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ADVANCES AND CHALLENGES IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASES: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: To understand the aspects of inflammatory bowel diseases, seeking to identify the best screening, treatment, and prevention strategies to improve patients' clinical outcomes. The guiding question, formulated based on the PVO (Population, Variable and Objective) strategy, is: "What are the best treatment and prevention strategies to improve clinical outcomes in patients with inflammatory bowel diseases?" Methodology: Literature review, using the PubMed database, with the descriptors combined with the Boolean term "AND": Inflammatory Bowel Diseases, Biological Therapy, Immunosuppressive Therapies, Crohn's Disease. The search strategies applied were: (Inflammatory Bowel Diseases) AND (Biological Therapy) AND (Immunosuppressive Therapies), (Crohn's Disease) AND (Immunosuppressive Therapies), and (Crohn's Disease) AND (Biological Therapy). A total of 369 articles were identified. After applying the inclusion and exclusion criteria, 41 studies were selected for analysis and 11 of these were selected to compose the collection. The inclusion criteria considered articles in English, Portuguese, and Spanish, published from 2019 to 2024, which addressed the themes proposed for this research; and review, observational and experimental studies, available in full. The exclusion criteria eliminated duplicate articles, available only in abstract form, that did not directly address the proposal studied or that did not meet the inclusion criteria. Results: Appropriate screening and

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treatment strategies are essential for the prevention of complications of inflammatory bowel diseases. Selected studies have highlighted that the correct use of biological and immunosuppressive therapies is effective in maintaining clinical remission and reducing inflammation. In addition, personalization of treatment based on therapeutic drug monitoring (TDM) and genomic testing can significantly improve patients' clinical outcomes. Conclusion: Early identification and treatment of inflammatory bowel diseases are essential to prevent associated complications and improve patients' quality of life. Effective screening strategies, adequate follow-up, and health education are key to reducing the incidence of these diseases and improving clinical outcomes. Health policies tailored to the needs of vulnerable populations and the strengthening of surveillance systems are crucial to achieving these goals.

Keywords: Inflammatory Bowel Diseases. Innovative Treatments. Systematic Review.

INTRODUCTION

Inflammatory Bowel Disease (IBD) represents a group of chronic inflammatory conditions that predominantly affect the gastrointestinal tract. This group includes Crohn's Disease (CD) and Ulcerative Colitis (UC), both of which are characterized by persistent inflammation that leads to debilitating symptoms and a significant impact on patients' quality of life. The pathogenesis of IBD is complex, involving a multifaceted interaction between genetic factors, gut microbiome, and immune dysregulation (Ghouri et al., 2020).

The pathogenesis of classic Inflammatory Bowel Disease (IBD) is a complex area of study that involves a multifaceted interaction between genetic factors, gut microbiome, and immune dysregulation.

Genetic mutations play a significant role in the predisposition to developing IBD. A well-known mutation is in the NOD2 gene, which encodes the nucleotide-binding oligomerization domain 2. This mutation is associated with a reduced immune response to bacterial lipopolysaccharides, resulting in an increased survivability of certain gram-negative bacteria that translocate to the intestinal epithelium and induce inflammation (Ghouri et al., 2020).

In addition, loss-of-function mutations in the alleles encoding fucosyltransferase 2 are linked to a higher risk of changes in the gut microbiome. The absence of this enzyme in the intestinal tract is associated with changes in microbial composition, which can promote inflammation (Ghouri et al., 2020).

Genetic defects that result in abnormal T cell function and macrophage activity can induce immune-mediated injury in the gut. These cellular changes cause the dysregulated production and release of cytokines, recruiting more inflammatory cells and perpetuating the immune-mediated inflammatory process (Ghouri et al., 2020).

The gut microbiome plays a crucial role in immune homeostasis. In IBD patients, there is a significant decrease in microbial biodiversity, a state known as dysbiosis, which contributes to the pathogenesis of the disease by allowing the proliferation of pathogenic bacteria and triggering an inflammatory response (Ghouri et al., 2020). This microbial imbalance exacerbates inflammation, perpetuating a vicious cycle of tissue injury.

In addition to genetic factors and microbiome, lifestyle also significantly influences IBD. Obesity, for example, is prevalent among IBD patients and is associated with a lower prevalence of clinical remission and higher anxiety and depression scores (Rozich et al., 2020). Similarly, sleep disturbances and chronic stress are factors that exacerbate disease activity, affecting patients' quality of life (Rozich et al., 2020).

There are some peculiarities in IBD, such as in the pediatric sphere, where it has shown a significant increase in incidence in recent decades, particularly in Europe and North America, which underlines the urgent need for effective management and treatment strategies for this vulnerable population (Ashton and Beattie, 2024). The etiology of paediatric IBD is equally complex, involving genetic, environmental and microbial factors, and requires a multifaceted approach to treatment.

In addition, there is secondary IBD, induced by external factors such as medications and surgeries, which presents an additional challenge in managing these conditions. Immunomodulators and anti-TNF agents, for example, can paradoxically induce or exacerbate IBD, highlighting the need for careful therapeutic management (Ghouri et al., 2020).

Inflammatory Bowel Disease, including Crohn's Disease and Ulcerative Colitis, presents significant management challenges due to its chronic and complex nature. Understanding the underlying pathogenic mechanisms and therapeutic strategies is crucial to improve patients' quality of life and reduce the burden of disease. Although several treatments are available, the efficacy and safety of many emerging therapies still need rigorous investigation. This systematic review will seek to consolidate current knowledge and identify gaps in the literature, providing a robust foundation for future research and clinical practice.

The aim of this systematic review is to evaluate and synthesize the existing evidence on treatments for Inflammatory Bowel Disease, focusing on emerging treatments and their clinical efficacy.

METHODOLOGY

This literature review aims to understand the aspects of inflammatory bowel diseases, seeking to identify the best screening, treatment, and prevention strategies to improve the clinical outcomes of patients. The guiding question, formulated based on the PVO (Population, Variable and Objective) strategy, is: "What are the best treatment and prevention strategies to improve clinical outcomes in patients with inflammatory bowel diseases?"

The searches were performed in the PubMed database, using descriptors combined with the Boolean term "AND": Inflammatory Bowel Diseases, Biological Therapy, Immunosuppressive Therapies, Crohn's Disease. The search strategies applied were: (Inflammatory Bowel Diseases) AND (Biological Therapy) AND (Immunosuppressive

Therapies), (Crohn's Disease) AND (Immunosuppressive Therapies), and (Crohn's Disease) AND (Biological Therapy).

In total, 369 articles were found, which were submitted to the selection criteria. The inclusion criteria considered articles in English, Portuguese, and Spanish, published between 2019 and 2024, which addressed the themes proposed for this research. Review, observational, and experimental studies were included, as long as they were available in full. The exclusion criteria applied eliminated duplicate articles, available only in abstract form, that did not directly address the proposal studied or that did not meet the inclusion criteria.

After the association of the descriptors in the searches, of the 369 articles found, 73 were excluded due to duplication. Applying the inclusion and exclusion criteria, 41 articles were selected and after individual reading, 11 were selected to compose the collection used in this systematic review.

RESULTS

Author	Major Contributions
Ashton and Beattie (2024)	They described the importance of therapeutic drug monitoring (TDM) to adjust biologic therapies in Inflammatory Bowel Disease (IBD). They highlighted the need for a more personalized approach, utilizing drug monitoring and genomic testing to adjust therapy based on individual patient response.
Balderramo (2022)	It explored the efficacy and mechanisms of action of mesalazine in inducing and maintaining ulcerative colitis (UC) remission. It described the potential adverse effects of mesalazine, including nausea, abdominal pain, and, in rare cases, pancreatitis and nephrotoxicity. He also addressed immunosuppressants, such as azathioprine and 6-mercaptopurine (6-MP), emphasizing the importance of regular monitoring of blood counts and liver function of patients.
Imbrizi, Magro and Coy (2023)	They looked at the role of thiopurines (azathioprine and 6-MP) and methotrexate in maintaining remission in IBD patients. They described the mechanism of action of thiopurines and associated adverse effects, such as myelosuppression and hepatotoxicity. They discussed the efficacy and side effects of vedolizumab, an anti-integrin monoclonal antibody, in the GEMINI 1, 2, and 3 clinical trials. They also explored the efficacy of ustekinumab, a monoclonal antibody targeting interleukins 12 and 23, in the UNITI-1 and UNITI-2 studies, and the efficacy of novel biologic agents targeting interleukin-23 (IL-23), such as risankizumab and mirikizumab.
Jefremow and Neurath (2023)	They investigated sphingosine-1-phosphate (S1P) receptor modulators in the treatment of IBD, including ozanimod, etrasimod, and amiselimod. They highlighted the efficacy of ozanimod in inducing and maintaining remission in patients with UC and the promising results of etrasimod. They discussed challenges related to the adverse effects of S1P modulators, such as bradycardia and elevations in liver enzymes. They addressed the need for further research to fully understand the therapeutic potential of amiselimod in IBD.
Nielsen et al. (2022)	They addressed the safety of biologics, especially TNF inhibitors, during pregnancy. They described that the continuation of biologics during pregnancy does not significantly increase the risk of adverse outcomes, such as premature birth, low birth weight, or congenital malformations. They highlighted the importance of maintaining biological therapy throughout pregnancy to minimize the risks of disease recurrence. They also mentioned the need for further studies on non-TNF biologics, such as vedolizumab and ustekinumab, during pregnancy.

Chapman et al. (2020)	They discussed the risk of relapse after withdrawal of immunomodulatory and biologic therapy in patients with IBD. They described the relapse rates after azathioprine withdrawal in patients with CD and UC, highlighting the importance of monitoring drug concentrations and biomarkers, such as fecal calprotectin, to predict recurrence. They suggested that phasing out immunomodulators from therapy combined with biologic agents may be an effective approach, as long as it is accompanied by close monitoring.
Conrad and Kelsen (2020)	They highlighted the efficacy of infliximab and adalimumab in the treatment of IBD. They described the importance of Therapeutic Drug Monitoring (TDM) to adjust the doses of infliximab and adalimumab based on serum levels and the presence of anti-drug antibodies. They discussed the safety of biologics during pregnancy and the importance of maintaining therapy to prevent recurrence of the disease.
Ghouri et al. (2020)	They compared treatments with IL-12/23p40 and IL-23p19 antagonists with TNF-α inhibitors, such as infliximab, adalimumab, certolizumab pegol, and golimumab. They discussed the efficacy and limitations of TNF-α inhibitors, emphasizing the need for new therapeutic approaches for patients who do not respond adequately to conventional treatments.
Vuyyuru et al. (2023)	They analyzed the efficacy and safety of novel biologics targeting interleukin-23 (IL-23), such as risankizumab and mirikizumab, in the treatment of IBD. They discussed the promising results of the ADVANCE, MOTIVATE, and FORTIFY clinical trials for risankizumab and LUCENT-1 and LUCENT-2 for mirikizumab. They highlighted the importance of personalizing the choice of biologic agent based on prior response to treatment and patients' comorbidities to maximize therapeutic benefits and minimize risks.
Higashiyama and Hokari (2023)	They discussed new and emerging therapies for IBD, including JAK inhibitors and anti-interleukin agents. They addressed the challenges in using these new treatments, including the associated adverse events such as severe infections and thrombotic events. They highlighted the importance of continuing to monitor adverse events and adjust treatment as needed to ensure patient safety.
Núñez, Quera and Yarur (2023)	They evaluated the safety of Janus kinase (JAK) inhibitors in the treatment of IBD, highlighting the efficacy of tofacitinib, filgotinib, and upadacitinib in inducing and maintaining clinical remission. They discussed the adverse effects associated with JAK inhibitors, such as infections, thrombotic events, and malignancies, and the need for careful monitoring of patients during treatment.

Source: table 1 - created by the author

DISCUSSION

Biologic therapies, such as infliximab and adalimumab, have revolutionized the treatment of IBD by targeting specific cytokines involved in the inflammatory response. However, optimizing the use of these therapies is critical. Infliximab, for example, has been a mainstay in the treatment of Crohn's disease and ulcerative colitis. The conventional dosage of 5 mg/kg administered at regular intervals has been revised to include accelerated induction and initial dosing of 10 mg/kg, guided by therapeutic drug monitoring (TDM). This adjustment is crucial to ensure adequate levels of the drug, reduce markers of inflammation, and minimize the risk of drug antibody formation (Ashton and Beattie, 2024).

IMMUNOMODULATORS

Immunomodulators play a critical role in maintaining remission in patients with Inflammatory Bowel Disease (IBD), especially in refractory or corticosteroid-dependent individuals. Immunosuppressants, including azathioprine, 6-mercaptopurine (6-MP), and methotrexate, play a crucial role in maintaining remission in patients with Inflammatory

Bowel Disease (IBD) who do not respond adequately to mesalazine or corticosteroids. These medications work by suppressing the immune system to control the chronic inflammation associated with IBD.

Mesalazine, also known as 5-aminosalicylic (5-ASA), is one of the most commonly used medications in the treatment of mild to moderate ulcerative colitis (UC). Its efficacy in inducing and maintaining UC remission is widely recognized, being a pillar in the management of this inflammatory bowel disease. Mesalazine acts locally on the lining of the gastrointestinal tract to reduce inflammation. The exact mechanism of action of mesalazine is not yet fully understood, but it is thought to involve inhibition of the synthesis of prostaglandins and leukotrienes, which are chemical mediators involved in the inflammatory process. In addition, mesalazine may exert antioxidant effects and alter the production of pro-inflammatory cytokines, contributing to the reduction of intestinal inflammation (Balderramo, 2022).

Clinical studies have shown that mesalazine is effective in inducing and maintaining remission in patients with UC. Topical administration of the drug allows a high concentration of mesalazine directly into the inflamed mucosa, reducing the symptoms of the disease and promoting mucosal healing. Mesalazine is available in various forms of administration, including oral tablets, suppositories, and enemas, which allows you to personalize treatment based on the location and extent of inflammation (Balderramo, 2022).

Mesalazine is generally well tolerated by patients, but side effects may occur. Among the most common are nausea, abdominal pain, and headache. In rare cases, more serious adverse reactions such as pancreatitis and nephrotoxicity may occur. Therefore, regular monitoring of renal function is essential in patients using mesalazine long-term (Balderramo, 2022).

Azathioprine (AZA) and its metabolized form, 6-mercaptopurine (6-MP), are thiopurines often used in the management of IBD. These agents act as immunosuppressants, inhibiting the proliferation of T and B cells, which play a central role in the inflammatory immune response. Azathioprine is converted to 6-MP in the body, which is then metabolized into thioguanine nucleotides, incorporating into the DNA and RNA of immune cells and inhibiting their replication (Balderramo, 2022).

These drugs are effective in maintaining remission in patients with IBD, especially those who are corticosteroid-dependent or who do not respond to 5-ASA therapy. However, azathioprine and 6-MP have a slow onset of action, and may take several weeks or months to reach full effectiveness. Therefore, they are often used as long-term maintenance therapies rather than rapid induction treatments (Balderramo, 2022).

The main side effects of immunosuppressants include myelosuppression (bone marrow suppression), hepatotoxicity, and an increased risk of infections. Myelosuppression can result in leukopenia, anemia, and thrombocytopenia, necessitating regular monitoring of patients' blood counts. Hepatotoxicity, which may manifest as elevations of liver enzymes, requires periodic evaluation of liver function. In addition, patients should be monitored for signs of infections, as immunosuppression can increase susceptibility to infectious diseases (Balderramo, 2022).

Azathioprine (AZA) and 6-mercaptopurine (6-MP) are the most frequently used thiopurines and act primarily as immunosuppressive agents. These drugs have a slow onset of action, often taking weeks to months to reach full clinical efficacy, and are therefore not recommended for rapid induction of remission, but rather for long-term maintenance (Imbrizi, Magro, and Coy, 2023).

The mechanism of action of thiopurines involves several immunosuppressive pathways, including the incorporation of 6-thioguanine into DNA and RNA, inhibiting DNA replication and repair, and protein synthesis. In addition, the metabolite 6-thioinosine 5-monophosphate (TIMP) inhibits purine synthesis by altering cell proliferation and T cell apoptosis via mitochondrial activation. The efficacy of thiopurines is strongly correlated with 6-thioguanine (6-TGN) levels (Imbrizi, Magro & Coy, 2023).

Methotrexate (MTX), another immunomodulator, is effective in maintaining remission in Crohn's disease (CD) and has been used in IBD. Its mechanism of action involves the inhibition of dihydrofolate reductase, interfering with the synthesis of DNA and RNA. MTX can also induce cell death through additional mechanisms, such as inhibition of enzymes involved in cell proliferation and induction of apoptosis (Imbrizi, Magro, and Coy, 2023).

Methotrexate is widely used as an immunosuppressant in the management of various autoimmune and inflammatory diseases, including Inflammatory Bowel Disease (IBD). Its efficacy in maintaining remission in patients with Crohn's Disease (CD) and Ulcerative Colitis (UC) is well documented, especially for those who do not respond adequately to conventional therapies such as mesalazine or corticosteroids (Balderramo, 2022).

One of the significant advantages of methotrexate is its ability to modulate the immune response, which is crucial for IBD patients, where chronic inflammation can lead to serious complications (Balderramo, 2022). By inhibiting the enzyme dihydrofolate reductase, methotrexate interferes with the DNA and RNA synthesis of immune cells,

reducing their proliferation and, consequently, the inflammatory response (Balderramo, 2022).

However, the use of methotrexate is not without its challenges. Its onset of action is relatively slow, taking several weeks or months to achieve full effectiveness, which can be a limitation in situations that require rapid control of inflammation (Balderramo, 2022). In addition, side effects such as myelosuppression, hepatotoxicity, and an increased risk of infections require careful monitoring (Balderramo, 2022). Patients being treated with methotrexate need regular follow-up with liver function tests and complete blood counts to ensure that the drug is being tolerated safely (Balderramo, 2022).

Despite these limitations, methotrexate remains a valuable option in the therapeutic arsenal for IBD. Its use should be carefully individualized, considering the potential benefits in maintaining remission against the risks associated with side effects (Balderramo, 2022).

NEW APPROACHES AND EMERGING DRUGS

In addition to traditional biological therapies, new approaches are emerging in the treatment of Inflammatory Bowel Disease (IBD). Drugs such as ustekinumab (anti-IL-12/23) and vedolizumab (anti-α4β7) are already used in pediatric practice, offering effective alternatives to anti-TNF therapy. These biologic agents are particularly useful for treating concomitant pathologies such as psoriasis and have an established safety profile (Ashton and Beattie, 2024). New drugs are constantly being developed, with risankizumab (selective anti-IL-23) expected to be available soon for younger patients. In addition, JAK-STAT inhibitors (filgotinib, tofacitinib, upadacitinib) and sphingosine-1-phosphate inhibitors (ozanimod) are emerging as potent options, especially for specific cases such as severe acute colitis. The efficacy of these agents varies with indication, but they are shown to be more effective when used as initial treatment compared to patients who have lost response to other agents (Ashton and Beattie, 2024).

ANTI-INTEGRIN THERAPIES

Anti-integrin therapies represent a significant advance in the treatment of IBD, especially for patients who do not respond to or cannot tolerate conventional anti-TNF treatments. Anti-integrins are monoclonal antibodies designed to inhibit the migration of leukocytes into the gastrointestinal tract by reducing local inflammation in a targeted manner. Vedolizumab, a humanized monoclonal antibody, blocks integrin α4β7, which interacts with the adhesion molecule MadCAM-1 present in the intestinal endothelium. This interaction is crucial for the trafficking of lymphocytes into the gut, a process that contributes

significantly to intestinal inflammation. By inhibiting this cell migration, vedolizumab effectively reduces inflammation, promoting clinical remission in IBD patients (Imbrizi, Magro & Coy, 2023).

Vedolizumab is a humanized monoclonal antibody, which belongs to the class of drugs known as anti-leukocyte trafficking agents. These agents are designed to inhibit the migration of leukocytes to the sites of inflammation, thereby reducing intestinal inflammation in a targeted and effective manner. In the case of vedolizumab, it specifically blocks integrin α4β7, preventing interaction with the adhesion molecule MadCAM-1 in the intestinal endothelium. This interaction is crucial for the trafficking of lymphocytes into the gut, a process that contributes significantly to intestinal inflammation. By inhibiting this cell migration, vedolizumab effectively reduces inflammation, promoting clinical remission in patients with Inflammatory Bowel Disease (IBD) (Imbrizi, Magro & Coy, 2023).

GEMINI 1, 2, and 3 clinical trials provided robust evidence of the efficacy of vedolizumab in both Crohn's Disease (CD) and Ulcerative Colitis (UC). In the GEMINI 1 trial, vedolizumab demonstrated a clinical response rate of 47.1% and a clinical remission rate of 16.9% at week 6. Maintenance of clinical response was observed in 56.6% of patients and clinical remission in 41.8% of patients at week 52. These results are particularly significant for patients who have failed previous anti-TNF therapies, highlighting the efficacy of vedolizumab in refractory cases (Imbrizi, Magro & Coy, 2023). One of the advantages of vedolizumab is its favorable safety profile compared to other biologic therapies, minimizing systemic immunosuppression and associated risks, such as severe infections. Due to its specific mechanism of action, targeting the gastrointestinal tract exclusively, vedolizumab minimizes systemic immunosuppression and the risks of serious side effects (Imbrizi, Magro & Coy, 2023).

Carotegrast, also known as AJM300, is an oral integrin α4 inhibitor that acts similarly to natalizumab, but without the same risks associated with PML. Experimental studies with colitis models in IL-10-deficient mice have shown that AJM300 can effectively reduce gut inflammation (Jefremow and Neurath, 2023).

Yoshimura et al. conducted a phase IIa clinical trial with AJM300 in patients with moderate UC, where a dose of 960 mg three times daily was administered. The results showed a clinical response rate of 62.7% and a clinical remission rate of 23.5%, compared with 25.5% and 3.9% in the placebo groups, respectively. Nasopharyngitis was the most observed adverse effect, being generally mild to moderate (Jefremow and Neurath, 2023). A subsequent phase III study led by Matsuoka et al. confirmed the efficacy of AJM300, with

45% of patients in the treated group achieving clinical response after 8 weeks, compared to 21% in the placebo group (Jefremow and Neurath, 2023).

Alicaforsen is an antisense oligonucleotide targeting intercellular adhesion molecule 1 (ICAM-1), which plays a role in the migration of leukocytes to the sites of inflammation. While initial clinical trials showed promising results, subsequent studies did not meet the primary endpoints for the treatment of mild to moderate UC (Jefremow and Neurath, 2023). Despite this, Alicaforsen continues to be investigated in different clinical settings, seeking to optimize its efficacy.

ANTI-INTERLEUKINS

Anti-interleukin therapies are a significant advance in the treatment of Inflammatory Bowel Disease (IBD) by targeting specific interleukins involved in the dysregulated inflammatory response. Ustekinumab, for example, is a human monoclonal antibody that binds to the p40 subunit shared by interleukins 12 and 23, blocking its interaction with receptors on T cells and other immune cells. This inhibition disrupts the differentiation and activation of Th1 and Th17 cells, which are key in the inflammatory response in IBD (Imbrizi, Magro & Coy, 2023).

Ustekinumab is a fully human IgG1 monoclonal antibody that targets the p40 subunit shared by interleukins 12 (IL-12) and 23 (IL-23). By binding to this subunit, ustekinumab prevents the interaction of these interleukins with their receptors on T cells and other immune cells, disrupting the differentiation and activation of Th1 and Th17 cells, which are key in the inflammatory response in Inflammatory Bowel Disease (IBD) (Imbrizi, Magro & Coy, 2023).

Clinical studies such as UNITI-1 and UNITI-2 have evaluated the efficacy of ustekinumab in patients with Crohn's Disease (CD) who have failed previous biologic therapies. In the UNITI-1 study, the response and clinical remission rates at week 6 were 33.7% and 18.5%, respectively. In the UNITI-2 study, which included patients with no previous experience with biologics, the response and clinical remission rates were 55.5% and 34.9%. Efficacy in maintaining remission was observed in 41.1% and 62.5% of patients in the UNITI-1 and 2 studies, respectively (Imbrizi, Magro and Coy, 2023).

In addition to the UNITI studies, the UNIFI study also demonstrated the long-term efficacy and safety of ustekinumab for the treatment of IBD. Ustekinumab was the first monoclonal antibody approved for the treatment of moderate to severe CD, showing superiority compared to placebo in inducing and maintaining clinical remission (UNITI I and II, IM-UNITI) (Vuyyuru et al., 2023). In the context of other Immune-Mediated Diseases

(IMIDs), such as psoriasis, ustekinumab has also been shown to be effective, albeit with variable response rates compared to TNF-α antagonists (Nielsen et al., 2022).

Ustekinumab has a well-established safety profile, making it a viable option for patients with moderate to severe IBD who do not respond to other therapies. Clinical studies indicate that ustekinumab is well tolerated, with fewer side effects compared to other biologic therapies. The choice of biologic agent should be personalized, considering the prior response to treatment and patients' comorbidities, to maximize therapeutic benefits and minimize risks (Imbrizi, Magro & Coy, 2023). Among the new emerging therapies, cytokine inhibitors such as anti-interleukin (IL) 12/23 agents, such as ustekinumab, have shown remarkable efficacy. Ustekinumab, by targeting the shared p40 subunit of IL-12/23, prevents its binding to receptors in cells, offering an effective approach for inflammation control in IBD (Higashiyama and Hokari, 2023).

NEW ANTI-INTERLEUKINS

In addition to ustekinumab, other antibodies targeting interleukin-23 (IL-23), such as risankizumab and mirikizumab, are emerging as effective options in the treatment of IBD. Risankizumab, for example, has shown significant efficacy in clinical trials, such as ADVANCE, MOTIVATE, and FORTIFY, for patients with CD. Similarly, mirikizumab has shown promising results in LUCENT-1 and LUCENT-2 studies for patients with Ulcerative Colitis (UC), with significant clinical response and remission rates (Imbrizi, Magro & Coy, 2023).

Risankizumab, on the other hand, focuses exclusively on the p19 subunit of IL-23, providing a more specific and higher-affinity binding. Clinical studies indicate that this treatment may offer a more robust response in patients with moderate to severe CD, especially those who have not responded to prior treatments, including TNF-α antagonists. Phase III trials have demonstrated that risankizumab is effective in achieving and maintaining clinical and endoscopic remission, showing superior efficacy compared to placebo (Vuyyuru et al., 2023).

These novel biologic agents are often well-tolerated and have established safety profiles, making them viable options for patients with moderate to severe IBD who do not respond to other therapies. The choice of biologic agent should be personalized, considering the prior response to treatment and patients' comorbidities, to maximize therapeutic benefits and minimize risks (Imbrizi, Magro & Coy, 2023).

Janus kinase (JAK) inhibitors, which is an anti-interleukin medication, have shown remarkable efficacy in treating Inflammatory Bowel Disease (IBD), which includes Crohn's

disease (CD) and ulcerative colitis (UC). These drugs block multiple cytokine-dependent immune pathways, providing rapid symptomatic relief and control of gut inflammation. Among the JAK inhibitors, tofacitinib, filgotinib and upadacitinib stand out.

Tofacitinib, a non-selective JAK inhibitor, has demonstrated high remission rates in patients with moderate to severe ulcerative colitis (UC). Studies such as OCTAVE 1 and 2 have evidenced the efficacy of tofacitinib in inducing and maintaining clinical remission, with significantly higher rates compared to placebo (Higashiyama and Hokari, 2023). However, the efficacy of tofacitinib in CD was not as robust (Núñez, Quera, and Yarur, 2023).

Filgotinib and Upadacitinib, selective JAK1 inhibitors such as filgotinib and upadacitinib, have also shown significant efficacy in clinical trials of induction and maintenance of remission in patients with UC and CD. Upadacitinib, in Phase 2 and 3 trials, has shown promising results in both inducing and maintaining remission (Núñez, Quera, and Yarur, 2023). Filgotinib showed similar efficacy, with safety profiles consistent with other JAK inhibitors (Núñez, Quera, and Yarur, 2023).

The safety of JAK inhibitors is a crucial aspect. Tofacitinib has been associated with serious adverse events (AEs), including infections, thrombotic events, and malignancies. The incidence of infections, especially herpes zoster (HZ), was significant, particularly in older patients and those with a history of immunosuppression, prompting the FDA to issue a "black box warning" about the increased risk of pulmonary embolism and mortality (Núñez, Quera, and Yarur, 2023).

Selective JAK-1 inhibitors, such as upadacitinib and filgotinib, have been developed to improve the safety profile. Upadacitinib has shown a lower incidence of serious adverse events compared to tofacitinib, although thrombotic events have still been observed (Núñez, Quera, and Yarur, 2023). Filgotinib had a similar safety profile, with infections being the most common AEs but without a significant increase in thrombotic events (Núñez, Quera, and Yarur, 2023).

The introduction of JAK inhibitors represents a significant evolution in the treatment of IBD, offering an alternative for patients who do not respond to traditional biological therapies. The efficacy of JAK inhibitors in UC and CD, combined with their safety profile, positions them as valuable therapeutic options. However, it is crucial to continue monitoring adverse events and adjust treatment as needed to ensure patient safety (Ghouri et al., 2020; Vuyyuru et al., 2023).

Sphingosine-1-phosphate (S1P) receptor modulators represent an innovative class of therapies in the management of Inflammatory Bowel Diseases (IBD), such as Crohn's Disease (CD) and Ulcerative Colitis (UC). These agents act on crucial lymphocyte

trafficking mechanisms, offering a promising approach to selectively and effectively reduce intestinal inflammation.

Sphingosine-1-phosphate (S1P) is a sphingolipid that binds to G-protein-coupled receptors (S1P1–S1P5), regulating the migration of lymphocytes from lymphatic tissue into the bloodstream. The binding of sphingosine-1-phosphate to these receptors plays a vital role in retaining lymphocytes in the lymph nodes and releasing them into the circulation. S1P modulators work by sequestering lymphocytes in lymph nodes, thereby reducing the amount of inflammatory cells entering peripheral intestinal tissues, promoting localized immunosuppression that minimizes systemic effects (Jefremow and Neurath, 2023).

Ozanimod is a selective modulator of S1P1 and S1P5, demonstrating efficacy in both inducing and maintaining remission in patients with UC. Clinical studies have demonstrated its effectiveness. In the TOUCHSTONE study, 16% of patients in the ozanimod 1 mg group achieved clinical remission by week 8, compared to only 6% in the placebo group. At week 32, maintenance of remission was achieved by 21% of patients in the ozanimod 1 mg group, evidencing the continued efficacy of the treatment (Jefremow and Neurath, 2023). The phase III True North study confirmed these findings, with 18.4% of patients treated with ozanimod achieving clinical remission during the induction phase, while only 6.0% of patients in the placebo group achieved the same result. In the maintenance phase, 37.0% of patients treated with ozanimod maintained clinical remission, compared to 18.5% in the placebo group (Jefremow and Neurath, 2023).

Etrasimod is another S1p modulator that has shown promising results in IBD. In the ELEVATE UC 12 and ELEVATE UC 52 studies, clinical remission was achieved by 27% of patients treated with etrasimod after 12 weeks, compared to 7% in the placebo group. After 52 weeks, 32% of patients in the etrasimod group maintained clinical remission, compared to 7% in the placebo group. These results highlight the effectiveness of etrasimod in maintaining long-term remission (Jefremow and Neurath, 2023). However, adverse effects such as upper respiratory tract infections, nasopharyngitis, and bradycardia were observed more frequently in the etrasimod group, indicating the need for careful monitoring of patients during treatment (Jefremow and Neurath, 2023).

Amiselimod, a selective modulator of S1P1, has been investigated in patients with CD. Unfortunately, it failed to achieve the expected clinical significance in terms of reduced disease activity. In the study conducted by D'Haens et al., 54.1% of patients in the placebo group achieved the desired reduction in Crohn's disease activity index (CDAI), compared to 48.7% in the amiselimod group. These results suggest that more research is needed to fully understand the therapeutic potential of amiselimod in IBD (Jefremow and Neurath, 2023).

While S1p modulators have significant potential in the treatment of IBD, there are challenges to be addressed. Adverse events such as bradycardia and elevations in liver enzymes are important concerns that may limit the clinical use of these agents. The varying efficacy between different S1p modulators also suggests the need for additional studies to optimize patient selection and dosing regimens (Jefremow and Neurath, 2023).

Future prospects include combining S1p modulators with other biologic or small molecule therapies to improve clinical outcomes and reduce adverse events. Ongoing clinical trials and future studies will provide valuable data to refine the use of these agents and potentially expand their therapeutic indications (Jefremow and Neurath, 2023).

ANTI-TNF-A THERAPIES

Anti-TNF-α monoclonal antibodies, such as infliximab and adalimumab, work specifically by blocking tumor necrosis factor-alpha (TNF-α), a proinflammatory cytokine central to the pathogenesis of IBD. By neutralizing TNF-α, these drugs reduce inflammation and help induce and maintain clinical remission. This class of therapies has shown impressive results in clinical studies, especially in those patients who do not respond adequately to conventional treatments.

Infliximab was the first biopharmaceutical approved for the treatment of IBD. It is a chimeric monoclonal IgG1 antibody that binds to TNF-α, a pro-inflammatory cytokine, blocking its activity. In addition to neutralizing TNF-α, infliximab prevents the migration of leukocytes to sites of inflammation and induces apoptosis of T lymphocytes and monocytes (Conrad and Kelsen, 2020).

Studies such as REACH have demonstrated the efficacy of infliximab in pediatric patients with moderate to severe CD, with 88% of children showing clinical response at week 10 and more than 50% maintaining clinical remission at week 54 with doses administered every 8 weeks (Conrad and Kelsen, 2020). Early introduction of infliximab has been shown to be advantageous, resulting in fewer structural complications and less need for surgical interventions (Conrad and Kelsen, 2020).

Adalimumab, a fully human monoclonal IgG1 antibody, is another anti-TNF therapy widely used in IBD. FDA-approved for pediatric CD, it has been shown to be effective in inducing and maintaining remission, including in cases of perianal fistulizing disease. Subcutaneous self-administration and the absence of infusion reactions are significant advantages of this drug (Conrad and Kelsen, 2020).

The efficacy of adalimumab compared to infliximab appears to be similar in anti-TNF-α-naïve patients, although non-response or loss of response to adalimumab may be more

common due to its pharmacokinetics. In cases of infliximab failure, adalimumab may still be effective, but the likelihood of remission is lower in non-primary responders to infliximab (Conrad and Kelsen, 2020).

COMPARISONS AND RELATIONSHIPS WITH OTHER TREATMENTS

Treatments with IL-12/23p40 and IL-23p19 antagonists are particularly relevant when compared to the previously discussed TNF-α inhibitors, such as infliximab (IFX), adalimumab (ADA), certolizumab pegol (CZP), and golimumab (GLM). Although TNF-α inhibitors have revolutionized the treatment of CD, many patients end up losing response over time or do not achieve the desired endoscopic remission (Ghouri et al., 2020).

The treatment of Inflammatory Bowel Disease (IBD) has evolved significantly in recent decades, driven by the development of new therapies that address complex inflammatory mechanisms. The introduction of anti-TNFα agents, such as infliximab and adalimumab, marked a crucial breakthrough in improving health outcomes and reducing the need for surgical interventions. However, treatment failure and adverse effects observed in many patients treated with these agents, including severe infections and increased risk of malignancy, highlight the need for new therapeutic approaches (Higashiyama and Hokari, 2023).

Therapeutic Drug Monitoring (TDM) Therapeutic Drug Monitoring (TDM) has emerged as a crucial tool in the management of biologic therapies for Inflammatory Bowel Disease (IBD). By monitoring serum drug levels and the presence of anti-drug antibodies, clinicians can adjust doses to optimize efficacy and minimize adverse effects (Conrad and Kelsen, 2020).

For infliximab, trough levels greater than 8.3 µg/mL at week 6 are associated with clinical remission at week 14. In the case of adalimumab, trough levels greater than 5 µg/mL are correlated with better clinical outcomes (Conrad and Kelsen, 2020).

In vedolizumab, although TDM is still in the research phase, higher serum concentrations have been associated with better clinical and endoscopic outcomes. Factors such as hypoalbuminemia and obesity may affect the pharmacokinetics of vedolizumab, highlighting the importance of MDT to adjust dosages in a personalized manner (Conrad and Kelsen, 2020).

TDM plays a vital role in tailoring therapy to the individual needs of patients. The measurement of drug levels and the formation of anti-drug antibodies, as in the case of infliximab, guide adjustments in dosage and frequency of administration. Utilizing TDM,

whether proactively or reactively, has shown clear benefits for patients, improving treatment efficacy and clinical response (Ashton and Beattie, 2024).

TREATMENT OF IBD IN PEDIATRICS

Treatment strategies for pediatric Inflammatory Bowel Disease (IBD) have evolved significantly, reflecting advances in both pharmacological therapies and multidisciplinary approaches. The central objective of these strategies is to provide effective management of the disease, prevent complications, and improve the quality of life of patients. Treatment of IBD usually begins with conventional therapies such as corticosteroids and immunosuppressants, which have been widely used due to their effectiveness in controlling inflammation. However, the need for a more personalized approach is becoming increasingly evident. Prediction and personalization of treatment, with the use of therapeutic drug monitoring and genomic testing, represent a crucial advance. These elements allow for adjusting therapy based on the patient's individual response, leading to more effective management of the disease (Ashton and Beattie, 2024).

SAFETY OF BIOLOGICS DURING PREGNANCY

Biologic treatments, especially tumor necrosis factor (TNF) inhibitors such as infliximab, adalimumab, certolizumab pegol, and golimumab, are crucial in the treatment of Inflammatory Bowel Disease (IBD). During pregnancy, there are concerns about the ability of these drugs to cross the placenta, especially in the third trimester, and possible adverse effects on fetal development.

Studies have shown that continuing biologics during pregnancy does not significantly increase the risk of adverse outcomes such as preterm birth, low birth weight, or congenital malformations (Nielsen et al., 2022). Discontinuation of TNF inhibitors before the third trimester may increase the risk of disease relapse, which is associated with elevated risks for fetal development. Thus, maintaining biologic therapy is recommended to minimize these risks (Nielsen et al., 2022).

Comparing different biologics, TNF inhibitors were shown to be safe. Non-TNF biologics, such as vedolizumab and ustekinumab, were also evaluated, but more studies are needed to clarify the results. These findings support the maintenance of biologic therapy throughout pregnancy in women with IBD, ensuring better outcomes for both mother and fetus. (Nielsen et al., 2022).

RISK OF RELAPSE AFTER WITHDRAWAL OF THERAPY IN INFLAMMATORY BOWEL DISEASE

Withdrawal of immunomodulatory and biologic therapy in patients with Inflammatory Bowel Disease (IBD) who have achieved sustained clinical remission is a complex issue, with the risk of relapse being a central concern. Randomized controlled trials (RCTs) have shown that withdrawal of azathioprine in patients with Crohn's disease (CD) and ulcerative colitis (UC) in remission results in substantially higher relapse rates. For example, relapse rates reach 62.7% at 5 years after azathioprine withdrawal in CD and 61% at one year in UC (Chapman et al., 2020).

The withdrawal of immunomodulators from combined therapy with biological agents presented mixed results. Although thiopurine withdrawal has not shown a significant increase in relapse rates within two years, observations suggest that the likelihood of relapse increases substantially over time, reaching 72% within five years (Chapman et al., 2020). Patients with sustained clinical remission for longer periods have a lower risk of relapse after withdrawal of treatment (Chapman et al., 2020).

Monitoring drug concentrations and biomarkers is essential to predict relapse. Low trough concentrations of infliximab are associated with a higher risk of relapse after withdrawal of the drug. Faecal calprotectin is a valuable biomarker, with increases in levels preceding clinical and endoscopic relapse (Chapman et al., 2020).

Actively monitoring patients during and after withdrawal of therapy, using biomarkers such as faecal calprotectin, can help detect relapse early and adjust treatment. A gradual, individualized approach to withdrawal from therapy may reduce the risk of relapse. Studies suggest that phasing out immunomodulators from combination therapy does not significantly increase the relapse rate at up to two years of follow-up, but the risk of biological immunogenicity should be considered (Chapman et al., 2020).

Withdrawal of immunomodulatory and biologic therapy in IBD patients who have achieved sustained remission should be carefully planned and monitored. The risk of relapse is substantial, but it can be mitigated through close monitoring, use of biomarkers, and an individualized approach, optimizing IBD management and providing better clinical outcomes (Chapman et al., 2020).

CONCLUSION

The treatment of pediatric Inflammatory Bowel Disease (IBD) has advanced significantly, driven by the development of new pharmacological therapies and monitoring strategies. Mesalazine continues to be a mainstay in the management of mild to moderate

ulcerative colitis (UC), while immunosuppressants such as azathioprine and 6-mercaptopurine play a critical role in maintaining remission. The introduction of biologic therapies, such as infliximab, adalimumab, and vedolizumab, has revolutionized IBD treatment, providing effective options for patients who do not respond to conventional therapies.

The use of Therapeutic Drug Monitoring (TDM) has been shown to be crucial to optimize the dosage and efficacy of biologic therapies, minimizing adverse effects and improving clinical outcomes. In addition, the safety of biologic treatments during pregnancy and the impact of withdrawal of therapy in patients in remission are areas that need careful monitoring to ensure better long-term outcomes.

Novel biologics targeting interleukins 12 and 23, such as ustekinumab, risankizumab, and mirikizumab, as well as sphingosine-1-phosphate (S1P) receptor modulators, represent promising advances in the management of IBD. However, the safety profile and efficacy of these agents need to be continuously evaluated through clinical studies.

Finally, the development of personalized therapeutic approaches, which take into account the individual response of patients and the use of biomarkers, represents the future of IBD management. The constant evolution of treatment strategies and the integration of new technologies are key to improving the quality of life of pediatric patients with IBD.

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