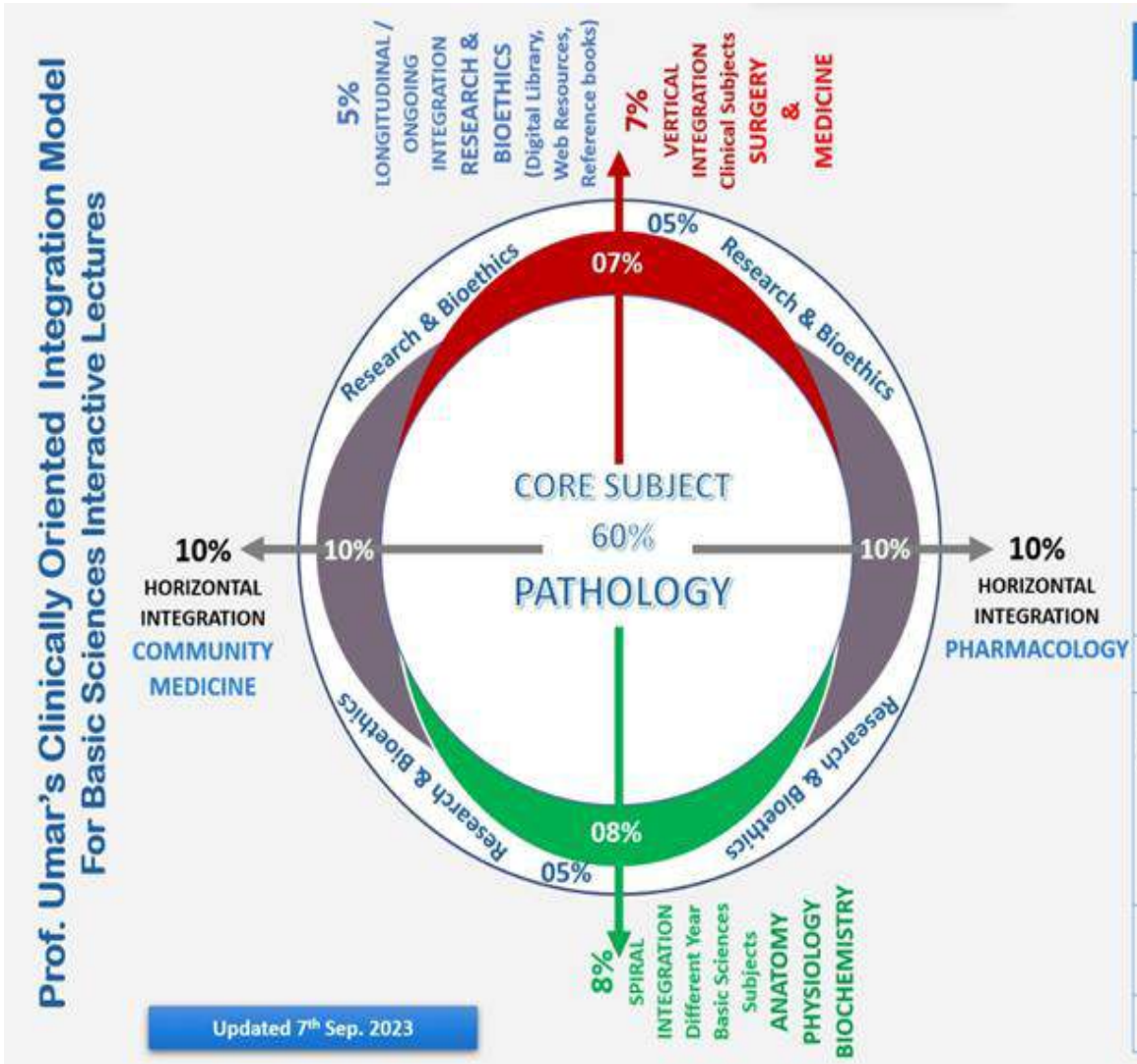

بسم الله الرحمن الرحيم
وَأَمَّا مَا يَنفَعُ ٱلنَّاسَ فَيَمْكُثُ فِى ٱلْأَرْضِ
but as for that which benefits the people, it remains on the earth.
Quran 13:17 (Surah ar-Ra'd)

MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine



Model 3rd Year Pathology LGIS (≈30 slides)	
Core Subject – 60% (≈ 18-20 slides)	
Pathology (≈ 18-20 slides)	
Horizontal Integration – 20% (≈ 5-6 slides)	
Same Year Subjects	• Pharmacology (10%) (≈ 2-3 slides) • Community Medicine (10%) (≈ 2-3 slides)
Vertical Integration – 07% (≈ 2-3 slides)	
Clinical Subjects	• Medicine (3-5%) (≈ 1-2 slides) • Surgery (3-5%) (≈ 1-2 slides)
Spiral Integration – 08% (≈ 2-3 slides)	
Different Year Basic Sciences Subjects	• Anatomy (1-3%) (≈ 1-2 slides) • Physiology (1-3%) (≈ 1-2 slides) • Biochemistry (1-3%) (≈ 1-2 slides)
Longitudinal / Ongoing Integration – 05% (≈ 1-2 slides)	
Research & Bioethics (≈ 1-2 slides)	

CNS,PSYCHIATRY &MSK MODULE
4th year MBBS

LGIS
ANTIRHEUMATIC DRUGS

DR.MUHAMMAD ZAHEER SHEIKH DATED: 16-11-24

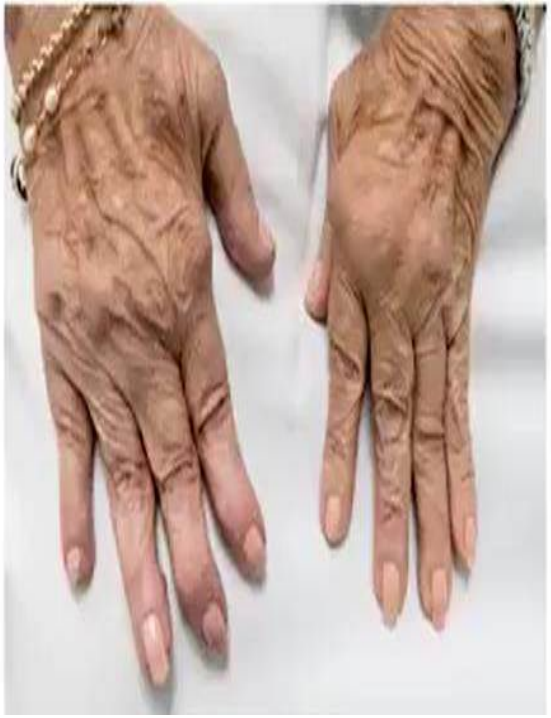
Sources

Bertram G. katzung Basic & Clinical Pharmacology 15th Edition
Goodman and Gilman's The Pharmacological Basis of Therapeutics 13th edition

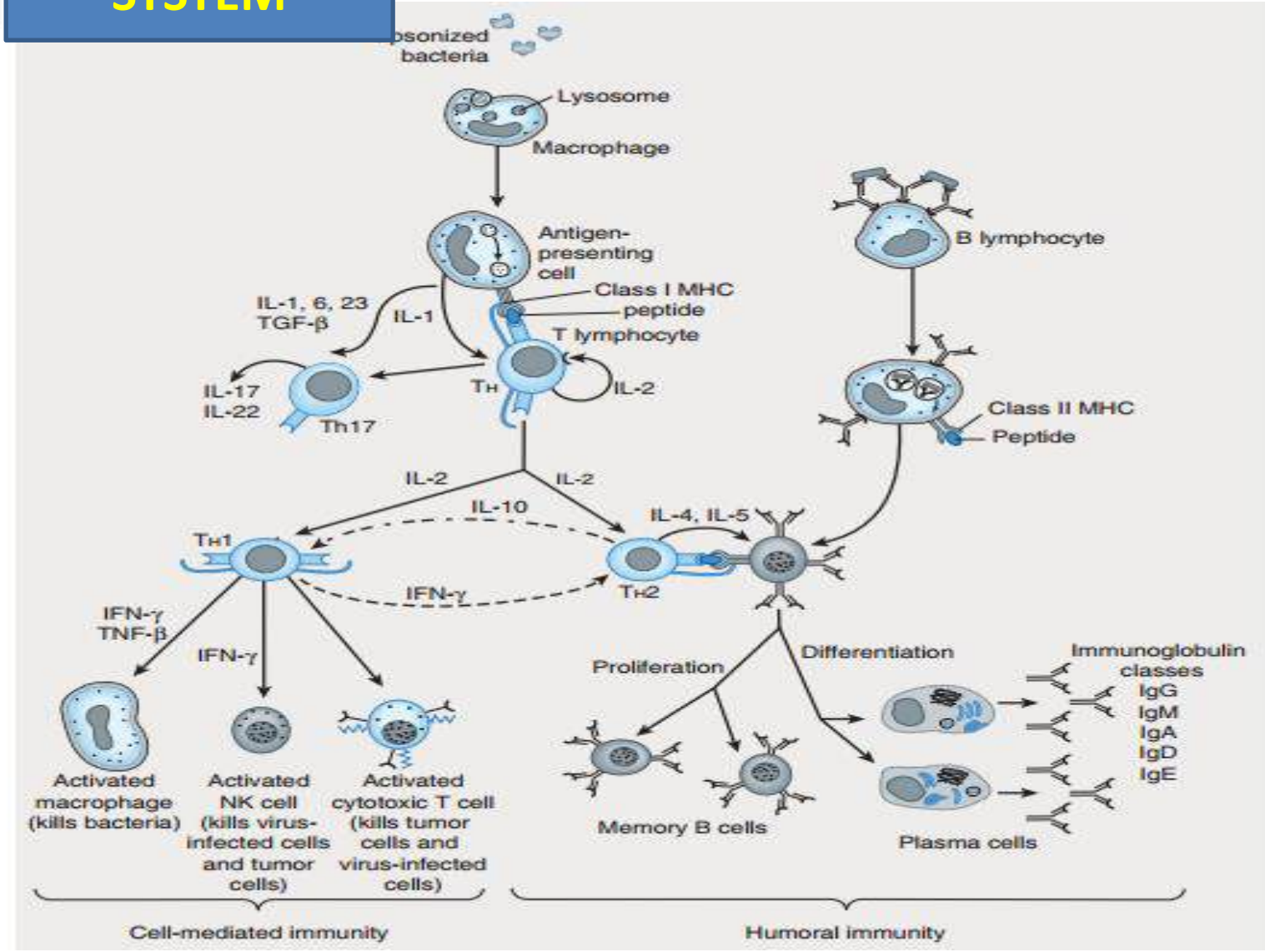
LEARNING OBJECTIVES

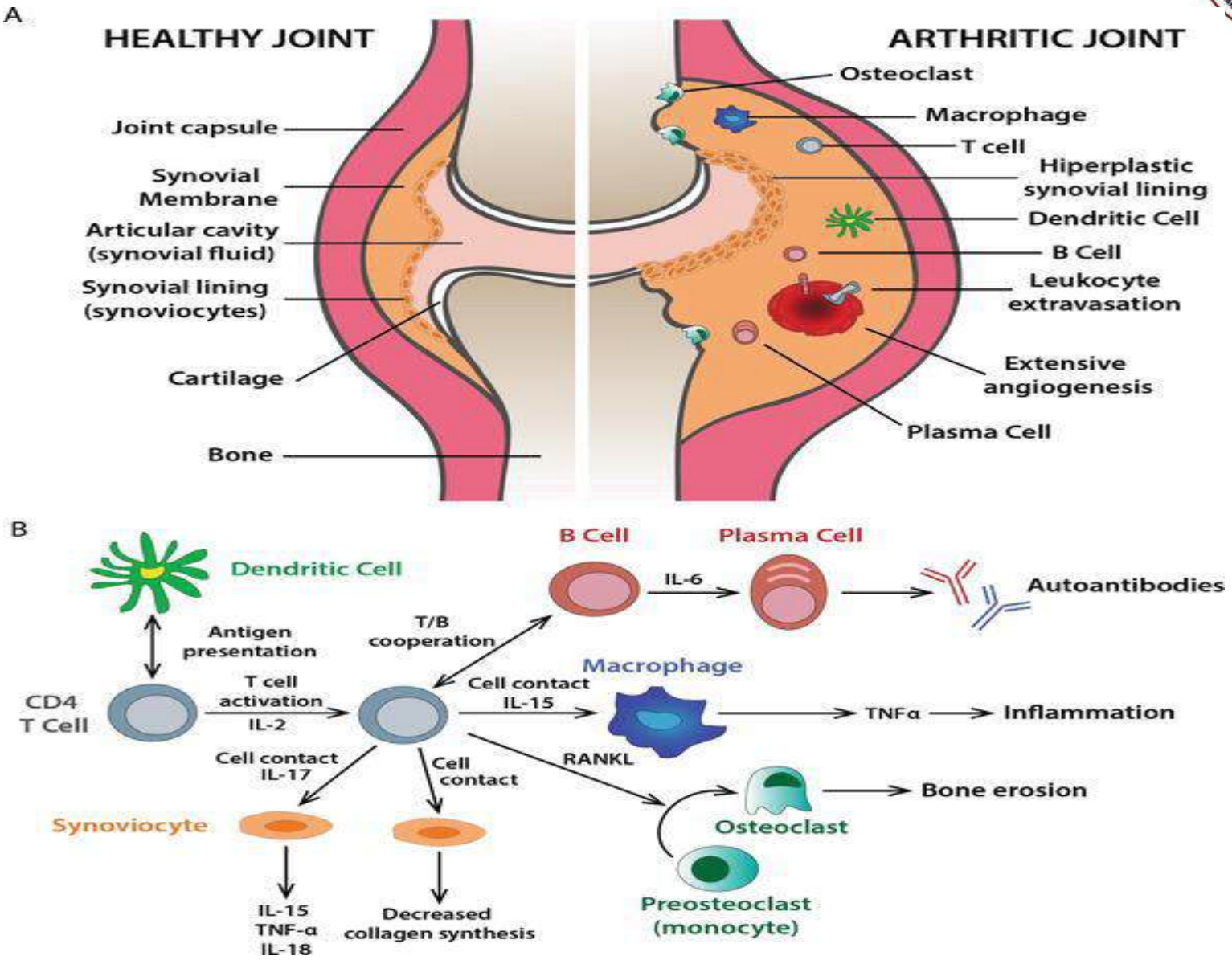
- Recall the pathophysiology of rheumatoid arthritis
- Classify DMARDS
- Describe salient features of conventionally synthetic and biological DMARDS

HAND DEFORMITY OF RA



IMMUNE SYSTEM




A
HEALTHY JOINT
ARTHRITIC JOINT
Joint capsule
Synovial Membrane
Articular cavity (synovial fluid)
Synovial lining (synoviocytes)
Cartilage
Bone
Osteoclast
Macrophage
T cell
Hiperplastic synovial lining
Dendritic Cell
B Cell
Leukocyte extravasation
Extensive angiogenesis
Plasma Cell
B
Dendritic Cell
B Cell
Plasma Cell
IL-6
Autoantibodies
Antigen presentation
T/B cooperation
CD4 T Cell
T cell activation
IL-2
Macrophage
Cell contact IL-15
TNFα
Inflammation
Cell contact IL-17
Cell contact
RANKL
Bone erosion
Synoviocyte
Osteoclast
IL-15
TNF-α
IL-18
Decreased collagen synthesis
Preosteoclast (monocyte)

CLASSIFICATION OF DMARDS

- **Synthetic DMARDs**

  a) Conventionally synthetic DMARDS(csDMARD)

  i) Immunosuppressive & immunomodulating agents

  Methotrexate
  Azathioprine
  Cyclophosphamide
  Cyclosporine
  Leflunomide
  Mycophenolate mofetil

  ii)**Anti-malarial :**

  Chloroquine, Hydroxychloroquine

  iii) Gold salts :

  Auro thiomalate, Aurothioglucose,Auranofin

  iv) NSAID:

  Sulfasalazine

  b) Targeted synthetic DMARDS(tsDMARDS)

  i) Janus Kinase inhibitor

  Tofacitinib (oral)

CLASSIFICATION OF DMARDS

❖ **Biological DMARD (bDMARD)**

a) Biolological original DMARD(boDMARD)

i. **TNF blocking agents**
   - Adalimumab
   - Golimumab
   - Certolizumab
   - Infliximab
   - Etanercept

ii. **B cell biologic**
   - Rituximab, Belimumab

iii. **T cell modulating biologic**
   - Abatacept

iv. **Interleukin inhibitors**

- **IL-1 inhibiting agents:** Anakinra,Canakinumab,Rilonacept
- **Anti –IL-6 receptor antibody:**Tolicizumab
- **IL-17 inhibiting antibody** :Secukinumab
- **IL-12 & IL-23 inhibiting antibody** :Ustekinumab

b) Biosimilar DMARD(bsDMARD)

Therapeutic goals

- Ameliorate pain, swelling and joint stiffness.

(immuno modulator + anti inflammatory)

- Prevent articular cartilage damage and bony erosions.

- Prevent deformity and preserve joint function.

METHOTREXATE

MECHANISM OF ACTION

- Inhibition of aminoimidazolecarboxamide ribonucleotide (AICAR) transformylase and thymidylate synthetase. AICAR, which accumulates intracellularly, competitively inhibits AMP deaminase, leading to an accumulation of AMP. The AMP is released and converted extracellularly to adenosine, which is a potent inhibitor of inflammation.
- It has direct inhibitory effects on proliferation and stimulates apoptosis in immune-inflammatory cells. Additionally, it has also been shown to have inhibition of proinflammatory cytokines linked to rheumatoid synovitis.

METHOTREXATE

RHEUMATOID ARTHRITIS | MEDICATION

Methotrexate: Monitor

- CBC, eGFR, SGPT
- Weekly until dose and monitoring are stable
- Then monthly for at least 1 year
- Frequency of monitoring may be decreased if disease / dose stable after 1 year
- Ask to report symptoms/ signs of infection—especially sore throat

Methotrexate Side Effects

Methotrexate is used to treat a variety of cancers, whilst also used for its immunosuppressant powers.

METHO!

M - **M**outh ulceration

E - **E**nd of white blood cells; leukopenia

T - **T**iredness / fatigue

H - **H**epatotoxicity

O - fibr**O**sis of the lung

METHOTREXATE

CLINICAL INDICATIONS

- Rheumatoid arthritis (The drug decreases the rate of appearance of new erosions)
- Juvenile chronic arthritis
- Psoriasis, psoriatic arthritis
- Ankylosing spondylitis
- Polymyositis
- Dermatomyositis
- Wegener's granulomatosis
- Giant cell arteritis
- Systemic lupus erythematosus
- Vasculitis.

CORTICOSTEROIDS MECHANISM OF ACTION

They have both anti-inflammatory action and immunosuppressant effects.

- Bind to glucocorticoid receptors and the complex interacts with DNA to inhibit gene transcription of inflammatory genes.
- Decrease production of inflammatory mediators as prostaglandins, leukotrienes, histamine, PAF, bradykinin.
- Decrease production of cytokines IL-1, IL-2, interferon, TNF.
- Stabilize lysosomal membranes.
- Decrease generation of IgG, nitric oxide and histamine.
- Inhibit antigen processing by macrophages.
- Suppress T-cell helper function
- Decrease T lymphocyte proliferation

CORTICOSTEROIDS
CLINICAL INDICATIONS

- Are first line therapy for solid organ allografts & haematopoietic stem cell transplantation.
- Autoimmune diseases as refractory rheumatoid arthritis, systemic lupus erythematosus, asthma
- Acute or chronic rejection of solid organ allografts.

CORTICOSTEROIDS
ADVERSE EFFECTS

- Adrenal suppression
- Osteoporosis
- Hypercholesterolemia
- Hyperglycemia
- Hypertension
- Cataract
- Infection

HYDROXYCHLOROQUINE

MECHANISM OF ACTION

- It is thought to suppress intracellular antigen processing and loading of peptides onto MHC class II molecules by increasing the pH of lysosomal and endosomal compartments, thereby decreasing T-cell activation
- Stabilization of lysosomal enzymes, inhibition of chemotaxis, interference with functioning of inflammatory cells

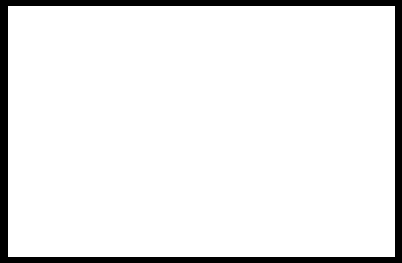
CLINICAL INDICATIONS

- Autoimmune disorders, e.g., rheumatoid arthritis and systemic lupus erythematosus.
- Treat and prevent graft-versus-host disease after allogeneic stem cell transplantation.
- Malaria

ADVERSE REACTION

- Dyspepsia, nausea, vomiting, abdominal pain, rashes, and nightmares

CONVENTIONAL DMARDS



GENERAL PROPERTIES

- **Nature** : Synthetic
- **Pharmacokinetics:** Oral, parental (methotrexate, azathioprine)
- **Mechanism:** Parent drug or active metabolite (leflunomide, azathioprine, cyclophosphamide, sulfasalazine, mycophenolate mofetil)

  Broad effect cell and cytokine mediated effect on the immune system

  Methotrexate: increase concentration of adenosine by inhibiting AICAR (amino imidazole carboxamide) transformylase which leads to suppression of inflammatory cells and reduction of proinflammatory cells

  Leflunomide: Active metabolite inhibits dihydroorate dehydrogenase and decrease de novo pyrimidine synthesis blocking T cell proliferation

  Sulfasalazine: Sulfapyridine suppress T & B cell function & inhibit release of IL-1IL-6,12 & TNFα

  HCQ/CQ: Stabilization of lysosomal enzymes, inhibition of chemotaxis, interference with functioning of inflammatory cells

  Azathioprine & Cylcophosphamide: T cell and B cell suppression

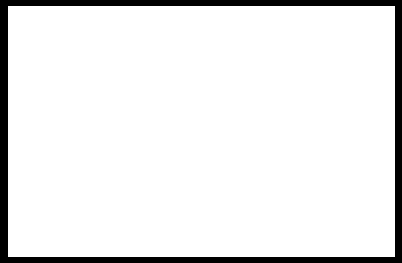
  Cyclosporine: Antigen receptor induced T cell differentiation & activation

  MMF: Mycophenolic acid suppress T and B cell function

GENERAL PROPERTIES

- **Response** : Months (3-6 months)
- **Toxicities:**
    - Hematological
    - Hepatotoxic
    - Ocular toxicity (HCQ, CQ)
    - GI disturbances (diarrhea)(lefluonamide)
- **Pregnancy:** HCQ and sulfasalazine (not in term as may cause kernicterus)
- **Combinations**: Can be given in combination with other csDMARDS and bDMARDS

BIOLOGICAL DMARDS



Drug	Type	Mechanism of action	Route of administration
Adalimumab	Humanized monoclonal ab	Binds with soluble TNF α & prevents binding to receptor	Subcutaneous (t1/2 10-20 days)
Certolizumab pegol	Pegylated Fab fragment	Neutralizes soluble and membrane bound TNF α	Subcutaneous (t1/2 14 days)
Golimumab	Humanized monoclonal ab	Neutralizes soluble and membrane bound TNF α	Subcutaneous (t1/2 14 days)
Etanercept	Fusion protein decoy receptor	Binds both TNF α, TNF β and lymphotoxin α	Subcutaneous (t1/2 4.5 days)
Infliximab	Chimeric monoclonal ab	Neutralizes soluble and membrane bound TNF α	Intravenous (t1/2 9-12 days)

ADVERSE EFFECTS

- Infusion Reactions with Infliximab
- Injection Site Reactions with Adalimumab and Etanercept
- Infection
  - Tuberculosis
  - Hepatitis B
- Malignancy
  - Increased risk of skin cancers (melanoma)
- Neurologic
  - Multiple Sclerosis, seizures, inflammation of the ocular nerve
- Autoimmune
  - Antibody formation – SLE like illness
- GIT intolerance (ulcers & perforation)
- Worsening of Congestive Heart Failure

INTERLEUKIN INHIBITORS

IL-I
IL-6
IL-12 & 23
IL-17

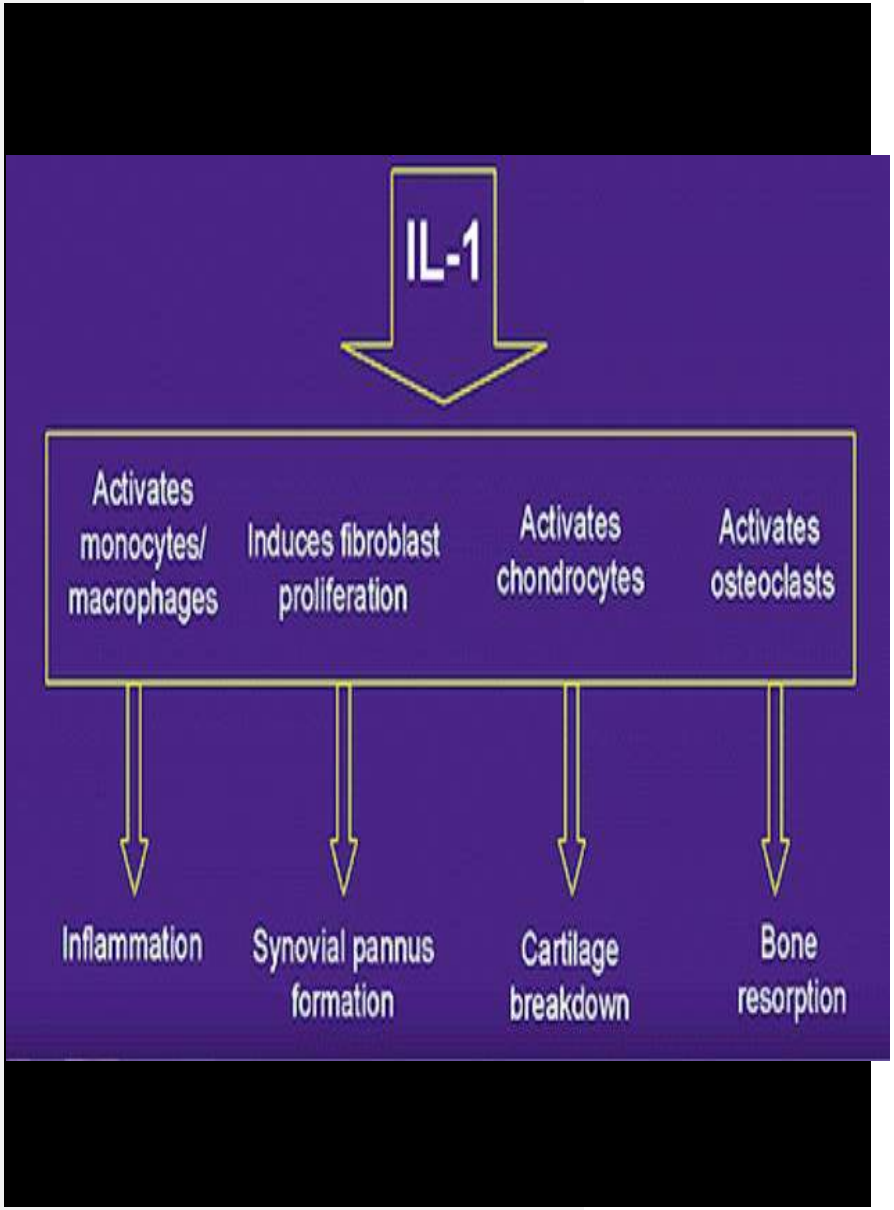
- **Anakinra**
- IL-1 receptor antagonist

- **Canakinumab**
- Monoclonal antibody that forms complex with IL-1b preventing binding to IL-1 receptor

- **Rilonacept**
- Neutralizes IL-1b and prevents attachment to IL-1 receptor

- **USES:**
- Gout
- SJIA

- **A/E:**
  Injection site reactions, RTIs, neutropenia & hypersensitivity



Tocilizumab — Humanized monoclonal antibody against IL-6

- Intravenous administration
- **A/E**: Infections, hematological complications, hypersensitivity, GIT intolerance & demyelinating disorders

Ustekinumab — Humanized monoclonal antibody that binds to p40 domain of IL-12 & 1L-23 preventing binding to IL-12 receptor on CD4 T cells & NK cells

- Subcutaneous & intravenous administration
- **A/E**: URTIs, malignancy & posterior leukoencephalopathy syndrome

Secukinumab — Human monoclonal antibody that binds to IL-17A

- Subcutaneous administration
- **A/E**: URTIs

❖ Belimumab

- Human monoclonal antibody which neutralized B cell activating factor/stimulator
- Intravenous administration
- SLE
- A/E:
  - Infusion site reactions
  - Respiratory tract infection
  - Depression and suicide

❖ Rituximab

- Chimeric monocloncal antibody that targets CD20 B lymphocytes causing lysis
- Intravenous administration
- SLE, vasculitis, lymphomas & leukemia
- A/E:
- Infusion site reactions (acetaminophen,antihistamines & steroids)
- Infections (new & dormant)
- Hypersensitivity (rash & anaphylaxis)

B CELL BIOLOGICS

- Selective inhibition of B cell function

❖ Abatacept

- Fusion protein that prevents activation of T cells by binding to cell surface markers (proteins) on leukocytes
- Intravenous & subcutaneous administration
- JIA, SLE, Sjogren's, IBD and psoriasis
- **A/E:**
  - Infusion site reactions
  - Infections (new and dormant)
  - Hypersensitivity

T CELL BIOLOGICS

- Selective inhibition of T cell function

- Oral bioavailability of 74%
- Metabolism in liver by CYP2C19
- Renal elimination

❖ **USES:**
- IBD
- Psoriasis
- Spondyloarthritis
- Graft rejection

❖ **A/E:**
- Infections
- Malignancies
- Lipid abnormalities
- Hematological problems
- Hepatic & GIT disturbances

JANUS KINASE INHIBITOR

Interrupts JAK/STAT signaling pathway

TOFACITINIB

BIOMEDICAL ETHICS

RA is fraught with ethical issues, regarding decision-making about care and treatment, patient–practitioner interaction, timely access to appropriate services, and opportunities to self-manage and live as full a life as possible

Research

- Katelani S, Fragoulis GE, Bakasis AD, Pouliakis A, Nikiphorou E, Atzeni F, Androutsakos T. HBV reactivation in patients with rheumatoid arthritis treated with anti-interleukin-6: a systematic review and meta-analysis. Rheumatology. 2023 Oct 1;62(SI3):SI252-9.

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