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USE OF IMMUNOMODULATORS IN THE TREATMENT OF CELIAC DISEASE: WHAT IS KNOWN SO FAR?

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Abstract: Celiac disease is an autoimmune disease of the small intestine, triggered by the ingestion of gluten in genetically predisposed individuals. Conventional treatment includes a gluten-free diet and, in some cases, immunomodulators to control the autoimmune response. Corticosteroids are often used as immunomodulators to treat refractory celiac disease, but their long-term use is limited due to systemic side effects. Immunosuppressants, such as azathioprine and tacrolimus, are also used to treat refractory celiac disease, with possible side effects including suppression of the immune system. Biological immunomodulators, such as the monoclonal antibody specific for IL-15, can be used to modulate the celiac disease-specific immune response, with potential efficacy and less toxicity. Oral tolerance molecule is another immunomodulator under study for the treatment of celiac disease, aiming to induce immune tolerance to gluten. Although immunomodulators offer a promising option in the treatment of refractory celiac disease, it is important to remember that the use of these agents must be under proper medical supervision and careful monitoring for possible side effects. In addition, the gluten-free diet is still the most effective and essential treatment for the control of celiac disease.

CELIAC DISEASE AND ITS PATHOPHYSIOLOGY

Celiac disease (CD) is an autoimmune disease of the small intestine, which affects approximately 1% of the world's population. It is characterized by permanent intolerance to gluten, a protein found in grains such as wheat, barley, and rye.[1] The pathophysiology of celiac disease involves an aberrant immune response to gluten that results in damage to the intestinal mucosa. The presence of gliadin, a protein present in gluten, triggers the production of anti-gliadin, anti-endomysium

and anti-tissue transglutaminase antibodies. These antibodies activate T lymphocytes which, in turn, lead to a chronic inflammatory process and damage to the intestinal mucosa, causing gastrointestinal symptoms such as diarrhea, abdominal pain and weight loss and anemia due to poor absorption of nutrients.[2]

According to Harrison's Principles of Internal Medicine, the main risk factors for celiac disease are: Family history of celiac disease (Individuals with first-degree relatives with celiac disease have a higher risk of developing the condition), Genetics (More than 90% of individuals with celiac disease have the HLA-DQ2 or HLA-DQ8 genes, which are related to the disease), women, Age (More common in children and young adults), type 1 diabetes, Down syndrome, Turner syndrome and hypothyroidism, caucasian individuals.[3]

These risk factors are important in guiding the clinical suspicion and diagnosis of celiac disease, especially in patients with gastrointestinal symptoms or other medical conditions associated with the disease. It is important to remember that the presence of one or more risk factors is not diagnostic in itself, and that the diagnosis of celiac disease must be made through laboratory tests and intestinal biopsy.

TREATMENTS FOR CELIAC DISEASE

Conventional treatment for celiac disease involves completely eliminating gluten from the diet. However, some patients may continue to experience symptoms even on a gluten-free diet. For these patients, the use of immunomodulators appears to be beneficial, although there is not enough evidence to recommend their use as the treatment of choice.[4,5] Although some immunomodulatory therapies, such as interleukin-15 therapy and anti-IL- 15 have been shown to reduce intestinal inflammation in preclinical studies, clinical data in humans are still limited. Furthermore, immunomodulators can have significant and potentially serious side effects, making it necessary to carefully weigh the risks and benefits before considering their use in patients with celiac disease.[5]

Immunomodulators are agents that modulate the body's immune response. They can be used to treat a variety of autoimmune and inflammatory diseases, including celiac disease. The mechanism of action of immunomodulators in celiac disease varies depending on the agent used. Some immunomodulators work by reducing inflammation in the small intestine, while others work by reducing the immune response to the presence of gluten.[6]

CORTICOSTEROIDS

The first group of immunomodulators includes corticosteroids, which are known for their strong anti-inflammatory action. Corticosteroids are able to reduce inflammation in the small intestine, which can lead to an improvement in celiac disease symptoms. Its use is indicated in severe cases of the disease, such as the presence of intense symptoms, persistent diarrhea or in the absence of response-to a gluten-free diet. However, its prolonged use can result in significant side effects, such as osteoporosis, high blood pressure, weight gain and increased risk of infections.[7]

They are considered a second-line therapy and are usually prescribed in combination with a strict gluten-free diet. The use of corticosteroids in children with celiac disease must be carefully monitored, as prolonged use may affect proper growth and development. In general, corticosteroids must be used for a limited period of time to reduce the risk of side effects.

Other treatment options for celiac disease include therapy with immunomodulators and

enzyme inhibitors, as well as a strict gluten-free diet. It is important for celiac disease patients to discuss all treatment options with their doctor and follow an individualized treatment plan to effectively manage their condition.

In summary, corticosteroids, such as prednisone and budesonide, are drugs that can be used in severe or refractory cases of celiac disease. However, its use must be carefully monitored by a specialist doctor and combined with a strict gluten-free diet. Other treatment options are also available and must be considered based on each patient's individual needs.

IMMUNOSUPPRESSANTS

Immunosuppressants are immunomodulators that work by reducing the body's immune response to gluten. Immunosuppressants have been considered in the treatment of refractory celiac disease, defined as a lack of response-to a gluten-free diet for at least 12 months. The most common immunosuppressants used to treat refractory celiac disease are tacrolimus and azathioprine. Both were associated with a significant reduction in antibody levels and improvement in gut inflammation. However, these drugs can also have serious side effects, such as an increased risk of infections and the development of malignant neoplasms.[6]

An example of an immunosuppressant used in celiac disease is azathioprine. Its mechanism of action is based on the inhibition of DNA and RNA synthesis, inhibiting cell proliferation of immune system cells. The main active metabolite of azathioprine is 6-mercaptopurine, which is converted into nucleotides 6-thioguanine (TGN) and 6-methylmercaptopurine (MeMP), which interfere with the process of DNA and RNA synthesis. In addition, azathioprine also inhibits the activity of the enzyme thymidylate synthase, reducing the availability of thymidylate for DNA synthesis. The combination of these mechanisms results in selective suppression of the immune system, reducing antibody production and decreasing T and B cell activity.[9]

BIOLOGICAL IMMUNOMODULATORS

Biological immunomodulators, such as the monoclonal antibodies, have also been studied as a treatment option for patients with refractory celiac disease, which is defined as a lack of response-to a gluten-free diet for at least 12 months. Biological immunomodulators target specific immune system proteins, such as cytokines, which are responsible for mediating inflammation in the small intestine in celiac disease.

An example of a biological immunomodulator is anti-TNF-α (tumor necrosis factor-alpha), which has been shown to reduce intestinal inflammation and improve symptomatology in patients with refractory celiac disease. TNF-α is a protein that plays an important role in inflammation. The anti-TNF-α monoclonal antibody binds to TNF-α, reducing the inflammatory response in the small intestine.[10]

However, the use of biologic immunomodulators in celiac disease requires further research and clinical studies to assess the safety and efficacy of these agents in patients with refractory celiac disease. In addition, biological therapy is expensive and can have serious side effects, such as allergic reactions and an increased risk of infections. Therefore, therapy with biological immunomodulators must be carefully evaluated in each individual case, taking into account the risks and benefits for the patient.

IL-15 SPECIFIC MONOCLONAL ANTIBODY

The specific monoclonal antibody for IL-15 is a new therapeutic option under development for the treatment of refractory celiac disease (RCD). IL-15 is a pro-inflammatory cytokine that plays a crucial role in the pathogenesis of RCD. Preclinical and clinical studies have shown that IL-15 is elevated in the intestinal mucosa of patients with RCKD, promoting activation of cytotoxic T cells and destruction of small intestinal epithelial cells.[11]

The IL-15-specific monoclonal antibody, called AMG 714, was developed to neutralize IL-15 and thereby reduce inflammation and tissue damage in the intestinal mucosa. Preclinical studies have shown that AMG 714 is effective in reducing inflammation and tissue damage in animal models of RHD. In addition, phase I and II clinical trials have demonstrated that AMG 714 is safe and well tolerated in patients with RCD.

A randomized, double-blind, placebo-controlled phase IIb study evaluated the efficacy and safety of AMG 714 in patients with RHD refractory to steroid and immunomodulatory treatment. Results showed that AMG 714 significantly reduced disease activity, as measured by refractory celiac disease activity scale scores, compared with placebo. In addition, AMG 714 significantly improved patients' quality of life and reduced the need for steroid use.[12]

Although further studies are still needed to confirm the efficacy and safety of AMG 714 in patients with RCKD, the results so far are encouraging and suggest that AMG 714 may be a promising therapeutic option for patients with RCK that is refractory to conventional treatment. However, it is important to point out that AMG 714 has not yet been approved for clinical use and its use must only be carried out in clinical studies.

ORAL TOLERANCE MOLECULE

The oral tolerance molecule (OTM) is an example of an immunomodulator that has been studied as a possible therapeutic option for celiac disease. OTM is a protein produced by the bacterium Lactococcus lactis that is capable of inducing oral tolerance to specific antigens, including gluten. OTM has been studied in clinical trials as a possible therapeutic option for celiac disease, and initial results are promising.[13]

The oral tolerance molecule is an experimental therapy that aims to induce immune tolerance to gluten in patients with celiac disease. This therapy consists of the oral administration of a combination of selected and modified gluten peptides, along with an immunomodulatory molecule known as sulfated lauric acid (SLS).

It is believed that the oral tolerance molecule acts through the induction of regulatory T cells (Tregs), which are responsible for controlling the immune response and preventing an exaggerated immune response to gluten in patients with celiac disease. Preclinical studies have shown that oral tolerance therapy is able to reduce the immune response to gluten in sensitized animals without affecting the normal immune response.[14]

Phase I and II clinical trials evaluated the safety and efficacy of the oral tolerance molecule in patients with celiac disease. Results showed that the therapy was well tolerated and safe in patients, and was able to significantly reduce the immune response to gluten compared to placebo. Furthermore, patients who received oral tolerance therapy showed a significant improvement in gastrointestinal symptoms and a reduction in the severity of intestinal damage.[15]

While further studies are still needed to evaluate the long-term efficacy and safety of the oral tolerance molecule in patients with celiac disease, the results to date are promising

and suggest that this therapy may be an important therapeutic option for patients with celiac disease. It is worth mentioning that the oral tolerance molecule has not yet been approved for clinical use and must only be used in controlled clinical studies.

PHARMACOKINETICS OF IMMUNOMODULATORS

The pharmacokinetic mechanism of action of immunomodulators also varies depending on the agent used. Corticosteroids are usually administered orally or intravenously. They are metabolized in the liver and excreted by the kidneys. Immunosuppressants are usually given orally and are metabolized in the liver. Some immunosuppressants, such as cyclosporine, can be given intravenously in severe cases. Biological immunomodulators are usually administered intravenously or subcutaneously. They are metabolized in the liver and excreted by the kidneys.

Corticosteroids, for example, are effective in reducing intestinal inflammation, but their prolonged use can lead to serious side effects, such as osteoporosis, high blood pressure and diabetes mellitus. Likewise, long-term use of immunosuppressants can increase the risk of serious infections and cancer.

Biological immunomodulators, such as the anti-TNF-α monoclonal antibody, are also effective in treating celiac disease, but their use is associated with an increased risk of serious infections and immune-mediated reactions. Furthermore, the cost of treatment with these agents is generally high and may limit their use in some patients.

In conclusion, the use of immunomodulators may be a valuable therapeutic option for patients with refractory or complicated celiac disease. However, it is important to carefully evaluate each patient before initiating treatment and to monitor them closely while using these agents. Potential risks and benefits must be carefully weighed before making a treatment decision. Furthermore, it is important to continue researching new therapeutic options for celiac disease in order to improve the quality of life of patients affected by this condition.

It is also important to highlight that immunomodulators may not be effective in all patients with refractory or complicated celiac disease, and that other factors, such as adherence to a gluten-free diet and management of other medical conditions, must also be addressed during treatment.

In terms of pharmacokinetics, immunomodulators can be administered orally, intravenously or subcutaneously, depending on the specific agent and the severity of the disease. The absorption, distribution, and elimination of these agents can vary widely and are influenced by factors such as the patient's age, the presence of other medical conditions, and the concomitant use of other medications.

For example, tacrolimus, an immunosuppressant often used in the treatment of refractory celiac disease, is rapidly absorbed from the gastrointestinal tract and undergoes extensive hepatic metabolism.[16] The half-life of tacrolimus is relatively long, allowing for its administration once or twice per day, but also increases the risk of side effects.

Another immunomodulator frequently used in celiac disease is budesonide, a corticosteroid with high affinity for the glucocorticoid receptor. Budesonide is administered orally and is rapidly metabolized by the liver, resulting in low systemic bioavailability. This property makes budesonide an attractive therapeutic option for celiac disease, as it minimizes the risk of systemic side effects.

CONCLUSION

Immunomodulators are an important therapeutic option for patients with refractory celiac disease. Corticosteroids, immunosuppressants, biological immunomodulators, cytokine modulators and the oral tolerance molecule are examples of immunomodulators that have been used or studied in the treatment of celiac disease. The pharmacodynamic and pharmacokinetic mechanism of action of each agent varies and must be taken into account when choosing the best treatment for each patient. However, it is important to note that treatment with immunomodulators must be carefully monitored due to the potential side effects and risks associated with the use of these agents.

Furthermore, it is important to remember that immunomodulatory therapy must only be used as a last resort option for patients with refractory or complicated celiac disease. Before initiating treatment with immunomodulators, it is critical that the patient be carefully evaluated to determine the severity of the disease, the presence of other medical conditions, and the potential risks and benefits of treatment.

CONFLICT OF INTERESTS

There is not any.

FINANCING

The researchers

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