Drugs and biological and immune therapy in inflammatory bowel disease (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**).

Inflammatory Bowel Diseases (IBD)

Ulcerative colitis (**UC**):

- Chronic mucosal inflammation of the colon

Crohn's disease (CD):

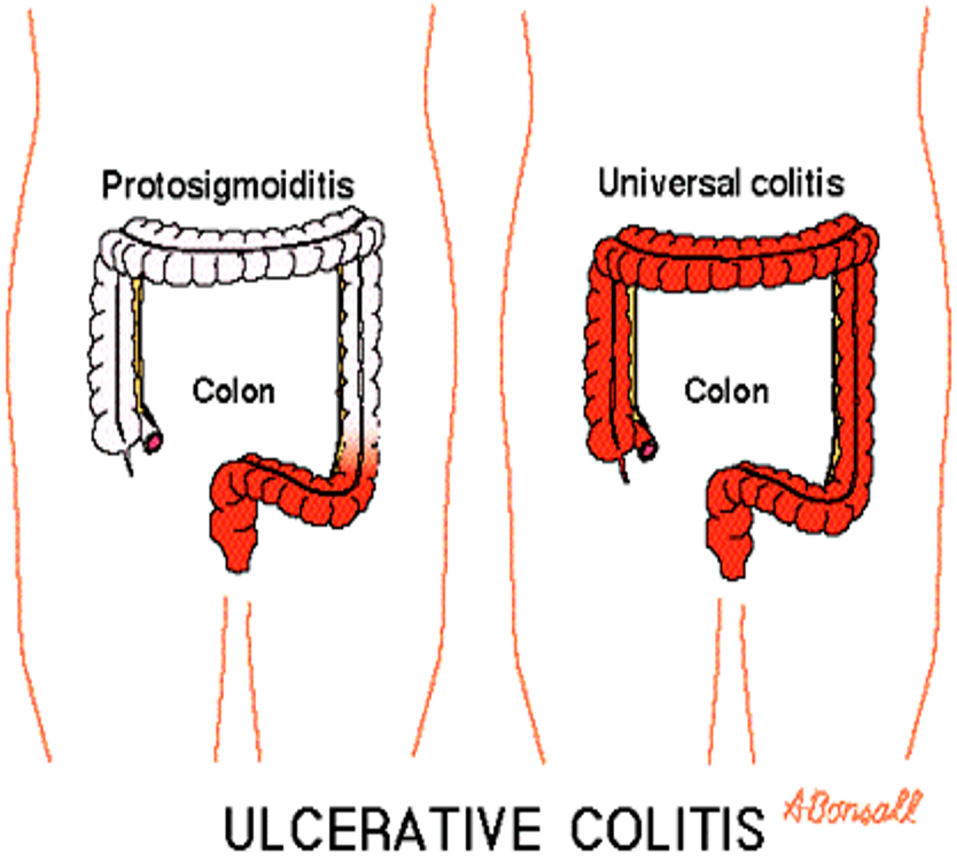
- Chronic transmural inflammation of gastrointestinal tract

Differences between Crohn's disease and UC

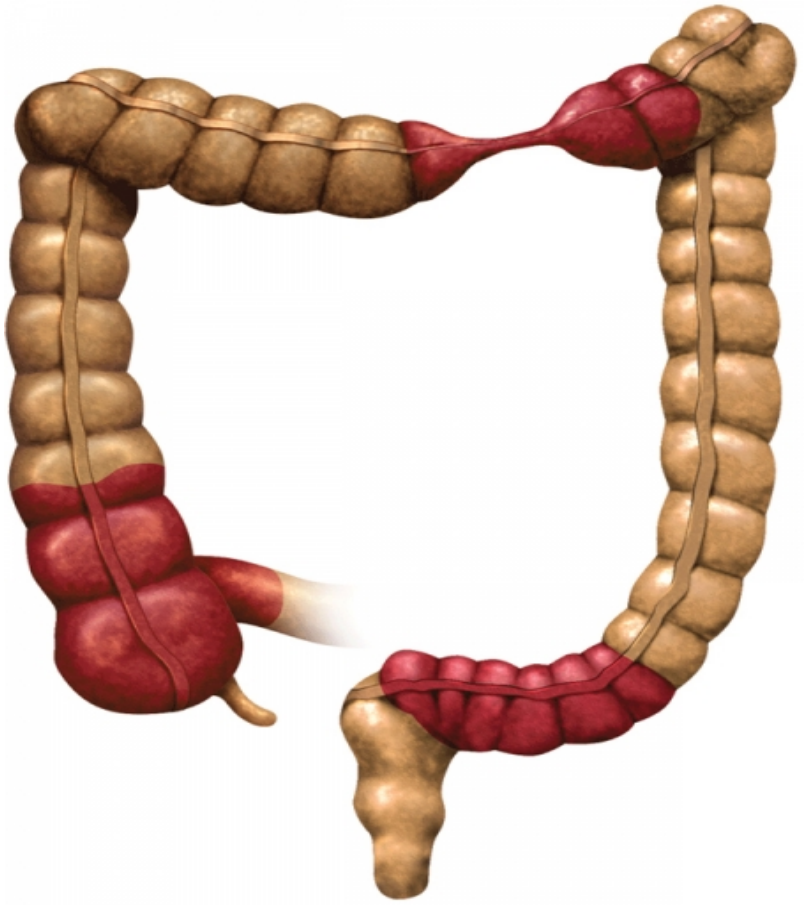
	Crohn's disease	Ulcerative colitis
Location	affect any part of the GIT, from mouth to anus	Restricted to colon & rectum
Distribution	Patchy areas of inflammation *(Skip lesions)*	Continuous area of inflammation
Depth of inflammation	May be transmural, deep into tissues	Shallow, mucosal
Complications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

Presentation

	Crohn Disease	Ulcerative Colitis
Bleeding	Occasional	Very common
Obstruction	Common	Uncommon
Fistulae	Common	None
Weight loss	Common	Uncommon
Perianal disease	Common	Rare



Ulcerative colitis



Crohn's disease

Causes

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

Symptoms

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

Complications

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

Treatment of IBD

Treatment objectives

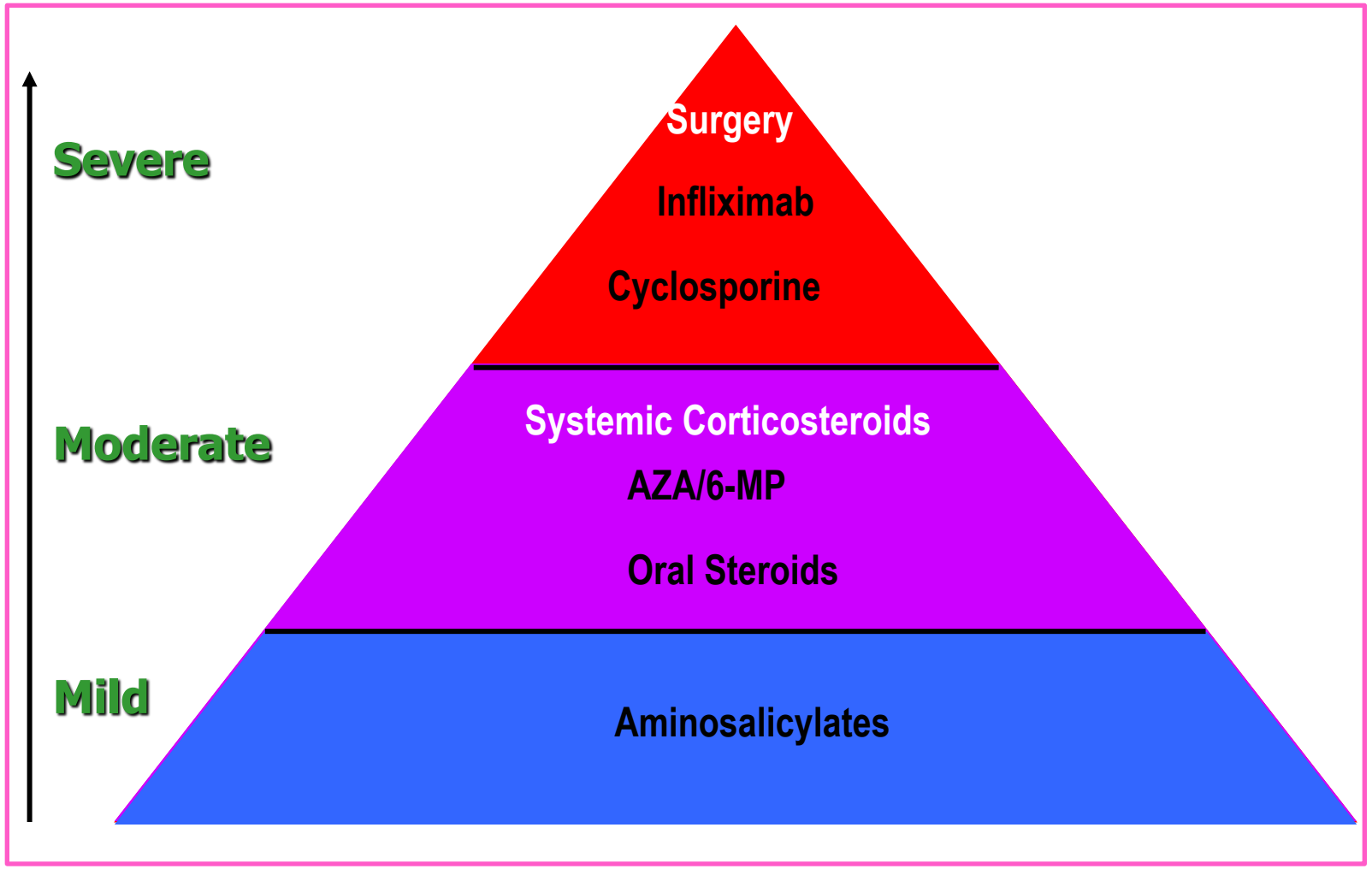
1. Achievement of remission (Induction).
2. Prevention of disease flares (maintenance).
3. Normalize bowel function.
4. Maintain nutritional status.
5. Improve quality of life.

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.**

Stepwise therapy For IBD



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.**

Mesalamines

- **Asacol** orally, delayed release tablets, distal ileum, colon, pH sensitive coating
- **Pentasa** orally, sustained release capsules, stomach, colon
- **Canasa** Rectally (suppository), rectum
- **Rowasa** Rectally (suspension as enema), rectum

Mesalamines

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 (delayed release).

Pentasa: microgranules that release 5-ASA throughout the small intestine (sustained release)..

Mesalamines

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

Mechanism of action of glucocorticoids

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

Glucocorticoids

Oral preparation: e.g. prednisone, prednisolone

Parenteral preparation: e.g. hydrocortisone, methyl prednisolone

- Higher rate of absorption
- More adverse effects compared to rectal administration

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
- Has low bioavailability
- Used in treatment of active mild to moderate Crohn's disease involving ileum and proximal colon.

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

Immunomodulators include:

- **Methotrexate**
- **Purine analogs include**
  - **Azathioprine**
  - **6-mercaptopurine**

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

Purine analogues

azathioprine & 6-mercaptopurine

Azathioprine is pro-drug of 6-mercaptopurine

- Inhibits 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 active IBD**

Adverse effects:

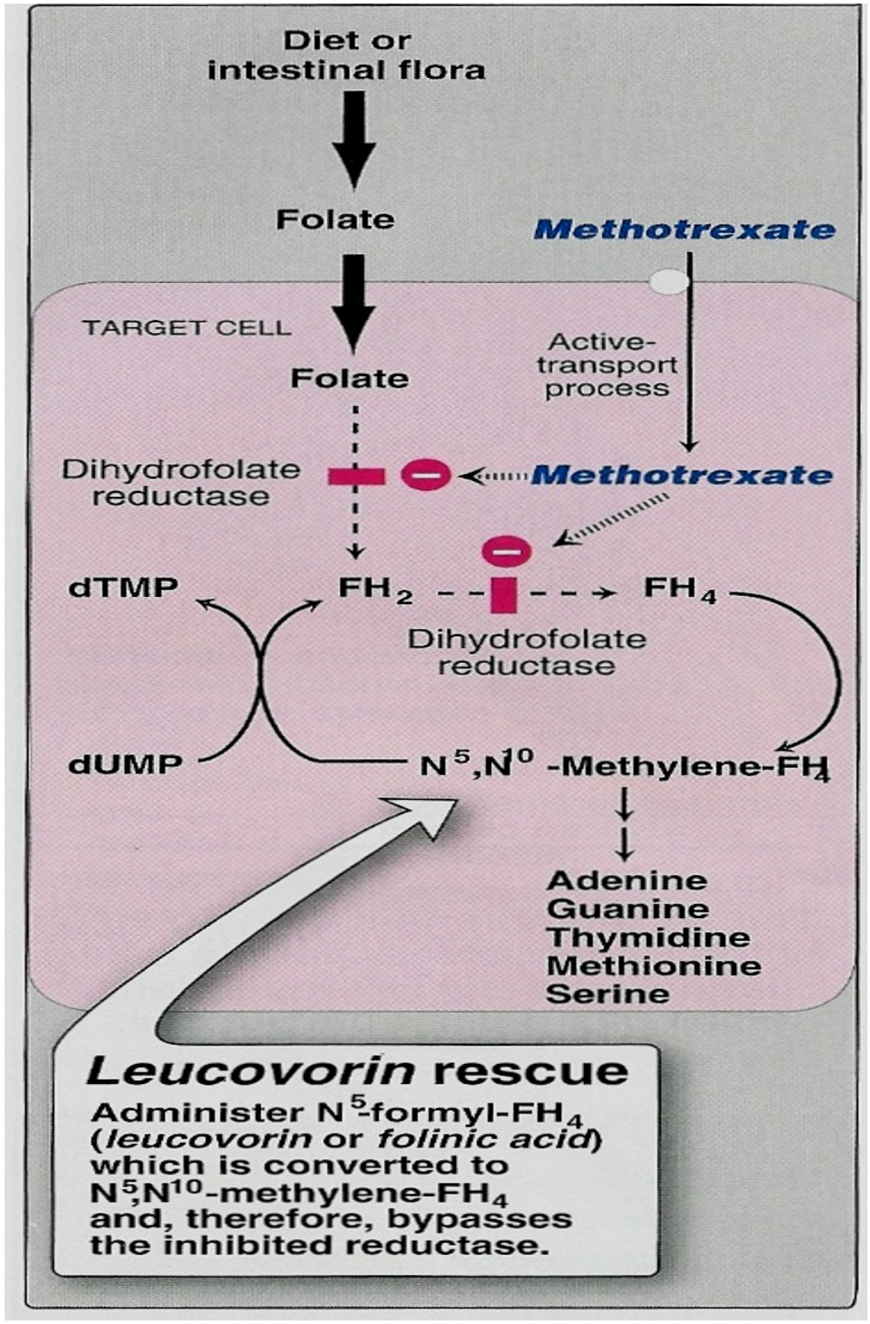
- **Bone marrow depression: leucopenia, thrombocytopenia.**
- **Gastrointestinal toxicity.**
- **Hepatic dysfunction.**
- **Complete blood count & liver function tests are required in all patients**

Methotrexate

- a folic acid antagonist
- Inhibits dihydrofolate reductase required for folic acid activation (**tetrahydrofolate**)
- Impairs DNA synthesis
- Orally, 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**
- **Teratogenic**

Monoclonal antibodies used in IBD (TNF-α inhibitors)

- **Infliximab**
- **Adalimumab**
- **Certolizumab**
- Act by binding to TNF-α thus preventing its binding to cell surface receptors.
- Increase apoptosis of T-lymphocytes and monocytes.

Infliximab

- a chimeric mouse-human monoclonal antibody
- 25% murine – 75% human.
- TNF-α inhibitor
- 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 infusion-related adverse reactions (Allergic reactions or anaphylaxis in 10% of patients).**
- **Delayed type hypersensitivity reaction (serum sickness-like reaction, in 5% of patients).**
- **Pre-treatment with diphenhydramine, acetaminophen, corticosteroids is recommended.**

Side effects (Cont.)

- **Increase risk of opportunistic infections (Latent tuberculosis, sepsis, hepatitis B, fungal infections).**
- **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

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**

Inductive Therapies

For UC

- Aminosalicylates
- Corticosteroids
- Immunosupressors
- Infliximab

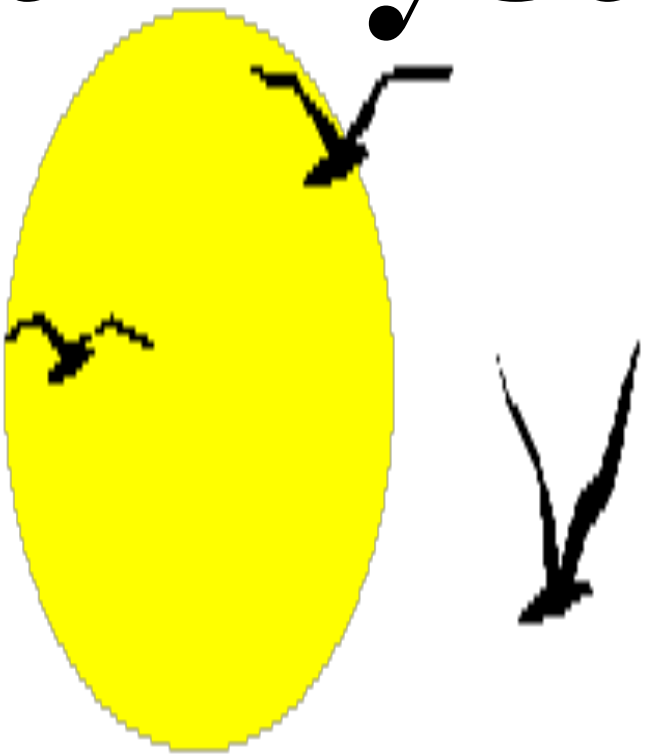
For CD

- Aminosalicylates
- Corticosteroids
- Antibiotics
- Biologics

Maintenance Therapies

- Aminosalicylates
- Immunosupressors
  Azathioprine
  6-MP
  Methotrexate
- Infliximab
- NO corticosteroids

Thank you



Questions ?