Chapter

Recent Advances in Diagnosis and Management of Crohn's Disease

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Abstract

The initiation of Crohn's disease, an inflammatory bowel disease, has been primarily associated with crypt inflammation and abscesses, which further progresses towards the development of mucosal lesion and ulcers followed by mucosal edema. Despite many years of research for the confirmatory role of inflammation in this disease, various pathways and diagnosis for this inflammatory cascade is still unrevealed, which in fact is of utmost importance in the assessment of disease activity and for tailoring the therapy. Till now, various histopathological as well as endoscopic examinations has been found to be effectively and accurately assess inflammatory activity, but they are invasive, time consuming and expensive and therefore are unsuitable for routine use. Consequently, the latest research is focusing on various biomarkers of intestinal inflammation and the corresponding biological therapy. So, this chapter will cover the recent advances in diagnosis and pharmacological therapies for the same.

Keywords: inflammation, biological therapy, fibrostenosis, stricture, immune response

1. Introduction

Crohn's disease (CD) is a chronic, inflammatory disease, mainly affecting the gastro-intestinal tract and is usually characterized as relapse-remitting condition with progressive bowel damage [1, 2]. Being first discovered in 1932 in the United States, its rising prevalence in Europe, North America and developing countries of East Asia and South America during the 20th century is of serious health concern [3–6]. The complex etiology of CD is still unresolved and the pathogenesis is supposed to involve various genetic, environmental, gut-mucosal and immune-mediated factors which ultimately causing the initiation of inflammatory cascade followed by altered epithelial barrier function and mucosal damage [7–9]. CD represents bowel inflammation at the time of diagnosis but with disease progression, various complications such as fibrotic stenosis and strictures occur which lead to the bowel blockages [10]. Several cohort studies have reported that in about 80% of the patients, CD is characterized by inflammation and approximately 5–28% of them presents with fibrotic structuring [11–13]. Also, in case of CD complications, the additional surgery cost presents a huge socioeconomic burden in developed as well as developing countries [6, 14].

The diagnosis of crohn's disease (CD) in clinical settings is still challenging because of the lack of accuracy and specificity of the currently available diagnostic tools, various serological, genetic and inflammatory biomarkers. Also the

heterogeneous nature of various fibrotic and inflammatory pathways involved in the disease limits the scope of such techniques [15, 16]. Preceding the inaccessibility towards the deep fibrotic site while using the invasive, expensive and time consuming conventional endoscopy, several advances have been made in the diagnosis of CD from both diagnostic and therapeutic perspectives. Diagnosis, disease activity, and therapeutic response are currently assessed by endoscopy, cross-sectional imaging, and biomarkers. Furthermore, because of paucity of effective drugs to treat inflammatory as well as complicated CD, a step-up approach of therapeutic management is required to not only to decrease disease activity but also to improve quality of life of the suffering population in clinical practice. Considering these points, this book chapter will discuss the recent advances in diagnosis and management of CD.

2. Diagnostic approach

2.1 Endoscopy and serological tests

Till now, the diagnostic process in clinical settings completely relied on various conventional techniques such as endoscopy and serological tests [7, 17]. Various antibodies against microbial antigens such as anti-Saccharomyces Cerevisiae antibodies (ASCA), outer membrane porin (anti-OmpC), flagellin (anti-Cbir1), and Pseudomonas flourescens- associated sequence 1–2 (anti-12) etcetera has been found to be involved in altered microbial biota in CD patients. IgA anti-OmpC, IgG anti-Cbir1 and IgA anti-I2 were found to be positive in approximately 55% of CD cases [18–20]. Furthermore, the elevated serum levels of various new antiglycan antibodies such as anti-aminaribioside (ALCA), anti-mannobioside carbohydrate antibody (AMCA) and anti-chitobioside carbohydrate antibody (ACCA) in CD patients has been remained an indicator for these antibodies as diagnostic biomarkers in patients suffering from CD [21]. A meta- analysis by Kaul et al., 2012, reported positive correlation between the number of positive anti-glycan antibodies and disease severity [22].

2.2 Inflammatory markers

As inflammation plays a prominent role in the initiation and progression of Crohn's disease, so determination of inflammatory state is crucial for the assessment of disease activity and for tailoring therapy. Non-invasive inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) have been used for these indications. CRP, an acute phase protein, produced primarily by hepatocytes in response to inflammatory trigger mediated by various other cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α, has proven its role as inflammatory biomarker from past decades but has since fallen out of favor as they are generally non-specific. More recently, markers of inflammation that are specific to the GI tract, such as fecal calprotectin (FC) and stool lactoferrin (SL), have been introduced as well established biomarker of intestinal inflammation. Various studies have reported the positive correlation between increased levels of FC and CD progression [23, 24]. In addition another research has documented that the increased levels of CRP, ESR in combination with fecal calprotectin proves best biomarker for the early diagnosis of crohn's disease in children suffering from abdominal pain and diarrhea [25]. Apart from this, various genetic biomarkers have evolved their role not only in the etiology of disease but also play a role in the disease pathogenesis as well as phenotype. Among genetic markers, the functional

polymorphs of the interferon regulatory factor 5 (IRF5) were found to affect the risk profile for CD [26]. The assessment of serological biomarkers and inflammatory biomarkers as an adjunct to genetic biomarkers such as extracellular matrix protein –1 (ECM1), signal transducer and activator of transcription 3 (STAT3) etcetera could help in the early diagnosis of complications associated with [27].

2.3 Advanced imaging techniques

Imaging techniques provides the platform not only to understand the pathology of the disease but are also able to provide detailed note about the molecular mechanism involved in the disease, thus helps in aiding better therapeutic decisions about the disease. Among conventional techniques, Barium follow-through (BaFT) has been used to diagnose luminal small bowel CD [28]. Nowadays, these have been replaced by new endoscopic developments such as double balloon endoscopy and capsule endoscopy as BaFTs assess only the intraluminal mucosal pathology, meanwhile obscuring the lesion caused by superimposition of the bowel loops. The development of cross-sectional imaging technologies facilitates the accurate and rapid assessment of not only the small bowel and adjacent tissues but also assess deep layers for strictures and extraintestinal complications such as abscesses & fistulas. Also the shift from techniques causing exposure of ionizing radiation such as computerized tomography (CT), towards safe non-radiating, non-invasive, cost efficient and safe cross sectional techniques such as ultrasound (US) and magnetic resonance imaging (MRI) have changed the clinical perspective towards the disease complication. The modified version of these techniques such as computerized tomography enterography (CTE), intestinal ultrasound (IUS), magnetic resonance enterography (MRE), contrast enhanced ultrasonography (CEUS) etcetera has been preferred diagnostic tools even for the early prediction of CD complications [29, 30].

2.3.1 Computed tomography enterography (CTE)

After its discovery in 1977 to assess the extent and severity of CD, CTE has evolved its role in the diagnosis of intraluminal and extraintestinal complications involved in CD patients [31, 32]. Moreover, it differs from the conventional abdominal CT scan techniques in a way that it involves the intake of enteric or oral contrast medium to achieve adequate luminal distension [33]. This technique involves the use of small bowel distension along with the mixture of low density or neutral contrast agents and an abdominal CT examination following the administration of intravenous contrast agents [29]. Apart from enabling the dynamic imaging, CTE provides additional advantages such as lower cost, lesser influence of bowel peristalsis, wide availability, and greater patient safety with lesser need of general anesthesia and better efficacy in patients sensitive to MRI [31]. However, the use of ionizing radiation make its use little disadvantageous but various new techniques has been developed which makes CT examinations at significantly lesser radiation rate in pediatrics and adolescents [34–36].

2.3.2 Small bowel ultrasound (SBUS)

This inexpensive, non-radiating and well-tolerated technique provides detailed evaluation of bowel and abdominal viscera [37]. This technique has been preferred for pediatric and young non-obese patients as obesity obscure the thorough examination. Irrespective of its dependency for use on special training and practice, it is still considered comparable to endoscopy and MRE [38, 39].

2.3.3 Magnetic resonance enterography (MRE)

As per the American College of Radiology's Appropriateness Criteria, MRE has become first line of choice for evaluating children or young patients of CD [40]. Also a recent study has demonstrated its greater sensitivity and specificity as compared to US and its superiority for disease mapping over other techniques [41]. Several studies have compared the use of CTE and MRE and reported that both the techniques have similar sensitivities and specificities in diagnosing CD [29, 42]. MRE has been reported to be more advantageous because of absence of ionizing radiations, high tissue contrast resolution, and less adverse effects because of use of intravenous contrast materials [29]. However, MRE technique also has some disadvantages including longer acquisition time, hindrance due to peristalsis and bowel movements and it has been found to be more expensive, time-consuming, and less well-tolerated than SBUS and CTE [31, 43].

Thus proteomics has emerged as an attractive approach not only to define the pathogenesis of disease but also to distinguish inflammatory and fibrostenotic phenotypes and predict the complications at an earliest. Coupling these protein biomarkers through proteomics with various non-invasive, non-radiating imaging techniques may aid in better diagnosis of CD and may provide a novel approach for the treatment of CD.

3. Therapy approach

3.1 Conventional therapeutic approach

The etiology and pathogenesis of CD is still complex and unresolved, curbing the development of new therapeutic agents for its treatment. The remission and recurrence of disease demands the effective induction and maintenance therapy while reducing the disease complications and improving the quality of life. Till date, aminosalicyclic acids, corticosteroids and various immunomodulators has been considered as therapeutic agents of choice, but lack of efficacy because of heterogenecity of disease and higher toxicity profile of these drugs have made these drugs inappropriate.

Among aminosalicylates, sulfasalazine and mesalamine has been effective in the treatment of CD. Various clinical studies have reported the role of sulfasalazine (3–6 gm/day) in the remission of mild to moderate CD [44, 45]. Mesalamine has been used routinely for decades in patients with Crohn's disease in clinical practice. A recent study have demonstrated that mesalamine at doses above 2.4 g/d was more effective than placebo for the induction of remission of Crohn's disease [46], but owing to less benefits, this class has gone out of favor in clinical practice [47]. Even various systematic reviews and meta-analyses remained inconclusive about the role of ASA in remission of active CD and preventing relapse of CD [48, 49]. Furthermore, broad spectrum antibiotics have been considered to be clinically efficacious as compared to narrow spectrum since the strain of intestinal bacteria involved in the progression of CD is still uncertain [50]. So, various clinical trials have reported the efficacy of antibiotics such as metronidazole, ciprofloxacin, clarithrmycin, rifaximin and anti-tuberculous regimen for the treatment of mild to moderately active CD [51, 52]. Rifaximin have shown its efficacy against majority of intestinal flora with relatively infrequent bacterial resistance. On the same pace, it has shown its effectiveness in CD with ciprofloxacin 500 mg, orally twice daily, given for the duration of 6 months [53]. Furthermore, a randomized controlled trial has shown the significant clinical efficacy with metronidazole [54]. As per recent

study, low-dose metronidazole in dose of 250 mg t.i.d. for the duration of 3 months even reduces the endoscopic postoperative recurrence rates in crohn's disease [55]. Moreover, Metronidazole in combination with ciprofloxacin 500 mg bid have shown promising rate of remission [56]. Furthermore, rifaximin, another broad spectrum antibiotic was found to be efficacious in various clinical trials. The double blind randomized controlled trials (RCT) were conducted by Prantera and coworkers 2006 & 2010. In these RCT's, 83 patients having 800 b.i.d. dose & 402 patients having 400–1200 b.i.d dose respectively for the duration of 3 months, have shown promising remission rate in CD [57, 58]. Various other studies have also demonstrated the same effects of rifaximin, in the dose of 800 mg b.i.d for the duration of 3 months [52, 59, 60].

Furthermore, corticosteroids were included in the algorithm of CD therapy. An accumulative body of literature has reported the preference of corticosteroid efficacy over conventional steroids and ASA's in CD, especially for ileocecal and ileal diseases [61–63]. Budesonide in combination with ciprofloxacin and metronidazole have shown effectiveness in induction of remission in CD patients but again the higher frequency of serious adverse reactions do not favor their use as routine therapy [64]. Moreover, the available data are limited to small uncontrolled trials that have not consistently demonstrated efficacy with these agents at inducing clinical remission for mild to moderate CD [54]. In addition, they are associated with a high potential for dependence and serious adverse effects [62, 65]. So, the rising detrimental effects of corticosteroids, which once has been used as first line therapy from the past decades, has led to stringent attempts to limit their use in the treatment of CD.

3.2 Advanced therapeutic approach

CD pathogenesis involves the breaching of epithelial barrier of mucosal layer and luminal microflora tend to stimulate the pro-inflammatory immune response leading to release of various proinflammatory cytokines such as interferon-gamma, interleukin 12, TNF- α and [66, 67]. Biologics therapy has been approved by FDA for the treatment of inflammatory cascade long time ago but the discovery of new molecules in this arena is still continued and represents a major breakthrough in the treatment of CD. The advanced therapeutic approach includes biologic agents such as immunomodulators, anti-TNF- α agents, IL-12, IL-23 antagonists, anti-adhesion molecules and monoclonal antibodies. Immunomodulators has been used primarily for inflammatory state of CD in clinical practice from many years. Among immunomodulators, Azathioprine (AZA) and 6-mercaptopurine (6-MP) has been included in the meta-analysis studies and have revealed their role in the remission in CD patients but with occurrence of serious adverse effects [68, 69]. On the other side, biologicals such as TNF-α antagonists and IL antagonists have been adopted for the treatment of CD complications such as fistulas and strictures. Moreover, these offer advantage over corticosteroids which tend to suppress the entire immune system and produce various adverse effects. Biologics target the inflammatory pathway specifically, with lesser unpredictable side effects. The US Food & Drug Administration (FDA) approved infliximab in 1998, followed by the approval of adalimumab and certolizumab. These TNF-α antagonist remained as an effective option among biologics since now for the treatment of CD. Systematic reviews and meta-analyses have evidenced about the role of adalimumab and infliximab in the maintenance and remission of CD [70–72]. Moreover, various optimization strategies have been given regarding the use of anti-TNF agents in CD patients. Likewise, as per SONIC study, infliximab was found to be more efficacious when given in combination with azathioprine as compared to monotherapy [73]. Although

TNF-antagonist therapy has greatly improved the management of CD, these drugs have some important limitations [74, 75]. Also, Up to one-third of patients do not respond to induction therapy, and an additional 40% lose response over the first year [76]. Treatment with a second TNF antagonist in patients failing these agents has only modest efficacy [77]. Thus, a need exists for alternative therapies. So, in recent years, a range of newer molecules has been discovered and implemented in clinical practice. Among these agents, Vedolizumab and Ustekinumab have shown effective and safe profile in the induction and remission of CD [78, 79]. Vedolizumab, the selective leukocyte adhesion molecule inhibitor was approved for CD in 2014, followed by ustekinumab, the monoclonal antibody that targets interleukin-12 and interleukin-23 in 2016. Furthermore, Pirfenidone and nintedanib which have been used for the treatment of pulmonary fibrosis have also proven their role in the management of fibrostenotic CD [80, 81]. Considering the efficacy of combination of immunomodulators with biologicals, it has been reported that inflixmab prescribed along with thiopurines is more efficacious as compared to infliximab alone or thiopurines alone [82].

Thus, 5-Aminosalicylic acid agents are not considered as first choice for treatment of CD. Corticosteroids such as Budesonide and Prednisone are now-a-days considered as the first line agents. Broad spectrum antibiotics such as metronidazole, ciprofloxacin, clarithrmycin and rifaximin have been considered to be clinically efficacious and remained as important adjuncts for the treatment of mild CD. Immunomodulators are used as second line agents in mild to moderate Crohn's disease. They act by modifying the immune system while inducing and maintaining remission. Biologicals such as Adalimumab, Infliximab, certolizumab, Vedolizumab eand Ustekinumab are used in moderate to severely active CD.

4. Conclusions

On concluding remarks, the diagnosis as well as management of CD and associated complications should remain the ultimate goal. From diagnostic perspective, CTE and MRE are at the forefront and providing new ways to quantify disease activity in order to provide more personalized therapy in clinical practice. Furthermore, from the diagnostic perspectives, the continuous evolvement of biologicals such as anti TNF-α and IL-antagonists has been proven as revolution in the treatment of inflammation as well as various complications associated with CD. Although the current therapy available for CD meets the safety as well as efficacy data requirements, still there is need of newer agents with high efficacy, less side effects and improved pharmacodynamic as well as pharmacokinetic profile. So, the anticipated discovery of new diagnostic biomarkers and therapeutic agents while minimizing the use of conventional endoscopic and radiologic examination will enable physicians to provide individualized treatment plans in order to improve the long-term prognosis of patients suffering from CD.

Conflict of interest

The authors declare no conflict of interest.

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