

Pharmacology team

Treatment of Inflammatory Bowel Disease.



Done by:

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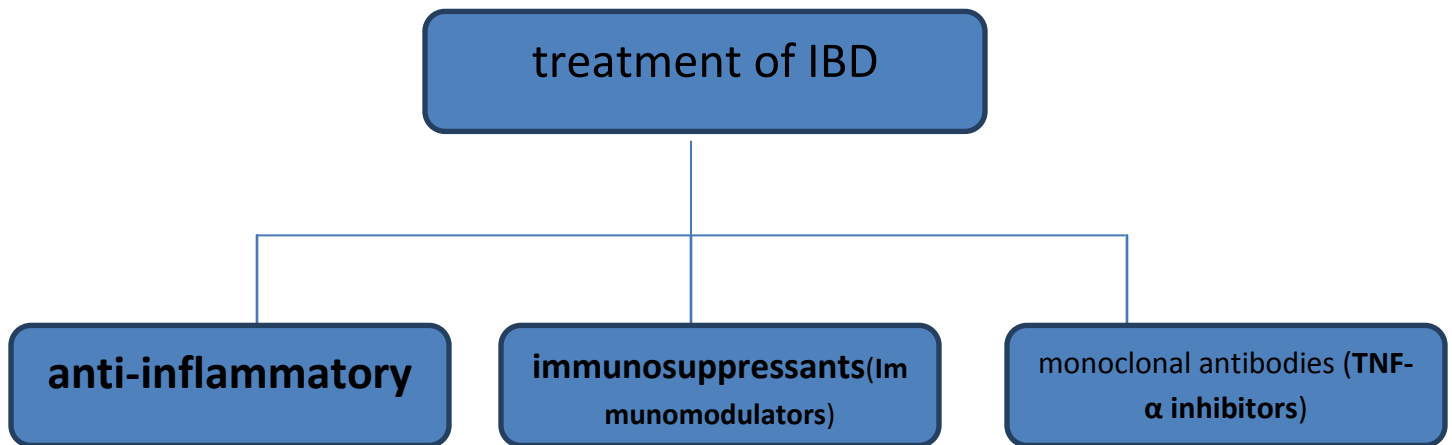
***Hamad Alkanhal**

Chronic inflammatory bowel diseases (IBD)

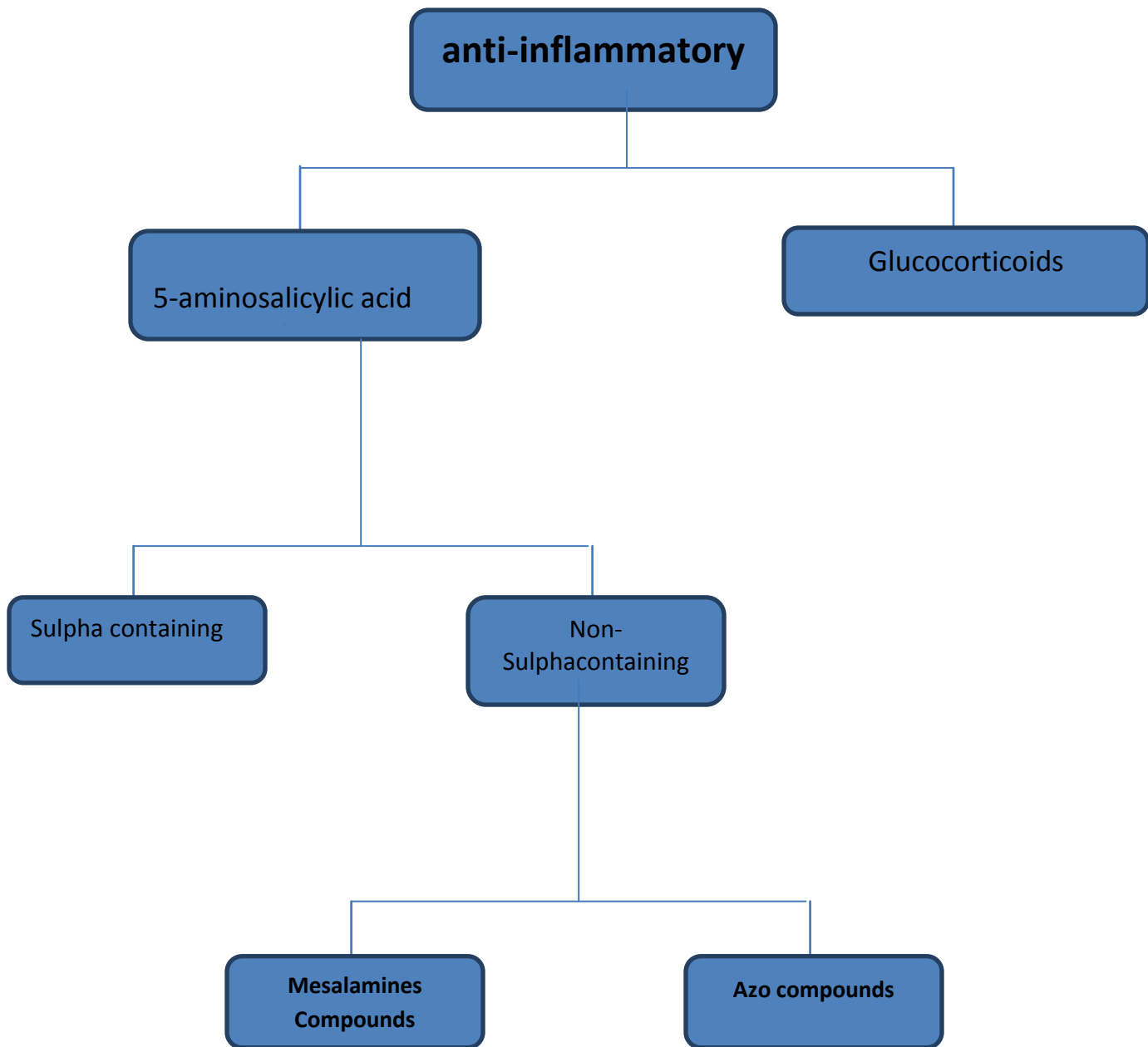
Introduction:

- IBD is a group of auto-immune disorders in which the intestines become inflamed.
- Are chronic inflammatory bowel diseases which have relapsing and limiting course.
- The major types of IBD are Crohn's disease and ulcerative colitis (UC).

	Crohn's disease	Ulcerative Colitis
Location	Affect any part of GI	Colon&rectum
Distibution	Skip lesions	Continous
Extent of the inflammation	Transmural(extends to deep tissue)	Mucosa
Diarrhea	No blood	Bloody diarrhea



a- Anti-inflammatory Drugs:

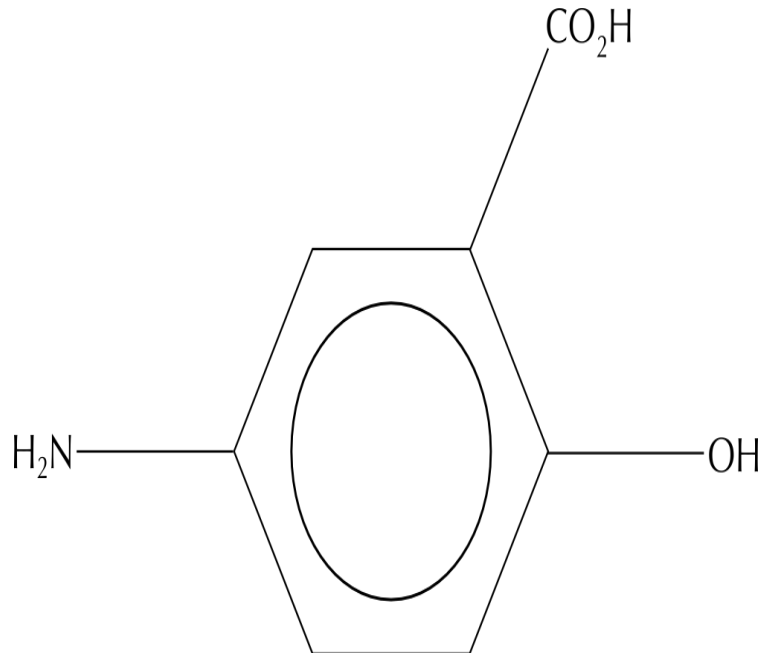


5-aminosalicylic acid compounds :

MOA: inhibits prostaglandin and leukotriens synthesis; decreases neutrophil chemotaxis and decreases free radicle production. scavenging free radical production.

Note: since it is an irritant to GIT(especially to the stomach).So, this drug should not be given orally as such.

Remember: NSAIDs makes IBD worse (not used in its treatment).



5-aminosalicylic acid Structure

Formulation:

a) Sulpha containing 5-Aminosalicylic Acid (e.g: **Sulphasalazine**).

We add sulfa group to avoid irritation of the

Sulphasalazine is a Prodrug, given orally (enteric coated tablets) (20-30 %) absorbed by intestine, secreted in the bile and hydrolysed in ileum and colon by isoreductase into: 5-ASA (not absorbed, active moiety) and Sulphapyridine (absorbed, side effects)
Sulphapyridine + 5- ASA (Linked by Azo group) -----> Hydrolyzed by bacteria in ileum and colon

Prodrug used in maintenance therapy, less effective in acute attack; **Used for U.colitis; Crohn's colitis but not Crohn's of small intestine.**

Because the bacteria that hydrolyses the drug are present in the distal ileum and colon, the places where the drug gives its therapeutic action.

Note: Nowadays it is seldom to be used for Crohn's disease (new 5-ASA are preferred but still use for UC).

Side Effects : **Prof. Alhaider said it is important**

- Muscular pain 29% caused by sulpha , N/V(nausea or vomiting), Diarrhea
- Crystalluria and interstitial nephritis.
- Hypersensitivity reactions as: skin rash, fever, aplastic anemia du to presence of sulfa group.
- Inhibit absorption of folic acid (megaloblastic anemia)
- Infertility in man (decrease sperm counts). However, **it is save in pregnancy .**

Note: 5-ASA differs from salicylic acid only by the addition of an amino group at the 5 (meta) position. Aminosaliclates are believed to work topically (not systemically) in areas of diseased gastrointestinal mucosa. Up to 80% of unformulated, aqueous 5-ASA is absorbed from the small intestine and does not reach the distal small bowel or colon in appreciable quantities. **To overcome the rapid absorption** of 5-ASA from the proximal small intestine, a number of formulations have been designed to deliver 5-ASA to various distal segments of the small bowel or the colon.

Note : most of adverse effects of sulfasalazine are attributable to (sulfapyridine)

B. Non-sulpha containing 5-Aminosalicylic Acid

1. Mesalamines Compounds: (used in patients sensitive \ allergic to sulpha drugs)

- Formulations that have been designed to deliver 5-ASA in small & large colon.
- e.g. pentasa (orally): time release microgranules that release 5ASA through the small intestine
- e.g. Asacol 5-ASA coated in pH sensitive resin that dissolved at pH 7 (controlled release).

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An enema (/)

- e.g. Rowasa (enema) or Canasa (suppositories)
- Treat and maintain remission in mild to moderate ulcerative colitis.
- Well tolerated, less side effects (sulfa free), useful in patient sensitive to sulfa drugs.

2. Azo compounds:

- Compounds contain 5-ASA and connected by azo bond to sulfapyridine moiety, another molecule of 5-ASA or to inert compound
- Azo structure (N=N)
- ✓ reduces absorption in small intestine
- ✓ Bacteria release azoreductase that cleave the azo dye and release 5-ASA in terminal ileum and colon

Because azocomunds are absorbed in **terminal ileum** and **colon** , It is more useful in ulcerative colitis than Crohn's D.

Examples:

- Olsalazine (Two molecules (dimer) of 5-ASA linked together by diazo bond which pass small intestine to ilium and colon).
- Balsalazide 5-ASA + inert carrier (Colazal).

Clinical Uses of 5-aminosalicylic acid compounds

Induction and maintenance of remission In mild to moderate ulcerative colitis & Crohn's disease (**First line of treatment**)

Are **NOT useful** in actual attack or severe forms of IBD.

Rheumatoid arthritis, psoriasis (*Sulfa - containing compounds only*)

Rectal formulations are used in **ulcerative proctitis and proctosigmoiditis**.

Ulcerative proctitis: It is the least severe form of inflammatory bowel disease. **Proctitis:** inflammation of the rectum and anus.

Proctosigmoiditis: inflammation of the sigmoid colon and rectum.

Glucocorticoids

MOA:

Inhibits phospholipase A2, inhibit gene expression of NO synthase, COX-2.
Inhibit inflammatory cytokines (TNF- α).

Prednisone, prednisolone (orally) :

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

Useful for acute attacks of U.C

Hydrocortisone (enema or suppository):

- 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 *first pass metabolism*
- Used in treatment of active mild to moderate Crohn's disease involving ileum and proximal colon.

Indications:

Treat moderate – severe ulcerative colitis. (Prednisone P.O. 40-60 mg/day for 2 weeks).

- Less effective as prophylactic (maintaining remission).
- Budesonide as controlled release oral (9 mg/day) formulation (Entocort).
- **Oral glucocorticoids is commonly used in active condition.**
- Hydrocortisone enema or suppository for rectum or sigmoid colon.
- Used also for extracolonic manifestations such as ocular lesion, skin disease, peripheral arthritis. Asthma, immunosuppressive drug for organ transplants , and antiemetics during cancer chemotherapy

Immunosuppressive Agents (Immunomodulators)

Are used to induce remission in IBD in active or severe conditions or steroid dependent or steroid resistant patients. (we use them when steroids fail to work since steroids have Immunosuppressive action)

Immunomodulators include:

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

A- Azathioprine :

MOA:

It is pro-drug of 6-mercaptopurine that inhibits purine synthesis.

Clinical indications:

for Rx and maintenance of remission of severe conditions and steroids dependent or resistant (ulcerative and Crohn's disease).

purines, along with pyrimidines, make up the nitrogenous bases in our DNA and RNA. Inhibiting purine synthesis will inhibit cell proliferation, especially leukocytes, therefore these agents are used as immunosuppressants

Side Effects:

- nausea and vomiting.
- **bone marrow depression** (leading to leukopenia, macrocytosis, anemia, or thrombocytopenia).
- LFT changes (it can cause hepatic toxicity). So, routine laboratory monitoring with complete blood count and liver function tests is required in all patients.
- Hypersensitivity reactions .

Very Important

azathioprine & mercaptopurine contain sulfa group

B- Methotrexate:

MOA:

(folic acid antagonist) dihydrofolate reductase inhibitor (an enzyme important in the production of thymidine and purines), Works as antimetabolite.

Clinical indications:

Crohn's disease (to induce and maintain remission); Rheumatoid Arthritis and cancer.

Side effects:

Bone marrow suppression and megaloblastic anemia.

Monoclonal antibodies used in IBD, (TNF- α inhibitors)

- Infliximab (source: chimeric: human/mice) 75% human .(may cause hypersensitivity reaction)
- Adalimumab (source: purely human) 100% human
- Certolizumab (source: humanized from mice) 95% human

Infliximab :

- Is a monoclonal IgG antibodies.
- 25% murine – 75% human.
- Anti-TNF- α : Inhibits soluble or membrane –bound TNF- α located on activated T lymphocytes.
- **Given as infusion** (5-10 mg/kg).
- has long half-life (8-10 days).
- 2 weeks to give clinical response.

Uses :

- 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, this reaction can be reduced by pretreatment with diphenhydramine, acetaminophen, corticosteroids.
- Delayed infusion reaction (serum sickness-like reaction, in 5% of patients). (It consists of myalgia, arthralgia, jaw tightness, fever, rash, urticaria, and edema and usually requires discontinuation of that agent).
- Infection complication (**Latent tuberculosis, sepsis, hepatitis B**). (due to suppression of the TH1 inflammatory response)
- Loss of response to infliximab over time *due to the development of antibodies to infliximab*. (Anti-body development is most commonly seen in infliximab because it is the least humanized among the three.)
- Severe hepatic failure.
- Rare risk of lymphoma.

Adalimumab (Humira) :

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

Certolizumabpegol (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

- IBD is a group of auto-immune disorders in which the intestines become inflamed. (chronic/relapsing).
- The major types of IBD are Crohn's disease and ulcerative colitis (UC).
- Treatment includes using 5-ASA, corticosteroids, purine analogs, methotrexate, and monoclonal antibodies.
- Sulphasalazine (5-ASA) is a Prodrug (20-30 %) absorbed by intestine, secreted in the bile and hydrolysed in ileum and colon by isoreductase .
- Sulphasalazine is used in maintenance therapy, less effective in acute attack; Used for U.colitis; Crohn's colitis but not Crohn's of small intestine.
- S/E include muscular pain and **hypersensitivity reaction because of the sulpha group. Safe in pregnancy.**
- pentasa (Mesalamine) (oral) it releases microgranules that release 5ASA through the small intestine.
- Mesalamines **treat and maintain remission in mild to moderate ulcerative colitis. Well tolerated, less side effects (sulfa free).**
- 5-ASA generally are NOT useful in actual attack or severe forms of IBD.
- Corticosteroids can treat moderate – severe ulcerative colitis.(prednisone). **Less effective as prophylactic (maintaining remission).**
- Immunomodulators (purine analogs and methotrexate) are used to induce remission in IBD in active or severe conditions or steroid dependent or steroid resistant patients.
- **Bone marrow depression is one of the most common S/E in immunomodulators.**

- Monoclonal antibodies (TNF- α inhibitors) include Certolizumab, Adalimumab (100% human), and Infliximab.
- Anti-TNF- α Inhibits soluble or membrane –bound TNF- α located on activated T lymphocytes.
- Uses include: **severe Crohn's disease, patients not responding to Immunomodulators or glucocorticoids.**
- S/E include: early adverse infusion reactions, serum sickness-like reaction, Infection complication, loss of response to infliximab over time, Severe hepatic failure, rare risk of lymphoma.
- Certolizumab is attached to PEG to increase its half-life.
- No corticosteroids used in maintenance therapy.

***Here I want to clarify some points:**

- 1- **Induce remission** means to treat the disease (**treatment**)
- 2- **maintain remission** means **prophylaxis**.

Special thanks to 430team. We quoted a lot from their work.

Questions:

1- Which of the following is a side effect of Sulfasalazine:

- A. Hepatic dysfunction**
- B. Megaloplastic anemia**
- C. Predispose to infection**

2-Which one of the following is a Clinical use of infliximab :

- A. Asthma**
- B. Crohn's disease**
- C. IBD with diarrhea**
- D. IBD with constipation**

Answers : 1-B 2-B