Alternative Drug Delivery Approaches for the Therapy of Inflammatory Bowel Disease

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ABSTRACT: This article shall give an overview on drug delivery systems for new therapeutic strategies in the treatment of inflammatory bowel disease. The various features of the different approaches allowing locally restricted drug delivery to the inflamed colon are discussed including the main physiological and pathophysiological limitations for the different systems. Conventional drug delivery systems are tightly adapted from developments for colonic delivery by oral administration triggered by release mechanisms owing to the physiological environment that these systems encounter in the colonic region. The newer developments in this context aim for an increased selectivity of drug delivery by targeting mechanisms which have a closer relation to pathophysiological particularities of the disease. Therefore, we were focused especially on new strategies for such treatment including liposomal formulations, cyclodextrins, micro- or nanoparticles, viral gene therapy approaches, and others. Effective and selective delivery even of an otherwise nonspecifically acting drug could provide new therapeutic pathways in the treatment of inflammatory bowel disease. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:2878–2891, 2008

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INTRODUCTION

Inflammatory bowel disease (IBD) encompasses several chronic inflammatory conditions of the gastrointestinal tract, which can impact the small or large bowel. The most known subtypes are Crohn's Disease (CD) and Ulcerative Colitis (UC). Highest incidence rates are in developed, more industrialized countries, traditionally reported in Northern and Western Europe as well as North America. Prevalence rates of IBD can reach up to 396/10000 inhabitants.[1] Both, UC and CD share many common features such as diarrhea, bloody stools, weight loss, abdominal pain, fever, and fatigue. However, distinct differences can be observed in the pathogenesis and the typical clinical manifestations. In UC, the inflammation affects the innermost mucosa with no segments of normal tissue and is usually restricted to the colon and rectum (Fig. 1). In the case of CD, the inflammation is transmural, extending through the bowel wall to the serosal layer, and can be found throughout the small and the

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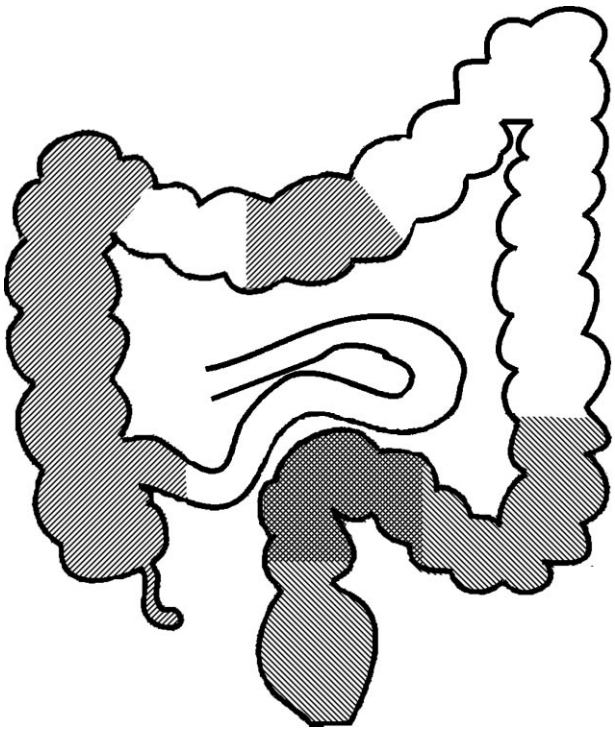

Figure 1. Schematic presentation of the large bowel indicating in black the most current affected areas in ulcerative colitis (▨) and Crohn's disease (▨) [50].

large intestine.[2,3] Phases of remission and exacerbation alternate, making life for the patients insupportable.

With a view to immunological aspects, a general disruption of the equilibration in the mucosal immune system is observed. In consequence, the deregulated, abnormal and uncontrolled immune response leads to chronic mucosal inflammation mainly characterized by the activation of lymphocytes and the overexpression of inflammatory cytokines.[2,4] CD appears to be primarily a condition of chronic Th1-lymphocyte activation with tissue damage induced by secondary macrophage activation and elevated levels of matrix metalloproteinases, which induce degradation of the lamina propria.[2,5] What kind of factors trigger the T-cell-activation remains unknown; antigens are considered to play an important roll, especially those originated from intestinal bacteria.[6] In UC there is no strong evidence for T-cell activation and humoral mechanisms predominate. The cytokine profile in UC patients provides more evidence of an exaggerated Th2 response—elevated interleukin-5 but no significant elevation of interferon-γ and other cytokines associated with an overactive Th1 response.[7] Also genetic factors have been investigated such as mutations in NOD2 encoding genes, which have been found to have a significant influence.[8,9]

THERAPY

Most of the current agents act by down regulating chronic inflammation in the intestinal mucosa and cannot cure the disease. Thus, the maintenance and reduction of remission is still the major aim of the therapy. The treatment of CD and UC are comparable though not always identical.

Conventional drugs for the treatment of IBD include aminosalicylates, corticosteroids, antibiotics, and immunosuppressive agents. Aminosalicylates are the most commonly used anti-inflammatory drugs to treat mild to moderate active CD or UC and to maintain remission.[2] Since 5-aminosalicylic acid (5-ASA) is known as the functionally active moiety of sulfasalazine, which inhibits NF-κB, IL-1, and IL-2, and sulfapyridine was suspect to be essentially responsible for certain adverse effects, sulfapyridine-free aminosalicylates have been developed (mesalamine, olsalazine, balsalazide).[3]

Administrated orally, rectally or intravenously, corticosteroids are effective in patients with active CD or UC. Their potent immunosuppressive effects include nonspecific effects on the humoral and cellular immune function as well as more specific effects on the production of cytokines and inflammatory mediators.[2] The short- and long-term adverse effects must be weight against the benefits of corticosteroids, and are principally related to the dose and duration of therapy. Meanwhile, other immune modulating agents are used and widely accepted in the treatment of IBD. In principle, these agents put patients at risk for opportunic infections. Besides the approved 6-mercaptopurine and its prodrug azathioprine, cyclosporine, and methotrexate,[10–12] newer immunosuppressive agents such as mycophenolate and tacrolimus are also starting to attract attention.[13] Antibiotics, especially metronidazole and ciprofloxacine have been used to induce remission of CD but are ineffective in UC.[10,14] Deeper insights into pathogenesis offered the opportunity to develop treatment options on the basis of antibody engineering. As tumor necrosis factor-α levels are in general highly elevated in both UC and CD,[15] many approaches have been made to invent therapy strategies against tumor necrosis factor-α.[16,17] The introduction of Remicade®