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MINIREVIEWS

Antibody markers in the diagnosis of inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is a chronic intestinal inflammation of unknown etiology. The diagnosis of IBD is based on endoscopic, radiologic and histopathologic criteria. Recently, the search for a noninvasive marker that could augment or replace part of this diagnostic process has become a focus of IBD research. In this review, antibody markers, including microbial antibodies, autoantibodies and peptide antibodies, will be described, focusing on their common features. At present, no single marker with qualities that are satisfactory for the diagnosis and treatment of IBD has been identified, although panels of some antibodies are being evaluated with keen interest. The discovery of novel IBD-specific and sensitive markers is anticipated. Such markers could minimize the use of endoscopic and radiologic examinations and could enable clinicians to implement individualized treatment plans designed to improve the long-term prognosis of patients with IBD.

Key words: Biomarker; Crohn's disease; Serological antibody; Ulcerative colitis

Core tip: The diagnosis of inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is based on endoscopic, radiologic and histopathologic criteria. Recently, the search for a noninvasive marker that could augment or replace part of this diagnostic process has become a focus of IBD research. In this review, antibody markers, including microbial antibodies, autoantibodies and peptide antibodies, will be described, focusing on their common features. The discovery of novel IBD-specific and sensitive markers

is anticipated. Such markers could minimize the use of endoscopic and radiologic examinations and could enable clinicians to implement individualized treatment plans designed to improve the long-term prognosis of patients with IBD.

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INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic relapsing disorder involving the gastrointestinal tract. The pathogenesis of IBD is complex, but the current model favors a dysregulated immune system that is triggered by luminal antigens, including intestinal bacteria and food antigens, in a genetically susceptible host. The diagnosis of IBD is based solely on invasive endoscopic, radiologic and histopathologic criteria. Recently, the search for a noninvasive test that could augment or replace part of this diagnostic process has become a focus of IBD research.

A biomarker is a traceable substance that is introduced into an organism as a means of examining organ function or other aspects of health. It can also be a physiological substance that, when detected, indicates a particular disease state. More specifically, a biomarker indicates a change in the expression or state of a protein that is correlated with the risk or progression of a disease or with the susceptibility of a disease to a given treatment. IBD is characterized by the production of several serological antibodies with distinct antigenic specificities, including microbial antibodies and autoantibodies. The challenge lies in finding one marker or a combination thereof that not only distinguishes IBD from non-IBD, or identifies at-risk populations, but that can also help clinicians distinguish between IBD subtypes (CD or UC) and, perhaps most importantly, predict the course of the disease over time and the impact of treatment outcomes.

The objective of this paper is to provide an overview of current knowledge on available clinical data and possible future perspectives for the use of antibody markers in the diagnosis of IBD. We also present data regarding a new marker that we have discovered in patients with CD.

CLASSIFICATION

Antibody markers in IBD can be classified into two groups: autoantibodies, which are antibodies to intestinal and non-intestinal self-constituents, and microbial antibodies, which are antibodies to microorganisms, including bacteria, yeasts and fungi (Table 1). In addition, antibodies against some peptides, the target antigens of which remain unclear, have also been reported.

Autoantibodies

Anti-neutrophil cytoplasmic antibody: Anti-neutrophil cytoplasmic antibody (ANCA) is classified according to two staining patterns: cytoplasmic ANCA (cANCA), in which the entire cytoplasm is stained, and perinuclear ANCA (pANCA), in which the area around the nucleus is stained. cANCA is expressed in Wegener's granulomatosis and other diseases, and pANCA is observed in IBD. In IBD, the antigen that corresponds to pANCA is thought to be histone 1, whereas in vasculitis, it is thought to be proteinase 3 and myeloperoxidase. pANCA is regarded as an autoantibody that is induced by a cross-reaction with intestinal bacterial antigens. pANCA is detected in 60%-70% of UC cases, 10%-15% of CD cases, and less than 5% of non-IBD colitis cases[1,2]. Moreover, patients with pANCA-positive CD exhibit a clinical phenotype resembling that of UC[3]. Unlike the pANCA in vasculitis, IgG from pANCA-positive UC was not able to activate a neutrophil respiratory burst[4].

Pancreatic antibody: Pancreatic antibody (PAB) is an antibody to a trypsin-sensitive protein in pancreatic secretions[5]. PAB is positive in 20%-40% of CD cases and 5% of UC cases[6]. PAB expression may exhibit racial differences. One study describes a positive rate of 46% among Chinese patients with CD, compared with 22% among Western patients[7]. The role of PAB in the diagnosis of IBD requires further study.

Microbial antibodies

Anti-*Saccharomyces cerevisiae* antibody: Anti-*Saccharomyces cerevisiae* antibody (ASCA), an anti-glycan antibody, is an antibody against mannan on the cell wall surface of baker's yeast (*S. cerevisiae*). The fact that CD is common in bakery workers (baker's disease) and that the disease activity of CD decreases in response to a diet low in baker's yeast suggest that ASCA is involved in the pathogenesis of CD. On the other hand, because mannan, which is the antigen recognized by ASCA, is a cell wall constituent of living organisms, including baker's yeast, and is also present as a protein in the human body, the immunogen may be something other than the yeast. Increases in IgG and IgA ASCAs have been reported in patients with CD, and although IgA ASCA has a high specificity, its sensitivity is not so high; instead, IgG ASCA is generally used as a biomarker[8]. The IgG ASCA-positive rate is 60%-70% in patients with CD, 10%-15% in patients with UC, and less than 5% in

Table 1 Target antigens and positive rates of antibody markers in inflammatory bowel disease

Antibody	Target antigen	Positive rate	
		Crohn's disease	Ulcerative colitis
Auto-antibody			
pANCA	Nuclear histone 1 of polymorphonuclear leukocytes	10%-15%	60%-70%
Anti-pancreas antibody	A trypsin-sensitive protein in pancreatic juice	20%-40%	About 10%
Microbial antibody			
ASCA	Mannan in the cell wall of bakers' yeast	60%-70%	10%-15%
ACCA	Chitobioside in the cell wall of yeasts and bacteria	20%-40%	About 10%
ALCA	Laminaribioside in the cell wall of yeasts, fungi, wheat and algae	20%-40%	About 10%
AMCA	Mannobioside in the cell wall of microorganisms	-	-
Anti-OmpC antibody	Outer-membrane protein OmpC of *Escherichia coli*	55%	5%-10%
Anit-Cbir1 antibody	Flagellin, a component of the flagella of indigenous bacteria in colitis mice	55%	10%
Anti-I2 antibody	I2 component of *Pseudomonas fluorescens* in mononuclear cells in the intestinal mucosa in Crohn's disease	55%	10%

pANCA: Perinuclear anti-neutrophil cytoplasmic antibody; ASCA: Anti-Saccharomyces cerevisia antibody; ACCA: Anti-chitobioside carbohydrate antibody; ALCA: Anti-laminaribioside carbohydrate antibody; AMCA: Anti-mannobioside carbohydrate antibody; OmpC: Outer-membrane porin C.

patients with non-IBD colitis[2,8]. ASCA also increases significantly in Japanese patients with CD, but the titers and positive rates are lower than those in Western CD patients, indicating that the expression of ASCA may also be affected by race[9].

Novel anti-glycan antibodies: New anti-glycan antibodies, including IgG anti-laminaribioside carbohydrate antibody (ALCA), IgA anti-chitobioside carbohydrate antibody (ACCA), and IgG anti-mannobioside carbohydrate antibody (AMCA), were reportedly elevated in the sera of CD patients in recent studies using GlycoChip microarrays[10,11]. These antibodies mainly target the cell wall components of microorganisms, including yeasts, fungi, and bacteria. The positive rate of both ALCA and ACCA is 20%-40% in CD and 10% in UC, but an improvement in CD diagnostic utility is expected using a combination of these new antibodies with ASCA. Laminaribioside, a laminarin component, is known to promote dectin-1-dependent cytokine production from macrophages and T-cell proliferation, and the increased expression of chitinase 3-like-1, which has the ability to bind chitin (containing chitobioside as a component), has been reported in intestinal epithelial cells and lymphocytes at sites of IBD. Both of these findings are very interesting and suggest that these cell wall components are involved in the pathogenesis of IBD.

Anti-outer-membrane porin C antibody: The anti-outer-membrane porin C (OmpC) antibody is an antibody to an outer-membrane protein of *Escherichia coli*. IgA anti-OmpC is positive in 55% of CD cases, 5%-10% of UC cases, and 5% of non-IBD colitis cases, and is even positive in 17%-36% of indeterminate colitis cases[12-16].

Anti-Cbir1 antibody (anti-flagellin antibody): Anti-flagellin (Cbir1) antibody is an antibody to a flagella component of indigenous bacteria in colitis mouse model[17]. Cbir1 has been cloned from the sera of colitis mice as a colitis-associated bacterial antigen. IgG anti-Cbir1 is positive in 55% of CD cases, 10% of UC cases, and 8% of non-IBD colitis cases[17-19]. After binding to Toll-like receptor-5, flagellin activates NF-κB and promotes the production of pro-inflammatory cytokines. Notably, colitis developed when flagellin-specific $CD4^+$Th1 cells were transferred into severe combined immunodeficiency mice, suggesting that the antigen is involved in the pathogenesis of colitis[18].

Anti-I2 antibody: Anti-I2 antibody is an antibody against *Pseudomonas fluorescens* component I2 isolated from mononuclear cells in the intestinal mucosa of patients with CD. IgA anti-I2 is positive in 55% of CD cases, 10% of UC cases, and 20% of non-IBD colitis cases[12,15,16]. Importantly, I2 is active as a T-cell superantigen.

Anti-*Mycobacterium avium* subspecies *paratuberculosis* antibody: *Mycobacterium avium* subspecies *paratuberculosis* (MAP) is the causative agent of Johne's disease, an intestinal infectious disease in ruminants and primates, in which non-caseating granulomas develop in the terminal ileum and colon. Based on the similarity to the pathohistological findings in CD and the fact that MAP has been isolated and cultured from intestinal tissue and breast milk in CD patients, MAP is thought to be involved in the pathogenesis of CD[20]. Naser *et al*[21] have reported increased titers of antibodies to MAP-specific proteins (p35 and p36) in the sera of CD patients. Nakase *et al*[22] prepared a recombinant protein produced by IS900 and observed elevated titers in CD patients when the recombinant protein was used as an antigen to measure the anti-IS900 level using an ELISA. However, MAP has been isolated from healthy subjects as well, and whether MAP itself has the ability to infect humans

remains unknown.

Anti-*Caenorhabditis elegans* antibody: Oshitani *et al*[23] analyzed HLA-DR-binding antigen peptides in the intestinal mucosa of IBD patients and discovered an antigen expressed by the nematode *Caenorhabditis elegans* (*C. elegans*), which lives in the soil. Subsequently, they reported an increase in anti-*C. elegans* antibody titers in the sera of patients with CD or UC[24].

Peptide antibodies

Anti-cocktail multiple antigenic peptide antibody: Saito *et al*[25] discovered 4 different peptides (cocktail multiple antigenic peptides, cocktail MAP) that reacted with the sera of CD patients by screening with a peptide phage library and established an ELISA that detects the anti-cocktail MAP antibody. The rate of positivity was 44% among CD patients, but positivity was rare among UC patients and healthy subjects. No reports of antigens corresponding to these peptides have been found.

Anti-TCP antibody: We used IgG in sera from CD patients to screen a T7 phage display library produced using colon cancer cDNA[26]. We selected a phage that specifically bound to a high percentage of sera samples from CD patients and then determined the amino acid sequence of the expressed peptide[2]. A previously unidentified, novel peptide (TCP peptide) was found, and an ELISA produced by converting the TCP peptide into a solid phase showed that while 61.7% of the CD patients who were examined exhibited positive seroreactivity, a positive result was less common among patients with UC (7.3%), non-IBD colitis (0%), colon cancer (11.4%), or healthy subjects (2.8%). These results demonstrated that an antibody to the TCP peptide is present in a high percentage of sera samples from CD patients.

Interestingly, when mononuclear cells are stimulated with the TCP peptide, they produce large amounts of pro-inflammatory cytokines, suggesting that antigens associated with this peptide are highly involved in the pathogenesis of CD. Homology has been found between the TCP peptide and rice- and microorganism-derived proteins, but no specific antigen has yet been identified. The major differences from the anti-cocktail MAP antibody described above[25] are the combination of four different, branched peptides in the cocktail MAP, whereas only a single, linear peptide is present in the TCP peptide.

CLINICAL SIGNIFICANCE

The addition of serological antibody measurements to endoscopic and radiographic examinations will enable clinicians to diagnose and treat IBD more conveniently, accurately and economically. Such measurements are expected to be of even greater significance to the pediatric population, in which invasive testing is less desirable. The role of serological antibody measurements in IBD is described below.

Contribution to diagnosis

At present, no single ideal serological antibody exists for the diagnosis of IBD, and the use of combinations of several markers has been attempted. In patients already diagnosed as having CD or UC, the predictive value of a pANCA-negative/ASCA-positive result was 95% for CD, while that of a pANCA-positive/ASCA-negative result was 90% for UC[1,27].

In patients with indeterminate colitis, the combination of pANCA and ASCA was useful for predicting whether the disease would progress to either CD or UC. A prospective study showed that the predictive value of this combination was 80% for progression to CD in pANCA-negative/ASCA-positive patients and 63.6% for progression to UC in pANCA-positive/ASCA-negative patients. Moreover, approximately 50% of the indeterminate colitis patients were pANCA-negative/ASCA-negative[28]. A poor postoperative outcome following ileal pouch-anal anastomosis surgery has also been reported in a patient with indeterminate colitis who progressed to CD[29].

Reportedly, 44% of CD patients who are negative for ASCA are ALCA-positive or ACCA-positive[10,11], and approximately 40% of CD patients who are negative for pANCA, ASCA, anti-OmpC, and anti-I2 are anti-Cbir1-positive[18]. These data indicate that the combination of several antibodies could further improve the diagnostic performance for CD.

Identification of subjects at risk

Israeli *et al*[30] assessed the availability of ASCA to predict the development of CD. During a 3-year observation of healthy Israeli soldiers who had enlisted in the army, 32 developed CD, and 10 (31.3%) of these soldiers were ASCA-positive at the time of enlistment. On the other hand, none of the 8 soldiers who developed UC were ASCA-positive[30]. Moreover, the fact that familial clustering is seen in the expression of ASCA and anti-OmpC in patients with CD and in the expression of pANCA in patients with UC and CD[31-34] suggests that a genetic predisposition is involved in the expression of these antibodies.

Classification of clinical phenotypes

The titers and numbers of microbial antibodies are closely associated with the clinical phenotypes of CD, including small bowel disease, intestinal complications (such as stricturing and internal penetrating disease behaviors), and the indications for small bowel surgery. Small bowel disease, a stricturing-type phenotype, a penetrating-type phenotype, and the need for small bowel surgery are common among ASCA-positive patients; a penetrating-type phenotype is

common among anti-OmpC-positive patients; small bowel disease, a stricturing-type phenotype, and a penetrating-type phenotype are common among anti-Cbir1-positive patients; and a stricturing-type phenotype and the need for small bowel surgery are common among anti-I2-positive patients. Moreover, patients who were triple positive for ASCA, anti-OmpC and anti-I2 were more likely to have undergone small bowel surgery than seronegative patients (OR = 8.6, $P < 0.001$)[35,36]. Similar results were obtained in a multicenter prospective study of pediatric patients with CD that utilized four antibodies: ASCA, anti-OmpC, anti-Cbir1 and anti-I2[37]. Thus, the greater the number of positive antibodies, the more likely that the stricture and penetration will develop as complications; of note, when all four antibodies are positive, the frequencies of these complications are 11 times higher than when all four antibodies are negative. Accelerated progression to a penetrating and/or stricturing disease has also been shown in patients in whom at least one antibody was positive, compared with seronegative patients. Furthermore, in a study that added novel anti-glycan antibodies, samples with higher titers of each antibody (ASCA, anti-OmpC, ALCA, ACCA and AMCA) were associated with more severe and complex complications (stricture and penetration) and a higher rate of surgery[14]. On the other hand, a need for early surgery and frequent complications associated with postoperative ileal pouchitis have been found in pANCA-positive UC cases[38,39].

In an autoantibody study, the frequencies of penetration, anal lesions and extra-intestinal complications were elevated in PAB-positive CD cases[5]. Autoantibodies to extra-intestinal components, including the pancreas, phospholipids, tissue plasminogen activator and sperm, which were reported in a minority of IBD patients, could conceivably contribute to the pathogenesis of some extra-intestinal complications, such as pancreatitis, thromboembolism, and infertility[40].

Prediction of response to treatment

It would be of great clinical and economic significance if clinicians could utilize serological antibody measurements to predict the response to treatment and to implement individualized treatment plans based on this information. This goal is particularly important because recent biologics are costly and can be associated with serious adverse events. Infliximab, an anti-tumor necrosis factor-α agent, has been reported to have little efficacy in pANCA-positive CD patients[41], and a subsequent study demonstrated a similar result in pANCA-positive/ASCA-negative CD patients[42]. Infliximab also has little efficacy in pANCA-positive/ASCA-negative UC patients[43]. Also, CD patients who responded to antibiotics were positive for anti-I2 or anti-OmpC, which are antibodies against intestinal bacteria[14]. Furthermore, pANCA-positive UC has been reported to be resistant to medical treatments[44].

PATHOGENIC ROLE

The presence of several types of antibodies in the sera of IBD patients suggests an immune-mediated nature of IBD. In IBD, tissue damage and antibody production to specific microorganisms occur as a result of a dysregulated innate immunity based on gene mutation. Differences in the type of gene mutation may alter subsequent immune responses, resulting in a change of the microorganism being targeted for "loss of tolerance" that may lead to the emergence of a different microorganism. Although IBD is characterized by the production of several antibodies with distinct antigenic specificities, the involvement of these antibodies in IBD pathogenesis is unclear. It seems likely that serological antibodies, thus far, are markers of an aberrant immune response, rather than direct effectors involved in the pathogenesis of the disease[45]. Further study is needed to determine the role of serological antibodies in the pathogenesis of IBD.

CONCLUSION

The clinical use of several antibody markers has been reviewed here. At present, no single marker of IBD with all of the above-mentioned qualities has been identified, although a few markers have come close. Furthermore, the expression of markers may be affected by race as well as the intestinal environment. An ideal marker should be easy to detect, rapid to quantify, cost-effective, minimally invasive or noninvasive, diagnostically accurate, and reproducible among patients and laboratories. Furthermore, markers should identify individuals at risk for the disease, be disease-specific, and aid the clinician in monitoring disease activity, evaluating response to therapy, and predicting disease relapse. The discovery of novel IBD-specific and sensitive markers is eagerly anticipated, and their use, in combination with the minimum use of endoscopic and radiologic examinations, will enable clinicians to create and implement individualized treatment plans designed to improve the long-term prognosis of patients with IBD.

REFERENCES

1 **Quinton JF**, Sendid B, Reumaux D, Duthilleul P, Cortot A, Grandbastien B, Charrier G, Targan SR, Colombel JF, Poulain D. Anti-Saccharomyces cerevisiae mannan antibodies combined with antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease: prevalence and diagnostic role. *Gut* 1998; **42**: 788-791 [PMID: 9691915 DOI: 10.1136/gut.42.6.788]

2 **Reese GE**, Constantinides VA, Simillis C, Darzi AW, Orchard TR, Fazio VW, Tekkis PP. Diagnostic precision of anti-Saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic antibodies in inflammatory bowel disease. *Am J Gastroenterol* 2006; **101**: 2410-2422 [PMID: 16952282 DOI: 10.1111/j.1572-0241.2006.00840.x]

3 **Ruemmele FM**, Targan SR, Levy G, Dubinsky M, Braun J, Seidman EG. Diagnostic accuracy of serological assays in pediatric

inflammatory bowel disease. *Gastroenterology* 1998; **115**: 822-829 [PMID: 9753483 DOI: 10.1016/S0016-5085(98)70252-5]

4 **Gionchetti P**, Vecchi M, Rizzello F, Ferretti M, Calabresi C, Venturi A, Bianchi MB, Brignola C, Sinico RA, De Franchis R, Miglioli M, Campieri M. Lack of effect of antineutrophil cytoplasmic antibodies associated with ulcerative colitis on superoxide anion production from neutrophils. *Gut* 1997; **40**: 102-104 [PMID: 9155584 DOI: 10.1136/gut.40.1.102]

5 **Lakatos PL**, Altorjay I, Szamosi T, Palatka K, Vitalis Z, Tumpek J, Sipka S, Udvardy M, Dinya T, Lakatos L, Kovacs A, Molnar T, Tulassay Z, Miheller P, Barta Z, Stocker W, Papp J, Veres G, Papp M. Pancreatic autoantibodies are associated with reactivity to microbial antibodies, penetrating disease behavior, perianal disease, and extraintestinal manifestations, but not with NOD2/CARD15 or TLR4 genotype in a Hungarian IBD cohort. *Inflamm Bowel Dis* 2009; **15**: 365-374 [PMID: 18972554 DOI: 10.1002/ibd.20778]

6 **Desplat-Jégo S**, Johanet C, Escande A, Goetz J, Fabien N, Olsson N, Ballot E, Sarles J, Baudon JJ, Grimaud JC, Veyrac M, Chamouard P, Humbel RL. Update on Anti-Saccharomyces cerevisiae antibodies, anti-nuclear associated anti-neutrophil antibodies and antibodies to exocrine pancreas detected by indirect immunofluorescence as biomarkers in chronic inflammatory bowel diseases: results of a multicenter study. *World J Gastroenterol* 2007; **13**: 2312-2318 [PMID: 17511029 DOI: 10.3748/wjg.v13.i16.2312]

7 **Lawrance IC**, Hall A, Leong R, Pearce C, Murray K. A comparative study of goblet cell and pancreatic exocine auto-antibodies combined with ASCA and pANCA in Chinese and Caucasian patients with IBD. *Inflamm Bowel Dis* 2005; **11**: 890-897 [PMID: 16189418 DOI: 10.1097/01.MIB.0000182872.76434.8c]

8 **Main J**, McKenzie H, Yeaman GR, Kerr MA, Robson D, Pennington CR, Parratt D. Antibody to Saccharomyces cerevisiae (bakers' yeast) in Crohn's disease. *BMJ* 1988; **297**: 1105-1106 [PMID: 3143445 DOI: 10.1136/bmj.297.6656.1105]

9 **Hisabe T**, Matsui T, Sakurai T, Murakami Y, Tanabe H, Matake H, Yao T, Kamachi S, Iwashita A. Anti-Saccharomyces cerevisiae antibodies in Japanese patients with inflammatory bowel disease: diagnostic accuracy and clinical value. *J Gastroenterol* 2003; **38**: 121-126 [PMID: 12640524 DOI: 10.1007/s005350300020]

10 **Dotan I**, Fishman S, Dgani Y, Schwartz M, Karban A, Lerner A, Weishauss O, Spector L, Shtevi A, Altstock RT, Dotan N, Halpern Z. Antibodies against laminaribioside and chitobioside are novel serologic markers in Crohn's disease. *Gastroenterology* 2006; **131**: 366-378 [PMID: 16890590 DOI: 10.1053/j.gastro.2006.04.030]

11 **Seow CH**, Stempak JM, Xu W, Lan H, Griffiths AM, Greenberg GR, Steinhart AH, Dotan N, Silverberg MS. Novel anti-glycan antibodies related to inflammatory bowel disease diagnosis and phenotype. *Am J Gastroenterol* 2009; **104**: 1426-1434 [PMID: 19491856 DOI: 10.1038/ajg.2009.79]

12 **Landers CJ**, Cohavy O, Misra R, Yang H, Lin YC, Braun J, Targan SR. Selected loss of tolerance evidenced by Crohn's disease-associated immune responses to auto- and microbial antigens. *Gastroenterology* 2002; **123**: 689-699 [PMID: 12198693 DOI: 10.1053/gast.2002.35379]

13 **Zholudev A**, Zurakowski D, Young W, Leichtner A, Bousvaros A. Serologic testing with ANCA, ASCA, and anti-OmpC in children and young adults with Crohn's disease and ulcerative colitis: diagnostic value and correlation with disease phenotype. *Am J Gastroenterol* 2004; **99**: 2235-2241 [PMID: 15555007 DOI: 10.1111/j.1572-0241.2004.40369.x]

14 **Ferrante M**, Henckaerts L, Joossens M, Pierik M, Joossens S, Dotan N, Norman GL, Altstock RT, Van Steen K, Rutgeerts P, Van Assche G, Vermeire S. New serological markers in inflammatory bowel disease are associated with complicated disease behaviour. *Gut* 2007; **56**: 1394-1403 [PMID: 17456509 DOI: 10.1136/gut.2006.108043]

15 **Joossens S**, Colombel JF, Landers C, Poulain D, Geboes K, Bossuyt X, Targan S, Rutgeerts P, Reinisch W. Anti-outer membrane of porin C and anti-I2 antibodies in indeterminate colitis. *Gut* 2006; **55**: 1667-1669 [PMID: 16687433 DOI: 10.1136/gut.2005.089623]

16 **Hui T**, Landers C, Vasiliauskas E, Abreu M, Dubinsky M, Papadakis KA, Price J, Lin YC, Huiying Y, Targan S, Fleshner P. Serologic responses in indeterminate colitis patients before ileal pouch-anal anastomosis may determine those at risk for continuous pouch inflammation. *Dis Colon Rectum* 2005; **48**: 1254-1262 [PMID: 15868228 DOI: 10.1007/s10350-005-0013-0]

17 **Lodes MJ**, Cong Y, Elson CO, Mohamath R, Landers CJ, Targan SR, Fort M, Hershberg RM. Bacterial flagellin is a dominant antigen in Crohn disease. *J Clin Invest* 2004; **113**: 1296-1306 [PMID: 15124021 DOI: 10.1172/JCI20295]

18 **Targan SR**, Landers CJ, Yang H, Lodes MJ, Cong Y, Papadakis KA, Vasiliauskas E, Elson CO, Hershberg RM. Antibodies to CBir1 flagellin define a unique response that is associated independently with complicated Crohn's disease. *Gastroenterology* 2005; **128**: 2020-2028 [PMID: 15940634 DOI: 10.1053/j.gastro.2005.03.046]

19 **Sitaraman SV**, Klapproth JM, Moore DA, Landers C, Targan S, Williams IR, Gewirtz AT. Elevated flagellin-specific immunoglobulins in Crohn's disease. *Am J Physiol Gastrointest Liver Physiol* 2005; **288**: G403-G406 [PMID: 15388489 DOI: 10.1152/ajpgi.00357.2004]

20 **Chiodini RJ**, Van Kruiningen HJ, Merkal RS, Thayer WR, Coutu JA. Characteristics of an unclassified Mycobacterium species isolated from patients with Crohn's disease. *J Clin Microbiol* 1984; **20**: 966-971 [PMID: 6511878]

21 **Naser S**, Shafran I, El-Zaatari F. Mycobacterium avium subsp. paratuberculosis in Crohn's disease is serologically positive. *Clin Diagn Lab Immunol* 1999; **6**: 282 [PMID: 10189224]

22 **Nakase H**, Nishio A, Tamaki H, Matsuura M, Asada M, Chiba T, Okazaki K. Specific antibodies against recombinant protein of insertion element 900 of Mycobacterium avium subspecies paratuberculosis in Japanese patients with Crohn's disease. *Inflamm Bowel Dis* 2006; **12**: 62-69 [PMID: 16374261 DOI: 10.1097/01.MIB.0000191671.12229.47]

23 **Oshitani N**, Hato F, Kitagawa S, Maeda K, Higuchi K, Matsumoto T, Arakawa T. Analysis of intestinal HLA-DR bound peptides and dysregulated immune responses to enteric flora in the pathogenesis of inflammatory bowel disease. *Int J Mol Med* 2003; **11**: 99-104 [PMID: 12469227 DOI: 10.3892/ijmm.11.1.99]

24 **Oshitani N**, Hato F, Kitagawa S, Watanabe K, Fujiwara Y, Higuchi K, Matsumoto T, Arakawa T. Distinct elevation of levels of anti-Caenorhabditis elegans antibody in sera of patients with inflammatory bowel disease. *Clin Diagn Lab Immunol* 2003; **10**: 856-861 [PMID: 12965916 DOI: 10.1128/cdli.10.5.856-861.2003]

25 **Saito H**, Fukuda Y, Katsuragi K, Tanaka M, Satomi M, Shimoyama T, Saito T, Tachikawa T. Isolation of peptides useful for differential diagnosis of Crohn's disease and ulcerative colitis. *Gut* 2003; **52**: 535-540 [PMID: 12631665 DOI: 10.1136/gut.52.4.535]

26 **Mitsuyama K**, Niwa M, Masuda J, Kuwaki K, Yamasaki H, Takedatsu H, Kobayashi T, Sata M. Isolation and characterization of a novel short peptide associated with Crohn's disease. *Clin Exp Immunol* 2011; **166**: 72-79 [PMID: 21797848 DOI: 10.1111/j.1365-2249.2011.04444.x]

27 **Peeters M**, Joossens S, Vermeire S, Vlietinck R, Bossuyt X, Rutgeerts P. Diagnostic value of anti-Saccharomyces cerevisiae and antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease. *Am J Gastroenterol* 2001; **96**: 730-734 [PMID: 11280542 DOI: 10.1111/j.1572-0241.2001.03613.x]

28 **Joossens S**, Reinisch W, Vermeire S, Sendid B, Poulain D, Peeters M, Geboes K, Bossuyt X, Vandewalle P, Oberhuber G, Vogelsang H, Rutgeerts P, Colombel JF. The value of serologic markers in indeterminate colitis: a prospective follow-up study. *Gastroenterology* 2002; **122**: 1242-1247 [PMID: 11984510 DOI: 10.1053/gast.2002.32980]

29 **Yu CS**, Pemberton JH, Larson D. Ileal pouch-anal anastomosis in patients with indeterminate colitis: long-term results. *Dis Colon Rectum* 2000; **43**: 1487-1496 [PMID: 11089581 DOI: 10.1007/BF02236726]

30 **Israeli E**, Grotto I, Gilburd B, Balicer RD, Goldin E, Wiik A, Shoenfeld Y. Anti-Saccharomyces cerevisiae and antineutrophil cytoplasmic antibodies as predictors of inflammatory bowel

disease. *Gut* 2005; **54**: 1232-1236 [PMID: 16099791 DOI: 10.1136/gut.2004.060228]
31 **Sutton CL**, Yang H, Li Z, Rotter JI, Targan SR, Braun J. Familial expression of anti-Saccharomyces cerevisiae mannan antibodies in affected and unaffected relatives of patients with Crohn's disease. *Gut* 2000; **46**: 58-63 [PMID: 10601056 DOI: 10.1136/gut.46.1.58]
32 **Halfvarson J**, Standaert-Vitse A, Järnerot G, Sendid B, Jouault T, Bodin L, Duhamel A, Colombel JF, Tysk C, Poulain D. Anti-Saccharomyces cerevisiae antibodies in twins with inflammatory bowel disease. *Gut* 2005; **54**: 1237-1243 [PMID: 15863472 DOI: 10.1136/gut.2005.066860]
33 **Mei L**, Targan SR, Landers CJ, Dutridge D, Ippoliti A, Vasiliauskas EA, Papadakis KA, Fleshner PR, Rotter JI, Yang H. Familial expression of anti-Escherichia coli outer membrane porin C in relatives of patients with Crohn's disease. *Gastroenterology* 2006; **130**: 1078-1085 [PMID: 16618402 DOI: 10.1053/j.gastro.2006.02.013]
34 **Török HP**, Glas J, Hollay HC, Gruber R, Osthoff M, Tonenchi L, Brückl C, Mussack T, Folwaczny M, Folwaczny C. Serum antibodies in first-degree relatives of patients with IBD: a marker of disease susceptibility? A follow-up pilot-study after 7 years. *Digestion* 2005; **72**: 119-123 [PMID: 16172548 DOI: 10.1159/000088366]
35 **Forcione DG**, Rosen MJ, Kisiel JB, Sands BE. Anti-Saccharomyces cerevisiae antibody (ASCA) positivity is associated with increased risk for early surgery in Crohn's disease. *Gut* 2004; **53**: 1117-1122 [PMID: 15247177 DOI: 10.1136/gut.2003.030734]
36 **Mow WS**, Vasiliauskas EA, Lin YC, Fleshner PR, Papadakis KA, Taylor KD, Landers CJ, Abreu-Martin MT, Rotter JI, Yang H, Targan SR. Association of antibody responses to microbial antigens and complications of small bowel Crohn's disease. *Gastroenterology* 2004; **126**: 414-424 [PMID: 14762777 DOI: 10.1053/j.gastro.2003.11.015]
37 **Dubinsky MC**, Lin YC, Dutridge D, Picornell Y, Landers CJ, Farrior S, Wrobel I, Quiros A, Vasiliauskas EA, Grill B, Israel D, Bahar R, Christie D, Wahbeh G, Silber G, Dallazadeh S, Shah P, Thomas D, Kelts D, Hershberg RM, Elson CO, Targan SR, Taylor KD, Rotter JI, Yang H. Serum immune responses predict rapid disease progression among children with Crohn's disease: immune responses predict disease progression. *Am J Gastroenterol* 2006; **101**: 360-367 [PMID: 16454844 DOI: 10.1111/j.1572-0241.2006.00456.x]
38 **Kuisma J**, Järvinen H, Kahri A, Färkkilä M. Factors associated with disease activity of pouchitis after surgery for ulcerative colitis. *Scand J Gastroenterol* 2004; **39**: 544-548 [PMID: 15223678 DOI: 10.1080/00365520410004668]
39 **Gupta N**, Cohen SA, Bostrom AG, Kirschner BS, Baldassano RN, Winter HS, Ferry GD, Smith T, Abramson O, Gold BD, Heyman MB. Risk factors for initial surgery in pediatric patients with Crohn's disease. *Gastroenterology* 2006; **130**: 1069-1077 [PMID: 16618401 DOI: 10.1053/j.gastro.2006.02.003]
40 **Vecchi M**, Spina L, Cavallaro F, Pastorelli L. Do antibodies have a role in IBD pathogenesis? *Inflamm Bowel Dis* 2008; **14** Suppl 2: S95-S96 [PMID: 18816674 DOI: 10.1002/ibd.20699]
41 **Taylor KD**, Plevy SE, Yang H, Landers CJ, Barry MJ, Rotter JI, Targan SR. ANCA pattern and LTA haplotype relationship to clinical responses to anti-TNF antibody treatment in Crohn's disease. *Gastroenterology* 2001; **120**: 1347-1355 [PMID: 11313304 DOI: 10.1053/gast.2001.23966]
42 **Esters N**, Vermeire S, Joossens S, Noman M, Louis E, Belaiche J, De Vos M, Van Gossum A, Pescatore P, Fiasse R, Pelckmans P, Reynaert H, Poulain D, Bossuyt X, Rutgeerts P. Serological markers for prediction of response to anti-tumor necrosis factor treatment in Crohn's disease. *Am J Gastroenterol* 2002; **97**: 1458-1462 [PMID: 12094865 DOI: 10.1111/j.1572-0241.2002.05689.x]
43 **Ferrante M**, Vermeire S, Katsanos KH, Noman M, Van Assche G, Schnitzler F, Arijs I, De Hertogh G, Hoffman I, Geboes JK, Rutgeerts P. Predictors of early response to infliximab in patients with ulcerative colitis. *Inflamm Bowel Dis* 2007; **13**: 123-128 [PMID: 17206703 DOI: 10.1002/ibd.20054]
44 **Sandborn WJ**, Landers CJ, Tremaine WJ, Targan SR. Association of antineutrophil cytoplasmic antibodies with resistance to treatment of left-sided ulcerative colitis: results of a pilot study. *Mayo Clin Proc* 1996; **71**: 431-436 [PMID: 8628021 DOI: 10.1016/S0025-6196(11)64083-4]
45 **Dotan I**. Serologic markers in inflammatory bowel disease: tools for better diagnosis and disease stratification. *Expert Rev Gastroenterol Hepatol* 2007; **1**: 265-274 [PMID: 19072419 DOI: 10.1586/17474124.1.2.265]

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