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Progress in the Diagnosis and Management of Inflammatory Bowel Disease

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ABSTRACT

Inflammatory bowel disease (IBD) is an idiopathic disease caused by chronic activation and inflammation within the gastrointestinal tract. Effectively induction and maintenance of disease remission and prevention of complications are the most important therapeutic goals in the IBD management. Recent advancement has provided new insights into the diagnosis and treatment option for patient with IBD. This review was aimed to present an overview of the current expanding knowledge about IBD diagnosis and management, including diagnostic and evaluation tools, such as genetic test, biochemical surrogate markers of activity, endoscopic techniques and radiological modalities, and therapeutic progress, which encompass medical, endoscopic and surgical interventions. With a better understanding of new information concerning IBD diagnosis and management will lead to the development of increasingly effective and individualized pharmacological treatment modality for IBD patients.

INTRODUCTION

Inflammatory bowel disease (IBD), including two main entities - ulcerative colitis (UC) and Crohn's disease (CD), is an idiopathic disease caused by chronic activation and inflammation within the gastrointestinal tract. It is reported that increased incidence and prevalence of IBD over the past 50 years, up to 8–14/100,000 and 120–200/100,000 persons, respectively, for UC and 6–15/100,000 and 50–200/100,000 persons, respectively, for CD [1,2]. Moreover, a lifelong relapsing and remitting course is commonly observed in patients with IBD, which could lower the quality of life and lead to long-term sequelae [3,4]. Therefore, effective early diagnosis and reasonable management of IBD is critical for these people suffered with IBD.

Among IBD, UC is limited to the superficial layers of the colon [5,6], whereas CD can involve any segment of gastrointestinal (GI) tract from the mouth to the anus. The clinical manifestations mainly include GI bleeding, toxic megacolon, or, with long-term unmanage disease, which could finally result in colorectal cancer (CRC), for UC [7,8], and diarrhea, abdominal pain and malnutrition, for CD[9-11], respectively. Furthermore, a wide range of extraintestinal manifestations such as sclerosing cholangitis, spondyloarthropathy, and metabolic bone disease, are also considered to be related with both UC and CD [12].

The therapeutic goal of IBD treatment is to reduce the inflammation that triggers signs and symptoms. Mucosal healing medications, including oral and/or rectal anti-inflammatory drugs, immunomodulators, or biologic agents, are firstly applied in the treatment of IBD [13-15]. When failure of above medications, surgical intervention in the form of colectomy or resection of the affected bowel segments is considered a cure for IBD [16,17]. However, certain detrimental complications could be caused in the long run and further management is required [18].

Recently, advancements have been made on both evaluation tool, which can assess proximal segments of the small bowel that are beyond the reach of standard ileocolonoscopy [19-21], and novel drugs, which have been proven safe and effective in IBD treatment [22]. However, certain evidences are still necessary to confirm the impact of these advancements on the overall outcome of IBD patients.

The aim of this review is to present the recently introduced diagnostic and therapeutic advancements in clinical practice and to discuss their impacts and limitations on the improvement of the overall care of IBD patients.

MATERIALS AND METHODS

We performed a comprehensive searching in two main literature databases PubMed and Web of Science by using following keywords: inflammatory bowel disease, ulcerative colitis, Crohn's disease, diagnosis, evaluation, testing, radiology, treatment, therapy, randomized controlled trials (RCTs), surgery, and endoscopy. After that, a more focused search was conducted for each section using additional relevant keywords. Inclusion criteria were not restricted to English papers, and

also relevant non-English paper was included. All retrospective studies, observational cohort studies, case control studies, RCTs, meta-analyses, and systematic reviews discussing the related topic were also included as sources of data. Moreover, a different single author performed data extraction for each section, in addition to the primary author (X.N.). Results were compared and conflicts were resolved by consensus.

RESULTS

IBD Diagnosis

Several aspects of challenges were presented in the early diagnosis of IBD, especially when the disease is limited to the small bowel. In reality world, presence of GI symptoms for months to years was usually reported by the patients prior to the diagnosis, which could result in the delay of the diagnosis. Several reasons, such as lack of gastroenterologist and resource [23,24], the vague and overlapping symptoms, might attribute to the delay.

In addition, recent progress in abdominal imaging, such as magnetic resonance (MR) imaging and computed tomographic enterography (CTE), as well as in endoscopic imaging, such as small bowel enteroscopy (SBE), should constitute adjunct investigational means to standard ileocolonoscopy. Currently, MR and CTE are considered as the key modality in the disease diagnosis and prognosis judgment [25].

Diagnostic and Evaluation Advances

Serological markers

Recent studies have identified several serological markers are associated with IBD, and these markers have been used in IBD and irritable bowel syndrome (IBS) discrimination, IBD subtypes and CD phenotypes identification, disease prognosis confirmation and prediction for requirement of surgery. The markers are *Escherichia coli* (OmpC), *Pseudomonas fluorescens* (I2), flagellin (CBir1), *Saccharomyces cerevisiae* (SCA), laminaribioside (LCA), chitobioside (CCA), mannobioside (MCA), laminarin (L), and chitin (C), for CD, and anti-neutrophil cytoplasmic autoantibodies (pANCA), antibodies against goblet cells (GAB) [26], anti-proteinase 3 (anti-PR3) [27], and high mobility group box 1 and box 2 non-histone chromosomal proteins (HMGB1 and HMGB2) [28], for UC, respectively. Several clinical trials have been performed to verify the effectiveness of these markers. Van Schaik et al [29] extracted the data from The international European Prospective Investigation into Cancer and Nutrition (EPIC) study demonstrated that the combination of the serological markers pANCA, ASCA, anti-CBir1, and anti-OmpC was able to predict the development of CD and UC (area under the curve 0.68 and 0.66, respectively) in individuals from a low-risk population. Moreover, the predictive value of the combination of these markers increased when time to the diagnosis of IBD decreased. However, the efficacy of these markers in IBD and IBS differentiation has not yet well examined. Other than IBD and IBS differentiation, biomarkers are also needed in differentiation of CD and UC. Kaul et al. [30] demonstrated in a recent published

meta-analysis anti-Saccharomyces cervisiae antibodies (ASCA) had the highest diagnostic odds ratio (DOR) for differentiating IBD from healthy (DOR 21.1; 1.8-247.3), and CD from UC (DOR 10.2; CI 7.7-13.7). Furthermore, they also showed that ASCA positive individuals developed stricturing or penetrating/fistulizing manifestation of CD with a sensitivity of 70.8% and specificity of 48.5%, while anti-chitobioside carbohydrate antibody (ACCA) exhibited the highest specificity of 75.1% but a lower sensitivity (43.3%), with a DOR of 2.7 (95% CI 2.0-3.6). The same study further showed that increased level of these anti-glycan markers were associated with a more aggressive disease course, complications and need for surgery. Zhang et al. [31] also demonstrated in their meta-analysis that the ASCA-positive status was associated with higher risk of early-onset age (OR 2.25, 95 % CI 1.41-3.57, P < 0.001), ileal involvement disease (1.70, 1.05-2.77, P = 0.03), complicated disease behavior (2.09, 1.71-2.57, P < 0.001), perianal disease (1.49, 1.14-1.94, P = 0.004), and risk for surgery (1.61, 1.29-2.01, P < 0.001). In a cohort study about pediatric patients with CD, Dubinsky et al. [32] showed that an increased and decreased frequency of penetrating and structuring phenotypes were associated with a positive statue of anti-anti-OmpC [hazard ratio (HR) 2.4, 95% CI 1.2-4.9] and anti-CBir1 (HR 2.5, 95% CI 1.2-5.2), and pANCA (HR 0.16, 95% CI 0.04-0.70), respectively.

Genetic markers

Other than serological markers, genetic markers also play a critical role in disease manifestation and progression. Multiple shared loci between immune-mediated inflammatory disorders were also presented in IBD. Interferon regulatory factor 5 (IRF5) polymorphisms was demonstrated to be associated with systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, multiple sclerosis, psoriasis and IBD [33]. IRF5 polymorphisms were also found to contribute to the risk profile for CD and UC along with ancestry and nucleotide oligomerization domain 2 (NOD2) genotypes. Lu et al. showed that no association between NOD1/CARD4 insertion/deletion polymorphism and IBD, CD, and UC. Stratification of cases by age showed that NOD1/CARD4 insertion/deletion polymorphism was associated with IBD in younger age group at onset (< 40 years) (GG vs T: OR = 0.68, 95% CI: 0.50-0.93, P = 0.02; GG/T + GG/GG vs T/T: OR = 0.71, 95% CI: 0.59-0.85, P = 0.0003).Several studies have demonstrated that the patient genotype was associated with the development of anti-glycan markers [30,34]. For examples, CARD 15 variant in CD was associated with an increased possibility of ASCA and ALCA positive (66% and 43%, respectively) [34], and high ASCA level [34, 35]. Additionally, combination use of serological markers and genetic markers, such as autophagy-related 16-like 1 (ATG16L1), the NK-2 homeobox NKX2-3, extracellular matrix protein-1 (ECM1), and signal transducer and activator of transcription 3 (STAT3) could increase the accuracy in IBD and non-IBD discrimination (area under the curve from 80% to 86%, $P < 0.001$), as well as UC and CD discrimination (area under the curve from 78% to 93%, $P < 0.001$) [36]. Lichtenstein et al. [37] demonstrated that increased frequency of complications in patients with single nucleotide polymorphism (SNP) 13 NOD2 risk alleles compared to those without NOD2 mutations. Also, use of the model combining serologic

and NOD2 genetic markers may provide physicians with a tool to assess the probability of patients developing a complication over the course of CD [37].

Noninvasive inflammatory markers

Other than serological and genetic markers, non-invasive inflammatory markers have earned more and more interest in IBD daily assessment. Application of these markers has expanded from initial diagnosis to differentiation between IBD and other disease, prognosis evaluation and relapse prediction. These inflammatory markers include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) [38] and, more recently fecal calprotein (FC) and stool lactoferrin (SL). As an iron-binding glycoprotein secreted by neutrophils, lactoferrin could be detected in stool as an indicator of inflammatory reaction generated on the mucosal surface [39]. Several studies have been shown that SL is a useful marker on IBD diagnosis in patients with lower GI symptoms, and disease statue differentiate (active or inactive) [40-42], especially in pediatric patients [43]. Moreover, SL is also well associated with endoscopic severity in colonic IBD (r=0.9) [44], and exhibit high positive predictive value (PPV; 100%) and negative predictive value (NPV; 83%) in small bowel CD diagnosis [45]. However, the association between SL and mucosal healing and disease relapse has not been examined yet. Calprotein is a protein possessed antimicrobial properties and is secreted by inflammation triggered white blood cells and squamous cells [46]. With the advantage of proteollytic enzymes and heat resistant, FC is considered as a good marker for disease detection. Roseth et al. [47] showed in their study that FC reflects the granulocyte migration through the gut wall in patients with IBD and hence might serve as a simple, inexpensive alternative to the indium-111 technique. Furthermore, several studies have also shown that FC could reflect disease severity and recurrence in UC patients with infliximab treatment [48,49]. However, due to lacking of direct evidece about the association between FC level and endoscopic remission, the real value of FC is still needed further evaluation.

Diagnostic imaging

The evolvement of imaging modality has resulted in the possibility to assess the bowel area that beyond the reach of the conventional ileocolonoscopy, to detect extraluminal involvement and complication of IBD, and to differentiate between UC and CD. However, thus far, these requirements could not be achieved by a single imaging modality. Over the past decades, small bowel follow through (SBFT) was used as alternative imaging modality to examine the area of small bowel that could not be reached by endoscopy. However, with the presence of cross-sectional imaging modalities, SBFT has gradually fallen out of favor.

MR imaging

As the most attractive imaging modality and promising investigatory tool for IBD patients, MR possesses the advantages of non-invasive and no ionized radiation. Masselli et al. [50] showed that MR enteroclysis can be served as the diagnostic procedure for initially evaluating in both adults and pediatric patients suspected of having CD because it allows accurate assessment of

both the proximal and distal small bowel. Several reports have studied the accuracy of MR imaging in CD, and the sensitivity and specificity were ranging from 88%-98% and from 78% to 100%, respectively. However, MR colonography exhibited a low efficacy colonic inflammation detection. Schreyer et al compared MR based colonography with conventional colonoscopy for assessing the presence and extent of colonic inflammation, and their results found that the sensitivity of MR colonography for correctly identifying inflammation on a per segment analysis of the colon was 31.6% for CD and 58.8% for UC. They concluded that MR based colonography is not suitable for adequately assessing the extent of colonic inflammation in patients with IBD. Furthermore, MR can be used for inflammatory and fibrostenoticstrictuing differentiation, and hence could be suitable for treatment guide. In addition, extraluminal manifestations related to CD, such as lymphadenopathy, fistulas and abscess, could also be determined by MR, with a high accuracy rate (100%) [51].

Computed tomographic enterography (CTE)

CTE shares the similar principles to MR modalities. Studies have shown that the accuracy of MR enterography and CTE was comparable in disease activity and bowel damage detection, extraluminal complications (especially intra-abdominal abscess), whereas MR exhibited a better anatomical structure description in intestinal strictures, fistulae and/or sinus tracts. Due to the availability and shorter examination time, CT is particular suitable for IBD diagnosis in the setting of acute and emergency condition.

Small bowel ultrasound

With the advantages of safe and inexpensive, Ultrasonography (US) is suitable for small bowel abnormalities detection. For the patients with a low risk of IBD, US could be used as the first-line imaging procedure due to it has a good NPV for IBD [52]. However, as shown in a previous study, detection of superficial lesions and deep intestinal loops evaluation could not be achieved by US [53].

Endoscopic advances

Capsule endoscopy

wireless capsule endoscopy (WCE) was approved by FDA in 2001 and was usually performed after ileocolonoscopy. CD diagnosis by WCE could be based on the criteria of European Crohn's and Colitis Organization (ECCO) [25], and Tukey et al. [54] found that the sensitivity, specificity, PPV and NPV was 77%, 89%, 50% and 96% for suspected CD diagnosis when using ECCO criteria.

Small bowel enteroscopy

Double balloon enteroscopy (DBE) is currently the most studied and established technique in deep small bowel enteroscopy. Intubation by DBE(240-360 cm antegrade and 102-140 cm retrograde) is deeper than enterscopy (90-150 cm) or ileocolonoscopy (50-80 cm) [55]. CD could

be detected in 5-13% patients who underwent DBE for suspected small bowel disease [55]. The limitation of DBE is relative lower success rate in patients with abdominal surgery history [56].

Spiral enterscopy

Enteroscopy equipped with the Endo-Ease System (Spirus Medical, Stoughton, MA, USA) uses a spiral-shaped overtube, 118 cm long, with a spiral ridge of 0.55 cm high and 22 cm long and is compatible with enteroscopes less than 9.4 mm in diameter [57]. Spiral enteroscopy takes less time to perform, but the less intubation depth than that of DBE. Limited studies have reported its use and safety in CD patients. Furthermore, the operative characteristics of spiral enteroscopy remained unclear.

Chromoendoscopy

Recently, the use of pan-colonic chromoendoscopy with targeted biopsies has been shown to improve adenoma detection rate [58,59]. In chromoendoscopy, application of dye solutions the mucosa of the colon could enhance the recognition of details to uncover the mucosal changes, which were not seen by the optical methods before targeted biopsy and histology [60]. Marion et al. [58] showed in a meta-analysis that colonoscopic surveillance of chronic colitis patients using methylene blue dye-spray targeted biopsies results in improved dysplasia yield compared to conventional random and targeted biopsy methods. Moreover, physician should avoid to use chromoendoscopy in patients with active disease and those with poor bowel preparation because of high rates of false-positive and false negative findings.

MANAGEMENT ADVANCES

Medical advance

TNF antagonist

IFX (Remicade®) is the first approved TNF antagonist, which has been shown to be effective in CD [61] and UC [62] treatment in multiple studies. IFX is given as an intravenous infusion of 5 mg/kg at weeks 0, 2, and 6 for induction, followed by 5-10 mg/kg every 8 weeks (often decreased to every 6 weeks) for maintenance. ADA (Humira®) is a humanized IgG1 monoclonal antibody (mAb) that irreversibly binds with high affinity and specificity to soluble TNF-α, which has been shown to be effective in patients with moderate severely active biologic-naïve CD and used as induction/maintenance agent for UC [63]. ADA is self-administered subcutaneously (SC) but given more frequently to maintain remission (every 2 weeks). CertolizumabPegol (CTZ) (Simzia®) is the third anti-TNF agent, and it possesses the advantages of a long half-life, not crossing the placenta, and not being excreted into breast milk, thus, it is suitable for pregnant females with IBD [64]. Golimumab (GOL) (Symponi®) is the newest anti-TNF agent, which is given by SC injection. The studies on GOL are ongoing, to date the data is encouraging and suggests that it is an effective agent for patients with moderate to severe UC [65].

Leukocyte trafficking inhibitors

Natalizumab (NTZ) (Tesabri®), a humanized IG4 mAb that inhibits leukocyte adhesion through antagonizing α4 integrin, was firstly shown effective in the treatment of relapsing multiple sclerosis (MS) [66]. Subsequently, NTZ showed effectiveness in the induction and maintenance of remission in patients with active CD [67]. Vedolizumab (VDZ; also known as MLN002) is a selective inhibitor of the integrin α4β7, which is considered as a central molecule in the process of leukocyte trafficking [68]. Previous phase I and II and recent phase III clinical trials of VDZ in IBD have proven the drug to be effective as an induction and maintenance agent for both UC and CD [69-71].

Interleukin (IL)-12/23 inhibitor

Ustekinumab (UKB) (Stelara®) is a fully human IgG1 mAb targeting p40 subunit to inhibits IL-12/23. After effectiveness confirmation in the treatment of psoriasis [72], two large multicenter RCTs has shown that UKB is an effective agent for the induction and maintenance of remission for patients with moderate to severely active CD refractory to anti-TNF therapy [73,74].

Probiotics

Normal colonic bacterial flora plays an important role in innate and adaptive immune regulation and the responses to foreign pathogens. In pouchitis, Probiotics have been shown to be effective in inducing and maintaining remission as well as pouchitis prevention [75,76]. Recently, probiotics have been shown to be an effective strategy to treat different severity (from mild to moderately) active UC [77] and CD through inducing and/or maintaining remission [78].

Endoscopic advances

More conservative approaches such as endoscopic balloon dilatation (EBD) and endoscopic stenting should be considered when fibrostenotic strictures do not typically respond to medical treatment and before consideration of surgical resection.

Endoscopic balloon dilatation

Couckuyt et al. [79] reported a procedure success rate of 90% and total long-term success rate of 62% in a prospective follow-up study of 55 CD patients with ileo-colonic stricture who underwent 78 dilatations. However, 6 patients were found with severe complications (11%, 8% of procedures). Their data showed that endoscopic dilatation using the through the scope hydrostatic balloon system could relieve obstructive symptoms resulting from ileocolonic Crohn's strictures. Recent published larger clinical trials showed a high success rate and a lower complication in the setting of similar operation. Thienpont et al. [80] studied 138 patients who underwent 237 dilatations for a clinically obstructive stricture; an immediate success rate was achieved in 97% with a 5% serious complication rate. After a median follow-up of 5.8 years, recurrent obstructive symptoms led to a new dilatation in 46% or surgery in 24%. Furthermore, in a recently published

larger clinical study with 776 dilatations involving 178 patients with CD, Gustavsson et al. [81] showed that a high technical success rated of 89% and a lower complication rate (5.3%). At 1, 3, and 5 years, no further intervention or one additional dilatation at the most occurred in 80%, 57%, and 52% patients, respectively. In a meta-analysis included 13 studies conducted between 1990 and 2007 showed that The technical success rate was 86%, long-term clinical success rate was 58%, and the rate of major complications was 2% in a total number of 347 CD patients and 695 dilation procedures [82]. Furthermore, Endo et al. [83] investigated the short and long-term outcomes of EBD for CD strictures and showed that a stricture length ≤ 4 cm was associated with a surgery-free outcome. They concluded that Anastomotic strictures were associated with better long-term outcomes than de novo strictures, indicating that stricture type might be useful for predicting the long-term outcomes of EBD.

Endoscopic stenting

Endoscopic stenting is another endoscopic approach available to treat cases of CD with refractory fibrostenotic stricture through placement of a temporary self-expandable metal stent (SEMS) under the endoscope [84]. Recent studies using stent with improved thearpeutic properties [85,86] also showed encouraging results, but their long-term efficacy and safety requires further studies.

Surgical advances for UC

Total colectomy with end ileostomy

Causey et al investigated the outcome of patients who underwent surgery for UC by analyzing The American College of Surgeons National Quality Improvement Project (ACS-NSQIP) database which included 1077 UC patients who underwent colectomy showed that laparoscopy was associated with lower morbidity (complication rate 21 vs. 32%, $P < 0.001$) and mortality rates (0.2 vs. 1.7%, $P = 0.046$) when compared to open surgical approaches [87]. They also showed that an 8.5% annual increase of utilizing laparoscopic colectomy in UC patients.

Restorative proctocolectomy with IPAA

Restorative proctocolectomy with an IPAA is currently considered the standard surgical treatment for patients with UC in certain condition [88]. Although IPAA is reported with excellent functional outcomes and improved quality of life, complications is still existed. Teixeira et al. [89] reported a 42% of early complications and a 36% late complications. They concluded that Ileal pouch-anal anastomosis is associated with a considerable number of early complications. There was no correlation between pouchitis and severe disease, operation with or without ileostomy, or early postoperative complications. The incidence of pouchitis was directly proportional to duration of time of follow-up.

Surgical advances for CD

Laparoscopic bowel resection

It is reported surgery is needed in 70-90% of patients despite the advancement in the medical management of CD during the course of their disease[90]. Makni et al compare laparoscopic-assisted and open ileocolic resection for primary CD and found that laparoscopic ileocecal resection is feasible and safe with a lower 5-year risk of small bowel obstruction compared to open approach (5% vs. 9%, *P*= 0.25), but the risk of recurrence is similar between them [91].

In conclusion, the care of IBD patients requires continuous care across the patient's lifetime, at various states of disease activity, with the goal of maintaining remission and preventing long-term complications. Rapid evolvement of more useful evaluation tool and effective drug therapies could result in a better management of IBD.

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