

Pharmacology 5

Drugs Used to Treat Inflammatory Bowel Disease

Aminosalicylates

[5 -aminosalicylic acid (5-ASA)]

- work topically
- 80% is absorbed from the small intestine before reaching the target site

the different formulations:

1- Azo Compounds

 [Sulfasalazine, Balsalazide, Olsalazine]

- it is a 5 -ASA bound by an azo (N=N) bond to another compound
- the bond will reduce absorption from the small intestine
- in colon bacteria cleave drug by azoreductase enzyme, releasing 5 -ASA in affected area

2- Mesalamine Compounds



 [Pentasa]

- release 5 ASA from granules gradually in small intestine

 [Asacol]

- 5 ASA coated with resin that dissolves at the pH of distal ileum and proximal colon

3- other formulations of 5-ASA

- Enema  Rowasa
- Suppositories  Canasa

Mechanisms of 5-ASA

- Inhibition of cytokine synthesis
- Inhibition of prostaglandin and leukotriene synthesis

- Free radical scavenging
- Immunosuppressive activity [T cell inhibition]
- Impairment of white cell adhesion and function

Clinical Uses of 5-ASA

- ulcerative colitis
- mild to moderate Crohn's

Adverse Effects:

- Nausea, headache, arthralgia, myalgia, bone marrow suppression, and malaise.
- allergic reactions, oligospermia, folate deficiency

Glucocorticoids

Mechanism:

- ↓ inflammatory cytokines and chemokines.
- ↓ inflammatory cell adhesion molecules.
- ↓ gene transcription of nitric oxide synthase
- ↓ phospholipase A 2
- ↓ cyclooxygenase 2
- ↓ NF- κ B.

Clinical Uses:

- Moderate to severe active IBD.
- Not for maintenance.

[Prednisolone]

- Orally or IV.

[Hydrocortisone]

- Rectally
- rectal & sigmoidal involvement

[Budesonide]

- orally, controlled release
- ileal and proximal colon involvement

Antimetabolites

[Azathioprim,6 -Mercaotopurine]

- purine analogs (produce thioguanine nucleotides)
- Immunosuppressants.
- leads to T lymphocyte inhibition

Clinical Use:

- Onset delayed for 17 weeks
- for remission [reduction of the signs and symptoms]
- Allow for dose reduction of steroids.

Adverse effect


- Nausea, vomiting, bone marrow suppression
- hepatic toxicity
- allergic reactions(fever, rash, pancreatitis, diarrhea and hepatitis).
- Allopurinol increases levels of the drugs.

[Methotrexate]

Clinical Use:

- remissions of Crohn's Disease
- cancer chemotherapy
- rheumatoid arthritis
- psoriasis.

Mechanism

- Inhibition of dihydrofolate reductase  purine inhibition

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

Adverse effects:

At high doses

- bone marrow depression, megaloblastic anemia
- alopecia
- mucositis.
- Renal insufficiency increases risk of hepatic toxicity.

🖋️ counteracted by folate supplementation.

Anti Tumor Necrosis Factor Therapy

🖋️ [Infliximab]

- chimeric immunoglobulin (mouse& human) neutralizes TNF α → helper T cell type 1 inhibition
- IV infusion

Uses:

- moderate to severe Crohn's disease.
- patients with refractory ulcerative colitis.

🖋️ body development of antibodies to infliximab → response is lost

Side Effects:

- Acute: fever, chills, urticaria, anaphylaxis
- Delayed: serum sickness- lupus like syndrome (rarely)
- respiratory infections; reactivation of TB.

🖋️ contraindicated in severe congestive heart failure.

🖋️ [Adalimumab]

- IgG (human)
- subcutaneously

[Certolizumab]

- Fab fragment of anti TNF α (human)
- subcutaneously


[Natalizumab]

- IgG4 monoclonal antibody against cell adhesion molecule (α 4 integrin subunit)

Clinical Use:

- moderate to severe Crohn's disease who have failed other therapies

Administration

- IV infusion every 4 weeks
- no other immune suppressants, otherwise  multifocal leukoencephalopathy

Adverse effects

- acute infusion reactions
- opportunistic infections.

Treat pancreatic enzyme insufficiency.



Pancreatic Enzyme Supplements

- mixture of amylase, lipase, and proteases.

[Pancrelipase]

- Available in (non enteric coated & coated preparation) , coat is to prevent dissolution in gastric secretion
- Administered with each meal and snack.

Adverse effect

- Excessive doses  diarrhea and abdominal pain.
- high purine content  hyperuricosuria & renal stones

Treat Variceal Hemorrhage

Somatostatin ,Octreotide

[Somatostatin ,Octreotide]

- for patients with cirrhosis and portal hypertension, to promote initial homeostasis in patients with esophageal varices


Clinical uses:



- reduces portal blood flow and variceal pressures
- inhibit the release of glucagon

Beta Receptor Blocking Drugs

Mechanism:

(β 1 blockade)  decrease cardiac output


(β 2 blockade)  splanchnic vasoconstriction

both effects   will reduce portal venous pressure


THUS , nonselective blockers  [propranolol ,nadolol] are more effective than selective β 1 blockers

Antidiuretic hormone



[Vasopressin]

- IV infusion
- causes splanchnic arterial vasoconstriction  lowered portal venous pressures.

Adverse effects:

- hypertension, myocardial infarction, or mesenteric infarction.
- nausea, abdominal cramps, and diarrhea (due to intestinal hyperactivity).
- promotes retention of free water  hyponatremia, fluid retention, and pulmonary edema.

 was used for acute variceal hemorrhage

 Now it is infused by angiographically-placed catheter in arteries [superior or inferior mesenteric] to promote vasospasm  for patients with bleeding from vascular ectasias or diverticulosis

[Terlipressin]

- Vasopressin analog
- similar efficacy
- fewer adverse effects.