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Crohn's Disease: General characteristics and treatment with Adalimumabe biopharmaceutical

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Abstract. Crohn's Disease (CD) is a chronic inflammatory disease that affects the gastrointestinal system. The etiology is not fully understood, however, genetic, immunological, microbiological and environmental factors are related to its genesis. The most common manifestations of this disease are diarrhea, abdominal pain, ulcers and fistulas. In the absence of adequate treatment it can evolve into extra intestinal complications and is also an important risk factor for colon and rectal cancer. The treatment of the disease is palliative and there is no cure for the disease, being considered only the period of remission of symptoms, as a good prognosis. The biopharmaceutical, Adalimumabe, produced by recombinant DNA technology has demonstrated efficacy in the treatment of this disease, as it prevents the action of TNF-α, a cytokine involved in inflammation and is abundant in individuals with CD. Although Adalimumabe has good results, its use leads to side effects that can be mild or fatal, such as the activation of tuberculosis.
Keywords: Crohn's disease, risk factors, Adalimumab; TNF-α

Introduction

Crohn's disease (CD) is a condition characterized by chronic inflammation of the intestines, thin (ileum) and thick (colon), or organs of the digestive system, affecting from the oral cavity to the anal region. It is a non-contagious disease that can affect adults and children, with a higher incidence in individuals between 15 and 30 years of age and with no predominance of gender (BRASIL, 2014, SANTOS, 2011).

The etiology of this pathology is not fully known, however, it is known that genetic, immunological, microbiological and environmental factors are involved in its genesis. The most common symptoms of CD include diarrhea (blood may be present), vomiting, abdominal cramps, fever, and weight loss. In addition, this disease also has extraintestinal manifestations, affecting several organs such as skin, joints, eyes and liver (CARDOZO et al, 2012; POLI, 2017; SANTOS, 2011).

It is known in the literature that tumor necrosis factor alpha (TNF-α) is an inflammatory cytokine involved in CD. Adalimumabe is a medicine, which has contributed to the control of the disease, avoiding hospitalizations and, consequently, improving the quality of life of patients with this pathology. The drug has demonstrated efficacy in remission of the disease because it is an antibody against this cytokine, anti-TNF-α (KOTZE et al., 2009). The objective of this work is to provide a literature review on Crohn's disease and its treatment with the biological treatament Adalimumabe.

Contextualization and Analysis

CD affects individuals worldwide, but not in the same proportion. In some countries, the number of cases is low, while in others the prevalence is high, becoming a public health problem due to high morbidity and the cost of treatment. DC is common in the countries of North America and Western Europe (CARDOZO et al., 2012; GONÇALVES, 2013).

According to Federal Government data, in Brazil, the Central-West region has the highest rate of hospitalizations related to the disease with 27.34%, followed by the South region with 25.28%, Southeast with 19.93%, Northeast with 17, 87% and, finally, the

North region with 9.5% of the cases. It should be taken into account that the South and Southeast regions are depreciated, since they have the largest number of patients attended by the private system, so a good part of the cases are probably not notified (BRASIL, 2010).

In recent years, Brazil has undergone changes in diet and increased hygiene and sanitary conditions, contributing to the increase in cases of CD. Industrialized foods, which have gained strength in the country, contain substances that can cause such an intense immune response that can be a determining factor for the onset of the disease, not to mention that, with less exposure to antigens in childhood, the immune system will not be well developed (CARDOZO et al., 2012).

CD affects all age groups, however, it is more common between 15 and 30 years. Some authors state that the predominance of the disease is slightly higher in women compared to men (GONÇALVES, 2013).

The racial and ethnic importance of the disease is significant, blacks are less affected than caucasians, and jews are at high risk of developing it. American, African and Asian Latinos are the least affected, however, there was an increase in the disease in these groups due to social changes that lead to new eating habits (GONÇALVES, 2013).

DC is critical because its cause is not yet understood. In addition, the treatments are high cost and palliative. Several hypotheses have been suggested to elucidate the cause of the disease, but none is convincing, but it is known that the disease is linked to immunological, genetic, environmental and microbial factors, but there is no single factor capable of generating CD. Thus, its onset is related to several causes, considered as a disease of multifactorial origin (CARDOZO et al., 2012).

Development

The presence of CD in several members of a family suggests a genetic predisposition, with research indicating that first-degree relatives are up to 12 times more likely to trigger the symptoms, this fact is related to the expression of abnormal genes (SANTOS, 2011).

The gene CARD15 encodes the NOD-2 protein, a protein that acts on the innate immune system, conferring an inflammatory response to the presence of Gram-negative bacteria and activating the NF-κB transcription factor of the monoclonal leukocytes. A mutation in this gene alters the production of these proteins and thus prevents the recognition and elimination of bacteria by keeping the inflammatory process active (SANTOS, 2011; RIBEIRO, 2009).

According to some authors, around 30% of patients with the disease have a mutation in the NOD2 / CARD15 gene. The changes that occurred in this gene relate to the behavior of the pathology, and confirm a link with the onset of the disease and the presence of stenosing lesions. Another protein that has also been associated with this pathology is NOD1 / CARD4, found in the small intestine and colon, important for the recognition of bacterial factors and acts similarly to NORD-2 / CARD15 (PINHO, 2008; SANTOS 2011).

Innate immunity is a type of defense that can prevent pathogens from accessing and repel those that enter the tissues. Epithelial barriers, specialized cells, some specific substances and organs are important because they block the access of the invaders. If they can penetrate the body, they will encounter cells of destruction such as lymphocytes and several proteins linked to protection (PARSLOW et al., 2004).

The intestinal barrier is part of the innate immunity, the microorganisms that have access to the digestive system will find this blockage. The intestinal barrier contains epithelium covered by protective mucus assists in protecting the system. In the case of the disease, the response to the invaders is exaggerated, with the recruitment of immune cells that destroy the tissue and consequently break the barrier of intestinal protection (PIRES et al., 2010; SANTOS, 2011).

Cytokines are a group of various types of peptides and intracellular signaling glycoproteins. TNF-α is a type of cytokine capable of generating inflammatory response, its main effects are: cytotoxicity, proliferation of T and B lymphocytes, apoptosis, septic shock, stimulation of the development of granulomas, summoning of neutrophils to the inflamed region, coagulation , immunoglobulin synthesis, adhesion cell production, and cytokines. However, this cytokine is abundant in patients with CD, being possible to detect its presence in the blood, feces and mucosa. Its activity is exaggerated prolonging the inflammatory activity characteristic of patients with DC (GOMES, 2004; PARSLOW et al., 2004).

The macrophage is the first cell to notice the presence of the foreign body and evidence, through the molecules of the larger histocompatibility complex (MHC), for $CD4^+$ T cells. When activated, macrophages manufacture inflammatory cytokines, especially TNF-α, which stimulates the Th1 action of the $CD4^+$ T cell. It is worth mentioning that when stimulated, the $TCD4^+$ cell differentiates into Th1 and Th2, which are subgroups of lymphocytes. But in the case of the disease, Th1 is quite expressive. Both Th1 and Th2 release different cytokines. Th1 cells manufacture IL-2, TNF-α, and INF-γ that are able to exacerbate inflammation, as Th2 reduces

inflammatory activity, yet its production is greatly reduced in DC. The cytokine INF-γ instigates the macrophage which, in turn, will stimulate TNF-α, thereby prolonging inflammatory activity (PIRES et al., 2010; PARSLOW et al., 2004; JUNIOR 2008; SANTOS 2011). Some factors can be considered as accelerated pathology, among them: diet, smoking, hygiene, microbial.

Exaggerated consumption of refined carbohydrates, milk, in the case of patients who have lactose intolerance, and gluten foods with gluten such as oats and barley as well as the exacerbated consumption of total fats, insoluble fibers that are able to increase fecal, and red meat are associated with DC crisis (SANTOS, 2011; SCHOFFEN et al., 2011).
Smoking worsens the course of the disease and is related to exaggeration of immune response, modification of mucus composition, alteration of cytokine levels, vascular, prothrombotic and other factors, besides increasing the presence of fistulas and stenoses, leading to more hospitalizations (CARDOZO et al., 2012; SCHOFFEN et al., 2011).

According to Stranccham (1989), with the improvement in basic sanitation the exposure to antigens is lower and, consequently, the individual at an early age when not in contact with pathogens, would develop an awkward defense system and therefore more vulnerable to the onset from DC (GONÇALVES et al., 2013). If there is more than desirable growth in the microbiota, genetically predisposed people may develop the disease (SANTOS, 2011).

Escherichia coli has been studied very hard because it is specifically associated with the ileal mucosa in the disease. The bacterium is able to enter and multiply within the macrophages, without causing the death of the host cell. Infected macrophages generate high amounts of TNF-α and stimulate cell aggregates. Other pathogens, such as *Pseudomonas maltophilia* and *Mycobacterium paratuberculosis*, have also been implicated as probable triggers of the disease. Response to commensal bacteria can activate the immune system (CARDOZO, et al., 2012; GONÇALVES 2013; SANTOS, 2011).

CD is also called a regional ileitis, granulomatous ileitis, which presents transmural inflammation and affects any part of the digestive system from the mouth to the anus. It is more common in the ileocolic, small intestine and colonic-anorectal regions. Those who have the disease have diarrhea, which is the most frequent complaint among patients who evacuate 4 to 6 times a day, with or without the presence of blood in the stool and mucus, weight loss, anemia, abdominal pain and in advanced situations, fecal incontinence that is linked to acute inflammation of the bowel wall as a consequence of the narrowing of the intestinal lumen. CD is divided into: ileus and cecum disease (40% of patients), disease in the small intestine (30%), disease restricted to the colon (25%) and others (5%). In regions such as the mouth, duodenum, esophagus and stomach, the manifestations of the disease are uncommon. Diarrhea is the most common symptom, followed by bleeding that affects 40% to 50% of the carriers, weight reduction (60%) and pain in the abdomen (70%). The most common signs are fever, weakness, paleness, fistulas and perianal fissures. It is suggested that six weeks with persistent diarrhea is enough to characterize it with acute infectious diarrhea (CARDOZO et al., 2000; MARANHÃO et al., 2015; SANTOS 2013).

In the intestinal segments, the serosa is granular with the dark gray tint and, in general, the mesenteric fat wraps around the surface of the intestine, also called the climbing fat. The mesentery often presents with fibrosis, thickening and edema. The intestinal wall is elastic and thick, since as a result of inflammation, fibrosis and hypertrophy of the region results in the narrowing of the intestinal lumen and one of the most common characteristics are the discontinuous lesions (CARDOZO et al., 2000; MARANHÃO et al., 2015; SANTOS 2013).

At the onset of the disease, aphthous ulcers, edema and loss of normal mucosal texture can be seen. With the evolution of the disease, the ulcers become long and curved linear. Due to nodular swelling of fibrosis and ulceration, a so-called 'cobble stone' appearance occurs. Narrow cracks extend into the folds of the mucosa and, innumerable times, enter through the intestinal wall causing intestinal adhesions. The prolongation of these fissures results in the presence of fistulas (COTRAN et al., 2000; SANTOS 2013).

The disease can affect the lips and mucosa of the mouth causing the appearance of mass in the abdomen with increased thickness of the loops. Hardening and redness may occur at the location of the anus. It is common for patients to have no desire to feed due to symptoms, leading to anorexia, anemia, and weight reduction. Signs and symptoms are crucial for noticing the disease, but it is not enough to diagnose it. (MARANHÃO et al., 2015; SANTOS, 2011).

It is important to emphasize that many of the patients with the disease are psychologically fragile, becoming a serious problem in the quality of life, since it is capable of triggering reduction of immune resistance, colic, hypertonia and mucosal ischemia (SCHOFFEN et al., 2011).

The diagnosis of CD is performed by means of examinations such as colonoscopy in which the presence of ulcerated lesions mixed with areas of the normal mucosa is verified. In the radiological examination it is possible to find the involvement of the fistula digestive system, and in the histological findings, there are non-caseous granulomas. In

laboratory tests, anemia is detected by malabsorption or blood loss, with leukocytosis, hypopotassemia in cases of severe diarrhea, increased erythrocyte sedimentation rate (ESR), and elevated C-reactive protein, a good marker of disease monitoring, currently fecal calprotectin and imaging tests such as nuclear magnetic resonance (MARANHÃO et al., 2015; BRASIL, 2014).

The fertility in some women with the disease is little reduced, this decrease is mainly related to tubal obstruction and scarce libido. There is no conclusive evidence that pregnancy can lead to complications, although in most cases patients prefer not to become pregnant due to the fragility of the disease. But for those who became pregnant, it is necessary that they present remission of the disease until the moment of delivery, as complications can occur (CARDOZO et al., 2012; MARCOLIN et al., 2011; JÚNIOR, RICCI et al., 2012).

There is an increase in cases of pediatric CD. About 30% of patients had onset of their symptoms before the age of 18, but a late diagnosis is common in children. The most common symptoms are: growth deficit, weight loss, diarrhea and delayed pubertal development, but in general, the behavior of the disease is similar to those presented in adults. CD causes reduction or stopping of sexual maturation, amenorrhea that is strongly linked to malnutrition (CARDOZO, et al., 2012).

Complications of the disease are common and the patient is subject to partial or total obstructions, fistulas, abscesses, perforations, hemorrhages, anemia, calculi, malnutrition, intestinal neoplasias among others (FLORA et al., 2009; SILVA et al., 2011).

Chronic inflammation can cause ulcers, which is more frequent in the ileum terminal, colon and rectum region. Depending on the inflammation situation, ulcers may be present on the surface or in all parts of the organ. If the area is very extensive it can reach the entire intestinal wall and form the fistula, which is the most frequent complication, the fistula is the aberrant junction between organs, such as enterovesical and enterovaginal. It may also happen to the union with the external part, such as the perianal intercutaneous fistula. By promoting this union between organs, they leave the patient vulnerable to complicated infections that cause death if left untreated. It is common in these individuals to detect anemia, often due to lack of interest in feeding. This complication is a consequence of several causes, such as lack of iron, folate and vitamin B12, which in its absence leads to bacterial proliferation. Diarrhea induces the loss of electrolytes, such as zinc that has beneficial activity in the activity of the immune system. In these patients the digestion of fats and fat-soluble vitamins are diminished, not to mention the malabsorption of carbohydrates (FLORA et al., 2009; SILVA et al., 2011).

DC can develop “Farmacobezoar”, which consists of drugs, usually tablets, which are not absorbed and are retained in any part of the digestive system, leading to the appearance of pockets, obviously the treatment is not being effective in these cases. This happens in view of inflammatory, tumor and post surgical stenose (MARANHÃO et al., 2015). Neoplasia is one of the most critical complications involving the disease, since there is an increased risk of mortality because only 10% of patients can recover because the tumor is usually classified as aggressive and infiltrative (CARDOZO et al., 2012; MARANHÃO et al., 2015).

In a more advanced state, there is a possibility of cystic pneumatosis, which is characterized by the appearance of several gaseous cysts in the intestinal wall, in which several factors are related, such as stenoses and obstruction of the intestine. Complications are: abdominal discomfort, bloody stools metabolic acidosis, intestinal ischemia (CARDOZO et al., 2012; MARANHÃO et al., 2015). Intestinal obstruction is also very common. It occurs because inflammation in the layers of the wall of the intestine causes it to thicken, making it impossible for the fecal cake to pass into the small intestine and colon, and surgery for the removal of feces is inevitable (SANTOS, 2011).

The occurrence of extra intestinal manifestations may occur due to clinical evolution or non-adherence to treatment. These manifestations are frighteningly serious, the most usual are: rheumatic, hepatic, dermatological diseases such as psoriasis, uveitis, hemolytic anemia, thrombosis, among others (CARDOZO et al., 2012; MARANHÃO et al., 2015).

Articular manifestations affect 60% of the cases, hepatobiliary around 17%, urological 15%, renal 4% to 23%, dermatological 6.8%, pulmonary 3%, vascular 1,5% and ophthalmologic 1,3%. These clues are very common in patients who are related to the disease in the region of the large intestine. These manifestations are diverse and can harm any organ of the individual, in this way it is necessary that an early diagnosis is made and that patients have a quality health care (SILVA et al., 2011).

Adalimumabe (HUMIRA®) is a type of biological medicine also known as a biopharmaceutical. The molecules of biopharmaceuticals are difficult to reproduce and replicate. According to DRC No. 55/2010, biological medicines, as they are peculiar, must present to the National Agency of Sanitary Surveillance (ANVISA) the reports of pharmacovigilance, reduction of the hazards and documentation of the immune response during the time they are in the Marketplace. Biological drugs are only prescribed in cases in which the

disease is moderate to severe (MORAIS et al., 2012; INTERFARMA, 2013; BRASIL, 2010).

The brand name of the drug is Humira®. Adalimumabe is an antibody derived from a single recombinant human (monoclonal) cell, from the mouse ovary cells of China, it is a therapeutic agent made from biotechnology. This drug was the first fully human monoclonal antibody to be approved for the treatment of CD. It is a fact that this type of drug class showed less toxic effects than conventional drugs. In 2002, Adalimumabe was accepted by the FDA and was introduced into the list of ideas drugs by the Unified Health System (SUS), according to the definition of Ordinance No. 2888, dated December 30, 2014 (COELHO, 2014; FUNED, 2015; INTERFARMA, 2013; RANG et al., 2011). The solution of the medicament is colorless, clear and sterile. It has a pH of 5.2 and there are no preservatives, it is in injectable form, pen and vial ampoule (pediatric use). The formula has 40 mg of active and 0.8 ml of excipients: water, sodium chloride, sodium citrate, mannitol, citric acid monohydrate, monosodium phosphate and disodium dihydrate and polysorbate (MANZANO, 2010).

Adalimumabe irreversibly binds to TNF-α, preventing its function and binding to the receptors on the surface of cells, and, moreover, articulates the biological responses attracted or controlled by TNF-α, such as changes in levels of adhesion molecules whose activity is to stimulate leukocyte migration. In addition, it induces the destruction of cells expressing TNF-α, such as macrophages and Th1 cells. Its administration is subcutaneously with an onset dose of 160 mg at week 0, followed by a dose of 80 mg at week 2, and thereafter the treatment proceeds with a maintenance dose of 40 mg every two weeks. For children, a dose-rate (mg / area) calculation is used, ie for small patients, 160 mg / 1.73 m^2 at week 0, 80 mg / 1.73 / m2 at week 2 In the maintenance dose 40 mg / 1.73 m2. However, it is not recommended for children up to 5 years of age, as there are no studies conducted for this age group. (ANVISA, 2016; CARDOZO et al., 2012).

The drug has a half-life of two weeks for patients who have not responded well to conventional therapy and / or who have not responded adequately to other biologicals, such as Infliximab. However, if the individual does not respond until the second application, treatment should be discontinued (CARDOZO et al., 2012; COELHO, 2014; MOTA, 2012; SANTOS et al., 2006). It is efficient in the treatment of this condition, bringing quality of life to the patients, as it does not present great toxicity as the conventional medicines and, if treated prematurely, the chances of controlling the pathology are high (CARDOZO, et al., 2012; COELHO, 2014; MOTA, 2012; SANTOS, et al., 2006).

Studies in 2006, called Classic I and Classic II, identified that patients who started treatment with the dose of attack reduced their signs and symptoms by up to 24% and those who immediately received the maintenance dose (40 mg every 2 weeks), 79% remained with pathologic regression. The use of this medication by pediatric patients guarantees the delay of the surgery, avoids the use of corticosteroids, promotes growth, improves the lesions and closes the fistulas (CARVALHO, 2012; CARDOZO et al., 2012).
Some patients require a change in dosage, which can be 40 mg every week. If no response occurs at the 12th week after dose change, the use of the drug should be reassessed. The use of corticosteroids, aminosalicylates and immunomulgence agents may be maintained in the course of Adalimumabe treatment but according to the guidelines, these medicinal products should be decreased (ANVISA, 2016).

In case the patient has any infection, such as flu or cold, than it should never apply the medicine, since its use could intensify the situation. Treatment should be discontinued if the patient manifests fever, weight loss, cough and wounds, as it may be an indication of infection. Its use is not advised for pregnant women and it is essential to avoid pregnancy because the substance can permeate the placenta, being considered of risk B (CARDOZO et al., 2012; MARCOLINO, 2010).

The drug is able to activate tuberculosis. For patients who have had contact with the tuberculosis causing bacillus, it is necessary that the prophylactic treatment be done, before starting with Adalimumabe (ANVISA, 2016). This substance acts to decrease the immune response, so the person using the medication is more vulnerable to opportunistic infections. Most worrying is the reactivation of tuberculosis as well as pneumonia and exaggeration of Herpes Zoster activity, but there are other complications such as the onset of anemia, hypertension, tiredness, skin problems, nausea, heart complications, etc. It is very common that after using the medication, the patient complains of itching, redness, pain at the application site, and also migraine (BARBOSA, 2015).

It is common for respiratory tract infections, such as pneumonia, sinusitis and pharyngitis, however, this event affects less than 10% of patients. Also other infections can happen such as, candidiasis, viral gastroenteritis, skin infections, vaginal fungal vaginal etc. There may be neoplasms, such as skin, breast, and thyroid cancer (SANTOS, 2011).

Conclusion

CD is a prominent disease because the number of patients is growing due to the various changes that have occurred in society, such as food and hygiene. Even with the increasing number of cases, the diagnosis is late because often the

pathology is confused with other diseases. Although its genesis has not yet been fully elucidated, several factors are known to be involved. TNF-α, an inflammatory cytokine whose function is to recruit more cells that will produce more cytokines and so on. The drug Adalimumabe acts against this cytokine, as it leads to apoptosis of the cells that manufacture it. Although it has recently been in the Brazilian market, it is one of the most prescribed for the treatment of Crohn's disease for patients in which the case is moderate to severe. The drug has not presented great toxicity to its users, however, there are very serious reactions associated with it, such as reactivation of the bacillus responsible for the development of tuberculosis.

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