Celiac Disease: Overview and Treatment Options

Authors:
Austen M. Junior, Pharm.D. Candidate 2015
Harrison School of Pharmacy, Auburn University;

Bryant W. Minor, Pharm.D. Candidate 2015
Harrison School of Pharmacy, Auburn University;

Brandon K. Sanford, Pharm.D. Candidate 2015
Harrison School of Pharmacy, Auburn University;

Bernie R. Olin, Pharm.D.,
Associate Clinical Professor and Director, Drug Information Center
Harrison School of Pharmacy, Auburn University

Universal Activity #: 0178-0000-15-102-H01-P | 1.25 contact hours (.125 CEUs)

Initial Release Date: March 1, 2015 | Expires: March. 1, 2017

Authors have no relevant financial relationships to disclose.

EDUCATIONAL OBJECTIVES

After the completion of this activity pharmacists will be able to:

- Define celiac disease and the burden of illness across patient populations.
- Define an at-risk patient of celiac disease.
- Cite the recommended diagnostic tests for celiac disease.
- Describe the pharmacist's role in celiac disease treatment.

INTRODUCTION

Celiac disease (CD), previously termed celiac sprue, non-tropical sprue, and gluten-sensitivity enteropathy, is an autoimmune enteropathy in which the ingestion of gluten results in damage to the tissues of the small intestine.[1,2] Consequently, this destruction leads to an increased risk of a variety of health concerns including malabsorption, malnutrition, failure to thrive, and extraintestinal manifestations. It is the only systemic autoimmune disorder with an identified environmental trigger, and the only currently accepted treatment is lifelong adherence to a gluten-free diet.[1-3] An increased understanding of the disease pathogenesis coupled with the fact that many patients display an incomplete clinical response to diet therapy has driven the development and testing of several pharmacological agents.

Celiac disease has long been considered to be a rare condition. It has recently been determined that it affects nearly 3 million Americans, or approximately 1% of the United States population. Worldwide, the region with the highest incidence is Western Europe, but the disease displays marked geographic variation. This disease primarily affects persons of the white, non-Hispanic demographic of European descent.[1,4] However, due to the evolving and coinciding diets among nations the worldwide prevalence in the non-Western nations appears to be similar, but further research regarding this topic is necessary.[5] CD has often been regarded as a pediatric disease; however, the concern and diagnosis in the adult population has increased substantially. Although the prevalence of this disease appears to be dramatically increasing, it could be the result of improved diagnostic techniques (genetic and serologic testing) and increased awareness.[1] Even with advances in technology and increased awareness of the disease many cases could remain undiagnosed. A 2012 study demonstrated that 82% of the patients found in the U.S. to have CD were unaware of their diagnosis.[6] Undiagnosed CD has the potential to lead to serious complications, especially in children, where it can result in stunted growth and/or delayed puberty.[7]

ETIOLOGY, RISK FACTORS, AND GENETICS

CD can be differentiated from other autoimmune diseases in that it encompasses several factors known to provoke a response. There is a clearly identified environmental trigger (gluten, a protein found in wheat, barley, and rye), a required dominant Human Leukocyte Antigen (HLA) contribution, and autoantibodies against tissue transglutaminase (tTG) (detectable in over 95% of celiac patients).[8] Although all of these have been identified as contributing factors to celiac disease the exact mechanism is still under investigation. Additional environmental factors, such as hepatitis B, hepatitis C, adenovirus, and others have been shown to have a role in celiac disease development.[1,5,9] Moreover, CD is characterized by a genetic component required for proper diagnosis.[1] This enteropathy is more commonly observed in individuals with a family history of CD, and essentially, all CD patients have variants of HLA-DQ2 or HLA-DQ8 heterodimers that are expressed on the surface of antigen-presenting cells.[1] Approximately 90% of patients with CD will have HLA-DQ2, and the remaining 8-10% of patients will have HLA-DQ8[9] Therefore, the absence of either of these excludes the diagnosis of celiac disease. However, the expression of these variants does not conclude that a patient will develop celiac autoimmunity as 40% of the general population also express these variants.[9] Additionally, concordance rates range between 8-18% in first-degree relatives and as high as 75-85% between monozygotic twins, which further accentuates the strong genetic component.[1,5,10]

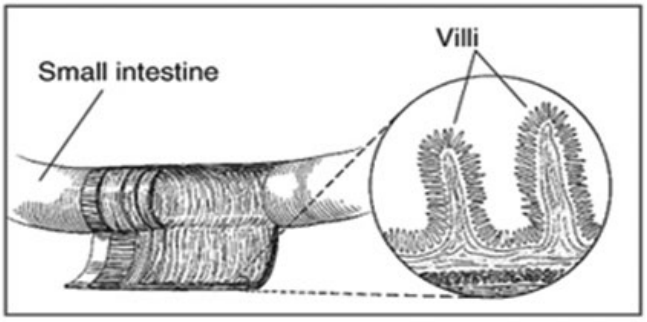
Additionally, many individuals with separate autoimmune disorders may be at a higher risk for developing CD. Autoimmune diseases such as type 2 diabetes, Addison's disease, thyroid disease, rheumatoid arthritis, or Sjogren's syndrome are a few identified risk factors.[5,7,9] This correlation has been useful for physicians to identify patients that could possibly benefit from routine screening and serology tests to unveil undiagnosed celiac disease and implement strategies to appropriately treat their conditions.

PATHOPHYSIOLOGY

Through years of targeted research our knowledge and understanding of celiac disease has accelerated. Clinical manifestations in patients affected with CD are a result of complex interplay of environmental exposure, genetic predisposition, and immunologic response.[10,11] Gluten (the known environmental trigger) is found in wheat, barley, rye, and other select grains. The gluten in wheat is composed of two proteins, gliadins (the primary toxic component) and glutenins. Gliadin is directly toxic to the enterocytes, the cells in the small intestine responsible for nutrient absorption, of individuals with celiac disease. Rye and barley contain similar storage proteins known as secalins and hordeins, respectively. In a patient without CD, when gluten is consumed it does not elicit an abnormal immune response locally or systemically. Normally, the intact intracellular tight junctions of the intestinal epithelium function as the primary barrier to the passage of molecules into the lamina propria.[1] Gluten and its associated peptides are broken down by enzymes and excreted before they are able to generate an immune reaction.

Contrarily, the ingestion of these storage proteins in a patient with CD can compromise the integrity of the tight junctions allowing gluten to penetrate to the lamina propria. This opening of the tight junctions and enhanced gluten transit ultimately induces an autoimmune response and cause enterocyte destruction and subsequent villous atrophy as elaborated below.[3,8] This loss in functioning villi limits the extent of nutrient absorption which can have detrimental effects to the individual.[9]

Figure 1.



Villi on the lining of the small intestine help absorb nutrients.

Figure taken from: NIHHS: celiac disease [Internet]. Bethesda: National Institute of Diabetes and Digestive and Kidney Diseases. What is celiac disease; 2008 [cited 2014 Jun 10]; [about 1 screen]. Available from: http://digestive.niddk.nih.gov/ddiseases/pubs/celiac/

A component that appears to be important in the pathogenesis of celiac disease is tissue transglutaminase. The expression of this enzyme and its associated activity is heightened in patients with CD.[1] This enzyme crosslinks ingested gliadin and causes specific deamidation of glutamine into glutamic acid. This diamidation leads to a more negatively charged gliadin peptide that is more capable of fitting into pockets of the HLA-DQ2 (or -DQ8) antigen-binding groove on the antigen-presenting cells, therefore increasing its immunogenicity.[1,9] Gliadin is then presented to gliadin-responsive CD4+ T cells resulting in a cascade of inflammatory activation and production of cytokines.[3,8] These T lymphocytes become activated and rapidly divide. Additionally, they secrete immunoglobulins, cytokines, interferons, tumor necrosis factor, and interleukin 15 and 17. This ultimately leads to tissue damage (villous atrophy, crypt hyperplasia, and increased antibody-producing B cells).[1] Without tTG, it is believed that gliadin is less immunogenic, and may not stimulate T cells as effectively.[9]

It is also proposed that celiac patients express an abnormal immunoglobulin A (IgA) receptor CD71 at the apical side of the enterocytes.[1,4] This abnormality allows for IgA and gliadin peptide immune complexes, protected from lysosomal acid proteases, to penetrate from the lumen of the intestine to the lamina propria and elicit an immune response. This suggested aspect is also under investigation as a culprit of celiac disease. The extensive research dedicated to the development of new pharmacologic therapy for CD is based on these proposed mechanisms for pathogenesis. Obtaining an improved understanding of the disease state and its pathogenesis will ultimately guide therapy and encourage the development of alternative therapeutic options.

CLINICAL FEATURES

Childhood

Celiac disease in infants is usually very distinguishable. The symptoms usually present in the first 1-2 years of life or after weaning when cereals are introduced into the diet. Classic symptoms include the child failing to thrive, apathetic and irritable appearance, and presentation of muscle wasting, hypotonia, and abdominal distention. Sometimes the child may present with watery diarrhea or constipation.[12] When the above abdominal symptoms are not present then diagnosis becomes a challenge. Therefore, in all children of relevant ethnic backgrounds that do not present with the "classic" symptoms, should be suspected of gluten sensitivity if they present with short stature or failure to thrive. Nutritional deficiency, such as anemia, is another common presentation, especially in older children. For many patients a brief, spontaneous remission of symptoms occurs in adolescence.[10]

Adulthood

The mean age of diagnosis in adults is approximately 45 years old. The increase in newly diagnosed adults with CD contradicts the past perception that celiac disease was mainly a pediatric complication. Some of the adults diagnosed may have had evidence of unrecognized gluten sensitivity in childhood, such as short stature and a symptom history consistent with unrecognized sensitivity.[10] However, many adults do not have evidence of a history of celiac disease, indicating that they developed gluten sensitivity for the first time in adult life. For theses adults there seems to be a correlation with the development of celiac disease and increased body mass indices and obesity.[10]

Table 1. Symptoms of Celiac Disease.[1,10]

Symptoms	
Gastrointestinal	Extraintestinal
• Diarrhea • Steatorrhea • Weight Loss • Flatulence • Abdominal Distension	• Osteopenia • Anemia • Neurologic (Ataxia, neuropathy) • Dermatitis herpetiformis

GASTROINTESTINAL AND EXTRAINTESTINAL SYMPTOMS

Symptoms vary tremendously between patients. The majority of symptoms are due to malabsorption, which is not specific to celiac disease and displays similar characteristics to other malabsorption disorders. Most adults present with diarrhea, steatorrhea, flatulence, and weight loss (similar to symptoms in a child).[10] As patients get older and with disease progression, they start to present with extraintestinal symptoms and clinical findings often from nutrient malabsorption. Virtually all organ systems may be affected by the progression, which may lead to anemia, osteopenia, neurologic issues, and menstrual abnormalities.

Often extraintestinal symptoms are more of a burden than gastrointestinal. Osteopenia is the most common complication (70% of untreated patients) relating from celiac disease. Prevalence increases with age and advances to osteoporosis in 25% of patients. Osteopenia is a result of impaired calcium absorption, vitamin D deficiency, and binding of intraluminal calcium and magnesium to unabsorbed dietary fatty acids. Patients present with bone pain in the lower back, rib cage, and pelvis. Lack of calcium and magnesium may also lead to muscle cramps, paresthesias, or tetany. Depletion of calcium may secondarily cause hyperparathyroidism, resulting in the mobilization of calcium from the bone, exacerbating the osteopenia. Despite this information, evidence of increased fracture risk of osteopenic celiac patients is still unclear.[10]

Anemia is a common complication in both children and adults. The main cause is due to a lack of iron or folate absorption from the proximal intestine. In severe disease the ileum becomes involved, which could lead to impaired absorption of vitamin B_{12}. Extensive progression of the disease may lead to bleeding into the skin, mucous membranes, or development of hematuria, epistaxis, vaginal or GI bleeding. Bleeding has the potential to exacerbate anemia and is most likely caused from impaired intestinal absorption of fat soluble vitamin-K.[10]

Neurologic symptoms caused by lesions of the central or peripheral nervous system occasionally occur in patients with severe disease and are not well understood. Ataxia is the most common neurologic manifestation, which is believed to be caused by immunologic damage to the cerebellum, posterior columns of the spinal cord, and peripheral nerves. Vitamin deficiencies have been proposed as causative agents of some neurologic symptoms, and administration of a multi-vitamin has shown some improvement in neurologic symptoms.[10]

Dermatitis herpetiformis is a skin manifestation caused by ingestion of gluten. It occurs in about 15-25% of patients with celiac disease and it is most frequently observed in 30-40 year old patients, although it can be found in children and the elderly.[1] The pruritic skin rash can occur anywhere on the body, but usually is seen on the elbows, knees, buttocks, and scalp. Patients with dermatitis herpetiformis usually do not exhibit the typical gastrointestinal symptoms, but they are at risk for developing intestinal damage. Dermatitis herpetiformis was thought to just be a skin disease that was often found in celiac disease. Now it is agreed that everybody with dermatitis herpetiformis also has celiac disease.[1,10] Patients can be diagnosed with dermatitis herpetiformis by taking a small skin biopsy from normal skin next to a blister site. The deposition of IgA granules at the dermal-epidermal junction confirms a positive biopsy result. The 2004 National Institutes of Health (NIH) Consensus Development Conference on Celiac Disease concluded that if a patient has a positive dermatitis herpetiformis skin biopsy, then a small intestine biopsy is not required.[1]

PHYSICAL EXAMINATION

Like the gastrointestinal and extraintestinal symptoms, the physical findings in CD patients are variable. In general, people with mild disease exhibit normal physical symptoms, but as the severity increases so do the physical abnormalities. In children, growth retardation is a main concern, but usually corrects itself if caught early and treated properly. The average CD patient is 3 inches shorter than the general population, they also may appear emaciated if untreated, and it is not abnormal for them to gain around 13 pounds after instituting a gluten free diet. If experiencing anemia due to an iron deficiency the patient may develop clubbing of the fingers and koilonychia (spoon nails). Patients may also experience pitting edema due to hypoproteinemia and hypotension that may cause dehydration and the drying out of the skin.[10]

The extremities of an untreated celiac patient reveal loss of sensory modalities, including light touch, vibration, and position. These symptoms are usually caused by peripheral neuropathy and very rarely demyelinating spinal cord lesions.[10]

DIAGNOSIS

A common theme in the presentation of celiac disease is patient variability based upon severity and extent of the intestinal lesions, and the diagnosis of the disease is no exception. Over the years the frequency of celiac disease diagnosis has increased, but it is estimated that 97% of patients with celiac disease have not been diagnosed. This is a cause for concern considering that undiagnosed celiac disease can lead to a four-fold increased risk of death compared to the normal population.[1] Another area of concern is that only 11% of celiac disease cases are diagnosed in a timely manner.[1] With an increased recognition of the many different common diseases that celiac patients are frequently misdiagnosed with clinicians can improve on that number. The most accurate diagnostic tests are serum IgA EMA or tTG antibody and the performance of a small intestine biopsy. A confirmed diagnosis of celiac disease requires both a positive histologic finding on the biopsy and improvement in response to gluten-free diet, which is usually carried out via serologic tests.[10]

SEROLOGY

There are many different assays that can be used to determine the presence of celiac disease, but the IgA EMA is the most sensitive (90%) and specific (99%), therefore, it is considered the gold standard. Due to the high specificity of the assay, the results are interpreted as a simple positive or negative. Antibody levels usually fall upon the initiation of a gluten-free diet, with the test often becoming negative in treated patients. The IgA tTG is slightly less reliable (sensitivity 93%, specificity 99%) than the IgA EMA. Both the IgA EMA and tTG target the tTG antigen, while other assay tests such as the IgA and IgG AGA tests target the antigladin antibody. The targeting of the antigladin antibody leads to the tests having lower diagnostic accuracy and are not recommended for initial diagnosis.

The clinical application of these tests includes the ability to evaluate the patients with suspected celiac disease, monitor diagnosed patients adherence to treatment, and may possibly be used in the future for screening asymptomatic patients for silent celiac disease. As previously stated the IgA EMA and tTG assays are preferred for the initial diagnosis. The EMA is more specific;

however, the tTG test is more readily available and less expensive, therefore more widely used.[10] The same is true when used for monitoring the adherence of celiac patients. Antibody levels decrease upon initiation of a gluten-free diet, which make the serology assays a perfect tool to monitor the compliance of celiac disease patients. Currently screening for silent celiac disease via the serologic test is not recommended due to the lack of studies pointing to benefits. Hypothetically there are plenty of benefits: reduction in risk of enteropathy associated T cell lymphoma, reversal of unrecognized nutritional deficiencies, avoidance of other autoimmune diseases, and general well-being.[10] These benefits however depend on the patients following a strict gluten free diet, which many asymptomatic patients may find difficult. The current standard screening process is reserved for those at high risk for developing celiac disease, such as family history (1st or 2nd degree relative), anemia, IBS, type 1 diabetes, autoimmune, connective tissue, or liver disorders, and subjects with Down syndrome.[10]

The European Society for Paedeatric Gastroenterology, Hepatology and Nutrition (ESPGAHN) released new guidelines in 2010 concerning the diagnosis in children. The new guidelines emphasized a more prominent role for serology testing and genetic testing in confirming the diagnosis for celiac disease. For symptomatic patients the guidelines still recommend initially using serology and biopsy as the primary way to confirm celiac disease.[13] The new fundamental aspect is that one may not have to perform a biopsy if the anti-tTG antibody levels are very high (>10 times ULN based on the child's specific age). If the choice is made to omit the intestinal biopsy, then both EMA and HLA levels should be drawn and be found positive to make an accurate diagnosis.[13]

Diagnosis for asymptomatic patients has changed from initially using the serology to now using genetic testing first (HLA -DQ2 and DQ8). The guidelines state that this would be more cost effective, because if the results came up negative these patients would be excluded from further testing. If they tested positive for DQ2 or DQ8 then testing with serology and biopsy would be initiated.

SMALL INTESTINE BIOPSY

Diagnosis of celiac disease may be apparent via clinical observation and positive serologic tests, but a confirmed diagnosis cannot be accomplished unless a positive biopsy for the disease is established. Endoscopic biopsy is the standard procedure, which takes multiple small samples from the distal duodenum. The mucosa of the small intestine is then analyzed via a dissecting microscope.[10] Normal small intestine mucosa have a villous structure, but in untreated celiac disease the mucosa takes on a flat and featureless shape, which is easily recognizable.[10] Clinicians use a standardized system to evaluate biopsy results called the Marsh classification system. Patients are placed in categories that rate form Marsh I to Marsh IV, with Marsh III being further divided into Marsh IIIa (partial villous atrophy), IIIb (subtotal villus atrophy), and IIIc (total villus atrophy). Most diagnosed celiac patients (50%-60%) are placed in one of the Marsh III subgroups.[1]

OTHER DIAGNOSTIC TOOLS

Stool studies, hematologic and biochemical tests, and radiologic studies may be performed, with an abnormal result appearing in celiac disease patients. The issue that arises is that these tests are not specific, due to the presence of these abnormalities seen in other intestinal malabsorption disease states.[10]

DIFFERENTIAL DIAGNOSIS

There are other malabsorption and gastrointestinal disorders that share similar characteristics as celiac disease, requiring the need to rule out these disorders when diagnosing celiac disease. The easiest way to do this is by performing one of the serologic tests mentioned above, as the IgA EMA and tTG are very specific in identifying celiac disease.

Malabsorption and steatorrhea may result from pancreatic insufficiency, cholestatic liver disease, and/or small intestinal bacterial cell overgrowth. Changes in the morphology of the small intestine similar to the findings in celiac disease may also be present in other disease states. Villus deterioration can occur via hypogammaglobinemia, viral gastroenteritis, or soy and milk intolerance found in infants.[10] Inflammatory bowel syndrome is another disorder that has overlap with celiac disease, specifically with genetics, but a 2014 article did not find a major correlation between the two compared to other autoimmune disorders.[5] Collagenous sprue is a rare condition that may cause confusion due to the fact that the symptoms and biopsy reveal identical results found in celiac disease, but the condition doesn't respond to gluten withdrawal. Patients may also develop diarrhea upon gluten ingestion, but the mucosa shows normal or small mucosal damage. This condition responds to a gluten free diet. Then, there are patients who have the classic symptoms of celiac disease and do not respond to a gluten free diet indicating a condition known as refractory sprue.

PROGNOSIS

If the condition is noticed and diagnosed early, patients with celiac disease have an excellent prognosis if they are willing to adhere to a lifelong gluten-free diet. Contrarily, if the condition is not recognized and proper diet restrictions are not implemented, affected patients may develop significant malnutrition and debilitation and possibly even die from complications such as infection or hemorrhage. Growth and development in infants and children with celiac disease proceed normally despite continued gluten insensitivity. Following initiation of a gluten-free diet, adults usually experience a return of absorptive functions and many of the manifestations of the disease disappear.[10]

Although malabsorption and malnutrition are mostly reversible, other complications of the disease may not be reversible, including peripheral neuropathy, ataxia, or pathologic fractures secondary to severe osteopenic bone disease.[10,14] Evidence gathered from previous studies suggests that celiac disease is not always a lifelong condition. A long-term follow-up of children with diagnosed celiac disease showed that a significant amount of them developed latent celiac disease and become "tolerant" to gluten during adolescence; however, the factors leading to the

appearance or disappearance of gluten-sensitive enteropathy are still unknown.[10]

TREATMENT

The overall goals of treatment include relieving symptoms, healing the intestine, and reversing the consequences of malabsorption. Currently, the only accepted treatment for celiac disease is a lifelong strict adherence to a gluten-free diet. Celiac patients must recognize the importance of completely avoiding gluten in their diet. This means not ingesting products containing gluten or any products that have been contaminated with gluten. Wheat, barley, and rye must be avoided. Oats are from a different plant family, but they have also been problematic in celiac patients. Patients must also commit to avoiding the ingestion of gluten found in nonfood items such as toothpaste, lip balm, lipstick, etc. Other potential sources of gluten that should not be overlooked are oral prescription or nonprescription drugs, vitamin and mineral supplements, and health and beauty aids and cosmetics that have oral ingestion.[1]

It is hard to determine a universal threshold under which patients need to keep their daily gluten, but as little as 10 to 50 mg/day is the minimum dose required to produce measurable damage to the small intestinal mucosa. The FDA has recently determined the tolerable daily gluten intake in celiac patients to be less than 0.4 mg/day for adverse morphological effects and less than 0.015 mg/day for adverse clinical effects.[1] The majority of celiac patients have substantial improvement following the elimination of gluten from their diets.[3] One study showed that cognitive impairment or "brain fog" was significantly improved in celiac patients who adhered to a gluten-free diet.[15]

Unfortunately, adhering to a strict gluten-free diet poses difficulties in everyday life including increased costs, social restrictions and stigmatization, which theoretically may impact negatively on the health-related quality of life.[16] Although the awareness of the gluten-free diet is increasing in the general public and the food manufacturing industry, it is still quite challenging to eliminate the "hidden gluten" which often contributes to the ongoing signs and symptoms and incomplete mucosal healing. Additionally, 7-30% of celiac patients have persistent symptoms, signs, or laboratory abnormalities typical of celiac disease despite being on a gluten-free diet for at least 6-12 months. This is nonresponsive celiac disease (NRCD), and unintentional gluten intake is often the cause accounting for 35-50% of the cases of NRCD. Refractory celiac disease (RCD) is another entity in the celiac disease spectrum, which is defined as persistent or recurrent malabsorptive symptoms and signs with small intestine atrophy despite a strict gluten-free diet for more than 12 months.[3] See Table 2 for a partial list of grains and botanicals that do and do not contain gluten.[3]

Newly diagnosed patients should be evaluated for nutritional deficiencies associated with vitamin and mineral malabsorption. Possible nutritional deficiencies include folic acid, vitamin B_{12}, fat-soluble vitamins, iron, and calcium. Iron-deficiency anemia may be the only presenting sign of disease in patients without diarrhea. If detected, these deficiencies should be supplemented in addition to treating the disease.[1]

Table 2. Gluten-containing/Gluten-free Grains/Botanicals

Contain Gluten	Gluten-Free
• Wheat • Barley • Rye • Bran • Triticale	• Amaranth • Arrowroot • Buckwheat • Corn • Millet • Quinoa • Rice • Soybeans

The bone disorders that result from the disease pose their own challenge for comprehensive treatment of celiac patients. The two main mechanisms are intestinal malabsorption and chronic inflammation. A gluten-free diet in addition to calcium and vitamin D supplementation is usually the initial approach for treating these bone disorders. However, in many cases, especially in severe osteoporosis, it might be useful to begin treatment with hormones or bisphosphonates.[14]

FUTURE THERAPIES

Because of the shortcomings of the gluten-free diet mentioned above, this approach is not the perfect solution for all celiac patients and leaves desire for additional treatment options for the disease. A few studies have addressed the use of systemic steroids (e.g. prednisone or enteric-coated budesonide), small intestinal release mesalamine, or immunosuppressive agents (eg, azathioprine) in patients with RCD. Unfortunately, these agents are not always successful in achieving symptom relief or mucosal healing.[3]

Due to an improved understanding of the pathogenesis of celiac disease potential therapeutic targets have emerged. Most of these novel therapeutic approaches are aimed at the treatment of patients with refractory celiac disease since the gluten-free diet is not effective for these patients. Future therapies can be directed at two general mechanisms for treating the disease: 1) decreasing the antigenic load and 2) modulating the immune response.[1]

Decreasing Antigenic Load

Potential methods include antigen presentation blockade via tTG inhibitors. However, their safety is questionable due to the presence of the enzyme throughout the body and its role in many functions necessary for homeostasis. In the intestinal lumen, gluten could potentially be detoxified by polymeric binders, probiotic bacteria, or glutenases that decrease the harmful effects of gluten peptides. Another approach to decrease the toxicity of gluten peptides is through the development of gluten proteins in which the proline residues were replaced by azidoprolines. These novel gluten peptides bound HLA-DQ2 but did not stimulate an immune response.[1,14]

Table 3. Celiac Disease Information Sources

For additional information, see the following CD Informational Sources:

- National Institutes of Health - http://www.nih.gov/
- For disease state overview, basic pathophysiology, and updates:
  - Celiac Disease Foundation http://celiac.org/
  - National Foundation for Celiac Awareness: Celiac Central http://www.celiaccentral.org/
  - Celiac Support Association http://www.csaceliacs.info/
  - American Celiac Disease Alliance http://americanceliac.org/
  - Celiac.com http://www.celiac.com/

Altering the permeability through the tight junctions in intestinal epithelium with zonulin inhibitors such as larazotide acetate (AT-1001) also appears to be a promising approach. Larazotide is a synthetic octapeptide that modulates the integrity of enterocyte tight junctions thereby reducing gluten transport across the epithelium.[1,3,17]

Modulating the Immune Response

Methods for modulating the immune response include the neutralization of inflammatory cytokines and regulation of T cells. Several endopeptidases have been developed which promote a more complete digestion of gluten peptides and thus destroy T cell activating epitopes. Lymphocyte blocking or anticytokine therapy may also be a potential approach to therapy. Finally, anti-inflammatory drugs and monoclonal antibodies that play a major role in immunomodulation have been tested and might become an approach in the future.[1,3]

PHARMACIST'S ROLE

Although there is a limited spectrum of drug therapy for CD, the pharmacist's role in therapy can be invaluable. The front line relationship that pharmacists have with their patients provides a great opportunity to:

1. Question/triage their patients based on their non-specific gastrointestinal complaints;
2. Potentially make connections to gastrointestinal and extraintestinal complaints to assist in a diagnosis;
3. Based on multiple observations of families, perhaps identify children that may be candidates for screening for celiac disease;
4. Educate patients, once a diagnosis of celiac disease is made, particularly for lifestyle changes and reinforce the importance of a gluten-free diet.
5. Assist patients in identifying gluten-free products and providing resources for this purpose.
6. Act as a source of information for the disease, including providing legitimate resources for the self-education of your patients. Table 3 lists sources where more information about CD can be found.

CONCLUSION

As the prevalence of celiac disease continues to rise and the clinical spectrum continues to evolve, the demand for further research and improved technology also increases. Advances in the utilization of diagnostic tests and screening tools will help to reduce the number of undiagnosed patients, leading to improved clinical outcomes and patient prognosis. The mainstay of therapy continues to be the implementation of a gluten-free diet; however, further understanding of the pathogenesis of the disease has led to new potential therapeutic approaches.

REFERENCES

1. Mangione RA, Patel PN. Celiac disease. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. *Pharmacotherapy: A pathophysiologic approach.* 9th ed. New York: McGraw-Hill Medical; c2014. p. 603-610.
2. Celiac disease foundation [Internet]. Woodland Hills; c2014 [cited 2014 Jun 6]. Available from: www.celiac.org
3. Vanga RR, Kelly CP. Novel therapeutic approaches for celiac disease. Discov Med [Internet]. 2014 May [cited 2014 Jun 6];17(95):285-93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24882720
4. Overview of celiac disease [Internet]. The University of Chicago Celiac Disease Center; c2014. [cited 2014 June 6]; [about 2 screens]. Available from: http://www.cureceliacdisease.org/
5. Pascual V, Dieli-Crimi R, Lopez-Palacios N, Bodas A, Medrano LM, Nunez, C. Inflammatory bowel disease and celiac disease: overlaps and differences. World J Gastroenterol [Internet]. 2014 May 7 [cited 2014 Jun 6]; 20(17):4846-56. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009516/?report=classic
6. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everheart JE. The prevalence of celiac disease in the United States. Am J Gastroenterol [Internet]. 2012 Oct [cited 2014 Jun 6];107(10):1538-44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22850429
7. Namatovu F, Sandstrom O, Ivarsson A. Celiac disease risk varies between birth cohorts, generating hypotheses about causality; evidence from 36 years of population-based follow-up. BMC Gastroenterol. [Internet]. 2014 [cited 2014 Jun 6];59(14): 1-23. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3977663/
8. Barker JM, Liu, E. Celiac disease: pathophysiology, clinical manifestations, and associated autoimmune conditions. Adv Pediatr. [Internet]. 2008 [cited 2014 Jun 7];55: 349-365. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2775561/
9. Pruessner HT. Detecting celiac disease in your patients. Am Fam Physician. [Internet]. 1998 Mar 1 [cited 2014 June 6];57(5):1023-1034. Available from: http://www.aafp.org/afp/1998/0301/p1023.html
10. Farrell RJ, Kelly CP. Celiac sprue and refractory sprue. In: Feldman M, Friedman LS, Brandt LJ, editors. Gastrointestinal and liver disease. 8th ed. Philadelphia: Elsevier Inc.; c2006. p. 2277-2306.
11. Celiac disease and malabsorption disorders [Internet].Cleveland: The Cleveland Clinic Foundation; c2000-2014. 2012 Oct [cited 2014 Jun 6]; [about 7 screens]. Available from: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/gastroenterology/celiac-disease-malabsorptive-disorders/#s0020
12. Hussain S, Sabir M, Afzal M, Asghar I. Coeliac disease- clinical presentation and diagnosis by anti tissue transglutaminase antibodies titre in children. J Pak Med Assoc. [Internet]. 2014 Apr 14 [cited 2014 Jun 9];64(4): 437-441. Available from: http://jpma.org.pk/PdfDownload/6301.pdf
13. Tonutti E, Bizzaro N. Diagnosis and classification of celiac disease and gluten sensitivity. Autoimmunity Reviews. [Internet] 2013 Nov [cited 2014 Jun 9]13:472-476. Available in: http://ac.els-cdn.com/S156899721400055X/1-s2.0-S156899721400055X-main.pdf?_tid=30bc1778-efe5-11e3-97d4-00000aab0f01&acdnat=1402325519_71c14e5bf717c16809710cf1040726ed
14. Krupa-Kozak U. Pathologic bone alterations in celiac disease: Etiology, epidemiology, and treatment. Nutrition. [Internet]. 2014 Jan [cited 2014 Jun 9];30(1): 16-24. Available from: http://ac.els-cdn.com/S089990071300289X/1-s2.0-S089990071300289X-main.pdf?_tid=c574b9be-f009-11e3-a433-00000aab0f02&acdnat=1402341231_387f756197810da5f7d69a38598aacc2
15. Lichtwark IT, Newnham ED, Robinson SR, Shepherd SJ, et al. Cognitive impairment in coeliac disease improves on a gluten-free diet and correlates with histological and serological indices of disease severity. Aliment Pharmacol Ther. [Internet]. 2014 May 28 [cited 2014 June 9];doi:10.1111. Available from: http://onlinelibrary.wiley.com/doi/10.1111/apt.12809/pdf
16. Myleus A, Peterson S, Carlsson A, Hammarroth S, et al. Health-related quality of life is not impaired in children with undetected as well as diagnosed celiac disease: a large population based cross-sectional study. BMC Public Health. [Internet]. 2014 [cited 2014 June 9];14(425): 1-9. Available from: http://www.biomedcentral.com/content/pdf/1471-2458-14-425.pdf
17. Zingone F, Capone P, Ciacci C. Celiac disease: Alternatives to a gluten free diet. WJGPT. [Internet]. 2010 Feb 6 [cited 2014 June 9];1(1): 36-39. Available from: http://www.wjgnet.com/2150-5349/full/v1/i1/36.htm