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

Pharmacology Unit
College of Medicine

Inflammatory Bowel Diseases (IBD)

- is a group of inflammatory conditions of the small intestine and colon.

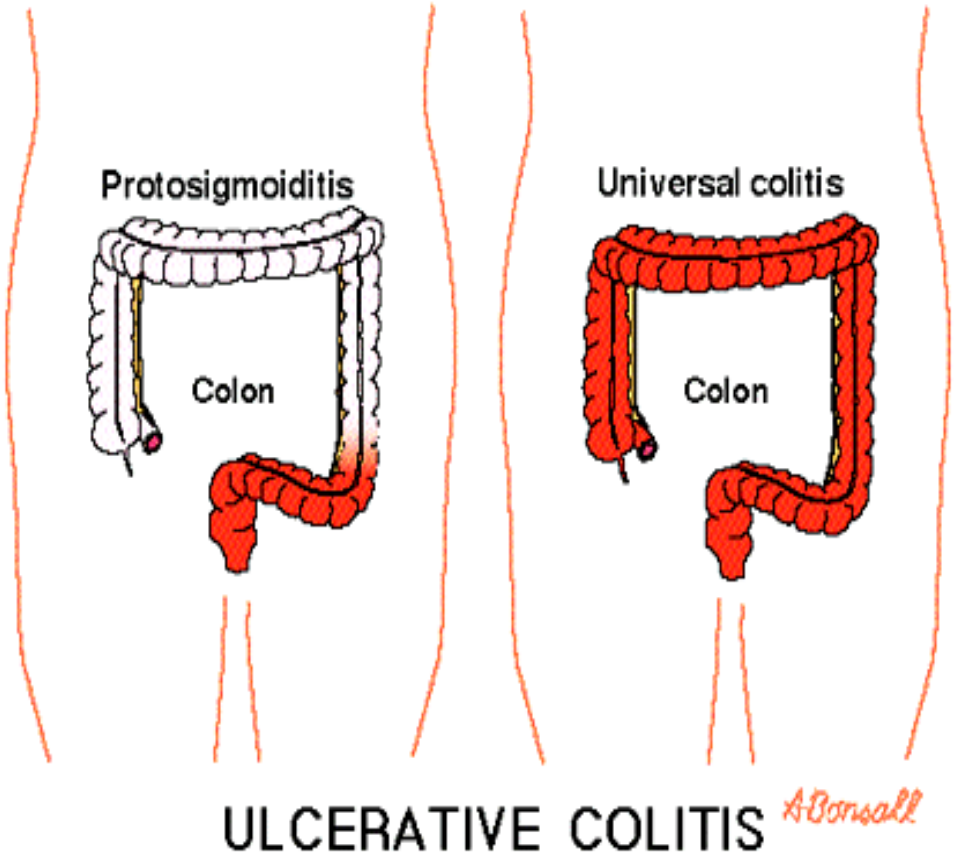
- The major types of **IBD** are Crohn's disease and ulcerative colitis (**UC**).

Causes

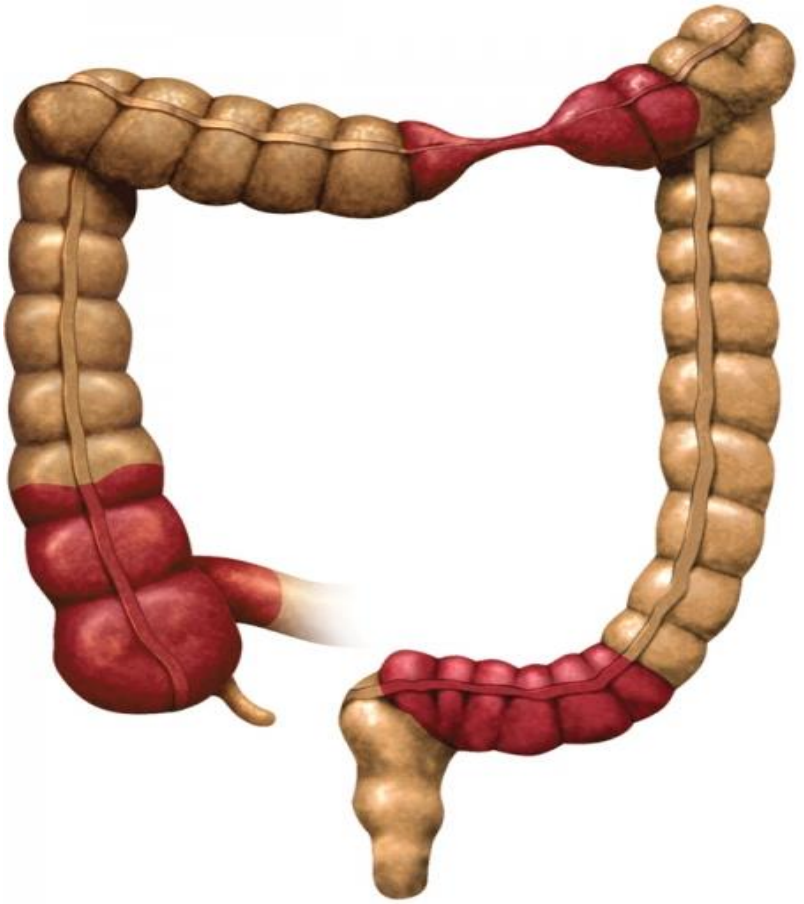
- **Not known.**
- **auto-immune disorder due to abnormal activation of the immune system.**
- **The susceptibility is genetically inherited.**

Differences between Crohn's disease and UC

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



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:

1. **5-amino salicylic acid compounds (5-ASA) or aminosalicylates.**
2. **Glucocorticoids**
3. **Immunomodulators**
4. **Biological therapy (TNF-α inhibitors).**
5. **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:

- **Azo compounds**
  - Sulfasalazine
  - Balsalazide
  - Olsalazine
- **Mesalamines**
  - Asacol
  - Pentasa
  - Canasa
  - Rowasa

The major differences are in mechanism and site of delivery.

Azo compounds

These compounds contain (5-ASA) that is connected by azo bond (N=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.**

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).

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:

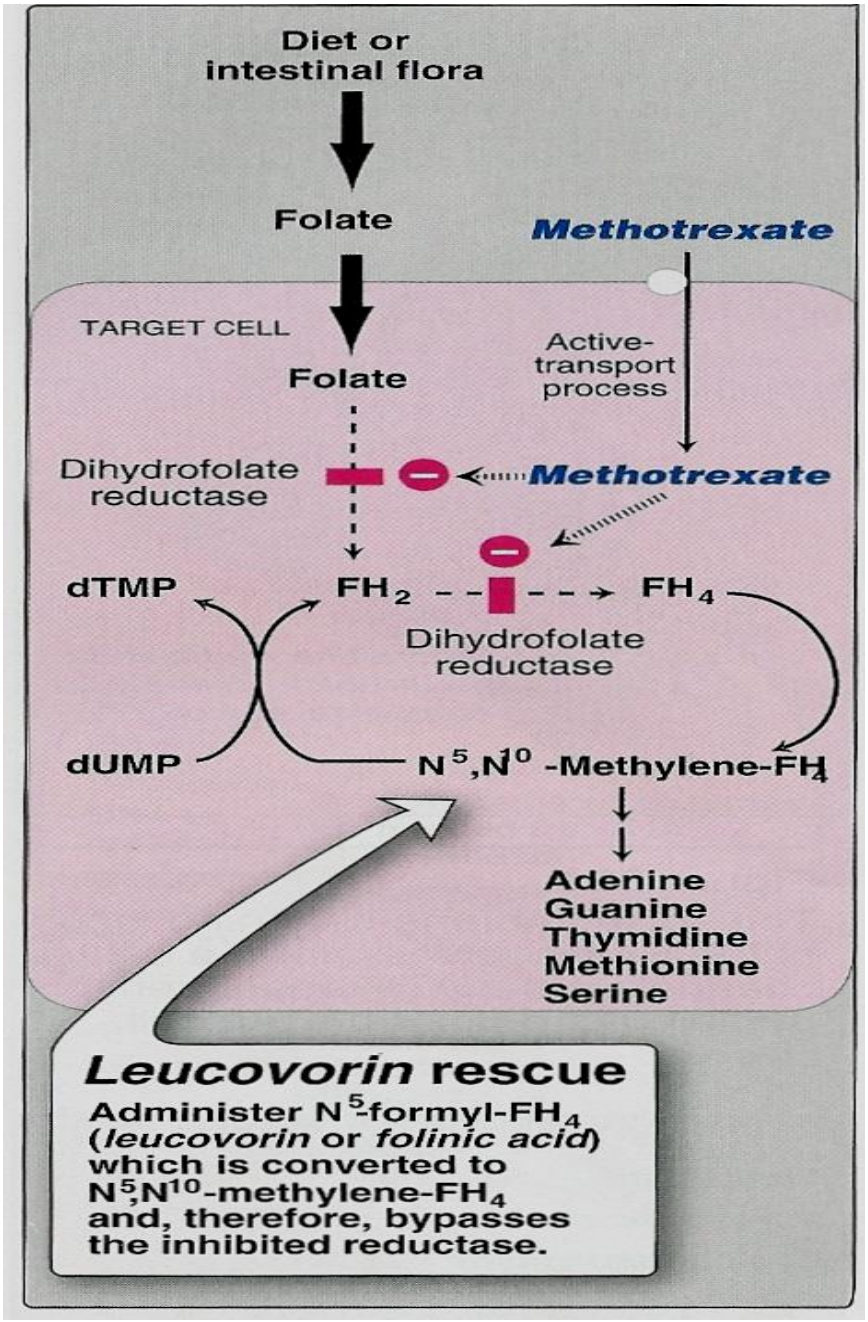
- **Bone marrow depression: leucopenia, thrombocytopenia.**
- **Gastrointestinal toxicity.**
- **Hepatic dysfunction.**
- **Complete blood count & liver function tests are required in all patients**

Methotrexate

- a 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


Diet or
intestinal flora
Folate
Methotrexate
TARGET CELL
Folate
Active-
transport
process
Dihydrofolate
reductase
Methotrexate
dTMP
FH2
FH4
Dihydrofolate
reductase
dUMP
N5,N10 -Methylene-FH4
Adenine
Guanine
Thymidine
Methionine
Serine
Leucovorin rescue
Administer N5-formyl-FH4
(leucovorin or folinic acid)
which is converted to
N5,N10-methylene-FH4
and, therefore, bypasses
the inhibited reductase.

Adverse effects of methotrexate

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

Monoclonal antibodies used in IBD (TNF-α inhibitors)

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

Infliximab

- a chimeric mouse-human monoclonal antibody
- 25% murine – 75% human.
- TNF-α inhibitors
- Inhibits soluble or membrane –bound TNF-α 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-reaction, in 5% of patients).***
- **Pretreatment with diphenhydramine, acetaminophen, corticosteroids is recommended.00**

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.**

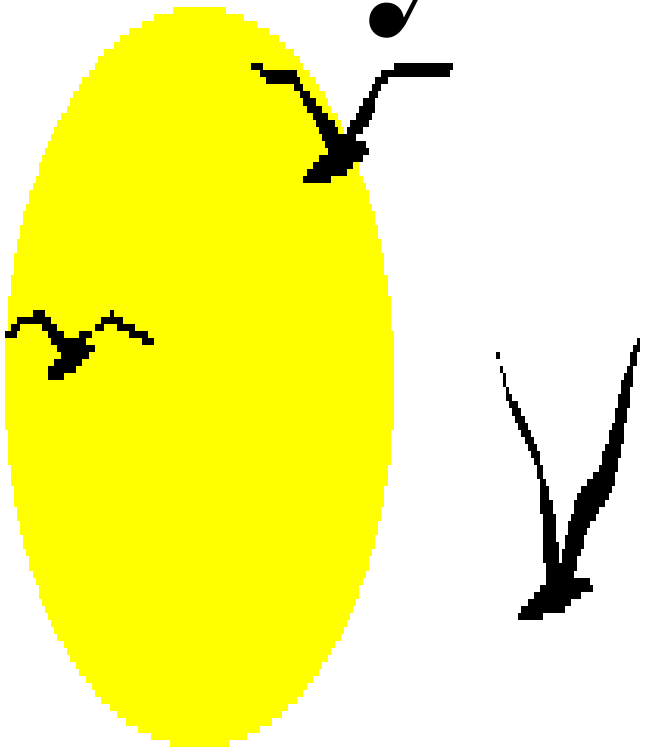
Adalimumab (HUMIRA)

- **Fully humanized IgG antibody to TNF-α**
- **Adalimumab is TNFα inhibitor**
- **It binds to TNFα, preventing it from activating TNF receptors.**
- **Has an advantage that it is given by subcutaneous injection**
- **is 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-α**
- **Certolizumab is attached to polyethylene glycol to increase its half-life in circulation.**
- **Given subcutaneously for the treatment of Crohn's disease & rheumatoid arthritis**

Thank you



Questions ?

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 - Cetrolizumab**