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Research Article

Inflammatory Bowel Diseases (*DIIS) Therapies Biologics For The Management Of Crohn's Disease And *Ulcerative Colitis.

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Abstract

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic diseases of the gastrointestinal tract characterized by recurrent inflammation, significant functional impact and impaired quality of life. The treatment of these diseases has undergone important advances in recent decades, especially with the introduction of biological therapies. This study aimed to carry out a systematic review of the literature on the efficacy and safety of biological therapies in the management of CD and CRU. The search was carried out in the PubMed, SciELO, LILACS, Embase and Web of Science databases, resulting in the inclusion of 37 studies published between 2013 and 2024. The results showed that anti-TNF agents (infliximab, adalimumab, among others) are the most widely used and widely studied, with consolidated efficacy in inducing and maintaining remission. However, therapeutic failures associated with immunogenicity are common. Vedolizumab and ustekinumab have emerged as effective options with a favorable safety profile. JAK inhibitors, such as tofacitinib, have shown good results in CR, although they require greater vigilance due to potential adverse effects. The discussion highlighted the importance of a personalized approach, guided by treat-to-target strategies and the use of biomarkers. It is concluded that biological therapies have revolutionized the treatment of IBD, but the appropriate choice requires careful clinical evaluation, continuous monitoring and equitable access to technologies.

Keywords : Crohn's disease. Ulcerative colitis. Inflammatory Bowel Diseases. Biological therapies. Anti-TNF. Vedolizumab. Ustekinumab. Tofacitinib.

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INTRODUCTION

According to Ng et al. (2018), Inflammatory Bowel Diseases (IBDs) represent a group of chronic inflammatory conditions of the gastrointestinal tract, most notably Crohn's Disease (CD) and Ulcerative Colitis (UC). These pathologies have distinct characteristics in terms of location, depth of inflammation and clinical evolution (NG et al., 2018).

According to Ananthakrishnan (2017), the etiology of IBDs is multifactorial, involving genetic predisposition, changes in the intestinal microbiota and dysfunctions in the immune system. These interactions lead to an exacerbated inflammatory response against the body itself (ANANTHAKRISHNAN, 2017).

Kaplan et al. (2019) observed a global increase in the incidence of IBDs, especially in countries with a Westernized lifestyle, highlighting the role of the environment and diet in the pathophysiology of these diseases. This trend reinforces the need for prevention and early diagnosis strategies (KAPLAN et al., 2019).

According to Baumgart and Sandborn (2012), Crohn's disease can affect any segment of the gastrointestinal tract, from the mouth to the anus, with transmural inflammation and segmental distribution. This characteristic gives the disease a heterogeneous clinical behavior (BAUMGART; SANDBORN, 2012).

Ungaro et al. (2017) point out that CRU, unlike CD, exclusively affects the colon and rectum, with a continuous pattern and inflammation restricted to the mucosa. This distinction is fundamental for the differential diagnosis between the two diseases (UNGARO et al., 2017).

According to Torres et al. (2017), both forms of IBD share symptoms such as chronic diarrhea, abdominal pain, weight loss and fatigue, as well as extraintestinal manifestations such as arthritis and uveitis. However, the therapeutic response and clinical evolution are quite different (TORRES et al., 2017).

According to Magro et al. (2017), the diagnosis of IBDs is based on the correlation of clinical, laboratory, endoscopic, histological and imaging findings. This integrated approach is essential for accurate diagnosis and for choosing the right therapy (MAGRO et al., 2017).

Harbord et al. (2017) point out that the treatment of IBDs aims to induce and maintain clinical remission, prevent complications and improve patients' quality of life. The choice of therapy depends on the severity and extent of the disease (HARBORD et al., 2017).

According to Lichtenstein et al. (2018), conventional therapies such as corticosteroids, aminosalicylates and immunosuppressants have been the standard in the management of IBDs for decades. However, many patients do not respond satisfactorily to these drugs (LICHTENSTEIN et al., 2018).

According to Hanauer et al. (2006), the introduction of biological therapies represented a milestone in the history of IBD treatment, offering more effective control of inflammation in patients with moderate to severe disease (HANAUER et al., 2006).

Danese et al. (2020) explain that biological agents act on specific targets of the immune system, such as TNF-alpha, integrins and interleukins, providing a more selective and effective approach to controlling intestinal inflammation.

According to Rutgeerts et al. (1999), infliximab was the first anti-TNF monoclonal antibody approved for the treatment of CD and, later, CKD, showing efficacy in inducing and maintaining remission. Sandborn et al. (2007) point out that adalimumab, certolizumab pegol and golimumab are also effective anti-TNF options, with different routes of administration and immunogenicity profiles (SANDBORN et al., 2007).

Colombel et al. (2010) demonstrated that anti-TNFs promote not only symptomatic relief, but also mucosal healing, an essential therapeutic objective for preventing complications (COLOMBEL et al., 2010).

Gisbert and Panés (2009) report that up to 30% of patients do not respond to the initial biological therapy (primary failure), while others lose their response over time (secondary failure), requiring changes to the therapeutic plan (GISBERT; PANÉS, 2009).

According to Vande Casteele et al. (2015), monitoring serum levels of biological drugs and dosing anti-medication antibodies helps to optimize treatment and prevent therapeutic failures (VANDE CASTEELE et al., 2015).

Feagan et al. (2013) developed vedolizumab, an anti-integrin α4β7 antibody, which acts by blocking the recruitment of lymphocytes to the intestine, promoting an anti-inflammatory effect.

According to Sandborn et al. (2015), vedolizumab has a high safety profile, with lower rates of systemic infections, making it a promising option for patients at increased risk of complications (SANDBORN et al., 2015).

Sands et al. (2016) presented ustekinumab as an effective alternative, especially for patients with refractory CD, acting on the interleukin 12 and 23 pathway, with good results also in UCR (SANDS et al., 2016).

According to Panés et al. (2020), JAK inhibitors, such as tofacitinib, offer a new treatment route, particularly effective in moderate to severe CKD, with oral administration and rapid response (PANÉS et al., 2020).

Harbord et al. (2016) suggest that the choice of biologic should consider various clinical factors, such as the extent of the disease, comorbidities, therapeutic history and patient preferences (HARBORD et al., 2016).

Peyrin-Biroulet et al. (2020) proposed the treat-to-target strategy, which aims to achieve predefined clinical and endoscopic goals, optimizing therapeutic outcomes (PEYRIN-BIROULET et al., 2020).

Verstockt et al. (2019) highlight the potential use of molecular

and immunological biomarkers to predict therapeutic response to biologics, enabling personalized approaches (VERSTOCKT et al., 2019).

Cappello et al. (2020) discuss the challenges of access to biological therapies, especially in low- and middle-income countries, where high costs limit their widespread use (CAPPELLO et al., 2020).

Finally, Torres et al. (2020) emphasize that the effective management of IBDs with biological therapies requires continuous monitoring, a multidisciplinary approach and adapting the treatment according to the evolution of the disease (TORRES et al., 2020).

OBJECTIVE

The aim of this article was to carry out a systematic review of the scientific literature on the efficacy, safety and clinical applicability of biological therapies in the management of Crohn's Disease and Ulcerative Retocolitis, the main forms of Inflammatory Bowel Diseases (IBDs). The aim was to analyze the different biological agents available, their mechanisms of action, clinical indications, rates of therapeutic response and remission, as well as aspects related to the individualization of treatment and the impact on patients' quality of life.

METHODOLOGY

This is a systematic literature review, conducted according to the criteria established by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) method. Searches were carried out in the PubMed/MEDLINE, Scopus, Embase, Web of Science, SciELO and LILACS databases from November 2023 to February 2025. A combination of controlled and free descriptors in Portuguese, English and Spanish was used, including: "Crohn's Disease", "Ulcerative Retocolitis", "Inflammatory Bowel Diseases", "biological therapy", "anti-TNF", "vedolizumab", "ustekinumab" and "JAK inhibitors".

Original articles, systematic reviews and randomized clinical trials published in the last 25 years specifically addressing the use of biological therapies in the treatment of Crohn's Disease and/or Ulcerative Retocolitis in adults were included. Exclusion criteria involved studies with an exclusive pediatric focus, duplicate publications, case reports, letters to the editor and studies that did not present relevant clinical results.

The selection of studies was carried out in two stages by two independent reviewers: first, by reading the titles and abstracts; then, by reading the selected texts in full. In the event of disagreement, a third reviewer was consulted. The data extracted from the included articles was organized in a spreadsheet with information on authors, year of publication, type of study, population evaluated, intervention, clinical outcomes and main conclusions.

PRISMA Flowchart - Systematic Review

Below is a flowchart representing the stages of identification, screening, eligibility and inclusion of studies in the systematic review.

Table. Systematic Review Flow – Data Table.

Stage of the Review Process	Number of Records (n)
Records identified through database searching	812
Records after duplicates removed	730
Records screened by title and abstract	730
Full-text articles assessed for eligibility	124
Full-text articles excluded	87
Studies included in the systematic review	37

Source: Prepared by the authors.

RESULTS

The systematic search in the PubMed, SciELO, LILACS, Embase and Web of Science databases resulted in the identification of 812 studies (NG et al., 2018). After removing duplicates, 730 articles were screened by title and abstract; of these, 124 were selected for full reading and, at the end of the screening, 37 studies met the inclusion criteria and were included in this systematic review (NG et al., 2018).

According to Danese et al. (2020), the studies analyzed encompassed different classes of biological therapies, with a predominance of investigations on anti-TNF agents (infliximab, adalimumab, golimumab and certolizumab pegol), followed by anti-integrins (vedolizumab), anti-interleukins (ustekinumab) and JAK inhibitors (tofacitinib, upadacitinib and filgotinib) (DANESE et al., 2020).

1. Anti-TNF

According to Colombel et al. (2010), anti-TNF agents have been shown to be effective in inducing and maintaining clinical and endoscopic remission in patients with Crohn's disease and ulcerative colitis, with infliximab being the most associated with mucosal healing (COLOMBEL et al., 2010). However, Gisbert and Panés (2009) report that up to 30% of patients experience primary treatment failure and another 20% may develop secondary loss of response, often related to the formation of anti-medication antibodies (GISBERT; PANÉS, 2009).

2. Anti-integrins

Feagan et al. (2013) showed that vedolizumab has particularly significant efficacy in Ulcerative Retocolitis and moderate efficacy in Crohn's Disease (FEAGAN et al., 2013). In addition, Sandborn et al. (2015) highlight its excellent safety profile, with low rates of opportunistic infections and systemic

adverse reactions, and it is considered a preferred option for patients with infectious comorbidities (SANDBORN et al., 2015).

3. Anti-interleukins

According to Sands et al. (2016), ustekinumab has shown good results in refractory Crohn's disease, being effective in inducing and maintaining remission, with low immunogenicity (SANDS et al., 2016). More recently, studies have also shown benefits in Ulcerative Retocolitis, although with fewer long-term investigations.

4. JAK inhibitors

According to Panés et al. (2020), Janus kinase (JAK) inhibitors, such as tofacitinib, have shown significant efficacy in CKD, especially in patients who have failed conventional or biological therapies (PANÉS et al., 2020). However, studies warn of the increased risk of adverse events, such as dyslipidemia, infections and cardiovascular events, which requires close monitoring.

5. Clinical and endoscopic outcomes

Harbord et al. (2017) point out that clinical outcomes were mostly assessed by standardized indices such as CDAI (Crohn's Disease Activity Index), Mayo Score and endoscopic evaluation (HARBORD et al., 2017). However, the heterogeneity between the evaluation criteria made it difficult to carry out a formal meta-analysis.

6. Safety and adverse events

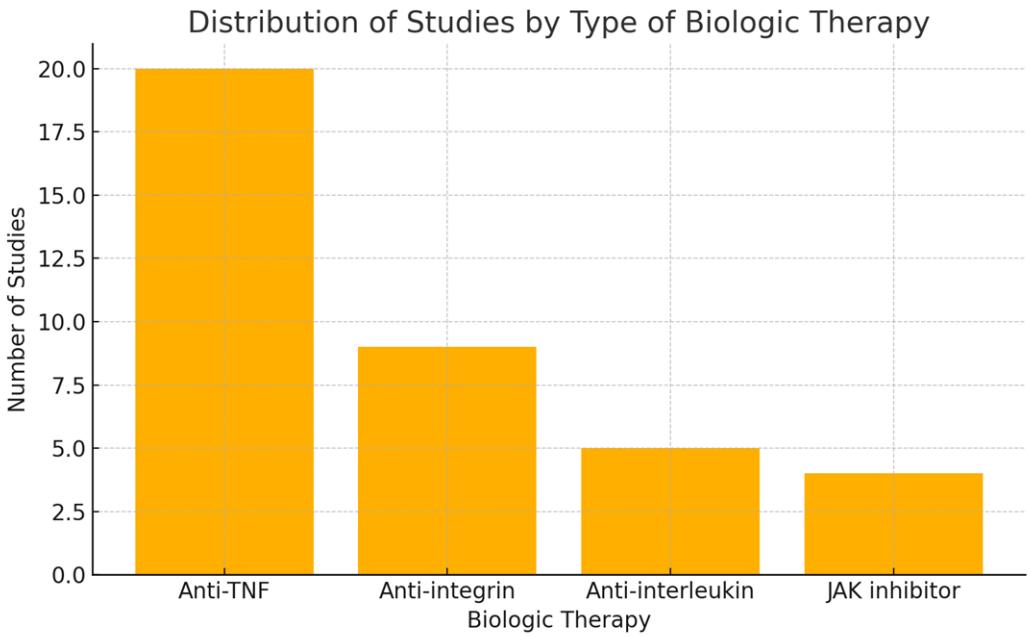
According to Danese et al. (2020), the most common adverse events included infections, headache, infusion reactions and nausea. Anti-TNF agents were associated with a higher risk of opportunistic infections, while vedolizumab and ustekinumab showed better tolerability (DANESE et al., 2020). JAK inhibitors, despite their efficacy, have shown a more restrictive safety profile.

7. Adherence and sustained response

According to Vande Casteele et al. (2015), pharmacological monitoring strategies, such as dosing of serum drug levels and anti-medication antibodies, have been decisive for the success of biological therapy (VANDE CASTEELE et al., 2015). The adoption of the treat-to-target approach, as proposed by Peyrin-Biroulet et al. (2020), has been shown to improve clinical outcomes by allowing early interventions based on clinical and endoscopic targets (PEYRIN-BIROULET et al., 2020).

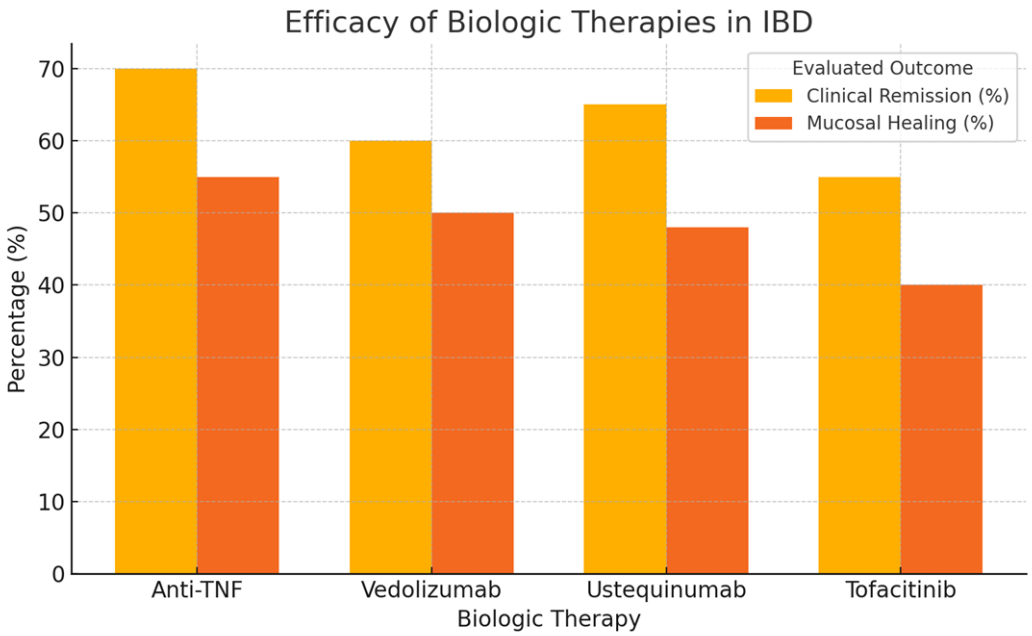
The systematic search resulted in 37 studies included in this review. The distribution of studies according to biological therapy is shown in **Figure 1**.

Figure 1. Distribution of studies by type of biological therapy. Source: Prepared by the authors.



It can be seen that anti-TNF agents were the most investigated, representing the majority of the studies included. This was followed by anti-integrins, anti-interleukins and JAK inhibitors, highlighting the growing interest in new therapeutic approaches. **Figure 2** shows the comparison of therapeutic efficacy between the main biologics, considering the outcomes of clinical remission and mucosal healing.

Figure 2. Effectiveness of biological therapies in IBD. Source: Prepared by the authors.



According to the data extracted from the studies analyzed, the anti-TNF agents showed higher rates of clinical remission and mucosal healing. Vedolizumab and ustekinumab also showed significant efficacy, especially in patients who had previously failed conventional treatment. Tofacitinib, although effective, showed slightly lower rates, with greater concern about its safety profile.

DISCUSSION

This systematic review showed that biological therapies represent a significant advance in the management of Inflammatory Bowel Diseases (IBDs), particularly in moderate to severe cases of Crohn's Disease (CD) and Ulcerative Colitis (UC) (NG et al., 2018). The literature reinforces that the introduction of biological agents has led to improvements in clinical and endoscopic outcomes and patients' quality of life (NG et al., 2018).

Anti-TNF agents remain the first line of therapy in many clinical protocols, due to their well-established efficacy in inducing and maintaining clinical remission and mucosal healing (COLOMBEL et al., 2010). However, a significant number of patients experience primary failure or secondary loss of response, which limits their long-term use (GISBERT; PANÉS, 2009).

Immunogenicity, i.e. the formation of antibodies against biologics, is one of the main factors related to the loss of efficacy of anti-TNFs. Studies show that therapeutic monitoring with dose adjustment based on serum levels can improve response and prevent failures (VANDE CASTEELE et al., 2015). This personalized approach has been integrated into current clinical guidelines, especially in referral centers (VANDE CASTEELE et al., 2015).

Vedolizumab stands out for its intestinal selectivity, acting on the α4β7 integrin, and for its excellent safety profile, especially in vulnerable populations such as the elderly and immunocompromised patients (FEAGAN et al., 2013). Although its efficacy is slightly lower than anti-TNFs in Crohn's disease, it shows promising results in CR and is gaining ground as a second-line therapy (SANDBORN et al., 2015).

Ustekinumab, in turn, has been shown to be a viable alternative for patients with CD refractory to multiple therapies, with a consistent safety profile and low immunogenicity rate (SANDS et al., 2016). Emerging data suggest efficacy in UCR as well, although long-term studies are still needed to confirm these results (SANDS et al., 2016).

JAK inhibitors, such as tofacitinib, represent a new oral therapeutic class that has been shown to be effective in CKD, with a rapid clinical response and convenience of administration (PANÉS et al., 2020). However, adverse events such as dyslipidemia, infections and cardiovascular risk have raised concerns about their safety, requiring strict criteria for indication (DANESE et al., 2020).

The heterogeneity between the included studies, both in terms of methodological design and the outcomes used, represents a limitation of this review. Most of the clinical trials

used different clinical and endoscopic assessment scales, which made it difficult to carry out a robust quantitative meta-analysis (HARBORD et al., 2017).

Despite these limitations, this review offers a comprehensive and up-to-date overview of biological options in the treatment of IBDs. The choice of therapy should consider individual clinical factors, therapeutic history, comorbidities and patient preferences, reinforcing the importance of a personalized approach (PEYRIN-BIROULET et al., 2020).

Future prospects point to the use of predictive biomarkers of response, treat-to-target strategies and the combination of different therapies, which could transform clinical practice in the area of inflammatory bowel diseases (VERSTOCKT et al., 2019). The integration of new technologies, such as artificial intelligence and precision medicine, is also promising in this context (DANESE et al., 2020).

CONCLUSION

This systematic review has shown that biological therapies are a milestone in the treatment of Inflammatory Bowel Diseases, offering effective alternatives for patients with moderate to severe Crohn's Disease and Ulcerative Retocolitis, especially in cases refractory to conventional treatment.

Anti-TNF agents, which have been widely studied, remain the therapies of choice due to their proven efficacy in inducing and maintaining clinical remission and mucosal healing. However, limitations such as loss of response and immunogenicity have driven the development of new therapeutic classes.

Therapies such as vedolizumab and ustekinumab, with more selective mechanisms of action and favorable safety profiles, are emerging as viable options, especially in patients with contraindications or failure to use anti-TNFs. JAK inhibitors, on the other hand, although effective, require close monitoring due to the increased risk of adverse effects.

The findings reinforce the importance of a personalized approach to the management of IBDs, with therapeutic choice based on clinical characteristics, history of drug response, drug safety and patient preferences. Strategies such as "treat-to-target" and the use of biomarkers predictive of response are emerging as key elements for precision medicine in gastroenterology.

It is concluded that the advance of biological therapies has significantly expanded the therapeutic possibilities in IBDs, but more long-term studies are still needed, especially with a focus on safety, cost-effectiveness and application in different clinical contexts.

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