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Drugs use in RA and their side effects

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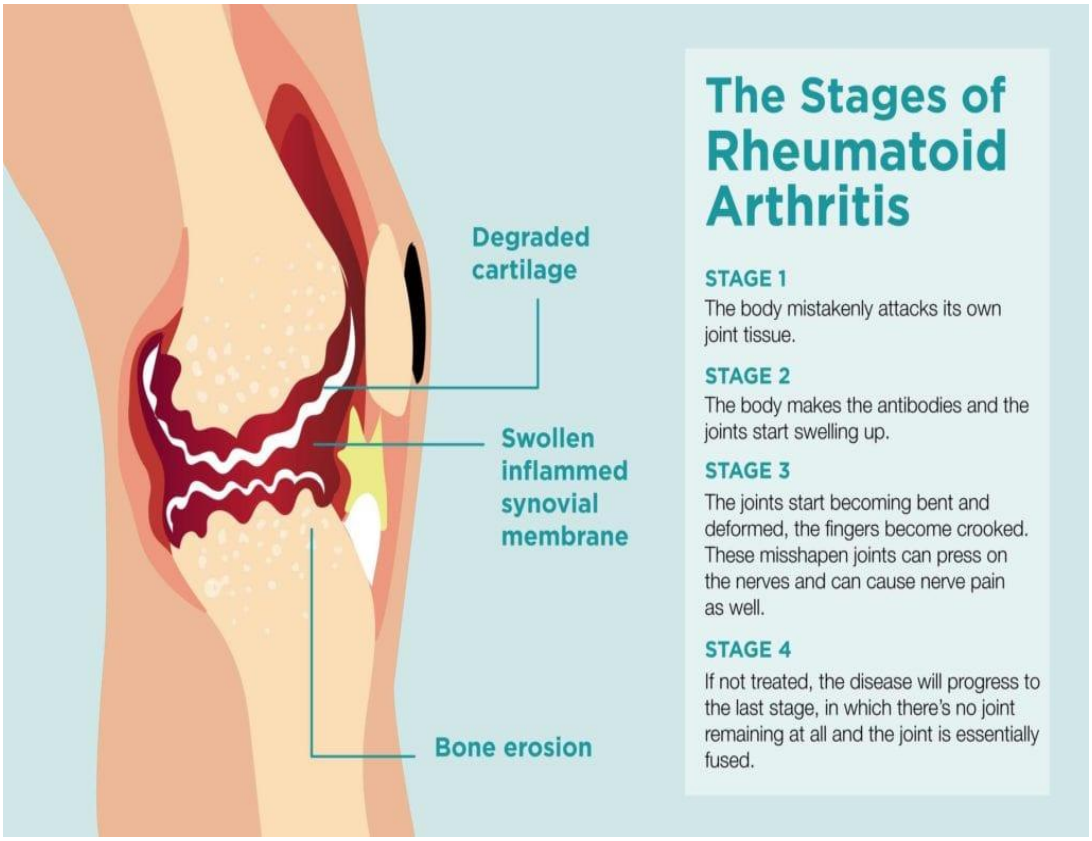
Rheumatoid arthritis (RA) is an autoimmune disease in which there is joint inflammation, synovial proliferation and and destruction of articular cartilage.



Immune complexes composed of IgM active complement and release cytokines (mainly TNF alpha and IL-1) which are chemotactic for neutrophils.These inflammatory cells secrete lysosomal enzymes which damage cartilage and erode bone,while PGs produced in the process cause vasodilation and pain.RA is a chronic progressive,cripping disorder with a waxing and waning course.NSAIDs are the first line drugs and afford symptomatic relief inpain,swelling,morning stiffness,immobility,but do not arrest the diseases process.

The goals of drug therapy in RA are :

- Ameliorate pain, swelling and joint stiffness
- Prevent articular cartilage damage and bone erosions
- Prevent deformity and preserve joint function

Though mild/early cases are still mostly treated only with NSAIDS, the current recommendation is to add DMARDS as soon as the diagnosis of RA is confirmed. However, use of DMARDS in early/mild RA should be weighed against their potential adverse effects, which may be serious. More than one DMARDS may be used concurrently ; advanced cases may required 2 or 3 drugs together, because all DMARDS tend to lose

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effectiveness with time. Rheumatoid arthritis medications are often most effective in combination

Following are main types of drugs used in RA.

- Nonsteroidal anti-inflammatory drugs (NSAIDS)
- Disease -modifying anti-rheumatic drugs (DMARDS)
- Biologic response modifiers
- Glucocorticoids
- Analgesics (painkillers)

NSAIDS is considered as first line drugs for Rheumatoid arthritis. Therapy with NSAIDS in patients of RA is used to relieve pain, inflammation and muscle stiffness. NSAIDS improve clinical indices of disease activity but have no effect on the underlying disease

process e.g plasma viscosity, joint swelling or its progression e.g joint destruction

Disease modifying anti rheumatoid drugs (DMARDS) are used to modify the course of the disease and induce remission, particularly when NSAIDS become ineffective and there is radiological evidence of joint destruction. The effects of this group of drug may take 4 weeks to 1 year to appear and thus they are slow acting compared to NSAIDS. Thus they are also called slow acting anti-rheumatic drugs (SAARDS). Systemic corticosteroids tend to be reserved for cases with inflammation so severe that it cannot be controlled by second line drugs.

NSAIDS mechanism of action

NSAIDS produce Anti-inflammatory and analgesia effects and thus are useful in the treatment of RA.

Analgesia: NSAIDS blocks painsensitizing mechanism induced by bradydykinin, TNF alpha, interleukins (ILS) and other analgesic substances primarily by inhibiting COX-2. This constitutes the peripheral component of the analgesic action of NSAIDS.

NSAIDS has also been shown to involve inhibition of PG synthesis in the spinal dorsal horn neurons as well as in brain, so that PG mediated amplification of pain impulse does not occur. They are therefore more effective against inflammation associated pain.

Antiinflammatory : The most important mechanism of anti-inflammatory action of NSAIDS is considered to inhibit COX-2 mediated enhanced PG synthesis at the site of injury. However, there is some evidence that inhibition of the constitutive COX-1 also contributes to suppression of inflammation, especially in initial stages.

Examples of NSAIDS :

Sr no	Name of the Drug	Mechanism of action	Dose	Side effects
1	Celecoxib	Selectively inhibits COX-2 enzyme	100-200mg BD.	• Diarrhea • Stomach pain • Increased risk of heart attack and stroke.
2	Diclofenac sodium	Inhibits PG synthesis and somewhat COX-2 selective inhibition	50-75 mg TDS, then BD oral, 75 mg deep i.m.	Generally mild: • Epigastric pain • Nausea • Headache • Dizziness • Rashes • Heartburn • Ulcer or bleeding, • Increased risk of blood clots and stroke. • Greater risk of complications for people with cardiovascular disease.
3	Ibuprofen	It is non selective COX inhibitor.	400- 600 mg TDS.	• Nausea • Vomiting ulcer etc.
4	Naproxen	Inhibits leucocyte	250 mg BD-	• Mild dyspepsia to

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		migration.	TDS.	nausea, vomiting, • Gastric bleeding, • Drowsiness • Headache • Depression • Jaundice • Renal impairment • Thrombocytopenia, • Agranulocytosis, • Angioneneurotic edema.
5	Sulindac	It inhibits both COX-1 and COX-2 which leads to inhibition of PG synthesis.	200 mg BD	• Nausea • Abdominal pain • Dizziness • Drowsiness and headache rashes are rare.
6	Etodolac	Inhibits PG synthesis	200- 300 mg TDS	• Abdominal pain and dyspepsia associated with low rate of GI ulceration.
7	Mephenamic acid	Non selective COX inhibition.	250-500 mg TDS.	• Diarrhoea • Epigastric distress • Skin rashes • Dizziness • Haemolytic anaemia is rare but serious complications.

DMARDS

DMARDS can often slow down or stop the progression of disease however they may take long time for showing their effect. DMARDS are often used with NSAIDS or glucocorticoids. It inhibits cytokine production, chemotaxis and cell-mediated immune reaction proliferation of immune-inflammatory cell is inhibited. Use of analgesic is not required while patient is taking DMARDS.

Examples of DMARDS :

sr no	Name of the Drug	Mechanism of action	Dose	Side effects
1	Methotrexate	inhibits cytokine production.	2.5 mg 2 to 4 times a week	• Oral ulceration • G.I. upset • Chills • Dizziness • Headache • Light sensitivity • Itching • Chest infection • Dose dependant progressive liver damage leading to cirrhosis.
2	Leflunomide	Inhibits proliferation of	It is given in loading dose of	• Diarrhoea • Headache

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		stimulated lymphocytes in patients with active RA. Arthritic symptoms are suppressed and radiological progression of disease is retarted.	100 mg daily for 3 days followed by 20 mg OD	• Nausea • Rashes • Loss of hair • Thrombocytopenia • Leucopenia • Chest infections • Dizziness • Gastrointestinal or liver problems • Neuropathy
3	Hydroxychloroquine	Their exact mechanism of action is not known, however they have been found to reduce monocyte IL-1,consequently inhibiting B lymphocytes.	400 mg/day for 4-6 weeks, followed by 200mg/day.	• Retinal damage • Corneal opacity • Rashes • Graying of hair • Irritable bowel syndrome • Myopathy • Neuropathy
4	Tofacitinib	It is a JAK-3 and JAK-1 kinase inhibitor, interferes with JAK-STAT signaling pathway, production of inflammatory meadiators and release of cytokines is inhibited	5 mg BD	• Headache • Insomnia • Diarrhoea • Hypertension • Anaemia • Susceptibility to respiratory infections • Flaring of tuberculosis • Liver damage.
5	Sulfasalazine	Exact MOA is not known, exerts anti-inflammatory effect.	1 to 3 g/day in 2-3 divided doses	• Neutropenia/ thrombocytopenia occurs in about 5-10% patients, • Hepatitis is possible
6	Baricitinib	It selectively inhibits Janus kinase mediator (JAK1 and JAK 2) which are essential mediators of for pro-inflammatory cytokines.	2 mg once a day.	• Upper respiratory tract infections • Headache • Diarrhea • Blood clots in intestine
7	Upadacitinib	Inhibits janus kinases (JAKs) mediators.	15-30 mg daily	• Upper respiratory tract infections • Cough • Fever • Nausea • Blood clotting

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Biological agents:

Biological agents or biologic response modifiers are a type of DMARDS, which target the part of immune system that produce inflammation and joint destruction. Biological agents can improve patient's condition and reduce symptoms. This drugs are recombinant proteins/ monoclonal antibodies that bind to and inhibit cytokines, especially TNF-alpha or IL-1 have been produced and found to afford substantial benefit in autoimmune disease like RA, inflammatory bowel disease, psoriasis, scleroderma, etc.

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

MOA : Most of biological agents used in RA works by inhibiting TNF alpha. Because cytokine TNF alpha plays a key role in the inflammatory cascade of RA by activating membrane bound receptors (TNFR1 and TNFR2) on the surface of T-cells, macrophages, etc., exogenously administered soluble TNF-receptor protein or antibody can neutralize it and interrupt the reaction. TNF inhibitor mainly suppress macrophage and T-cell function; inflammatory changes in the joint regress and new erosions are slowed. Quicker response than nonbiologic DMARDS has been obtained.

With this drugs, susceptibility to opportunistic infections, including tuberculosis and pneumocystis pneumonia is increased, because TNF alpha plays important role in combating bacterial infection.

Examples of biological agents:

Sr no	Name of the drug	Mechanism of action	Dose	Side effects
1	Etanercept	It binds and prevents TNF alpha from activating TNF receptors on the membrane of T-cells/ macrophages	25-50 mg s.c. once or twice weekly.	• Pain, redness, itching and swelling occur at injection site • Fatigue • Neurological events Rare complications: • Increased risk of malignancy • Chances of chest infections, TB, and bacterial and fungal infections.
2	Infliximab	It is a chimeral monoclonal antibody which binds and neutralizes TNF alpha.	3-5 mg/kg is infused i.v every 4-8 weeks.	• Headache • Rashes • Fatigue • An acute reaction comprising of fever, chills, urticaria, bronchospasm , rarely anaphylaxis may follow the infusion. • Susceptibility to respiratory infections is increased and worsening of CHF has been noted. Rare complications include : • Development of tuberculosis • Fungal infections
3	Adalimumab	It is a recombinant human monoclonal anti-TNF antibody	40 mg s.c every 2 weeks.	• Redness ,pain ,itching, brushing at site of administration • Upper respiratory tract

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				infection • Other infections like TB, bacterial, viral and fungal infections.
4	Anakinra	It is a recombinant human IL-1 receptor antagonist	100 mg s.c daily.	• Local reactions at site of administration − Redness, swelling, pain, bruising etc. • Low white blood cell count • Upper respiratory infections • TB • Infections from bacteria, fungi or viruses.
5	Abatacept	It is a recombinant fusion protein which combines part of Fc domain of human IgG with extracellular domain of T-cell inhibitory receptor CTLA4. By binding to CD80 and CD86 molecules, it prevents the 2nd signal for constimulation of T-cells. It is used in severe active RA.	250 mg by i.v. infusion as well as s.c. injection	• Cough • Dizziness • Headache • Increased chances of infections
6	Rituximab	This chimerized monoclonal antibody depletes B- lymphocytes.		• Abdominal pain • Chills of fever • Headache • Itching • Infections Serious side effects includes: • Infusion reaction • Tumor lysis syndrome • Severe skin reaction • Serious infections such as- TB, bacterial, viral and fungal infections.

Corticosteroids:

Glucorticoids or corticosteroids have potent immunosuppressant and anti-inflammatory activity. They can be induced almost at any stage in RA along with first or second line drugs.

Their symptomatic relief is prompt and marked, but they do not arrest the rheumatoid process, though joint destruction may be slowed and bony erosions delayed

Since long term use of corticosteroids carries serious risk of side effects, it is generally recommended that this drugs should be used only for brief periods.

In case of single or few joint involvement with severe symptoms, intraarticular injection of a

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soluble glucocorticoid affords relief for several weeks; joint damage may be slowed. This procedure should not be repeated before 3-4 months.

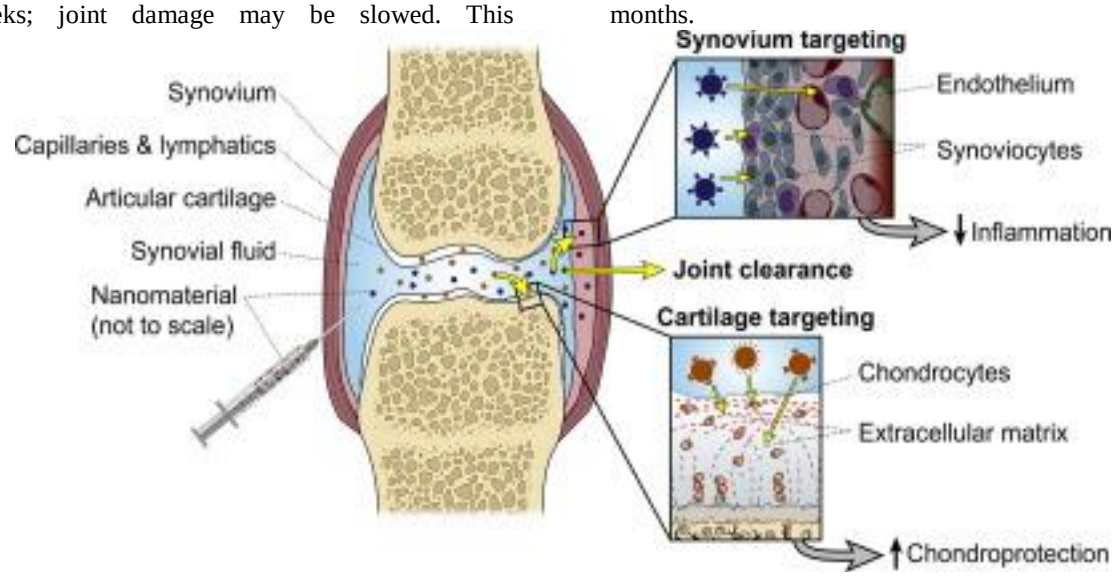

Fig: Intra-articular corticosteroid injection for RA

Sr no	Name of the drug	Mechanism of action	Dose	Side effects
1	Prednisone	Inhibits clonal proliferation of Th1 cells through decreasing the transcription of the gene for IL-2 and decrease many cytokine transcription (TNF alpha and IL-1) during the phase of immune response	5-60 mg/day oral, 10 -40 mg i.m., intraarticular.	• Bruising • Cataracts • Increased cholesterol level • Atherosclerosis • High blood pressure • Increased appetite • Mood swings • Muscle weakness • Osteoporosis • Infections
2	Methyl prednisolone	Decreases cytokine transcription (TNF alpha and IL-1) during the phase of immune response.	4-32 mg/ day oral i.v − 1g infused every 6-8 weeks	• Upset stomach • Vomiting • Headache • Trouble sleeping • Depression • Anxiety • Bruising • Skipped or irregular periods.
3	Betamethasone	Decrease cytokine transcription during the phase of	0.5- 5 mg/day oral, 4-20 mg i.m, i.v injection for	• Bruising • Cataracts • Increased

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		immune response.	infusion.	cholesterol • Atherosclerosis • High blood pressure • Increased appetite • Mood swings, nervousness • Muscle weakness • Osteoporosis • Infections

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