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Inflammatory bowel disease: pathogenesis, diagnosis and current therapeutic approach

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ABSTRACT

Inflammatory bowel disease is a group of conditions of unknown etiology, represented by Crohn's disease and ulcerative colitis and characterized by the presence of intestinal wall inflammation. From the first cases described to date, several studies have been performed to elucidate the cause of inflammatory bowel disease. Generally, the genetic factors predispose to their occurrence while epigenetic and environmental factors trigger them. Genetic factors are mutations of the genes involved in the response and recognition of immune cells to different pathogens. The most studied epigenetic and environmental factors are smoking (which predisposes to Crohn's disease and can be protective for ulcerative colitis), lack of vitamin D, a diet rich in sugars and low in flavonoids and fibers. The diagnosis is usually established by endoscopy and biopsy. Recent technologies can perform live biopsies such as endocytoscopy or confocal laser endomicroscopy, with an accuracy of 100% compared to classical methods. Therapy involves several classes of drugs, preferably in association with diet and lifestyle changes. In case of complications or in non-responsive diseases, surgery must be considered, as documented for ulcerative colitis that can be cured by removing the entire colon. The purpose of this review is to present recent findings on pathology, as well as modern diagnosis and treatment methods for IBD.

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Introduction

Inflammatory bowel disease (IBD) is a group of diseases characterized by the inflammation of the intestinal wall. This can include a layer (mucosa) or all intestinal layers, with severe complications such as perforations, stenosis, bleeding, all of which having a major impact on the patients' life quality. The economic impact is major due to the chronic treatment, high hospitalization rates and recurrence [1-3]. This group of diseases includes Crohn's disease/ CD, characterized by the presence of transmural inflammation in any segment of the digestive tract (clinically expressed as diarrhea with steatorrhea, weight loss, fever, abdominal pain, etc.), and ulcerative colitis/ UC, pathology located mainly in the colon - most often rectally, where only the mucosal layer is affected (the main symptom being the occurrence of bloody stools) [4-7]. A subtype of inflammatory bowel disease has also been described, which borrows the characteristics from the CD and UC, or which cannot fall into either of the two major categories. It is classified as unqualified inflammatory disease [8,9]. Their incidence has increased in recent years, occurring in both developed and developing countries, with a different distribution by sex. Crohn's disease is more common in women and is associated with other autoimmune diseases/manifestations (irises, irido-cyclitis, autoimmune thyroiditis, etc.), as well as more frequent digestive complications (perforation with abscess, stenosis and fistula formation) [10].

The etiology of the disease remains unknown today, most likely due to the interaction between immunological genetic factors (imbalance between anti-inflammatory and pro-inflammatory factors, with a predominance of the latter). Other factors are represented by microbiotics (patients with IBD have a microbial flora with a prosthesis activity 9-10 times higher than that of healthy individuals), smoking, a low-fiber diet and a rich processed food diet/ refined food [11,12]. The diagnosis of patients with inflammatory bowel disease is established through colonoscopy (which can reveal the appearance of the

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mucosa, the presence of ulcerations, stenosis and, at the same time, it can procure bioptic material for histopathological examination), computed tomography or MRI scanning [13-15]. The current diagnosis by serologic markers is possible by fecal calprotectin that can distinguish between irritable bowel syndrome and inflammatory bowel disease, with the mention that the fecal level can be influenced by several factors (sex, age, fiber, the presence of blood in the stool, etc.) [16,17].

The treatment of inflammatory bowel disease has undergone significant changes since the discovery of the pathological entity so far, with several classes of drugs being available for administration (amino salicylates, corticosteroids, immunological and molecular treatment). In case of complications, surgical intervention is also required. A breakthrough was the discovery of the treatment that can interfere with the TNF pathway, drugs that can induce the long-term remission. The new therapeutic approach is based on the direct influence of the cellular mechanisms that lead to the gastro-intestinal lesions, the final goal being the healing of the mucosa (elimination of inflammation with the appearance of normal mucosal structure) [18-21].

The purpose of this review is to provide an update on the literature on the causes of IBD, as well as modern methods of diagnosis and treatment.

Discussion

Pathogenesis

The occurrence of IBD is determined by the interaction between several factors, such as: genetic, immunological, environmental and microbiota factors.

Genetic factors

To date, 163 genes have been discovered in patients with inflammatory bowel disease, of which 30 genes are common for UC and CD, suggesting the existence of a common pathological pathway [1]. The NOD-2 gene encodes a protein that functions as an intracellular receptor and it structurally resembles the peptidoglycan on the surface gram-positive and gram-negative bacteria. It helps the immunogenic cells in the process of autophagy, which can control the bacterial replication and modulate the innate and adaptive immune system. It has been observed that mutations of NOD-2 gene can predispose to the occurrence of CD [2]. In the study of the pathophysiology of IBD, it was discovered that autophagy plays a central role, because it can control the intracellular homeostasis by degrading cytosolic elements and organs [3], ATG16L1 also appears to be involved in the intracellular process, and T300A point mutation may predispose to CD. IRGM is a protein which belongs to the p47 immunity-related GTP-ase family, its expression on the epithelial and dendritic cells being often decreased in CD patients [3,4].

Genetic sequencing methods have been used to identify the IL-23 receptor, in order to establish a possible association between its mutations and CD [5]. IL-23 is a pro-inflammatory cytokine that is involved in the generation of T-helper-17 (Th17) cell, being related to the pathogenesis of IBD (with gene loci: IL-23R, IL-12B, JAK-2 and STAT-3) [6,7]. In addition, genetic defects of IL-10, CARD-9, IL-1R2 REL SMAD3 and other immune markers also predispose to IBD [4].

Environmental factors

Environmental factors are involved in the onset and evolution of IBD, among the most studied being: smoking, a diet rich in processed foods, a diet low in fiber and flavonoids, drug use, and psychological factors [8]. Smoking is the most investigated environmental factor, smokers having less often and less severe episodes of UC [9,10], while chronic disease is a risk factor for postoperative IBD [11].

The chronic administration of non-steroidal anti-inflammatory compounds/ NSAIDs and the large-scale use of antibiotics have long been considered risk factors for the development of IBD. It has been shown that the use of aspirin, regardless of the duration of administration, rhythm and doses, does not trigger nor impair the condition of patients with IBD, while the long duration of the treatment and high doses of NSAIDs have been associated with relapses [12]. Chronic antibiotics administration can cause changes in the bacterial flora, predisposing to infections with potentially pathogenic bacteria which further lead to colitis. The dose and the period of administration that would lead to the occurrence of IBD are not yet determined, remaining to be established in future studies [13].

The incidence of IBD has increased proportionally with the level of economic and industrial development, the confirmation being based on epidemiological and ecological studies. It is suggested that air pollution can lead to the increased incidence of IBD (the pathophysiological mechanism being the increase in the plasma levels of cytokines and circulating cells) [14-16], while the increased level of SO2 and NO2 secondary to the burning of fossil fuels can lead to frequent and severe relapses [17].

Vitamin D plays a role in the pathogenesis of IBD, its deficiency being considered a risk factor for their occurrence [18]. The World Health Organization (WHO) classifies the low intake of vitamin D into deficiency (the plasma level of 25-hydroxyvitamin D [25(OH)D] being below 10ng/ml) and insufficiency (in which the level varies between 10-25ng/ml) [19]. In the digestive tract, Vitamin D maintains the integrity of the enteric mucosa, by increasing the number of tight and adherent junctions [20], E-cadherin and also some components of tight junctions (such as occludin and claudin) [21]. Another effect of Vitamin D is to decrease the kinase activity which can

degrade the myosin chain (due to its binding to the nuclear receptor) and prevents the degradation of the tight junctions [22]. Studies concerning the number and the activity of vitamin D receptors in patients with IBD are controversial. Thus, there is only one study that finds a lower number of receptors for vitamin D in subjects with active IBD than in those who did not suffer from it [23], while other two studies do not find statistically significant data between the groups, although they find different numbers of receptors between the normal and the affected mucosa [24,25]. In patients with active IBD, there is a decrease in the expression of Vitamin D receptors, secondary to the mucosal inflammation mediated by TNFα and over-expression of CYP27B1 [26]. Binding the vitamin to the receptor can reduce the activity of claudin-2 (the protein involved in non-specific trans-cellular permeability and apoptosis), thus being a protective factor for IBD [27]. This was confirmed by Garg et al., who administered 10,000 IU of vitamin D daily; after 12 weeks, the serum levels of this vitamin in patients varied between 40-50ng/ml, being accompanied by a reduction of the disease activity on the clinical and endoscopic scale [28].

The consumption of flavonoids in food is considered a protective factor against inflammatory bowel disease, as they have antioxidant properties by decreasing the amount of free radicals (causing changes in the microbiota), thus protecting the mucosal barrier [29]. The antioxidant properties of flavonoids are favorable in inflammatory bowel disease, where the free radicals of oxygen are overproduced secondarily to myeloperoxidase (MPO) and NADPH system activity [30]. In vivo studies have shown that most flavonoids reduce colonic MPO levels by lowering free radical levels, which can be considered a marker for leukocyte invasion and inflammation [31]. Daidzein, hesperidin and naringenin flavonoids are found in citrus fruits, bitter fruits and tomatoes, having a protective capacity on the enteric mucosa by maintaining the integrity of tight junctions. It is currently considered that the hyper permeability of the mucosa is the initiating factor of inflammatory bowel disease [32]. Flavonoids are also involved in modulating the immune system at the intestinal level, decreasing the amount of pro-inflammatory cytokines including TNFα, IL-6, IL-1b via Epigallocatechin gallate [33].

Quercitin is a flavonoid found ubiquitously in fruits and vegetables, and causes a decrease in the amount of macrophages and neutrophils infiltrated in the colon mucosa of patients with CD or UC, thus decreasing the activity of the disease [34]. In patients with IBD, severe dysbiosis occurs with a decrease in the biodiversity of the colon, the main species found being Proteobacteria [35]. This aspect has been identified in mice with induced colitis; addition of Quercetin as a supplement appears to be a favorable factor, by enhancing the biodiversity in the colon and reducing the inflammation [36].

Immunological factors

In the pathogenesis of inflammatory bowel disease, there are changes in the innate and acquired immune system that led to chronic inflammation, secondary to the impaired barrier function of the mucosal layer, changes in the intestinal microbiota and disorders of autophagy [4]. Innate immunity is the first line of defense, being nonspecific and causing a rapid immune response. Its main role is to recognize various antigens through the NOD and TLR receptors, which are found on the surface and in the cytoplasm of various immune cells (neutrophils, dendritic cells, monocytes, etc.) [37]. In patients with IBD, there is an alteration of these two types of receptors. The mutation NOD2 3020insC 2 predisposes to CD. The mechanisms presumed to be involved are the lack of response of the receptor to bacterial lipopolysaccharides [38]. In addition, the lack of activation of the NF-Kb pathway can reduce the antibacterial response and will lead to the appearance of bacterial overpopulation [39,40]. Yet, the lack of inhibition of the RLR2 pathway leads to an excessively immune response modulated by T helper cell 1(Th1) [41].

Interleukin-23 plays an important role in the function of both the innate and adaptive immune system, intervening early in the response to a pathogen; its receptor polymorphism is often associated with the presence of both UC and CD [4].

The acquired immune response is highly specific and it requires a long time to perform the function. Through the Th1 cell, large amounts of IL-12 and IFN-γ are produced, and through Th2 helper cells, IL-4, IL-5 and IL-13 are released [42]. In CD, there are high levels of IL-2 and IFN-γ secondary to increased Th1 cell activity; in contrast, UC has high serum concentrations of IL-13 secondary to natural killer-T cell hyper activation [43,44]. The classical assumption in CD is that the immune response is mediated by Th1 cells, while in UC by Th2 cells [45]. In vivo studies have shown that there are similar levels of INF in both pathologies [46] and that low levels of IL-13 (with anti-inflammatory function) are similar [47]. Bernando et al. identified a mixed cytokine profile with predominancy of IL-6 and the absence of IL-13 in the mucous cell culture of patients with IBD, which therefore leads to a change in the classical conception [48]. Th17 cells are capable of synthesizing large amounts of IL-17, IL-21 and IL-22, which are the result of the concomitant action of IL-6 and transforming growth factor β. IL-17A can be found in large amounts in both CD and UC [49]. The definite role of these cells in the pathogenesis of IBD remains to be investigated, especially in that they express surface receptors for IL-23.

Clinical aspects of IBD

Intestinal manifestations of IBD

The characteristic of **Crohn's** disease is the ubiquitous involvement of the digestive tract from the oral cavity to the rectum and anal canal, which can take great variability.

In classical semiology, a relatively specific pattern is described - the appearance of abdominal pain with colic, weight loss and watery diarrhea [50]. Frequently, abdominal pain occurs prior to the diagnosis of the disease for several years, its location being in the lower-right quadrant because the terminal ileum is affected. The character of the pain is colicky and the intensity is medium to severe. It can often be confused with appendicitis [51]. Diarrhea may be watery, sometimes with the presence of bloody streaks, more frequently in case of rectal damage [52]. Bleeding can also occur many years before the diagnosis of the disease, with 1-2% of cases with a vital threat due to high flow [53]. Weight loss is the third major symptom with a multifactorial cause, presence of chronic inflammation leading to malabsorption and anorexia.

Chronic disease is often associated with the presence of fistula and stenosis. The most frequent type of fistula is between the separate segments of the jejunum, defined as entero-enteral fistula. Most of them are asymptomatic; if the diameter of fistula enlarges, the process can lead to an accelerated intestinal transit with the occurrence of watery diarrhea. The leakage of intestinal fluid through the vagina shows the presence of an entero-vaginal fistula. In a few cases, there may be abnormal communication between the digestive tract and the urinary tract or even the skin. The processes located in the digestive tract can be manifested by colic pain, abdominal bloating or early satiety. For those placed in the stomach or the duodenum, symptoms vary depending on the location [51]. In one third of the cases, patients with CD have anal suffering through the presence of fistulas, abscesses and fissures [54]. The presence of anal fistulas is suggestive for a special clinical form, as these patients have relapses with high and severe recurrence rates that require prompt therapeutic intervention [55].

Regarding **ulcerative colitis**, the symptoms are more stable, the spread of the disease being exclusively in the colon. The time until the diagnosis being much shorter than in the case of CD. The main clinical manifestation of UC is marked by diarrhea (that occurs most often postprandial and at night), its severity correlating with the severity of the inflammation. Regarding the extent of the disease in the colic region, if the proximal part of the colon is affected, a large quantity of mucus and blood will come along with the stool [51]. Massive bleeding with hemodynamic instability is rare, and can be found in cases of ischemic colitis or toxic mega colon, accounting for 15% of the patients [56].

Other symptoms present in patients with UC are abdominal colic pain along with other general symptoms such as asthenia, fatigue and fever. With the long-term evolution of the disease, the appearance of strictures and stenosis can be seen, which can lead to colonic constipation. It can occur in the distal locations of the disease, when the stool is associated with lower digestive bleeding [57].

Extra-intestinal manifestations of IBD

IBD is actually a veritable systemic disease, distant manifestations occurring in addition to the local lesions. Their incidence varies between 6.2-46.6%, thus affecting the quality of life of the patient [58]. It is considered that if one extra-intestinal manifestation appears, the patient is likely to develop other systemic manifestations over time. The way they appear in relation to the time of diagnosis of inflammatory bowel disease can be variable. That is, before the onset of digestive symptoms (8.7-10% of patients, according to the study), concomitantly or in the first month after diagnosis (about 25% of the cases) and in the next two months after the diagnosis for the rest of the patients [59].

The course of extra-intestinal manifestations is not well documented. It is considered that antigenic structures presenting similarities with epitopes of cells in the skin, synovial capsule or periarticular tissue, can pass through the intestinal mucosa triggering a local immune response [60-62]. Patients with CD presenting HLA-A2, DR-1, DQw5 have a significant predisposition to develop extra-intestinal manifestations, which are similar to patients with UC presenting HLADR103 [63]. In the major histocompatibility complex, there are certain subtypes that predispose to several extra intestinal manifestations. For example, HLA-DRB1*0103, HLA-B*27 and HLA-B*58 predispose to articular, dermal and ocular diseases [64,65].

Musculoskeletal manifestations are the most common form of injury in IBD patients (small and axial joints are often affected), being present in approximately 40% of the cases. These include arthritis and peripheral arthritis where there is no joint damage, as opposed to psoriatic arthritis or rheumatoid arthritis [66,67]. This form of arthritis is divided into two subtypes. Type 1 of polyarticular condition usually is pauciarticular, with fewer than 5 joints being affected and associated with HLA-B27, B35, and HLA-DR103 [68]. Large joints (especially the knee) are damaged, and the treatment administered for intestinal manifestations can improve and relieve the joint pain [67]. Type 2 polyarticular condition is characterized by the affliction of more than 5 joints, which does not necessarily correlate with the evolution of the digestive disease, but is instead associated with uveitis [69]. In general, arthritis responds to the NSAIDs (especially COX_2), with the metacarpophalangeal joint being most commonly involved [67,70].

Axial atrophies include ankylosing spondylitis and sacroiliitis, which are less common in incidence (only 25% of patients presenting such symptoms) [71]. In general, men are more likely to develop such arthropathies, especially HLA-B27 positive patients [72]. The evolution is generally progressive and causes significant skeletal damage without treatment [67]. Sacroiliitis usually occurs in HLAB27 negative patients and often causes chronic pain and incapacity of work, which lead to decreased work

capacity and quality of life [73]. In the case of axial arthropathy, the recommended treatment is methotrexate in combination with sulfasalazine and azathioprine, or anti-TNF antibodies of different generations in refractory cases [74-76].

Mucocutaneous damage occurs in about 15% of the patients, the main forms of manifestation being erythema nodosum, pyoderma gangrenosum, sweet syndrome and lesions of the oral mucosa [77].

Erythema nodosum is a nodular skin lesion (with dimensions varying between 0.5-4.5 cm) that is found on the anterior surface of the lower limbs and less often on the trunk or face; it usually appears in patients with CD. Healing is most often possible without scarring. The diagnosis is made clinically based on the characteristic appearance [78]. Regarding the treatment, they respond well to the systemic and/or the local treatment with corticosteroids (CSs) [79]. In severe cases that do not respond to the treatment, the suspicion of another cause of nodules (such as bacterial infections with pseudo tuberculosis, enterocolic, sarcoidosis, tertiary syphilis or drug reactions) may be considered. After their exclusion, there is an upgrade of the treatment with the administration of CSs in immunosuppressant doses, or the treatment with anti TNF. It is worth mentioning that the effect of Infliximab and Adalimumab is superior to other anti-TNF drugs [80-82].

Pyoderma gangrenosum occurs by the presence of a nodule or morbillus that grows rapidly in size and affects the adjacent skin tissue, with the development of a purplish ulcer at the edges with the elimination of sterile pus [83]. The size of the lesions varies from a few centimeters to the surface of a limb. Elective locations are on the extension surface, near the postoperative stoma, but they can occur anywhere on the body surface [84]. It is often associated with UC, with damage of the entire colon and affecting especially woman [85]. The declassifying factor is represented by skin trauma, including venous punctures or biopsies [86].

Regarding the treatment of pyoderma gangrenosum, along with the remission of the colonic manifestations, its remission also appears. The mild forms respond to the local injectable treatment with CSs, the local wound cleaning with wet pads [87]. Sulfasalazine, dapsone or immunomodulatory drugs are administered in refractory cases, in the form of azathioprine, cyclophosphamide, methotrexate, tacrolimus and anti-TNF agents. Most of the time, healing occurs with residual scars [87-89].

Sweet's syndrome is a rare manifestation associated with IBD, characterized by a papular-scaly rash on the hands, feet, torso, or face being associated with fever, arthropathy and ocular symptoms [90,91]. At the histopathological examination, large infiltrates with neutrophils appear. It is often associated with chronic diseases and possible malignancies [67]. The treatment consists in the topical or systemic administration of CSs [92].

The lesions at the level of the oral cavity appear in approximately 10% of the IBD cases, determining the appearance of periodontitis, foot-and-mouth disease, or in severe cases pyosomatitis vegetans (characterized by pustular rashes anywhere on the surface of the oral mucosa) [93]. The treatment requires the administration of local CSs and/ or an antiseptic treatment [94].

Ocular manifestations occur in 2-5% of the patients [68,95], being more common in patients with CD than in UC, especially in subjects younger than 40 years [58,68]. Generally, uveitis and episcleritis (which affects the anterior chamber of the eye) can advance to the retina and the choroid, this process being known as panuveitis. Without a prompt diagnosis, uveitis can lead to vision loss. The treatment with topical steroids can be life-saving; in cases of refractory disease, cyclosporine A can be used [67]. The treatment with Infliximab appears to be the best solution for the patients with uveitis, sacroiliitis and CD [96].

Hepato-biliary damage in IBD consists of stricture and dilatation of the bile ducts, which can lead to intrahepatic lithiasis, cholecystitis, granulomatous hepatitis or hepatic steatosis [97]. It occurs more often in patients with UC than in CD [98]. The dilatations and strictures in the bile ducts appear before the diagnosis of CD and, once formed, they lead to altered bile leakage with the appearance of cholestasis and biliary cirrhosis [99]. The treatment of the underlying disease does not improve the dilatation and the stenosis. However, the administration of ursodeoxycholic acid improves liver functioning. In the case of extra hepatic strictures, the insertion of stents by ERCP procedure can be performed. In the final stage of the disease, a liver transplant is necessary [100].

The diagnosis of IBD

The diagnosis of inflammatory bowel disease is made by correlating the clinical signs and the symptoms with the paraclinical investigations (abdominal ultrasound, lower digestive endoscopy, CT, MRI, etc.) and serological tests, which are used both as a method of initial diagnosis and to monitor the disease evolution.

The endoscopic procedures

Endoscopic procedures play a major role in the diagnosis of inflammatory bowel disease. They are used for diagnosis/ biopsies (to differentiate between CD and UC) on the one hand, and for monitoring the disease evolution (response to treatment and complications) on the other hand [101]. In patients with IBD upon the initial evaluation, colonoscopy is performed in order to evaluate the terminal ileum with the collection of 2 biopsies from 5 different places, including the rectum and the terminal ileum [102]. It is a simple procedure with minimal side

effects, which must be limited on patients with severe forms of colitis or with toxic megacolon. In such cases, it is possible to perform only rectosigmoidoscopy to obtain tissue for the histopathological examination [103]. The classical aspect of UC is the loss of vascularity, erythema of the mucosa with granular and friable appearance, ulcers, erosions and pseudo-polyps. This aspect evolves from the rectum to the proximal level where the intensity gradually disappears [104]. In CD, the classical lesions are represented by the presence of discontinuous ulcers, which give the appearance of paving stone/ cobblestone [105].

In the last decade, the endoscopic equipment has been developed to highlight the presence of inflammation in the colonic and intestinal mucosa, being used to better diagnose/ evaluate the activity of the disease compared to classical endoscopy [106]. Dye-chromoendoscopy uses staining agents (methylene blue/ indigo carmine) that are applied to the mucosa, thus increasing the detective rate of any changes [107]. This investigation helps detect the early and various adenomas that could become malignant, secondary to the inflammation of the mucosa. The sensitivity of the endoscopic examination is correlated with the histopathological data [108,109].

Dye less-chromoendoscopy uses several working systems such as narrow band imaging (a narrow spectrum of light that is absorbed by hemoglobin from the vessels), thus leading to a better highlighting of the vascularization at the level of the organ of interest [110,111]. Compared to classical endoscopy, it is much better in assessing the vascularity which appears to correlate with histological inflammation [112]. The shape of the blood vessels can predict the risk of recurrence. Patients with vessels like bare branches have active disease, while in subjects presenting a honeycomb pattern the disease is often inactive [113]. Other dye-less chromoendoscopy technologies are represented by I-scan, blue light imaging, linked color imaging [110]. The correlation between the histopathological evolution and the endoscopic appearance on the I-scan has been recently investigated. The results are conclusive, with the OE score being largely correlated with two histological activity scores (Robarts histopathology index and ECAP for UC) [114]; similar results have been found in CD [115].

Endocytoscopy is a diagnostic method that allows the in vivo evaluation of the appearance of the mucosa; by obtaining virtual biopsies, it can reach up to 50μm in size [106]. It also correlates 100% with the activity investigated by classical methods (on Riley score) [116]. Recent studies have concluded that endoscopy is able to differentiate between patients with active disease and subjects in remission, without taking biopsies [117]. Confocal laser endomicroscopy is an endoscopic evaluation method that allows the evaluation tissues up to 250 μm [118]. Patients with remitted UC may show distorted crypts, inflammation and abnormal vascular pattern [119]. In patients treated with TNF-alpha inhibitors, the number of affected crypts, the degree of vascular permeability and the degree of inflammation compared to the Gupta score could be assessed, with similarities in 95% of the cases [120].

Upper digestive endoscopy is useful in the evaluation of patients with CD, which can affect the upper portion of the digestive tract in 16% of the cases [121]. In such cases, two biopsies should be obtained from the esophagus, stomach and duodenum when the damage is suspected [122]. The results are characterized by the presence of ulcers, strictures, fistulas and erythema. These damages may be simultaneous or may occur later, when the manifestations appear in the distal part of the digestive tract [123]. In the pediatric population, it is recommended that the initial assessment be made regardless of the onset of the disease and whether upper digestive endoscopy is performed or not [124].

Small bowel capsule endoscopy is a sensitive method of highlighting small bowel damages, being recommended for patients with CD [125]. Since its introduction, technological leaps have been made in terms of image resolution and capsule size, which has led to their widespread use [126]. It is a useful investigation especially in the follow-up of patients, because it is able to diagnose patients with intestinal ulcers, thus allowing a step forward in terms of treatment and preventing the risk of intestinal stenosis and fistulas. At the same time, it evaluates the IBD evolution and response to treatment, allowing thus an anticipation of 6 months before the appearance of a new active form of the disease [127].

Artificial intelligence refers to the ability of computers to function similarly to the human mind, which can be useful for the endoscopic diagnosis of IBD [128]. A Google-based computer aided diagnosis (CAD) system was used to identify the normal mucosa and the presence of mucosal healing (Mayo score 1 for 114 patients with UC), this system recognizing more than 90% of the processed images [129]. Furthermore, with the help of artificial intelligence and based on the appearance of red areas on the endoscopic examination (given by the vascular pattern), the same team developed a red density score. This score correlates with endoscopic (Mayo) and histological activity data, which suggest that the system may intervene in the subjectivity of the investigator in the evaluation of the disease [130].

Imaging evaluation

In the IBD, a large number of imaging methods are used, such as: abdominal plain radiography, barium contrast studies, computed tomography, ultrasound and MRI.

Plain radiography is a simple, easy and inexpensive investigation, being used especially in emergency departments for the occurrence of IBD complications. The

digestive perforation induces pneumoperitoneum, while stenosis on intestinal ulcers appears with hydro-aerial levels and marked distension of the loops above the stenotic area [131]. This is most often completed by a spiral assessment of the abdominal floor such as CT/ MRI or abdominal ultrasound [132]. Fluoroscopic imaging is a method of assessing the digestive tract damages in CD and can be used to investigate both the small intestine and the colon. Regarding the upper digestive tract, the method of investigation has recently been replaced by CT, MRI or enterocapsule [133]. In order to highlight the lesions, it is necessary to mount a nasal-jejunal probe and to insufflate the air or methylcellulose (with the formation of a characteristic double contrast), the appearance of thickening of the intestine suggesting the presence of stenosis [134]. Contrast-based enemas can also be performed, highlighting erosions, ulcers or irregularities in the colon, with the mention that suggestive images result only in the presence of double contrast [135].

Computed tomography

Computed tomography (CT) is one of the first methods of evaluating patients with IBD, due to its availability and effectiveness. It can diagnose both the local complications of diseases (fistulas, abscesses, etc.) and the extraintestinal manifestations (pancreatitis, cholangitis, sacroiliitis, etc.) [131]. By administering intravenous contrast, several changes can be observed, such as the thickening of the mucosa and the mucous layer, the presence of adenopathy/ large nodules obvious in the middle of the affected region or Comb-sign, which is characterized by a turgescent vasa recta [136]. The CT can also be used to evaluate the activity of CD, with a sensitivity of 81% and a specificity of 88%, being able to detect strictures or damage to the peri-intestinal tissues [137]. Regarding UC, the results are moderate, the tomographic evaluation being less correlated with the activity of the disease (a sensitivity of 74%) [138] It is more useful in detecting acute complications of the disease such as toxic megacolon, digestive perforations, etc. [139]. However, CT has limited utility in monitoring disease activity in young patients with IBD, as the effect of ionizing radiation may increase the risk of colon cancer by 7% (in young people) and 16% (in the elderly) [140].

Magnetic resonance imaging

MRI is an imaging diagnostic method that uses non-ionizing radiation. Its availability has recently increased, but it is not frequently used due to the extended time required for a complete evaluation [131]. It can be used to evaluate the small intestine and the perineal area (highlighting lymphadenopathy, fistulas and fissures with different trajectories), thus becoming the gold standard in identification of periintestinal complications [141]. Other signs observed by imaging methods may reveal the parietal thickening of the small intestine, hyper vascularization, abscesses and stenosis [142].

In IBD, the evolution can be investigated by MRI, with a sensitivity and specificity of over 80% in CD [143], and over 85% in UC [144]. An activity score was developed by Rimola-Magnetic Resonance index of Activity/ MaRia score, in which several parameters are included (intestinal wall thickness, contrast loading, edema and ulceration) [145]. The MaRIA score is obtained by quantifying these parameters at the ileal level, colon and rectum. These results are correlated with Crohn's Disease Endoscopic Index of Severity (CDEIS), so the MaRIA score correlates with the disease activity and evolution (a score > 7 appears in the active medium forms, while a score > 11 in the severe forms of the disease) [145,146].

The treatment of IBD

Several medications are currently available for therapy of IBD, such as: amino salicylates, immunomodulators, corticosteroids, biological treatments and small molecules.

Aminosalicylates

Aminosalicylates are represented by sulfasalazine and other 5-aminosalicylic acid derivatives. Sulfasalazine is a compound that has been used for over 80 years in the treatment of IBD [147]. Its mechanism of action is related to the arachidonic acid system, which causes a decrease in the amount of leukotrienes and prostaglandins, the inactivation of reactive and nitrogen reactive species, and the activation of the aryl hydrocarbon receptor pathway (which determines the activation of the tissue growth factor with the accentuation of the tissue recovery) [148,149]. The action of aminosalicylates in UC is documented, as it can induce the remission of the disease regardless of the rate of administration (1 or 2 doses daily) [150]. At the same time, it represents a protective factor for malignant complications, reducing the risk of colon cancer by 75% [151]. Regarding CD, studies have shown that the oral administration of aminosalicylates does not induce remission nor it maintains it [152]. However, their administration for more than 1 year has led to decreased medical costs of hospitalization for severe forms or surgery [153]. Mesalamine, when administered in high doses, induces remission of the disease (in patients with moderate and severe forms of CD) and prevents the administration of steroids [154].

Adverse reactions caused by aminosalicylates are moderate (headaches, abdominal pain and diarrhea) and can be easily managed [148].

Corticosteroids

Corticosteroids (CSs) have the property of inducing the remission of inflammatory bowel disease through a systemic anti-inflammatory effect. It is mediated by the binding of the steroid molecule to the nuclear receptor, which results in low transcription of genes responsible for the pro-inflammatory proteins and stimulation of genes

that are responsible for the anti-inflammatory effects [155]. In IBD, CSs are recommended for patients who have been receiving mesalazine for more than 4 weeks for moderate forms, and only after the complete cycle of the treatment [156]. The systemic route of corticosteroid administration can cause different effects: diabetes, hypertension, immunosuppression predisposing to infections with opportunistic germs, osteoporosis, etc. [157,158]. In the case of long-term use, corticosteroid dependence may also occur, being defined by the use of high doses of steroids for the same or no effect [159]. The second generation of corticosteroids (butensonide) has a higher safety profile than the others, being administered orally with gradual release in the terminal ileum and ascending colon (the pH-dependent capsules decreasing its systemic effects) [160]. For mild or severe forms of CD, with lesions placed on the ascending colon or the terminal ileum, 9 mg daily therapy for 8 weeks is generally effective [156].

Immunomodulators

Thiopurines

T-lymphocytes are an important element in the pathogenesis of inflammatory bowel disease, penetrating the mucosa and releasing pro-inflammatory cytokines, which further cause local lesions. Thiopurines, such as azathioprine and mecaptopurine, inhibit T-lymphocytes proliferation and activation [161]. In an observational study, thiopurines can maintain the remission of UC for 7 years in 43.8% of the cases, and prevent colectomy in 88% of the cases [162]. The effect of azathioprine is favorable in both UC and CD, reducing the rate of hospitalization and preventing postoperative complications [163-165]. In the case of CD, azathioprine determines the remission of the disease and reduces the need for steroids to no dose for 60 months [166]. However, the side effects of thiopurines are multiple and can be life-threatening. Such adverse effects are represented by the suppression of bone marrow, hepatic cytolysis with hepatitis [167] and gastrointestinal disorders [168]. For this reason, 39% of patients discontinue the treatment with thiopurine within the first 3 months [169].

Methotrexate

At low doses, methotrexate causes the inhibition of DNA synthesis, as well as the lowering of the plasmatic levels of IL-1, IL-2, IL-6, IL-18, all this leading to a decrease in the inflammatory response and the activity of T-lymphocytes [170]. Administration of 25mg methotrexate/week can maintain the remission of CD for 40 weeks, the remission being noted in 72% of the patient after 3 months of treatment [171]. Methotrexate side effects are represented by nausea, vomiting, fatigue, and immunosuppression which can lead to atypical pneumonia. Regarding UC, methotrexate has not been proven its efficacy as an inductor treatment [172].

Calcineurin inhibitors

The calcineurin inhibitors used in the treatment of IBD are cyclosporine A and tacrolimus, which inhibit the NEAT system by binding to specific receptors (Cyclophilin A and FK binding protein 12) [173]. In addition, tacrolimus induces macrophage apoptosis and inhibits the release of pro-inflammatory cytokines IL-12, IL-23 and TNFα [174]. Cyclosporine A is indicated in severe forms of UC refractory to treatment, by administration of 4mg/kg. Remission can be achieved in 80% of the patients over 8 days, relatively similar results being obtained with a dose lower than 2mg/kg [175,176]. Regarding the association of CSs with cyclosporine A in the relapses of patients with CD, no advantages were observed compared to the CSs monotherapy [177].

In comparison with cyclosporine, tacrolimus has a 10-20-time stronger effect in vivo and 30-100 times in vitro [178]. It has the ability of inducing the remission of UC and maintaining it for more than 30 days in 70.4% of the cases [179]. At the same time, it prevents the surgical therapy in the evolution of the patients, with rates of up to 69% at 1 year from the beginning of the treatment [180]. Regarding the effect of tacrolimus in CD, the data are controversial; the remission rates is obtained on about 44.3% of the patients, regardless of the route of administration (topical or systemic) [181]. The side effects of tacrolimus are kidney and liver damages, predisposition to infections and hyperkaliemia. The maximum benefit can be obtained by monitoring the plasma level of the drug, which must be maintained at concentrations between 10-15ng/ml [182].

Biologics

Biological treatments target either pro-inflammatory cytokines (TNFα, IL-12, IL-23) or several proteins (integrins). TNFα is a cytokine involved in inflammation, apoptosis and cell proliferation; the overexpression of TNFα gene can lead to various autoimmune diseases [183]. Treatments with anti-TNFα monoclonal antibodies are useful in non-responding patients to immunomodulatory therapy with CSs, or in patients who become dependent on CSs [147]. Infliximab has been shown to be effective; after 54 weeks of treatment, rates of colo-rectectomy and hospitalization decrease by 7% for the patients with mild and severe forms of UC [184]. In CD, 5mg/kg of intravenous infliximab led to remission in 68% of the patients, and the fistula cure rate was 55% [185]. Golimumab, a human monoclonal antibody against TNFα, determines a better cure rate than placebo [186,187], so it is currently used in patients with severe forms of UC and non-responding to conventional treatment [188,189]. Although TNFα plays a central role in the pathogenesis of inflammatory bowel disease (its inhibition being very important for successful treatment), there are patients who

do not respond to treatment in 40% of the cases, and between 23-46% of subjects lose their response to treatment over time [190]. This leads to several strategies of improving the therapeutic efficacy, such as de-escalation after remission, or increasing the period between administrations [191].

IL-12 and IL-23 are pro-inflammatory cytokines released in the antigen recognition reaction by the immune cells, being involved in UC and CD in the onset and maintenance of intestinal inflammation [192]. Structurally, IL-12 and IL-23 have two components, p40 that is a common component, and p35 for IL-12 or p19 for IL-23.

Monoclonal antibodies have been developed, with ustekinumab binding to the common component p40. This component prevents cytokine from binding to its own receptor on the surface of T/ NK cells, thus leading to the inhibition of inflammation. Randomized studies have shown the effectiveness of ustekinumab in moderate and severe cases of UC and CD [193]. By administering it for 8 weeks, the endoscopic activity score of the disease decreased by 2.8 points compared to the control group ($p = 0.012$) [194]. Mirikizumab is a monoclonal antibody against the p19 subunit of IL-23, which leads to the clinical remission of the disease by administration of 200 mg for 12 weeks. No major adverse reactions were observed during the administration of these monoclonal antibodies for treatment induction and/or maintenance [195].

Integrins are surface cell receptors that intervene in the leukocytes localization by binding them to specific cellular receptors, called cell adhesion molecules. Integrin a4b7 is present in the intestine and lymphoid tissue, which allows the migration of leukocytes in the mucosa and adhesion to this level. Patients with inflammatory bowel disease have a high number of such receptors [196]. The accumulation of inflammatory cells aggravates local inflammation by the massive release of INF-γ, TNF-α, IL-17A, which decrease the tissue repair system [197]. Anti-integrin treatment blocks the effect of integrin on endothelial cells/ leukocytes at the time of contact with the intestinal mucosa.

Vedolizumab is a monoclonal antibody that binds to α4β7, thus preventing the migration of lymphocytes to the intestinal receptor and further reducing the degree of inflammation. Phase 3 studies have shown that vedolizumab can maintain and induce the remission of the disease with a high tolerance for patients, without the risk of immunosuppression. The drug has a high selectivity for receptors [198,199], being indicated for patients with moderate or severe UC/CD that do not respond to conventional or anti-TNFα therapy [200]. If the remission of the disease is not achieved, it can be associated with calcineurin or TNFα inhibitors [201,202].

Etrolizumab is an ultra-selective monoclonal antibody that inhibits the β7 subunit of the integrin α4β7 and αEβ7 [197], thus leading to the remission of moderate or severe forms of UC and CD [203].

Biological agents are highly effective, selective and have a low toxicity. Such agents are expensive and the patients may be intolerant or unresponsive to the treatment if used improperly, due to JAK inhibitors that block multiple intercellular or intracellular signaling pathways. However, it can be a solution for unresponsive patients [147]. Tofacitinib is an inhibitor of JAK1 which is found ubiquitously and JAK3 that is found in hematopoietic cells, being useful in the treatment of severe forms of UC [204]. It is able to induce remission after 8 weeks of treatment, the rate of remission in the investigated group being 18.5% higher than in patients in the control group. The best rates of remission of the disease were obtained by administering 10 mg on a daily basis. Long-term side effects are still under investigation; however, thrombosis, infections or the reactivation of varicella-zoster virus may occur in the acute period [205].

Another molecule which was developed and with similar results and uses is filgotinib, which can be administered orally in CD with satisfactory results [206]. If administered in 45 mg doses for moderate/ severe cases of UC, upadacinib may induce the remission of the disease and improve endoscopic score, but with the risk of developing pulmonary embolism or deep vein thrombosis [207].

Novel Therapies

In refractory or unanswered cases, new methods of inducing the remission of the disease have been developed, including apheresis, cell therapy or exome therapy. They are the starting points for possible new therapeutic methods [147]. Apheresis can reduce the local inflammatory response by isolating and absorbing leukocytes from peripheral blood [208], which can induce the remission of the disease in UC. It has a better efficiency than in the case of CSs administration [209]; in some patients, mucosal healing can be achieved with a low rate of incidence of adverse reactions [210].

Changing the intestinal microbiota

In patients with IBD, there is an imbalance between pathogenic and potentially pathogenic bacteria, which determines an abnormal immune response. Several data suggest that changing the microbiota can improve symptoms and even remit the disease [211]. The antibiotic therapy can be considered a future treatment option, by changing the bacterial flora. Administration may induce some additional beneficial effects, such as the reduction of the risk of postoperative complications [212,213]. In patients with CD, the administration of the antibiotic treatment as the inductor of the remission may lead to modest results, inducing a degree of remission of the disease but without marked symptomatic improvement. Consequently, this class of drugs is not indicated in initiating and maintaining the remission of IBD [214].

Administration of probiotics (living microorganisms-lactobacillus and bifid bacterium), prebiotics and symbiotics have a beneficial effect in IBD, especially in UC. Symbiotics can induce and maintain the remission of the disease better than pro and prebiotics [215], and their association with conventional drugs leads to a superior effect compared to single drug administration [216]. The regular consumption of kefir containing lactobacilli can increase the quality of life of patients with IBD [217]. The effects of probiotics are demonstrated especially in UC. As for CD, the effects of the probiotic therapy are controversial [218].

Fecal material transplant (FMT) is a procedure in which the feces of a healthy donor are transferred to a patient with IBD, in order to improve the intestinal microecology and thus to improve/cure the disease [147]. Fecal transplantation is efficient in the treatment of refractory and recurrent IBD with a success rate of up to 90% [219]. The Australian Consensus approved the transplantation of fecal matter in moderate forms of UC for the first time, in order to induce remission of the disease, the efficiency being superior to placebo after 7 weeks of administration [220]. The main advantage of FMT is the restoration of a quasi-normal ecosystem in patients with IBD, by administration of a wide and varied spectrum of bacteria. The higher the success rate and response to treatment of the disease, the greater the variety of bacteria from the donor [221]. The method of administration of transplant material can influence the efficiency of the treatment. The best results are obtained by administering fecal matter through enemas, being able to administer larger quantities and in a more efficient way (than the administration by superior route or by colonoscopy) [222]. One of the shortcomings of fecal transplantation is the inability to determine long-term efficacy, because studies have not monitored patients for more than 1 year [223]. There may be some side effects such as bloating and diarrhea [224], or other reactions related to the oral route of administration: aspiration pneumonia and the perforation of the colon [225].

Stem cells have the ability of differentiating and proliferating on a particular cell line. They have the ability of repairing damaged tissue in IBD, helping to restore the mucosal barrier. The cells involved in the pathophysiological mechanisms of UC and CD are related to hematopoietic/ mesenchymal line, as well as to intestinal mucosa that can be restored (reducing inflammation and inducing the remission of the disease) [147].

Hematopoietic stem cells have the ability of migrating to damaged tissues, helping them with the restoration and regeneration process. In IBD, the cells used for transplant are harvested from the bone marrow, umbilical cord or peripheral blood with CD34 surface marker [226]. Several studies have been published on this topic. For example, 82 patients with CD received stem cell transplants, which led to remission and relief of symptoms in 68% of patients, with a disease-free period of 6-174 months [227]. At the same time, stem cell transplants resulted in a 38% reduction in the need for steroids in these patients after 3 months, half of all subjects achieving mucosal healing [228].

Regarding the safety of this new method of treatment, literature data show that patients need maintenance or rescue treatment after 1 year of treatment [229]. About 80% of the patients reach the initial stage of the disease or require a new transplant after 5 years [230]. All this are associated with an increased risk of severe immunosuppression, leading to viral infections, sepsis and pneumonia. For this reason, it is considered that autologous transplantation may be useful in the refractory forms of the disease that do not refer to other therapeutic methods [231].

ABX464 is an antiviral drug that can be used as the only treatment for HIV patients [232]. It may increase the expression of miR-124 and may inhibit the immune response of patients with IBD [233]. By administering 50 mg/ day of ABX464 orally for 8 weeks, an improvement in the endoscopic appearance can be achieved, without severe side effects [234].

IL-10 is a pro-inflammatory cytokine that may be interfered, decreasing UC and CD activity but leading to long-term anemia or thrombocytopenia [235]. AMT101 is a chimeric protein fragment binding to the IL-10 receptor in lamina propria, which appears to stimulate/ exert anti-inflammatory proteins without side effects [236].

Conclusions

From the initial description of inflammatory bowel disease, many pathophysiological mechanisms have been elucidated and presented. These mechanisms can be interfered with by different therapeutic classes of drugs. To note, such mechanisms are induced by several (genetic, environmental, immunological, and microbiotics) factors, which are interdependent and should not be addressed separately. This means that IBD should be considered a multifactorial systemic disease, which must be treated by complex therapeutic methods.

The diagnosis must take into account the digestive manifestations, including their complications, as well as the extradigestive manifestations, which may be difficult for the clinician to detect.

The treatment must be multimodal on all possible levels, by gradually initiating an appropriate therapy. A treatment upgrade may be necessary in the case of non-responsive forms, and even a rescue therapy when life-threatening complications occur.

Finally, a healthy lifestyle without exposure to stress, pollutants, with a rich diet in flavonoids, regular exercise can help the patients relieve their symptoms and induce/ maintain the remission of the disease.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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