WHAT IS "INFLAMMATORY BOWEL DISEASE" & HOW CAN IT BE TREATED?

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Abstract

Ulcerative colitis and Crohn's disease are chronic diseases of the gastrointestinal tract, which are usually grouped together as inflammatory bowel disease (IBD). Despite many researches, the etiology is still unknown, but it is believed that IBD is caused by a combination of genetic and environmental factors that interact with the immunological system. Many people worldwide (around 4 million) suffer from a form IBD and the incidence of Crohn's disease is still increasing. Aminosalicylates, corticosteroids, immunomodulators, biologic medicines reduce the inflammation, relieve symptoms, prevent flare-ups, but new, more effective drugs with smaller amount of side effects are wanted and examined.

Keywords: Inflammatory bowel diseases, Ulcerative colitis, Crohn's disease, Etiology, Therapy

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Introduction

Inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic, idiopathic, progressive and often relapsing inflammatory diseases of gastrointestinal tract. Clinically, they are often considered together with similar etiology and symptoms, but they affect different parts of the digestive tract and they differ in the nature of the inflammation. UC is characterized by inflammation and ulcerations in the large bowel mucosa and submucosa, while CD is a trans-mural inflammatory disorder that may involve various parts of the gastrointestinal tract, but mainly the terminal ileum.

Tab. 1 Differences between CD and UC [13].

	Crohn's Disease	Ulcerative colitis
Involves terminal ileum	Commonly	Never
Involves colon	Usually	Usually
Involves rectum	Seldom	Always
Peri-anal involvement	Commonly	Never
Distribution of disease	Various areas of inflammation	Continuous areas of inflammation
Endoscopy	Linear and serpiginous ulcers	Continuous ulcer
Depth of inflammation	Transmular	Mucosal
Fistulae	Commonly	Never

IBD can appear at any time from early childhood to late adulthood, but more than 80% of cases are diagnosed between the age of 50 and 80 years.

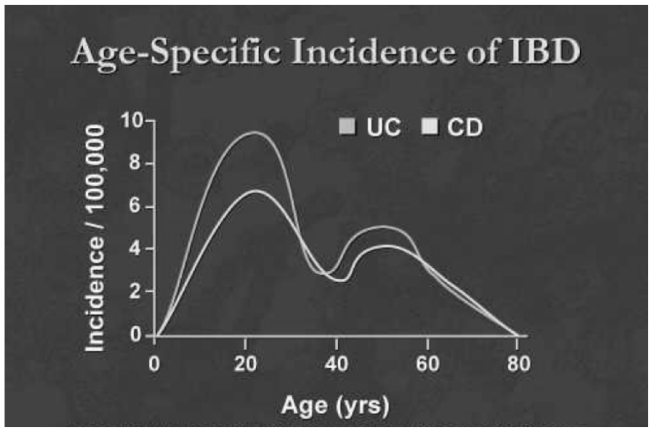

Figure 1. Age specific Incidence of IBD

Their incidence is increasing worldwide and is the highest in Northern Europe, The United Kingdom and North America [1, 2].

Figure 2 The global map of inflammatory bowel disease [1].

IBD still remain incurable, moreover they reduce quality of life, capacity for work and cause disability.

Diarrhea, abdominal pain, rectal bleeding and weight loss are the most often clinical manifestations of IBD. The chronic loss of blood from the gastrointestinal tract can cause anemia. Systemic symptoms include also fever, malabsorption and growth failure. Seronegative spondyloarthropathy, pyoderma gangrenosum, autoimmune hemolytic anemia and neurological complications such as peripheral neuropathy and depression are extraintestinal manifestations. Symptoms appear when lesions are extensive or distal, what is associated with a systemic inflammatory response, or they can be associated with local complications such as dilatation (toxic megacolon), massive hemorrhage, strictures, perforation (abscesses and fistulas) and cancer. Colorectal lesions usually present more and early manifestations, while small bowel lesions may remain latent for several years. The disease proceed with flares and remission of varying duration, but approximately one-fifth of these patients undergo a chronic, active, continuous disease course [2, 3, 8].

Inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD) is a multifactorial disease with probable genetic heterogeneity. In addition, smoking, stress, diet, antibiotics, NSAID, infections are risk factors, which contribute to the pathogenesis. Twin studies confirmed the role of genetics and the environment in the disease's etiology. Combining results produces Crohn's disease concordance rates of 37% and 7% for monozygotic and dizygotic twins, respectively, with equivalent results for ulcerative colitis of 10% and 3%. Another studies showed that between 6% and 32% of patients with IBD have an affected first- or second-degree relative and those patients are more likely to be younger at diagnosis and have small bowel disease. Presumably 170 genes localized on 12 chromosomes can be connected with this group of disorders. Meaningful areas of replicated linkage have been found on chromosomes 6p (IBD3), 12q (IBD2), 14q, 16q (IBD1). IBD3 appears to confer susceptibility to both ulcerative colitis and Crohn's disease, while IBD1 and IBD2 seem to determine susceptibility specifically to Crohn's disease and ulcerative colitis, respectively.

NOD2, a gene located at chromosome 16q12, encodes a protein with homology to plant disease resistance gene and is related to immune response to bacteria. A frameshift mutation caused by a cytosine insertion, 3020insC, which is expected to encode a truncated NOD2 protein, is associated with Crohn's disease [4,5,6,7].

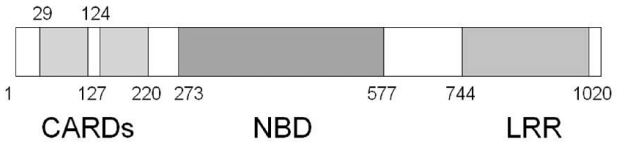

Figure 3 The representation of NOD2 domain structure and the position of the polymorphism associated with Crohn's disease [7].

IBD Therapy

Studies conducted in experimental models of colitis suggest that IBD-associated tissue damage can be caused by an excessive immune response directed against to normal components of the bacterial microflora, which is inappropriately

controlled by counter-regulatory mechanisms. Transforming growth factor (TGF)-β1, a pleiotropic cytokine with potent immune-suppressive activity, is an example of such mechanisms. Mice deficient in TGF-β1 unable to respond to the cytokine develop intestinal inflammation, while induction of TGF-β1 attenuates colitis in some murine models of IBD. TGF-β1 bind to a heterodimeric transmembrane serine/threonine kinases receptor, consisting of type I (TGF-βRI) and type II (TGF-βRII). In particular, binding of TGF-β1 to TGF-βRII promotes phosphorylation and activation of TGF-βRI, which in turn phosphorylates/activates Smad2 and Smad3. Smad proteins create then a heterocomplex with Smad4, which translocates to the nucleus and regulates the functional activities of many target genes. Deficiency of Smad3 in mice reduces cell responsiveness to TGF-β1 and causes spontaneously the development of a chronic inflammation in gastrointestinal tract. Smad6 and Smad7 are two inhibitors, which also belong to Smad family. Up-regulation of Smad7 is associated with inhibition of TGF-β1-induced Smad2/3 activation, so the diminished activation of TGF-β1-associated Smad signaling in IBD could be related to high Smad7. Studies showed that Smad7 was over-expressed in whole mucosal and LPMC samples of CD patients and UC patients in comparison to controls. Moreover knockdown of Smad7 with a specific antisense oligonucleotide allows endogenous TGF-β1 to act and suppress inflammatory signals [9, 10, 11, 12].

In the past, the main aim of medical treatment was an improvement in IBD symptoms, but nowadays the objective is to achieve a clinical remission and cessation of steroid administration. The best result, which can be reached is clinical and endoscopic remission. The location, extent, severity, and disease behavior, both in UC and CD, will determine the medical treatment options.

Medical therapy relies on classic antinflammatory and immunosuppressant drugs: corticosteroids, mesalamine compounds, azathioprine, and derivatives of the latter. Mesalazine suppress the production of IL-1, IL- 6 and inhibit IL-2 receptors. Combining oral and rectal administration of mesalamine was found in the past to be the most effective for the treatment of mild–moderate left-sided UC. If lesions are located in distal part of gastrointestinal tract, patients can be treated with glucocorticosteroids locally, what can reduce additionally their side effects. The prevalence of corticosteroid resistance or dependence in patients is estimated at about 30%, so that was the main reason to start the treatment with conventional immunomodulatory agents (azathioprine, mercaptopurine, methotrexate) [18].

In active IBD, many proinflammatory cytokines are released within the mucosal compartment, of which tumour necrosis factor α (TNF-α) have a particularly important role. Therefore anti–TNF-α antibodies, such as infliximab, abdalimumab can control IBD. Infliximab, a chimeric IgG4 monoclonal anti-TNF-α antibody, is effected in moderately to severely active luminal Crohn's disease and in CD with draining fistulas. The response to treatment was found in 65% of patients, and complete remission in 33% compared with 17% and 4%, respectively, in placebo treated patients. Infliximab induced rapid closure of enterocutaneous fistulas in 55%, which was significantly better than the 13% closure in Crohn's disease patients on standard medical treatment. The therapeutic effect of infliximab treatment appears almost immediately after infusion and sustain for 8–12 weeks. This monoclonal antibody suppresses mucosal

inflammation by a reduction the number of lamina propria cells producing TNF-α and the chemokines RANTES and MIP-1α. In controlled studies of TNF-alpha blocking agents, including infliximab, more cases of lymphoma and other malignancies have been observed among patients receiving the agents than among control group patients [13,14,15].

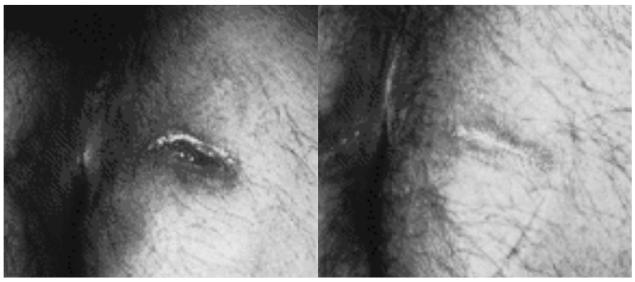

Figure 4 Closure of a perianal fistulae in a 60anal 60-year old man with treatment of Infliximab (5mg/kg) [16]. Baseline versus 10 weeks of healing.

Adalimumab, a human monoclonal anti-TNF antibody, has demonstrated efficacy in inducing remission in patient with moderate to severe CD. Adalimumab is effective in naïve patients and also in patients with loss of response or intolerance to infliximab. After 20 weeks of treatment 79% of patients had resolution of at least one extra intestinal manifestation and 51% were free of any sign and symptom [17].

Table 1. Comparison of in vitro properties of different tumor necrosis factor-α blockers in clinical practice for inflammatory bowel disease [20]

Agent	Binds	Mediates		Increases proportion of apoptotic cells	Inhibits cytokine production	Effective in IBD patients
	TNF	CDC	ADCC			
Infliximab	Yes	Yes	Yes	Yes	Yes	Yes
Etanercept	Yes	Yes	Yes	Yes	No	No
Adalimumab	Yes	Yes	Yes	Yes	Yes	Yes
Certolizumab pegol	Yes	No	No	No	Yes	Yes

The more patients are treated with anti-TNF agents, the more of them have primary and secondary failures, what require the development of novel therapies. Natalizumab, a α4-integrin inhibitor that blocks the extravasation of leukocytes from the vessels to sites of inflammation, has been found to be effective in the treatment of refractory CD. However, due to the rare risk of progressive multifocal leukoencelopathy caused by the John Cunningham virus, its use is restricted to CD patients refractory to multiple immunosuppressive treatments. Further studies regard α4β7-integrin inhibitors such as vedolizumab, which are gut specific and do not carry the risk of progressive multifocal leukoencelopathy [19].

The efficacy of anti-TNFα is limited. Studies showed, that 20%-30% of patients with refractory CD and roughly 40% of patients with refractory UC do not respond to anti-TNFα treatment [20].

A gene therapy using regulatory T cells or MSCs offers an alternative treatment for inflammation of gastrointestinal tract. Regulatory T lymphocytes were effective in both the cure and the prevention of experimental colitis in multiple animal models. One of studies showed, that transfer of regulatory T cells into mice with

colitis led to resolution of the lamina propria infiltrate in the intestine and reappearance of normal intestinal architecture. The phase II/III of clinical trials for the treatment of refractory CD with cells therapy are in progress. Concerning gene therapy, further development of viral vector delivery to the gut and long term efficacy are still needed, but pre-clinical data are promising [21, 22].

Main aims of new, alternative treatments are IL-12/IL-23, IFN-γ, or IL-6 and IL-10. Anti–IL-12p40 is an antibody that targets IL-12 and IL-23 (the major cytokines underlying the Th1 response) and it demonstrated impressive efficacy in Crohn disease during preliminary studies. Recent reports suggested that experimental colitis is more dependent on IL-23 and IL-17 than on IL-12 and IFN-γ, so anti–IL-23p19, which targets IL-23 (and not IL-12), is tested in clinical trial. An elimination of effector cells by leukocytapheresis, administration of anti-CD3 antibodies and autologous hematopoietic stem cell transplant is other strategies aim. Other new approaches in treatment of IBD are: restoring the lack of immunoregulation, (e.g., extracorporeal photophoresis, adipose stem cell infusion, and administration of probiotics), enhancing innate immune function (via use of GM-CSF), or activating the innate immune system by administration of microbe-derived agents. These treatments should reduce the number of inflammatory mediators that cause tissue damage, maintenance of the active inflammation and exacerbation of dysfunction of the epithelial barrier. The challenges for development of new therapies of IBD include the identification of new molecular defects such as NOD2 mutations, the elucidation of the functional impact of these defects on mucosal immune responses and epithelial cell barrier function. Such approaches hold the promise of more effective therapies with fewer side effects.[13]

Table 2. Selected examples of clinical experience with emerging IBD therapies [13] Deno, N. C.; Richey, H. G.; Liu, J. S.;. J. Am. Chem. Soc. 1965, 87, 4533-4538.

Agent	Target or action	Reported efficacy in:	Reference
Anti-IL-12p40/ABT874	IL-12/IL-23	Active CD	10
Anti-IL-6 receptor	IL-6	Active CD	69
Fontolizumab	IFN-γ	Active CD	68
Visilizumab	CD3/apoptosis-activated T cells	Active UC	73
Basiliximab	IL-2 receptor	Active UC	79
Daclizumab	IL-2 receptor	No effect in active UC	80
Natalizumab	α 4 integrins	Active CD	67
MLN02	α4β7 integrin	Active UC	64
Alicaforsen	ICAM-1 (antisense oligonucleoide)	Active UC, maintenance of remission	81
GM-CSF	Innate immune system	Active CD	77
EGF	Epithellium	Active UC	82
Porcine whipworm oocysts	Innate immune system	Active UC	83

Resumo

Ulcerema kolito kaj la malsano de Crohn estas kronikaj malsanoj de la gastrointesta trakto, kiujn oni kutime arigas kiel inflamaj intestaj malsanoj (IIM). Spite de multaj esploroj, la etiologio estas ankoraŭ nekonata, sed oni kredas ke IIM estas kaŭzata per

kombinacio de genetikaj kaj mediaj faktoroj, kiuj interrilatas kun la imuna sistemo. Multaj homoj sur la tuta tero (ĉirkaŭ 4 milionoj) suferas de ia speco de IIM kaj la ekmalsaniĝo kaŭze de la malsano de Crohn estas ankoraŭ plimultiĝanta. Aminosalicilatoj, kortikosteroidoj, imunomodudulaĵoj, biologikaj kuraciloj malpliigas la inflamon, plibonigas simptomojn, malhelpas novajn atakojn, sed novaj pli efikaj kuraciloj kun malpli da flankaj efikoj estas bezonataj kaj esplorataj.

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