



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

objectives

- 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

● extra information and further explanation

● important

● doctors notes

● Drugs names

● Mnemonics



[Kindly check the editing file before studying this document](#)

Inflammatory Bowel Diseases (IBD)

Definition

is a group of **inflammatory** conditions of the small **intestine** and **colon**. **or all GIT**

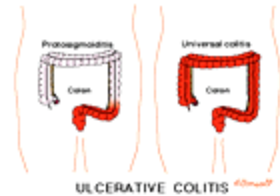
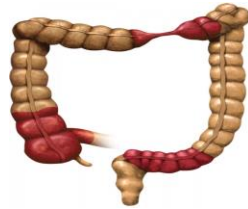
Causes

- Not known.
- auto-immune disorder due to abnormal activation of the immune system.
- The susceptibility is genetically inherited.

Types

The major types of **IBD** are **Crohn's disease** and **ulcerative colitis (UC)**.

	Crohn's disease	Ulcerative colitis
Location	affect any part of the GIT, From mouth to anus	Restricted to colon & rectum
Distribution	Patchy areas of inflammation (Skip lesions) not Continuous	Continuous area of inflammation
Depth of inflammation	May be transmural, deep into tissues	Shallow, mucosal
Complications	Strictures, Obstruction, Abscess, Fistula	Toxic megacolon, Colon cancer



Symptoms	Complication
- Abdominal pain - Diarrhea - Rectal bleeding. - vomiting - Weight loss	- Anemia - Abdominal obstruction (Crohn's disease). - Colon cancer - Mega colon

Treatment

There are two goals of therapy

1- Achievement of remission (**Induction**).

2-Prevention of disease flares (**maintenance**).

Stepwise therapy: (in order we start from less ADRs to the ones that have more ADRs)

اعالج خطوة بخطوة وإذا
مانفع اعالج باللي بعده

- 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

Inflammatory Bowel Diseases treatment OVERVIEW



Aminosalicylates

Drug	5-amino salicylic acid compounds (5-ASA) Aminosalicylates <small>aspirin-like</small>	
M.O.A	<p>Have topical anti-inflammatory action due to inhibition of prostaglandins and leukotrienes.</p> <ul style="list-style-type: none"> ○ decrease neutrophil chemotaxis. ○ Antioxidant activity (scavenging free radical production). 	<ul style="list-style-type: none"> • it has to applied topically . • Should come in contact with the inflamed area directly.
P.K	<ul style="list-style-type: none"> ○ 5-ASA itself is absorbed from the proximal small intestine. ○ 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 	<p>we have to keep the drug unabsorbed until it reach the inflamed area</p>
Clinical uses	<ul style="list-style-type: none"> ○ 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 	

formulations of aminosalicylates

The major differences are in the **mechanism** and the **site** of delivery.

Azo compounds

- Balsalazide
- Sulfasalazine
- Olsalazine

أزوا الزين ؟ Azo.. alazine

Mesalamines

- Asacol
- Pentasa
- Canasa
- Rowasa

آسه.. هذي مسألة مين؟! Asa .. Mesala-mine

بلاش تسولف لي عن علا

Aminosalicylates

Azo compounds

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

1- to sulfapyridine moiety (Sulfasalazine) → “Sulfasalazine = 5-ASA + sulphapyridine”

OI = all 2- to another molecule of 5-ASA (Olsalazine) → “Olsalazine = 5-ASA + 5-ASA”

علا دایم تسکتني
وتقول لي اصة اصة

3- to inert compound (Balsalazide) → “Balsalazide = 5-ASA + inert carrier” has no ADR

- Azo structure **reduces absorption of 5-ASA in small intestine.**

بلاش إضافات ووجع راس

- 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.

This enzyme exist only in the terminal ileum & colon → it cleaves the double bond of nitrogen thus releasing its components

Drug	Sulfasalazine (Azulfidine)	
M.O.A	<ul style="list-style-type: none"> ○ Pro-drug activated by enzyme 	<ul style="list-style-type: none"> ○ A combination of 5-ASA + sulfapyridine
P.K	5-ASA has anti-inflammatory action due to: <ul style="list-style-type: none"> ○ inhibition of prostaglandins and leukotrienes. ○ decrease neutrophil chemotaxis. ○ Antioxidant activity (scavenging free radical production). 	
ADRS	<ul style="list-style-type: none"> ○ Is given orally (enteric coated tablets). ○ Little amount is absorbed (10%) the 90% left is saved until it reaches the terminal ileum ○ In the terminal ileum and colon, sulfasalazine is broken by azoreductase into: <ul style="list-style-type: none"> • 5-ASA (not absorbed, active moiety acting locally). • Sulphapyridine (absorbed, <u>causes most of side effects</u>) 	<ul style="list-style-type: none"> ○ Bone marrow depression ○ Folic acid deficiency (should be provided). ○ Interstitial nephritis due to 5-ASA.
	(Oligospermia). <div style="border: 1px solid green; border-radius: 10px; padding: 5px; display: inline-block; margin-top: 10px;"> Most of the ADRs are caused by Sulfapyridine </div>	

Aminosalicylates

Mesalamine compounds

They are Formulations (oral & rectal) that have been designed to deliver 5-ASA in terminal small bowel & large colon.

These formulations have the **following characteristics:**

- Sulfa free
- well tolerated
- have less side effects compared to **sulfasalazine**
- useful in patient sensitive to sulfa drugs
- Coated with material that is sensitive to PH or time

Oral formulations

Control the release either by time or PH

- Releases **5-ASA** in the distal **small bowel** secondary to pH changes. → they release it in alkaline PH, stomach is acidic, therefore they won't release 5-ASA (coated with PH sensitive coat)
- Releases start at the pylorus and continues throughout the small bowel and colon.
- **Asacol**: 5-ASA coated in **pH-sensitive resin***** that dissolve at pH 7.
- **Pentasa**: micro granules**** that release **5-ASA** throughout the **small intestine** time sensitive

Rectal formulations

- Release **5-ASA** in the **distal colon**.
- **Canasa** (suppositories *)
كان يدعمني (can) دائماً (support me)
- **Rowasa** (enema **)
Rawan has anemia

*Suppository → a solid, conical mass of medicinal substance that melts upon insertion into the rectum or vagina

**enema → the injection of a fluid into the rectum to cause a bowel movement.

*** resin is not an absorbable molecule يمسك حاجات على سطحه بس

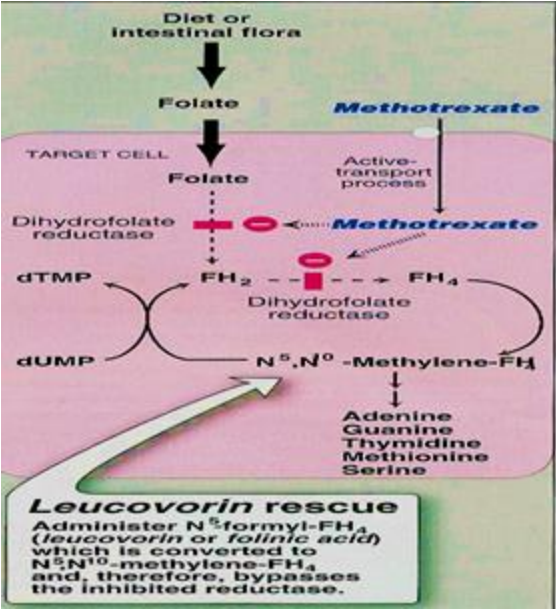
**** each granule has a different coat that releases its components on different **time intervals** to sustain/prolong the action

Glucocorticoids

Drug	Oral preparation <u>prednisone</u> , <u>prednisolone</u>	Parenteral preparation <u>hydrocortisone</u> , methyl <u>prednisolone</u>	Rectal preparation <u>Hydrocortisone</u>	Budesonide حامل تقوّل أبغى (بدي) أجيب (ولّد)
M.O.A	<ul style="list-style-type: none"> Inhibits phospholipase A2 Inhibits gene transcription of NO synthase, cyclo-oxygenase-2 (COX-2) Inhibit production of inflammatory cytokines 			
Indications	<ul style="list-style-type: none"> Indicated for acute flares of disease (moderate –to- severe active IBD). Are NOT useful in maintaining remission (not effective as prophylactic therapy). Asthma Rheumatoid arthritis immunosuppressive drug for organ transplants Antiemetic during cancer chemotherapy 			
	<p>Oral glucocorticoids</p> <p>is commonly used in active condition.</p>	<p>_____</p>	<p>Rectal glucocorticoids are preferred in IBD involving rectum or sigmoid colon.</p>	<p>Used in treatment of active mild to moderate Crohn's disease involving ileum and proximal colon. Not use in prophylactic</p>
Notes	<ul style="list-style-type: none"> Higher rate of absorption More adverse effects compared to rectal administration Gradually given 		<ul style="list-style-type: none"> As enema or suppository, give topical effect. Less absorption rate than oral. Minimal side effects & maximum tissue effects 	<ul style="list-style-type: none"> A potent synthetic prednisolone analog Given orally (controlled release tablets) so release drug in ileum and colon. Low oral bioavailability (10%). Is subject to extensive first pass metabolism

- 90% will reach the site of inflammation
- the 10% absorbed percentage is the cause of ADRs

Immunomodulators

Drug	Methotrexate	Purine analogs: azathioprine & 6-mercaptopurine <small>Inactive form</small> <small>Active form</small>
Action/Mech. of action	<ul style="list-style-type: none"> a folic acid antagonist Inhibits dihydrofolate reductase required for folic acid activation (tetrahydrofolate) Impairs DNA synthesis Induction and maintenance of remission in IBD 	<p>Azathioprine is pro-drug of 6-mercaptopurine. In the body it become active which is 6-mercaptopurine</p> <ul style="list-style-type: none"> Inhibit purine synthesis and inhibits synthesis of DNA, RNA, and proteins. It may decrease proliferation of immune cells, which lowers autoimmune activity. Suppress the inflamed cells Induction and maintenance of remission in IBD
indications	<p>Are used to induce remission in IBD in active moderate-to-severe conditions or steroid dependent or steroid resistant (refractory) Patients and to maintain remission. Prophylactic therapy</p> <ul style="list-style-type: none"> Inflammatory bowel disease Rheumatoid arthritis Cancer Given Orally, S.C., I.M. 	
ADRs	<ul style="list-style-type: none"> Megaloblastic anemia. Bone marrow depression 	<ul style="list-style-type: none"> Bone marrow depression: leucopenia, thrombocytopenia. Gastrointestinal toxicity. Hepatic dysfunction. Complete blood count & liver function tests are required in all patients

Monoclonal antibodies used in IBD

Mab = Monoclonal

(TNF- α inhibitors)

Certo=certain target

Drug	Infliximab	Adalimumab (Humira)	Certolizumab (Cimzia)
Mech. of action	<ul style="list-style-type: none"> - a chimeric mouse-human monoclonal antibody - 25% murine – 75% human. - TNF-α inhibitors - Inhibits soluble or membrane-bound TNF-α located on activated T lymphocytes. <p>The foreign protein (murine) lead to hypersensitivity reaction</p>	<ul style="list-style-type: none"> - Fully humanized IgG antibody to TNF-α -it binds to TNFα, preventing it from activating TNF receptors. • (Better than Infliximab) 	<ul style="list-style-type: none"> - Fab fragment of a humanized antibody directed against TNF-α - Certolizumab is attached to polyethylene glycol to increase its half-life in circulation.
P.K	<ul style="list-style-type: none"> • Given intravenously as infusion (5-10 mg/kg). Not given orally • has long half life (8-10 days) • 2 weeks to give clinical response. <p>Delayed action</p> <p>Infinity (∞) = infliximab</p>	<p>Has an advantage that it is given by subcutaneous injection</p>	<p>Given subcutaneously</p>
indications	<ul style="list-style-type: none"> • In moderate to severe active Crohn's disease and ulcerative colitis. • Patients not responding to immunomodulators or glucocorticoids. • Treatment of rheumatoid arthritis • Psoriasis الصدفية 	<p>is approved for treatment of, moderate to severe Crohn's disease, rheumatoid arthritis, psoriasis.</p>	<p>for the treatment of Crohn's disease & rheumatoid arthritis</p> <p>Longer action than adalimumab and BETTER</p>
ADRS	<ul style="list-style-type: none"> • <u>Acute</u> or <u>early</u> adverse infusion reactions (Allergic reactions or anaphylaxis in 10% of patients). • <u>Delayed</u> infusion reaction (serum sickness-like reaction, in 5% of patients). <p>Pre-treatment with diphenhydramine, acetaminophen, corticosteroids is recommended.</p> <ul style="list-style-type: none"> • Infection complication (Latent tuberculosis, sepsis, hepatitis B). • Loss of response to infliximab over time due to the development of antibodies to infliximab. • Severe hepatic failure. • Rare risk of lymphoma. 	<p>_____</p> <p>_____</p>	<p>_____</p> <p>_____</p>

لاني اتعامل مع دواء يقلل المناعه

Summary

Stepwise therapy of IBD → in order, we move to the next step when the previous did not work (pt. unresponsive)

1. Aminosalicylates "5-ASA"

- It has anti-inflammatory reaction.
- Used for **induction** & **maintenance** of remission
- 1st line of treatment mild to moderate IBD

Azo compounds: Sulfasalazine	Mesalamine compounds	
<ul style="list-style-type: none"> • azo bond is cleaved by azoreductase enzyme produced by bacterial flora releasing 5-ASA in the terminal ileum and colon • Sulphapyridine is responsible for the ARDs: <ul style="list-style-type: none"> ◦ Crystalluria. ◦ Megaloblastic anaemia. ◦ Impairment of male fertility • 5-ASA ARDs: Interstitial nephritis 	They are Formulations designed to deliver 5-ASA in terminal small bowel & large colon.	
	Oral formulation	Rectal formulation
	Releases 5-ASA in the distal small bowel <ul style="list-style-type: none"> • Asacol: PH sensitive coat • Pentasa: time sensitive coat 	Release 5-ASA in the distal colon <ul style="list-style-type: none"> Canasa -suppositories Rowasa - enema

2. Glucocorticoids

- Inhibits phospholipids A2 & gene transcription of NO synthesis
- Used for **indications** "treating" **ONLY** → not for maintaining remission

Oral glucocorticoids Prednisone Prednisolone	Parenteral preparations Hydrocortisone Methyl, Prednisolone	Rectal glucocorticoids Hydrocortisone	Budesonide
Commonly used in Active conditions	————	Used in IBD involving the rectum/sigmoid colon	Used in active Crohn's disease in ileum & proximal colon

3. Immunomodulators

- Used for **induction** & **maintenance** of active moderate to severe IBD.
- Used for steroid dependent & steroid resistant patients to maintain remission.

Methotrexate	Purine analogs : Azathioprine & 6-mercaptopurine
Folic acid antagonist → it inhibits Dihydrofolate reductase required for folic acid activation	<ul style="list-style-type: none"> • Inhibits purine synthesis • Lower autoimmune activity

Summary (cont.)

4. TNF- α inhibitors		
Used for induction "treating" only		
Infliximab	Adalimumab (humira)	Certolizumab (cimzia)
<ul style="list-style-type: none"> • Mouse-human monoclonal antibody \rightarrow has 25% murine (foreign protein lead to hypersensitivity reaction). • Used for moderate to severe active Crohn's disease. • It lowers the immunity so it's contraindicated for immunocompromised pts. 	<ul style="list-style-type: none"> • Fully humanized • Binds to TNF-α preventing it from activating TNF receptors • Treat moderate to severe Crohn's disease 	<ul style="list-style-type: none"> • Fab fragment of humanized antibody directed against TNF-α • Treat Crohn's disease • Better than Adalimumab and has a longer action

MCQs

- 23 y/o 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. What drug do you recommend for him first?**

a) Asacol b) Methotrexate c) Sulfasalazine
- Which of the following is the action of Azo structure?**

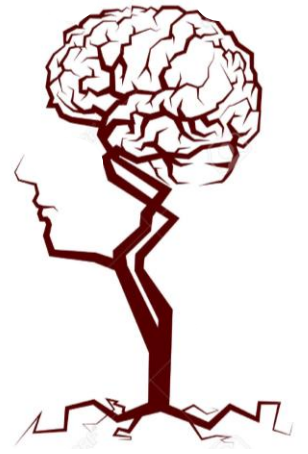
a) Deliver 5-ASA in terminal small bowel b) reduce absorption of 5-ASA c) inhibits phospholipase
- Which of the following isn't used for maintaining remission of IBD ?**

a) 5-ASA b) Immunomodulators c) TNF alpha inhibitors
- Recently diagnosed pt. with IBD and was prescribed a treatment. After weeks he started developing hepatic dysfunction. What drug caused this adverse reaction?**

a) Azathioprine b) Methotrexate c) certolizumab
- Which of the following drugs id better used for Crohn's disease pt. ?**

a) Infliximab b) Certolizumab c) Adalimumab

5.	B
4.	A
3.	C
2.	B
1.	C



إِنَّ فِي ذَلِكَ لَآيَاتٍ لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٣﴾

قادة فريق علم الأدوية :

- جومانا القحطاني - اللولو الصليهم
- فارس النفيسة

الشكر موصول لأعضاء الفريق المتميزين :

عبد الكريم العتيبي

روان القحطاني

وجدان الزيد

رحاب العنزي

شوق الأحمري

References :

1- 436 Prof. Hanan's slides and notes



pharma436@outlook.com



@pharma436



[Your feedback](#)