce symptoms in one or more body systems, particularly the gut, but this reaction has nothing to do with food allergy (1). Gluten and lactose intolerances are the most common. Among the diseases that are directly related to food, there is celiac disease; which is defined as « an autoimmune enteropathy that causes destruction of the villi of the small intestine (villous atrophy) in relation to the ingestion of a food antigen: gluten » (2). Currently, celiac disease exists all over the world, its prevalence is between 0, 7% and 2% in Western countries and it affects between 3 and 6% in people who have type 1 diabetes (3). In Morocco, the Moroccan Association of Autoimmune and Systemic Diseases announced that this disease would affect more than 1% of the population, compared to this average, the south of Morocco had revealed an estimated prevalence of 5,6% according to a study conducted on Sahrawi children in 1999 (4). Its spectrum of clinical manifestations differs depending on the person affected, but generally the most common digestive signs in adults include ; diarrhea, undernutrition and weight loss (5), and in children, this disease manifests itself by abdominal bloating, bulky stools and stunted growth (6). In addition to these symptoms, there are hematological (anemia), bone (osteoporosis),gynecological (fertility disorders),cardiovascular (venous thrombosis), hepatic (cirrhosis) and neurological (cerebellar ataxia) complications (7), and sometimes if the prognosis is late, the occurrence of certain digestive cancers and lymphomas may be increased (8-9). Its diagnosis is based on a series of analysis preceded by serology; which is the first test to be requested once the disease is suspected (10), based on the dosage of antibodies anti-transglutaminases tissue IgA and IgG and anti-endomysium antibodies (11) and subsequently the anatomopathological analysis of intestinal biopsies is necessary for the confirmation of the diagnosis. Today, the recognized treatment for celiac disease is the lifelong gluten-free diet, which has been shown to correct biological, histological and clinical abnormalities and to prevent potential complications including small bowel lymphoma (12). However, this diet seems to be

very easy but, in reality, its strict adherence remains difficult for patients. Among the factors that contribute to the failure of the treatment: some food products may contain traces of gluten, such as cold cuts and spice mixtures, the extra cost of substituted products, and the difficulties encountered when preparing dishes with gluten-free ingredients, especially the preparation of dough, because gluten is considered a texture agent (13-14). For this, it is necessary to develop new therapeutic approaches that are alternative and complementary to dietary treatment. Among them : 1- genetic modification of cereals, 2- enzymatic approaches based on the hydrolysis of gluten, into fragments unrecognizable by the body; by using propyl-endopeptidase and ALV003, 3- consumption of pseudo-cereals, such as: quinoa, buckwheat and amaranth ; because they play multiple roles, for example : the reduction of symptoms, the correction of nutritional deficiency and improvement of the inflammatory profile, 4- finally the use of a key molecule which is elafin, to reduce the inflammatory reaction characteristic of the celiac disease. These therapeutic approaches, some of which are currently being studied, aim to give hope for a better quality of life in the future for people with celiac disease. In this review, we would like to present the new therapeutic approaches that have been suggested as alternatives to the gluten-free diet for people with celiac disease.

The gluten free-diet and the search for new therapies

The appearance of agriculture in general dates back more than ten thousand years to the Neolithic revolution, and the agriculture of cereals appeared 2.3 million years ago. The five most cultivated cereals in the world, which represent almost 97% of the total, are corn, wheat, rice, barley and sorghum (according to the tonnage of grain produced worldwide). Over time, the two most known types of wheat are: soft wheat called Triticum aestivum is present in mid-latitudes for example: Canada, Germany.., and durum wheat also known as Triticum durum is also cultivated in Europe, North America and the Middle East and widely used in the Mediterranean region (15). While rice is considered a more popular cereal in the East, in part of Asia (16), maize is also grown in Asia, Africa and Latin America. Early epidemiological studies considered celiac disease affect only people of Caucasian origin because they consume more wheat, especially the European, Mediterranean and Middle Eastern population (17), which partly explains the high prevalence of celiac disease in these regions. However, several studies have identified celiac disease with a comparable prevalence in different regions of the world (18-19); and this can be explained by the high consumption of wheat, which is considered a central component of the human diet, and the Food and Agriculture Organization (FAO), has announced that the daily consumption of wheat varies between 21 to 564g-person-day (20). The Dutch doctor Dicke was the first to note that celiac disease has a close relationship with the consumption of wheat and similar cereals and from the middle of the 20th century; the gluten-free diet was advocated for patients with celiac disease. The Codex Alimentarius Commission and the Food and Agriculture Organization of the United Nations have authorized the consumption of products made from ingredients that do not contain any prolamine from wheat, any Triticum species, or their crossbred varieties with a gluten content not exceeding 20ppm. In addition, the amount of gluten that can be tolerated on a daily basis depends on the individual with celiac disease, but studies have suggested that consumption of less than 10 mg of gluten per day is unlikely to cause harm to celiac disease (21). Despite the benefits of the gluten-free diet, adherence to it remains very complicated and costly, and cross-contamination of gluten remains a major concern because wheat is so widely used in most diets (22). Adding to its disadvantages, the unintentional introduction of gluten can occur during the synthesis and marketing of certain food products and drugs (23). Thus, in some patients with celiac disease, dietary treatment sometimes does not work well because these patients may either not respond or need additional therapies (24). In recent decades, several studies have suggested that following a gluten-free diet by celiac patients may lead to weight gain (25-26). This is due to the reduction of dietary fiber, the excessive consumption of high- calorie fats and drinks and high-glycemic cereals (27-28-29). In addition, several studies have shown that the poorly balanced gluten-free

diet can lead to nutritional deficiencies, especially in iron, calcium, folic acid, zinc, vitamin D and vitamin B (30), and can lead to an increase in total cholesterol, LDL, triglycerides and a decrease in HDL (31). However, complete histologic resolution is not always possible, or may take longer. For these reasons, the search for new alternative therapies seems to be desirable by patients, as some of them were dissatisfied with the gluten-free diet (32). So the development of new therapies may help patients to induce immune tolerance to gluten not only for celiac disease but perhaps apply to other autoimmune diseases, thus, giving hope to patients to resume a normal diet and enjoy a better quality of life in the future. Moreover, of course, the safety and efficacy of these approaches must be proven and extensive toxicology testing will be required.

New therapeutic approaches

Development of genetically modified cereals

This approach aims to develop grains with reduced pathogenicity without affecting the baking properties of the transgenic wheat. Normally, the composition of wheat grains is essentially made of a complex mixture of proteins that possess viscoelastic properties essential for the manufacture of cereal foods. However, wheat flour contains a variety of proteins including gluten and in particular those of the alpha gliadin group, which have been considered as triggers of celiac disease (33). For this reason, scientists aimed to develop genetically modified grains to reduce their pathogenicity. In this sense, a successful transformation of bread wheat Triticum aestivum Butte 86 was reported. In this study, an RNA interference was used to silence the expression of genes coding for omega-gliadin responsible for food allergy. Protein analysis of the transgenic wheat showed that omega-5 gliadins either were absent or reduced compared to untransformed controls (34). Thus, several studies have been conducted on modifications introduced into the barley genome, for example, the deletion of hordeins B and C, has allowed the production of barley lines with very low levels of toxicity for celiac disease patients compared to the wild type (35).

Elafin

Elafin is a human protein synthesized by gut cells, and its expression and induction are decreased in patients with inflammatory bowel disease (36-37). It decreases the inflammatory response characteristic of celiac disease and may interact with transglaminase-2, a protein involved in the gluten degradation mechanism in celiac patients (38). Since, transglutaminase-2 (TG-2) plays an important role in the pathogenesis of celiac disease, due to its enzymatic activity which allows the introduction of negatively charged residues into gluten proteins contained in cereals by deamidation, (39), therefore, the principle of this strategic target is based on the inhibition of TG-2 by Elafin. Researchers from the National Institute for Agricultural Research (INRA) and the National Institute of Health and Medical Research (INSERM) in collaboration with researchers from MC Master University in Canada and the Swiss Federal Institute of Technology in Zurich have demonstrated that elafin is a key protein against the inflammatory reaction characteristic of celiac disease. They also developed a recombinant strain of a probiotic bacterium, Lactococcus lactis that is able to express and deliver elafin to the intestinal mucosa. In this study, the researchers administered the bacteria to gluten intolerant mice and observed a strong decrease in the inflammatory response to elafin delivered by the probiotic (40). This innovation, published online on April 8, 2014 in the American Journal of Gastroenterology, opens the door to new strategies for treating gluten intolerance.

Gluten degrading enzymes: oral protease to complement gluten luminal digestion

This approach is based on the fact that gluten proteins contain peptide sequences that resist gastric, pancreatic and intestinal proteolytic digestion in the gastrointestinal tract (41). This difficult digestion is due to the high content of amino acids, especially prolines and glutamines (42). Consequently, these residues rich in high molecular weight proline persist in the intestinal lumen and can trigger the inflammatory reaction (42). Therefore, the main goal of the enzymatic approach is to use exogenous enzymes or enzyme supplementation to promote the cleavage and inactivation

of immunogenic gluten peptides that are incompletely degraded by human proteases quickly enough that an inflammatory reaction is not triggered in the small intestine of the patient (43). It should be noted that these enzymes retain their structure and function in the ph ranges of the gastrointestinal tract (44).

The two therapeutic agents that have been proposed in the new therapy are endoproteases of the propyl-endopeptidase (PE) family, and ALV003, which has been shown to be effective in vitro and in vivo, non-toxic, and without allergic reaction (45).

3-1-propyl- endopeptidases

Propyl-endopeptidase (PE) also known as propyl oligopeptidase or post-proline cleavage enzyme is an endoproteolytic enzyme expressed by various microorganisms and plants and in humans encoded by the PREP gene (46). These proline-specific enzymes are able to degrade gluten into smaller peptides that can be digested by the enzymes of the intestinal brush border (aminopeptidases and carboxypeptidases). As the prolamins are more resistant to digestive enzymes, researchers have proposed to administer oral doses of propyl endopeptidase to celiac disease to remedy this problem. In this sense, a study was conducted to determine the feasibility of this treatment; the effect of PE on wheat proteins (gliadins) was evaluated in vitro for 3 hours. At high concentrations of PE, the amount of gliadin peptides was decreased (47). In the same sense, another study was performed during 2 phases over a period of 14 days in 20 asymptomatic patients with celiac disease to evaluate whether treatment of pre-treated dietary gluten with PE decreases intestinal dysfunction. During phase 1, patients ate one slice of bread daily and one slice of bread pre-treated with PE during phase 2. The pretreatment of gluten with PE prevented the development of malabsorption in these patients (48). Therefore, further studies are needed to determine the amount of enzyme dose suitable for protein digested.

3-2-ALV003

Latiglutenase is also known as ALV003 is a mixture of two proteases that degrade gluten; Endoprotease B, isoform-2; also known as ALV001 (EP-B2) is a glutamin-specific cysteine endoprotease derived from germinated barley seeds and SC-PEP (also known as AVL002) is a PEP from Sphingomonas-capsulate (49-50). A phase 2-controlled clinical trial was conducted in patients with celiac disease. These adults received either ALV003 or a placebo daily for a period of 6 weeks upon ingestion of two g of gluten-containing bread. This study demonstrated that AVL003 appeared to attenuate gluten-induced small intestinal mucosal damage in patients with celiac disease (51). After 6 weeks, the biopsies of the subjects in the placebo group showed intestinal mucosal damage after gluten challenge, however, no mucosal damage was observed in the biopsies of the ALV003 group (51). Similarly, 81 patients were enrolled in a clinical study to evaluate the safety, tolerability and activity of AVL003 in two phase 1 clinical trials. In this first trial, 28 patients received AVL003 in the fasting state, and in the second trial, 53 patients received AVL003 along with a gluten-containing meal. AVL003 was administered in escalating doses per cohort (100,300,900 and 1800 mg). The results showed that all doses were well tolerated and no adverse effects or allergic reactions were observed and that gastric aspirates showed that doses 100 and 300 mg of AVL003 degraded 75± 10% and 88± 5% respectively of a gram of wheat bread (52).

Pseudo-cereals

Celiac disease can cause a deficiency in macro and micronutrients. For this reason, this approach focuses on the use of a group of gluten-free cereals known as pseudo-cereals, due to their high nutritional value, which can be used as alternatives to diversify and optimize the gluten-free diet also it can improve the nutritional status, well-being and health of patients with celiac disease (53).

Pseudo-cereals are non-grass plants that do not contain gluten and include amaranth, quinoa, millet and buckwheat. They are increasingly considered an interesting option for the gluten-free diet because they are recognized for their high nutritional value. They are very rich in minerals, vitamins; contain complex carbohydrates and important fiber for our body (54). Studies have shown that amaranth and quinoa contain more digestible proteins, more relevant and contribute

to nutritional balance (55). Similarly, buckwheat has a high fiber content (56). Pseudo-cereals contain a variety of minerals such as iron, calcium and zinc (56), especially amaranth rich in calcium, which is useful and beneficial for patients with celiac disease who are predisposed to nutritional deficiencies (57).

Quinoa

Quinoa is a flowering pseudo-cereal plant belongs to the amaranth family. Its seeds are rich in protein, dietary fiber and minerals (58). Quinoa has a very high nutritional value (83%) similar to that of milk and higher than that of fish and wheat (59). Quinoa proteins contain low concentrations of prolamins (≤ 7%). A study was conducted with 19 patients with celiac disease to evaluate the effects in vivo when consuming quinoa. These adults were received 50g of quinoa daily for 6 weeks. The results showed that the addition of quinoa to the diet of celiac disease patients was well tolerated and they found that gastrointestinal parameters were normal and the ration of villi height to crypt depth improved (60).

Buckwheat

Buckwheat is also known as Fogopyrum esculentum, is an annual cereal of the Polygonaceae family. It is also called buckwheat when it is processed into flour (61). It is rich in protein and its grains qualified as having high nutritional value because they contain all the essential amino acids, soluble fiber and antioxidant compounds (62-63). The dry weight of buckwheat contains 10% to 12% of protein (64). A study was conducted on 19 patients with non-celiac gluten sensitivity to evaluate the effect of buckwheat products on intestinal and extra-intestinal symptoms and biochemical parameters over a period of 12 weeks. During the experimental period, the participants' diet was based on the consumption of buckwheat products and during the control phase, the patients were asked to continue their normal gluten-free diet. Symptom assessment was done by two questionnaires. The results showed that the severity of abdominal pain and bloating was significantly reduced in these patients compared to the control group. The buckwheat diet also let to a significant increase in serum magnesium levels (+4, 7%) and a significant reduction in the levels of certain pro-inflammatory cytokines (-4.5%). Thus, the study confirmed the positive effects of buckwheat for gluten intolerant patients, showing that this pseudo-cereal can contribute to the reduction of symptoms, correct nutritional deficiencies, and improve the inflammatory profile (65).

Amaranth

The amaranth is an annual plant native to Latin America and belongs to the Amaranthaceaes family and not to the grass family. It has very interesting nutritional qualities and is naturally gluten-free. It is characterized by its high protein content (17.7% of dry weight) (66), fiber (4.91% of dry weight) (67), lipids (7.32% of dry weight) (68). Regarding the mineral content, this plant is relatively rich in calcium, manganese and iron (69). In fact, celiac people have used amaranth for some times, because it does not cause allergic reactions in the intestinal mucosa (70).

Therefore, better characterization of these pseudo-cereals is needed in order to recommend them to patients with celiac disease.

Conclusion

Celiac disease is an autoimmune disease of the small intestine, linked to gluten intolerance, which is most often observed in genetically predisposed individuals and its incidence is constantly increasing. This chronic enteropathy is associated with intestinal and extra-intestinal manifestations. Since its appearance, the only available treatment is the gluten- free diet. In recent years, the pathophysiology of celiac disease has undergone great progress, which has led to the search for new therapies complementary or alternative to dietary treatment. These approaches are being developed and have given preliminary results, so it is necessary to conduct clinical trials and increase scientific research in this area. At this time, the gluten- free diet remains the only key to celiac disease while waiting for confirmation of the safety and efficacy of these therapies to allow celiac patients to tolerate gluten at well-defined quantities or to able to eat it at least occasionally.

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