Drugs For Arthritis

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DMARDs

- Group of agents has anti-inflammatory actions in several connective tissue diseases.
- They are called disease-modifying drugs because shows slowing or even reversal of joint damage, an effect never seen with NSAIDs.
- They are also called slow-acting antirheumatic drugs because it may take 6 wk to 6 mo for their benefits to become apparent.

Abatacept

- Abatacept is regulate immune response to prevent autoimmune disease (block T cell function)
- Abatacept can be used as monotherapy or in combination with other DMARDs.
- For patients with moderate to severe rheumatoid arthritis who have had an inadequate response to other DMARDs.
- Abatacept is given as three intravenous infusion doses (day 0, week 2 and week 4), followed by monthly infusions.

Adverse Effects of Abatacept

1. Infection (the upper respiratory tract)

   Note: Concomitant use with TNF-α antagonists is not recommended due to the increased incidence of serious infection.
2. Infusion-related reactions & hypersensitivity reactions, anaphylaxis (rare).
3. Lymphomas

Azathioprine

Mechanism of Action

- Synthetic DMARD
- Acts through its major metabolite, 6-thioguanine by.
  - Suppression of B-cell and T-cell function
  - Suppression of immunoglobulin production
  - Suppression of interleukin-2 secretion.

Pharmacokinetics of Azathioprine

- Azathioprine metabolize to rapid metabolizers & slow metabolizers.
- Production of 6-thioguanine is dependent on thiopurine methyltransferase (TPMT)
- Patients with low or absent TPMT activity are at high risk of myelosuppression by excess concentrations of the parent drug, if dosage is not adjusted.

Indications of Zathioprine

- Rheumatoid arthritis
- Psoriatic arthritis
- Reactive arthritis
- Polymyositis
- Systemic lupus eythematosus
- Behcet’s disease.

Adverse Effects of Azathioprine

- Bone marrow suppression
- GI disturbances
- Infection
- Lymphomas
- Fever, rash and hepatotoxicity acute allergic reactions (rarely)

Chloroquine and Hydroxychloroquine

- Malaria (mainly used)
- Rheumatic diseases.

Mechanism of Action

The anti inflammatory mechanisms have been proposed:

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

Pharmacokinetics of Chloroquine and Hydroxychloroquine

- Rapidly absorbed
- 50% protein-bound in the plasma.
- Extensively tissue-bound, particularly in melanin-containing tissues such as the eyes.
- Half-lives of up to 45 days
- The drugs are deaminated in the liver

Indications of Chloroquine and Hydroxychloroquine

- Treatment of malaria , improve symptoms
- Rheumatoid arthritis , it usually takes 3-6 months to obtain a response.

  Note: they are not alter bony damage in rheumatoid arthritis at their usual dosages (dose-loading may increase rate of response).
- Skin manifestations, joint pains of systemic Lupus erythematosus.
- Sjogren's syndrome

Adverse Effects of Chloroquine and Hydroxychloroquine

- Ocular toxicity (rarely occurs at low doses).

  Note: Ophthalmologic monitoring every 12 months
- GIT adverse effect, dyspepsia, nausea, vomiting and abdominal pain
- Rashes
- Nightmares
- Relatively safe in pregnancy.

Cyclophosphamide

Mechanism of Action of Cyclophosphamide

- Synthetic DMARD
- Its major active metabolite is phosphoramide mustard, which cross-links DNA to prevent cell replication.
- It suppresses T-cell and B-cell function by 30-40%

Indications of Cyclophosphamide

- Rheumatoid arthritis when given orally at dosages of 2 mg/kg/d but not intravenously.
- Systemic lupus erythematosus
- Vasculitis
- Wegener's granulomatosis
- Other severe rheumatic diseases.

Cyclosporine
Mechanism of Action

- Cyclosporine is a peptide antibiotic
- Regulats gene transcription
- Inhibits interleukin-1 and interleukin-2 receptor production
- Inhibits macrophage-T-cell interaction and T-cell responsiveness

Pharmacokinetics

- Cyclosporine absorption is incomplete and erratic
- Bioavailability is 20-30%
- Grapefruit juice increases cyclosporine bioavailability by as much as 62%.
- Cyclosporine is metabolized by CYP3A
- Have drug interactions

Indications of Cyclosporine

1. Rheumatoid arthritis, retards the appearance of new bony erosions.
2. Systemic lupus erythematosus
3. Polymyositis
4. Dermatomyositis
5. Wegener's granulomatosis
6. Juvenile chronic arthritis.

Adverse Effect of Cyclosporine

- Leukopenia, thrombocytopenia and anemia
- High doses can be cardiotoxic
- Sterility after chronic dosing at anti-rheumatic doses, especially in women.
- Bladder cancer (rare), must be looked for, even 5 years after cessation of use.

Leflunomide

Mechanism of Action of Leflunomide

- Undergoes rapid conversion, both in the intestine and in the plasma, to its active metabolite, which decrease in ribonucleotide synthesis
- Arrest of stimulated cells in the G1 phase of cell growth.
- leflunomide inhibits T-cell proliferation and production of auto antibodies by B cells.

Pharmacokinetics of Leflunomide

- It is completely absorbed
- Half life of 19 days.
- Its active metabolite, have the same half-life and is subject to enterohepatic recirculation.
- Cholestyramine can enhance leflunomide excretion and increases total clearance by approximately 50%.

Indications of Leflunomide

- Rheumatoid arthritis (inhibition of bony damage)

  Note: Combintion treatment with methotrexate and leflunomide resulted in increase response than treatment with methotrexate alone.

Adverse Effects of Leflunomide

- Diarrhea & elevation in liver enzymes Both effects can be reduced by decreasing the dose of leflunomide.
- Mild alopecia, weight gain & increased blood pressure.
- Leukopenia and thrombocytopenia (rarely)
- Teratogenic

Methotrexate

- A synthetic antimetabolite
- The first-line DMARD for treatment of rheumatoid arthritis
- Doses of methotrexate required for this treatment are much lower than those needed in cancer chemotherapy (once a week)

Mechanism of Action

Methotrexate's principal mechanism of action at the low doses used in the rheumatic diseases

- Accumulation of AMP and its conversion extracellularly to adenosine (a potent inhibitor of inflammation)
- Suppress the inflammatory functions of neutrophils, macrophages and lymphocytes
- Secondary effects on polymorphonuclear chemotaxis.
- Direct inhibitory effects on proliferation
- Stimulates apoptosis in immune-inflammatory cells.
- Inhibition of proinflammatory cytokines linked to rheumatoid synovitis.

Pharmacokinetics of Methotrexate

- 70% absorbed after oral administration
- It is metabolized to a less active hydroxylated metabolite.
- Half-life 6-9 hours, it may be as long as 24 hours in some individuals.
- Hydroxychloroquine, reduce the clearance or increase the tubular reabsorption of methotrexate.
- Drug is excreted in the urine, 30% in bile.

Indications of Methotrexate

1. Rheumatoid arthritis (decreases the rate of appearance of new erosions).
2. Juvenile chronic arthritis
3. Psoriatic arthritis
4. Ankylosing spondylitis
5. Polymyositis, dermatomyositis
6. Wegener's granulomatosis
7. Systemic lupus Erythematosus
8. Vasculitis.

Adverse Effects

- Nausea and mucosal ulcers (most common toxicities)
- Leukopenia, anemia, stomatitis, GI ulcerations and alopecia as a result of inhibiting cellular proliferation.
- Liver enzyme elevation, cirrhosis is rare (<1%).
- Rare hypersensitivity-acute shortness of breath
- The incidence of GI and liver function test abnormalities can be reduced by the use of leucovorin 24 hours after each weekly dose **or** daily folic acid

  Note: this may decrease the efficacy of the methotrexate by about 10%.
- Teratogenic

Sulfasalazine

Mechanism of Action

- Synthetic DMARD
- Metabolized to sulfapyridine and 5-aminosalicylic acid.
- The sulfapyridine is the active moiety when treating rheumatoid arthritis, unlike inflammatory bowel disease.
- Sulfasalazine, cause decrease IgA and IgM rheumatoid factor production, Suppress of T-cell responses
- Sulfasalazine or its metabolites inhibit the release of inflammatory cytokines (interleukins-1 &TNF-α)

Pharmacokinetics of Sulfasalazine

- Absorption of oral dose is 10-20%
- Half-life is 6-17 hours
- Undergoes enterohepatic recirculation
- Intestinal bacteria liberate sulfapyridine and 5-aminosalicylic acid
- Sulfapyridine is well absorbed while 5-aminosalicylic acid remains unabsorbed.
- Sulfapyridine is excreted after hepatic metabolism
- Some of it excreted unchanged in the urine

Indications of Sulfasalazine

- Rheumatoid arthritis
- Juvenile chronic arthritis
- Ankylosing spondylitis

Adverse Effects of Sulfasalazine

- Nausea, vomiting, headache and rash.
- Neutropenia, Hemolytic anemia. Methemoglobinemia, thrombocytopenia and are very rare.
- Pulmonary toxicity
- Drug-induced lupus (rare)
- Reversible infertility occurs in men
- Teratogenic.

TNF-α blocking agents

TNF-α

- It is cytokine that play important role in the immune response and in inflammatory process of rheumatoid arthritis
- TNF-α activate TNFR 1 & TNFR 2
- When secreted by synovial macrophages, TNF-α stimulate synovial cells to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption and inhibiting proteoglycan synthesis.
- Biologic DMARDs interfering with TNF-α and used for treatment of rheumatoid arthritis and other rheumatic diseases

Adalimumab

- It is a fully human IgG 1 anti-TNF monoclonal antibody.
- It complexes with soluble TNF-α and prevents its interaction to cell surface receptors.
- This results in down-regulation of macrophage and T-cell function.
- Administered subcutaneously weekly or every other week
- Indicated for treatment RA, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis
- It is effective both as monotherapy and in combination with methotrexate and other DMARDs.

Adverse Effects

- Tuberculosis and other opportunistic infections
- Leukopenia, vasculitis & lupus (rare)

Infliximab

- It is a chimeric (25% mouse, 75% human) IgG 1 monoclonal antibody
- The same mechanism of action of adalimumab
- Binds with high affinity to soluble and possibly membrane-bound TNF-α.
- Infliximab is given as an intravenous infusion with “induction” at 0, 2 and 6 weeks and maintenance every 8 weeks
- Infliximab elicits human antichimeric antibodies in up to 62% of patients.
- Concurrent therapy with methotrexate markedly decreases the prevalence of human antichimeric antibodies.

Indications of Infliximab

- Rheumatoid arthritis
- Ankylosing spondylitis
- Psoriatic arthritis
- Crohn's disease
- Ulcerative colitis
- Juvenile chronic arthritis
- Wegener's granulomatosis

Note: In rheumatoid arthritis, a regimen of infliximab plus methotrexate decreases the rate of formation of new erosions more than methotrexate alone

Adverse Effects of Infliximab

- Bacterial infections, including upper respiratory tract infections (because it is a potent macrophage inhibitor)
- Activation of latent tuberculosis
- Demyelinating syndromes (rare), patients with multiple sclerosis or neuro-uveitis should not use infliximab.
- Rare cases of leukopenia, hepatitis, activation of hepatitis B and vasculitis
- Lupus erythematosus
- Infusion site reactions correlate with anti-infliximab antibodies.

Etanercept

- It is a recombinant agent
- Binds TNF-α molecules & also inhibits lymphotoxin-α.
- It is given subcutaneously
- Slowly absorbed
- Peak concentration 72 hours after drug administration Etanercept is approved for the treatment of rheumatoid arthritis, juvenile chronic arthritis, psoriasis, psoriatic arthritis and ankylosing spondylitis & Wegener's granulomatosis.
- It can be used as monotherapy, although over 70% of patients taking etanercept are also using methotrexate.

Adverse Effects of Etanercept

- Bacterial infections
- Activation of latent tuberculosis

  Note: Patients should be screened for latent or active tuberculosis before starting this medication.
- Opportunistic infections
- Solid malignancies, lymphomas
- Injection site reactions

Corticosteroids

- Corticosteroids can be considered anti-inflammatory drugs with an intermediate rate of action (ie, slower than NSAIDs but faster than other DMARDs).
- The corticosteroids are too toxic for routine chronic use and give temporary control of severe exacerbations.
- Slow the appearance of new bone erosions.
- When prednisone is required for long-term therapy, the dosage should not exceed 7.5 mg daily, and gradual reduction of the dose should be encouraged.
- Intra-articular corticosteroids are often helpful to alleviate painful symptoms