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.
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 $\gamma$ (IFN-$\gamma$), lymphotoxin $\beta$ and TNF-$\alpha$ whereas $T_H^2$ cells predominately secret interleukin (IL)-4, IL-5, IL-6, IL-10 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-$\alpha$, 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 (binds 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: Tofacitinib (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 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.
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 arthritis. (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.
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 up to 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

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Type</th>
<th>Mode of action</th>
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<tbody>
<tr>
<td><strong>Soluble TNF-α</strong></td>
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<td></td>
<td>Adalimumab</td>
<td>Humanised monoclonal antibody</td>
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<td></td>
<td>Certolizumab pegol</td>
<td>Pegylated antibody fragment</td>
<td>Neutralisation</td>
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<td></td>
<td>Infliximab</td>
<td>Chimeric neutralising antibody</td>
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<td></td>
<td>Etanercept</td>
<td>Fusion protein decoy receptor</td>
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<td><strong>Soluble IL-1</strong></td>
<td>Anakinra</td>
<td>Recombinant human IL-1 receptor antagonist</td>
<td>Neutralisation</td>
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<tr>
<td><strong>Soluble IL-6</strong></td>
<td>Tocilizumab</td>
<td>Humanised monoclonal antibody</td>
<td>Neutralisation</td>
</tr>
<tr>
<td><strong>T cells</strong></td>
<td>Abatacept</td>
<td>Fusion protein</td>
<td>Prevents co-stimulation of T cells (binds to CD80/86 on T-cells)</td>
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<tr>
<td><strong>B cells</strong></td>
<td>Rituximab</td>
<td>Chimeric monoclonal antibody</td>
<td>Causes B cell lysis</td>
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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.
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