

# **Drugs used in inflammatory bowel disease and biological and immune therapy of IBD**

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# Inflammatory Bowel Diseases (IBD)

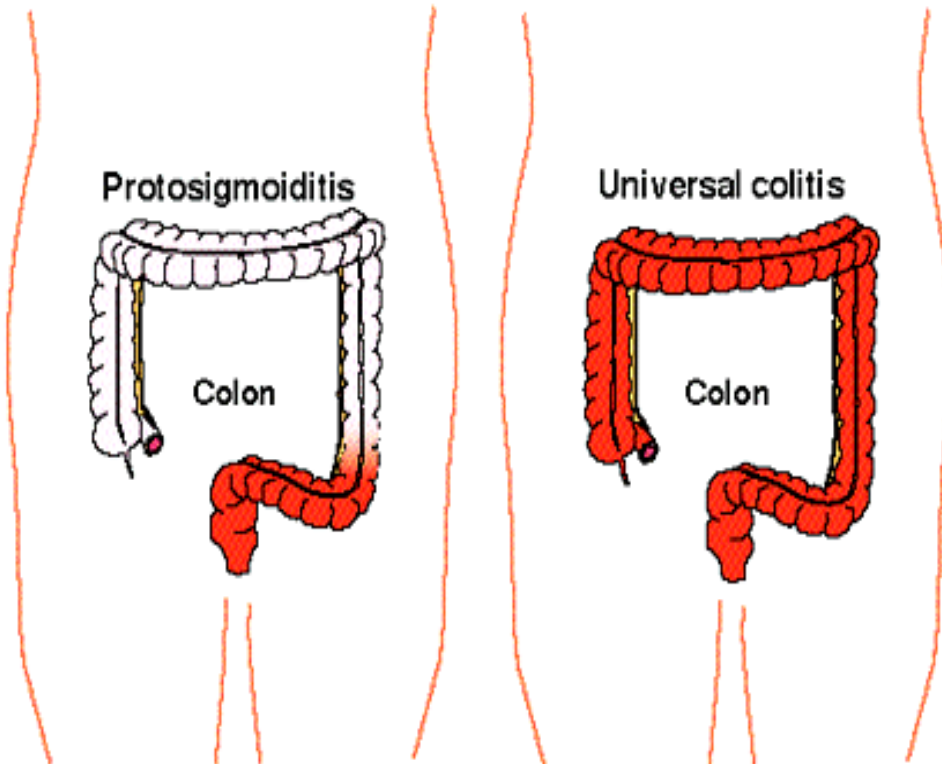
- Is a group of inflammatory conditions of the small intestine and colon.
- The major types of **IBD** are Crohn's disease and ulcerative colitis (UC).

# Causes

- **Not known.**
- **Auto-immune disorder due to abnormal activation of the immune system.**
- **The susceptibility is genetically inherited.**

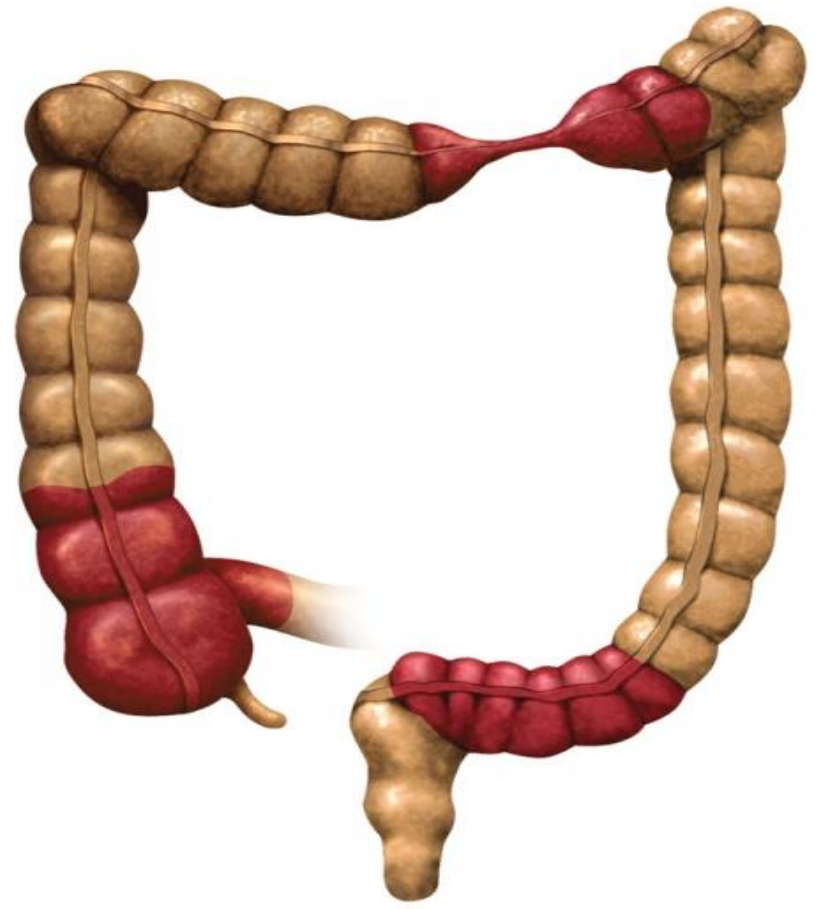
# Differences between Crohn's disease and UC

	<b>Crohn's disease</b>	<b>Ulcerative colitis</b>
<b>Location</b>	Affects any part of the GIT, from <b>mouth</b> to <b>anus</b>	Restricted to colon & rectum
<b>Distribution</b>	<b>Patchy areas</b> of inflammation ( <i>Skip lesions</i> )	<b>Continuous area</b> of inflammation
<b>Depth of inflammation</b>	May be transmural, deep into tissues	Shallow, mucosal
<b>Complications</b>	Strictures, Obstruction Abscess, Fistula	Toxic megacolon Colon cancer



ULCERATIVE COLITIS *A. Bonsall*

# Ulcerative colitis



# Crohn's disease

# Symptoms

- **Abdominal pain**
- **Vomiting**
- **Diarrhea**
- **Rectal bleeding.**
- **Weight loss**

# Complications

- **Anemia**
- **Abdominal obstruction (Crohn's disease)**
- **Mega colon**
- **Colon cancer**

# Treatment of IBD

**There are two goals of therapy**

- 1. Achievement of remission (Induction).**
- 2. Prevention of disease flares (maintenance).**



# Treatment of IBD

## Stepwise therapy:

- A. 5-amino salicylic acid compounds (5-ASA) or aminosalicylates.
- B. Glucocorticoids
- C. Immunomodulators
- D. Biological therapy (**TNF- $\alpha$  inhibitors**).
- E. Surgery in severe condition.

# 5-amino salicylic acid compounds (5-ASA) Aminosalicylates

## Mechanism of action

Have **topical anti-inflammatory** action due to:

- Inhibition of prostaglandins and leukotrienes.
- Decrease neutrophil chemotaxis.
- Antioxidant activity (scavenging free radical production).

# **Aminosalicylates (5-ASA)**

- **5-ASA itself is absorbed from the proximal small intestine.**
- **Different formulations are used to overcome rapid absorption of 5-ASA from the proximal small intestine.**
- **All aminosalicylates are used for induction and maintenance of remission**

# Aminosalicylates

**Different formulations of aminosalicylates are:**

## **1. Azo compounds**

- Sulfasalazine
- Balsalazide
- Olsalazine

## **2. Mesalamines**

- Asacol
- Pentasa
- Canasa
- Rowasa

**The major differences are in **mechanism** and **site** of delivery.**

# 1. Azo compounds

These compounds contain (5-ASA) that is connected by azo bond ( $\text{N}=\text{N}$ ) :

- ✓ to sulfapyridine moiety (**Sulfasalazine**)
- ✓ to another molecule of 5-ASA (**Olsalazine**)
- ✓ to inert compound (**Balsalazide**).

**Sulfasalazine** : 5-ASA + sulphapyridine

**Olsalazine**: 5-ASA + 5-ASA

**Balsalazide**: 5-ASA + inert carrier

# Azo compounds

- **Azo structure** reduces absorption of 5-ASA in small intestine.
- **In the terminal ileum and colon**, azo bond is cleaved by azoreductase enzyme produced by bacterial flora releasing 5-ASA in the terminal ileum and colon.

## Sulfasalazine (Azulfidine)

- **Pro-drug**
- **A combination of 5-ASA + sulfapyridine**
- **Is given orally (enteric coated tablets).**
- **Little amount is absorbed (10%)**
- **In the terminal ileum and colon, sulfasalazine is broken by azoreductase into:**
  - **5-ASA** (not absorbed, active moiety acting locally).
  - **Sulphapyridine** (absorbed, causes most of side effects).

# **Mechanism of action of sulfasalazine**

**5-ASA has anti-inflammatory action due to:**

- **Inhibition of prostaglandins and leukotrienes.**
- **Decrease neutrophil chemotaxis.**
- **Antioxidant activity (scavenging free radical production).**



## Side effects of sulfasalazine

- **Crystalluria.**
- **Bone marrow depression**
- **Megaloblastic anemia.**
- **Folic acid deficiency (should be provided).**
- **Impairment of male fertility (*Oligospermia*).**
- **Interstitial nephritis due to 5-ASA.**

## **2.Mesalamine compounds**

**Formulations that have been designed to deliver 5-ASA in terminal small bowel & large colon.**

*Mesalamine formulations are*

- **Sulfa free**
- **Well tolerated**
- **Have less side effects compared to sulfasalazine**
- **Useful in patient sensitive to sulfa drugs.**

# Mesalamine compounds

## Oral formulations

- which releases 5-ASA in the distal small bowel secondary to pH changes.
- Releases start at the pylorus and continues throughout the small bowel and colon.
- **Asacol:** 5-ASA coated in pH-sensitive resin that dissolve at pH 7.
- **Pentasa:** micro granules that release 5-ASA throughout the small intestine.

# Mesalamine rectal formulations

release 5-ASA in the distal colon.

**Canasa** (suppositories)

**Rowasa** (enema)

# Clinical uses of 5-amino salicylic acid compounds

- Induction and maintenance of remission in mild to moderate IBD (First line of treatment).
- Rheumatoid arthritis (**Sulfasalazine only**).
- Rectal formulations are used in distal ulcerative colitis, **ulcerative proctitis** and **proctosigmoiditis**.

# Glucocorticoids

- I) **Oral preparation: e.g. prednisone, prednisolone**
- II) **Parenteral preparation: e.g. hydrocortisone, methyl prednisolone**
  - Higher rate of absorption
  - More adverse effects compared to rectal administration
- III) **Rectal preparation e.g. Hydrocortisone**
  - As enema or suppository, give topical effect.
  - Less absorption rate than oral.
  - Minimal side effects & maximum tissue effects

# Budesonide:

- A potent synthetic prednisolone analog
- Given orally (**controlled release tablets**) so release drug in ileum and colon.
- Low oral bioavailability (10%).
- Is subject to extensive **first pass metabolism**
- Used in treatment of active mild to moderate Crohn's disease involving ileum and proximal colon.

# **Mechanism of action of glucocorticoids**

- **Inhibits phospholipase A2**
- **Inhibits gene transcription of NO synthase, cyclo-oxygenase-2 (COX-2)**
- **Inhibit production of inflammatory cytokines**



# Uses of glucocorticoids

- **Indicated for acute flares of disease (moderate –to- severe active IBD).**
- **Are not useful in maintaining remission (not effective as prophylactic therapy).**
- **Oral glucocorticoids is commonly used in active condition.**
- **Rectal glucocorticoids are preferred in IBD involving rectum or sigmoid colon.**

# Uses of glucocorticoids

- **Asthma**
- **Rheumatoid arthritis**
- **Immunosuppressive drug for organ transplants**
- **Antiemetic during cancer chemotherapy**

# **Immunomodulators**

Are used to induce remission in IBD in active moderate-to-severe conditions or steroid dependent or steroid resistant (refractory) Patients and to maintain remission.

## **Immunomodulators include:**

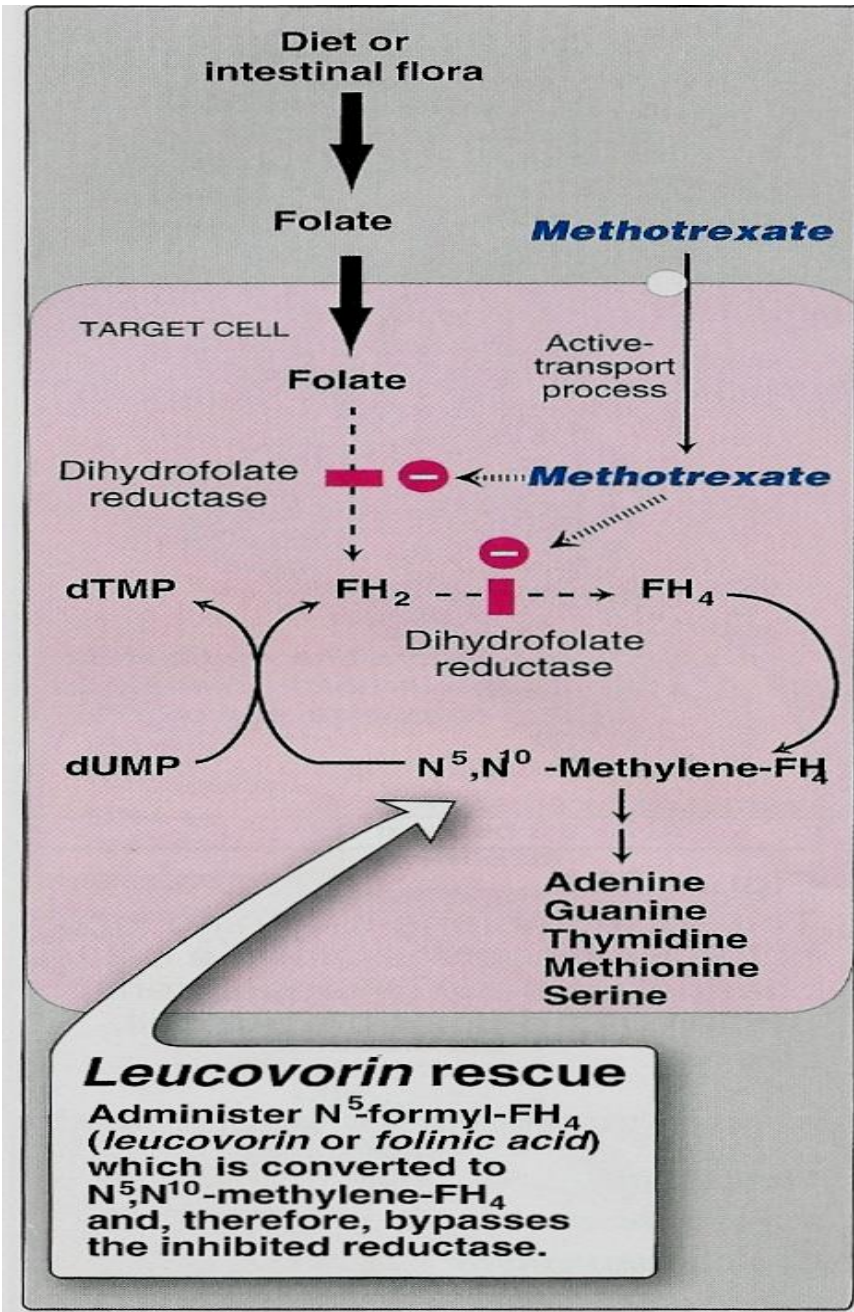
- **Methotrexate**
- **Purine analogs:**  
**(azathioprine & 6-mercaptopurine).**

# Methotrexate

- Folic acid antagonist
- Inhibits dihydrofolate reductase required for folic acid activation (tetrahydrofolate)
- Impairs DNA synthesis
- Orally, S.C., I.M.
- Used to induce and maintain remission.

## Uses

- Inflammatory bowel disease
- Rheumatoid arthritis
- Cancer



# **Adverse effects of methotrexate**

- **Megaloblastic anemia**
- **Bone marrow depression**

# Purine analogues

(azathioprine & 6-mercaptopurine)

**Azathioprine is pro-drug of 6-mercaptopurine**

- Inhibit purine synthesis and inhibits synthesis of DNA, RNA, and proteins.
- It may decrease proliferation of immune cells, which lowers autoimmune activity.
- **Induction and maintenance of remission in IBD**

## **Adverse effects:**

- Bone marrow depression: leucopenia, thrombocytopenia.**
- Gastrointestinal toxicity.**
- Hepatic dysfunction.**
- Complete blood count & liver function tests are required in all patients**



# **Monoclonal antibodies used in IBD**

## **(TNF- $\alpha$ inhibitors)**

- **Infliximab**
- **Adalimumab**
- **Certolizumab**

# Infliximab

- a chimeric mouse-human monoclonal antibody
- 25% murine – 75% human.
- TNF- $\alpha$  inhibitors
- Inhibits soluble or membrane –bound TNF- $\alpha$  located on activated T lymphocytes.
- Given intravenously as infusion (5-10 mg/kg).
- has long half life (8-10 days)
- 2 weeks to give clinical response.

# Uses of infliximab

- **In moderate to severe active Crohn's disease and ulcerative colitis.**
- **Patients not responding to immunomodulators or glucocorticoids.**
- **Treatment of rheumatoid arthritis**
- **Psoriasis**

# Side effects

- **Acute or early adverse infusion reactions**  
*(Allergic reactions or anaphylaxis in 10% of patients).*
- **Delayed infusion reaction** *(serum sickness-like reaction, in 5% of patients).*
- **Pretreatment with diphenhydramine, acetaminophen, corticosteroids is recommended.**

## **Side effects (Cont.)**

- **Infection complication (Latent tuberculosis, sepsis, hepatitis B).**
- **Loss of response to infliximab over time due to the development of antibodies to infliximab.**
- **Severe hepatic failure.**
- **Rare risk of lymphoma.**

# Adalimumab (HUMIRA)

- Fully humanized IgG antibody to TNF- $\alpha$
- Adalimumab is TNF $\alpha$  inhibitor
- It binds to TNF $\alpha$ , preventing it from activating TNF receptors.
- Has an advantage that it is given by subcutaneous injection
- Approved for treatment of, moderate to severe Crohn's disease, rheumatoid arthritis, psoriasis.

# Certolizumab pegol (Cimzia)

- Fab fragment of a humanized antibody directed against TNF- $\alpha$
- Certolizumab is attached to polyethylene glycol to increase its half-life in circulation.
- Given subcutaneously for the treatment of Crohn's disease & rheumatoid arthritis

# Summary for drugs used in IBD

- **5-aminosalicylic acid compounds**
  - Azo compounds:  
sulfasalazine, olsalazine, balsalazide
  - Mesalamines:  
Pentasa, Asacol, Rowasa, Canasa
- **Glucocorticoids**  
prednisone, prednisolone, hydrocortisone, budesonide
- **Immunomodulators**
  - Methotrexate
  - Purine analogues: Azathioprine & 6mercaptopurine
- **TNF-alpha inhibitors (monoclonal antibodies)**
  - Infliximab – Adalimumab - Certolizumab



Thank you