بسم الله الرحمن الرحيم

MMS module

Pharmacology of Disease modifying anti-rheumatic drugs

by

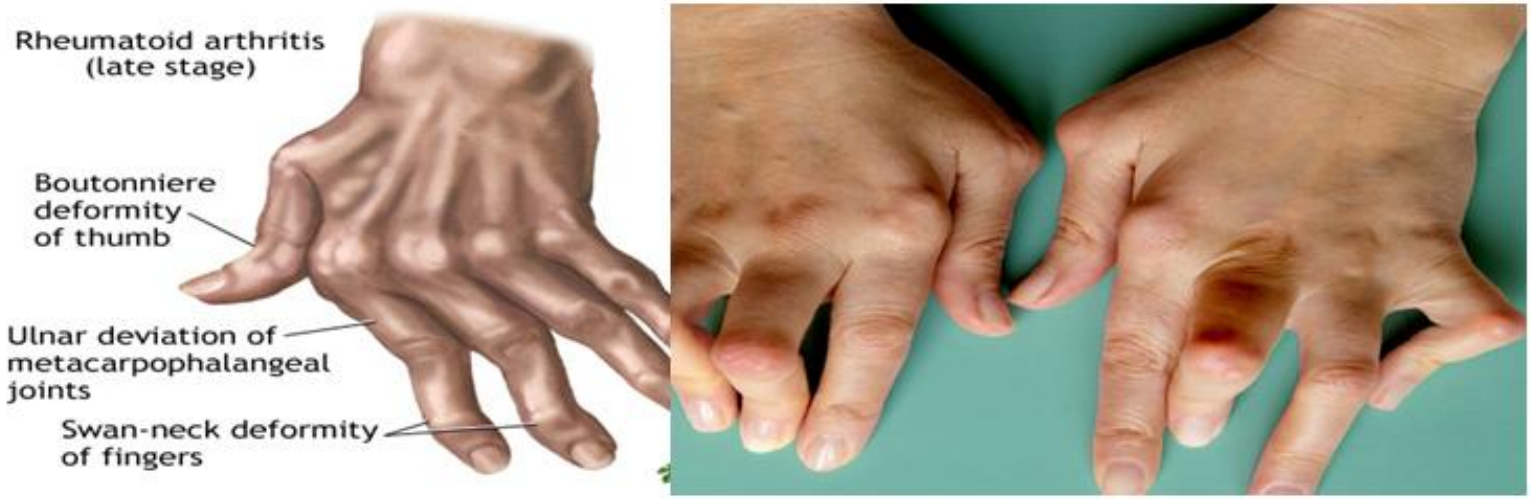
Dr. Mohamed Salem

2024

Introduction

Rheumatoid arthritis (**RA**) is a progressive autoimmune disease that causes significant systemic effects, shortens life, and reduces mobility and quality of life. RA has flares (relapses or activity) & **remissions** (decreased manifestations) periods

RA affects the synovial lining of joints, causing a painful swelling, stiffness especially in the morning, and finally bone erosion and joint deformity. These deformities cause physical disabilities.



Drug therapy of rheumatoid arthritis

Till now there is **no curative treatment**. Available medications might **arrest** or at least **slow** the **progression of RA** by modifying the disease itself.

First line drugs (Fast-acting drugs)

They are given during flare (disease activity) till remission occurs

(1) NSAIDs and analgesics.

(2) Corticosteroids

-They cause rapid and marked anti-inflammatory effect

-Oral prednisone is used during severe flares (the smallest effective dose for short time) or if there is poor response to NSAIDs.

-the **intraarticular injection of triamcinolone** can be used instead of oral therapy but not used for more than 4 times /year.

-The repeated intraarticular injection of corticosteroids may **cause painless destruction of joints.**

Second line drugs (Slow-acting drugs)

(Disease modifying anti-rheumatic drugs, DMARDs)

- DMARDs have slow onset of action (weeks or months).
- DMARDs have little or **no direct anti-inflammatory** or analgesic effects.
- They act mainly through suppression of immunological functions.
- They promote rapid **remission and decrease relapse**.
- DMARDS **retard the progression of joint destruction & deformity.**
- DMARDs may increase the risk of secondary infections.
- Most DMARDs suppress bone marrow.

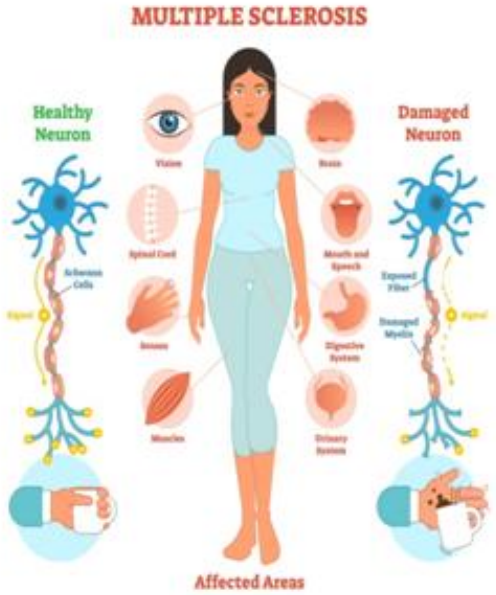
Therapeutic uses of DMARDs

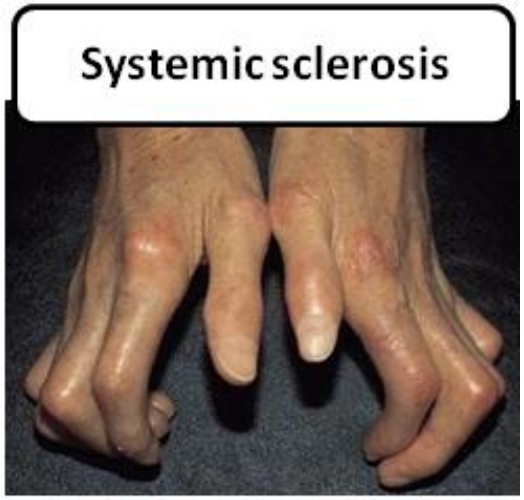
DMARDs are known for treating **RA** but also used for:

1. Ankylosing **spondylitis**.
2. Psoriatic arthritis and **psoriasis**.
3. Systemic lupus erythematosus (**SLE**).
4. Juvenile idiopathic **arthritis**.

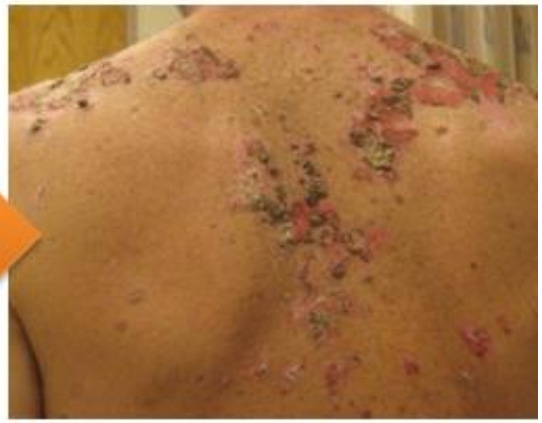
Ankylosing spondylitis

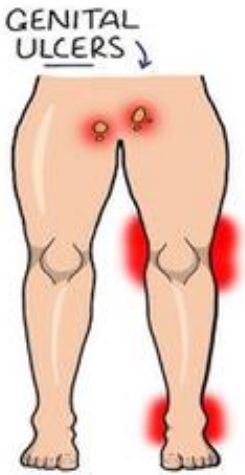
5. Systemic sclerosis.
6. Multiple sclerosis.
7. Sjögren's syndrome.
8. **Myositis**.
9. **Vasculitis**.
10. **Uveitis**.
11. **Inflammatory bowel disease**.
12. Other diseases (e.g. **myasthenia**, pemphigus, and Behcet disease).
13. Cancers (**leukemia & lymphomas**).

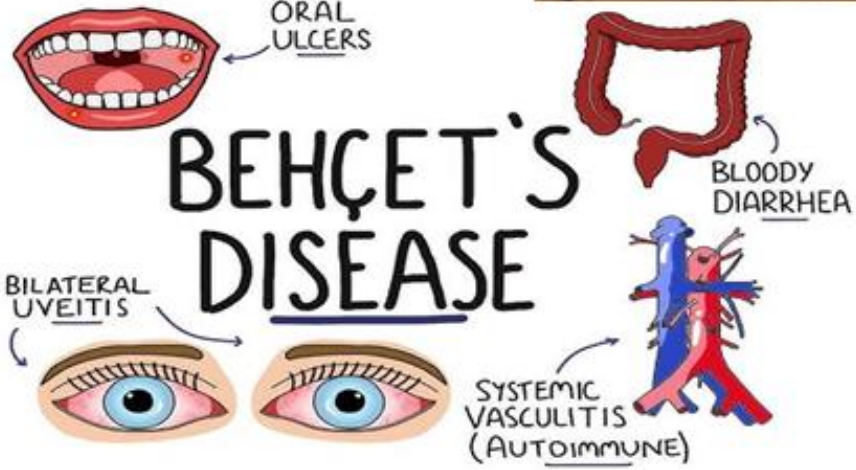


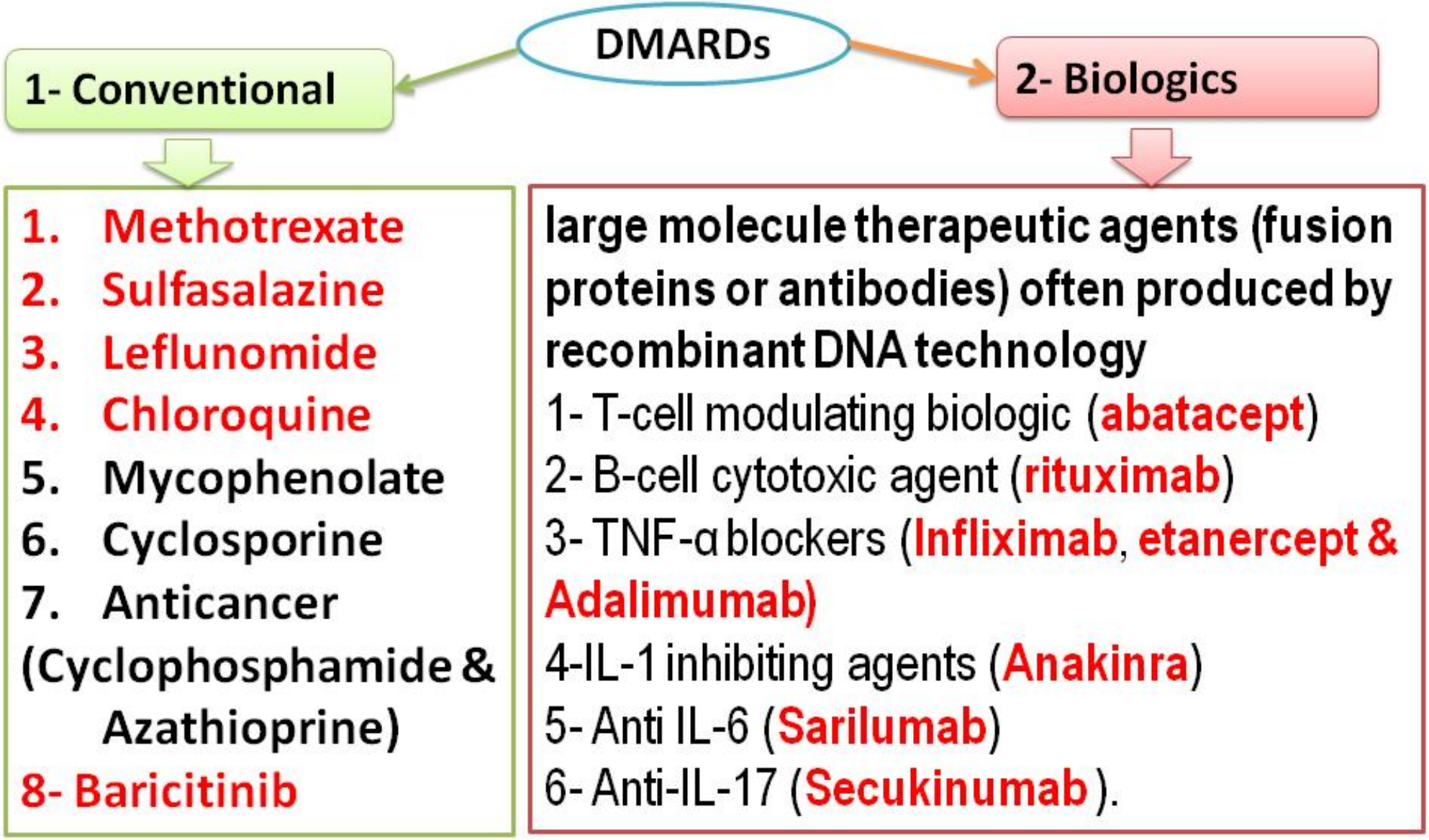


pemphigus









N.B. Gold salts and penicillamine, which were once extensively used, are no longer recommended because of their significant toxicities.

N.B. Minocycline is a weak DMARD effective in early RA.

1-Methotrexate (MTX)

-It **inhibits folic acid** and hence DNA synthesis. This lead to decreased number of lymphocytes and leukocytes.

-It is the treatment of choice in patient with severe RA who failed to respond to NSAIDs.

-MTX is relatively a rapid acting DMARD (within 2-4 weeks) compared with 2-6 months with other **DMARDs**.

-It is approved for treating psoriasis & other diseases.

-Generally, it is well tolerated in the recommended dose.

- It is given **oral or IM** in doses less than the anticancer doses.
- Adverse effects: bone marrow depression, Crystalluria, **hepatotoxicity**, & GIT irritation and ulceration.

- **It is contraindicated during pregnancy.**

2-Sulfasalazine

- It is widely used in treating **inflammatory bowel diseases** & **RA.**
- It has some anti-inflammatory and immunosuppressant activities.
- 30% of patients discontinue the drug because of toxicity:

1- hypersensitivity reaction (Stevens Jonson syndrome).

2- Blood toxicity: Hemolytic anemia & agranulocytosis.

3-Reversible infertility occurs in men, but not in women.

- **Sulfasalazine appears relatively safe in pregnancy.**

3-Leflunomide

- It is used either alone or in combination with MTX.
- It inhibits the synthesis of pyrimidine leading to suppression of the activity of immune cells.
- It is a widely used DMARD for treating RA and other diseases.

Adverse effects: **Diarrhea** (common) and hepatotoxicity.

It is contraindicated during pregnancy.

4- Antimalarial drugs (Chloroquine and hydroxychloroquine)

- They have long half-lives (40–50 days) due to large VD.
- They are **Less toxic** but **less effective** than other drugs.
- They **suppress T-lymphocyte**, **stabilize lysosomal enzymes**, and **prevent antigen presentation** to immune cells. Used in **RA & SLE**

The serious adverse effects include:

1-Eye (keratitis, and retinal damage with irreversible blindness).

2-Hepatotoxicity and Cardiac arrhythmias.

3- Hemolysis in patients suffering from **G6PD deficiency.**

These drugs are relatively safe in pregnancy.

5- Mycophenolate mofetil

It **inhibits inosine monophosphate dehydrogenase** (IMPDH), leading to suppression of T and B lymphocyte proliferation.

It is used after organ transplantation & for treatment of RA.

Adverse effects: Hepatotoxicity, infections & **bone marrow depression**.

It is contraindicated during pregnancy.

6- Cyclosporine

- It is immunosuppressive drug & used in treatment of **RA , psoriasis**, and other autoimmune diseases. It is used after organ transplantation also.
- Mechanism: **inhibition of calcineurin** → inactivation of T-cells.
- Adverse effects: **hypertension**, **nephrotoxicity,** hypertrichosis, hyperuricemia, gum hyperplasia, severe immunosuppressant effect (leads to infections and lymphomas).
- **It is safe during pregnancy (Category C).**

7-Anticancer drugs used as DMARDs

- Examples: **Cyclophosphamide**, and **Azathioprine.**
- They decrease lymphocytes 'number and hence decrease the production of auto-Antibodies that attacking joints and other tissues.
- They are used in treating RA and other autoimmune diseases but in doses less than the doses used for treatment of cancer.
- The major adverse effect is bone marrow suppression.
- **Cyclophosphamide is contraindicated during pregnancy.**
- **Azathioprine is relatively safe in pregnancy.**

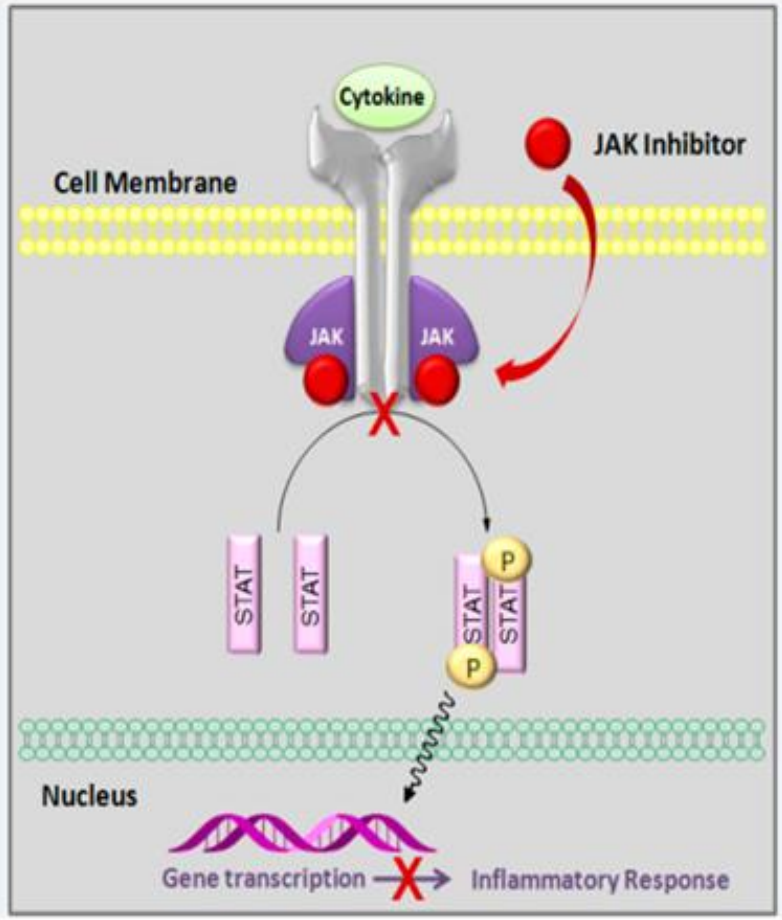
8- Baricitinib

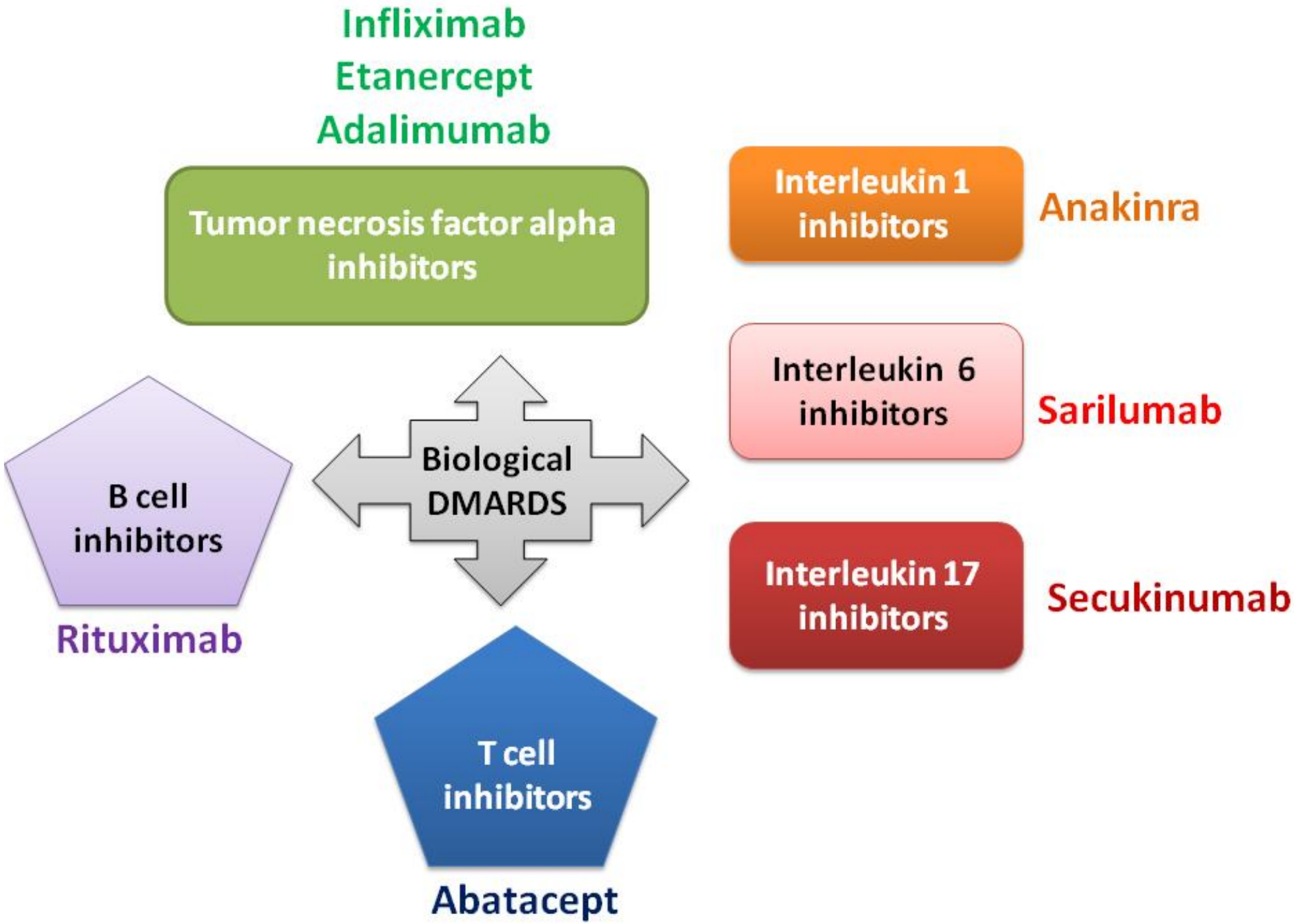
Tyrosine or Janus kinase (JAK) inhibitors

They inhibit the signaling (JAK-STAT) of different inflammatory cytokines.

- **Oral baricitinib** is approved for treating **Alopecia areata**, **and RA.**
- Adverse effects: Infections are common.
- All JAK inhibitors have FDA **"black box warning"** of increased **venous thrombotic events** including (deep vein thrombosis, pulmonary emboli , and could lead to myocardial infarction)

- **N.B. Baricitinib is not a true biologic drug** (although marketed as a biologic)**. It is smaller in size than biological drugs.**




Infliximab
Etanercept
Adalimumab
Tumor necrosis factor alpha inhibitors
Interleukin 1 inhibitors
Anakinra
Interleukin 6 inhibitors
Sarilumab
Biological DMARDS
B cell inhibitors
Rituximab
Interleukin 17 inhibitors
Secukinumab
T cell inhibitors
Abatacept

Abatacept

It **inhibits T-cell activation** by blocking interaction with CD28 on T cells.

It is used SC or IV.

Uses:

1- control RA, and other forms of arthritis.

2- The prophylaxis of acute **graft-versus-host disease.**

3- Treatment of **systemic lupus erythomatosus** (SLE)

4-Primary Sjögren syndrome

5- Delay progression of **Type 1 diabetes**

6- **Inflammatory bowel disease**

7- **Psoriasis**

8-Dermatomyositis.

Adverse effects:

1- Infections (activation of viral hepatitis & **T.B**).

2- hypersensitivity and **anaphylaxis**.

Rituximab

A monoclonal antibody targeting **CD20 on B lymphocytes** leading to their apoptosis and decreasing **B cell counts.**

✓Used in **RA,** Lymphomas, leukemia, myasthenia, and pemphigus.

Adverse Effects:

1- Rash, Urticaria, anaphylaxis & **Stevens Johnson syndrome.**

2-Serious & even fatal infections (bacterial, fungal, viral) reported rarely. Reactivation of hepatitis B is common.

➢Rituximab has **not** been associated with activation of tuberculosis.

➢Rituximab is category C during pregnancy.

Tumor necrosis factor (TNF α) inhibitors

➢TNF - α is a cytokine that is markedly increased in the synovial fluid of the joints in cases of RA. TNF- α has an important role in facing infections; so, its inhibition may increase the **risk of infections as T.B by 4-fold.**

➢These drugs should stopped if any signs of infection appear.

➢Infliximab & etanercept (in 1998 & 1999), **Adalimumab** (in 2002).

Adalimumab

- It is a TNF alpha inhibitor. Given SC (half-life; 10–20 days).
- It decreases the rate of formation of new erosions in **RA.**
- Adalimumab has also been used in **Behçet disease**, **sarcoidosis**, **psoriasis**, **inflammatory bowel disease** and **uveitis**.

Adverse Effects of Adalimumab:

1- It increases the risk of serious infections (in particular latent **T.B** reactivation, and deep **fungal infections)**.

2- It worsen or initiate **multiple sclerosis/neurologic** diseases, and **heart failure.**

3- Headache, rash, **lymphoma**, and **lupus like syndrome** are uncommon.

Interleukin1 (IL-1) Inhibitor (Anakinra)

- Anakinra is blocks IL-1 receptor. It blocks the effect of both IL-1α &1β, hence decreasing the immune response in inflammatory diseases namely RA.

✓ It was approved for treating **COVID-19 pneumonia**.

➢ The most common adverse effects of IL1 inhibitors are injection site reactions (up to 40%), Serious infections including **T.B and opportunistic or fungal infections** could occur.

IL-6 receptor antagonist (Sarilumab)

➢ Sarilumab appears to be **superior to Adalimumab** in **RA.**

➢ Given once every 2 weeks, administered subcutaneously.

Adverse Effects:

1- The most common adverse effect is infections.

2- Neutropenia, thrombocytopenia, and anemia.

3- **Elevated triglycerides and LDL** have been reported.

4- Perforation with diverticulitis has been reported.

5- Malignancies have been observed.

IL-17 inhibitors (e.g. Secukinumab)

- Secukinumab selectively binds to the IL-17A cytokine, inhibiting its interaction with the IL-17A receptor.
- **It is given SC injection** (half-life is 22–31 days).
- ✓ Secukinumab is indicated for **psoriasis**, **psoriatic arthritis**, **RA**, ankylosing spondylitis, and other diseases.
- Adverse Effects: Infection (especially Nasopharyngitis).
- T.B status should be evaluated prior to therapy.

Secukinumab may cause or exacerbate inflammatory bowel disease.


Thank you