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THE INFLUENCE OF IMMUNOBIOLOGICALS AND SMALL MOLECULES ON THE MANAGEMENT OF CROHN'S DISEASE

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Abstract: Introduction: Crohn's disease (CD) is a chronic inflammatory bowel disease that mainly affects adolescents and young adults, affecting the entire gastrointestinal tract, with specific foci of greater inflammation. In addition, there may be extra-intestinal manifestations in the joints, eyes, skin and liver. The pathogenesis is multifactorial, including genetic and environmental factors such as eating habits and previous infections. Polymorphisms in genes that encode inflammatory cytokines, adhesion molecules and influence the production of intestinal mucus are fundamental in the pathogenesis and are therapeutic targets. CD is diagnosed using laboratory, imaging and endoscopic tests, with endoscopy being fundamental for diagnosis, predicting severity and controlling the disease. Treatment involves a series of medications aimed at controlling tissue inflammation, such as corticosteroids, immunosuppressants and immunobiologicals. The main classes of immunobiologicals that will be discussed are: Anti-TNF-alpha, Anti-integrins and p40 inhibitors. **Methodology**: Qualitative review of articles on CD, more specifically on the importance of immunobiologicals and small molecules and the need for more in-depth research on this aspect. The terms "Crohn's Disease"; "Immunobiologicals"; "Inflammatory Bowel Disease"; "Therapeutic Targets for CD" were used as descriptors for the search on the PubMed and Google Scholar platforms. **Discussion**: CD is an autoimmune inflammatory disease characterized by inflammation of all intestinal histological layers. The pathophysiology of Crohn's disease is explained by hypersensitivity to symbiont bacteria in the GIT, characterized by a predominantly Th1 immune response. This autoimmunity is caused by mutations with gain of function in lymphocyte adhesion proteins, cytokines such as TNF-α and IL-2, as well as decreased mucin production in the mucosa. The therapeutic goal of CD is to achieve a state of clinical and laboratory remission, requiring behavioral and drug treatment, involving therapies with immunomodulators and immunobiologicals, the focus of this review. Tumor necrosis factor (TNF) antagonists, Infliximab and Adalimumab, act by inhibiting TNF-alpha, reducing the intestinal pro-inflammatory state. Currently, Infliximab is a chimeric antibody and Adalimumab is a fully humanized antibody. Natalizumab and Vedolizumab are monoclonal antibodies that act by inhibiting the role of integrins. Ustekinumab, an inhibitor of the p40 subunit common to IL-12 and IL-23, acts by blocking the chronic inflammatory response in CD, interfering with the functions of these cytokines in the inflammatory pathways. **Conclusion**: Immunobiological therapy with small molecules can improve the prognosis of patients with CD, being a conservative treatment with the aim of inducing remission of the disease, reducing the need for surgical interventions. However, patients tend to lose their response to immunobiologicals over time. Immunotherapy with monoclonal antibodies is a vast field of research in high demand. Finally, the search for an understanding of the loss of response to immunobiologicals, the variety of drugs and the reduction of adverse effects is necessary.

Keywords: Crohn's Disease; Immunobiologicals; Inflammatory Bowel Disease; Crohn's Disease Therapeutic Targets; Basic Immunology; Applied Immunology.

INTRODUCTION

Crohn's disease (CD) is an inflammatory, autoimmune and chronic disorder with a pattern of periods of activity alternating with remission. This disease can have multiple etiologies, among them: genetic alterations that interfere with the intestinal microbiota, irregular diet, infections and failure of the immune defense and intestinal barrier.

> Baêta (2023) observed that the incidence and prevalence of CD has increased mainly in Western countries, including Brazil, which may be directly influenced by Western diets with low nutritional potential and industrialized foods. In addition, an important factor is age, which has a higher incidence between the 20th and 40th decade, mostly afflicting adolescents and young adults.

With regard to the risk factors for CD, it is possible to mention that there is no gender preference for the disease; on the other hand, studies suggest that men are more susceptible to developing the most severe form of CD. In addition to these factors, it is important to note that smoking, exposure to antibiotics in early childhood, the use of oral contraceptives, non-steroidal anti-inflammatory drugs and a diet rich in saturated fats also contribute to an increased risk of developing the disease. It can also be seen that the intestinal microbiota is closely linked to the risk of CD, since in the disease there is an imbalance in the population of intestinal bacteria.

There are protective factors associated with a lower risk of developing CD, such as physical exercise, a balanced diet with fruit and fiber, a family with more than two siblings and exposure to pets.

> According to Santos (2013), among the most affected sites in the digestive system, it was mentioned that the small intestine was the region with the highest occurrence of involvement (75% of patients) and in these cases, the terminal ileum was the most affected by the disease with around 90% of patients presenting the disease in this region, considered the center of the disease generally sparing the rectum and duodenum.

The predominant manifestations can be inflammatory, obstructive and/or fistulizing, varying in their prognostic impact. Episodes of chronic diarrhea with mucus or blood, pallor of the skin and mucous membranes, distension or fistulization through the abdominal wall, weight loss, rectal bleeding, abdominal pain and impairment of the mucosal barrier result in nutritional and functional deficiencies, guiding clinical evaluation. Thus, nutritional therapy becomes essential in treatment.

Morphologically, Crohn's disease is characterized by well-defined segmental lesions alternating with areas of normal tissue. In addition, there are aphthous ulcers, edema in the mucosa and submucosa, and an increase in the number of lymphocytes, plasma cells and macrophages.

Extra-intestinal manifestations can also occur frequently and are directly related to the severity of the intestinal inflammation. These manifestations can affect the skin (erythema nodosum and pyoderma gangrenosum), the peripheral joints (arthritis) or axial joints (ankylosing spondylitis and sacroiliitis), the eyes (conjunctivitis and uveitis) and the liver (primary sclerosing cholangitis).

Among the tests used to diagnose CD are endoscopic, histological, imaging and biochemical examinations. Colonoscopy is recommended as the gold standard for describing the severity of the disease and its healing.

Endoscopy shows a pattern of discontinuous ulcerative lesions with erythema and mucosal edema, which may or may not show luminal narrowing, and biopsy and therapeutic intervention are possible. Histology shows inflammation of the transmural layer with granulomas and disorganized architecture, which is essential for diagnosing CD.

In conjunction with endoscopy, imaging tests such as nuclear magnetic resonance or tomography and ultrasound can be used to complement the endoscopic assessment. In addition, correlation with inflammatory markers including C-reactive protein, fecal lactoferrin and fecal calprotectin can also help with the diagnosis. A complete blood count, pregnancy test, stool parasitology and a stool test for Clostridium difficile should also be requested.

Research indicates the possibility of nutritional intervention to reduce the inflammatory activity of Crohn's Disease through the use of immunomodulatory nutrients, which aim to restore and/or maintain nutritional status, ensure adequate nutrient intake, contribute to symptom reduction and minimize complications in the postoperative period. These include specific nutrients such as arginine, glutamine, fatty acids, nucleotides, as well as probiotics and probiotics.

The aim of CD treatment is to achieve remission of the disease by controlling symptoms and enabling the intestinal mucosa to heal. The aim is to reduce complications and offer the patient a better quality of life. The therapeutic management of CD is divided into two stages, the first being a rapid induction of clinical remission to contain symptoms using high doses of corticosteroids. The second stage, the maintenance stage, consists of the use of immunobiologicals and is the focus of this study. Currently, three types of biological therapies are used to treat CD: tumor necrosis factor (TNF) antagonists, such as Infliximab and Adalimumab; the interleukin 12/23 inhibitor, Ustekinumab; and the integrin inhibitor, Vedolizumab. The study aims to understand the mechanisms of action of immunobiologicals by understanding the pathogenesis of the disease, as well as their role in the prognosis of CD.

METHODOLOGY

This study was based on bibliographic research in the SciELO, Virtual Health Library, Google Scholar and PubMed virtual databases. The articles selected as references consist of publications made between 2009 and 2024 in Portuguese, and articles cited as bibliographical references of the most relevant articles were also used. The search focused on the two main aspects of this work: Crohn's disease and immunobiologicals. The descriptors used in the search for articles were: "Crohn's Disease"; "Immunobiologicals"; "Inflammatory Bowel Disease"; "Therapeutic Targets for CD". Articles with the highest degree of relevance to the subject and which addressed not only the use of immunobiologicals in treatment, but all aspects of Crohn's Disease, were selected.

DISCUSSION

Crohn's disease is a multifactorial inflammatory bowel disease whose pathophysiology is based on chronic tissue inflammation. This inflammation is related to an intense immune response to bacterial antigens in the intestinal lumen with the recruitment of numerous immune cells such as TCD4 and TCD8 lymphocytes, B lymphocytes, CD14 monocytes and Natural Killers (NK). Associated with this is a deficiency in the production of intestinal mucus by the innate response related to variants in the Muc2 gene.

In addition, CD patients show hyperactivity of T cells in the intestinal tract, which results in increased production of pro-inflammatory cytokines such as IL-2, TNF-α, IFN gamma, with a TH1 lymphocyte phenotype prevailing. The humoral immune system also plays a role in the pathogenesis, with the production of T(Th1) cells, which express B-type granzymes with cytotoxic activity in the intestinal mucosa and contribute to epithelial damage.

Another important contributing factor to pathogenesis is intestinal dysbiosis, an imbalance in the microbial community. The increased permeability of the intestinal barrier makes it easier for bacteria and their toxic products to come into direct contact with intestinal tissue, intensifying the immune response.

In summary, according to the studies by Baêta (2023), it is essential to understand all aspects of the pathophysiology that involves the interaction between genetic, environmental and immunological factors and the

intestinal microbiota, resulting in chronic inflammation, in order to develop a more effective therapeutic approach and to increasingly improve the prognosis of patients.

The aim of conventional treatment for CD is to suppress the exacerbated immune response in order to control the disease and achieve remission. To this end, therapy may involve the use of corticosteroids, immunosuppressants, biological therapies and immune system modifiers.

When it comes to biological medicines, it refers to active ingredients obtained from biological material, such as fluids, human tissues, animals or microorganisms.

There are currently several lines of treatment for CD, and one of the main classes used in the autoimmune disease scenario is immunobiological therapy. However, it is still unclear when exactly it should be started, as it is indicated for moderate or severe disease that has not responded to other drugs, but the point at which the disease is considered moderate or severe is imprecise.

At present, three types of biological therapies are widely used in the treatment of Crohn's disease, each acting on different inflammatory pathways: tumor necrosis factor (TNF) antagonists, such as infliximab and adalimumab; the interleukin 12/23 inhibitor, ustekinumab; and the integrin inhibitor, vedolizumab, all with different efficacy profiles.

Biological therapies play an established role in the treatment of moderate to severe CD. The goal of treatment is to achieve symptom remission, promote mucosal healing, improve patients' quality of life and reduce the need for surgical interventions.

Despite developments in biological and small molecule therapies over the years, some patients remain refractory to treatment, and a significant proportion lose their response over time.

As for the tumor necrosis factor (TNF) antagonists infliximab and adalimumab, they will act through a monoclonal antibody that binds to TNF-α and inhibits it, preventing it from carrying out its pro-inflammatory effects on the intestinal immune response that play an important role in CD. Thus exerting an anti-inflammatory effect, increasing efficacy in inducing and maintaining remission. They promote healing of the mucosa and closure of fistulas, as well as optimizing the patient's nutritional status. This treatment can also alter the course of the disease, reduce hospitalization rates and the need for surgery, as well as improving patients' quality of life. Currently, the anti-TNF-α variations approved for treatment include the chimeric human-mouse IgG1 monoclonal antibody, the fully humanized ADA monoclonal antibody and the CZP antigen-binding fragment of the humanized polyethylene glycol monoclonal antibody. There are some adverse reactions related to the use of anti-TNF-α preparations such as allergic reactions, drug-induced lupus erythematosus, lymphoma and infections, with special care for hepatitis B and Mycobacterium tuberculosis; therefore, it is necessary to screen for tuberculosis before administration and to monitor during treatment.

The class of anti-integrin monoclonal antibodies, on the other hand, will act by inhibiting the role of integrin, a selective adhesion molecule that has the function of aiding the chemotaxis of leukocytes at sites of systemic inflammation. Natalizumab and vedolizumab, examples of drugs in this class, have been approved to treat Crohn's disease and are effective in CD patients who do not respond to treatment with monoclonal antibodies (mAb) against TNF-α. The most frequent side effects during treatment of CD with natalizumab include headache, nausea, abdominal pain, nasopharyngitis, dizziness and fatigue, among others. It is important to be aware of the risk

of serious infections associated with the use of the medication, such as the John Cunningham virus (JCV), also known as the JC virus, which can cause progressive multifocal leukoencephalopathy (PML).

As for drugs in the interleukin 12/23 inhibitor class, they act through a monoclonal antibody against IL-12/23. In the pathogenesis of Crohn's disease, intestinal microorganisms activate macrophages and dendritic cells, leading to excessive production of IL-12/23. These cytokines stimulate the proliferation and differentiation of various effector T cells, such as Th1, Th17 and Th22, which produce pro-inflammatory factors, including IFN-γ, IL-17, IL-22 and TNF-α . These factors play a crucial role in the chronic inflammatory response of CD. Ustekinumab, an inhibitor of the p40 subunit common to IL-12 and IL-23, acts by blocking the chronic inflammatory response in Crohn's disease, interfering with the functions of these cytokines in the inflammatory pathways. This drug is a fully human monoclonal antibody with low immunogenicity. It was initially approved in 2008 by the FDA for the treatment of psoriasis and later in 2016 for the treatment of CD.

An international multicenter phase III clinical trial of ustekinumab in CD, including two 8-week intravenous administration trials of remission induction, in patients who failed or were intolerant to anti-TNF-α therapy (UNITI-1) and in patients with failure or intolerance to traditional therapy (UNITI-2), both trials and its follow-up maintenance trial (IM-UNITI, 44w) showed that ustekinumab was effective and safe in the treatment of CD.

CONCLUSION

Immunobiological therapy is the main approach to autoimmune diseases, aimed at alleviating the disease and improving the patient's quality of life. These include the three main classes used in treatment. Tumor necrosis factor (TNF) antagonists are effective in slowing down the progression of the disease, promoting healing of mucous membranes and closure of fistulas, thus contributing to the remission of the disease and consequently reducing the number of hospitalizations and surgical procedures. The anti-integrin monoclonal antibody class was approved due to its mechanism of integrin inhibition and consequent inhibition of inflammation, making it the best choice for CD patients who do not show improvement after therapy with TNF antagonists. Interleukin 12/23 inhibitor drugs include ustekinumab, an inhibitor of the p40 subunit, as a drug capable of interfering with the functions of pro-inflammatory cytokines in chronic inflammation, reversing the condition. This drug is a safe approach for patients who have been unsuccessful with TNF antagonists, and is therefore considered effective in treating CD. On the other hand, even with therapeutic advances, there are patients who do not respond to treatment and it is possible for the response to become desensitized after a certain period of time. That said, the aim of treatment is always to achieve remission, with a positive impact on the patient's quality of life without the need for surgery.

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