GIS

PHARMACOLOGY

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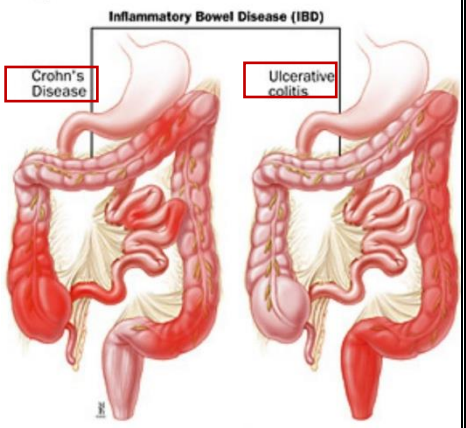
Drugs Used to Treat Inflammatory Bowel Disease

There are 2 types of inflammatory bowel disease (both Etiology & pathogenesis are unknown):

1. **Ulcerative colitis:** Restricted to the colon and the rectum. Also, it is restricted to the mucosa.
2. **Crohn's disease:** more dangerous it can affect any part of GIT. But most cases start in terminal ileum, and it affects the whole bowel wall.



Both of them present with extra-intestinal manifestations (such as liver problems, arthritis, skin manifestations and eye problems) in different proportions.

To Treat these conditions:

1.Aminosalicylates

(5-ASA) which works topically not systemically (so it has to get to the infected area) and if it is given unformulated about 80% of 5-ASA is absorbed Leaving only 20% to reach the small intestine and the distal small bowel or colon to get to the infected area and work there.

***That is why there is a number of formulations deliver 5-ASA to various distal segments of the small bowel or the colon:*

Azo Compounds (Sulfalazine, Balsalazide, olsalazine)

These are 5-ASA bound by an azo (N=N) bond to an inert (drug or agent having no pharmacologic or therapeutic action) or to another 5-ASA molecule.

The azo structure markedly reduces absorption of the parent drug from the small intestine (which is good because all the side effects comes from the absorption). In the terminal ileum and colon, resident bacteria Cleave the azo bond by an azoreductase enzymes, releasing 5-ASA toward the affected area.

Mesalamine compounds

there are several Mesalamine Based agents including:

A. Pentasa: Timed-release microgranules that release 5-ASA Throughout the small intestine

B. Asacol: 5-ASA coated in a pH-sensitive resin that dissolves at the pH of the distal ileum and proximal colon)

5-ASA also delivered as:

- Enema (Rowasa): an injection of fluid into the lower bowel by way of the rectum
- Suppositories (Canasa): is a solid dosage

📌**mechanism of action of 5-ASA is unknown but several mechanisms of action were proposed. So, it might work by**:

1. Inhibition of cytokine synthesis
2. Inhibition of PG and leukotriene synthesis
3. Free radical scavenging
4. Immunosuppressive activity: 5-ASA inhibits both T-cell proliferation and subsequent activation and differentiation.
5. Impairment of white cell adhesion and function

📌**Clinical uses**

5-ASA drugs are **first-line** agents for treatment of **mild to moderate active ulcerative colitis.**
Their efficacy in Crohn's disease is unproven, although used as first-line therapy for mild to moderate disease involving the colon or distal ileum.

📌**Adverse Effects**

These effects are due to systemic absorption and they are more severe in slow acetylators they include:
Nausea, headache, arthralgia (pain in joint), myalgia (pain in muscles) , bone marrow suppression, and malaise. Also, allergic reactions, oligospermia (low sperm count), and folate deficiency.

💊2.Glucocorticoids

Potent anti-inflammatory drugs

📌**Mechanism of action,**

they suppress immune system by

A. Inhibit production of inflammatory cytokines and chemokines
B. Reduce expression of inflammatory cell adhesion molecules.
C. Inhibit gene transcription of nitric oxide synthase, phospholipase A2, cyclooxygenase-2, and NF-B.

📌**Clinical uses: Moderate to severe** active IBD. Not useful for maintenance (for maintenance we need to give Glucocorticoids for a long time and longtime treatment with Glucocorticoids brings out many side effects that are not wanted).

📌 Ex:

Prednisolone Orally or IV 💉

Hydrocortisone Rectally for rectal and sigmoid involvement.

Budesonide which is a controlled-release oral formulation, releases the drug in the distal ileum and colon for ileal and proximal colon Involvement.

💊 3. Antimetabolites:

Azathioprim, 6-Mercaotopurine.

These Are purine analogs; which produce thioguanine nucleotides (Active form).

Immunosuppressants. Inhibit purine nucleotide metabolism and DNA synthesis and repair, resulting in inhibition of cell division and proliferation and may promote T-lymphocyte apoptosis

📌 **Clinical Use:**

Onset delayed for 17 weeks so. Used in induction and maintenance of remission.

Allow dose reduction or elimination of steroids.

📌 **Adverse Effects:**

Nausea, vomiting, bone marrow suppression, Hepatic toxicity and allergic reactions (fever, rash, Pancreatitis, diarrhea and hepatitis).

**Allopurinol increases levels of the drugs.

Methotrexate

Antimetabolite, Used in cancer chemotherapy, Rheumatoid arthritis and psoriasis.

📌 **Mechanism of action:**

Inhibition of dihydrofolate reductase enzyme which is important in the synthesis of thymidine and purines.

- At high doses it inhibits cellular proliferation.
- At **low doses** used in IBD, it interferes with the inflammatory actions of interleukin-1, stimulates adenosine release, apoptosis and death of activated T lymphocytes.

📌 **Uses**

Induction and maintenance of remissions of Crohn's Disease.

📌**Adverse effects**: these effects could be produced at higher doses, but we use lower doses for IBD, SO high doses can cause:
Bone marrow depression,
Megaloblastic anemia,
Alopecia and mucositis.
Renal insufficiency may increase risk of hepatic
Accumulation and toxicity. But Side effects counteracted by folate supplementation.

💊Anti-Tumor Necrosis Factor Therapy

TNF-α is one of the principal cytokines mediating the TH1 (helper T cell type 1) immune response characteristic of **Crohn's disease**.

Infliximab

- A chimeric [means it comes from different types of animals] **immunoglobulin** (25% mouse, 75% human) **that binds to and neutralizes TNF-α**.
- Infliximab binds to both soluble & transmembrane forms of TNF- α and inhibits their ability to bind to TNF receptors and may cause lysis of these cells.
- Given by IV infusion.
- Half life 8-10 days with persistence of antibodies formed in plasma for 8-12 weeks.
- Used in moderate to severe **Crohn's disease**.
- Also used in acute and chronic treatment of patients with for **refractory ulcerative colitis**.
- Response might be lost due to development of antibodies to infliximab.

📌 **Side Effects:**
Acute:
fever, chills, urticaria, or even anaphylaxis
Delayed:
serum sickness–like reactions may develop after infliximab infusion, but **lupus-like syndrome** occurs only rarely.

- **Antibodies** to infliximab can decrease its clinical efficacy.
- Therapy is associated with increased incidence of **respiratory infections; reactivation of TB.**
- so, it shouldn't be given to patients with history of TB and respiratory infections
- Infliximab also is contraindicated in patients with severe congestive heart failure.

Adalimumab
Fully humanized IgG antibody, given SC [subcutaneously].
Certolizumab
Polyethylene glycol Fab fragment of humanized anti- TNF-α, also given SC.
For both, immunogenicity appears to be less of a problem than that associated with infliximab.

Natalizumab
- Humanized IgG4 monoclonal antibody against the cell adhesion molecule α 4-integrin subunit.
- Prevents binding of several integrins on circulating inflammatory cells to vascular adhesion molecules
- Used for patients with moderate to severe Crohn's disease who have failed other therapies
- Given by IV infusion every 4 weeks, and patients should not be on other immune suppressants to prevent the risk of progressive multifocal leukoencephalopathy (rare and usually fatal viral disease)
📌 **Adverse effects** include acute infusion reactions & a small risk of opportunistic infections.

pancreatic enzyme supplement
- Contain a mixture of **amylase, lipase, and proteases**.
- Used to treat pancreatic enzyme insufficiency.

Pancrelipase
- Available in both non-enteric-coated (given with acid suppression therapy) & enteric-coated preparations.
- Administered with each meal and snack. Excessive doses may cause diarrhea and abdominal pain.
- The high purine content of pancreas extracts may lead to hyperuricosuria and renal stones.

Drugs Used to Treat Variceal Hemorrhage
- Portal hypertension commonly occurs as a consequence of Chronic liver disease.
- Portal hypertension is caused by increased blood flow within the portal venous system & increased resistance to portal flow within the liver.
- blood accumulate in the veins and take the shape of balloons, the wall in these veins is thin, so, they might rapture causing hemorrhage
- Splanchnic blood flow is increased in patients with cirrhosis.

- The extra blood flow causes the veins in the esophagus to balloon outward.
- Varices can rupture, leading to massive upper GI bleeding

Somatostatin & Octreotide

- In patients with cirrhosis and portal hypertension, intravenous somatostatin or octreotide reduces portal blood flow and variceal pressures.
- They inhibit the release of glucagon and other gut peptides that alter mesenteric blood flow.
- They promote initial homeostasis from bleeding esophageal varices.
- They are generally administered for 3–5 days.

Beta-Receptor-Blocking Drugs

- Beta-receptor antagonists reduce portal venous pressures via a decrease in portal venous inflow.
- This decrease is due to a decrease in cardiac output (β1 blockade) and to splanchnic vasoconstriction (β2 blockade) caused by the unopposed effect of systemic catecholamines on α receptors.
- Thus, nonselective blockers such as **propranolol** and **nadolol** are more effective than selective β1 blockers in reducing portal pressures.
- Nonselective β blockers significantly reduce the rate of recurrent bleeding.

Vasopressin (antidiuretic hormone)

- Is a potent arterial vasoconstrictor.
- IV infusion causes splanchnic arterial vasoconstriction that leads to reduced splanchnic perfusion and lowered portal venous pressures.
- Vasopressin was commonly used to treat acute variceal hemorrhage. Because of its high adverse-effect profile, it is no longer used for this purpose.
- Patients with acute gastrointestinal bleeding from small bowel or large bowel vascular **ectasias** or **diverticulosis**, vasopressin may be infused—to promote vasospasm—into one of the branches of the superior or inferior mesenteric artery through an angiographically placed catheter

📌 **Adverse effects**

Are common. hypertension, myocardial ischemia or infarction, or mesenteric infarction.

Other common adverse effects are nausea, abdominal cramps, and diarrhea (due to intestinal hyperactivity).

vasopressin promotes retention of free water, which can lead to hyponatremia, fluid retention, and pulmonary edema

Terlipressin

is a vasopressin analog that have similar efficacy to vasopressin with fewer adverse effects.