Update in the diagnosis and management of inflammatory bowel disease.

A Research Project

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(اقْرَأْ بِاسْمِ رَبِّكَ الَّذِي خَلَقَ (1) خَلَقَ الإنسَانَ مِنْ عَلَقٍ (2) اقْرَأْ وَرَبُّكَ الأَكْرَمُ (3) الَّذِي عَلَّمَ بِالْقَلَمِ (4) عَلَّمَ الإنسَانَ مَا لَمْ يَعْلَمْ (5))سورة العلق

صدق الله العظيم

Abstract

Inflammatory bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder, which can affect all members of a society, regardless of age, sex, race or socioeconomic status. Because of its high prevalence and chronic nature, it represents a significant economic burden. In fact, these patients have a relevant impairment of their quality of life, which limits their work productivity and daily social activities, especially when it is associated with other disorders, such as anxiety and depression. The diagnosis of IBS relies on symptom-based diagnostic criteria with normal results on a limited number of complementary tests that rule out other possible diagnoses. The aetiology of this condition is incompletely established. However, evidence suggests that it is a multifactorial disorder with several different mechanisms that have been implicated as responsible for the symptoms. Since the treatment strategy is usually based on predominant symptoms and their severity, it is important to recognise the underlying mechanisms in order to successfully relief the visceral pain and altered bowel habits. The aim of this review was to explore the update in the diagnosis and management of inflammatory bowel disease.

Contents

LIST OF ABBREVIATIONS

IBD	Inflammatory Bowel Disease
UC	Ulcerative Colitis
CD	Crohn's disease
PSC	Primary sclerosing cholangitis
TB	Tuberculosis
CBC	Complete blood count
HBV	Hepatitis B virus
HIV	Human immunodeficiecy virus
HCV	Hepatitis C virus
VZV	varicella zoster virus
IgG	Immunoglobulin G
p-ANCA	Perinuclear antineutrophil cytoplasmic antibody
ASCA	anti-saccharomyces
TPMT	thiopurine methyltranferase
TNF	Tumor necrosis factor
CMV	cytomegalovirus

SES-CD	simple endoscopic score for Crohn’s disease
CDAI	Crohn’s disease Activity Index
CXR	chest x-ray
SCD	specific carbohydrates diet
CBT	cognitive-behavioral therapy
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
5-ASA	5Aminosalicylates
6-MP	6 mercaptopurine
HACA	Human anti-chimeric antibodies
PPD	purified protein derivative
CDP-870	Certolizumab pegol
MS	multiple sclerosis
S1PR	sphingosine-1-phosphate receptor
PDEs	phosphodiesterases

CHAPTER 1
INTRODUCTION

1.1Introduction

Inflammatory bowel disease (IBD) is a group of idiopathic chronic inflammatory intestinal conditions. The 2 main disease categories are Crohn's disease (CD) and ulcerative colitis (UC), CD and UC are characterized by a course of remission and relapse with complex interactions among genes, the environment, and immunity(1)The pathogenesis of IBD is incompletely understood. Genetic and environmental factors such as altered luminal bacteria and enhanced intestinal permeability play a role in the dysregulation of intestinal immunity, leading to gastrointestinal injury.(2)subtypes of IBD are Crohn's disease (CD) and ulcerative colitis (UC). CD can affect any portion of the Gl tract from the mouth to the anus in a non continuous fashion and is characterized by transmural inflammation. UC usually affects the rectum. It may extend continuously to affect other parts of the colon, and is characterized by inflammation limited to the mucosal layer (3)Distribution patterns of disease with (A) skip lesions in Crohn's disease and (B) continuous involvement of the colon, beginning with the rectum, in ulcerative colitis.(4)Crohn's disease is a chronic, inflammatory bowel disease that mainly affects the gastro-intestinal tract. It is characterised by thickened areas of the gastro-intestinal wall with inflammation extending through all layers, deep ulceration and fissuring of the mucosa, and the presence of granulomas; affected areas may occur in any part of the gastro-intestinal tract, interspersed with areas of relatively normal tissue. Crohn's disease may present as recurrent attacks, with acute exacerbations combined with periods of remission or less active disease. Symptoms depend on the site of disease but may include abdominal pain, diarrhoea, fever, weight loss and rectal bleeding. Complications of Crohn's disease include intestinal strictures, abscesses in the wall of the intestine or adjacent structures, fistulae, anaemia, malnutrition, colorectal and small bowel cancers, and growth failure and delayed puberty in children. Crohn's disease may also be associated with extra-intestinal manifestation: the most common are arthritis and abnormalities of the joints, eyes, liver and skin .Crohn's disease is also a cause of secondary osteoporosis and those at greatest risk should be monitored for osteopenia and assessed for the risk of fractures.(5)Ulcerative colitis is a chronic inflammatory

condition characterised by diffuse mucosal inflammation—it has a relapsing-remitting pattern. It is a life-long disease that is associated with significant morbidity. It most commonly presents between the ages of 15 and 25 years, although diagnosis can be made at any age. The pattern of inflammation is continuous, extending from the rectum upwards to a varying degree. Inflammation of the rectum is referred to as proctitis, and inflammation of the rectum and sigmoid colon as proctosigmoiditis. Left- sided colitis refers to disease involving the colon distal to the splenic flexure. Extensive colitis affects the colon

proximal to the splenic flexure, and includes pan-colitis where the whole colon is involved. Common symptoms of active disease or relapse include bloody diarrhoea, an urgent need to defaecate, and abdominal pain. Complications associated with ulcerative colitis include an increased risk of colorectal cancer, secondary osteoporosis,

venous thromboembolism, and toxic megacolon.(6)

1.2.Clinical features of IBD

IBD is a chronic, intermittent disease. The symptoms range from mild to severe during relapses, and they may disappear or decrease during remissions. In general, the symptoms depend on the segment of the intestinal tract involved.

1.3.Symptoms Related to Inflammatory Damage in the Digestive Tract

- Diarrhea
- Stool may contain mucus or blood. Nocturnal diarrhea.
- Incontinence
- Constipation:

May be the primary symptom in UC limited to the rectum (proctitis). Obstipation with no passage of flatus can be seen in cases of bowel obstruction. Pain or rectal bleeding with bowel movement. Bowel movement urgency.

- Tenesmus.

- Abdominal cramps and pain: In the right lower quadrant of the abdomen common in CD, or around the umbilicus, in the lower left quadrant in moderate to severe UC
- Nausea and vomiting may occur, but more so in CD than UC. (7)

1.4.General Symptoms Associated With UC and CD in Some Cases

- Fever.
- Loss of appetite.
- Weight loss.
- Fatigue.
- Night sweats. Growth retardation.
- Primary amenorrhea.

1.4.1.Extraintestinal manifestations include

Musculoskeletal conditions (erythema nodosum, pyoderma gangrenosum), ocular conditions (scleritis, episcleritis, uveitis), and hep- atobiliary conditions (PSC) (8)

1.4.2.Complications

1.4.2.1.Intestinal Complications

Hemorrhage: profuse bleeding from ulcers occurs in UC. Bleeding is less common in CD. Massive bleeding in CD is more often seen due to ileal ulceration than in colitis.

About 5% to 10% of individuals with CD show ulceration in the stomach or duodenum.

Bowel perforation is a concern in CD, and in both CD (if the colon is involved) and UC if megacolon ensues. Intra-abdominal abscesses in CD. Strictures and obstruction (narrowing of the bowel may be due to acute inflammation and edema, or due top

chronic fibrosis):

1.4.2.2.in CD are often inflammatory:

(i) Inflammatory strictures can resolve with medical treatment .

(ii) Scarring (fixed or fibrotic) strictures may require endoscopic or surgical intervention to relieve the obstruction.Colonic strictures in UC are presumed to be malignant until proven otherwise.

1.4.2.3Fistulas and perianal disease:

These are a hallmark of CD.

(i) Surgical intervention is required in cases that do not respond to medical treatment, or when abscesses have developed. Sometimes surgical treatment should be pursued concomitantly with medical therapy, especially in instances of complex fistulas.

(ii) There is a high risk of recurrence. Fistulas to the urinary tract or vagina are not uncommon and can lead to pneumaturia or fecaluria, or passage of air from the vagina. This may result in urinary tract infection or gynecologic inflammation.(9)

1.4.2.4.Toxic megacolon:

This is a relatively rare, life-threatening complication of colitis (characterized by dilation of the colon)diagnosed on plain abdominal radiography) that requires aggressive medical therapy and urgent surgical intervention if there is no response within 24 hours (more common in UC than CD). (11)

1.4.2.5.Extraintestinal Complications

Extraintestinal complications should be differentiated from extraintestinal manifestations, and they may be related to disease or to drugs used for IBD, for example, drug-induced arthropathies (corticosteroids, biologicals);

- ocular complications (corticosteroid-induced glaucoma or cataracts);
- hepatobiliary complications (gallstones, fatty liver);

- renal complications (drug-induced tubulointerstitial nephritis); anemia (iron or vitamin B12 deficiency, or thiopurine-induced cytopenia); bone complications (osteoporosis and fractures); venous thromboembolic

disease; and mood and anxiety disorders. They affect up to 25% of those with IBD, although 15% to 20% have arthralgias, whereas the remainder have frank inflammatory disease in other organ systems. Some complications may antedate the diagnosis of IBD, and some may run an independent course from the IBD (even colectomy in UC does not affect the course of ankylosing spondylitis or PSC—although for many, arthralgia activity parallels the activity of the bowel disease).(10)

1.5.DIAGNOSIS OF IBD

The diagnosis of IBD in adults requires a comprehensive physical examination and a review of the patient's history. Various tests, including blood tests, stool examination, endoscopy, biopsies, and imaging studies help exclude other causes and confirm the diagnosis.(12)

- Patient History

Ask about symptoms—diarrhea (blood, mucus), abdominal pain, vomiting, weight loss, extraintestinal manifestations, fistulas, perianal disease (in CD), and fever. Inquire as to whether any of the presenting symptoms has occurred at any time in the past (not uncommonly, flares of disease have gone undiagnosed in the past). Duration of current complaints, nocturnal awakening,missing work, or usual social activities. Inquire about possible extraintestinal manifestations including, but not limited to, arthritis, inflammatory ocular disease, skin diseases, osteoporosis and fractures, and venous thromboembolic disease. Identify whether mood disorders are present, or stressful situations known to precipitate IBD. Recent and past medical problems intestinal infection. History of TB and known TB contacts.(13)

- Travel history.

- Medications—antibiotics, nonsteroidal anti-inflammatory drugs, and others like corticosteroids for acne. Family history (IBD, celiac disease, colorectal cancer, TB).
- Cigarette smoking.
- Physical Examination General:
- General well-being. Pallor.
- Cachexia. Clubbing.
- Nutritional status.
- Pulse rate and blood pressure. Body temperature.
- Body weight and height

Abdominal region:

- Mass. Distension.
- Tenderness, rebound, guarding. Altered bowel sounds (obstruction). Hepatomegaly.
- Surgical scars. Perianal region: Tags.
- Fissures.
- Fistulas.
- Abscess.

Digital rectal examination (assess for anal strictures, rectal mass).

Extraintestinal inspection

mouth, eyes, skin, and joints:

- Aphthous ulcers. Arthropathy.
- Uveitis, episcleritis. Erythema nodosum.

- Pyoderma gangrenosum.
- Sweet's disease (acute neutrophilic dermatosis).
- PSC (manifestations of chronic liver disease). Metabolic bone disease. (14)

1.5.1.Laboratory Tests

1.5.1.1.Stool Examination

Routine fecal examinations and cultures should be carried out to eliminate bacterial, viral, or parasitic causes of diarrhea.Testing for Clostridium difficile (should be considered even in the absence of antecedent antibiotics) should be carried out within 2 hours of passage of stools.A check for occult blood or fecal leukocytes should be carried out if a patient presents without a history of blood in the stool, as this can strengthen the indication for lower endoscopy.Where lower endoscopy is readily available, these tests are rarely indicated.(15)Lactoferrin, a1-antitrypsin. The main reason for listing this test is to rule out intestinal inflammation, rather than using it as a positive diagnostic test. It may not be available in developing countries, but it can be under taken relatively inexpensively and easily with rapid turnaround slide-based enzyme-linked immunoassay (ELISA) tests. Calprotectin a simple, reliable, and readily available test for measuring IBD activity—may be better for UC than CD; the rapid fecal calprotectin tests could be very helpful in developing countries.17 If available, a home test may be useful as a routine for follow-up.(15)

1.5.1.2.Blood Examination

Complete blood count (CBC).Erythrocyte sedimentation rate, C-reactive protein (CRP), and orosomucoid; levels correlate imperfectly with inflammation and disease activity. Electrolytes and albumin, ferritin (may indicate absorption or loss problems), calcium, magnesium, and vitamin B12. Serum ferritin may be elevated in active IBD, and may be

in the normal range even in the face of severe iron deficiency. Transferrin saturation can also be assessed to evaluate anemia. The soluble transferrin receptor assay is also a good measure of iron stores, although it is expensive (and also involves an acute-phase protein) and not commonly available. Decreased serum cobalamin may indicate malabsorption. Liver enzyme and function testing international normalized ratio, bilirubin, and albumin. Human immunodeficiency virus (HIV)additional opportunistic infection work-up, hepatitis B virus (HBV), hepatitis C virus (HCV), varicella zoster virus (VZV), and immunoglobulin G (IgG).)18 (Perinuclear antineutrophil cytoplasmic antibody (p-ANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA) for cases of unclassified IBD. Positive p-ANCA and negative ASCA tests suggest UC. Negative p-ANCA and positive ASCA tests suggest CD.It is recommended that thiopurine methyltransferase (TPMT) enzyme levels should be measured before initiating thiopurine therapy. In whites, the rate of mutations at both TPMT alleles, resulting in inadequate TPMT levels, is approximately 0.3%. The rates of very low to unmeasurable TPMT levels in other ethnic groups are unknown. Serum levels of thiopurine metabolites and of circulating levels of biological agents [to date mostly only available for antibodies to tumor necrosis factor (TNF)], as well as circulating levels of antibodies to biological agents, can help guide the dosage and monitoring of drug adherence.(16)

1.5.2.Histopathology

Biopsies are routinely obtained during endoscopy. It is important for the endoscopist to consider what specific question he or she is asking of the pathologist with each biopsy sample submitted for evaluation. Some of the important reasons for obtaining biopsies include:

- Assessment of crypt architecture distortion, “crypt runting,” increased subcryptal space, and basal plasma- cytosis. These are features of chronic colitis and would be atypical in acute infectious colitis.

- Assessment of noncaseating granulomas, which would be suggestive of CD. Large or necrotic/caseating granulomas should alert the physician to the diagnosis of TB, especially in regions in which TB is endemic.

Identifying histologic changes in areas of normal endoscopy to fully stage the extent of disease. Cytomegalovirus (CMV) can be sought on tissue biopsy in patients receiving immunosuppressive agents or chronic corticosteroids—both for RNA, and on histology in colonic tissue. Serology can be useful as an adjunctive measure (CMV IgM).

A search for dysplasia can be carried out if routine biopsies are being obtained for dysplasia surveillance, or if mass lesions are biopsied. Identifying lymphocytic colitis or collagenous colitis in an otherwise endoscopically normal-appearing colon. These diagnoses may coexist with small-bowel CD, and should be sought in patients with diarrhea. (16)

1.5.3.Imaging and Endoscopy

1.5.3.1.Plain abdominal radiography:

Can establish whether colitis is present and its extent in some cases. Used when bowel obstruction or perforation is expected. Excludes toxic megacolon. Barium double-contrast enema/barium small-bowel radiography:

- Not typically recommended in severe cases.
- Can be useful for identifying fistulas that arise from or bridge to the colon.
- Barium small-bowel radiography is still widely used to assess the gastrointestinal tract as far as the distal small bowel.
- Can provide an anatomic “road-map” before surgery.(17)

1.5.3.2.Sigmoidoscopy, colonoscopy:

Examine for ulcers, inflammation, bleeding, and stenoses. Multiple biopsies from the colon and terminal ileum. Colonoscopy in severe or fulminant cases may be limited in

extent, due to the increased risk of perforation. When there is a lack of response to usual therapy, these examinations can be used to assess for CMV infection if the patient is receiving chronic immunosuppressant medication, or for C. difficile infection if stool tests are equivocal. A screening colonoscopy for dysplasia surveillance is indicated after 8 years of UC or Crohn's colitis The new consensus statement published by the American Society for Gastrointestinal Endoscopy should be consulted for recommendations on surveillance for and management of dysplasia in patients with IBD. (18)

1.5.3.3.Upper gastrointestinal endoscopy:

In case of upper gastrointestinal symptoms (nausea, vomiting, epigastric pain). As upper gastrointestinal disease may be more common in pediatric CD, this is more routine in children.

1.5.3.4.Capsule endoscopy:

Helpful in patients with suspected CD and negative initial work-up. Allows evaluation of the entire small intestine, thus improving the diagnosis and differential diagnosis of IBD24—lesions found should be interpreted in the context of the differential diagnosis. M ay have a role in known CD—assessing disease distribution and the extent and response to therapy (mucosal healing). Its current role in UC is still debatable. For patients with CD who have stenoses or when there is uncertainty regarding stenosis, a patency capsule can be used first to determine whether there is a functional structure that would not allow passage of the real capsule endoscope. Rarely available and unaffordable in underprivileged countries. (19) Double-balloon, single-balloon, and spiral enteroscopy: To assess small-bowel disease when other modalities have been negative and when a condition is strongly suspected or if there is a need for biopsies; also to obtain tissue to rule out TB if the findings are beyond the reach of standard

endoscopy. To treat small bowel strictures or for assessment of obscure bleeding in CD. Rarely available in underprivileged countries.(18)

1.6.Clinical and endoscopic scoring system

Various scoring systems integrating clinical symptoms, physical findings, and endoscopic or imaging studies have been used to assess the disease severity of IBD as objective indices to guide therapy and monitor the disease condition. For CD, the scoring systems commonly used in Taiwan are the CDEIS and Simple Endoscopic Score for CD (SES-CD) (which integrate endoscopy findings for assessment; the SES-CD is more clinical and practical and thus preferred), and CD Activity Index (CDAI) or pediatric CDAI (which does not integrate endoscopy findings as part of assessments). For UC, the most common scoring systems used in Taiwan are the Mayo score, which integrates clinical symptoms; endoscopic findings; and physicians' global assessments. (20)

1.7.CASCADE FOR IBD DIAGNOSIS

Cascade 1: Choices for Diagnosis Relative to Available Resources Limited Resources Available

- Physical examination.
- Stool tests for infective sources and fecal leukocytes.
- CBC and serum albumin.
- HIV and TB testing in high-risk populations—and other opportunistic infection work up, HBV, HCV, and chest x-ray (CXR).
- Flexible full-length colonoscopy and ileoscopy with biopsies if histologic interpretation is available.
- If endoscopy is not available but barium studies are, then both a small-bowel barium study and a barium enema should be obtained.

1.8.Medium Resources Available

- Physical examination.
- Stool tests for infection.
- Stool for fecal leukocytes, fecal calprotectin (not necessary if endoscopy available, but may help select for further investigation including with endoscopy). (4) CBC, serum albumin, serum ferritin, and CRP.
- HIV and TB testing in high-risk populations—serology to HAV, HBV in patients with known IBD to vaccinate if necessary before therapy. Opportunistic infection work-up, HBV, HCV, VZV IgG, and CXR.
- Colonoscopy or ileoscopy, if available.
- Abdominal ultrasound scan.
- CT scan of the abdomen.

- Physical examination
- Stool tests for infection.
- CBC, serum albumin, serum ferritin, and CRP.
- HIV and TB testing in high-risk populations serology to HAV, HBV in cases with known IBD to due to the potential risk of- vaccinate before therapy, if needed. Opportunistic infection work-up, HBV, HCV, VZV IgG, and CXR
- Colonoscopy and ileoscopy.
- Abdominal ultrasound scan.
- Abdominal MRI is preferable to abdominal CT, due to the lack of radiation exposure.

- TB polymerase chain reaction testing and culture are essential during lower endoscopy in areas with a high prevalence of TB.

- If there is uncertainty whether the patient has small bowel disease, cross-sectional imaging with MRI, small- bowel capsule endoscopy, or CT should be carried out.

- Barium enema if a colonic fistula is expected and not identified on cross-sectional imaging, or if colono-

scopy is incomplete.

- In the setting of incomplete colonoscopy, CT colonography has become a preferred choice for examining the entire colon. Some radiology units have reservations about pursuing this technique in the setting of CD.

Colon capsule studies are another alternative in cases of incomplete colonoscopy, unless a colonic stricture is known or highly likely.

- Capsule endoscopy if the suspected diagnosis of CD is still unclear.

- Double-balloon endoscopy (antegrade or retrograde, depending on the suspected site) if areas of the mid- small bowel.(21)

CHAPTER 2

MANGEMENT

2.1.goals of IBD therapy:

- Induce and maintain remission: The primary objective is to reduce inflammation and achieve remission, which involves the absence of symptoms and normalization of inflammatory markers. This helps alleviate symptoms such as abdominal pain, diarrhea, and rectal bleeding.
- Control inflammation: The main focus is to suppress the inflammatory response in the gastrointestinal tract. By controlling inflammation, therapy aims to prevent disease progression, reduce the risk of complications, and maintain long-term remission.
- Improve quality of life: IBD can significantly impact a person's quality of life due to symptoms, physical limitations, and emotional distress. Therapy aims to alleviate symptoms, enhance overall well-being, and improve daily functioning.
- Prevent complications: IBD is associated with various complications, including strictures, fistulas, abscesses, and colorectal cancer. Treatment seeks to minimize the occurrence of these complications through effective management of inflammation and timely interventions when necessary.
- Individualize treatment: Therapy should be tailored to the individual patient, taking into account factors such as disease severity, location, behavior, response to previous treatments, comorbidities, and patient preferences. The goal is to find the most appropriate treatment approach for each person to optimize outcomes.

It's important to note that the goals of therapy may evolve over time, and treatment plans may be adjusted based on the individual's response to treatment and disease course.(22)

2.2.non-pharmacological interventions

can play a supportive role in the management of inflammatory bowel disease (IBD). While these interventions may not replace medication, they can help improve symptoms, enhance overall well-being, and complement the medical treatment. Here are some non-pharmacological treatment options for IBD.(23)

1-Dietary modifications: Certain dietary changes may help manage IBD symptoms and promote gut health. While specific recommendations may vary based on individual needs, some common approaches include:

- Low-residue or low-fiber diet: This can help reduce bowel movements and alleviate symptoms such as diarrhea and abdominal pain. It involves avoiding high-fiber foods, raw fruits and vegetables, nuts, seeds, and whole grains.
- Specific Carbohydrate Diet (SCD): This diet restricts complex carbohydrates to reduce inflammation and balance gut bacteria. It eliminates grains, lactose, refined sugars, and certain vegetables and fruits.
- Elimination diets: Identifying and eliminating trigger foods that worsen symptoms through trial and error or under the guidance of a healthcare professional or registered dietitian.**(24)**

It's important to work with a healthcare professional or registered dietitian to develop an individualized dietary plan based on specific needs and tolerances.

2-Stress management: Stress and emotional factors can exacerbate IBD symptoms. Strategies to manage stress and promote emotional well-being may include:

- Relaxation techniques: Practice techniques such as deep breathing, meditation, mindfulness, and progressive muscle relaxation to reduce stress levels.

- Exercise: Engage in regular physical activity, as exercise has been shown to improve overall well-being, reduce stress, and possibly alleviate symptoms.
- Psychological support: Seek counseling, therapy, or support groups to address the emotional challenges associated with IBD. Cognitive-behavioral therapy (CBT) may be particularly helpful.

3-Regular exercise: Physical activity can have a positive impact on IBD symptoms and overall health. It can help reduce inflammation, improve mood, enhance cardiovascular fitness, and promote better digestion. However, it's important to tailor exercise routines to individual capabilities and consult with a healthcare professional before starting a new exercise program.

4-Complementary and alternative therapies: Some individuals with IBD find relief with certain complementary and alternative therapies. These may include acupuncture, probiotics, herbal supplements, and mind-body practices like yoga or tai chi. It's essential to discuss these options with a healthcare provider before initiating any complementary therapies.

5-Supportive care: Adequate rest, maintaining proper hydration, and getting sufficient sleep can contribute to overall well-being and symptom management in IBD.**(25)**

2.3.Pharmalogical treatment

2.3.1.Aminosalicylates 5- (5-ASA)

5-ASA are bowel-specific drugs that are metabolized in the gut where the predominant actions occur. As a derivative of salicylic acid, 5-ASA is also an antioxidant that traps free radicals, which are potentially damaging by-products of metabolism. In the radical induction theory of ulcerative colitis, 5-ASA functions

as a free radical trap as well as an anti-inflammatory drug. 5-ASA is considered to be the active moiety of sulphasalazine, which metabolizes to it. Oral and/or topical 5-ASA is recommended for mild to moderate ulcerative colitis to induce and maintain remission. The dosage of 5-ASA should be no less than 3 g/d. In practice, most patients do not like a topical treatment, but in left-sided disease, an enema with 4 g of 5-ASA 2 times per day or suppositories with 500 mg 5-ASA 3 times per day are most effective. Sometimes it is helpful for the patient to use the enema only in the evening and the suppositories in the morning.**(26)** 5-ASA is a standard treatment for ulcerative colitis, but not for Crohn's disease.In most patients, the side-effects are not very severe with headache as one of the most common side-effects. However, in some cases nephritis, pancreatitis and hair loss have been reported, which suggests regular monitoring of renal and liver enzymes at least once in three months.(27)

2.3.2.Antibiotics

Antibiotics (e.g. metronidazole) play only a minor role in the additional treatment of fistulizing disease.(28)Although metronidazole (for up to 3 mo in a dosage of 400 mg 2 times per day) is often used in post-operative management after an ileocecal resection or fistula/abscess operation for Crohn's disease, this therapy is not based on study evidence. A side-effect of long-term treatment with metronidazole is polyneuropathy and monitoring is, therefore, required. Antibiotics are also used in the conservative treatment of small abscesses. Understanding the role of microbiota and antibiotics in IBD may become important in the future, but currently clinical studies have not provided support for this concern.

2.3.3.Corticosteroids

In patients with moderate to severe Crohn's disease or ulcerative colitis, corticosteroids are effective for the induction of clinical response and

remission[11-16]. Dosages from 40-60 mg/d or 1 mg/kg per day orally are effective for the induction of remission. After the induction of remission, the steroid dose should be tapered (10 mg/wk until 40 mg; 5 mg/wk until 20 mg, followed by a tapering of 2.5 mg/wk). In severe disease, the application of parenteral glucocorticoids as soon as possible is useful for an anti-inflammatory response. Before the initiation of steroid treatment, the presence of an abscess should be excluded. In patients who have been on glucocorticoids for more than one month, an ACTH(Adrenocorticotropic hormone)-Test should be performed before beginning tapering of the steroid. The ACTH-test can detect deficient cortisol production in the body. If there is a deficiency, hydrocortisone should be used as a substitute.The benefits of glucocorticoid therapy should be carefully balanced against possible side-effects. Budesonide can reduce typical steroid side effects by a 90% first-pass metabolism in the liver and erythrocytes. Due to a special structural formulation, budesonide achieves the best anti-inflammatory effect in ileocecal inflammation[17-20]. Therefore, it is useful in therapy for Crohn's disease with ileocecal inflammation only. However, neither budesonide nor any other glucocorticosteroid should be used for a maintenance therapy due to the side-effects (e.g. Cushing-syndrome, osteoporosis or cardiomyopathy[21,22]). All patients treated with corticosteroids should additionally receive vitamin D and calcium substitution to avoid bone loss.

2.3.4.Immunosuppressives

Immunomodulators are, therefore, recommended for the treatment of chronic active IBD. Studies have shown an efficacy for immunosuppressives that is similar to azathioprine and its metabolite, 6-mercaptopurine (6-MP; 2-3 mg/kg per day, resp. 1-1.5 mg/kg per day), in the long-term use of chronic active disease. Immunomodulators have been shown to be efficient for the control of

inflammation and remission maintenance. Only limited data exists on the efficacy of immunosuppressants in fistulizing Crohn's disease and the prevention of post-operative recurrence[24-30]. Evidence-based data is missing on the post-operative use of azathioprine and many IBD referral centers are using azathioprine for the prevention of post-operative recurrence. Prior to an initiation of treatment with azathioprine or 6-MP, patients should be thiopurine methyltransferase (TPMT) genotype assessed in order to detect for a homozygous deficiency in TPMT in an effort to avert AZA or 6-MP-induced potential adverse events. All patients on azathioprine or 6-MP should be monitored weekly in the first month and after that once a month regarding their white blood count and liver enzymes because a myelosuppression or an elevation of liver enzymes subsequent to the use of azathioprine or 6-MP can occur. In such cases, the dosage of azathioprine or 6-MP should be reduced or paused until lab values are normal. In patients with gastrointestinal side-effects after the intake of azathioprine, a change to 6-MP should be considered.

2.3.4.1.Methotrexate and cyclosporine

Methotrexate is another immunomodulatory agent that is used in long-term treatment of IBD. The dosage for induction of remission in chronic active disease is 25 mg i.m. per week for 16 wk, followed by a maintenance treatment of 15 mg i.m. per week. In contrast to azathioprine and 6-MP [31-33]. Cyclosporine is reserved for the treatment of severe steroid-refractory ulcerative colitis only. Intravenous cyclosporine (2-4 mg/kg) was able to prevent a decidered colectomy in two of three patients with severe ulcerative colitis. Due to its toxicity, use should be considered carefully; i.e. it should be used only in very severe active disease

cases to avoid a colectomy. In Crohn’s disease, cyclosporine has been shown to be effective only in fistulizing, but not luminal disease[34-37].

2.3.5.Biological therapies,

especially anti-TNF agents, play a pivotal role in the treatment of chronic active IBD and fistulizing disease[40-43]. The first anti-TNF agent on the market 1998, infliximab, is a chimeric IgG1 mouse/human monoclonal antibody. Randomised, placebo-controlled trials (ACCENTIand II) demonstrated the efficacy of infliximab (5 mg/kg, i.v.) in the induction of clinical response and remission in patients with active Crohn´s disease. In fistulizing disease, complete fistula closure of at least 50% of the fistulas could be seen in 55% of the patients after three infusions of infliximab at wk 0, 2 and 6 (ACCENT II). Given on a regular basis in intervals of 8-12 wk (5 mg/kg i.v.), infliximab is able to maintain remission[44-50].In ulcerative colitis, Contraindications and side-effects should be taken into consideration carefully prior to infliximab therapy[53]. Due to immunogenicity, infliximab can lead to the formation of human anti-chimeric antibodies (HACA) in 30% to 75% of the patients. Additional administration of immunosuppressants; e.g. azathioprine and/or pretreatment with intravenous prednisolone, can reduce the risks of HACA formation. The main reported side-effect is an infusion reaction, which can occur as an acute allergic/anaphylactic reaction or a delayed hypersensitivity reaction. In clinical trials, observations have included infections, drug-induced lupus, cardiac failure, non-Hodgkin's lymphoma and, in post-marketing surveillance, tuberculosis, pneumonia, histoplasmosis, listeriosis and aspergillosis. To avoid a potential tuberculosis reactivation, a purified protein derivative (PPD) skin test and a chest-X-ray should be performed prior to infliximab treatment[54-67].Patients with perianal or enterocutaneous fistulizing

Crohn’s disease should be treated first with infliximab. The effect of infliximab is not as effective on entero-enteral or recto-vaginal fistulas. Patients with steroid-refractory or chronic active Crohn’s disease or ulcerative colitis who do not respond to immunosuppressive therapy alone should also be treated with infliximab. The recommended treatment regimen is an induction scheme with three infusions (5 mg/kg i.v.) at 0, 2 and 6 wk, followed by a maintenance treatment of infliximab every 8 wk (5 mg/kg i.v.). Additionally, immunosuppressive therapy with azathioprine, for example, is recommended. HACA testing is not recommended routinely for every patient on infliximab, but it is recommended if there is a delayed hypersensitivity reaction or if the last infliximab infusion was more than 12 wk previous.

2.3.5.1.Adalimumab

Other TNF agents also showed efficacy in Crohn’s disease. The human IgG1 antibody adalimumab, which is a therapeutic agent used for rheumatoid arthritis, was effective in open-label experience. A placebo-controlled, randomised trial was also conducted. One advantage, in comparison to infliximab, might be the completely human structure of the antibody, which leads to better tolerance and a subcutaneous route of administration. Data on adverse reactions in Crohn’s disease patients are still not available, but adalimumab is well-tolerated in patients with rheumatoid arthritis[68-71].

2.3.6.CDP-870

Certolizumab pegol (CDP-870)(Cimzia), FDA approved for Crohn’s disease in 2008.which is a polyethylene-glycolated Fab-fragment of the anti-tumour necrosis factor, has been shown to be effective in the treatment of Crohn’s disease in a

recent published, randomised, placebo-controlled trial. At week ten, 52.8% of the certolizumab (400 mg) treated patients showed a clinical response versus 30.1% in the placebo treated group (the high placebo response was seen in a large patient subgroup with low C-reactive protein levels; this might have been due to statistical separation between treatment and placebo group[72]). The antibody was well tolerated. Ongoing trials, however, are necessary to establish efficacy in Crohn's disease.

2.2.5.Probiotics

A different group of therapeutic agents for therapy of IBD are probiotics. The use of probiotics has been advocated in colonic inflammatory disease for a long time. Only recently, two controlled trials demonstrated that E. coli nissle is as effective as 5-ASA for remission maintenance in ulcerative colitis[83,84]. For remission maintenance and pouchitis, studies demonstrated the benefit of probiotics[85,86]. Due to a better understanding of the molecular events and the pathophysiological processes of this disease, it is hoped that more probiotic agents will be developed in the near future.

2.3.7.Newer drugs

2.3.7.1.Inhibition of Immune Cell Trafficking Anti-Adhesion Agents

The trafficking of T lymphocytes from SLOs to the site of inflamed intestine in IBD is mediated by several en- hanced chemokines and selectins, leading to the adhesion of integrins expressed on T cells to ligands on HEVs, fol- lowed by their transmigration into intestinal tissue. New pharmacological agents have been developed to prevent leukocyte trafficking by selectively targeting the adhesion

molecules involved in the pathogenesis of IBD [3]. Among several adhesion molecules, integrin α4β7 is preferential- ly expressed on lymphocytes activated in gut SLOs and interacts with mucosal addressin cell adhesion mole- cule-1 (MAdCAM-1), which is highly expressed on HEVs [3]. Natalizumab, a recombinant humanized monoclonal antibody against α4-integrin, was initially approved to treat multiple sclerosis (MS), followed by CD [4]. Vedol- izumab is a humanized monoclonal antibody against α4β7 that selectively prevents lymphocyte migration and improves chronic intestinal inflammation. Vedolizumab effectively induces and maintains remission in IBD pa- tients refractory to conventional therapies, with a gener- ally favorable long-term safety profile (GEMINI LTS study), offering an advantage over natalizumab because of no association with the occurrence of PML [6]. Etrolizumab is a humanized monoclonal antibody against the β7 subunit of the heterodimeric integrins α4β7 and αEβ7 expressed on lymphocytes, thus concurrently inhibiting their interaction with MAdCAM-1 and E-cadherin, re- spectively, leading to the reduction of inflammatory T cells and cytotoxic intraepithelial lymphocytes in the gut mucosa via blockade of intestinal tissue entry and reten- tion [7]. Carotegrast methyl is an orally active, small mol- ecule with a similar action mechanism to natalizumab and was approved in Japan for UC treatment in 2022 [8]. Theoretically, carotegrast methyl can lead to an increased risk of PML as mentioned above. Therefore, the treat- ment duration was limited to <6 months and there was no case of PML reported. Ontamalimab is a monoclonal IgG2 antibody against MAdCAM-1, thus preventing lymphocyte migration into sites of intestinal inflamma- tion and is efficacious for IBD treatment [4]. Other po- tential targets of adhesion molecules for the treatment of IBD include intercellular adhesion molecules, vascular cellular adhesion molecule-1, P-selectin, and P-selectin glycoprotein ligand-1 [9]

2.3.7.2.Sphingosine-1-Phosphate Modulators

The sphingosine-1-phosphate receptor (S1PR) com- prises 5 subtypes and plays several important roles, in- cluding cell proliferation and migration, intercellular communication, vascular tone maintenance, and other cardiovascular effects. S1PR1 plays an essential role in controlling lymphocyte egress from the thymus, SLOs, and bone marrow [10]. Several S1P modulators have been developed to treat immune-mediated diseases, including IBD, MS, rheumatoid arthritis (RA), systemic lupus ery- thematosus, and psoriasis, with promising results [10]. Ozanimod, an orally administered small molecule and se- lective immunomodulator of the S1PR1 and S1PR5 re- ceptors, is effective as an induction and maintenance therapy for IBD by receptor internalization and degrada- tion, thus inhibiting the migration of lymphocytes along a gradient of S1P concentration from SLOs into the sys- temic circulation [10]. Other S1P modulators, including etrasimod and amiselimod, have also been developed and used in clinical trials [10].

2.3.7.3.Inhibition of Cytokines

i.Targeting IL-12/23 Pathways

IL-12, a heterodimer of p40 and p35, and IL-23, a het- erodimer of p40 and p19, are released from myeloid cells, including dendritic cells (DCs) or macrophages, induce differentiation of naïve CD4+ T cells into T-helper 1 (Th1) and T-helper 17 (Th17) cells, and play important roles in the pathogenesis of IBD [11]. Ustekinumab is a fully hu- man IgG1 monoclonal antibody that targets the

IL-12/23 shared p40 subunit, preventing its binding to the recep- tors on cells [11]. UNITI and UNIFI studies have shown ustekinumab's long-term efficacy and safety for IBD. Ri- sankizumab is a humanized IgG1 monoclonal antibody that selectively binds the IL-23 p19 subunit with a high affinity. Theoretically, risankizumab may confer fewer side effects than ustekinumab by specifically targeting the IL-23-mediated inflammatory pathway without blocking the IL-12-dependent T cell activation pathway, which is vital for infection and cancer immunity. Studies targeting the IL-23 p19 subunit by other biologics, such as miriki- zumab, brazikumab, and guselkumab, also showed effec- tiveness in controlling intestinal inflammation [11].

ii.JAK Inhibitors

Cytokines promote intracellular signaling through induction of the JAK/signal transducer and activator of transcription (JAK/STAT) signaling pathway. JAKs, a family of intracellular tyrosine protein kinases, are comprised of 4 members: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). Inhibition of the JAK/STAT signaling pathway gets a lot of attention for developing novel IBD therapies [13]. JAK inhibitors are small molecules and the first IBD- targeted therapy administered orally. JAK inhibitors are characterized by a rapid onset of action after entering sys- temic circulation and may provide fast symptomatic relief. In contrast to the aforementioned monoclonal antibodies that target a single cytokine (TNF-α, IL-12, or IL-23), JAK inhibitors have the potential to affect multiple cytokine- dependent immune pathways (for example, JAK1, JAK2, and TYK2 mediate signaling of IL-6, while JAK2 and TYK2 also mediate signaling of IL-23) [13]. Several JAK inhibi- tors have already been approved for treating RA. Among them, tofacitinib is a highly effective nonselective JAK in- hibitor (preferentially inhibits JAK1 and JAK3) that was first approved for induction and maintenance

therapy in UC. The risk of herpes zoster in- fection increases in patients aged >65 years with previous failure of TNFα agents and Asian ethnicity [13]. In phase 2b clinical trials of CD, primary efficacy endpoints were not significantly different from placebo. The selective JAK1 inhibitors, filgotinib and upadacitinib, are also efficacious for IBD [14, 15]. In the maintenance study of filgotinib (SELECTION trial), clinical remission rate at 58 weeks of moderately and severe UC patients taking 200 mg were 37.2% compared to 11.2% in placebo ($p < 0.0001$). Filgotinib was assessed in CD in the phase 2 FITZROY study, which showed 47% of patients taking 200 mg achieved clinical remission at week 10 compared to 23% in placebo ($p = 0.0077$). In the U-ACHIEVE study, clinical remission rate at 8 weeks of moderately and severely UC patients taking upadacitinib 45 mg was 19.6% compared to 0% in placebo ($p = 0.002$). In the CELEST trial assessing upadacitinib in patients with moderate to severe CD, the clinical remission at week 16 was 27% of patients receiving 6 mg upadacitinib twice daily compared to 11% in placebo ($p < 0.1$). Deucravacitinib in phase 2 clinical trials of CD and UC is a highly selective TYK2 inhibitor that targets IL- 12, IL-23, and type 1 interferon (IFN) [13].

iii.Phosphodiesterase Inhibitor

Phosphodiesterases (PDEs) are a heterogeneous and large family of enzymes that catalyze the degradation of cAMP and cGMP. PDE4 is expressed in DCs, macro- phages, monocytes, and T cells. The inhibition of PDE4 elevates intracellular cAMP levels, reducing the expression of the inflammatory cytokines TNFα, IL-17, IFN-γ, and IL-23, while increasing regulatory cytokine levels, such as IL10. Therefore, the PDE4 inhibitor apremilast has been evaluated as a therapeutic agent in treating ac- tive UC and proved effective [18].

2.3.8.Future Perspectives

Since multiple inflammatory pathways are activated in the inflamed intestine, blocking one of them might not be sufficient to control inflammation, as we now do with tar- geted monotherapies. Therefore, in the future, we will need to establish treatment strategies, such as sequential/ combination therapy, to optimize the efficacy of each drug [20]; for example, using combination therapies in the induction phase of early IBD followed by monotherapy in remission. Meanwhile, therapeutic approaches with different mechanisms of action have been investigated from various perspectives. In this section, we dis- cuss several possible future therapeutic targets.

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