Antirheumatoid drugs

Disclaimer

All the content material provided here is only for teaching purpose.

Rheumatoid arthritis

- Autoimmune disorder
  - Joint inflammation
  - Non-Suppurative Proliferative Synovitis
  - Articular cartilage destruction

- Disabling Arthritis - pain, swelling, stiffness and loss of function in the joints .

Rheumatoid arthritis - Mechanism

- Immune complexes composed of IgM activates Complements
- Release of cytokines – mainly TNFα, IL-1 – chemotactic for neutrophils
- Inflammatory cells secrete lysosomal enzymes – Cartilage damage and erosion of bones
- PGs produced – Vasodilatation and pain

Antirheumatoid Drugs

- Drugs which (except corticosteroids) can suppress the rheumatoid process and bring about a remission, but do not have nonspecific antiinflammatory or analgesic action - Used in addition to NSAIDS

- Disease Modifying Antirheumatoid Drugs (DMARDs) or Slow acting Antirheumatoid Drugs (SAARDs)
  – Slow onset and relapses

- Biologic Response Modifiers (BRMs)

DMARDs:

1. Immunosuppressants: Methotrexate, Azathioprine and Cyclosporine
2. Salfasalazine
3. Chloroquine/Hydroxychloroquine
4. Leflunomide
5. Gold sod. Thiomalate, Auranofin
6. D-Penicillamine

BRM:

1. TNFα inhibitors: Etanercept, Infliximab and adalimumab
2. IL-1 antagonist: Anakinra

Adjuvant: Corticosteroids, Prednisolone and others

Treatment Goals

1. Relief of pain

2. Reduction of swelling & stiffness

3. Protection of articular structures – cartilage damage

4. Maintenance of function

5. Control of systemic involvement

Methotrexate

- One of the oldest and highly efficacious antineoplastic drug
- Primarily kills cells in S phase – inhibits DNA synthesis – also RNA and protein

MOA:

- Inhibitor of dihydrofolate reductase enzyme –immunosuppressant and potent antiinflammatory (blocks conversion of DHFA to THFA – de novo purine synthesis and amino acid interconversion) – affects lymphocyte and macrophage function

- **Kinetics:**

  Absorbed orally (variable) - 70%, affected by food. Binds to plasma protein 50%, little metabolized and largely excreted unchanged in urine – renal diseases, interaction with aspirin and probenecid (plasma protein bound)

- **Dose:**

  7.5 to 15 mg weekly Vs 15-30 mg per day

- **Uses:**

Autoimmune diseases:

RA, Psoriasis, Pemphigus, Chronic active hepatitis, Myasthenia gravis

Cancer:

Choriocarcinoma, Leukemia, NHL, Ca Breast, Bladder, Head & neck Cancer,

- Osteogenic Sarcoma

Azathioprine

- Purine antimetabolite – acts after getting converted to 6-mercaptopurine by enzyme Thiopurine methyl transferase (TPMT)

- **MOA**: Suppressions of CMI – selectively affects differentiation and function of T-cells and natural killer cells – also suppresses inflammation
- **Drawback**: Smaller percentage of success rate of treatment – less commonly used
- **Uses**: Along with Corticosteroids - Steroid sparing effect – however not to be combined with Mtx
- **ADRs**: Bone marrow suppression, GI disturbances, infection risk, Lymphomas, fever, rash, and hepatotoxicity

Sulfasalazine

- Compound of sulfapyridine and 5-amino salicylic acid (5-ASA) – antiinflammatory – used in ulcerative colitis

MOA: sulfapyridine splits off in colon by bacterial action and active compound gets (5-ASA is active in ulcerative colitis) absorbed systemically – generation of superoxide radicals and cytokine liberation suppressed

- **Uses**: 2nd line of drug in RA

- **ADRs**: Neutropenia, Thrombocytopenia, Hepatitis

BRMs – Biological Response Modifier

- TNFα has key role in RA – activates membrane bound receptors TNFR1 and TNFR2 on surface of T-cells and macrophages etc.
- Exogenously administered inhibitors or antibodies can neutralize it and interrupt reaction
- Mainly suppress Macrophage and T-cells
- Inflammatory changes and bone erosion – slowed down and also new erosions slowed down
- Effective as monotherapy, but given with Mtx – in low Mtx responsive and highly rapidly progressing cases
- Few side effects – but opportunistic infections

Infliximab

- Infliximab is a chimeric (25% mouse, 75% human) IgG1 monoclonal antibody
- Binds with high affinity to soluble and membrane-bound TNF-α.
- 3–5 mg/kg every 8 weeks intravenous infusion
- ADRs: Acute reactions – fever, chills, urticaria, bronchospasm, anaphylaxis
- Susceptibility to respiratory infections
- Combined with Mtx – improved result

Common toxicities of BRMs

- Bacterial infections and macrophage-dependent infection (TB and other opportunistic infections)
- Leukopenias and vasculitis
- Demyelinating syndromes (multiple sclerosis)
- Hepatitis, activation of hepatitis B
- Infusion/ injection site reactions
- Rarely lymphomas

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