ANTIRHEUMATOID DRUGS

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RHEUMATOID ARTHRITIS (RA)

- Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown aetiology marked by a symmetric, peripheral polyarthritis.

- The wrists, metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints stand out as the most frequently involved joints.

- RA may result in a variety of extraarticular manifestations, including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis and hematologic abnormalities.

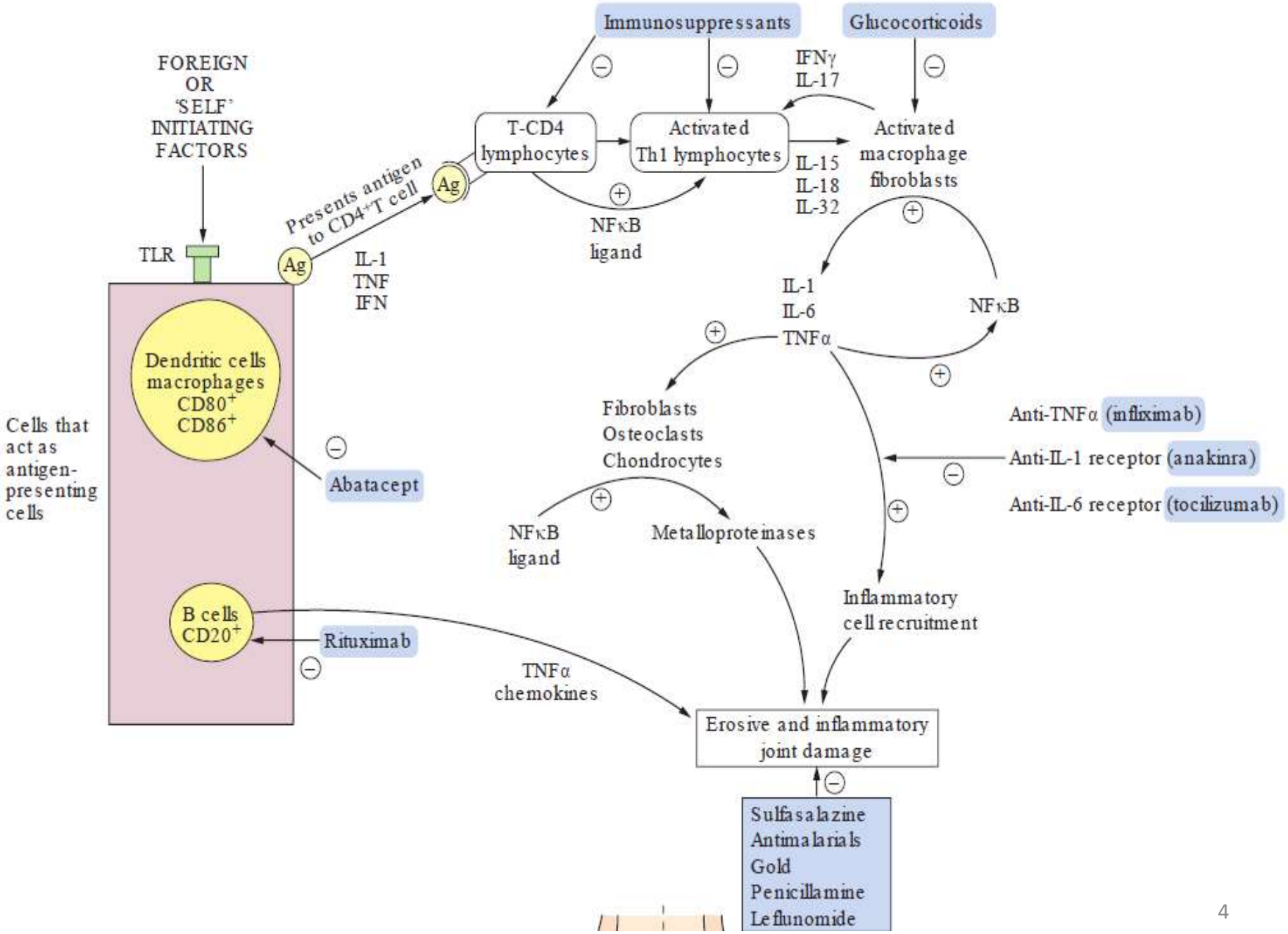
RHEUMATOID ARTHRITIS (RA)

- The pathogenic mechanisms of synovial inflammation result from a complex interplay of genetic, environmental and immunologic factors that produces dysregulation of the immune system and a breakdown in self-tolerance.

- RA is associated with allelic variation in the HLA-DRB 1 gene, which encodes the MHC IIβ - chain molecule.

- In RA preclinical stage is characterized by a breakdown in self-tolerance, supported by the finding that autoantibodies RF and anti-CCP (cyclic citrullinated peptide) antibodies may be found in sera.

- The pathologic hallmarks of RA are synovial inflammation and proliferation, focal bone erosions and thinning of articular cartilage.


Immunosuppressants
Glucocorticoids
FOREIGN OR 'SELF' INITIATING FACTORS
IFNγ
IL-17
T-CD4 lymphocytes
Activated Th1 lymphocytes
Activated macrophage fibroblasts
IL-15
IL-18
IL-32
Presents antigen to CD4+ T cell
Ag
TLR
IL-1
TNF
IFN
NFκB ligand
IL-1
IL-6
TNFα
NFκB
Dendritic cells macrophages CD80+ CD86+
Cells that act as antigen-presenting cells
Abatacept
Fibroblasts
Osteoclasts
Chondrocytes
Anti-TNFα (infliximab)
Anti-IL-1 receptor (anakinra)
Anti-IL-6 receptor (tocilizumab)
NFκB ligand
Metalloproteinases
Inflammatory cell recruitment
B cells CD20+
Rituximab
TNFα chemokines
Erosive and inflammatory joint damage
Sulfasalazine
Antimalarials
Gold
Penicillamine
Leflunomide

RHEUMATOID ARTHRITIS (RA)

- The inflammatory infiltrate is made up of: T cells, B cells, plasma cells, dendritic cells, mast cells and granulocytes.

- Activated T cells stimulate macrophages and fibroblast-like synovocytes to generate proinflammatory mediators and proteases that drive the synovial inflammatory response and destroy the cartilage and bone.

- T_H 1 cells produce interferon γ (IFN- γ), lymphotoxin β and TNF-α whereas T_H 2 cells predominately secret interleukin (IL)-4, IL-5, IL-6, IL- I0 and IL- 13.

- Activated B cells give rise to plasma cells, which in turn produce antibodies, including RF and anti-CCP antibodies.

- Macrophage is the predominant source of proinflammatory cytokines TNF-α, IL- 1, IL-6, IL- 12, IL- 15, IL- 18 and IL-23.

ANTIRHEUMATOID DRUGS

I. Disease-modifying antirheumatic drugs (**DMARDs**)/slow acting antirheumatic drugs (**SAARDs**)-

A. Nonbiological drugs-

1. Immunosuppressants: Methotrexate, Azathioprine, Cyclosporine
2. Sulfasalazine
3. Chloroquine or Hydroxychloroquine
4. Leflunomide

B. Biological agents-

1. TNF-α inhibitors: Etanercept, Infliximab, Adalimumab
2. IL-1 antagonist: Anakinra(rarely used in RA)
3. T cell Co-stimulation inhibitors: Abatacept (bind B7 protein of APC)
4. IL-6 inhibitor: Tocilizumab
5. B-Cell depleter: Rituximab (Ab towards CD20, cytotoxic to B cells)
6. small-molecule inhibitor: Tofactinib (inhibits JAK 3 & JAK 1)

II. Adjuvant drugs

Corticosteroids: Prednisolone and others

METHOTREXATE

- Methotrexate, a synthetic nonbiologic antimetabolite, is the first line DMARD for treating RA and is used in 50–70% of patients.

Mechanism of action:

- Principal mechanism of action in RA relates to inhibition of amino-imidazolecarboxamide 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.

METHOTREXATE

Mechanism of action (continue….):

- Methotrexate has secondary effects on polymorphonuclear chemotaxis.
- There is some effect on dihydrofolate reductase and this affects lymphocyte and macrophage function.
- Methotrexate has direct inhibitory effects on proliferation and stimulates apoptosis in immune-inflammatory cells.
- Additionally, it inhibits proinflammatory cytokines linked to rheumatoid synovitis.

METHOTREXATE

Adverse Effects:

- Nausea and mucosal ulcers are the most common.
- Many other side effects such as leukopenia, anaemia, stomatitis, GI ulcerations, and alopecia are the result of inhibiting cellular proliferation.
- Progressive dose-related hepatotoxicity in the form of enzyme elevation occurs frequently.
- A rare hypersensitivity-like lung reaction with acute shortness of breath has been documented.
- This drug is contraindicated in pregnancy.

AZATHIOPRINE

- Azathioprine is a synthetic nonbiologic DMARD.
- converting to 6-mercaptopurine (active metabolite)
- It selectively affects differentiation and function of T cells and inhibits cytolytic lymphocytes; CMI is primarily depressed.

Adverse Effects:

- Bone marrow suppression, GI disturbances, and some increase in infection risk.

- Lymphomas may be increased.

- Rarely, fever, rash and hepatotoxicity.

Cyclosporine

- CALCINEURIN INHIBITORS (Specific T-cell inhibitors)
- profoundly and selectively inhibits T lymphocyte proliferation,
- IL-2 and other cytokine production as well as response of inducer T cells to IL-1, without any effect on suppressor T-cells.
- Lymphocytes are arrested in G0 or G1 phase.
- Cyclosporine binds to an intracellular protein ‘Cyclophilin’ and this complex inhibits Ca^{2+}-Calmodulin (Ca^{2+}-CAM) activated phosphatase ‘Calcineurin’.
- Normally, after activation through T-cell receptor, calcineurin dephosphorylates a ‘nuclear factor of activated T-cells’ (NFAT) which translocates to the nucleus and triggers transcription of cytokine genes resulting in production of IL-2 and other cytokines.

SULFASALAZINE

- It is a compound of 5-aminosalicylic acid (5-ASA) with sulfapyridine linked through an azo bond.

- The azo bond is split by colonic bacteria to release 5-ASA and sulfapyridine.

- Sulfapyridine absorbed systemically appears to be the active moiety for rheumatoid ararthritis. (contrast ulcerative colitis, in which 5-ASA acting locally in the colon is the active component).

Mechanism of Action

- In vitro, sulfasalazine or its metabolites inhibit the release of inflammatory cytokines produced by monocytes or macrophages, eg, IL-1, -6, and -12, and TNF-α.

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SULFASALAZINE

Adverse Effects

- Common side effects include gastrointestinal disturbances, malaise and headache
- Skin reactions and leukopenia
- Absorption of folic acid is sometimes impaired
- Reversible decrease in sperm count
- Bone marrow depression and anaphylactic-type reactions

Haematological monitoring may be necessary.

CHLOROQUINE AND HYDROXYCHLOROQUINE

- These are antimalarial drugs found to induce remission in upto 50% patients of RA, but takes 3-6 months.

Mechanism of action:

- Suppression of T-lymphocyte responses to mitogens
- Inhibition of leukocyte chemotaxis
- Stabilization of lysosomal enzymes
- Inhibition of DNA and RNA synthesis
- and the trapping of free radicals.

CHLOROQUINE AND HYDROXYCHLOROQUINE

- For RA these drugs have to be given for long periods: accumulate in tissues and produce toxicity.

- These are used in milder nonerosive disease, especially when only one or few joints are involved, or they are combined with Mtx/sulfasalazine.

Adverse Effects:

- This is less common and reversible in case of hydroxychloroquine.

- Rashes, graying of hair, irritable bowel syndrome, myopathy and neuropathy are other adverse effects

- These drugs are relatively safe in pregnancy.

LEFLUNOMIDE

- Leflunomide is as effective as methotrexate in RA, including inhibition of bony damage.

Mechanism of Action:

- Leflunomide undergoes rapid conversion to its active metabolite which inhibits dihydroorotate dehydrogenase, leading to a decrease in ribonucleotide synthesis and the arrest of stimulated cells in the G1 phase of cell growth.

- Consequently, leflunomide inhibits T-cell proliferation and reduces production of autoantibodies by B cells.

- Secondary effects include increase of IL-10 receptor mRNA, decreased IL-8 receptor type A mRNA, and decreased TNF-α-dependent nuclear factor kappa B (NF-κB) activation.

LEFLUNOMIDE

Adverse Effects:

- Diarrhea occurs in approximately 25% of patients given leflunomide.
- Elevation in liver enzymes
- Other adverse effects are mild alopecia, weight gain, and increased blood pressure.
- Leukopenia and thrombocytopenia occur rarely.
- This drug is contraindicated in pregnancy.

Biologic DMARDs

Target	Drug	Type	Mode of action
Soluble TNF-α	Adalimumab	Humanised monoclonal ab	Neutralisation
	Certolizumab pegol	Pegylated ab fragment	
	Golimumab	Humanised monoclonal ab	
	Infliximab	Chimeric neutralising ab	
	Etanercept	Fusion protein decoy receptor	
Soluble IL-1	Anakinra	recombinant human IL-1 receptor antagonist	Neutralisation
Soluble IL-6	Tocilizumab	Humanised monoclonal ab	Neutralisation
T cells	Abatacept	Fusion protein	Prevents co-stimulation of T cells (binds to CD80/86 on T-cells)
B cells	Rituximab	Chimeric monoclonal ab	Causes B cell lysis

Biologic DMARDs

- They are protein therapeutics designed mostly to target cytokines and cell-surface molecules.

- All of them produce prominent adverse effects, are expensive, and are used only as reserve drugs for severe refractory disease.

TNF-α-BLOCKING AGENTS

Adalimumab

- Fully human IgG1 anti-TNF monoclonal antibody.

- Complexes with soluble TNF-α and prevents its interaction with p55 and p75 cell surface receptors.

- This results in down-regulation of macrophage and T-cell function.

TNF-α-BLOCKING AGENTS

Infliximab

- A chimeric (25% mouse, 75% human) IgG1 monoclonal antibody that binds with high affinity to soluble and possibly membranebound TNF-α.

- Its mechanism of action probably is the same as that of adalimumab.

Etanercept

- A recombinant fusion protein consisting of two soluble TNF p75 receptor moieties linked to the Fc portion of human IgG1.

- It binds TNF-α molecules and also inhibits lymphotoxin-α.

TNF-α-BLOCKING AGENTS

Golimumab

- A human monoclonal antibody with a high affinity for soluble and membrane-bound TNF-α.

- Effectively neutralizes the inflammatory effects produced by TNF-α seen in diseases such as RA.

Certolizumab

- A recombinant, humanized antibody Fab fragment conjugated to a polyethylene glycol (PEG) with specificity for human TNF-α.

- Certolizumab neutralizes membrane-bound and soluble TNF-α in a dose-dependent manner.

TNF-α-BLOCKING AGENTS

Certolizumab

- Additionally, certolizumab does not contain an Fc region, found on a complete antibody, and does not fix complement or cause antibody dependent cell-mediated cytotoxicity in vitro.

Adverse Effects of TNF- α -Blocking Agents

- TNF-α-blocking agents have multiple adverse effects in common.

- The risk of bacterial infections and macrophage-dependent infection (including tuberculosis, fungal, and other opportunistic infections) is increased.

- Activation of latent tuberculosis is lower with etanercept than with other TNF-α-blocking agents.

Adverse Effects of TNF- α -Blocking Agents (Cont…)

- Increased risk of HBV reactivation.
- Increased risk of skin cancers—including melanoma
- In patients with borderline or overt heart failure (HF), TNF-α-blocking agents can exacerbate HF.
- TNF-α-blocking agents can induce the immune system to develop anti-drug antibodies in about 17% of cases.

Adverse Effects of TNF- α -Blocking Agents (Cont…)

- Injection site reactions occur in 20–40% of patients.
- Cases of alopecia areata, hypertrichosis, and erosive lichen planus have been reported.
- May increase the risk of gastrointestinal ulcers and large bowel perforation including diverticular and appendiceal perforation.
- Rarely nonspecific interstitial pneumonia, psoriasis, sarcoidosis, leukopenia, neutropenia, thrombocytopenia, and pancytopenia.

ABATACEPT

- Abatacept binds to CD80 and 86, thereby inhibiting the binding to CD28 and preventing the activation of T cells.

Adverse Effects:

- There is a slightly increased risk of infection (as with other biologic DMARDs), predominantly of the upper respiratory tract.

TOCILIZUMAB

- Tocilizumab, a humanized antibody, binds to soluble and membrane-bound IL-6 receptors, and inhibits the IL-6-mediated signaling via these receptors.

Adverse Effects:

- Similar to those of TNF-α blocking agents.

RITUXIMAB

- Rituximab is a chimeric monoclonal antibody biologic agent that targets CD20 B lymphocytes.

- Depletion of B lymphocytes reduces inflammation by decreasing the presentation of antigens to T lymphocytes and inhibiting the secretion of proinflammatory cytokines.

Adverse Effects:

- About 30% of patients develop rash with the first treatment; this incidence decreases progressively with each course of therapy and usually do not require discontinuation of therapy.

- Increased risk of infection and reactivation of hepatitis B virus (HBV) infection, not associated with either activation of tuberculosis or the occurrence of lymphomas or other tumors.

GLUCOCORTICOID DRUGS

- Corticosteroids have been used in 60–70% of rheumatoid arthritis patients. They are capable of slowing the appearance of new bone erosions.

- The corticosteroids used in arthritic conditions are usually **prednisone**, **methylprednisolone** and **prednisolone**.

- However, the short-acting **hydrocortisone** and the long-acting **dexamethasone** and **betamethasone** can also be used.

- Intra-articular corticosteroids are often helpful to alleviate painful symptoms .

- Prolonged use of these drugs leads to serious and disabling toxic effects.

NSAIDs

- NSAIDs provide analgesic and anti-inflammatory benefits for joint pain and swelling.

- However, they do not prevent joint damage or change the underlying disease.

- It is appropriate for a patient to begin taking an NSAID along with a DMARD for “bridge therapy” to provide symptomatic relief until the therapeutic effect of the DMARD is observed.

- Selecting NSAID depends on multiple patient-specific factors including cardiovascular risk, potential for gastrointestinal-related adverse events.

THANK YOU