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INFLAMMATORY BOWEL DISEASE

Sonia Kassana*
Research scholar, Galgotias University, Greater Noida, Pin-201308, India.
Email: soniakasana12@gmail.com

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Abstract

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract with a multifactorial pathophysiology. The gastrointestinal tract plays a central role in maintaining immune homeostasis i.e. tolerance to non- pathogenic commensal bacteria, self- antigens, while also protecting the host against pathogenic organisms by mounting an inflammatory response.

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract with a multifactorial pathophysiology. Inflammatory bowel disease is a disorders that involves chronic inflammatory of digestive tract that includes a ulcerative colitis (UC) and chron's disease (CD)[1]. Inflammatory bowel disease pathology is still out of reach and therefore, treatment is far from idea. In addition to genetic susceptibility, environment exposures, genetic microbial and immunological factor are continuously being investigated and the improved knowledge contributes to the new therapies development [2,3]. All these environmental factors are part of a western, lifestyle, thus high incidence rates of IBD in Europe and the United States are found. The gastrointestinal tract plays a central role in maintaining immune homeostasis i.e. tolerance to non- pathogenic commensal bacteria, self- antigens, while also protecting the host against pathogenic organisms by mounting an inflammatory response. Inflammatory bowel disease develops as the coupled reaction of both respiratory burst and inflammatory burst; both factors collectively lead to the pathogenesis of disease[1,2].

The most common forms of IBD are ulcerative colitis (UHL- sur -uh - tiv koh – LEYE- tiss) and crohn's (krohnz) disease. Ulcerative colitis affects the top layer of the large intestine[4]. The disease causes swelling and tiny open sores, or ulcer to form on the surface of the lining of large intestine, including bacteria, spill into the abdominal cavity or leak into the blood. This causes a serious infection and emergency surgery. In crohn's disease, swelling and scar tissue causes thickness of the intestinal wall. This narrows the passageway for food that is being digested.

The area of the intestine that narrowed is called stricture (STRIK – choor)[5,6]. Also, deep ulcers may turn into tunnels, called fistulas (FISS – choo-luhss) and they connect different parts of the intestine. CD and colitis have been postulated with defects in the intestinal barrier and an impaired immune function. In addition, symptom includes rectal bleeding diarrhoea often with blood, abdominal pain, and weight loss. With CD, affected areas range from the mouth to the anus with symptoms of transmural granulomas and aphthous ulcers with histological feature of fistula fissures and symptoms of abdominal pain, diarrhoea, fever, weight loss, and fistulas.

Causes of IBD

IBD is an autoimmune disorder which collectively results due to environmental factors, genetic factors, immune dysregulation, hormonal changes causing imbalance between central nervous sytem and digestive tract [7,8].

Symptoms

Symptoms of IBD ranges from mild to severe going away from months or even years basic symptoms includes at a time with relapse/ flare up. On the basis of symptoms 3 main types of IBD has been classified as IBD with constipation (IBD-C) revealed by stomach pain, discomfort, bloating, infrequent or delayed bowel movements, or hard or lumpy stools. IBD with diarrhea (IBD-D) revealed by stomach pain, discomfort, an urgency of urination, frequent bowel movement, watery or loose stools. IBD, with stool pattern involves both constipation and diarrhea[9,10].The other symptoms which signifies its manifestation includes severe to chronic pain in the abdomen; diarrhoea-sometimes with blood, Joint pain, fever, skin problem, bleeding from the rectum, loss of appetite, unexplained weight loss, changes in bowel habits, swelling, cramping, headache[11].

Pathophysiology of IBD:

As earlier suggested numerous factors play an important role in cause of IBD as environmental, microbial attack, immune imbalance and genetic factors. An environmental factor includes improper diet, routine, pollutants, synthetic drug as NSAIDs and antibiotics and deficiency of Vitamin D. Among many smoking, junk food and improper life style sickly adheres to cause of IBD[12,13,14].

Immune Imbalance

IBD pathogenesis has been result of

- The immune cell increases the permeability of intestinal epithelials and recognizes bacterial antigens via toll like receptor (TLRs) and activates macrophages, B cells and inflammatory T cells[15].
- Natural killer T cells produce interleukins, further disrupting the epithelial barrier. Mechanism such as upregulation of pro-inflammatory chemokines (CXCL) and binding of integrin bearing t cells to colonic endothelial cells via mucosal vascular adhesion occurs
- Stimulate the nuclear factor Kappa B pathway (NF-KB), and is transcription of pro-inflammatory antigen.
- Increased levels of pro-inflammatory cytokines, tumor necrosis factor alpha (TNFa), interleukin (IL)-1beta, IL-6, IL-12, and IL-23 occurs.
- Presented the T helper cells via T cell receptor antigens facilitating an adaptive immune response [10].

Innate immunity

Different cell we have:

- Epithelial cells
- Neutrophilis
- Eiosinophilis cells
- Monocytes, macrophages and natural killer cells

Initiated by recognition of microbial antigen toll like receptor (cell system) and NOD-like receptor/ cytotoxic.

NOD mutation reduced activation of NF-KB. Reduced protection of NOD and results in lactation of inhibition of TLR2, this activates IBD TL23 cytotoxin plays key roles in case of IBD too, it activates TH17 cells, IL-23 and initiates cytotoxin productions by innate lymphoid cells (ILCs) [2,5].

CD also associated with genes ATG16LI and IRGM genes. Involved in autophagy and coding mutation T300A, associate with increased rises of CD Auto phages process is essential to maintain balance between bactericidal effects and antigens. This mutation of NOD2 deactivates autophagy and promotes the case of IBD

Adaptive immunity:

Adaptive immunity specifically depends on T cells. In process inflammatory cells produces larger amount of IFN-Y, TH2-Cell release IL-4, IL-5,IL-13.TH1 protects inflammation in CD and VC peptides and produces large quantities of IL-2, IFN-Y and T cells[2,8,]. It has been also postulated that CD is result of Th1 immune response and UC is result of TH2 immune response TH17 cells alsoplays key role in case of IBSD, TH17 cells leads to production of IL-17A, IL-17F, IL-21, IL-22, and up regulates the inflamed mucosa in IBD [16].

Treatment approaches

Treatment approaches for IBD has been classified into two forms i.e. conventional therapy and novel therapy. Convention therapy involves direct/indierct modification of drug to release the content at site of action in presence of hydrolytic enzymes or alteration in pH. Treatment approaches has been further discussed below [17].

Conventional therapy

Conventional therpies and their characteristics

1. **Chemical modification**

- **PEGylation**: Masks antigenic epitope, inhibits uptake by RES, and prevents degradation by proteolytic enzymes. Examples are Intron, Oncaspar[18]
- **Glycosylation**: Oligosaccharides are attached to proteins or other organic molecules. Examples are Alglucosidase (Myozyme) -alpha-1-antitrypsin (Prolastin) [19]
- **Hydrophobization**: Reduces immunogenicity and immune response. Examples: Enzyme glucose oxidase coupled to hexyl aliphatic chains reduces antibody production[20,21].

- **Amino acid substitution:** Alters physiological properties by substitution techniques. Examples: Substitutes D-amino acid for L-amino, enhancing enzymes stability.

2. Prodrug (Active molecules +carrier molecules)

- **Sulfasalazine**: Sulfapyridine and 5-ASA (Azo linkage, metabolized by intestinal bacteria). Examples are Salazopyrin, Me
- salazine, Azulfidine, Sulazine, Salazopyrin.[22,23]
- **Olsalazine**: Sulfa prodrug of two 5-ASA molecules (AZo linkage more efficient in terms of therapy, safety, and acceptability). Examples are Dipentum[24,25].
- **Balsalazide**: Sulfa Prodrug 5-ASA linked via diazo bond to 4-aminobenzoyl-beta- alanine(4-ABA) (Azo linkage reduces adverse reaction and more is accepted) Example is Colazal[26].
- **Glucuronide conjugated:** Budesonide with glucuronic acid (Glucuronide linkage, more effective then p Examples are Morphine, paracetamol, steroids, Bilirubin, Oxazepam.[27]

3. Polymer-coated solid dosage

- **Matrix tablet:** Indomethacin cross-linked with chondroitin sulphate and causes slow erosion of matrix, followed by drug release. Example are Indomethacin[28].
- **PH-sensitive polymer coating:** (5-ASA coated with Eudragit S copolymer (Asacol);Budesonides coated with Eudragit L100-55 (Entocort) + Drug release occurs at colonic PH. Examples ae Asacol, Budesonides[29].
- **Time-dependent formulation:** Pellets of 5-ASA coated with ethylcellulose (Pentasa) and reduces UC Score. Example is Pentasa[30]
- **Double coated drugs** -ASA coated with calcium. Examples are Disprin, Omprazole[26,27]

NOVEL DRUG- DELIVERY SYSTEMS

Initial stages of IBD are treated with probiotics, antibiotics, corticosteroids, 5-ASAs, biologicals,chemically modified drug enzymatics, prodrug therapy, enteric coated drugs,and technique-based solid dosage forms. The release of drug from these conventional systems depends on factor such as Intestinal motility, Time, PH, and

Microbial and Enzymatic degradation[30]. These novel drug- delivery systems are advantageous for the treatment of IBD for the following reasons:

- Innovative systems help to target the activities at the site of action, minimize drug loss, and increase drug bioavailablity and targeting at the site of action.
- An inflamed intestinal barrier loses tight junction and allows sufficient localization and adsorption of vesicular and particulate systems.
- Particulate systems are adsorbed by paracellular transport/endocytosis across the intestinal epithelial cells[31,32]
- Macrophages and lymphocyte-bioengineered cells can directly target to sites and release activities because they are themselves inflammatory cells.

Novel carrier systems could be classified into vesicular, particulate, and polymer systems as well as emulsions and cellular. Brief descriptions are discussed further [33]

3.2.1. Vesicular systems

1. **Liposomes**

Liposomes are phospholipid-based, bilayered, vesicular structures enclosed in an aqueous volume. Liposomes are highly compatible phospholipid vesicular system, giving the ability to carry both hydrophilic and lipophilic drugs due to the amphiphilic nature. liposome of drug in polymer we have Dexamethasone phosphate[34]

a. **Gel-bead-Entrapped liposomes**

A novel formulation for oral administration using calcium alginate gel beads-entrapped liposome and prednisolone as drug has been investigated for colon-specific drug delivery in vitro. Gel-bead-Entrapped of drug in polymer have doxorubicin and sodium alginate[35]

b. **Mucoadhesive polymers**

Mucoadhesive polymers have the ability to adhere to the mucous lining through various forces and interactions. A Mucoadhesive system enhances the bioavilability of poorly soluble drugs and protein -based drugs by providing stability from the protease system. Mucoadhesive polymers are PVP and MC (methyl cellulose) bind to the protein of the cell [32].

3.2.2. **Particulate carrier**: Particulate carriers are very small carrier-based lipid and polymer matrix systems in which the drug is dispersed or dissolved in a lipid or polymer matrix. on the basis of systems are termed either nanoparticulate or microparticulate.nanoparticulate systems measure in nanometersare un two types: solid lipid nanoparticles ans nanostructured lipid particles.[36]

a. **Solid lipid nanoparticles(SLNs)**

SLNs are beneficial in terms are drug protection and prevention of degradation.an increase bioavailability of entrapped drug to improved encapsulation efficiency and increase in the initial release. Example of drug in polymer have Triglycerides, Trilaurin, Tristearin[34,35].

b. **Nanostructured lipid carriers (NLCs)**

Nanostructured lipid carriers are part of nanomatrix systems. These are composed of solid and liquid lipids. Liquid lipids generate flexibility in carrier system and improved drug-loading capacity. Solid lipid with higher melting points crystalline to form of lipid core and liquid lipid form of higher melting point and lipophilic drug. Examples of drug bind to the polymer have Castor oil, oleic acid, Davana oil, Cetiolv, Miglyol[37,38]

c. **Microsphere**

Microsphere is spherical polymer ranging from 1 to 1000um. Microsphere provide steady and sustained release, reducing dose frequency with improved therapeutic effect and patient compliance. Example of drug bind to the polymer Serum albumin.[39]

3.2.3. Self-Assembled polymer systems

1. **Hydrogel**

Hydrogels are cross-linked network of hydrophobic polymers that physically or chemically link with one other. Drugs are released through diffusion after swelling or degrading polymers.[40]

3.2.4. Emulsion-Based carriers

1. **Microemulsion**

Microemulsions are thermodynamically stable isotropic dispersions. microemulsion either oilin water and oater in oil with ranging from 5 to 100. Example of drug in polymer we have Lecithin, sodium lauryl sulphate [26,28].

2. **Nanoemulsion**

Nanoemulsion is uniform droplet particles composed of lipid and surfactants that are thermodynamically stable for long periods of time. Examples are oil in water and water in oil.

3.2.5. Cellular carriers

1**. Eukaryotic Resealed Erythrocyte cells**

Erythrocytes cells having vesicular system like properties, used to target inflamed intestinal lining.

2. **Eukaryotic Macrophages and Lymphocytes cells**

Macrophages and lymphocytes used to target inflammatory sites, both macrophages and lymphocytes can be bioengineered to entrap a drug via pinocytes and phagocytes[30,31].

3**. Bacterial-cell-Based delivery systems**

Bacterial cells could be modified and bioengineered to be used as efficient target delivery systems with polysaccarides capsules and flagella. They can be modified by forming a recombinant or by encapsulating a drug-loaded bacterial cell into a nanocapsule.

Table 1: Novel Carries Used For Administration of Drug And Enzymes In IBD [31,32,36].

S.NO	Carrier system	Drug
Liposome	Long-circulating liposomes(LCLs)	Dexamethasone phosphate
	negatively charged liposomes	Superoxide dismutase
	Eudragit S 100-coated calcium alginated gel	Prednisolone
	Phospholipid bilayer system	Verteporfin
	Topical drug delivery, transport tamoxifen molecules	Tamoxifen
		Dutasteride

Particulate systems	Bearing liposomes loaded vesicular system and topical liposomes	Finasteride
	Silicon nanoparticles	Methylated 5-ASA
	PEG-PLA polymer carriers (PNC)	PEG-catalse
	Mannosylated cystamine bisacrylamide branched polyetylenimine	siRNA for TNF-a
	polyethylene glycol nanoparticles	
	5-aminosalicyclic (5SAS) localized chemotherapy	Sulfasalazine
	Eudragit S-100 coated Capsules	5-fluoro-uracil
	Polyvinyl chloride-based medical devices	DEHP di(2-ethylhexy phthalate
Entrapped systems	cationic chitosan and microparticles proteins	Budesonide
	Nanoparticles with the high encapsulation	Phosphorthioate oligodeoxy nucleotides Rifaximin
Emulsions	efficiency and high loading capacity microemulsion	
	Hydrogels prepared by	Cyclosporin
Self-assembled systems	coplymerization of 2-Hydroethyl methacrylate	Brilaciden

	with 4-methacryloyloxy azobezene	
	Lacotococcus lactis	NF-a-neutralizing nanobody protein
Cells		
(Prokaryotics	Human RBC cells	Dexamethanse
and	Leukocyte-directed	
eukaryotics)	anotargeted	siRNA against CyDl mRNA

Conclusion:

Inflammatory bowel disease that causes considerable morbidity in the united states and Europe. In recent years, important advances have been made understanding of the imm une mediators of intestinal inflammation. this has new approaches to IBD. There is no doubt that an unprecedented progress in our understanding of IBD pathogenesis has been achieved during the past few years.

The key factors responsible for IBD include genetic components, environmental elements, microbial flora and immune responses. An extremely complex interaction among genetic and environmental elements, dysregulated immune response and alterations of the microbiome, and that none of these factors alone is likely to cause the disease.

More detailed information on their composition, function, and interaction is increasingly accessible through high genomic approaches, investigation of environmental changes, molecular analysis of gut bacteria flora, and a more integrated interaction between innate and adaptive immune responses. This review provides an overview of the experimental studies done using monoclonal antibodies and anti-inflammatory drug. Most of the results reported in the papers show anti-inflammatory compounds inhibit the proliferation of cytokines such as TNF-a and IFN-y, but unfortunately have potential side effect, including vomiting, diarrhea, and nausea. the information obtained from ongoing and future clinical trails will help us better understand the pathophysiology of intestinal inflammation in IBD and may have a significant impact on treating patients with the disease.

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Corresponding Author:

Sonia Kassana*

Research scholar, Galgotias University, Greater Noida, Pin-201308, India.

Email: soniakasana12@gmail.com