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APPLICABILITY OF MONOCLONAL IMMUNOMODULATORS IN INFLAMMATORY BOWEL DISEASES: WHAT DOES THE FUTURE PROMISE?

Vinicyus Eduardo Melo Amorim
Faculdade Pernambucana de Saúde. Recife, Pernambuco, Brazil
ORCID: 0000-0003-4541- 690X
http://lattes.cnpq.br/3530467921354204

Renata Vitória de França Sales
Faculdade Pernambucana de Saúde. Recife, Pernambuco, Brazil
ORCID: 0000-0002-0795-4179
http://lattes.cnpq.br/7356014364843598

Felipe Santos da Silva
Faculdade Tiradentes. Jaboatão dos Guararapes, Pernambuco, Brazil
ORCID: 0009-0009-9290-3250
http://lattes.cnpq.br/6140390189023815

Priscila Cardoso Alves Aureliano
Centro Universitário Maurício de Nassau. Recife, Pernambuco, Brazil
ORCID: 0000-0003-2453-363X
http://lattes.cnpq.br/7588181068576583

Beatriz Vilaça de Queiroz Valença
Faculdade Pernambucana de Saúde. Recife, Pernambuco, Brazil
ORCID: 0009-0005-8487-4956
http://lattes.cnpq.br/4829835215346873

José Adriano de Oliveira
Faculdade de Medicina de Olinda. Olinda, Pernambuco, Brazil.
ORCID: 0009-0000-4636-0181
http://lattes.cnpq.br/7405125917598980

Paula Vitória Tabosa de Lima
Faculdade Pernambucana de Saúde. Recife, Pernambuco, Brazil
ORCID: 0009-0006-2357-9969
https://lattes.cnpq.br/7872943767208921

Allana Victória Pereira Alves
Centro Universitário Maurício de Nassau. Recife, Pernambuco, Brazil
ORCID: 0009-0000-3979-140X
http://lattes.cnpq.br/3980037112810294

Elinando Ferreira da Silva
Faculdade de Medicina de Olinda. Olinda, Pernambuco, Brazil
ORCID: 0009-0004-2204-6955
http://lattes.cnpq.br/8054061809072893

Ricardo Oliveira De Andrade
Centro Universitário Maurício de Nassau. Recife, Pernambuco, Brazil
ORCID: 0009-0001-0500-3628
http://lattes.cnpq.br/8871414248616026

Renato Barbosa Pinheiro
Faculdade medicina de Olinda. Olinda, Pernambuco, Brazil
ORCID: 0009-0003-8112-1591
http://lattes.cnpq.br/8572511779455352

Wagner de Martino Filho
Faculdade medicina de Olinda. Olinda, Pernambuco, Brazil
ORCID: 0009-0005-7445-4392
https://lattes.cnpq.br/8044551069986304

Abstract: Monoclonal immunomodulators are a class of drugs that regulate the immune system and are used in the treatment of various autoimmune and inflammatory diseases, including Crohn's disease and ulcerative colitis. These two diseases are chronic inflammatory bowel diseases that affect the gastrointestinal tract, causing symptoms such as diarrhea, abdominal pain and weight loss. Monoclonal immunomodulators work by blocking specific molecules involved in the immune response, thereby reducing intestinal inflammation. An example of a monoclonal immunomodulator used in the treatment of these diseases is infliximab, which binds to the TNF-α molecule, reducing inflammation in the intestine. Other monoclonal immunomodulators include adalimumab, certolizumab, and golimumab. These medications are typically prescribed for patients with Crohn's disease or moderate to severe ulcerative colitis who do not respond well to other treatments, such as corticosteroids and immunosuppressants. They are given intravenously or subcutaneously, with frequency varying according to the specific drug and the severity of the condition. Despite being effective in treating Crohn's disease and ulcerative colitis, monoclonal immunomodulators have some side effects, such as allergic reactions, infections, reactivation of latent infections, and increased risk of certain types of cancer. Therefore, it is important that patients receiving these drugs are carefully monitored by a physician specializing in gastroenterology. In summary, monoclonal immunomodulators are an effective treatment option for patients with Crohn's disease and moderate to severe ulcerative colitis who do not respond well to other therapies. However, these drugs can have significant side effects and must be prescribed and monitored carefully, taking into account the risks and benefits to the patient.

INTRODUCTION

Inflammatory bowel diseases (IBD) are a group of chronic conditions that affect the gastrointestinal tract, with Crohn's disease and ulcerative colitis (UC) being the most common forms. Both are characterized by chronic inflammation of the intestinal lining, which can lead to symptoms such as the abdominal pain, diarrhea, weight loss and fatigue. The exact cause of IBD is still unknown, but it is believed that a combination of genetic, environmental and immunological factors may play an important role in its development. The diagnosis of IBD is made based on clinical, imaging, and laboratory tests, as well as an evaluation of the patient's medical history.[1]

CROHN'S DISEASE AND ITS REPERCUSSIONS

Crohn's disease is a chronic inflammatory disease that predominantly affects the gastrointestinal tract and can affect anywhere from the mouth to the anus. Its pathophysiology is complex and multifactorial, involving interactions between genetic, immunological, environmental and microbial factors.[2] Its development is believed to be triggered by an abnormal immune response to components of the intestinal flora in genetically predisposed individuals. Chronic inflammation resulting from the abnormal immune response can damage the intestinal wall, which can progress to ulcers, strictures, and fistulas.[1]

Chronic inflammation can also lead to changes in intestinal motility, resulting in diarrhea and abdominal pain. In addition, inflammation interferes with nutrient absorption, resulting in malnutrition in some patients.3 Malnutrition is a common consequence of malabsorption disorders, as the body is not receiving adequate amounts of nutrients needed for good health. Vitamin and mineral deficiency is also common in people with malabsorption disorders, which can lead to serious health problems. For example, vitamin B12 deficiency can cause anemia, fatigue, and neurological problems, while iron deficiency can cause iron-deficiency anemia. Calcium and vitamin D deficiency can lead to bone problems such as osteoporosis.[4,5,6]

Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are chronic conditions that affect the gastrointestinal tract and can have several complications, including the formation of intestinal strictures, which can lead to intestinal obstructions and perforations. Inflammation can also cause the intestinal walls to weaken, increasing the risk of fistulas, which are abnormal connections between organs or between the intestine and the skin. IBD can also increase the risk of colorectal cancer, particularly in patients with long-standing ulcerative colitis and psychiatric disorders such as depression and anxiety. In addition, chronic inflammation can affect other organs and systems of the body, such as joints, eyes, skin and liver, leading to extraintestinal diseases and causing significant impacts on patients' quality of life.[7]

Involvement of different parts of the gastrointestinal tract is a hallmark of Crohn's disease, and the inflammation can be transmural, reaching all layers of the intestinal wall, however, the inflammation can also be discontinuous, leaving areas of apparently normal mucosa between the areas. affected. The inflammatory response is initiated by an imbalance between beneficial and pathogenic bacteria in the gastrointestinal tract, which stimulate the production of inflammatory cytokines and the cellular immune response. T cells play an important role in the pathogenesis of Crohn's disease, with increased production of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-12 and IL-23.[2]

Furthermore, evidence indicates that

mutations in genes that regulate the immune response, such as NOD2, ATG16L1 and IRGM, may be associated with the development of the disease in some patients. These mutations can affect the immune response to the gut flora and lead to an exaggerated inflammatory response. Changes in intestinal permeability are also characteristic of Crohn's disease, with increased expression of tight junction proteins and increased intestinal permeability. This allows entry of antigenic substances into intestinal tissue, leading to an exacerbated inflammatory response. Furthermore, intestinal epithelial cells play an important role in the pathogenesis of Crohn's disease with increased apoptosis and decreased cell renewal, thus increasing the exposure of immune cells to intestinal antigens and contributing to the chronicity of the disease.[2]

THE EMERGENCE OF ULCERATIVE COLITIS

Ulcerative colitis (UC) is a chronic inflammatory disease that affects the gastrointestinal tract, with symptoms ranging from mild to severe. The pathophysiology of UC involves an imbalance in the immune system, leading to an uncontrolled inflammatory response in the mucosa of the colon and rectum. Several studies suggest that the complex interaction between genetic, environmental and immunological factors play a key role in the pathogenesis of UC.[8]

The hallmark of UC is ongoing inflammation of the rectal mucosa, which may extend along the colon. Inflammation is characterized by infiltration of inflammatory cells, including lymphocytes, plasma cells, neutrophils and eosinophils. These cells release inflammatory mediators, including cytokines and chemokines, which attract more inflammatory cells to the affected area and cause epithelial cell damage.[9]

The specific mechanisms that trigger inflammation in UC are still not completely understood, but several factors are known to be involved. Genetic studies have identified several genes associated with UC, including genes related to the immune system and the intestinal epithelial barrier. Furthermore, the immune response to commensal intestinal bacteria may also play an important role in the pathogenesis of UC.[10]

Other environmental factors, such as smoking, use of non-steroidal anti-inflammatory drugs and diet, can also influence the development of UC. For example, a diet high in fats and sugars can increase the risk of developing the disease. Treatment options for UC include anti-inflammatory medications, immunosuppressants, and biologic therapies, depending on the severity of the disease. The main goal of treatment is to control inflammation and prevent complications, such as colorectal cancer.[11,12]

CURRENT TREATMENT OF INFLAMMATORY BOWEL DISEASE

Treatment of IBD usually involves a combination of medications to reduce inflammation and manage symptoms, as well as dietary and lifestyle changes. Another treatment option is surgery, which may be necessary in severe cases of IBD, such as the intestinal obstruction, perforation, or bleeding. Surgery may involve removing parts of the intestine or creating a stoma.[13] Although there is no cure for IBD, many patients manage to control their symptoms and lead normal lives with proper treatment. However, the management of IBD can be challenging and requires an individualized approach for each patient.[14]

Treatment may include medications to reduce inflammation, manage pain and diarrhea, as well as nutritional supplements and dietary and lifestyle changes. The most

common medications used to treat IBD include anti-inflammatories, corticosteroids, and immunomodulators. Furthermore, nutrition can play an important role in the treatment of IBD, especially in cases of malnutrition or nutritional deficiencies. Diet can be modified to include foods that help reduce inflammation and provide essential nutrients.[14] In severe cases, biological therapy, which uses monoclonal antibodies, can be used to treat the inflammation.[15]

Monoclonal antibodies are laboratory-made proteins that bind to specific proteins in the body, including cytokines, which are inflammatory proteins involved in the pathogenesis of Crohn's disease. Monoclonal antibody therapy may help reduce intestinal inflammation and improve symptoms in patients with active Crohn's disease.[16,17]

Monoclonal immunomodulators represent one of the major developments in the treatment of inflammatory bowel diseases in recent years. With the improvement in the understanding of the pathophysiology of these diseases, new therapeutic targets were identified, allowing the development of new monoclonal antibodies with different mechanisms of action. There is still much to be explored in this field, and the future of monoclonal immunomodulators looks very promising. Some of the main expected advances include the use of personalized therapies based on biomarkers, the improvement in the efficacy and safety of existing drugs and the discovery of new therapeutic targets.[18]

In addition, monoclonal antibody technology has been evolving rapidly, with the development of new production techniques and molecular modification, which can lead to new drugs with better pharmacokinetic properties and efficacy. Research in this area continues to evolve, and clinical trials at an advanced stage are already being carried out with several new monoclonal immunomodulators. It is hoped that these new drugs can bring even more benefits to patients with inflammatory bowel diseases.[19]

Furthermore, it is important to highlight that monoclonal immunomodulators are being studied in other autoimmune diseases in addition to inflammatory bowel diseases, such as rheumatoid arthritis, psoriasis and systemic lupus erythematosus. With the advancement of research, it is possible that new therapeutic targets will be identified and new monoclonal immunomodulators will be developed.[20]

MONOCLONAL IMMUNOMODULATORS IN IBD

There are several monoclonal antibodies available for the treatment of Crohn's disease, including infliximab, adalimumab, golimumab, and vedolizumab. Infliximab is a monoclonal antibody that binds to tumor necrosis factor alpha (TNF-α), an inflammatory cytokine, reducing intestinal inflammation. Adalimumab and golimumab also bind to TNF-α, while vedolizumab binds to the α4β7 integrin, preventing the migration of inflammatory cells into the intestine.[16]

A study published in 2018 evaluated the efficacy and safety of infliximab in patients with active Crohn's disease. 1476 patients were randomized to receive infliximab or placebo for a period of 30 weeks. Results showed that 56.8% of patients treated with infliximab achieved clinical remission, compared with only 12.5% of patients treated with placebo. An older study evaluated the use of infliximab in patients with moderate to severe Crohn's disease. 108 patients were randomized to receive infliximab or placebo for a period of 12 weeks. Results showed that 81% of patients treated with infliximab experienced clinical improvement, compared with only 17% of patients treated with placebo. In addition, infliximab was also effective in reducing the

risk of hospitalization and surgery, thereby improving patients' quality of life.[21] The drug is also used in patients with moderate to severe ulcerative colitis who are unresponsive or intolerant of other treatments.

When evaluating the use of golimumab in 771 patients with moderate to severe ulcerative colitis randomized to receive golimumab or placebo for a period of 54 weeks, a significant improvement in the therapeutic outcome was observed. Results showed that 17.8% of golimumab-treated patients achieved clinical remission as well as improved bowel symptoms compared to only 8.4% of placebo-treated patients.[22]

Studies have shown that monoclonal antibody therapy can be especially useful in patients with Crohn's disease refractory to other therapies. Combination therapy with more than one monoclonal antibody has been studied as a treatment option for patients with active Crohn's disease.[24] However, it is important to note that this therapy may increase the risk of infections in patients. Therefore, it is necessary to closely monitor patients receiving this type of therapy and take measures to minimize the risk of infections, such as vaccination against specific pathogens. Furthermore, the therapy is associated with a high cost, which may limit access to this form of treatment for some patients.[25].

Vedolizumab has also been shown to be effective in the treatment of UC.[26,27] One study evaluated its use in patients with moderate to severe ulcerative colitis who had not responded to or were intolerant of previous treatments. 1115 patients were randomized to receive vedolizumab or placebo for a period of 52 weeks. Results showed that 47.1% of patients treated with vedolizumab achieved clinical remission, as well as improvement in bowel symptoms and quality of life compared to only 25.5% of patients treated with placebo.

The VARSITY trial compared the efficacy and safety of vedolizumab with adalimumab in the treatment of patients with moderate to severe ulcerative colitis. 769 patients were randomized to receive vedolizumab or adalimumab for a period of 52 weeks. The results showed that the rate of clinical remission was higher in the group treated with vedolizumab compared with adalimumab (31.3% versus 22.5%, respectively). Its use was also associated with a lower rate of serious adverse events.[28]

Ustekinumab is another monoclonal antibody that has been used in the treatment of ulcerative colitis. This drug binds to the p19 subunit of interleukin 23 (IL-23), a cytokine that plays an important role in the inflammatory response, therefore reducing inflammation in the colon and improving the symptomatology of the disease.[29] A more recent study evaluated the use of ustekinumab in patients with active Crohn's disease. 961 patients were randomized to receive ustekinumab or placebo for a period of 16 weeks. Results showed that 53.1% of ustekinumab-treated patients achieved clinical remission, compared to only 35.9% of placebo-treated patients.[30]

The UNITI-1 study evaluated the use of ustekinumab in patients with moderate to severe Crohn's disease. We randomized 741 patients to receive ustekinumab, placebo or adalimumab (a conventional anti-TNF) for a period of 52 weeks. The results showed that the clinical remission rate was significantly higher in the ustekinumab-treated group compared to placebo and adalimumab (34.3%, 16.5% and 19.2%, respectively). In addition, ustekinumab was also associated with a higher rate of healing of intestinal lesions.[31] The UNIFI study evaluated the use of ustekinumab in patients with moderate to severe ulcerative colitis refractory or intolerant of conventional or biological treatments. 961 patients were randomized to receive ustekinumab or

placebo. Results showed that the rate of clinical remission was significantly higher in the ustekinumab-treated group compared to placebo (45.1% versus 19.6%, respectively).[32]

A recent study evaluated the use of etrolizumab in patients with moderate to severe Crohn's disease. 124 patients were randomized to receive etrolizumab or placebo for a period of 12 weeks. The results showed that the clinical remission rate was significantly higher in the etrolizumab-treated group compared to placebo (21.8% versus 6.8%, respectively).[33] However, despite being effective in treating ulcerative colitis, monoclonal antibodies can have side effects, including an increased risk of infections, allergic reactions, and risk of developing certain types of cancer. Therefore, it is important to carefully assess the risks and benefits of each treatment in each individual patient.

CONCLUSION

Monoclonal antibodies can be used as a treatment for inducing or maintaining remission in patients with active Crohn's disease. These drugs are generally well tolerated, although some patients may experience side effects such as infusion site reactions, infections, and allergic reactions. In summary, monoclonal antibody therapy may be an effective treatment option for patients with active Crohn's disease, reducing inflammation and improving symptoms. However, it is important that treatment be individualized for each patient, taking into account the severity of the disease, response to treatment, and other individual factors.

CONFLICT OF INTERESTS

There is not any.

FINANCING

The own researchers

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