Drugs Used in IBD & Biological & Immune Therapy of IBD

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- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objectives

- No objectives

Dr. Fouda Videos

Inflammatory Bowel Disease (IBD)

What is IBD?

- A group of inflammatory conditions of the small intestine and colon.
- The major types of IBD are: **Crohn's disease** and **ulcerative colitis** (UC)
- Causes:
  1. Unknown
  2. Autoimmune disorder due to abnormal activation of the immune system
  3. The susceptibility is genetically inherited.

Symptomes

- Abdominal pain
- Vomiting
- Weight loss
- Diarrhea
- Rectal bleeding

Complications

- Megacolon
- Colon cancer
- Abdominal Obstruction **(Crohn's disease)**
- **Anemia** (due to bleeding)

The Major Types of IBD

Disease	Crohn's disease (CD)	Ulcerative Colitis (UC)
Definition	Chronic transmural inflammation of gastrointestinal tract	Chronic mucosal inflammation of the colon
Location	Affects any part of the GIT, from mouth to anus	Restricted to colon & rectum
Distribution	Patchy areas of inflammation (Skip lesions)	Continuous area of inflammation
Depth of inflammation	May be transmural, deep into tissues	Shallow, mucosal
Complications	Strictures, Obstruction, Abscess, Fistula	Toxic megacolon (colon dilatation), Colon cancer

Treatment of Inflammatory Bowel Disease (IBD)

There are 2 goals of therapy:

01 — Achievement of remission (Induction).
control of symptoms

02 — Prevention of disease flares (maintenance)
control of inflammation

Treatment of IBD (stepwise therapy)

1. 5-amino salicylic acid compounds (5-ASA) or aminosalicylates.
2. Glucocorticoids
3. Immunomodulators
4. Biological therapy (TNF-α inhibitors).
5 .Surgery in severe condition.

1- Aminosalicylates

MOA

Have TOPICAL anti-inflammatory action needs to have direct contact with the inflamed tissue due to:

- Inhibition of prostaglandins and leukotrienes.
- Decrease neutrophil chemotaxis
- Antioxidant activity (scavenging free radical production)

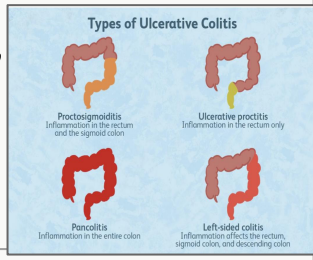
P.K

- 5-ASA itself is absorbed from the proximal small intestine.
  442: 5-asa is acidic drug which is best absorbed in acidic medium and our goal is to overcome its absorption in the stomach & proximal small intestine. therefore we use different formulations so it can reach the inflamed area only "terminal ileum & colon
- Different formulations are used to overcome rapid absorption of 5-ASA from the proximal small intestine
- All aminosalicylates are used for induction and maintenance of remission

Uses

Have other uses not only IBD

1. Induction and maintenance of remission in mild to moderate IBD (First line of treatment)
2. Rheumatoid arthritis (Sulfasalazine only)
3. Rectal formulations are used in distal ulcerative colitis, ulcerative proctitis inflammation of the rectum and proctosigmoiditis inflammation of the rectum and sigmoid colon



Formulations of Aminosalicylates

Aminosalicylates

- **Azo Compounds**
  1. Sulfasalazine
  2. Balsalazide
  3. Olsalazine
- **Mesalamines**
  1. Asacol
  2. Pentasa
  3. Canasa
  4. Rowasa

The major differences are in mechanism and site of delivery

1- Aminosalicylates

A) Azo compounds (Combination)

Overview	These compounds contain (5-ASA) that is connected by azo bond (N=N) : - to sulfapyridine moiety (Sulfasalazine) : **5-ASA + Sulphapyridine** - to another molecule of 5-ASA (Olsalazine): **5-ASA + 5-ASA** - to inert compound (Balsalazide): **5-ASA + Inert carrier** - Azo structure reduces absorption of 5-ASA in small intestine. - In the terminal ileum and colon, azo bond is cleaved by azoreductase enzyme produced by bacterial flora releasing 5-ASA in the terminal ileum and colon.

Sulfasalazine (Azulfidine)

A combination of 5-ASA + Sulfapyridine

P.K	• Pro-drug • Given orally (enteric coated tablets) • Little amount is absorbed (10%) • ★In the terminal ileum and colon, sulfasalazine is broken by azoreductase Into: 1. 5-ASA (not absorbed, active moiety, acting locally) 2. Sulphapyridine (absorbed, causes most of side effects)
MOA	5-ASA has anti-inflammatory action due to: • inhibition of prostaglandins and leukotrienes. • decrease neutrophil chemotaxis. • Antioxidant activity (scavenging free radical production).
ADRs	• ★Crystalluria (because Sulfa mainly affects the kidney) • Folic acid (B9) deficiency (should be provided) • Megaloblastic anemia • Bone marrow depression • Impairment of male fertility (oligospermia) • Interstitial nephritis due to 5-ASA

1- Aminosalicylates

B) Mesalamine compounds

Overview

- Formulations that have been designed to deliver 5-ASA in terminal small bowel & large colon.
- **Mesalamine formulation are:**
  1. Well tolerated
  2. less side effects compared to sulfasalazine
  3. Sulfa free
  4. Useful in patient sensitive to sulfa drugs

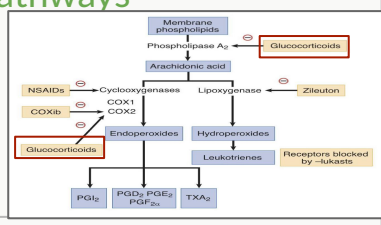
Oral formulations	**Rectal** formulations
• Which releases 5-ASA in the distal small bowel secondary to pH changes. • Releases start at the pylorus and continues throughout the small bowel and colon.	• Release 5-ASA in the **distal colon.**
1. Asacol: • 5-ASA coated in pH-sensitive resin that dissolve at pH 7 2. **Pentasa:** • micro granules that release 5-ASA throughout the small intestine at specific time	**1. Canasa:** (suppositories). **2. Rowasa:** (enema)

2- Glucocorticoids

Important

MOA

- Inhibits phospholipase A2 inhibition of all inflammatory pathways
- Inhibits gene transcription of NO synthase, cyclooxygenase-2 (COX-2)
- Inhibit production of inflammatory cytokines



Uses

Indicated for acute flares of disease (active moderate to severe IBD).
Not useful in maintaining remission (not effective as prophylactic therapy).

Other uses:

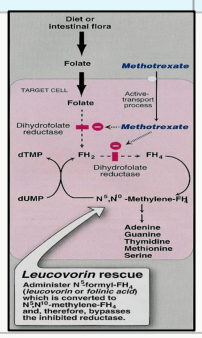
1. Asthma
2. Rheumatoid arthritis
3. Immunosuppressive drug for organ transplants
4. Antiemetic during cancer chemotherapy

2- Glucocorticoids

They can be used for inflammation in any disease. (ex: asthma)

	Systemic Preparations			Local Preparation
ROA	**Oral**		**Parenteral**	**Rectal**
Drug	**Prednisone** **Prednisolone**	**Budesonide** A potent **synthetic** prednisolone analog	**Hydrocortisone** **Methylprednisolone**	**Hydrocortisone**
P.K.	good oral bioavailability	-Controlled release tablets so release drug in **ileum and colon.** -Low oral bioavailability (10%) -Extensive first pass metabolism -Low bioavailability	-Higher rate of absorption -More adverse effects compared to rectal administration	As enema or suppository, give topical effect. Less absorption rate than oral. Minimal side effects & maximum tissue effects
Uses	Oral glucocorticoids are commonly used in active condition.	Used in treatment of **active mild to moderate** Crohn's disease involving ileum and proximal colon	-	Rectal glucocorticoids are preferred in IBD involving rectum or sigmoid colon

3-Immunomodulators

	Methotrexate Orally, I.M, S.C	Purine analogs **Azathioprine, 6-mercaptopurine**
MOA	• Folic acid antagonist • ★Inhibits **dihydrofolate reductase** required for folic acid activation (tetrahydrofolate) FH4 (active form) • Impairs DNA synthesis 	• Azathioprine is **pro-drug** of 6-mercaptopurine. • Inhibit **purine** synthesis and inhibits synthesis of DNA, RNA, and proteins. • It may decrease proliferation of immune cells (T lymphocytes), which lowers autoimmune activity.
Uses	• **Induce and maintain** remission in **IBD** in active **moderate to severe** conditions or steroid dependent or steroid resistant patients (refractory). • Inflammatory bowel disease • Rheumatoid arthritis • Cancer	-
ADRs	• Bone marrow depression • Megaloblastic anemia • Teratogenic "since it inhibits DNA synthesis, it inhibits proliferation of fetal cells"	• Bone marrow depression: leucopenia, thrombocytopenia. • Hepatic dysfunction • Gastrointestinal toxicity. ➔ Complete blood count & liver function are required in all patients "before and after giving the drug"

4- Monoclonal antibodies used in IBD

Drugs	TNF **α inhibitors: 1. Infliximab 2.Certolizumab 3. Adalimumab** strongly linked to inflammation
Uses	• Act by binding to TNF-α thus preventing its binding to cell surface receptors • Increase apoptosis of T-lymphocytes and monocytes

A chimeric mouse-human monoclonal antibody, 25% murine – 75% human

Drug	**Infliximab**
Overview	• Inhibits soluble or membrane–bound TNFα located on activated T lymphocytes. • Given intravenously 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
ADRs (Important)	1. Allergies : - Acute or **early** infusion reactions(**Allergic reactions or anaphylaxis** in 10% of patients) - **Delayed** type hypersensitivity reaction (**serum sickness- like reaction**, in 5% of patients). - **Pre-treatment** with diphenhydramine, acetaminophen, corticosteroids is recommended **2. Loss of response to infliximab** over time due to the development of antibodies to infliximab. 3. ★ Infection complication (Latent TB, sepsis, hepatitis B) (make sure that the patient doesn't have these diseases because once they takes this medication these diseases will flare up) 4. Severe hepatic failure. 5. Rare risk of lymphoma .

Humanized Antibodies

Drug	**1. Adalimumab (Humira)**	**2. Certolizumab pegol (Cimzia)**
Uses	• Moderate to severe Crohn's disease • Rheumatoid arthritis • Psoriasis.	• Crohn's disease • Rheumatoid arthritis
P.K.	• **Has an advantage in that it is given by subcutaneous injection**	
	• Fully **humanized** IgG antibody to TNF-α • It binds to TNF-α, preventing it from activating TNF receptors (TNF-α inhibitor)	• **Fab fragment** of a **humanized** antibody directed against TNF-α • Attached to polyethylene glycol to increase its half-life in circulation

Summary From the slides

5-aminosalicylic acid compounds	**Azo compounds**	- sulfasalazine - olsalazine - balsalazide
	Mesalamine:	- Pentasa - Asacol - Rowasa - Canasa
Glucocorticoids		- prednisone, - prednisolone - hydrocortisone - budesonide
Immunomodulators		- Methotrexate - Purine analogues: Azathioprine & 6-mercaptopurine
TNF-alpha inhibitors (monoclonal antibodies)		- Infliximab - Adalimumab - Certolizumab

MCQ

1.What is the first line of treatment in case of IBD:			
A. Glucocorticoids	B. aminosalicylic acid	C. Methotrexate	D. TNF-alpha inhibitors
2. Which of the following the **main** side effect of sulfasalazine:			
A.Crystalluria	B. Psoriasis	C. Bone marrow depression	D. hepatic failure
3. Which of the following is likely to produce flare up of latent TB:			
A. Methotrexate	B. Prednisone	C. Sulfasalazine	D. Infliximab
4. 17 YO boy is complaining of bloody diarrhea and tenesmus. He is diagnosed to have ulcerative colitis. His history indicate allergy to sulfonamides. Which of the following will be appropriate for this case?			
A.Infliximab	B. Mesalamine	C. Prednisone	D. Sulfasalazine
5. Which of the following release 5-ASA in the distal colon:			
A.Methotrexate	B. Canasa	C. Pentasa	D.Prednisone
6. Which of the following Indicated for acute flares of disease:			
A. Glucocorticoids	B. aminosalicylic acid	C. Methotrexate	D. TNF-alpha inhibitors

1:B ,2: A ,3:D ,4:B ,5:B ,6: A

SAQ

01

Write one MOA of each of the following :
A- 5ASA
B- Glucocorticoides
C- Methotrexate

A-1- Inhibition of prostaglandins and leukotrienes.
2-Decrease neutrophil chemotaxis
3-Antioxidant activity (scavenging free radical production)
B- inhibition of cyclooxygenase, NO synthase and phospholipase.
C-inhibition of folate reductase

02

Write one side effect of Infliximab

Infection reaction

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