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Drugs Used in Inflammatory Bowel Diseases

- IBDs are **auto-immune** disorders, major types are **Crohn's disease** and **Ulcerative colitis**.
- **Symptoms**: vomiting, abdominal pain, diarrhea, rectal bleeding and weight loss.
- **Complications**: anemia, obstruction in CD, colon cancer in UC and mega colon.
- **Crohn's disease**: affects any part, skip lesions, deep, and may cause fistulas, strictures, etc.
- **Ulcerative colitis**: affects the colon only, continuous inflammation, shallow, may cause colon cancer and toxic mega colon.
- Treatment is only for maintaining remission and preventing relapse, it is **not curative**.
- **Tx:**
  1- 5-amino salicylic acid compounds (5-ASA).
  2- Glucocorticoids.
  3- Immunomodulators.
  4- Biological therapy
  5- Surgery if severe.

1- 5-ASA

- Topical.
- Formulations are used to **overcome 5-ASA early absorption** and thus delivered to the terminal ileum and colon, by being:
  a- Azo compounds.
  b- Mesalamine compounds.
- 5- ASA inhibits T-cell activation and proliferation and PG/LT/cytokine synthesis.

	Drug	Mechanism	Side effects	Notes
A- Azo compounds 5-ASA connected by an azo bond (N=N) to: *+ Sulphapyridine → Sulfasalazine.* *+ 5-ASA → Olsalazine* *+ Inert carrier → Balsalazide*	**Sulfasalazine**	- Oral pro-drug. In the terminal ileum and colon, flora releases azoreductase forming: **a- 5-ASA:** (not absorbed, active moiety) **b- Sulphapyridine:** (absorbed, side effects)	- Can be Dose related or Idiosyncratic (rare). **Idiosyncratic:** **1- Blood disorders:** Agranulocytosis, anemia, leukopenia, thrombocytopenia. **2- Skin reactions:** Lupus like syndrome, Stevens-Johnson syndrome, alopecia. **Contraindications:** - **5-ASA →** Salicylate hypersensitivity + interstitial nephritis. - **Sulfapyridine →** G6PD deficiency + slow acetylator status.	**1-** Induction and maintenance of remission. **2-** Used in **UC** more (First line of treatment). - Used for rheumatoid arthritis. - Rectal formulations are used in active distal UC ulcerative proctitis and proctosigmoiditis. **More side effects:** Folic acid deficiency + male infertility (**oligospermia**)

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	Drug	Mechanism	Notes
B- Mesalamine compounds *Coated*	*Oral:* **Asacol** **Pentasa** *Rectal:* **Rowasa** **Canasa**	- Oral formulations: 1- **Asacol** (controlled release): coated in pH-sensitive resin that dissolved at pH 7. 2- **Pentasa** (delayed release): time-released 5-ASA throughout the small intestine.	1- Induction and maintenance of remission. 2- Used for **UC** more. **Advantages:** Well tolerated and sulfa free, thus less side effects and useful in patient sensitive or allergic to sulfa drugs.

2- Glucocorticoids

- **Mechanism of action:** Inhibits phospholipase A2 // Inhibits gene transcription of NO synthase, cyclooxygenase-2 (COX-2). Inhibit production of inflammatory cytokines // Decrease antigen-antibody reaction.

- **Uses of glucocorticoids:**

1- Induction of remission only; **not** used for maintaining remission.
2- Used for **both** UC and CD.
3- Oral glucocorticoids is commonly used in active disease conditions.
4- Rectal glucocorticoids are preferred in IBD involving rectum or sigmoid colon.

Drug	Mechanism	Notes
Prednisone, prednisolone.	- Orally. - Has higher rate of absorption.	- More adverse effects compared to rectal administration.
Budesonide	- Orally, controlled release tablets in ileum and colon. - Low oral bioavailability (10%), thus less side effects.	- Subject to **first pass metabolism**.

3- Immunomodulators

- Used in IBD active severe conditions and in **steroid resistant patients**.

Drug	Action	Side Effects
Purine analogs *(azathioprine and 6-mercaptopurine)*	- It **inhibits purine synthesis**. 1- Induction and maintenance of remission. 2- Used in **both** UC and CD. - **Important**: Azathioprine is a pro-drug of 6-mercaptopurine, a substance that is metabolized into a cytotoxic 6-thioguanine, while an enzyme (TPMT) inactivates 6-mercaptopurine through methylation, thus deficiency in TPMT causes a life-threatening bone marrow suppression due to the accumulation of an active cytotoxic 6-thioguanine.	- **Bone marrow suppression**: leucopenia, thrombocytopenia, and myelotoxicity, determined by TPMT activity. - Gastrointestinal toxicity. - Hepatic dysfunction. - Pancreatitis. - Complete blood count and liver function tests are required in all patients
Methotrexate *Orally, SC., IM*	- **Folic acid antagonist**. - Inhibits dihydrofolate reductase required for folic acid activation. 1- Used to induce and maintain remission. 2- For **CD** only. - Used for Rheumatoid arthritis and Cancer.	- Bone marrow depression. - Megaloblastic anemia.

4- Biological Therapy

- Monoclonal antibodies **(TNF-α inhibitors).**

Drug	Mechanism	Side Effects	Notes
Infliximab *IV*	- Inhibits TNF-α. - Long half-life (8-10 days) - 2 weeks to give clinical response.	- **Allergic reactions** 10% of patients. - Delayed infusion reaction (serum sickness-like reaction). → *Pretreatment with diphenhydramine, acetaminophen, corticosteroids is recommended.* - **Reactivation** of Tuberculosis and HBV. - Patient may become resistant. - Severe hepatic failure and rare risk of lymphoma.	- A **chimeric mouse-human** monoclonal antibody (25% murine – 75% human). **1-** Induction and maintenance of remission. **2-** Used for **both** UC and CD. **Used for:** - Patients not responding to immunomodulators or glucocorticoids. - Treatment of rheumatoid arthritis and Psoriasis.
Adalimumab *Subq (advantage)*	- Inhibits TNFα.	-	- **Fully humanized** IgG antibody to TNF-α **1-** Induction and maintenance of remission. **2-** Used for **both** UC and CD. Used for: Rheumatoid arthritis and Psoriasis.
Certolizumab *Subq* *(The Dr. didn't emphasize on it)*	-	- Immunogenicity appears to be **less** of a problem than with infliximab.	- Polyethylene glycol Fab fragment of **humanized** anti-TNF-α.

The doctor emphasized on:

- Knowing: **1- Induction/Maintenance? 2- For CD/UC?** for each drug, showed in the table with the respective number.
- **TPMT activity** and its influence on purines analogs' side effect.
- Budesonide is subject to the first bypass effect.
- Infliximab is chimeric (mouse + human antibodies), while Adalimumab and Certolizumab are fully humanized.
- **Asacol** → pH-dependent, mainly on colon. **Pentasa** → Time-dependent, mainly on terminal ileum.
- Understand the side effect of steroids, as shown in the figure to the right: