Treatment of Inflammatory Bowel Disease

Prof. Hanan Hagar & Prof. Abdulqader Alhaider

PHARMA TEAM

Eman Alrashidi, Badra`a Almuharib

Ibrahim Alshiddi, Ismail Raslan, Suhail Assiri

Team notes are in purple

Introduction to IBD:

- **is a group of inflammatory conditions of the small intestine and colon**.

	Ulcerative colitis	Crohn's disease
Location	Rectum and colon	All the GIT
Distribution	Continuous area of inflammation	Patchy areas of inflammation (Skip lesions)
Depth of inflammation	Affect whole thickness of wall (transmural)	Affect mucosa only
Symptoms	bloody Diarrhea	No Blood

- **Symptoms complications**:

Symptoms	Complications
· Abdominal pain	– Mega colon
· Rectal bleeding >>>>>>>>>>>>>	– Anemia
· Diarrhea >> >>>>>>>>>>>>>>>>>	– dehydration
· Vomiting	– Intestinal obstruction (with Crohn's)
· Weight loss	– Colon cancer (especially with UC)
- Fever	

- **Causes:**

Unknown! but we know that there is **Abnormal** activation of the immune system which leads to **inflammation**. It's believed that IBD is genetically inherited.

Treatment of IBS:

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

} ***Antiinflammatory drugs***

The main goal of treatment is by stopping the inflammation

1st class: 5-amino salicylic acid compounds (5-ASA), also known as aminosalycates:

- **MoA:** inhibit prostaglandin and leukotriens synthesis; decreases neutrophil chemotaxis and decreases free radical production.
- 5-ASA itself is absorbed from small intestine so different formulations are used to overcome rapid absorption of 5-ASA from the proximal small intestine → it can reach site of inflammation and produce effect.
- Remember that salicylates are irritant to gastric mucosa so it is advised to be taken after meals.
- So what are these formulations called?

  → **Azo compounds: Compounds that contain 5-ASA and connected by azo bond (N=N) to sulfapyridine, another molecule of 5-ASA or to inert compound.**

  Sulfasalazine : 5-ASA + sulphapyridine

  Olsalazine: Two molecules of 5-ASA (Colazal)

  Balsalazide: 5-ASA + inert carrier (*Dipentum*)

  - As we said, Importance of Azo structure is to reduce absorption in small intestine. Later, *in the terminal ileum and colon*, bacterial flora release azoreductase that cleave the azo bond and release 5-ASA in <u>terminal ileum and colon.</u>

- **Uses of Azo and mesalamine compounds are**

  1. **Treat and maintain* remission in mild to moderate ulcerative colitis & Crohn's disease (First line of treatment).**
  2. **Rheumatoid arthritis (Sulfasalazine only)**

  *** Maintenance therapy (used to prevent acute attacks not during acute attacks)**

- **Azo compounds** are of **two types:**

  A)Sulpha containing 5-ASA (E.g. sulphasalazine)

  B) **Non-sulpha containing 5-ASA**

A. **Sulphasalzine:** (5-ASA + sulphapyridine)

- Prodrug - It is safe in pregnancy
- Is given orally (enteric coated tablets to protect against gastric juices)
- In the terminal ileum and colon, sulfasalazine is broken by folra (azoreductase) to
  - 5 amino salicylic acid (active compound)
  - Sulphapyridine (inactive , causes side effects)

- **ADR's :**

1. **Hypersensitivity reactions due to sulpha**
2. **Crystalluria.**
3. **Folic acid deficiency** (should be provided).
4. **Megaloblastic anemia.** (due to Inhibition of absorption of folic acid)
5. **Bone marrow depression.** >> aplastic anemia
6. **Impairment of male fertility** (Oligospermia=decreased sperm count).
7. **Interstitial nephritis due to 5-ASA**
8. **Muscular pain**

B. Non-sulpha 5-ASA: 1) **Mesalamine**

- Mesalamine formulations are well tolerated, have less side effects (sulfa free), useful in patient sensitive to sulfa drugs.
- irritant for upper GIT thus given rectally or by these oral formulations:

Oral formulations		*Rectal formulations*	
i. **Pentasa**	ii. **Asacol**	i. **Rowasa** (enema)	ii. **Canasa** (suppositories)
Time-release microgranules that release 5-ASA throughout the small intestine (delayed-release) < delayed release so large doses don't irritate mucosa.	**5-ASA coated in pH-sensitive resin that dissolved at pH 7 (controlled release) < controlled so they don't dissolve in the stomach and cause irritation.**		

2) **Mesalazine** (Oral control release form of 5-ASA; less side effects but expensive)

3) **Olsalazine** [Two molecules (dimer) of 5-ASA linked together by diazo bond which pass small intesitne to ileum and colon]

2nd class: **Glucocorticoids** (Anti-Inflammatory + Immunosuppresent)

- **MoA:**

· Inhibits phospholipase A2,

· Inhibit gene expression of NO synthase, COX-2 so reduces the inflammation

· Inhibit production of inflammatory cytokines (TNF-a)

- Less effective as a prophylactic (maintaining remission) → used in acute attacks.

- **Uses** of corticosteroids :

· **Treat moderate – severe <u>active</u> IBD**

→ Glucocorticoids are less effective as prophylactic therapy (maintenance)

· **Also used for extracolonic manifestations** such as ocular lesion, skin disease and arthritis.

A. **Prednisone**, prednisolone:	B. **Hydrocortisone**	C. **Budesonide**
- Oral - Higher rate of absorption → ↑adverse effects compared to rectal administration	- enema or suppository - rectal administration reduce absorption → maximize tissue effects and minimize side effects	- A potent synthetic analog of prednisolone - Given orally as controlled releas tablets that release drug in ileum and colon where it is absorbed - Is subject to first pass metabolis (CYP3A4) so Low oral bioavailability (10%)

- **Administration methods:**
  - **Oral** administration is commonly used in **active condition**.
  - IBD involving rectum or sigmoid colon (**UC**), **rectal** administered glucocorticoids are preferred.
  - **Budesonide** is used in treatment of active mild to moderate **Crohn's disease** involving ileum and proximal colon.

3rd class: **Immunomodulators**:

- **MoA:** Suppress the body's immune system
- **Used** in severe conditions or Steroid-dependent or steroid resistant patients

  in treatment and prophylaxis (to continue the remission)

- 2 types : A) purine analogs and B) methotrexate

A. Purine analogs :

- **Azathioprine** (*Imuran®*) and **Mercaptopurine**
- **MoA:** Inhibit purine synthesis → inhibit DNA synthesis →no proliferation of inflammatory cells
- Induction and maintenance of remission in IBS
- **ADR's:**
  i. leukopenia, thrombocytopenia. (BONE MARROW DEPRESSION)
  ii. Hepatic dysfunction.
  iii. Gastrointestinal toxicity. .(nausea & vomiting)
  iv. Complete blood count & liver function tests are required in all patients
  v. Hypersensitivity reactions due to thio (thio=sulpha)

<< CBC & LFT monitoring is required

B. Methotrexate

- Orally, S.C., I.M (not I.V.)
- **MoA:** Inhibit dihydrofolate reductase important in production of purines **(**works as antimetabolite.)
- **Uses:** Crohn's disease to induce and maintain remission (used in acute attacks and as maintenance) and Rheumatoid Arthritis and cancer
- **ADR's:**

1) Bone marrow suppression >> 2)Megaloblastic anemia

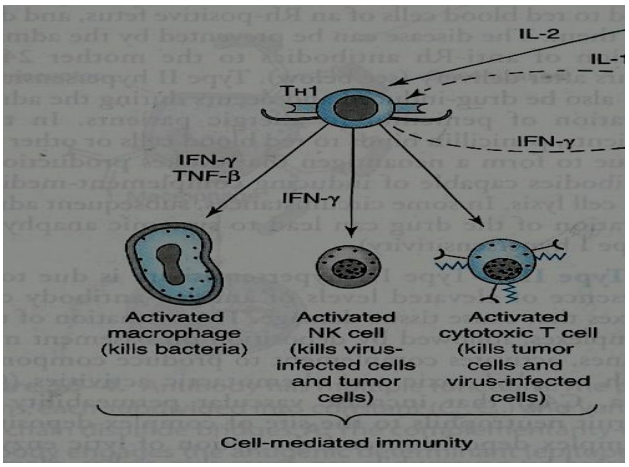
Biological therapy of IBD

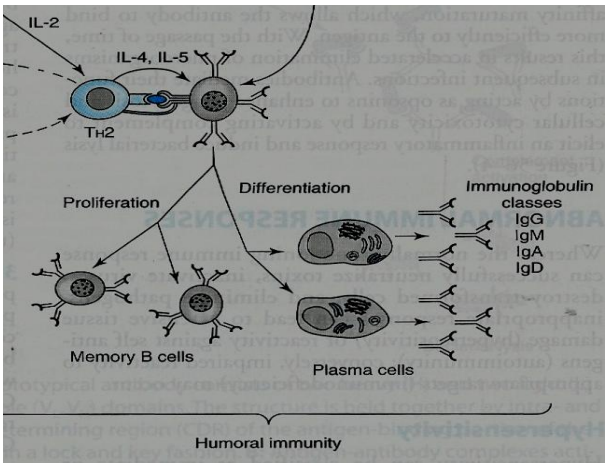
- **Introduction on Immunology**: *it's extra knowledge.You only need to know what's in red:*

- Immune system include two main arms

- Cell –mediated immunity by TH1 << TH1 response is mediated by proinflammatory cytokines as TNF-α.

- Humoral (antibody –mediated immunity) TH2.





- **Cytokines are soluble signaling proteins that bind to receptors on a variety of cells and are involved in many inflammatory conditions.**
- **Cytokines include**
  - **Interleukins**
  - **Tumor Necrosis Factors (TNFs)**
  - **Interferon (IFNs) and others**

Tumor Necrosis Factors (TNF-α)

- **It is one of the key pro-inflammatory cytokines involved in Th1 response.**
- **TNFα inactivation has proven to be important in down-regulating the inflammatory reactions associated with autoimmune diseases.**
- **Inhibition of TNFα action is done by antibodies against TNFα (TNFα inhibitors)**

- **Types of biological antibodies used in treatment of autoimmune diseases:**

1. Polyclonal antibodies (Antisera):	**2. Monoclonal antibodies:**
are a **combination** of immunoglobulin, each identifying a **different** epitope. **Preparation** 1) Immunization of animals with **antigen** that induces the B-lymphocytes to produce immunoglobulins (**IgGs**) specific for that antigen. >> 2) This polyclonal IgG is purified from the mammal's serum and given to human.	are **monospecific** antibodies that are the **same** because they are made by identical immune cells that are all clones of a unique parent cell. **Preparation** Prepared by **recombinant DNA technology.**

We'll focus on ***Monoclonal antibodies****:*

They're classified according to their source to:

- **Mo**use antibodies contain suffix (**mo**mab) e.g. Odulimomab , muromonab.
- **Chimeric [mixed]** (humanized mAbs & non-human mAbs) contain suffix (**xi**mab) e.g. infli**xi**mab , Abci**xi**mab; Rutu**xi**mab , bacili**xi**mab)
- H**um**anized mAbs contain suffix (**mu**mab or **zu**mab) e.g. Adali**mu**mab, certoli**zu**mab pegol, Dacli**zu**mab; Transtu**zu**mab

Which ones do use to treat IBD?

(TNF-α inhibitors), and those are:

i. Infliximab

ii. Adalimumab

iii. Certolizumab

i: Infliximab

- a mixed mouse-human monoclonal antibody.
- 25% murine – 75% human.
- **Directed against TNF-α**
- Binds to soluble or membrane –bound TNF-α located on activated T lymphocytes and neutralizes its activity.
- Given **I.V.** as infusion (5-10 mg/kg).
- has long half life (8-10 days)
- 2 weeks to give clinical response.

Uses:

1. In patient with moderate to severe active Crohn's disease and ulcerative colitis (*reduce frequency of acute flare*).
2. Patients not responding to immunomodulators or glucocorticoids.
   ↳ Because it is very expensive 20 thousans $/year.
3. Treatment of rheumatoid arthritis
4. Psoriasis (الصدفية)
5. ankylosing spondylitis, psoriatic arthritis,

ADR's:

1. Acute or early adverse infusion reactions *(Allergic reactions or anaphylaxis in 10% of patients).*
2. Delayed infusion reaction *(serum sickness-like reaction, in 5% of patients)**.
3. Infection complication *(!!Latent tuberculosis, sepsis, hepatitis B).* << *SO* it is contraindication with positive TB test
4. Loss of response to infliximab over time *due to the development of antibodies to infliximab* (*termed human anti-chimeric antibodies*).*
5. Severe hepatic failure.
6. Rare risk of lymphoma.

* Treat serum sickness with:
-diphenhydramine (antihistamine),
-acetaminophen (paracetamol)
-corticosteroids is recommended.

* 25% of Infliximab is murine (animal source) so it is expected to form antibodies against the drug its self (antibody against the antibody) . When those antibodies are too elevated and affect the Inflixmab action.

ii: Adalimumab (Humira®)

- Fully humanized IgG antibody to TNF-α
- **Adalimumab is TNFα inhibitor**
- It binds to TNFα, preventing it from activating TNF receptors
- Has an advantage that it is given by **subcutaneous injection** (. less hypersensitivity reaction than infliximab which is given by IV only)
- **Used** for treatment of, moderate to severe Crohn's disease*, rheumatoid arthritis and psoriasis

* This drug is new and its affect against UC is unknown, so it is used mainly for Crohn.

iii: Certolizumab pegol (Cimzia®)

- !! Fab fragment of recombinant, humanized antibody with specificity for human tumor necrosis factor alpha (TNFα),
- Certolizumab **is attached to polyethylene glycol to increase its half-life** in circulation.(it has longer duration of action than Adalimumab)
- **Given subcutaneously**
- for the treatment of Crohn's disease & rheumatoid arthritis . It may be used alone or combined with methotrexate (or other drugs used for treating rheumatoid arthritis.
- !! Fab fragment means part of the antibody not fully as Adalimumab * each antibody has 2 Fabs*)

* Structure of antibody consist of 2 fabs
In Certoliz**um**ab. Only one fab of the antibody
While Adalimumab. Is fully antibody which means 2 fabs