Turk J Gastroenterol *2015; 26: 93-4*

Use of elafin in celiac disease

Novel Role of the Serine Protease Inhibitor Elafin in Gluten-Related Disorders

Galipeau HJ, Wiepjes M, Motta JP et al. Am J Gastroenterol 2014; 109: 109: 748-56.

Celiac disease (CD) is a gluten-sensitive enteropathy that develops in genetically susceptible individuals with permanent intolerance to wheat gliadin. CD is characterized by the presence of typical, though not specific, histopathological changes in the small intestinal mucosa. Reported CD prevalence among different countries varies between 1:70 and 1:200. Non-diarrhea-associated forms (silent, oligosymptomatic, or atypical CD) are the major mode of presentation. Gluten withdrawal is highly effective for most patients, but the necessity of a lifetime gluten-free diet (GFD) makes the diagnosis challenging because of the various presentations encompassed by the disease (1-3).

In real life, "gluten free" is a misnomer because of the contamination of foods with various amounts of gluten during production. Even a small amount can increase long-term morbidities in susceptible patients. On the other hand, adhering to a limited diet could be very hard for asymptomatic or surveillance-diagnosed patients. The social lives of the patients are also affected because of the restriction and lack of knowledge about the healthy alternatives to gluten. Development of alternative therapies such as glutenases that degrade the ingested gluten and immunotherapy are on the way.

In the May issue of American Journal of Gastroenterology, Galipeau and colleagues (4) investigated the novel role of elafin in gluten-related disorders. Elafin is a serine protease inhibitor that acts on various forms of elastases and proteinases. The aim of the study was to determine the inhibitory effect of elafin on the activity of tissue transglutaminase (TTG), which has an important role in the pathogenesis of CD. The study was designed in three steps: 1) to evaluate tissue expression of elafin by immunofluorescence in patients with CD before and 1 year after the initiation of a GFD; 2) the inhibitory effect of Elafin on human TTG was tested by measuring the decrease in deamidation of 33-mer gliadin peptide by TTG in the presence of elafin; 3) evaluation of barrier-enhancing properties in the transgenic gliadin-sensitized mice model of CD via delivery of elafin with the *Lactobacillus. lactis* (LI-E) vector, and subsequent measurement of small intestinal inflammation and permeability.

Elafin expression and intensity were much lower in patients with active CD compared to controls. Elafin levels in treated CD patients were lower than controls and higher than active patients, but were not statistically different. The inhibitory effect of elafin on TTG was shown by the slowing of the kinetics of deamidation of 33-mer gliadin peptide in a dose- and time-dependent manner. Delivery of LI-E to the treatment group in the animal model normalized intraepithelial lymphocyte counts compared to the control group. Moreover, small intestinal permeability in the treatment group, as indicated by 51Cr-EDTA flux, was lower as well with the tissue conductance compared to controls.

It is a promising study, and thus, as a consequence of this investigation, clinicians may use elafin-producing recombinant probiotics in the future as an adjuvant therapy in CD. However, we wish to put an emphasis on the word "adjuvant".

In this study, it was shown that elafin expression throughout the small intestine was lower in patients with active CD compared to control groups (4). It seems to us that-as suggested in the study-decreased elafin expression is a result of the processes occurring in CD, rather than the cause of CD, as proposed in the manu-

Address for Correspondence: Taylan Kav, Department of Gastroenterology, Hacettepe University, Ankara, Turkey
E-mail: tkav@hacettepe.edu.tr
Received: October 29, 2014 **Accepted:** November 12, 2014

script. One of the sources of elafin in the alimentary tract is the epithelial cells (5), and destruction of these cells may lead to low expression. Additionally, consumption of elafin caused by chronic inflammation probably contributes to the decreased levels of the molecule, and so replacing the consumed molecule may be a good idea. However, we think that elafin therapy will not completely replace a GFD in patients with evident and/or active CD. It can be used as an adjuvant to the diet in evident CD. Once a gluten exposure occurs, susceptible patients will always stay "sensitized", and we hypothesize that elafin will not terminate the state of being sensitized, since gluten-specific CD4+ T cells will always be ready to start an immune reaction (6). Besides this, in the study, it was shown that elafin moderately inhibited tissue TTG (4). So, according to our hypothesis and data given in the study, we postulate that elafin will not make patients free of a GFD.

However, if the ultimate purpose is to get rid of the GFD in CD therapy, we think that the ideal way is to prevent sensitization by gluten. This may be achieved by using elafin in patients by inhibition of TTG, which in turn will decrease formation of gliadin peptides, and thereby will inhibit introduction of gluten residues, and therefore, sensitization may be prevented. Of course, there is a long way to go before researchers can make elafin available in clinical practice as a drug to treat CD. If it is achieved, we postulate that non-sensitized susceptible patients or patients at risk, in which CD occurs more frequently than in the general population (7), may benefit much more from elafin than patients with evident and/or active CD.

Taylan Kav

Department of Gastroenterology, Hacettepe University Faculty of Medicine, Ankara, Turkey

REFERENCES

1. Murray JA, Rubio-Tapia A, Van Dyke CT, et.al. Mucosal atrophy in celiac disease: Extent of involvement, correlation with clinical presentation, and response to treatment. Clin Gastroenterol Hepatol 2008; 6: 186-125. **[CrossRef]**
2. Rubio-Tapia A, Murray JA. Celiac disease. Curr opin Gastroenterol 2010; 26: 116-22. **[CrossRef]**
3. Hopper AD, Cross SS, Sanders DS. Patchy villous atrophy in adult patients with susupected gluten sensitive enteropathy: is a multiple duodenal biopsy strategy appropriate? Endoscopy 2007; 39: 219-24.
4. Galipeau HJ, Wiepjes M, Motta JP, et al. Novel role of the serine protease inhibitor elafin in gluten-related disorders. Am J Gastroenterol 2014; 109: 748-756. **[CrossRef]**
5. Schmid M, Fellermann K, Fritz P, Wiedow O, Stange EF, Wehkamp J. Attenuated induction of epithelial and leukocyte serine antiproteases elafin and secretory leukocyte protease inhibitor in Crohn's disease. J Leukoc Biol 2007; 81: 907-915. **[CrossRef]**
6. Han A , Newell EW , Glanville J, et al. Dietary gluten triggers concomitant activation of CD4+ and CD8+ αβ T cells and γδ T cells in celiac disease. Proc Natl Acad Sci USA 2013; 110: 13073-8. **[CrossRef]**
7. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA; American College of Gastroenterology. ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease. Am J Gastroenterol 2013; 108: 656-76. **[CrossRef]**