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Review article

Current scenario in inflammatory bowel disease: Drug development prospects

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ABSTRACT

Background: Inflammatory bowel disease (IBD) pathophysiology have led to the development of various compounds that might ameliorate the disease process. Recently several failures in terms of developing disease-modifying therapies needs to be communicated effectively as per their process and cause which have led to a debate about the potential deficiencies in our understanding of the pathogenesis of IBD and choice of therapeutic targets. So that the thoroughly development of drug candidates and study design of clinical trials is done.

Methods: Various online medical databases were searched for relevant study and publications. Different clinical trials were reviewed and the available data in clinical trials describing the effective drug development status of IBD medications.

Results: The aminosalicylates, anti-inflammatory and biological molecules tested for the treatment of Crohn's disease (CD) and ulcerative colitis (UC) but the risks of common and rare adverse events were found with treatment. Antibiotics and steroid help in reducing the immune response but further studies required on each molecule to substantiate treatment strategies. There has been significant research on different drug molecules as per the phase, which is summarized in this review.

Conclusions: Preclinical research on the complex IBD puzzle coupled with an active and vibrant research agenda in recent decades which might reveal patterns of pharmacological interactions instead of single potential drug targets. The increased collaboration between pharmaceutical companies, basic researchers and clinical researchers has the potential to bring us closer to developing an optimum pharmaceutical approach for the treatment of IBD.

Contents

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; Fab, Fragment antigen-binding; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; IBD, inflammatory bowel disease; IBDQ, Inflammatory Bowel Disease Quality of Life Survey; IGF, insulin like growth factor; IOIBD, International Organization for the Study of Inflammatory Bowel Disease; LPAM, lymphocyte Peyer's patch adhesion molecule; mAb, monoclonal antibody; MMX, multi-matrix system; NSAIDs, Nonsteroidal Antiinflammatory Drugs; PEG, Polyethylene glycol; QoL, quality of life; SCCAI, Simple Clinical Colitis Activity Index; SONIC, Study of Biologic and Immunomodulators Naive Patients in CD; TNF, tumor necrosis factor; UC, ulcerative colitis.

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Introduction

Inflammatory bowel disease (IBD) is a group of complex inflammatory condition which comprises of two chronically reverting diseases ulcerative colitis (UC) and Crohn's disease [CD] [1]. Usually distal ileum and colon can be affected by CD, whereas UC affects only the colon [2]. Europe reported highest prevalence values for IBD (UC, 505/1 Lac persons; CD, 322/1 Lac persons), North America (UC, 249/1 Lac persons; CD, 319/1 Lac persons) and least found in the Middle East Asia (6.3/1 Lac person) [3].

Hypercoagulable state and pathologic clotting is a significant cause of morbidity and mortality in patients of IBD [4]. The etiology of IBD is still unknown, but evidence has intimated that both CD and UC result from the interaction of genetic and environmental factors that ultimately, elevate an excessive and poorly controlled mucosal immune response that is directed against a component of gut micro-biota. The production of distinct visibilities of cytokines in experimental models studies of IBD have also shown that CD4+ T cells initiating and shaping this immunopathologic process [5]. There is also a hyperbolized production of IL-12 in the same tissue which is the major helper T cell 1 (Th1)-inducing factor in patients [6].

A comprehensive physical exam and review of the patient's history with various tests (blood tests, stool examination, endoscopy, biopsies and imaging studies) avail to confirm the diagnosis of IBD. Symptoms related to inflammatory scathe of the digestive tract includes diarrhea, proctitis, pain or rectal bleeding with bowel movement, tenesmus, abdominal cramps and the pain associated in the right lower quadrant of the abdomen common in CD or in the lower left quadrant (around the umbilicus) in moderate to severe UC [7].

Substantial progress has been made for the treatment of IBD over the last decade. In the early of the disease course, the treatment algorithm of starting with safe but weaker medications but advancing to more potent medications has been challenged when those treatments fails. Medications may be used either to bring on or maintain remission in patients. The introduction of different types of antibiotics, steroids, immunomodulators, biologics and other anti-inflammatory agents has been the most significant addition to the spectrum of therapeutic options in IBD. Other medications like anti-diarrheal, nutrition, carbohydrates and vitamin D supplements used in addition to controlling inflammation and relieving signs and symptoms [2]. Ingestion of probiotics and prebiotics may provide some clues in developing a new class of therapeutic agents for the treatment/prevention of IBD [8]. Nowadays, therapeutic recommendations for the management of dysplasia in IBD are based on macroscopic pattern and microscopic characteristics [9]. Alternative of therapy depends entirely on the severity of disease with disease location, adverse events and side effects.

Further introduction of new biological therapy is helping to optimize the available medications better. However, several compounds currently under development that could become drugs with additional proficient innovations and methodological meliorations for clinical trials. Fig. 1 shows the different pharmacotherapeutic targets for treatment in IBD.

Phase-I (Table 1) trials are designed almost exclusively to safety of the therapy in human populations and long time span between Phase-I testing is the potential introduction of a new therapy into clinical practice. However, the agents identified in same section comprise a broad representation of compounds in Phase-II, III trials, including agents with presumptive and novel mechanisms of action.

This review aims to provide a brief overview on the current status of different therapeutic drugs for the treatment of IBD used in clinical trials and to highlight the adverse challenges associated with them for the patient safety.

Methods

The screening of the relevant articles includes various online databases such as PubMed, Medline, Cochrane etc. The search was conducted using the following key words and phrases: Crohn's disease, ulcerative colitis, inflammatory bowel disease, clinical trials, drugs in IBD. The different clinical trials were searched using the keyword 'inflammatory bowel disease' in "www.clinicaltrials.gov".

The data is listed in table according to the relevant phases of the clinical trial studies. There we found 1238 studies in IBD till February 2014, out of which 513 (44%) were conducted in United States and 457 (39%) in Europe. We discussed the studies which are completed and few on the basis of publications. Reference lists from identified manuscripts were searched for further publications.

As per the published literature from databases and clinical trial registries, it was found that there are many interventions are approved from regulatory and many more are still under trials.

Approved drugs

Many drugs are approved for the treatment of IBD till now. As per FDA reference some drugs i.e. Golimumab, Vedolizumab, Mesalamine, Certolizumab pegol, Budesonide, Ciprofloxacin etc. are approved for use against the epidemiology of UC and CD. Majority of them are biologicals that are preferred by the physician.

1. CNTO-148 (Golimumab)

   Golimumab is a new tumor necrosis factor (TNF) antagonist recently approved by the FDA in May 2013. It is created using genetically engineered mice immunized with human TNF i.e. a human anti-TNF antibody. In the treatment of ulcerative colitis, Golimumab, binds to both the bioactive forms of soluble and transmembranal human TNF-α and inhibits the activity by preventing its binding to receptors [10,11].
2. MLN0002 (Vedolizumab)

   It is a monoclonal antibody which may also humanized. It is developed for the treatment of UC and CD and approved in May 2014 by FDA. It is an integrin antagonist that targets the gut-specific α4β7 integrin LPAM 1 for inhibition. It appears that Vedolizumab is not associated with any signs of systemic

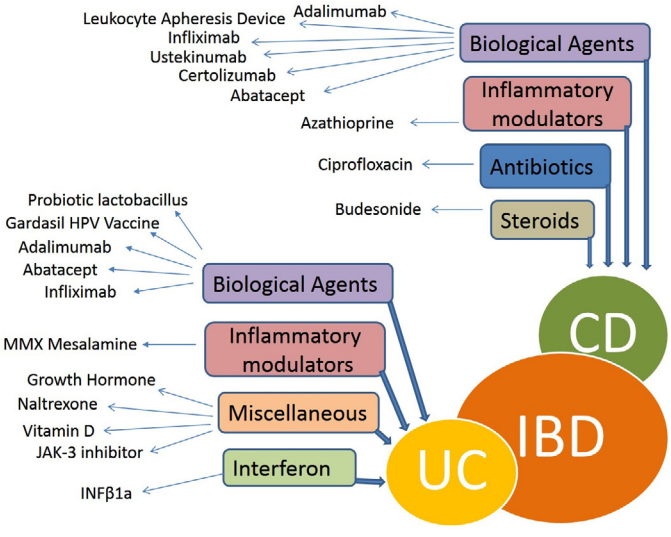

Fig. 1. Recent pharmacotherapeutic targets in drug development of inflammatory bowel disease (IBD).