

Current Advances in the Management of Crohn's Disease

Yousef Ajlouni,^{*1} Mustafa M. Shennak²

Abstract

Crohn's disease is a chronic relapsing and remitting inflammatory bowel disease believed to develop as a result of the stimulation of a dysfunctional immune response in genetically susceptible individuals. Crohn's disease is most commonly diagnosed in young adults (15 to 30 years) with a female-to-male ratio between unity and 1.2: 1. Prevalence of Crohn's disease rapidly increased all through the world as different countries adopt a Western lifestyle. The incidence is 5.8 cases per 100,000 people per year and the prevalence is 133 cases per 100,000 people.

Mortality in Crohn's disease is now low, but morbidity is considerable. Thirty to sixty per cent of patients with Crohn's disease who attain medically induced remission will relapse within 1 year. It is estimated that 50% and 75% of Crohn's disease patients will require surgery within 5 to 15 years of diagnosis. Surgical resection is not curative as evidenced by the near universal recurrence of neo-terminal ileal Crohn's disease following ileocolonic resection.

In the absence of a definitive cure, the aim of therapy is to induce and maintain clinical remission at an acceptable cost, avoidance of surgeries, and improvement of health-related quality of life. The first line treatment is still based on combinations of steroids, amino-salicylic acid derivatives, immunomodulators, and nutritional regimens. Biological drugs have opened new therapeutic horizons for treating Crohn's disease, but have also brought with them issues related to immunogenicity, long-term efficacy, safety and cost.

This review will highlight the current advances in the management of Crohn's disease as well as discuss areas that remain controversial and are awaiting resolution.

Keyword: Crohn's disease, Ulcerative colitis, Inflammatory bowel disease, IBD, Advances.

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Pathogenesis

Chronic intestinal inflammation in Crohn's Disease (CD) results from the interactions of genetic, immunologic, microbial and environmental factors. It is proposed that Crohn's disease results from the failure to appropriately

downregulated nonspecific inflammation initiated by an environmental trigger, such as an acute, self-limited infection or NSAID use.¹

Normal hosts quickly clear infections of invasive enteric bacteria, downregulate innate immune responses and heal the injured mucosa without stimulating effector T-cell responses.

1. IBD, Consultant Gastroenterologist, King Hussein Medical Center, Amman, Jordan.

2. Professor of Medicine and Gastroenterology, Chief, GI and Liver Division, Faculty of Medicine, Jordan University and Hospital.

* Correspondence should be addressed to:

Yousef M. Ajlouni

P.O.Box : 1047, Jubaiha 11941, Amman, Jordan

E-mail: yousefajlouni@yahoo.com

By contrast, genetically susceptible hosts who are unable to clear an invading pathogen and/or generate tolerogenic immune response to commensal microbial agents by mounting appropriate innate immunity, downregulating immune responses or healing the mucosal barrier-subsequently activate pathogenic T-cell responses to commensal bacteria and proceed to chronic, relapsing intestinal inflammation. Resistance to T-cell apoptosis, lack of response to downregulatory signals and continuous exposure to luminal antigens and adjuvants help sustain this inflammatory response.²

Many environmental factors can influence mucosal immune responses and enteric bacteria composition, including diet, smoking, stress, altered microenvironment and NSAID exposure. Although postulated that self-limited, nonspecific infections can initiate the onset of chronic inflammation and reactivate quiescent disease, it is possible that a persistent pathogen could cause disease in individuals unable to clear infections, or that the commensal bacteria of some patients could acquire virulence factors (e.g. toxins, adherence and/or invasion properties) that might cause chronic intestinal inflammation.³

Epidemiology

The incidence rate of Crohn's disease is increasing in different parts of the world. The factors contributing to this trend have not been completely elucidated but probably do not merely reflect improved diagnostic capabilities and the discovery of greater numbers of mild cases.⁽⁴⁾ In both Europe and North America, higher incidence rates have been noted in more northern latitudes. In the United States, recent estimates of incidence rates ascertained by various methodologies have ranged from 3.6 to 8.8 per 100,000. In Japan, the incidence rate has remained low, with estimates between 0.08 and 0.5 per 100,000, whereas in Australia and New Zealand, incidence rates have ranged from 1.75 to 2.1 per 100,000. Crohn's disease is thought to be extremely rare in much of South America and Africa, with the exception of South Africa, where the most recent estimate of the incidence rate for

the white population is 2.6 per 100,000 and is considerably lower among nonwhite populations.⁵

Crohn's disease is diagnosed most frequently among persons aged 15 to 30, although the age of diagnosis may range from early childhood through the entire lifespan. Many, though not all, studies have shown a smaller second peak in incidence later in life, generally in the seventh decade. There is a small excess risk of Crohn's disease among women. Most reports show a female-to-male ratio between unity and 1.2:1.⁶

Differences in clinical presentation among younger and older patients suggest that distinct risk factors are operative at different ages at onset.⁷ The pathologic findings in young and old patients are not discernibly different, yet some studies have identified a greater proportion of colonic disease among older patients, whereas younger patients tend to have ileal disease with greater frequency. The tendency for small intestinal localization in younger patients may correlate with familial Crohn's disease, suggesting that additional nongenetic factors play a greater role in disease of later onset.⁸

Diagnosis

To confirm a diagnosis and to exclude the presence of other conditions that can cause similar symptoms and mimic Crohn's disease, such as other inflammatory bowel disorders, colitis, celiac disease, or irritable bowel syndrome, a number of specific clinical maneuvers and tests may be undertaken. These include performing a complete physical examination as well as appropriate diagnostic medical tests, such as stool samples for enteric pathogens, stool samples for ova and parasites, and stool collection for *Clostridium difficile* toxin assay.

1. Serologic Testing

Perinuclear anti-neutrophilic cytoplasmic antibody (pANCA), and anti-Saccharomyces cerevisiae antibody (ASCA) have been proposed as screening tools for patients who present with

signs and symptoms of IBD and also has been proposed as a method to reach a definitive diagnosis of Crohn's disease or ulcerative colitis in patients with indeterminate colitis.⁹ However, pANCA and ASCA testing does not have the specificity needed to distinguish ulcerative colitis from Crohn's disease in these patients. It should be stressed that ASCA IgA is present in 50% to 70% of patients with Crohn's disease and in 6% to 14% of patients with ulcerative colitis. The presence of both ASCA IgG and IgA is highly specific for the presence of Crohn's disease.¹⁰

Anti-OmpC IgA (outer membrane porin from *Escherichia coli*) is an autoantibody directed against outer membrane porin C on the cell wall of *E. coli*. This marker enhances detection of Crohn's disease. The presence of this antibody is associated with a subset of patients who have a more severe form of Crohn's disease. Antibodies to OmpC IgA have been reported in 46% of Crohn's disease patients who were ASCA-negative.¹¹

Antibody to CBir1 (anti-CBir1 flagellin); CBir1 is a flagellin-like antigen associated with the presence of IBD. In particular, serum response to anti-CBir1 identifies the presence of Crohn's disease and is associated with a subset of patients with this form of IBD. This marker has been shown to differentiate pANCA-positive results in ulcerative colitis vs ulcerative colitis-like Crohn's disease, and identifies a unique subset of patients with Crohn's disease not previously identified with other serologic markers. Serum responses to CBir1 identifies patients with complicated Crohn's disease (such as small bowel, internal penetrating, and fibrostenosing disease). Levels of anti-CBir1 are increased in 50% to 55% of patients with Crohn's disease.¹²

2. Endoscopy

Colonoscopy represents the primary modality to obtain tissue for histologic evaluation. It is of paramount importance that biopsies be procured, even from tissue that appears endoscopically normal. Histology represents the most sensitive measure of disease extent and activity.

Colonoscopy with biopsy of involved and endoscopically normal areas is important in determining whether patients with indeterminate colitis have Crohn's colitis or ulcerative colitis. In 10% of all patients, colonoscopy with biopsy is unable to differentiate between Crohn's colitis and ulcerative colitis.¹³

In Crohn's disease, characteristically, there are focal ulcers, skip areas with normal-appearing mucosa, and deep longitudinal ulcers in severe disease. It should be stressed that endoscopic findings do not correlate well with clinical disease activity. Endoscopic evaluation of strictures should include multiple biopsies and brushing cytology. Patients who have significant Crohn's disease have transmural inflammation present. The mucosa demonstrates evidence of chronic inflammatory changes, atrophy, and metaplastic change within the epithelium, i.e., Paneth cell metaplasia in the colon. The hallmark of Crohn's disease is the presence of noncaseating granulomas within the bowel wall or in regional lymph nodes. The end result of this disease is transmural inflammation leading to fibrosis and stricturing.¹⁴

An upper gastrointestinal endoscopy and gastro-duodenal biopsies may have utility in patients with Crohn's disease for the possibility of upper gastrointestinal involvement which occur in about 5% of the cases.¹⁵

3. Radiographic Studies

Barium studies, can identify the extent of disease and the presence of complications such as fistulas or strictures. Small-bowel radiography may be of adequate sensitivity to detect advanced changes of Crohn's disease in the terminal ileum; however, mild changes confined to the terminal ileum, such as aphthous ulcerations, may be missed unless a peroral pneumocolon or air-contrast enteroclysis is performed. These studies, however, may miss subtle luminal disease. In some patients, a small-bowel air-contrast study (enteroclysis) can provide additional information for evaluating jejunal and ileal disease.

Enteroclysis is suggested for those individuals who have suspected fistulizing disease not well demonstrated on small-bowel follow-through radiographic study, or for evaluating small intestinal stricturing disease. Enteroclysis is excellent for the detection of Crohn's disease-related fistulas.¹⁶

Abdominal or pelvic abscesses or masses can be visualized using ultrasound, either abdominal or transrectal, as well as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). MRI is often used to detect perianal disease, such as fistulas or abscesses. In addition to evaluating for potential abdominal abscess, CT is a useful adjunct to barium small-bowel studies for evaluating extraintestinal abnormalities, fistulas, phlegmon, and colorectal cancer. It should be emphasized that colonoscopy is the best modality for the detection of colorectal carcinoma. CT scan can also assess bowel-wall thickening and transmural inflammation, differentiating ulcerative colitis from Crohn's disease, and allowing at least some rudimentary assessment of Crohn's disease activity. Finally, interventional CT can be used to percutaneously drain abdominal abscesses.¹⁷

4. Capsule endoscopy, Push enteroscopy and Double-balloon enteroscopy

The technique of video capsule endoscopy has enabled physicians to visualize the terminal ileum with a higher sensitivity as compared with small-bowel radiology. Pushing enteroscopy frequently has difficulty in reaching the terminal ileum, the most common site of Crohn's disease. However, double-balloon enteroscopy has recently demonstrated success in this setting.¹⁸

Video capsule endoscopy should be considered in those individuals suspected of having Crohn's disease who have had a negative work-up, including a negative small-bowel radiographic study. It should be emphasized that not all aphthous ulcerations represent Crohn's disease. Caution should be exercised to avoid overinterpretation of the presence of aphthous ulcerations in the small bowel, because individuals with other disorders, such as celiac

sprue, as well as normal individuals may also have these lesions. Thus, it appears that currently the most appropriate use of capsule endoscopy is in patients with an unknown diagnosis and a negative work-up (EGD, colonoscopy, and small-bowel radiographic study) for Crohn's disease. In terms of considering this technology as a screening study for abdominal pain or diarrhea in the general population, the prevalence of IBD seems too low to make it an appropriate first test. Capsule endoscopy may also be used in patients who have gastrointestinal bleeding of uncertain etiology.¹⁹

Biological Markers of Crohn's disease activity **1. Acute Phase Reactants**

Haemoglobin, platelet count, mean platelet volume, erythrocyte sedimentation rate (ESR), serum thrombopoietin, serum erythropoietin, C-reactive protein and orosomucoid (α_1 -acid glycoprotein) have been used for the assessment of disease activity singly or in combination. ESR and C-reactive proteins are the most commonly used markers.

Erythrocyte Sedimentation Rate is not rapidly responsive to change in clinical status (ESR may take several days to decrease even when rapid clinical improvement occurs). Hence, the ESR is a crude assessment of disease activity. In Crohn's disease (CD), the ESR appears to be a less accurate measure of disease activity. The ESR does appear to increase with increasing disease activity but this correlates more with colonic disease and does not reflect the disease activity of small bowel.

Orosomucoid (α_1 -acid glycoprotein) is an acute phase protein synthesized predominantly in the liver in response to tissue injury, inflammation or infection, and it may have a physiological role such as immunomodulation. The levels of circulating orosomucoid correlate with disease activity of IBD as assessed by standard disease activity indices but a long half life of 5 days limits its usefulness as an indicator of improvement in disease activity.²⁰

C-Reactive Protein is produced as an acute phase reactant predominantly in the liver in response to stimulation by interleukin (IL)-6, TNF- α and IL-1 β , which are produced at the site of inflammation. CRP functions as an opsonin for bacterial sequences and nuclear material expressed during apoptosis. CRP has been used as a marker to diagnose and to predict the activity of inflammatory disease. CRP synthesis by the liver is the only factor determining plasma CRP concentration. Hence, only the liver failure or therapies affecting acute phase stimulus may decrease CRP. The normal value of CRP for systemic inflammation is 0.8 mg/dL (8 mg/L). In the presence of acute phase stimulus, CRP production is rapidly upregulated. Once the acute phase stimulus disappears, CRP concentrations quickly decrease due to short half-life of 19 h. This makes CRP a valuable marker to detect the activity of IBD. In CD, serum levels of CRP correlate with disease activity. For UC, same trend can be observed although CRP is overall lower than in CD.²¹

Leucocytosis is not a useful marker of disease activity in clinical practice as there are many factors besides disease activity (systemic steroids, immunosuppressants, presence of abscess) that affect it.

Platelet count correlates with disease activity in IBD but it is not used in clinical practice in IBD as there are other factors such as haemorrhage from other sites and iron deficiency anaemia which can cause elevation of platelet count.

Neopterin, an intermediate metabolite in the synthetic pathway of bipterin, is synthesized and released from monocytes/macrophages upon non-specific stimulation. The level of neopterin in urine and serum has been shown to correlate with disease activity of UC and CD but this is not IBD specific.²²

2. Cytokines

The expression of proinflammatory cytokines is markedly increased in the intestinal mucosa in patients with active IBD, although not always accompanied by increased concentration of cytokines in the serum.

Interleukin-1 is a proinflammatory cytokine. Interleukin receptor antagonists (IL-1RA) levels are increased in patients with active IBD and IL-1RA/IL-1 ratio decreases with increasing IBD activity. Interleukin-2 receptor (IL-R) is shed by activated T cells into circulation along with IL-2. IL-2 receptor is more stable than IL-2 and hence more reliable than IL-2 for detection in circulation. It also has advantage over acute phase proteins in that it more accurately reflects the underlying immunopathogenic process. IL-2 receptor has three different subunits, which behave differently with respect to inflammation and UC or CD. IL-2 receptor- α correlates positively with increasing disease activity in both UC and CD.

Interleukin-6 possesses both anti-inflammatory and proinflammatory effects. Elevated serum IL-6 concentrations are found in active CD but not always in UC.

A recent study found higher concentrations of soluble TNF receptor I, soluble TNF receptor II, soluble IL-1 receptor I, IL-6 and soluble IL-6 receptor in patients with active CD when compared with inactive CD and healthy controls. Soluble IL-1 receptor II concentrations were profoundly decreased in patients with active CD compared to patients with inactive CD and healthy controls, and negatively correlated with CRP concentrations. Deficient production of soluble IL-1RII was specific to CD and not observed in UC.

Interleukin-8 is produced by polymorphonuclear cells, macrophages and epithelial cells, it is important for neutrophil chemotaxis. Serum IL-8 is elevated in patients with active UC but many patients have concentration below the detectable level. Serum IL-8 not elevated in patients with active CD. Thus, serum IL-8 level is a poor marker of disease activity in patients with IBD.

Interleukin-10 and IL-15 are anti-inflammatory cytokines. The concentration of IL-10 is elevated in serum of patients in active UC and CD, suggesting that IL-10 acts as a naturally occurring immunosuppressant in the acute inflammatory process of IBD.

A study evaluated 78 cytokines, growth factors and receptors using antibody-based protein microarrays amplified by rolling circle amplification and found no differences in circulating concentrations of proinflammatory cytokines but found that paediatric IBD patients in remission compared to those with active disease had higher concentrations of specific circulating cytokines, including the regulatory cytokines IL-12p40 and TGF- β 1.

The cytokines, cytokines receptors and/or cytokine transcripts have also been studied in the intestinal mucosa. IL-1 β , IL-2, soluble IL-2 receptor, IL-6, IL-8, IL-23, IL-27, TNF- α and IL-15 (anti-inflammatory cytokine) have been found to be elevated and may correlate with endoscopic and disease activity.²³

3. Faecal Markers

As serum markers can be elevated in a variety of conditions, it seems likely that faecal marker of inflammation, in absence of enteric infection would be more specific for IBD. Faecal markers can be divided into faecal excretion of leucocytes, serum proteins or leucocyte products. Faecal excretion of leucocyte products (faecal lactoferrin and calprotectin) are more promising. Calprotectin was first isolated from granulocytes. The name calprotectin comes from the fact that it binds to calcium and it has antimicrobial properties. It represents 50-60% of neutrophilic cytosolic protein. It is released from cells during cell activation or death. It is stable in faeces for several days after excretion. Faecal calprotectin measurement correlates well with the more difficult and more expensive measurement of [¹¹¹I]Indium-labelled leucocyte excretion. The median faecal calprotectin level is 2 mg/L in healthy individuals with an upper limit of 10 mg/L. Faecal calprotectin level has been shown to be a sensitive marker of activity in CD and to correlate well with endoscopic and histological activity in UC. Faecal calprotectin normalizes along with endoscopic healing in CD. Faecal calprotectin level of 50 μ g/g was found sensitive and specific marker of relapse in both CD and UC (sensitivity of 90% and specificity of 83%).

Lactoferrin is a glycoprotein found in many body fluids as well as in granules of neutrophil granulocytes. Faecal lactoferrin levels quickly increase after influx of neutrophils into intestinal lumen during inflammation. Faecal lactoferrin concentration is increased in patients with active IBD when compared to those with inactive IBD with specificity between 85% and 90%. Faecal lactoferrin levels may rise significantly prior to a clinically evident relapse and may be a good marker to predict subsequent IBD flares. Recent studies comparing faecal lactoferrin and calprotectin have suggested that both tests are similarly useful in the assessment of the disease activity of IBD. Faecal excretion of calprotectin correlated with finding of colonic inflammation at endoscopy while faecal excretion of lactoferrin correlated with histological inflammation.²⁴

4. Intestinal Permeability

Intestinal permeability using differential 5 h urinary excretion ratio (ratio of lactulose and l-rhamnose) and CrEDTA have been used for assessment of disease activity as well as for prediction of relapse in patients with CD. This assay has been of limited value in assessing the disease activity but does appear to predict relapse. Less than 20% of patients who have normal intestinal permeability relapse in 6 months.²⁵

5. White Cell Scan and 4-Day Faecal Excretion Test

Abdominal scanning with ¹¹¹Indium white cell technique visualizes segments of inflamed bowel and quantitates the degree of intestinal inflammatory activity. When combined with 4-day faecal excretion of labelled white cells, the inflammatory activity can be quantified accurately and can be used to document the response to treatment. Faecal excretion of [¹¹¹I]Indium-labelled white blood cells has a good correlation with colitis but not ileitis and poor correlation with the CD activity index. The disadvantage is that these are expensive and more technically demanding.²⁶

6. Whole Gut Lavage

Gut lavage fluid proteins have been studied as marker of disease activity in IBD and gut lavage IgG was found to be a more specific disease marker than albumin in the lavage fluid.²⁷

Treatment

The goals of management are to improve or maintain quality of life. This can be achieved by improvement or prevention of symptoms, avoidance of side-effects/ adverse events and a decrease in complications. Finally, and of great importance to the patient, an important goal is to avoid surgery.²⁸

A. Conventional treatment

Antibiotics: The bacterial flora in the intestine likely plays a role in the pathogenesis of CD. Thus, antibiotics have been explored as a therapeutic agent. Metronidazole and ciprofloxacin are the most widely used antibiotics in clinical practice for the treatment of CD; however, the efficacy of these agents has not been convincingly demonstrated in controlled clinical trials. Other antibiotics, such as clarithromycin and ethambutol, have been investigated for CD treatment in randomized controlled trials and did not offer benefit to patients. Rifaximin is a nonabsorbable antibiotic that has undergone multiple open-label studies examining its utility in the treatment of IBD.²⁹

Antibiotics are clearly indicated where there is evidence of sepsis. They are also widely used in 'nonseptic' flares of Crohn's disease, although the evidence for benefit in this latter group is less convincing. Metronidazole (200-400 mg t.d.s.) is the antibiotic most frequently used for a 7-10 day course. However, two well designed trials have demonstrated that its effect is at best only marginally greater than placebo when used as monotherapy. Ciprofloxacin (500 mg b.d.) is increasingly being used as an alternative due to better tolerability, and there are emerging data that the combination of these antibiotics may be an efficacious treatment for active Crohn's disease.

Metronidazole has also been demonstrated to reduce post-operative relapse rates, but it is not widely used in this context and treatment for more than 3 months is limited by peripheral neuropathy.

Mirroring the use of antibiotics is the increasing interest being shown in the use of probiotics as treatment for active disease. In the absence of any currently available commercial preparations and particularly for patients whose disease is complicated by recurrent small bowel overgrowth, live yoghurt may help and is unlikely to harm.³⁰

5-ASA / Mesalamine

It is obvious that there is conflicting evidence on the efficacy of oral aminosalicylates in active CD and their use in treating mild to moderate CD has been debated.³¹

The efficacy of sulfasalazine is greatest in patients with active colonic or ileocolonic disease. Sulfasalazine has a slower onset of action than prednisone or 6-methylprednisolone and is substantially less effective. As an adjunctive therapy, sulfasalazine is not more effective than prednisone alone, nor is it steroid-sparing.³²

Adverse events in patients treated with sulfasalazine include headache, epigastric pain, nausea, vomiting, cyanosis, skin rash, fever, hepatitis, autoimmune haemolysis, aplastic anaemia, leucopenia, agranulocytosis, folate deficiency, pancreatitis, systemic lupus erythematosus, sulphonamide-induced toxic epidermal necrolysis, Stevens-Johnson syndrome, pulmonary dysfunction and male infertility. Most of the side effects of sulfasalazine can be attributed to the systemic absorption of sulfapyridine and the adverse effects occur more frequently in patients who are genetically predisposed to 'slow' acetylation of sulfapyridine to N-acetylsulfapyridine in the liver. Some of the side effects (headache, nausea, vomiting, and epigastric pain) are dose-related and can be minimized by gradual dose escalation.³³

It is unknown whether the active component of sulfasalazine in CD is 5-aminosalicylate or sulfapyridine, and the possibility that sulfapyridine may contribute to the efficacy of sulfasalazine in CD could explain the observed differences in efficacy between sulfasalazine and mesalazine.³⁴

Although mesalazine has been used as first-line treatment of mild to moderate CD for many years, the efficacy of this treatment has not been consistently demonstrated in randomized, placebo-controlled studies.³⁵ Adverse events in patients treated with mesalazine occur infrequently. Rare, but serious adverse events include pulmonary toxicity, pericarditis, hepatitis and pancreatitis. Interstitial nephritis has also been reported to occur infrequently in patients treated with mesalazine; however, it is unclear if mesalazine is the cause of the renal lesions.³⁶

Corticosteroids: Corticosteroids (CS) have a role in the treatment of active Crohn's disease but have no role in maintaining remission. The inability of Corticosteroids to heal mucosa, coupled with the plethora of associated side effects makes decisions concerning their commencement and cessation immensely important.³⁷

While CS are not recommended as first-line therapy in mild to moderate Crohn's disease, they may be used when patients fail to respond to standard therapy such as 5-aminosalicylic acid (5-ASA), or a topically acting CS such as budesonide (depending on the site of inflammation). For moderate-severe disease, oral CS are viewed as first-line therapy for the induction of remission, while parenteral steroids are recommended when there is no response to oral steroids after 7-14 days, and for severe-fulminant disease.³⁸

CS are not indicated for the treatment of fistulating Crohn's disease. Their use in such patients may increase the need for surgery. There is also evidence to suggest that when used for enterovesical fistulae, steroids may decrease the chance of healing the fistula medically. Similarly, in patients with an abdominal mass resulting

from an abscess, steroid usage is associated with an increased risk of sepsis and even death. It has traditionally been thought that maintenance therapy with CS is ineffective.³⁹

Clinical characteristics associated with steroid resistance include prior bowel resections, perianal disease and a high pretreatment CDAI. Likewise, steroid dependence is more likely to occur in patients who smoke, with colonic and nonfibrostenotic disease, and whose disease onset occurred early in life. Furthermore, recurrent courses of steroid over the preceding 3 years, or a recent course of steroids, predict relapse after steroid withdrawal. Despite this, it is not currently possible to predict who will fail to respond to CS therapy; advances in the field of pharmacogenetics, combined with further definition of clinical features may one day allow identification of steroid-refractory and steroid-dependent patients prior to treatment. Finally, CS should not be used recurrently. Any patient requiring steroids more frequently than yearly should be started on a steroid-sparing agent.⁴⁰

Budesonide, unlike prednisolone and prednisone, undergoes extensive first-pass hepatic metabolism and is, therefore, associated with fewer systemic side effects. Its efficacy as a treatment for mild to moderate ileocaecal Crohn's disease has been demonstrated in high quality, randomized, placebo-controlled trials and comparative trials with either mesalazine or conventional CS. A Cochrane review has shown that budesonide is less effective than conventional CS at inducing remission. This may, in fact, be related to the high first-pass metabolism of budesonide. Crohn's disease is a transmural disease and also affects lymph nodes and mesenteric fat. As only 11% of budesonide is systemically available, steroid delivery to areas other than the mucosa will presumably be lesser with budesonide than with prednisolone. However, budesonide is associated with fewer (albeit dose-related) side effects (such as moon face, hirsutism and acne) than conventional CS, and is less likely to cause suppression of endogenous cortisol production. Therefore, it is indicated in preference to conventional CS to

induce remission in patients with mild to moderate ileocaecal Crohn's disease. There is little to choose between prednisone and prednisolone (the active form).

However, in patients with severe liver disease prednisolone should be used in preference to prednisone because the latter requires hepatic conversion to the former. Likewise, methylprednisolone and hydrocortisone are both acceptable intravenous treatments for severely active Crohn's disease; the former steroid has a lesser mineralocorticoid effect and is, therefore, preferred by some. Although dexamethasone has negligible mineralocorticoid effects, its use is less widespread. Adrenocorticotrophic hormone (ACTH) 120 U/day has been shown to be as effective as hydrocortisone 300 mg/day in inducing remission in severe Crohn's disease. Its use is not, however, widespread, perhaps in part due to its association with adrenal haemorrhage.⁴¹

The commonly used practice of weaning steroids over several weeks after a 1-2-week induction period is thought to decrease the chance of relapse. Steroid withdrawal regimens, should be over 4-12 weeks. Nevertheless, experience suggests that, at least in a proportion of patients, weaning decreases the chance of rapid relapse. Furthermore, weaning is normally necessary because of the effects of exogenous CS on the HPA axis.⁴²

Immunosuppressive Agents: Azathioprine (2.0-2.5 mg/kg/day) and mercaptopurine (1.0-1.5 mg/kg/day) are not indicated for use as induction therapy in patients with mild to moderately active CD due to their relatively slow onset of action (≥ 3 months). However, these agents have been found to be effective as a maintenance therapy following corticosteroid-induced remission of patients with mild to moderate CD. However, these agents are currently reserved for patients who are steroid-dependent or have complications such as fistulizing disease because of their potential for serious toxicity.⁴³

Azathioprine 2.5 mg/kg was more effective than placebo at maintaining remission for up to 15 months. Furthermore, withdrawal of azathioprine

maintenance therapy leads to a greater rate of relapse than continuation of azathioprine. Azathioprine therapy may also be advantageous for weaning CD patients off conventional corticosteroid therapy.⁴⁴

A concern of long-term, maintenance therapy is the potential for adverse side effects. Approximately 2% to 8% of patients report mercaptopurine-induced toxicity events including pancreatitis, bone marrow depression, allergic reactions and infectious complications. Others have also reported pancreatitis, allergy, and opportunistic infection, plus additional adverse events such as leucopenia and neutropenia. Furthermore, there is an increase in the rate of lymphoma during treatment with azathioprine. Approximately, half the patients who do not tolerate azathioprine will tolerate mercaptopurine.⁴⁵

Methotrexate: Methotrexate, like azathioprine and mercaptopurine, it has a slow onset of action. Thus, it is not recommended as an induction treatment for mild to moderately active CD. Methotrexate is an effective therapy for maintaining methotrexate-induced remission.⁽⁴⁶⁾ Nausea is the most common minor side effect of methotrexate treatment, and it tends to occur for a period of 24-48 h following weekly injections. Leucopenia and associated opportunistic infection have been reported, but rarely. Other concerns include hypersensitivity pneumonitis (occurs in up to 1% of patients) and hepatotoxicity (clinically important hepatotoxicity rarely occurs when treatments are administered weekly versus daily). Methotrexate cannot be used by pregnant women, as it is teratogenic. No high quality data indicate that methotrexate is associated with malignancy.⁴⁷

Calcineurin Inhibitors: Ciclosporin and tacrolimus have had a very positive impact on the success of organ transplantation, and treating certain immune-related diseases. This has created interest in these medications for the treatment of Crohn's disease. A meta-analysis of the four clinical trials evaluating ciclosporin concluded that this treatment was not effective for inducing remission in patients with active Crohn's disease.

However, there may be a role for this medication in the acute management of fistulizing Crohn's disease. The side effects of ciclosporin include: hypertension, headache, hirsutism, hypertrichosis, hypertriglyceridaemia, nausea, gingival hyperplasia, tremor, paresthesia, nephropathy and immunosuppression. Similar to ciclosporin, tacrolimus is an inhibitor of T-helper cell activation.⁴⁸

Tacrolimus has demonstrated efficacy in the treatment of severe steroid-refractory IBD, but questions persist as to the long-term outcomes of those patients treated with the "salvage" agent. Tacrolimus has been studied to determine its effect on the treatment of fistulizing Crohn's disease which end with a conclusion that using tacrolimus may alter the course of fistulizing Crohn's disease. The safety and efficacy of tacrolimus was also retrospectively studied in 47 IBD patients treated over a 5-year period, 32 of whom were receiving concomitant antimetabolites. Successful cessation of corticosteroid therapy was achieved in only 4 of the ulcerative colitis patients; remission was achieved in only 3. None of the Crohn's disease patients were able to stop corticosteroids, and only 1 achieved remission. There were 44 adverse events noted, mostly hypermagnesaemia. Although useful as a "rescue therapy," on the basis of these results, tacrolimus did not appear to be a durable option.⁴⁹

In particular, tacrolimus or ciclosporin may be appropriate as induction agents, while waiting for other therapies (such as MP/azathioprine) to start helping. Prophylaxis against *Pneumocystis carinii* pneumonia is strongly recommended when using the calcineurin inhibitors.⁵⁰

B. Anti tumour necrosis factor (TNF)-alpha

While these drugs have opened new therapeutic horizons for treating Crohn's disease (CD), they have also created new classes of adverse events related to their immunogenic properties. Other issues brought to the fore include long-term efficacy, safety and cost. Those drugs of proved benefit fall predominantly into the mechanistic domains of tumour necrosis factor (TNF)-alpha

inhibition [the chimeric antibody infliximab, the humanized antibody (certolizumab) and the human antibody adalimumab].⁵¹

Infliximab: When treating luminal disease with infliximab, approximately two thirds of patients respond initially. The efficacy of scheduled infliximab therapy was better than episodic treatment. A lower proportion developed antibodies to infliximab in the scheduled groups than in the episodic group [9% (5 mg/kg), 6% (10 mg/kg), 28% (episodic), respectively]. Scheduled strategy patients had fewer CD-related hospitalizations and surgical episodes than episodic strategy patients. Both scheduled groups had higher rates of mucosal healing.⁵²

Fistulas occur in 30–50% of CD patients at some stage during their lifetime. Most are anorectal fistulas. This complication is associated with substantial morbidity and is often very difficult to treat. Infliximab has had a major impact on the management of Crohn's anorectal fistulas. Two thirds of patients respond initially. When treating fistulas with infliximab, magnetic resonance imaging (MRI) scanning allows the extent of deep healing to be assessed. It may be useful to help decide on the duration of treatment.⁵³

Treatment with infliximab commonly results in the formation of antibodies against infliximab. Concomitant immunosuppressive therapy was predictive of low titres of antibodies against infliximab ($P < 0.001$) and high concentrations of infliximab 4 weeks after an infusion ($P < 0.001$).

Antibodies were associated with a 12% absolute increase in infusion reactions but no increase in serious infusion reactions or serum-sickness-like reactions. In effect, reduced antibody formation and greater clinical benefit were observed with an induction regimen followed by maintenance treatment compared with a single dose followed by episodic re-treatment in CD patients treated with infliximab. Loss of initial response and infusion reactions post-infliximab are strongly related to antibody formation and level. Administering a second infusion within 8 weeks of the first and concurrent immunosuppressant therapy significantly reduce antibody formation.

Intravenous hydrocortisone premedication significantly reduces antibody levels but does not eliminate antibody formation or infusion reactions.⁵⁴

Infliximab is associated with an increased incidence of infections. In the case of increased incidence of tuberculosis (TB), in most patients this is thought to be related to activation of previously dormant disease. This has been shown to occur with an incidence of approximately 1 in 2000. Experience with screening for latent or previous TB prior to treatment with infliximab, has demonstrated a marked reduction in the incidence of active TB with treatment. Such screening with a chest radiograph and skin testing should form part of standard screening practice prior to the treatment with infliximab. Other opportunistic infections are also seen after treatment with infliximab. Data regarding malignancy are conflicting. The drug carries a possible increase in the risk of lymphoma.⁵⁵

About 30% of patients with refractory Crohn's disease have consistently been found to be resistant to infliximab therapy. Moreover, not all responders display a full response. A number of clinical, biological and genetic risk factors have been investigated in randomized controlled trials to predict the outcome of infliximab therapy. Patients with biologically active inflammation as witnessed by increased CRP have the best chance of responding to infliximab therapy. Patients with non-stricturing disease and with pure colonic disease respond better to infliximab therapy. Patients treated with concomitant immunosuppression are more likely to respond both short- and long-term to infliximab therapy. Whether this additive effect is because of improved combined efficacy or to suppression of the formation of antibodies to infliximab (ATI) is not clear. Smokers are less likely to respond to infliximab. The value of smoking and immunosuppression has not been identified as clinical risk factors in all studies. Infliximab is highly effective in achieving improvement and inducing and maintaining remission in paediatric patients with Crohn's disease in fistulizing as well as luminal disease. It seems that children with early Crohn's disease have a higher chance

of prolonged response to infliximab than children with longstanding Crohn's disease.

This suggests that early introduction of the drug might be particularly efficacious to change the long-term course of Crohn's disease. The presence of a rectovaginal fistula was a poor prognostic indicator for successful infliximab therapy, but this was not suggested by the Accent II study. Several genetic factors have been studied and interesting data have been gathered but genetic predictors need to be confirmed in different cohorts of patients.⁵⁶

Adalimumab: In the CLASSIC I dose-ranging RCT comprised a total of 299 patients with moderate-to-severe CD naive to TNF α inhibitor therapy who were randomized to receive adalimumab (40/20mg, 80/40mg, or 160/80 mg) or placebo at weeks 0 and 2; the authors concluded that adalimumab was superior to placebo for inducing remission in CD patients with moderate-to-severe disease who were naive to TNF α inhibitor therapy with the 160/80mg having the most robust response.

There were 275 patients from CLASSIC I who were entered into the CLASSIC II trial. CLASSIC I and II showed that adalimumab induced and maintained clinical remission in patients with moderate-to-severe CD naive to TNF α inhibitor treatment.⁵⁷

In CHARM, 854 patients with moderate-to-severe CD received open-label adalimumab SC at doses of 80mg at week 0 and 40mg at week 2. Patients who had been exposed to infliximab in the past and either lost response or had become intolerant to infliximab were eligible for this trial. Approximately 60% of patients responded at week 4 and were then randomized to one of three treatment arms: adalimumab 40mg eow, adalimumab 40mg weekly, or placebo. There was no difference in the proportion of patients who were able to maintain remission or response according to their previous infliximab exposure. A subgroup analyses from CHARM showed that adalimumab demonstrated steroid-sparing efficacy comparable to that reported for infliximab.

Within the CHARM study population, 117 patients had active perianal fistulizing disease; one third of patients treated with adalimumab had complete and maintained healing of fistula. Results of a 12-month, open-label extension study from CHARM that assessed long-term efficacy at fistula healing (100% closure) and response ($\geq 50\%$ closure) ; showed that fistula healing rates from the start of CHARM were 50% (6 and 12 months), 56% (18 months), and 60% (24 months), while fistula response rates were 64% (6 months), 59% (12 months), and 71% (18 and 24 months). A separate analysis of the extension study showed that of the 40 patients with healed fistulas at the end of CHARM, healing persisted in 79% at 6 months and 76% at 12 months, while response occurred in 87% at 6 months and 79% at 12 months.⁵⁸

Several small trials have suggested that adalimumab may be effective in patients who have lost response or become intolerant to infliximab. Further findings from CHARM showed that adalimumab was effective in sustaining clinical remission in CD regardless of concomitant immunosuppressant therapy or history of TNF α inhibitor therapy. This issue was addressed in the GAIN study, a placebo-controlled RCT in 325 patients with moderate-to-severe CD who had failed infliximab therapy (i.e., intolerant of infliximab or must have previously responded then lost response to infliximab). Patients were treated with adalimumab (160mg at week 0 then 80mg at week 2) or placebo. At week 4, of the 301 patients who completed the trial, induction of remission was greater for adalimumab than for placebo (21% vs 7%, $p < 0.001$). Adalimumab was, well tolerated and clinically effective in patients with CD who had previously lost their response to, or could not tolerate infliximab.⁵⁹

Certolizumab: Certolizumab pegol (a polyethylene-glycolated Fab' fragment of anti-TNF) offers the prospect of infrequent subcutaneous anti-TNF antibody administration. Certolizumab 400 mg is effective and well-tolerated in patients with active CD.⁶⁰

The indications for certolizumab therapy in Crohn's disease include: (1) induction of response and induction of remission in outpatient adults with moderate-to-severe Crohn's disease; (2) maintenance of response to certolizumab and maintenance of remission after certolizumab treatment; and (3) loss of response to infliximab.⁶¹

Nutritional Therapy: There is obvious importance in ensuring adequate nutritional provision in the patient with Crohn's disease who is malnourished, but in this respect most patients with Crohn's disease differ little in assessment or intervention from other patients with malnutrition of intestinal origin. There have been interesting observations in Crohn's therapy from the use of probiotics, prebiotics and short chain fatty acids, each of which may be considered to have some nutritional component.⁶²

Complete bowel rest and concomitant exclusive parenteral nutrition can result in as many as 95% of patients with active Crohn's disease entering clinical remission, and response rates from 65% to over 90% are recorded, even for steroid-refractory disease. However, it has subsequently been realized that elemental nutrition, oligomeric and other pre-digested feeds, and polymeric liquid formula diets can yield results very similar to those obtained from exclusive parenteral feeding.⁶³

There is no robust evidence that the likelihood of induction of remission is greatly influenced by the nature of the nutritional regimen employed, beyond confidence that simple liquidized food is insufficient to yield useful responses. It is probable that a component of the response is from mechanical factors, and also that a reduction in exposure of the intestine to foreign antigenic material is important. Accordingly, the various nutritional regimens have been critically compared to determine what factors are important in the therapeutic response. Somewhat surprisingly there does not appear to be any major difference between polymeric feeds based on whole protein and complex carbohydrate, and the true elemental feeds based on amino acids and glucose.⁶⁴

The place of exclusive nutritional therapy in the maintenance of remission is even less clear-cut. Exclusion diets, with systematic slow introduction of foods once remission has been achieved have, nonetheless, been advocated. The issues of compliance take on a much greater significance to the patient when the end-point is indefinite, rather than the 4 or 8 week time course normally considered in the therapy of acute relapse. Even in patients brought into remission by nutritional therapy there will be understandable resistance to such an option. Given the impracticality (in most observers' minds) of persisting with exclusion or exclusive defined formula diets for more than a few weeks, attention has moved to studying the value of a prolonged administration of supplementary feeds (for purposes other than of countering malnutrition). There is now evidence that this may help to maintain remission. This is likely to be of real practical value, since it was previously difficult to give evidence-based advice on whether and for how long nutritional therapy should be continued once remission was achieved. All patients wish to recommence normal eating as soon as possible, but this, in combination with dietary supplements may now be considered highly legitimate if not mandatory, and can be encouraged even in the patient who is not malnourished.⁶⁵

Smoking Cessation Therapy: Case-control studies indicate that smokers have almost twice the risk of developing Crohn's disease. Studies demonstrated a decreased need for oral steroids in those quit smoking comparing with smokers over mean follow-up period of 6-10 years. The actuarial colectomy rate noticed also lower in non smokers at 10 years follow up.⁶⁶

The first report that clearly demonstrated the association between the most severe courses of Crohn's disease and smoking was in 1990. It was shown that in patients that had required surgery for Crohn's disease, smokers had a greater risk of the need for further surgery than non-smokers over 10 years. The increased risk was more marked in females than males. Heavy smokers more likely to have small bowel Crohn's disease than lighter smokers and non-smokers.⁶⁷

Smokers are more likely to have perforating complications than nonsmokers, with a greater accumulated number of fistulae. The risks of clinical, endoscopic and surgical recurrence after surgery are all greater in smokers. Heavy smokers have been shown to have significantly more recurrences than light smokers and daily consumption of tobacco seems to be more important than previous pack years.⁶⁸

Quitters indeed has a lower risk of flare up than continued smokers. A similar pattern emerged when the need for steroids or further immunosuppressive therapy is considered; smokers need more intense treatment than quitters and non-smokers. In conclusion, smoking cessation is highly beneficial to patients with Crohn's disease. The benefits become significant within 1 year of quitting and are long lasting. The effect of stopping smoking is of the same magnitude as commencing immunosuppressive therapy.⁶⁹

Acute Severe Crohn's Disease: Patients presenting acutely with severe diarrhoea, abdominal pain, anorexia or fever should be admitted to hospital. Corticosteroids provide the mainstay of treatment, together with intravenous fluids and bowel rest in the form of nil by mouth or enteral nutrition with elemental or polymeric diet only. Antibiotics (for example metronidazole) are also given if there is any suggestion of sepsis, in the form of fever, a palpable inflammatory mass, discharging fistula or severe perianal disease. Anti-emetics may be required, and opiate analgesia with pethidine can be given, albeit cautiously if there is any suggestion of toxic dilatation. DVT prophylaxis is important in view of the increased risk of thromboembolism in active inflammatory bowel disease. Stool frequency should be recorded, as should temperature and pulse. Patients must be examined at least daily, and electrolytes (especially potassium), albumin and inflammatory markers [erythrocyte sedimentation rate (ESR) and C reactive protein (CRP)] should be monitored. Plain abdominal X-rays need repeating unless symptoms settle promptly. Most patients respond well within 5-7 days, after which treatment can be changed to an oral regimen and

normal diet recommenced. For patients with acute severe disease who do not respond well to steroids, the options lie between surgery and possibly ciclosporin (4 mg per kg body weight per day as a continuous infusion). For patients with extensive disease, complex fistulae or possibly first presentation of steroid refractory Crohn's colitis, ciclosporin use is probably warranted although more data from randomized trials are required. For patients with disease that is limited in extent, early surgery is often the preferred option, as it clearly is for those whose symptoms are of obstruction which has failed to settle. Following surgery, symptoms recur at a rate of approximately 15% per year, compared to a 30-40% relapse rate at 1 year following medically induced remission.⁷⁰

Clinical Predictors Of Relapse in Crohn's disease: Different studies have specifically examined clinical markers of relapse in Crohn's disease. An age less than 25 years, interval since first symptoms of > 5 years, interval since last relapse of less than 6 months and colonic involvement as poor prognostic markers. Young age has been identified as a marker of relapse. The time since last relapse has similarly been identified, but the data are conflicting.⁽⁷¹⁾ A long interval since diagnosis was identified in a large study, but not in smaller cohorts. The disease distribution that is most consistently associated with frequent relapse is colonic disease, but ileal disease and ileocolonic disease have also been identified. Perianal disease appears to be an independent marker of a poor prognosis. The need for corticosteroids, previous surgery and the type of presentation (inflammatory or obstructive) have also been identified as prognostic markers.⁷² Most of the clinical predictors of relapse are either immutable or inconsistent. The exception is smoking, the single most important environmental influence conferring a poor prognosis in Crohn's disease. Smoking is not only associated with an increased susceptibility for the disease, but current smoking leads to an increased frequency of relapse, more surgery, more rapid recurrence post-surgery, more severe recurrent anastomotic lesions, a poorer quality of life and an overall greater mortality.

The use of oral contraceptives has been proposed as a poor prognostic marker, although the data are far less convincing.⁷³

Surgery in Crohn's disease: The majority of patients affected by Crohn's disease will require surgery during the course of their illness; 50% after 5 years and from 74% to 96% after 10-20 years of follow up. The aim of the surgery is to correct the complications of the disease or to relieve symptoms not controlled by medical therapy. In earlier times, a complete resection of the macroscopic disease was considered essential. Despite this radical surgery many patients required repeated intestinal resection over time with the consequent potential for short bowel syndrome. Several studies demonstrated an increase in the recurrence rate with the follow-up, without adverse influence of the residual microscopic disease at the margins of resection.⁷⁴

At least 75% of patients are operated on for one or more of the following complications: abdominal abscesses, internal or external fistulae, bleeding and (rarely) free perforation. These conditions have to be treated with resection. What has changed over time is the length of the resection, following the concept that as recurrence is almost inevitable; the main aim is to save as much intestinal tissue as possible. Other common complications which have to be treated by surgery are intestinal obstruction and failure of medical therapy.⁷⁵

Unfortunately, recurrences at the anastomotic site are in many instances perforating recurrences and the disease often extends for more than 20 cm, making it technically impossible to fashion a stricturoplasty. This is why the number of strictured ileocolic anastomoses treated conservatively is small compared to the number of patients presenting with this symptom.⁷⁶

In cases of patients who had undergone previous ileocolonic resections with perforating recurrent disease a combination of small resection and conservative surgery could be advocated. The ileocolic anastomosis involved with recurrent Crohn's disease is isolated and resected along with the pre-anastomotic fistulous tract.

The remaining stenotic segment is divided into two halves and a side-to-side entero-enteric isoperistaltic anastomosis is performed.⁷⁷

The frequency of post-surgical relapse has been estimated to be 37% of patients at 3 years. The estimated risk of recurrence requiring surgery to be 3.9% per annum with a cumulative risk of 41.8% at 15 years.⁷⁸

Preventing post-operative recurrence in Crohn's disease is a complex problem. The decision regarding treatment after surgery first requires a good estimation of the risk of recurrence. It is also important to consider the consequences of recurrence for the patient, and the risks and benefits of treatment, bearing in mind that it will be given over a long period. Several drugs have been tried to decrease the risk of recurrence. Corticosteroids and budesonide have proved to be ineffective. Mesalazine has significant efficacy in some, but not all trials, and a meta-analysis has established that it decreases the absolute risk by 10–15% after 1-2 years.⁷⁹ Mercaptopurine seemed to be effective in a recent study. Metronidazole and ornidazole have significant efficacy, but cannot be tolerated for long periods. Probiotics represent a new approach, but evidence for their efficacy in CD is still lacking. In the past, the strategy was to give no treatment until clinical recurrence. Another approach is to give no treatment, and then to treat the patient according to severity of endoscopic recurrence. Alternative strategies include treating all patients with mesalazine until either severe endoscopic or clinical recurrence occurs, and then to use azathioprine/ mercaptopurine, or to give azathioprine/mercaptopurine immediately, especially in high-risk patients.⁸⁰

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التطورات الحديثة الحالية في معالجة مرض كرون

يوسف العجلوني¹، مصطفى الشناق²

1- استشاري أمراض الجهاز الهضمي، مدينة الحسين الطبية، عمان، الأردن؛ 2- أستاذ في الطب وأمراض الجهاز الهضمي، رئيس قسم الجهاز الهضمي والكبد في كلية الطب، مستشفى الجامعة الأردنية، الجامعة الأردنية، عمان، الأردن

الملخص

مرض كرون مرض التهابي مزمن يؤثر على نحو رئيس في الأنسجة المخاطية للقولون، وهو في معظم الأحوال يصيب من هم في العمر بين 15 و35 سنة من الجنسين، وليس هنالك عمر مستثنى من المرض. أما سبب هذا المرض فغير معروف للآن، وهو في الدول الغربية يصيب سنوياً من 5.8 حالة في كل 100000، وتعادل نسبة شيوعه -133 حالة لكل 100000. فضلاً عن أنه يمتاز بفترات شديدة وأخرى هادئة. حالات الوفاة بسبب المرض قليلة، ولكن المعاناة معتبرة؛ إذ إن 30-60% من الحالات الشافية بالعلاج تنتكس خلال سنة. ويتوقع أن ما نسبته من 50-75% من حالات مرض كرون تحتاج إلى جراحة خلال 5-15 سنة من التشخيص. علماً أن القصد الجراحي لا يشفي من هذا المرض؛ إذ يعود في معظم الحالات بعد القصد.

مع التطور العلمي وازدياد الخيارات وعدم وجود شفاء كامل من المرض، يبقى القرار بتحديد نوع العلاج ووقته أكثر صعوبة. وفي الوقت نفسه يجب أن تكون هنالك خطة علاجية واضحة لعلاج صحيح كامل، بحيث لا تكون هناك حلقة مفرغة ننتقل من خلالها من علاج إلى آخر من غير فائدة. يأمل المريض دائماً تطوير علاج جديد يشفي المرض، كما يأمل تحسين مستوى معيشتة بعيداً عن المضاعفات ودخول المستشفى والعمل الجراحي.

تتفحص هذه المقالة التطورات الحديثة الحالية لمرض كرون من جوانب عدة.

الكلمات الدالة: مرض كرون، التهاب القولون التقرحي، أمراض الأمعاء الالتهابية، تطورات.