MED438

pharmacology
Team 438

Reviewed by Razan AlRabah & Ibrahim AlDakhil

Drugs and biological and immune therapy in inflammatory bowel disease (IBD)

Objectives:

By the end of the lecture , you should know:

- Define inflammatory bowel disease
- Differentiate between ulcerative colitis and Crohn' disease.
- Define the stepwise treatment of IBD
- Discuss the pharmacokinetics, pharmacodynamics, uses and adverse effects of 5-amino salicylic acid compounds (5-ASA), glucocorticoids, immunomodulators and biological therapy (TNF-α inhibitors)
- Compare between drugs used for induction of remission and those used for maintenance of remission

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Purple: Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

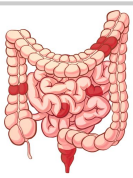
Inflammatory Bowel Disease IBD

- 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

Unknown — Autoimmune — Genetically inherited

The Major Types of IBD

	Crohn's disease	Ulcerative Colitis
Definition	Chronic transmural inflammation of gastrointestinal tract	Chronic mucosal inflammation of the colon
Location	affect any part of the GIT, From mouth to anus	Restricted to colon & rectum
Distribution	Patchy areas of inflammation 	Continuous area of inflammation 
Depth of inflammation	May be transmural, deep into tissues	Shallow, mucosal
Complications	Strictures, Obstruction, Abscess, Fistula	Toxic megacolon, Colon cancer
Presentation		Females only
Bleeding	Occasional	Very common
Obstruction	Common	Uncommon
Fistulae		None
Weight loss		Uncommon
Perianal disease		Rare

1 Symptoms of IBD

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

2 Complications

- Anemia
- Megacolon (mainly for UC)
- Colon cancer (mainly for UC)
- Abdominal obstruction(Crohn's disease)

Treatment

Treatment objectives[1]

1. **Achievement of remission (Induction)**
2. **Prevention of disease flares (maintenance)**
3. Normalize bowel function
4. Maintain nutritional status
5. Improve quality of life

Stepwise[2] therapy

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

Aminosalicylates (5-ASA)

Classes	Azo Compound	Mesalamines (More common)
Drugs	• Sulfasalazine • Olsalazine • Balsalazide	• Asacol • Pentasa • Canasa • Rowasa
	• The major differences are in **mechanism** and **site** of delivery	
MOA	• Have **TOPICAL**[3] anti-inflammatory action due to: ○ inhibition of prostaglandins[4] and leukotrienes. ○ decrease neutrophil chemotaxis ○ Antioxidant activity (scavenging free radical production)	
P.K	• 5-ASA itself is absorbed from the proximal small intestine[5] ★ Different formulations (Azo component & Mesalamines) are used to **overcome rapid absorption** of 5-ASA from the proximal small intestine ★ All aminosalicylates are used for **induction (treatment) and maintenance (prophylaxis)** of remission	
Uses	• Induction and maintenance of remission in **mild to moderate** IBD **(First line of treatment)** • Rheumatoid arthritis (**Sulfasalazine** only) • **Rectal** formulations are used in distal ulcerative colitis, ulcerative proctitis and proctosigmoiditis	

1: no actual cure, aim is to reduce or get rid of the inflammation = reduce disease manifestations.
2: "do not go for option 2 unless you try option 1 and it does not work".
3: the drug has to come in contact with the affected tissue to produce its effect (which means that there is no need for the drug to be absorbed in case of IBD=less systemic side effects)
4: all prostaglandins will be inhibited, including I&E that are physiologically beneficial for the stomach (by protecting against acidity).
5: not effective in UC unless given in a different formulation that will prevent its absorption in the SI.

Aminosalicylates (5-ASA)

A) Azo Compound

These compounds contain (5-ASA) that is connected by azo bond (N=N) into :

1- sulfapyridine moiety (Sulfasalazine)	Sulfasalazine: 5-ASA + sulphapyridine
2- another molecule of 5-ASA (Olsalazine)	Olsalazine: 5-ASA + 5-ASA
3- inert compound (Balsalazide)	Balsalazide: 5-ASA + inert carrier[1]

- **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[2].**

Drug	Sulfasalazine (Azulfidine)

P.K	• Pro-drug
	• A combination of 5-ASA+sulfapyridine
	• Given orally (enteric coated tablets)
	• Little amount is absorbed (10%[3])
	• In the terminal ileum and colon, sulfasalazine is broken by azoreductase Into:
	  ○ 5-ASA (not absorbed, active moiety, **acting locally**)
	  ○ Sulphapyridine (absorbed, **causes most of side effects**)

ADRs	• **Due to Sulfapyridine:** 1. Folic acid deficiency (should be provided) 2. Impairment of male fertility (oligospermia) (Temporary) 3. Megaloblastic anemia[4] 4. Crystalluria[5] 5. Bone marrow depression • **Due to 5-ASA:** 1. Interstitial nephritis (rare)

B) Mesalamine Compound

Formulations that have been designed to deliver 5-ASA **in terminal small bowel & large colon.**

Features of Mesalamine compounds are:

- Well tolerated
- Sulfate free
- Less ADRs than sulfasalazine
- Useful in patient sensitive to sulfa drugs

1 Oral[6] Formulations

- Releases 5-ASA in the distal small bowel secondary to pH changes.
- Release starts at the pylorus and continues throughout the small bowel and colon.

Pentasa: micro granules that release 5-ASA throughout the small intestine.(sustain released [7])

Asacol: 5-ASA coated in pH-sensitive resin that dissolve at pH 7. (delayed release tablet[8])

2 Rectal Formulations

- release 5-ASA in the distal colon.

Canasa (suppositories)

Rowasa (enema)

1: Inert carrier has no pharmacological importance, only helps ASA reach the colon. 2: The desired site of action
3: this 10% is powerful enough to produce systemic side effects
4: Due to folic acid antagonism. 5: Advice patient to stay hydrated to avoid crystalluria.
6: ASA release should be controlled to avoid absorption in the SI, which is established by the following:
7: "Sustained release capsules": the capsules contain different colored granules, each color is meant to disintegrate at a specific part of the GIT (helpful in case of Crohn's disease where the stomach is affected).
8: "delayed release tablet": the tablet only disintegrate when exposed to a specific pH (basic pH of the distal SI in this case)

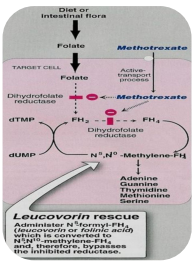
Glucocorticoids[1]

Drugs	• Prednisone • Prednisolone	• Hydrocortisone • Methylprednisolone	• Hydrocortisone
Route	Orally	Parenteral (I.V , I.M)	Rectal
M.O.A	• Inhibits phospholipase A2 • Inhibits gene transcription of NO synthase cyclooxygenase-2 (COX-2) • Inhibit production of inflammatory cytokines		
P.K	• Higher rate of absorption		• Less absorption rate than oral. • As enema or suppository, give topical effect
Uses	★ Indicated for **ACUTE flares** of disease (**moderate to severe active IBD**). ★ Are **NOT** useful in **maintaining** remission • **Oral glucocorticoids:** ○ are commonly used in active condition. • **Rectal glucocorticoids:** ○ are preferred in **IBD** involving rectum or sigmoid colon. • **Other uses:** ○ Asthma ○ Rheumatoid arthritis ○ immunosuppressive drug for organ transplants ○ Antiemetic during cancer chemotherapy		
ADRs	• More adverse effects compared to rectal		• Minimal side effects and maximum tissue effects

Drug	Budesonide
M.O.A	★ A potent synthetic **prednisolone** analog
P.K	• Given orally **(controlled release tablets)** so release drug in ileum and colon • Low oral bioavailability[2] • Subject to extensive first pass metabolism
Uses	★ Used in treatment of **active mild to moderate crohn's disease** involving **Ileum** and **Proximal colon**

1: systemic release = more side effects than ASAs
2: lower bioavailability = less release into the systemic circulation (considered an advantage since the site of action is GIT) = topical action in contact with the inflamed tissues .

Immunomodulators

Drug	Methotrexate	Purine analogs: Azathioprine | 6-mercaptopurine
M.O.A	★ a folic acid antagonist • Inhibits dihydrofolate reductase required for folic acid activation (tetrahydrofolate) • 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, which lowers autoimmune activity.
P.K	• Orally, I.M	-
Uses	★ **Induce and maintain** remission in **IBD** in active **moderate to severe** conditions or steroid dependent or steroid resistant patients.	
	• Inflammatory bowel disease • Rheumatoid arthritis • Cancer	-
ADRs	• Megaloblastic anemia [1] • Bone marrow depression [1] • Teratogenic	★ Bone marrow depression: leucopenia, thrombocytopenia. ★ Hepatic dysfunction • CBC & liver function tests are required in all patients • Gastrointestinal toxicity.

Monoclonal antibodies used in IBD (TNF-α inhibitors)[2]

MOA	• Act by binding to TNF-a thus preventing its binding to cell surface receptors. • Increase apoptosis of T-lymphocytes and monocytes.	
Drug	Adalimumab (Humira)	Certolizumab (Cimzia)
Over-view	• Fully humanized[3] IgG antibody to TNF-α (TNF-α inhibitor) • It binds to TNF-a, preventing it from activating TNF receptors • Has an advantage in that it is given by subcutaneous injection	• 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
Uses	• moderate to severe Crohn's disease • rheumatoid arthritis • psoriasis	• Crohn's disease • Rheumatoid arthritis

1: both due to folic acid antagonism
2: the suffix (mab) means that the drug is composed of antibodies (protein) so it cannot be given orally because it is going to be degraded before reaching the side of action.
3: less risk of early sensitivity seen in infliximab.

Monoclonal antibodies used in IBD (TNF-α inhibitors) cont...

Drug	Infliximab
Over-view	• a chimeric mouse[1]-human monoclonal antibody, 25% murine – 75% human. • Inhibits soluble or membrane –bound TNF-α located on activated T lymphocytes. • Given intravenously as infusion (5-10 mg/kg). • has long half life (8-10 days) ★ 2 weeks[2] to give clinical response.
Uses	• In **moderate to severe**[3] active Crohn's disease and ulcerative colitis. ★ Patients **NOT** responding to immunomodulators or glucocorticoids. • Treatment of rheumatoid arthritis. • Psoriasis.
ADRs	★ Acute or **early** infusion ADRs(**Allergic reactions or anaphylaxis** in 10% of patients) Type 1 allergic reaction ★ **Delayed** type hypersensitivity reaction (**serum sickness- reaction**, in 5% of patients). • **Pre-treatment**[4] with diphenhydramine, acetaminophen, corticosteroids is recommended ★ **Loss of response to infliximab** over time due to the development of antibodies to infliximab. • ↑risk of opportunistic infection[5] (Latent TB, sepsis, hepatitis B, fungal infection). • Severe hepatic failure. • Rare risk of lymphoma[6].

Summary from Doctor slides

Treatment of IBD

Inductive Therapy

A) For Ulcerative colitis:
- Aminosalicylates
-Corticosteroids
-Immunomodulators
-Infliximab

B) For Crohn's disease:
-Aminosalicylates
-Corticosteroids
-Antibiotics
-Biologics

Maintenance Therapy

-Aminosalicylates
-Immunomodulators: Azathioprine & 6-Mercaptopurine & Methotrexate
-Infliximab
NO corticosteroids

1: leads to allergic manifestations (early)
2: because some T-cells have been already activated, and patient should be aware of the **delayed** response.
3: not given to mild due to its side effects. 4: to avoid allergic reactions.
5: patients should be tested for those infections before starting the treatment.
6: due to the lower immunity produced by the drug.

Quiz

MCQ

1- A patient suffering from prostate cancer and he is also having IBD which one of the following is drug of choice ?

A- Methotrexate B- Infliximab C- Azathioprine

2- Which of the following drugs is fully humanized IgG antibody to TNF-α?

A- Infliximab B- Adalimumab C- Certolizumab

3- Patient on treatment of IBD comes with oligospermia and Crystalluria, which drug he used?

A- Sulfasalazine B- Canasa C- Methotrexate

4- Which of the following side effects is a result of treatment rheumatoid arthritis using infliximab?

A- Glaucoma B- Vomiting C- Activation of latent tuberculosis

5- A patient came to the ER due to abdominal pain and rectal bleeding, examination and investigations revealed that he has active crohn's disease. Which drug can be use?

A- Budesonide B- Sulfasalazine C- Azathioprine

SAQ

-A 35 years old patient Recently diagnosed with IBD and was prescribed a treatment, After weeks he started developing hepatic dysfunction.

Q1-What drug caused this adverse reaction?

Q2-What is the mechanism of action of that drug?

-A 84 years old male was diagnosed with IBD, after some investigations the doctor found that his proximal colon and ileum were affected.

Q3-What drug is the best to be used in this case?

-43 years old man visited the physician complaining of abdominal discomfort, rectal bleeding and diarrhea for the past month. Endoscopy of the colon showed patchy inflamed areas along the colon.

Q4-What drug do you recommend for him first?

Q5-Mention three side effect.

Answers:

MCQ

Q1	A
Q2	B
Q3	A
Q4	C
Q5	A

SAQ

Q1	Azathioprine
Q2	Inhibit purine synthesis and the synthesis of DNA, RNA, and proteins
Q3	Sulfasalazine or Budesonide
Q4	Sulfasalazine
Q5	Bone marrow depression-Megaloblastic anemia-Folic acid deficiency

Share with us your ideas !

Good Luck , Future Doctors!

Team Leaders:

May Babaeer

Zyad Aldosari

This Amazing Work is By:

May Babaeer

Raghad AlKhashan

Noura AlMazrou

Shahad AlSahil