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REVIEW IN GASTROENTEROLOGY

New coeliac disease treatments and their complications☆

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Abstract The only accepted treatment for coeliac disease is strict adherence to a gluten-free diet. This type of diet may give rise to reduced patient quality of life with economic and social repercussions. For this reason, dietary transgressions are common and may elicit intestinal damage. Several treatments aimed at different pathogenic targets of coeliac disease have been developed in recent years: modification of gluten to produce non-immunogenic gluten, endoluminal therapies to degrade gluten in the intestinal lumen, increased gluten tolerance, modulation of intestinal permeability and regulation of the adaptive immune response. This review evaluates these coeliac disease treatment lines that are being researched and the treatments that aim to control disease complications like refractory coeliac disease.

PALABRAS CLAVE
Enfermedad celiaca;
Dieta sin gluten;
Enteropatía sensible al gluten

Nuevas terapias en la enfermedad celiaca y sus complicaciones

Resumen El único tratamiento aceptado para la enfermedad celiaca es el seguimiento de forma estricta de la dieta sin gluten. Este tipo de dieta puede ocasionar una disminución de la calidad de vida de los pacientes, dificultades sociales y económicas. Por lo tanto, son frecuentes las transgresiones dietéticas que pueden perpetuar el daño intestinal. En los últimos años se han desarrollado numerosos tratamientos, dirigidos hacia diferentes dianas en la patogenia de la enfermedad celiaca: modificación del gluten para conseguir un gluten no inmunogénico, terapias endoluminales que degraden el gluten en la luz intestinal, favorecer la tolerancia al

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gluten, modulación de la permeabilidad intestinal o regulación de la respuesta inmune adaptativa. En esta revisión se evalúan estas líneas terapéuticas que se están investigando para la enfermedad celiaca y los tratamientos enfocados al control de las complicaciones de la enfermedad, como la enfermedad celiaca refractaria.

Introduction

Coeliac disease (CD) is an enteropathy triggered by the ingestion of gluten that affects genetically predisposed subjects.[1,2] Gluten is a polypeptide that is insoluble in both water and dilute saline solutions, with a high prolamin and glutenin content.[3] This protein causes chronic inflammation in the small intestine mediated by the HLA system, specifically HLA-DQ2 and HLA-DQ8. The intestinal inflammatory process leads to malabsorption of different nutrients. Clinical manifestations vary according to the patient's age.[4] In paediatric patients, classic symptoms characterised by diarrhoea, abdominal distension and growth retardation predominate. In adults, symptoms are more atypical with oligosymptomatic manifestations,[5] such as anaemia, early osteoporosis, abdominal distension or abnormal intestinal motility, which means this disease should always be considered when making a diagnosis.[6]

CD affects around 1% of the population in developed countries.[7] However, it is estimated that a proportion of patients may not be diagnosed correctly due to the procedures commonly used, which are based on serological techniques (mainly anti-transglutaminase, anti-endomysial and anti-gliadin antibodies).[8] As a result, strategies have been designed in recent years to optimise early detection of the disease in high-risk groups, such as first-degree relatives of individuals with coeliac disease.[9–12]

At present, the only effective treatment for CD is strict adherence to a gluten-free diet (GFD) for life. However, it has been demonstrated that mucosal recovery is not immediate and there is even a significant proportion (30–50%) of patients who have persistent intestinal lesions and recurrent symptoms despite apparently correct adherence to a gluten-free diet (known as non-responsive coeliac disease [NRCD]).[13,14] Strict adherence to a GFD requires enormous personal sacrifice and has an impact on patients' psychological and social spheres, which often makes strict adherence difficult.[15] Also, a small proportion of coeliac patients (~1%) does not respond to GFD at all (refractory CD [RCD]). These subjects are mainly diagnosed at an adult age after eating gluten for a prolonged period of time, and are at risk of developing complications such as Type II RCD (RCD-II, an *in situ* small bowel lymphoma) or the most severe complication, enteropathy-associated T-cell lymphoma (EATL).[16,17] Table 1 shows the main features that make it possible to differentiate between CD, RCD-I, RCD-II and EATL.

Although a strict GFD is the primary treatment for CD, various alternative therapeutic measures have been investigated in recent years. A description of the different treatments being developed and their mechanism of action in relation to the aetiopathogenesis of CD is given below.

Pathogenesis

CD arises in genetically predisposed individuals as an immune response to ingested gluten. This immune response comprises an innate response (direct *toxic* effect of the gluten on the epithelium) and an adaptive or specific response (involving CD4+ T-cells in the lamina propria or underlying tissue) and the two appear to be responsible for histological damage to the intestinal mucosa.[18]

Some gluten fragments, such as α-gliadin, induce an innate, toxic and immediate immune response that is not related to T-cells or HLA-DQ2/8 presentation.[19,20] As a result, oxidative stress is triggered, mediated primarily by the formation of nitric oxide, which is produced by inducible nitric oxide synthase (iNOS) in enterocytes,[21–24] causing expression of ligands, such as MICA, in these cells.[25] Gliadin is also able to weaken intercellular bonds between the enterocytes.[26,27] However, the main mechanism depends on IL-15 being released by these enterocytes in the event of stress.[28] This cytokine induces NKG2D expression in intraepithelial lymphocytes, which is capable of interacting with its ligand, the MICA molecule of enterocytes, enhancing intestinal damage.[29,30] The NKG2D/MICA bond induces enterocyte apoptosis, resulting in the disappearance of microvilli and flattening of the intestinal epithelium. This process activates cytotoxicity phenomena in the epithelium, which, together with the weakening of the intercellular bonds, increases intestinal permeability and the passage of gluten into the lamina propria, where the adaptive response is triggered.

The adaptive immune response is mediated by specific T-cells that have been presented with antigens by antigen-presenting cells (APC) carrying HLA-DQ2/DQ8 restriction elements. Macrophages (20%), and especially dendritic cells (DC) (80%), are the main APC of the lamina propria and accumulate in active coeliac lesions.[31] These APC are also activated as a result of IL-15 induction due to the innate response.[32–34] CD4+ T-cells in the lamina propria recognise gluten fragments, such as α-gliadin, presented in the context of HLA-DQ2 or DQ8 molecules,[31,35,36] and after being modified by the enzyme transglutaminase 2 (tTG2).[37,38] Therefore, the final effect will be mediated by CD4+ T-cells, which are responsible for a response dominated by pro-inflammatory cytokines, such as IFN-γ, TNF-α and IL-18, and a proportional decrease in regulatory or anti-inflammatory