REVIEW

NEW MEDICAL APPROACHES IN CROHN'S DISEASE TREATMENT

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Abstract: *Crohn's disease is a lifelong, relapsing systemic inflammatory disease of unknown etiology, mainly caused by an impaired immune response, characterized by chronic inflammation of any part of the gastrointestinal tract, with an increasing incidence worldwide. This disease is associated with multiple extraintestinal manifestations and patients frequently present persistent diarrhea, abdominal pain and weight loss. It affects people of all ages, but its onset generally occurs at a young age. Several triggers have been implicated in the etiopathology of Crohn's disease, including a dysregulated immune system, an altered intestinal microbiome, genetic susceptibility and environmental factors, but the main cause of the disease still remains an enigma. Due to its debut at a young age, in most cases, a long-term and early established treatment is undoubtedly required to prevent its progression with multiple intestinal and extraintestinal complications. Nowadays, novel biologic therapies or small-molecule drugs may deeply change the innate history of this pathology and could also decrease the rate of complications and the need for surgery. In order to establish the proper diagnosis, endoscopy with the histological evaluation of biopsy specimens represents the most reliable method, even if less invasive biomarkers are being developed. Crohn's disease is a comprehensive disease and the treatment should be adapted to each patient's underlying pathogenetic mechanism.*

Keywords: *Crohn's disease, inflammatory bowel disease, diagnosis, small molecules drugs.*

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Introduction

Chron's Disease (CD) is a life-long, disabling inflammatory disorder that is often diagnosed at a young age and continues to increase in prevalence worldwide [1]. Patients with CD encounter periods of flares and remissions influenced by a complex pathogenesis, where inflammation maintains a decisive role [2]. Since its first description in modern medical literature as regional ileitis by Crohn, Ginzburg, and Oppenheimer in a case series presented at the annual meeting of the American Medical Association in 1932 [3], this pathology has persisted as an unresolved problem for both gastroenterologists and immunologists [3]. Nowadays, powerful brand-new investigative techniques are gradually leading to a better understanding of the major pathophysiological processes underlying this disease, providing this way the necessary means to access new efficient therapies [4].

Epidemiology

This disease arises from a complex interplay between genetic predisposition and environmental influence. Its prevalence has continually increased over the past 50 years,

and despite its worldwide distribution, the highest incidence has been reported in Northern Europe, the United Kingdom and North America [5]. A recent British study, published in 2020, revealed that the prevalence of Crohn's disease has increased from 220 to 400 per 100 000 and that the prevalence of inflammatory bowel disease will likely reach 1.1% by 2025 [6]. This disease has a bimodal distribution, with the onset occurring between 15 - 30 years old and 40 - 60 years old [7].

Etiology

Crohn's Disease is a chronic inflammatory condition that can affect any part of the gastrointestinal tract, from the mouth to the anus, but has a predilection to affect the distal ileum and ascending colon. Although its etiology is still unknown, the interaction between several factors, such as genetic susceptibility and the host's immune response, along with various environmental factors and the intestinal microbiome, is considered to be the main factor that may trigger the apparition of this disease [8].

Its primary patho0physiology is tissue inflammation, which is induced by an uncontrolled immunological response to luminal bacterial antigens. Immune cells like CD4 T-Cells, CD8 T-Cells, B-Cells, CD14 monocytes, and natural killers are involved in this process as they infiltrate the gut of CD patients [3]. There have been identified multiple awareness loci and many genetic factors for CD, including the NOD2 (CARD 15) gene, present on chromosome 16, which is expressed in the bacterial cell wall; people with FUT2 variants, responsible for the secretion of soluble forms of the ABO antigens, have an altered interaction with bacteria and are more prone to developing CD 8 and specific defects in the IL-10 receptor pathway and the Th17 pathway. Moreover, anomalies in the autophagy genes ATG16L1, IRGM, IL-23 receptor gene also increase the risk of CD [8,9].

Environmental factors, including cigarette smoking, a high sugar and fat income, and the so-called „Hygene hypothesis" are involved in the development of this disease. Cigarette smoking has been shown to double the risk of exacerbating CD and also to increase the risk of recurrence. A „clean" environment, which means a reduction in the body's exposure to enteric infections, may also affect the mucosal immune response, resulting in an impairment between the effector and regulatory immune responses [8,9].

Although the microbiome alterations in CD patients still remain unclear, new evidence advocates that the gut microbiota plays a crucial role in developing CD. Even if a single causative infectious agent has not been detected, there have been shown a decreased numbers of bifidobacteria and Faecalibacterium prausnitzii with a higher concentration of Bacterioides and Escherichia Coli in the samples from patients with CD compared to healthy patients. Similarly, listeria, mycobacteria, and measle-like viruses have been involved in the pathogenesis of CD, and their etiologic role is highly disputed. While the search for an infectious cause is still in progress, it seems more reasonable that its etiology is polyfactorial [8,9,10].

Clinical Features

Whereas CD most often has an insidious debut, this condition can also present as an acute toxic illness and its symptoms can be heterogeneous and subtle. One of the most common seen scenarios of Crohn's Disease is a young patient, typically complaining of abdominal pain (right lower quadrant), flatulence or bloating, diarrhea (which can include mucus and blood) or steatorrhea (in small bowel disease), fever, malabsorption, notable weight loss, even anorexia and anemia. Moreover, aphtous ulcerations of the mouth are usually observed [7]. In children, delayed puberty and a stagnation in the growth rate can also be perceived [8]. The

anus should always be examined because, in some cases, CD can become complicated by anal and perianal disease, such as abscesses, ulcers, fistulas, scarring, and cutaneous fistulas. Enteric fistulae to the bladder, abdominal wall, or vagina may also occur in 20-40% of cases, with the patient presenting pneumaturia, repetitive urinary tract infections, and feculent vaginal discharge [7,8]. Furthermore, in certain circumstances, Crohn's Disease is associated with extraintestinal features, that can affect different sites of the body, such as:

- Eyes: episcleritis, uveitis, conjunctivitis;
- Liver and biliary tree: fatty liver, chronic hepatitis, cirrhosis, gallstones, cholangitis, primary sclerosing cholangitis;
- Kidneys: nephrolithiasis, hydronephrosis, urinary tract infections;
- Joints: arthritis (spine - sacral, knee, ankles, hips, wrist, elbows), ankylosing spondylitis, arthralgia, inflammatory back pain;
- Skin disorders: erythema nodosum and pyoderma gangrenosum;
- Venous thrombosis: deep vein thrombosis, stroke or pulmonary embolism.

Diagnosis

The diagnosis of Crohn's Disease is established on the basis of endoscopy, radiological imaging, and/or histologic findings that prove the transmural inflammation of the luminal gastrointestinal tract in a patient with notable clinical manifestations (abdominal pain, chronic diarrhea). Blood and stool tests are complementary in assessing the severity and complications of Crohn's Disease, but they do not indicate the final diagnosis [11].

Routine laboratory tests may reveal anamia, which is commonly found, and it can be normocytic, normochromic, with an elevated C-reactive protein and erythrocyte sedimentation rate (ESR), hypoalbuminemia, iron and/or folate deficiency, and vitamin D deficiency [8,11]. If diarrhea is present, stool tests should always be performed. Fecal calprotectin is known to be extremely sensitive in detecting colonic inflammation, being raised in an active intestinal disease and it is also useful to predict the relapses of the disease [12]. Positive ASCA and negative pANCA antibodies represent a specific and sensitive test for Crohn's Disease, also being effective when taking into consideration the differential diagnosis with ulcerative colitis [5]. Epithelioid granulomas, transmural inflammation, "skip lesions," active and chronic inflammation, such as neutrophil-predominant cryptitis, and crypt abscesses or ulcers with chronic architectural changes are some of the classic histological signs [13].

Although the diagnosis of Crohn's Disease does not involve a single test and there is no single gold standard investigation being used, a full ileocolonoscopy with biopsies is the most universally used diagnostic investigation [5]. A solitary normal finding on ileocolonoscopy is insufficient to exclude the diagnosis of CD because approximately 27% of patients have disease situated to the terminal ileum. A relatively new and quite simple imaging technique, having the advantage of being non-invasive, is that of capsule endoscopy, which is gaining acknowledgement for small bowel exploration [5,8]. Colonoscopy or sigmoidoscopy, used in patients with severe disease, are performed when the colonic involvement is taken into consideration. As CD can also affect the upper gastrointestinal tract, upper gastrointestinal endoscopy may be required to exclude the involvement of the oesophagus or duodenum. Ultrasound scanning is a radiation-free method that can be performed at the bedside and if there is suspicion of small bowel involvement as an area affected by the disease, another non-invasive imaging technique that must be included in the local expertise is computed tomography enterography (CTE). This

technique utilizes neutral oral contrast agents and intravenous contrast medium in pursuance of identifying small bowel inflammation and visualizing the extra-enteric structures. In order to decrease the ionizing radiation that the use of the CT involves, the MRI, including MR enterography (MRE) and enteroclysis (MREC), is capable of demonstrating a wide range of pathological features of CD. F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) or radionuclide scans, such as Indium or Technetium-labeled leucocytes, may be performed in some highly specialized centers not only for initial diagnosis and for a more targeted overview of the small intestine and colonic inflammation but also for therapeutic response monitoring, suspected recurrence and to identify extraintestinal abcesses [8,14,15].

Differential Diagnosis

In order to establish a proper diagnosis of CD, especially if the pathology is uncertain, a few other differential diagnoses must be taken into consideration a few other differential diagnosis, such as ulcerative colitis, amebiasis, intestinal tuberculosis, drug-induced colitis and other conditions that are associated with small bowel fissuring ulcers [9].

CD and ulcerative colitis (UC) are two idiopathic inflammatory bowel disorders which are defined by chronic and relapsing inflammation of the bowel. Between these two conditions, there is a high degree of overlap in their clinical features, aetiopatogenesis and histological abnormalities. In UC the inflammation is generally limited to the colon, suffering a mucosal continous process, worse distally, with an increased span of involvement distal to proximal, as the disease progresses apart from minimal distal "back-wash" ileitis. The mucosa may appear reddened and inflamed and it can have a high degree of friability. The presence of granulomas is not often encountered. Moreover, UC usually includes only the mucosal layer of the bowel, and, in some cases, the superficial submucosa, unless there is fulminant colitis (toxic megacolon). In addition, the serologic findings in UC are usually positive for pANCA antibodies and negative for ASCA [8,9].

Amoebiasis is one of the diseases that must be taken into considerations in the differential diagnosis of CD. Amoebic colitis, which is a parasitic disease caused by the protozoa Entamoeba histolytica, is normally subacute and, in some cases, even asymptomatic, manifesting itself with diarrhea, abdominal pain, and rectorrhagia. Given these symptoms, infections like Escherichia Coli, Campylobacter, or Shigella should be taken into account to perform a differential diagnosis. The liver abscess is its most common extraintestinal manifestation, which is frequently associated with high fever and pain in the right hypochondrium [16].

Nonsteroidal anti-inflammatory drugs (NSAIDs), methyldopa, gold and penicillins can produce granulomatous reactions that can mimic CD. They can lead to a so-called drug-induced colitis, with several disorders that can manifest with full-thickness ulcers and resultant chronic crypt architectural remodeling. Mucosal injury can be focal or extensive, involving the entire colonic mucosa, and sometimes it can involve other parts of the gastrointestinal tract. In some cases, this type of colitis may resolve with the discontinuation of medication [9,17].

Gastrointestinal tuberculosis can occur as a primary infection or in the context of active pulmonary disease, caused by sputum ingestion or by hematogenous or lymphatic spread through infected lymphatic nodes, with the ileocecal region as its most frequently affected site. The diagnosis is often a difficult one, and it can be delayed because of its non-specific presentation. In order to detect intestinal tuberculosis, at least one of the following criteria must be encountered: acid-fast bacilli may be isolated from clinical specimens, the presence of caseating

granulomas on the histopathological investigation or the complete clinical recovery along with the healing of the gastrointestinal mucosa after 6 months, or even longer, of antituberculosis treatment [18,19].

Fissuring ulcers may also be observed in other pathologies, such as Behcet's disease, celiac sprue, or malignant lymphoma. Behcet disease is a very rare vasculitic disorder, characterized by the presence of oral and genital aphthous ulcers and uveitis, and the ability to affect small, medium and large vessels. Its diagnosis is based on clinical criteria, as there is no specific diagnostic test that can be used [9,20].

Treatment

In order to obtain proper management of CD, decisions should always be reached through a discussion between a multidisciplinary team and, of course, the patient itself. Smoking should be avoided and a healthy diet, rich in fruits and fibers, has been demonstrated to have numerous benefits [13].

1. Pharmacological treatment:

Corticosteroids: The use of oral corticosteroids such as Prednisone was once a mainstay of IBD treatment, but now it is typically reserved to induce remission in moderate to severe attacks of CD. These medications are associated with many unfavorable side effects, such as osteoporosis, high blood pressure, Cushing's disease and diabetes. Budesonide, being a glucocorticoid with a limited intestinal action and a lower systemic bioavailability, may be a better option [21].

5-aminosalicylates: In patients with inflammation limited to the rectum and sigmoid colon, this class of drugs, which contains 5-aminosalicylic acid, such as Sulfasalazine and Mesalamine, is often prescribed. These drugs are usually well tolerated, but blood tests should be performed every few months, in order to monitor hepatic and renal function [8,21].

Immunosuppresive drugs: These agents have variable efficacy and different indications. Azathioprine, methotrexate, 6-mercaptopurine, tacrolimus and cyclosporin are the most frequently used, representing conventional maintenance remission therapy. These medications have the ability to reduce inflammation in the gastrointestinal tract by suppressing the immune system. Due to their numerous side effects (liver injury, bone marrow suppression), their usage is declining, and sometimes it is more preferable to use them in lower doses with biologic medications for a better enhancement of treatment [22].

Biologic therapies: Although this class of medications was historically reserved for the treatment of severe cases, the modern approach to CD nowadays suggests that they should be used as a first-line approach, becoming the standard first-line therapy in the care of patients. With many ongoing trials and newly discovered agents, this therapeutic approach is promising and proving to be a rapidly developing area [23].

1. Anti-TNF alpha therapies: Notwithstanding the fact that the exact mechanism of action is still not fully defined, these medications block the tumor necrosis factor (TNF) and induce cell apoptosis. Available anti-TNF agents consist of infliximab, adalimumab and certolizumab pegol, and they have led to improved rates of both response and remission in patients. These drugs can induce anti-drug antibodies and can become less effective if they are not used on a regular basis [24].

2. Anti-IL-12/23: These therapies have the ultimate goal of treating Crohn's Disease while minimizing the side effects that commonly appear and reducing intestinal inflammation by inhibiting specific pro-inflammatory proteins, such as interleukin-12 and interleukin-23. They are currently used to treat moderately to severley active CD in those patients who are not responding enough to anti-TNF-alpha agents. Ustekinumab is already FDA-approved to treat CD and it has

proven its efficiency. Risankizumab was FDA-approved in June 2022 to treat patients with moderately to severely active Crohn's disease. Three other monoclonal antibodies, mirikizumab, brazikumab and guselkumab are currently in advanced clinical trials for CD [25].

3. Anti-Integrin: Vedolizumab (Entyvio), which is an anti- α4β7 integrin therapy, reduces leucocyte recruitment to the inflamed intestine. It is used both in induction and maintenance therapy. This drug may be administered as IV infusions or subcutaneous injections. It was approved worldwide as an intravenous [IV] 300 mg formulation to treat moderately to severely active CD and in 2020 a SC formulation of Vedolizumab [Vedolizumab SC] was developed to provide an alternative route of Vedolizumab administration for use in UC and CD in Europe, Canada and Australia as maintenance therapy (108 mg every 2 weeks) [8,26].

Small molecule drugs (SMDs): Despite the fact that the anti-TNF-alpha, anti-integrin, and anti-IL12/13 medications have substantially improved the management of Crohn's Disease, because of the anti-drug antibody formation, their effectiveness is not always as expected. In order to tackle this issue, therapy with SMDs, which are orally administered, has been newly established. These medications use a broad range of novel pharmacological pathways and they may even lack of immunogenity [23,27].

1. JAK inhibitors: These therapies interfere with the activity of Janus kinases (JAK), being targeted therapies that work on the body's inflamatory immune response. Upadacitinib is the first oral agent and distinguishes itself from the injectable biological therapies used in CD, by being well-tolerated both in the induction and maintenance phases, representing a promising agent. It was FDA-approved in March 2022 and it was associated with superior endoscopic outcomes at 12 weeks and 1 year compared with placebo among people with moderately to severely active CD, and it was efficient in patients with previous failure of biologic therapy. Upadacitinib has the main advantages of a single oral daily administration, a fast onset and a low risk of immunogenicity [28,29].

2. S1P receptor modulators: This class of medication blocks the receptor of a signaling fat molecule called S1P and its effect is to reduce inflammation and the immune response. Ozanimod, an oral agonist of the S1P receptor subtypes 1 and 5 decreases the number of circulating activated lymphocyteswas and was approved in May 2021 for the treatment of moderate to severe UC. Ponesimod and Etrasimod, which are currently in phase 3 trials for the treatment of IBD, are another two selective S1P modulators that are on the verge of proving their effectiveness in IBD treatment [30].

3. Anti-sense oligodeoxynucleotide to SMAD7- Monsergen, an oral anti-sense oligonucleotide, that restores TGF-beta 1 signaling and decreases the output of pro-inflammatory markers, is another promising new treatment for CD, phase 3 studies ongoing [8,31].

Stem cell therapy, mostly including hematopoietic stem cell therapy and mesenchymal stem cell therapy, has shown the potential to improve the clinical disease activity of patients when pharmacological treatments are not effective. Nevertheless, this type of therapy is still in the research stage. Stem cell therapy, an emerging therapy for IBD, may have the ability to both repair and regenerate the damaged tissue and may ease the mucosal inflammation. In this manner, this therapy can help to enhance symptoms such as abdominal pain and diarrhea and may even hinder the disease's advancement. Darvadstrocel (Cx601), the only commercially available mesencymal stem cell preparation approved by The United States Food and Drug Administration (FDA), can be used in the treatment of CD, complicated by perianal fistula [32,33].

Surgical management: While pharmacological treatment remains the first

treatment option, almost 80% of people with Crohn's disease will eventually require surgery at some point in their lives. As recurrence is almost unavoidable, surgery should be performed only under special medical conditions and minimal resections are preferred. Some common types of surgeries implemented in Crohn's Disease include:

- Stricturoplasty, where some strictures, which are complications commonly encountered, can be widened;
- Fistula removal;
- Colectomy or panproctocolectomy with ileostomy, when the disease involves the colon; the ileostomy may be temporary, in order to reduce the inflammation, or permanent;
- Bowel resection;
- Abcess drainage [8].
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Prognosis

The life expectancy in those with Crohn's Disease is mildly reduced compared to the general population, due to the risk of developing malignancies and multiple complications of different organs (liver, genitourinary tract, biliary tract). Almost half of the patients will need a surgical resection within the first 5 years of the disease, and pharmacological treatment should be initiated in the first years of the disease. An extensive small bowel disease, young adults (<20 years old), serious ulcerations, and complicated perianal disease represent some of the poor prognosis factors [8,34].

Conclusions

The management of this disease requires a multi-speciality team, including gastroenterologists, primary care physicians, surgeons, oncologists and many others. Despite the fact that there is no cure for Crohn's Disease, nowadays the overall mortality has decreased steadily, owing to new pharmacological therapies, that have greatly expanded the treatment options available for the management of this disease.

Author Contributions:

M.I.M. conceived the original draft preparation. M.I.M. was responsible for conception and design of the review. M.I.M. was responsible for the data acquisition and for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content.

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