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EXTRAINTESTINAL NEOPLASMS RELATED TO THE TREATMENT OF INFLAMMATORY BOWEL DISEASES

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Abstract: The main representatives of Inflammatory Bowel Diseases (IBD) are Crohn's Disease (CD) and Ulcerative Colitis (UC), which occur with dysregulation of the immune system and chronic inflammation of the digestive tract. Treatment includes aminosalicylates, immunosuppressants, corticosteroids and biological agents. There is already evidence that IBD patients have a higher risk of developing colorectal cancer. However, the association with extraintestinal cancer is still poorly studied. The use of drugs to treat IBD, associated with systemic immune dysregulation, can decrease the body's defense against the development of malignancies. **Objective:** To conduct an integrative review on extraintestinal neoplasms that may occur as a consequence of the treatment of inflammatory bowel diseases. **Methods:** An integrative review was carried out to investigate the possible relationship between the treatment of inflammatory bowel diseases and the increased incidence of extraintestinal neoplasms. Data sources included PubMed, Scielo and Elsevier/ScienceDirect, with specific search strategies. The selection of studies was based on analyzing the titles and reading the full texts. Cohort studies published between 2013 and 2023 were included. Exclusion criteria were applied to eliminate out-of-scope studies. Data collection was conducted using a validated questionnaire, and seven articles were finally included in the review. **Results:** Yadav et al. found no statistically significant increase in overall cancer risk with the use of aminosalicylates, corticosteroids, immunosuppressants or anti-TNF agents. However, there was an increased risk of melanoma in patients treated with corticosteroids and immunosuppressants. Ostermann et al. showed an increased risk of non-melanoma skin cancer and other malignancies with the use of combination therapy of adalimumab with immunosuppressants. However, they found no significant

results with the use of adalimumab monotherapy. Khan et al. showed a higher risk of lymphoma in patients treated with thiopurines, increasing significantly after 4 years of therapy. Ölen et al. showed an increased risk of lymphoma in CD patients undergoing combined therapy (immunosuppressant and biologic) and second-line biologics. Lopez et al. found no increased risk of myeloid disorders with thiopurines, but there was an increased risk in patients with past exposure to these. Rungoe et al. observed an increased risk of high-grade squamous intraepithelial lesions in patients who used TNF- α and azathioprine for a prolonged period. Long-term exposure did not affect the risk of low-grade intraepithelial lesions or cancer in CD or RCU. Finally, Rouvroye et al. found no association between immunosuppressive therapy and the risk of vulvovaginal cancer. Patients who used immunobiological drugs had a younger age at diagnosis of vulvar or vaginal cancer. **Conclusions:** This integrative review reveals diverse results on the impact of treatments for Inflammatory Bowel Diseases on extraintestinal malignancy rates. The complexity of cancer risk assessment highlights the need for a personalized therapeutic approach, considering individual factors, duration of treatment and specific choice of drugs, highlighting the importance of further research to guide safer and more effective therapeutic strategies for IBD patients.

Keywords: Inflammatory Bowel Diseases; Crohn's Disease; Ulcerative Colitis; Therapeutics; Neoplasms.

INTRODUCTION

The main representatives of inflammatory bowel diseases (IBD) are Crohn's Disease (CD) and Ulcerative Colitis (UC). Although the pathogenesis of these diseases is not fully understood, it is believed that genetically predisposed individuals, when interacting with

environmental factors, trigger a dysregulation of the immune system, from which chronic inflammation of the digestive tract originates to varying extents(1).

The typical course of inflammatory bowel diseases is one of recurrent outbreaks and remissions. The extent of mucosal inflammation is related to the severity of the course of the disease(2). Intestinal symptoms are the most characteristic of these diseases, but extraintestinal manifestations can also be present (3).

The treatment of IBD includes aminosalicylates (sulfasalazine, mesalazine), immunosuppressants (azathioprine, 6-mercaptopurine, methotrexate), corticosteroids (prednisone, hydrocortisone, methylprednisolone, budesonide) and biological agents (anti-TNF α , anti-integrin, anti-interleukin and JAK inhibitors) (4).

Patients with IBD are more likely to develop colorectal cancer due to chronic inflammation in the intestine (5,6). However, the association with extraintestinal cancer is still poorly studied. The use of drugs to treat IBD, combined with systemic immune dysregulation, can reduce the body's defense against the development of malignancies (7).

Thus, the aim of this study is to conduct an integrative review on extraintestinal neoplasms that can occur as a result of the treatment of inflammatory bowel diseases.

METHODOLOGY

An integrative review was carried out with the aim of answering the following guiding question: “Can the treatment of inflammatory bowel diseases be related to an increase in the incidence of extraintestinal neoplasms?”.

DATA SOURCES AND SEARCH STRATEGY

The databases used were PubMed, Scielo and Elsevier/ScienceDirect.

The search was conducted using the descriptors “Inflammatory Bowel Diseases” AND “Neoplasms”; “Inflammatory Bowel Diseases” AND “Immunosuppressive Agents” and “Inflammatory Bowel Diseases” AND “Malignancy”.

SELECTION OF STUDIES

The selection of studies was initially carried out by analyzing the titles, followed by reading the full texts of potentially eligible studies.

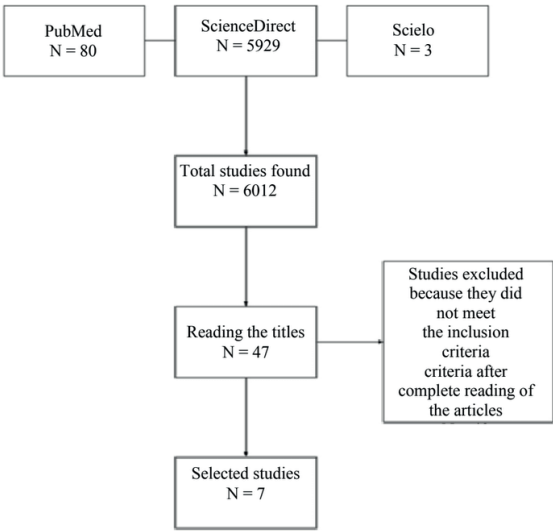


Image 1: Article selection process

INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria were based on the following aspects: high methodological accuracy, prospective or retrospective cohort studies, studies published between 2013 and 2023, which included men and women over the age of 18.

Exclusion criteria were established to eliminate studies that did not answer the guiding question, had low methodological accuracy and included the pediatric population.

DATA COLLECTION

Data collection from the studies found in the literature search was carried out using a model instrument in the form of a questionnaire, validated by Ursi (8). This instrument covers the objectives of the research, the characteristics of the sample, the results and the implications of the results.

Subsequently, the academic advisor was consulted to ensure the methodological quality of the selected studies. The studies were finally chosen by the authors of this study together with the academic advisor, who carried out a critical evaluation of all the eligible articles to identify possible biases. In the end, seven articles were included in the review.

ORGANIZATION OF THE ARTICLES

The articles were organized chronologically with their respective authors, year of publication, title, type of study, country, number of participants and summary of results. All the articles were published in English.

RESULTS

The study by Yadav et al. (9), which included 839 patients with IBD, followed up for an average of 18 years, sought to estimate whether IBD drugs modify the risk of cancer. The diagnosis of CD and CR was confirmed based on clinical, endoscopic, radiological and/or histological criteria. The drugs were categorized as: sulfasalazine and aminosaliclates, corticosteroids, immunomodulators (Azathioprine, Mercaptopurine, Methotrexate, Cyclosporine and Tacrolimus) and anti-TNF α agents (Infliximab, Adalimumab, Certolizumab pegol).

No statistically significant values were found for increased overall cancer risk in patients treated with aminosaliclates (versus patients with no previous treatment with aminosaliclates; RR 1.0; 95% CI, 0.5-1.8), corticosteroids (versus patients with no previous tre-

atment with corticosteroids; RR 1.4; 95% CI, 0.5-3.4) immunomodulators (versus patients without previous treatment with immunomodulators; RR 0.9; 95% CI, 0.3-2.3) or anti-TNF α agents (versus patients without previous treatment with anti-TNF α agents; RR 0.6; 95% CI, 0.1-4.5).

There was also an increased risk of melanoma in the group of patients treated with corticosteroids (RR 8.2; 95% CI, 1.4-49.2) and in the group treated with immunomodulators (RR 5.3; 95% CI, 1.1-24.8). There was a numerically, but not statistically, higher risk of hematological malignancies in patients treated with corticosteroids (RR 4.9; 95% CI, 0.9-25.1) and immunomodulators (RR 4.2; 95% CI, 0.9-19.2). In addition, the overall risk of cancer was not significantly different in former users of aminosaliclates (RR 1.2; 95% CI, 0.7-1.9), corticosteroids (RR 1.2; 95% CI, 0.8-1.8), immunomodulators (RR 1.1; 95% CI, 0.5-2.2) or anti-TNF α agents (RR 1.0; 95% CI, 0.3-3.1), compared to IBD patients who had never been treated with these drugs.

Seeking further evidence of the relationship between malignancies and IBD treatment, the study by Ostermann et al. (10) aimed to determine the relative risk of malignancy in CD patients receiving adalimumab monotherapy, compared to patients receiving adalimumab associated with immunomodulatory therapy and the general population. This study included 1594 patients with CD who took part in clinical trials with adalimumab, followed up for an average of 1.5 years, with 66% of the population analyzed receiving adalimumab monotherapy and 44% receiving concomitant immunomodulators (563 with thiopurines and 131 with methotrexate).

There were 44 malignant events reported in 34 patients (2.1%). In the adalimumab monotherapy group, 10 patients (1.1%) had 12 events, while in the combination therapy group, 24 patients (3.5%) had 32 events. The

Authors (year)	Original article title	Type of study, country and number of participants (N)	Summary of results
Yadav et al. (2015)	Effect of Medications on Risk of Cancer in Patients With Inflammatory Bowel Diseases: A Population-Based Cohort Study from Olmsted County, Minnesota	Cohort study, United States, N = 839	No statistically significant values were found for an increase in the overall risk of cancer with the use of aminosalicylates, corticosteroids, immunosuppressants or anti-TNF agents. However, there was an increased risk of melanoma in patients treated with corticosteroids and immunosuppressants.
Osterman et al. (2013)	Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease	Cohort study, United States, N = 1594	Shown an increased risk of non-melanoma skin cancer and other malignancies with the use of combination therapy of adalimumab with an immunosuppressant. However, it did not find significant results with the use of adalimumab monotherapy.
Khan et al. (2013)	Risk of lymphoma in patients with ulcerative colitis treated with thiopurines: a nationwide retrospective cohort study	Cohort study, United States, N = 36.891	Shown a higher risk of lymphoma in patients treated with thiopurines, increasing significantly after 4 years of therapy.
Ölen et al. (2023)	Increasing risk of lymphoma over time in Crohn's disease but not in ulcerative colitis: a Scandinavian cohort study.	Cohort study, Denmark and Sweden, N = 109.289	It showed a higher risk of lymphoma in CD patients undergoing combined therapy (immunosuppressant and biologic) and second-line biologics.
Lopez et al. (2014)	Increased risk of acute myeloid leukemias and myelodysplastic syndromes in patients who received thiopurine treatment for inflammatory bowel disease	Cohort study, France, N = 19.486	Did not find an increased risk of myeloid disorders with continuous use of thiopurines, but there was an increased risk in patients with past exposure to this drug.
Rungoe et al. (2014)	Inflammatory Bowel Disease and Cervical Neoplasia: A Population-Based Nationwide Cohort Study	Cohort study, Denmark, N = 27.408	Observed increased risk of high-grade squamous intraepithelial lesion in patients who used TNF- α and azathioprine for a prolonged period. Long-term exposure did not affect the risk of low-grade intraepithelial lesions or cancer in CD or RCU.
Rouvroye et al. (2019)	Vulvar and vaginal neoplasia in women with inflammatory bowel disease	Cohort study, Netherlands, N = 55	Did not find an association between immunosuppressive therapy and risk of vulvovaginal cancer. Patients who used immunobiological drugs had a lower age at diagnosis of vulvar or vaginal cancer.

Image 2: Organization of the articles

study showed that patients treated with adalimumab monotherapy have an increased risk of non-melanoma skin cancer (NMSC) (SIR 1.2; 95% CI, 0.39-2.80), but not for other malignancies (SIR 0.63; 95% CI, 0.17-1.62), when compared to the general population, although none of the values are statistically significant.

However, patients treated with combination therapy of adalimumab with an immunomodulator had an increased risk of NMSC (SIR 4.59; 95% CI, 2.51-7.70) and other malignancies (SIR 3.04; 95% CI, 1.66-5.10), when compared to the general population. The research also showed that patients treated with combined adalimumab and immunomodulator therapy had an increased risk of NMSC (RR 3.46; 95% CI, 1.08-11.06) and other malignancies (RR 2.82; 95% CI, 1.07-7.44), compared to patients treated with adalimumab alone. These data suggest that the increased risk of malignancy may be attributable to immunomodulatory therapy.

In agreement with the data just presented, the study by Khan et al. (11) sought to determine whether the treatment of CKD patients with thiopurines (azathioprine and mercaptopurine) increases the risk of lymphoma. This study analyzed data from 36,891 patients diagnosed with CKD in the US Department of Veterans Affairs healthcare system, followed up for a median of 6.7 years. In total, 4,734 patients with CKD were treated with thiopurines. Lymphoma developed in 119 patients who were not treated with thiopurines, in 18 who were treated with thiopurines and 5 who discontinued treatment with thiopurines.

There was a greater development of lymphoma in patients during treatment with thiopurines (HR 4.2; 95% CI, 2.5-5.8), compared to unexposed patients. In contrast, there was no increase in lymphoma in patients who discontinued treatment with thiopurines (HR 0.5; 95% CI, 0.2-1.3), compared to unexposed patients. The study also looked at whether

there was an increased risk of lymphoma during successive years of thiopurine therapy. It was found that the risk of this malignancy in the first 3 years of therapy varied between 1.2-3.8, but without statistical significance. However, after 4 years of therapy, the risk increased significantly to 14.4 times (95% CI, 5.9-14.4) compared to those not treated with thiopurines. These data suggest an increased risk of lymphoma in patients treated with thiopurines and that this risk increases with successive years of therapy with these drugs.

With regard to hematological neoplasms, the study by Ölen et al. (12), carried out in Sweden and Denmark, aimed to analyze the occurrence rates of lymphoma in IBD patients. One of the analyses in this study related the risk of developing lymphoma in patients being treated for CD and UCR compared to matched individuals in the general population. Over the years 2007 to 2019, 38,512 CD patients and 70,777 CKD patients were compared with a tenfold larger group of individuals without IBD. This cohort study showed that in the last 20 years, when the use of immunosuppressants and biological agents became more common, there was a higher risk rate for lymphoma, especially in CD patients exposed to combined therapy of immunosuppressants and biological agents (HR, 2.58; 95% CI, 1.48-4.48) and second-line biologicals (HR, 3.16; 95% CI, 1.90-6.86) compared to individuals without IBD. The same increase in the rate was not observed in UCR. The researchers associated this increase with the greater use of immunomodulatory drugs in CD.

(13) conducted in France, analyzed the impact of thiopurines on the risk of developing myeloid disorders (MD), such as acute myeloid leukemia and myelodysplastic syndromes, in a cohort of IBD patients followed up for 3 years. The study was carried out with 19,486 patients, 60% of whom had CD and 45% had UCR or unclassified IBD, in which

the incidence of DM was calculated considering that the cohort is affected by an incidence similar to that of the general population. The incidence in the general population was estimated using specific rates according to sex, age and subtype of hematological malignancy. The observed number of incident DM cases was divided by the expected number to obtain an estimate of the standardized incidence ratio (SIR). The expected number of DM cases in the cohort was obtained by multiplying the patient-years at risk in each 5-year age group by the corresponding sex- and age-specific incidence rate. Finally, to calculate the incidence of myeloid diseases according to thiopurine exposure, patients who had never received thiopurines were selected from those who had discontinued thiopurines and those who were receiving thiopurines at the start of the cohort.

This study did not find an increased risk of DM in IBD patients being treated with thiopurines compared to patients who had never received the medication, with a SIR of 1.54 (95% CI, 0.05-8.54) and 0.59 (95% CI, 0.02-3.28), respectively. In addition, there was no increase in the risk of DM among IBD patients compared to the general population, with an SIR of 1.80 (95% CI, 0.58-4.20). However, it was observed that patients with previous exposure to thiopurines had an increased risk of DM SIR of 6.98 (95% CI, 1.44-20.36).

Other studies have looked at the relationship between the treatment of inflammatory bowel diseases and gynecological neoplasms. The study by Rungoe et al. (14), carried out in Denmark, assessed the risk of cervical cancer in CD and UC women. In this study, the researchers analyzed the risk of developing cervical neoplasia and the use of drugs for IBD. A national cohort of women diagnosed with UCR (n=18,691 patients), CD (n=8,717 patients), and a control group of women from the general population (n=1,508,334) was established. The drugs in-

cluded for IBD were azathioprine, mesalazine, oral and topical corticosteroids and tumor necrosis factor (TNF- α) antagonists and the patients were divided as users and non-users and followed up during the years 1979 to 2011. Finally, the risk of cervical dysplasia or cancer was investigated according to the number of previous prescriptions, during the years 1994 to 2011.

Thus, in this study, CD patients who had used anti-TNF α had a significantly increased risk of high-grade squamous intraepithelial lesion (LEAG) (RR, 1.85, 95% CI, 1.12-3.04) compared to non-users. This was also not found for UCR (RR, 1.12; 95% CI, 0.45-2.79). None of the cervical cancer cases had received TNF- α antagonists. In addition, the use of mesalazine, azathioprine and corticosteroids had no impact on the risk of cervical neoplasia in CD or UC.

In the analysis of the impact of the number of prescriptions on the risk of cervical neoplasia, the research showed an 8% increase in the RR for LEAG per azathioprine prescription in CD patients (RR, 1.08; 95% CI, 1.04-1.13). In addition, the number of prescriptions for oral corticosteroids (RR, 1.02; 95% CI, 0.98-1.06) or TNF- α antagonists (RR, 1.16; 95% CI, 0.87-1.55) had no significant impact on risk. Finally, cumulative exposure to any of these drugs did not affect the risk of low-grade squamous intraepithelial lesion (LEBG) or cancer in DC or RCU.

The study by Rouvroye et al. (15) aimed to assess the risk of vulvar and vaginal cancer in IBD patients. The study was carried out in the Netherlands with 55 IBD patients (37 with CD and 19 with UCR) who were diagnosed with vulvar intraepithelial neoplasia, vaginal intraepithelial neoplasia or vulvar or vaginal cancer between 1991 and 2015. To analyze the data, the Kaplan-Meier curve was used, which is a graphical representation that describes the cumulative probability of an event

over time in a group of patients. In the article, this method was produced to represent the cumulative incidence of a first recurrence in female IBD patients after successful treatment of their vulvar or vaginal lesion. In addition, a statistical measure (p) was used to assess whether the differences observed in the Kaplan-Meier curves are statistically significant or may have occurred at random. In this study, p -values of less than 0.05 were considered statistically significant.

One of the analyses carried out in this study was the use of immunosuppressive therapy (thiopurines, methotrexate, biological agents) with patient characteristics and vulva-vaginal malignancy. In this sense, it was observed that the use of immunosuppressive therapy is not associated with the risk of vulvar or vaginal cancers and their precursor lesions. Furthermore, the use of immunosuppressive drugs did not influence the risk of recurrence of malignancy, nor did it influence the frequency of recurrence or the years until recurrence.

Furthermore, the subgroup analysis of immunosuppressive drugs showed that for patients who used biological drugs, the age at diagnosis was lower ($p = 0.022$). The mean age at diagnosis in the group of thiopurine users was 58 years, compared to 43 years for the biological drug users and 34 years for the two patients who received both.

Finally, there was no significant difference between users of immunosuppressive drugs and those who had never used them ($p = 0.662$) in the cumulative incidence of a recurrence of vulvovaginal malignancies after successful therapy for the neoplasm.

DISCUSSION

TREATMENT OF INFLAMMATORY BOWEL DISEASES

The treatment of inflammatory bowel diseases is usually carried out in two stages. The

first is induction of remission, which aims to reduce or abolish the patient's symptoms during periods of crisis. The second is maintenance of remission, which aims to ensure that the individual remains relapse-free, symptom-free and with healing of the mucosa (16).

This discussion covered the therapies observed in the results of the studies in order to provide an understanding of the treatment and then discuss the results found.

CLINICAL TREATMENT OF ULCERATIVE COLITIS

Treatment to induce remission

Induction and remission treatment for mild to moderate ulcerative colitis (UC) involves the use of aminosalicilate derivatives and corticosteroids. Traditional therapy includes aminosalicilates such as sulfasalazine and mesalazine (5-ASA). The efficacy of sulfasalazine is comparable to that of mesalazine, but the former has a higher incidence of side effects. Corticosteroids are indicated for mild to moderate active CKD in patients without an adequate response to aminosalicilates at an adequate dose. Immunomodulators such as azathioprine, mercaptopurine and methotrexate are not recommended for inducing remission in CKR due to their slow onset of action and lack of evidence for their effective use (17) .(18)

Treatment of moderate to severe CKD involves corticosteroids for remission induction as the first line, for up to 8 weeks. For patients with no response to corticosteroids, immunobiological therapy is indicated. The choice between anti-TNF α , anti-integrin, anti-interleukin or JAK inhibitor should be made individually, considering patient preference, cost, likely compliance and safety. Aminosalicilate derivatives and thiopurines are not recommended due to lack of evidence or late onset of action (17)(18).

Remission maintenance treatment

Maintenance treatment for CRU mainly involves aminosalicylate derivatives and immunomodulators. Mesalazine compounds are the first choice for patients who respond to mesalazine or steroids, and combination therapy with 5-ASA is more effective than oral or topical monotherapy with 5-ASA. Patients on maintenance high doses of mesalazine, requiring multiple cycles of corticosteroids or becoming dependent or refractory to them, can be escalated to thiopurines or advanced therapy. Thiopurines are useful in preserving remission in steroid-dependent patients (17) (18)

Biological agents are effective in maintaining remission in moderate to severe CKD, increasing the chances of avoiding surgical procedures. In relation to anti-TNF α , infliximab has shown superiority in inducing clinical remission compared to adalimumab. In patients who have achieved remission with anti-interleukin, anti-integrin or JAK inhibitors, these drugs should be maintained in the maintenance phase (17) .(18)

CLINICAL TREATMENT OF CROHN'S DISEASE

Treatment to induce remission

The treatment options for inducing remission in mild to moderate Crohn's disease (CD) are corticosteroids and immunosuppressants. Corticosteroids have a rapid effect and are preferred initially, but prolonged use should be avoided due to side effects. Immunosuppressants are not indicated in monotherapy for remission of luminal CD. However, the combined use of corticosteroids with immunosuppressants can save prolonged corticosteroid therapy, and they are indicated early on (19,20).

In cases of severe CD, the early use of immunobiological agents, such as infliximab and adalimumab, is recommended in the first

2 years after diagnosis, promoting mucosal healing and reducing relapses compared to conventional treatments. The combination of infliximab with thiopurines is more effective than infliximab alone. Anti-integrins and anti-interleukins are used when there is an inadequate response to conventional or anti-TNF α therapy (19,20).

Remission maintenance therapy

Remission maintenance therapy in Crohn's disease (CD) aims to prolong relapse-free periods. Immunosuppressants are used as monotherapy to maintain remission in steroid-dependent and refractory patients. Long-term use of thiopurines is recommended to prevent relapses after reaching clinical remission, while parenteral methotrexate can be used as maintenance therapy if used initially to induce remission. Cyclosporine and tacrolimus are not recommended (19,20).

In moderate to severe CD, immunosuppressants and biological agents are effective in maintaining remission. For patients who have achieved remission with anti-TNF α agents, continued maintenance treatment with the same drug is suggested. The combination of anti-TNF α and thiopurines is effective for both induction and maintenance of remission, with the possibility of maintaining remission with a single biological agent after combination therapy. Anti-integrins and anti-interleukins are used in patients who have achieved remission with these drugs (19,20).

TREATMENT OF INFLAMMATORY BOWEL DISEASES AND THE RISK OF MALIGNANCY

IMMUNOSUPPRESSANTS

Among immunosuppressants, thiopurines are the most widely used in the treatment of IBD. Azathioprine is the most widely used

thiopurine and the most cited drug in the selected studies. It was therefore the drug chosen to be described. This drug acts through its main metabolite, 6-tiguanine, which inhibits DNA synthesis and induces cytotoxicity/immunosuppression (21). This direct alteration of DNA can lead to the activation of oncogenes, a reduction in cancer immunosurveillance and impaired immune control of oncogenic viruses (22).

Several studies conducted with transplant patients have shown that prolonged treatment with thiopurines is associated with an increased risk of various malignancies. In view of this, the International Agency for Research on Cancer (IARC) has classified azathioprine as a human carcinogen (23).

Research has therefore been conducted to assess the safety of thiopurines and the risk of malignancies in IBD patients. Among the studies included in this review, there was an increased risk of skin cancer melanoma (9), lymphoma (11), myeloid disorders (past exposure to thiopurines) (13). However, there was no increased risk of cervical neoplasms (14), vulvovaginal neoplasms (15) and other neoplasms (9).

BIOLOGICAL AGENTS

Tumor necrosis factor alpha antagonists

The anti-TNF α agents available for the treatment of CD mainly include infliximab and adalimumab. These drugs have a dual effect on tumor progression through different predominant molecular pathways triggered after binding to the cell receptor. In this sense, anti-TNF α can stimulate apoptosis through the caspase pathway and tumor necrosis. In addition, anti-TNF α can facilitate the survival and proliferation of neoplastic cells through the NF- κ B cascade (24).

Several studies have been carried out to assess the risk of malignancy associated with anti-TNF α . Currently, there is no evidence of

an overall increase in cancer risk in IBD patients treated with anti-TNF α monotherapy, although the risk of lymphoma and melanoma may be increased (25) (22). In addition, combination therapy between anti-TNF α and thiopurine has shown a higher risk of lymphoma compared to monotherapy with thiopurine or anti-TNF α (25).

From this perspective, studies were analyzed to investigate the safety of anti-TNF α in relation to the risk of malignancies in IBD patients. Among the studies included in this review, it was observed that CD patients, evaluated for cervical neoplasia, on anti-TNF α monotherapy had an increased risk of high-grade squamous intraepithelial lesion (14). However, no increase in malignancy was observed in other types of gynecological cancers, such as vulvar or vaginal (15). Another study showed that IBD patients treated with combined therapy (immunosuppressants and biological agents) had a higher risk of lymphoma (12). However, a second study on the same subject showed that the increased risk of lymphoma in combination therapy was due to immunomodulators (10). Finally, one study showed that there is no increase in the overall risk of cancer in patients treated with anti-TNF α or former users of these drugs (9).

Anti-integrins, anti-interleukins and JAK inhibitors

Biological agents such as anti-integrins, anti-interleukins and JAK inhibitors were not included in the studies analyzed. However, current evidence does not show an increased risk of malignancy in IBD patients treated with these drugs (25).

Anti-interleukin is a monoclonal antibody that blocks pro-inflammatory responses. In this sense, the drug ustecinumab acts by inhibiting the bioactivity of IL-12 and IL-23, which are cytokines that stimulate cells and pathways in the immune system (26).

In addition, anti-integrin is a monoclonal antibody that targets extracellular integrins expressed by intestinal lymphocytes, modulating intestinal inflammation. Vedolizumab binds specifically to the $\alpha 4\beta 7$ integrin, which is expressed on T helper lymphocytes in the gut, inhibiting inflammation (18).

JAK inhibitors are a family of small molecules that block intracellular tyrosine kinases. Tofacitinib inhibits JAK1, JAK3 and, to a lesser extent, JAK2. This inhibition blocks signals from various inflammatory cytokines involved in the pathogenesis of IBD and participates in many immune signaling pathways, including lymphocyte activation, function and proliferation (18)

CORTICOSTEROIDS

Corticosteroids have broad anti-inflammatory effects, as they bind to receptors inside cells and regulate the transcription of various genes. They have immunosuppressive effects by inhibiting the formation of pro-inflammatory cytokines and reducing chemotaxis and the release of lysosomal enzymes by neutrophils and monocytes (27). They can also inhibit apoptosis, allowing cells with cancerous potential to proliferate, and promote angiogenesis, which is an important process in the development of tumors (28).

In this sense, studies have been carried out to investigate the relationship between the development of malignancies and the use of corticosteroids, especially in patients with rheumatological diseases, who use this class of drugs for long periods. The main concern is that their use may promote cancers related to the immune system, such as non-melanoma skin cancer, melanoma skin cancer and non-Hodgkin's lymphoma (29).

However, in the treatment of IBD, the prolonged use of corticosteroids is discouraged. Thus, the carcinogenic effect of these drugs in IBD is not a major problem (24). Among the

studies included in this review, there was an increased risk of melanoma skin cancer, but no increase in the overall risk of neoplasms (9). There was also no increased risk of cervical (14) or vulvovaginal (15) neoplasms.

AMINOSALICYLATES

This group of drugs includes sulfasalazine and mesalazine (5-ASA) and are mainly used for ulcerative colitis. These drugs are no longer used to maintain remission in Crohn's disease because their anti-inflammatory effects are limited topically to the mucosa, with limited effects on deeper inflammation. The mechanism of action underlying the efficacy of sulfasalazine and mesalazine in IBD has not yet been identified. However, in vitro studies have shown effects on immune and inflammatory functions. In this sense, the drug promotes inhibition of IL-1 and TNF α production, inhibition of the lipoxygenase pathway, elimination of free radicals and oxidants, inhibition of PPAR- γ , and inhibition of NF- κ B, a transcription factor fundamental to the production of inflammatory mediators (27) .(19)

Furthermore, no studies were found linking aminosalicylates to extraintestinal neoplasms. In colorectal cancer in IBD patients, recent meta-analyses have shown that the drug 5-ASA may have an antineoplastic effect (30). In this sense, the drug inhibits the pathways that support colon carcinogenesis by negatively regulating the COX-2/PGE2 axis, inhibiting EGFR, NF- κ B and Wnt/ β -catenin signaling, and activating PPAR- γ in colorectal cancer cells, thus modulating cell cycle-related proteins and improving replication fidelity (31) (32).

Thus, studies were analyzed to investigate the safety of aminosalicylate derivatives in relation to the risk of malignancies in IBD patients. The studies showed that there was no increase in the overall risk of cancer in patients treated with aminosalicylates or former users of these drugs (9). With specific regard to cervical neoplasia, mesalazine had no impact on increasing the risk of this neoplasm (14).

CONCLUSION

This integrative review has therefore shown that the studies reviewed present varying results on the impact of treatments for Inflammatory Bowel Diseases (IBD) on extraintestinal malignancy rates.

While some studies do not show a significant increase in the overall risk of cancer with the use of certain drugs, others point to worrying associations. Specifically, an increase in the risk of melanoma was observed in patients treated with corticosteroids and immunosuppressants, as well as an increase in the risk of non-melanoma skin cancer with the use of combined therapy of adalimumab with immunosuppressant. In addition, there is a greater increase in the risk of lymphoma in CD patients undergoing combined therapy of immunobiological agents with immunosuppressants and second-line biologics. As well as an increased risk of myeloid disorders after 4 years of thiopurine use by IBD patients. Past exposure to thiopurines was associated with an increased risk of myeloid disorders. Finally, although an association between immunosuppressive therapy and the risk of vulvovaginal cancer was not identified, the use of anti-TNF α agents increased the risk of high-grade squamous intraepithelial lesions.

This study highlights the complexity in as-

sessing the risk of cancer associated with IBD therapy, since patients are exposed to different drugs throughout their treatment, making it difficult to accurately identify the drug that contributes to the increased risk of cancer. However, although no study has suggested discontinuing medication, preference should be given to those with a more favorable safety profile. Thus, a personalized therapeutic approach to the care of these patients is necessary, taking into account individual factors, the duration of treatment and the specific choice of drugs. Further research is essential for a comprehensive understanding of these associations and to guide safer and more effective therapeutic strategies for IBD patients.

LIST OF ABBREVIATIONS

5-ASA: mesalazine

Anti-TNF: tumor necrosis factor antagonist

CD: Crohn's Disease

IBD: Inflammatory Bowel Disease

MD: myeloid disorders

HR: hazard ratio

JAK: janus kinase

UCR: Ulcerative colitis

RR: relative risk

SIR: standardized incidence ratio

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