

## Drugs used in IBD

Drug	MOA	Pharmacokinetics and Uses	ADRs
<b>5-aminosalicylic acid compounds:</b> Topical anti-inflammatory drugs. 5-ASA itself is absorbed from small intestine. Different formulations are used to overcome rapid absorption of 5-ASA from the proximal small intestine <b>Uses:</b> Induction and maintenance of remission in mild to moderate ulcerative colitis & Crohn's disease ( <b>First line of treatment</b> ). Are <b>NOT USEFUL</b> in actual attack or severe forms of IBD. <ul style="list-style-type: none"> <li>Rheumatoid arthritis, psoriasis (<i>Sulfasalazine only</i>)</li> <li>Rectal formulations are used in <u>ulcerative proctitis</u> and <u>proctosigmoiditis</u>.</li> </ul>			
<b>Azo compounds :</b> <b>Sulfasalazine</b>	<b>5-ASA has anti-inflammatory action due to:</b> <ul style="list-style-type: none"> <li>inhibition of prostaglandins and leukotrienes.</li> <li>decrease neutrophil chemotaxis.</li> <li>Antioxidant activity (scavenging free radical production).</li> </ul>	<ul style="list-style-type: none"> <li>Pro-drug</li> <li>A combination of 5-ASA and sulfapyridine</li> <li>Is given orally (enteric coated tablets).</li> <li>Little amount is absorbed (10%), secreted in the bile</li> <li><i>In the terminal ileum and colon</i>, sulfasalazine is broken by azoreductase into: 5-ASA (not absorbed, active moiety) and Sulphapyridine (absorbed, side effects)</li> </ul>	<ul style="list-style-type: none"> <li>Muscular pain 29% caused by sulpha. N/V(nausea or vomiting), Diarrhea</li> <li><b>Crystalluria and interstitial nephritis.</b></li> <li>Hypersensitivity reactions as: skin rash, fever, aplastic anemia. caused by sulpha.</li> <li>Inhibit absorption of folic acid (megaloblastic anemia)</li> <li>Infertility in man (decrease sperm counts). However, it is safe in pregnancy .</li> <li>Bone marrow depression</li> </ul>
<b>Mesalamine compounds:</b>  Well tolerated, less side effects (sulfa free), useful in patient sensitive to sulfa drugs.	<ul style="list-style-type: none"> <li>Treat and maintain remission in mild to moderate ulcerative colitis .</li> </ul>	<ul style="list-style-type: none"> <li>Formulations that have been designed to deliver 5-ASA in terminal small bowel &amp; large colon.</li> <li><u>Oral formulations</u>  <b>-Asacol:</b> 5-ASA coated in pH-sensitive resin that dissolved at pH 7 (<i>controlled release</i>).  <b>-pentasa:</b> time-release microgranules that release 5-ASA throughout the small intestine (<i>delayed release</i>).</li> <li><u>Rectal formulations</u> <b>Canasa</b> (suppositories), <b>Rowasa</b> (enema)</li> </ul>	
<b>Glucocorticoids</b>	<ul style="list-style-type: none"> <li>Inhibits phospholipase A2</li> <li>Inhibits gene transcription of NO synthase, cyclooxygenase -2 (COX-2)</li> <li>Inhibit production of inflammatory cytokines</li> </ul>	<ul style="list-style-type: none"> <li>Treat moderate – severe ulcerative colitis. (<b>Prednisone P.O.</b> 40-60 mg/day for 2 weeks ).</li> <li><b>Less effective as prophylactic</b> (maintaining remission).</li> <li>Budesonide as controlled release oral (9 mg/day) formulation (Entocort).</li> <li><u>Oral glucocorticoids</u> is commonly used in active condition.</li> <li><b>Hydrocortisone enema</b> or suppository for rectum or sigmoid colon.</li> <li>Used also for extracolonic manifestations such as ocular lesion, skin disease, peripheral arthritis. Asthma, immunosuppressive drug for organ transplants , and antiemetics during cancer chemotherapy</li> </ul>	

### Immunomodulators

**Uses:** Are used to induce remission in IBD in active or severe conditions or steroid dependent or steroid resistant patients.

Purine analogs (azathioprine & 6-mercaptopurine)	Inhibit purine synthesis	Azathioprine is pro-drug of 6-mercaptopurine  <b>Used in</b> Induction and maintenance of remission in IBD	<ul style="list-style-type: none"> <li>Bone marrow depression: leucopenia, thrombocytopenia.</li> <li>Gastrointestinal toxicity.</li> <li>Hepatic dysfunction.</li> <li>Hypersensitivity reaction</li> </ul> <p>Complete blood count &amp; liver function tests are required in all patients</p>
Methotrexate	<ul style="list-style-type: none"> <li>a folic acid antagonist</li> <li>Inhibits dihydrofolate reductase required for folic acid activation (tetrahydrofolate)</li> </ul>	<ul style="list-style-type: none"> <li>Orally, S.C., I.M.</li> </ul> <p><b>Uses:</b></p> <ul style="list-style-type: none"> <li>Used to induce and maintain remission.</li> <li>Inflammatory bowel disease</li> <li>Rheumatoid arthritis</li> <li>Cancer</li> </ul>	<ul style="list-style-type: none"> <li>Megaloblastic anemia</li> <li>Bone marrow depression</li> </ul>

### Monoclonal antibodies used in IBD (TNF- $\alpha$ inhibitors)

Infliximab	<ul style="list-style-type: none"> <li>TNF-<math>\alpha</math> inhibitors</li> <li>Inhibits soluble or membrane -bound TNF-<math>\alpha</math> located on activated T lymphocytes and</li> </ul>	<ul style="list-style-type: none"> <li>a chimeric mouse-human monoclonal antibody</li> <li>25% murine - 75% human.</li> <li>Given intravenously as infusion (5-10 mg/kg).</li> <li>has long half life (8-10 days)</li> <li>2 weeks to give clinical response</li> </ul> <p><b>Uses</b></p> <ul style="list-style-type: none"> <li>In moderate to severe active Crohn's disease and ulcerative colitis</li> <li>Patients not responding to immunomodulators or glucocorticoids.</li> <li>Treatment of rheumatoid arthritis</li> <li>Psoriasis</li> </ul>	<ul style="list-style-type: none"> <li>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.</li> <li>Delayed infusion reaction (serum sickness-like reaction, in 5% of patients). Infection complication (Latent tuberculosis, sepsis, hepatitis B</li> <li>Loss of response to infliximab over time due to the development of antibodies to infliximab Severe hepatic failure.</li> <li>Rare risk of lymphoma.</li> </ul>
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#### Adalimumab (Humira)

- Fully humanized IgG antibody to TNF- $\alpha$ .
- Adalimumab is TNF $\alpha$  inhibitor.
- It binds to TNF $\alpha$ , 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.

#### Certolizumab pegol (Cimzia)

- Fab fragment of a humanized antibody directed against TNF- $\alpha$ .
- Certolizumab is attached to **polyethylene glycol** to increase **its half-life in circulation.**
- Given **subcutaneously** for the treatment of Crohn's disease & rheumatoid arthritis.