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RESEARCH ARTICLE OPEN ACCESS

Comprehensive Review on Rheumatoid Arthritis

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Abstract

Immunosuppressant drugs are a class of drugs that suppress, or reduce the strength of the body immune system. Some of these drugs are used to make the body less likely to reject a transplanted organ such as liver, heart, kidney.Rheumatoid arthritis is an inflammatory diseases mainly affect the joints . A chronic progressive disease causing inflammation in joints and resulting in painful deformity and immobility in joints .It also called as RA.RA is affecting 1% of population worldwide This review discusses our understanding of RA pathogenesis, disease modifying drugs, and provides perspective on next generation therapeutics for RA.

Keywords- RA , pathogenesis, deformity, immobility.

Introduction

Immunity is resistance of an organism to infection or disease , immunity is state of sufficient biological defences to avoid infection , disease or other unwanted biological invasion . Immunosuppressant drugs are weaken your immune system to reduce your body reaction against foreign organ.

Immunosuppressive drugs also known as immunosuppressive agents, immunosuppressant and antirejection medication are drugs that inhibits or prevent activity of immune system.

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Other disease treated with immunosuppressant drug

- Psoriasis
- Rheumatoid arthritis
- Crohn's disease
- Multiple sclerosis
- Alopecia areata

A autoimmune chronic inflammatory disorders affecting many joints including those in hands and feet. In RA body's immune system attacks it's own tissue, including joints. In severe cases it attack internal organs.

RA commonly affects joints in hands, wrists, knees. In joint RA, lining of joint becomes inflamedcausing damage to joint tissue; which causes long lasting or chronic pain, lacks of balance and deformity.

RA is best characterized as immune mediated inflammatory diseases (IMID). There is no cure for RA; most cases can be managed with class of medication called anti-rheumatic drugs (DMARDS).

The goals of drug therapy in RA are-:

- Ameliorate pain
- Swelling pain
- Joint stiffness
- Prevent articular cartilage
- Bony erosion
- Prevent deformity
- Preserve joint function

History

First description of RA found by **Augustin Jacob landre- beauvais** from year 1800.he was resident physician in France when he first noticed symptoms and sign of RA .he examined and treated a handful of patients with joint pain that cannot explained by other at the time (rheumatism or osteoarthritis) . He hypothesized that patients were suffering from a such conditions , which he name "**Goutte asthenique primitive or primary asthenic gout".**

Next important contributor to study of RA was **Alfred garrod** at late 19th century an English physician , 1st to distinguish gout from other arthritic condition. He found excess

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uric acid in patients blood which suffering from gout, but not in other which suffering from arthritis. 1859 he wrote treatise on **"Nature of good and rheumatic gout".** This work differentiated arthritis from gout and categorized RA as rheumatic gout.

The name rheumatoid arthritis was coined in 1859 by British rheumatologist **Dr.Alfred baring garrod.**

Etymology

Rheumatoid arthritis is derived from the Greek word ῥεύμα-rheuma(nom), ῥεύματος-rheumatoid (gen) ("flow current). The suffix -oid ("resembling") gives the translation as joint inflammation that resembles rheumatic fever .Rhuma which means watery discharge might refer to the fact that the joints are swollen or that the disease may be made worse by wet weather.

Classification

1.Disease modifying antirheumatic drug

A .Nonbiological drugs

1.Immunosuppressants -methotrexate, azathioprine, cyclosporine

2.sulfasalazine

3.chloroquine

4.leflunomide

B. Biological agents

1.TNF{ inhibitors:- Etanercept, Infliximab, Adalimumab

2. IL- 1 antagonist -Anakinra

2.Adjuvant drugs

Corticosteroid- prednisolone, and others

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Etiology

The cause of RA is unknown .The tendency to develop RA may be genetically inherited certain environment factor may trigger the immune system to attack body's own tissue , resulting in inflammation in various body organs such as lungs or eyes.

For example:- Smoking tobacco increase the risk of developing RA.

Other factors involved in RA as follows

1) **Environmental influences-:** infections or trauma ,trigger the development of RA
2) **Genetic markers-:** human leukocytes antigen DR4 (HCA- DR4) associated with triggering the inflammatory process in RA.
3) **Antigen- dependent activation of T lymphocytes-:** activation of proinflmmatory cells from bone marrow cytokine and protease secretion, autoantibody production.
4) **Anticitrullinated protein and peptides -:** are highly specific to RA
5) **Tumor necrosis factor-:** TNF, IL-1, IL-6, IL-8, growth factor propagate the inflammatory process.
6) **Inflamed synovium-:** hallmark of pathophysiology of RA. Synovium- proliferates abnormally , growing into joints space and into bone, forming a pannus, pannus migrates to articular cartilage leading to destruction of cartilage , bone, blood vessels.

B) Predisposing factors

1) Gender- before the menopause woman are three times more affected than men. The use of oral contraceptive pill has no effect on RA.

2) Familial – In occasional families it affects several generations.

C) Genetic Factor- 60% of disease susceptibility.

Pathophysiology

1) In RA, immune system identifies the synovial membrane as "**foreign and begins"** attacking it.
2) With long term exposure to antigen normal antibodies become auto- antibodies that Target antigen in synovial membrane.
3) Once it reaches antigen presenting cell deals with it.

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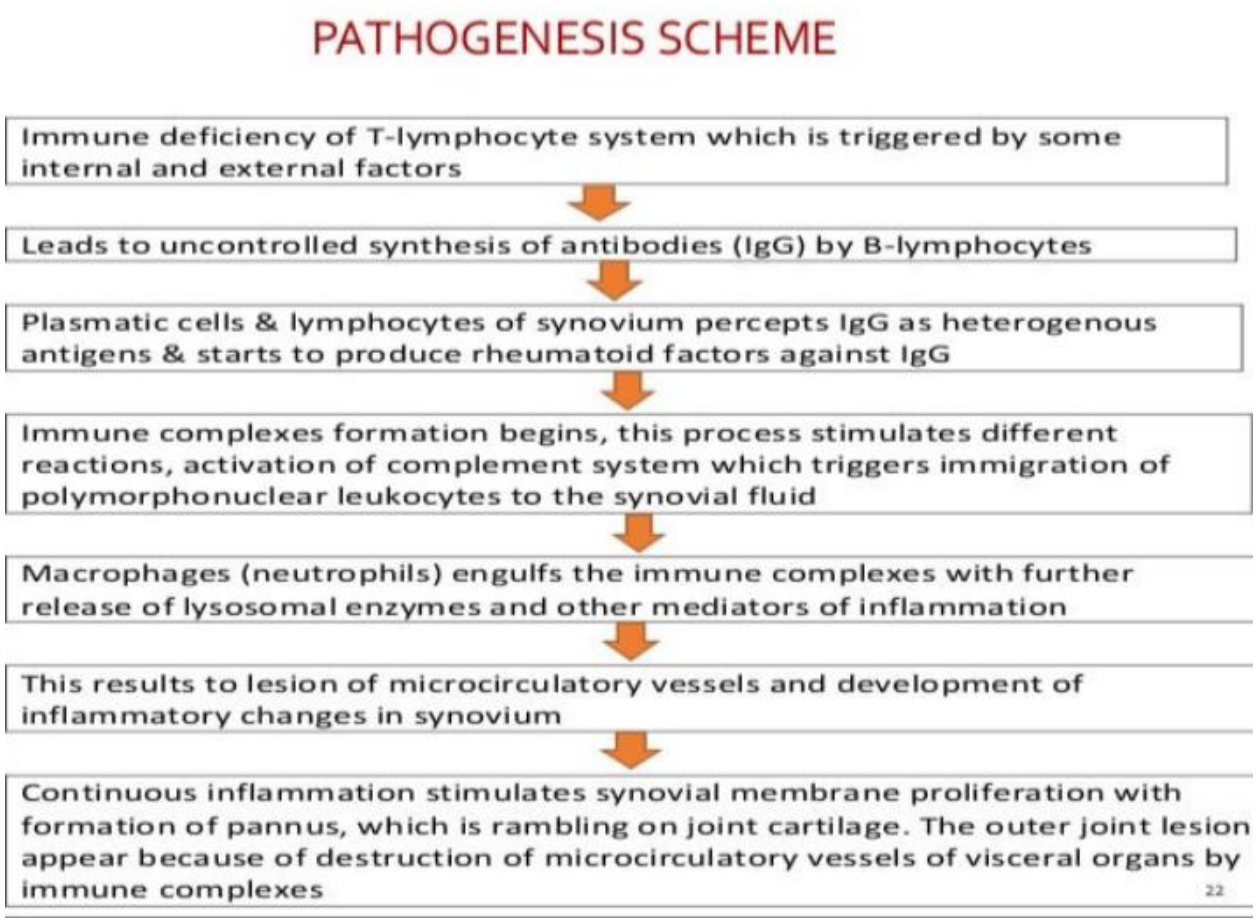
4) APC usually a macrophage in synovium- engulfs the antigen.
5) Peroxide inside APC break down antigen into smaller particles.
6) Antigen transported to surface of APC binds with MHC
7) This complex persecuted to T cells which T cell receptor recognizes and binds to .
8) Once T cell binds to MHC complex, APC secrete cytokines like IL-1, IFN-a, IFN-9 , TNF.



Signs and symptoms

- Pain
- Swelling

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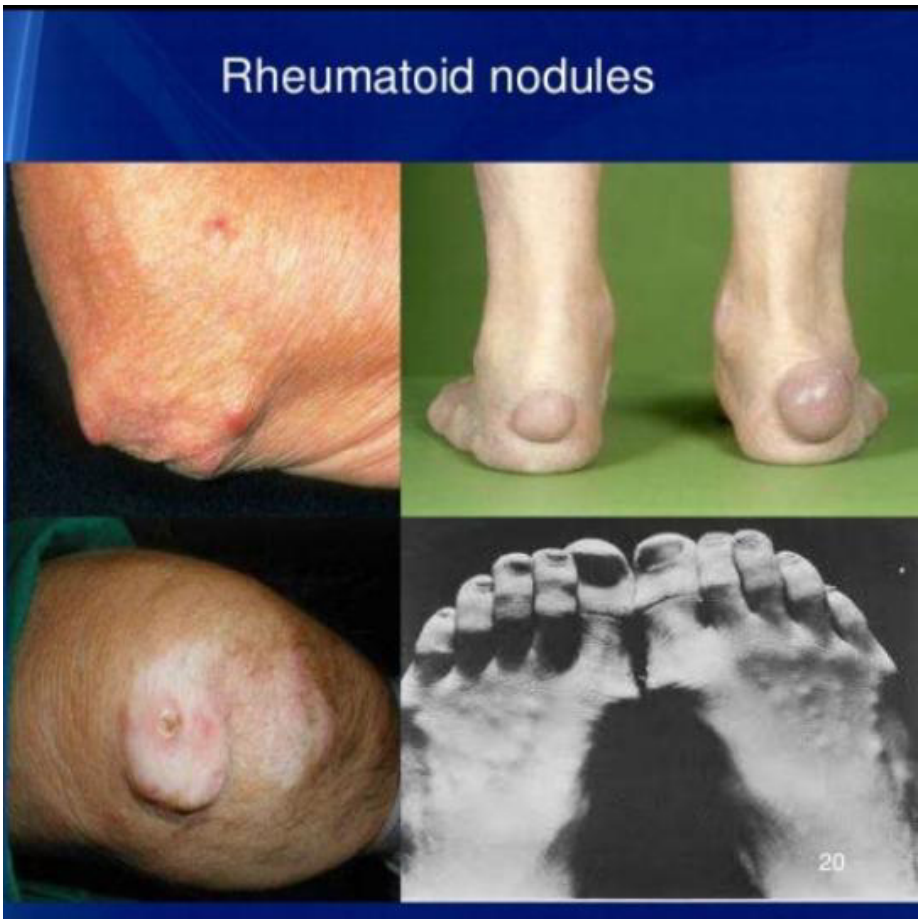
- Stiffness and tenderness in more than one joint
- Stiffness especially in morning or after sitting for long periods.
- Pain and stiffness in same joints on both sides of your body
- Fatigue
- Weakness
- Fever
- Rheumatoid nodules
- Raynaud'sPhenom



Progressive changes in joints-

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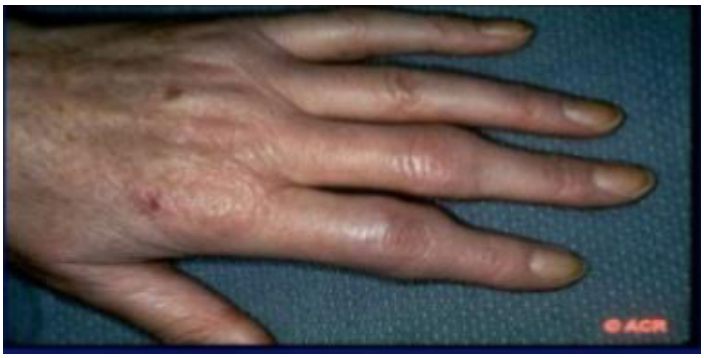
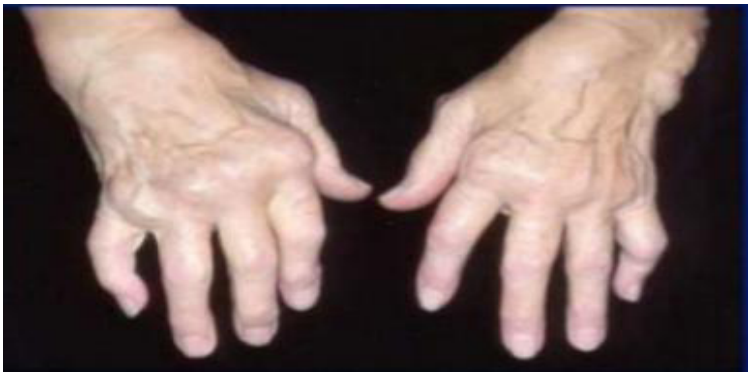
Stage I- Inflammation of synovial membrane spread to other soft tissue and cartilage , causes pain and reduce joint movement and spasm in muscle.

Stage II- Granulation tissue formation within synovial membrane and spread to periarticular tissue, cartilage disintegration and joint filled with granulation . Thickening joint and impaired joint movement permanently.

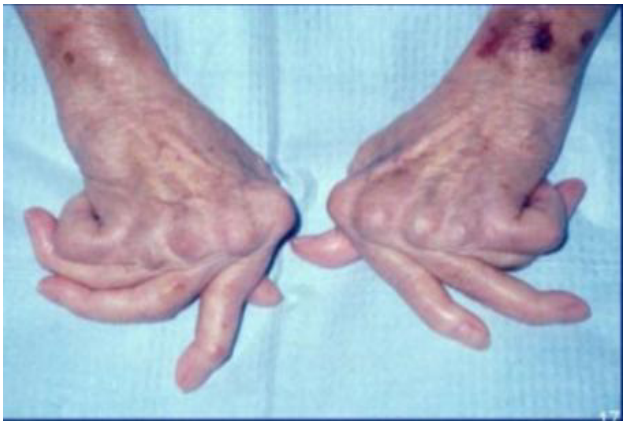
Stage III- granulation tissue converted into fibrous tissue with adhesion formation between tendon , joint capsule articular surface. Articular surface cover by cartilage and fibrous tissue.



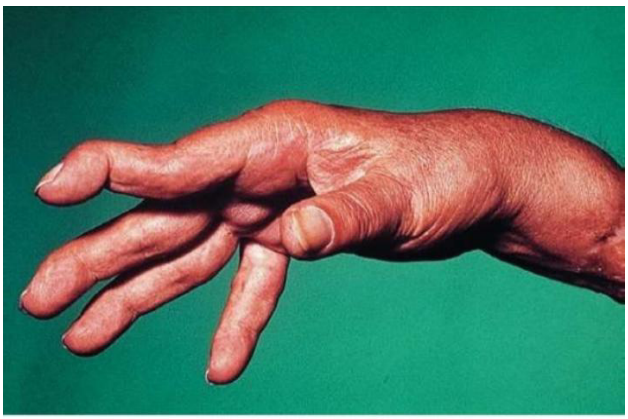


Stage IV- permanent joint damage and deformity causes disability.

Stage- I.



Stage-Ii



'Swan neck' deformity of the fingers.

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Stage-III

Joint involvement in RA

- Hand
- Wrists
- Shoulder
- Elbow
- Feet
- Knees
- Hips
- Cervical spine

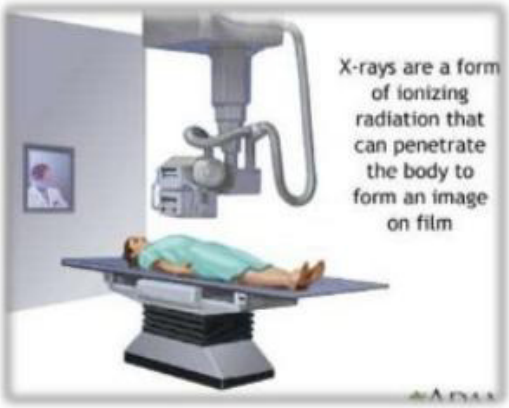
Diagnosis

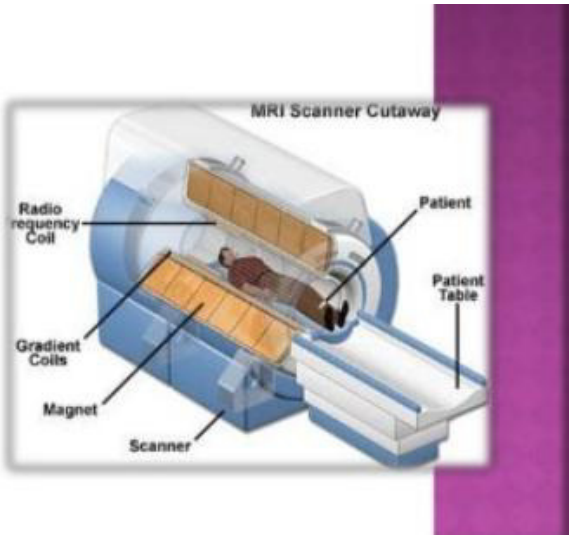
A) **Personal and family medical history-** doctor asked your past and your relatives , if someone in your family tree has RA.

B) **Physical exam-** Doctor check your joints for swelling tenderness, range of motion.

C) **Imaging tests**

- **X-rays** – show how much joint damage.
- **Magnetic resonance imaging (MRI) and ultrasound-** give detailed pictures of joints. These scan aren't diagnose RA, but helps doctors find it early.





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D) Blood tests

- **Rheumatoid factor (RF)-** RF is specific antibody in blood negative RF does not rule out RA, called sero negative.
- **Anti- citrullinated protein antibodies (ACPAS)-** This testing is positive in proportion of all RA cases. This test is rarely positive , if RA is not present , give specificity about 95%.

Other blood tests performed when RA is suspected

- **Erythrocytes sedimentation rate (ESR)-** rate at which RBC precipitate in one hour period.
- **C- reactive protein-** protein found in blood in response to inflammation.
- **Full blood count-** information about all blood cell .
- **Renal function-** kidney function
- **Liver enzymes-** information about on which state patients liver is.

Fig- synovial fluid examination

Type	WBC per mm^3	% neutrophils	Viscosity
Normal	<200	0	High
Osteoarthritis	<5000	<25	High
Trauma	<10,000	<50	Variable
Inflammatory	2,000–50,000	50–80	Low
Septic arthritis	>50,000	>75	Low
Gonorrhea	~10,000	60	Low
Tuberculosis	~20,000	70	Low

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Treatment

There is no cure for RA but clinical studies Indicate that remission of symptoms is more likely when treatment begins early with medications as disease modifying antirheumatic drug (DMARDS).

Medication

Drug class	Example		Uses
NSAID	Ibuprofen, naproxen sodium		Relieve pain and reduce inflammation
Steroids	Prednisolone		Reduce inflammation, pain, slow joint damage
Conventional DMARDS	Methotrexate, sulfasalazine, hydroxy chloroquine	Slow the progression of RA and save joint and tissue from permanent damage	
Targeted synthetic DMARDS	Tofacitinib	Reduce inflammation	
Biologic agents	Anakinra , Infliximab, Etanercept	Reduce pain and inflammation	

Therapy

Occupational therapist who can teach you exercise to help keep your joints flexible.

Surgery

If medications fails to prevent or slow joint damage, then doctor consider surgery to repair damaged joints.

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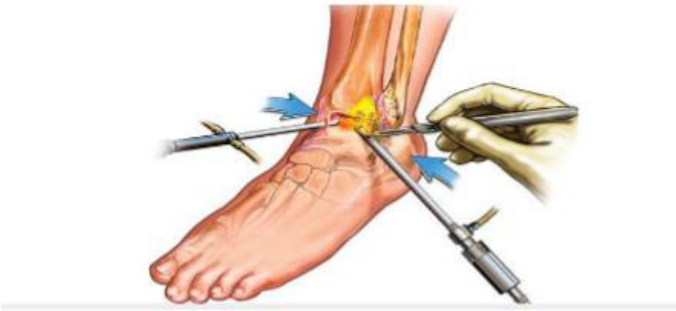
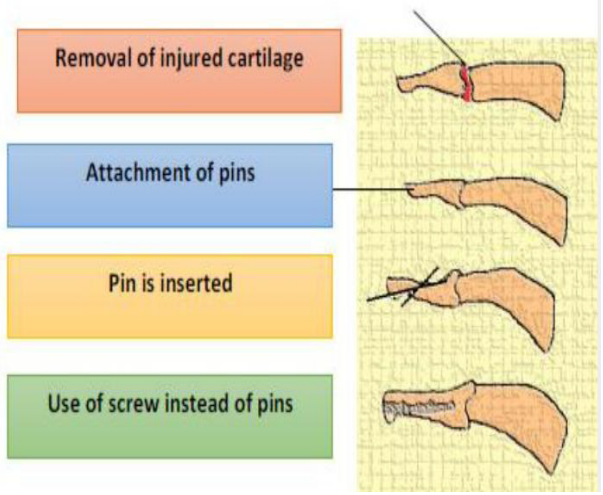
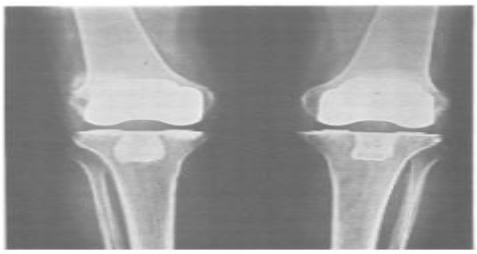
- **Tendon repair**



- **Joint fusion –**for the purpose of stabilization of joints, relieving from the pains, joint are fused



- **Total joint replacement-** dented part was replaced with Fake material made from metal and plastic.



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***Non pharmaceutical treatment**

Diet, exercise, acupuncture, herbal medicine, massage, stress reduction techniques, prayer, meditation, yoga, hypnosis .

Nutrition

Most common observed vitamin and mineral deficiency in patients with RA

- Folic acid
- Vitamin C
- Vitamin D
- Vitamin B6
- Vitamin B12
- Vitamin E
- Calcium
- Magnesium
- Zinc
- Selenium

Exercise

Being overweight strains joints and leads to further inflammation

- Walking
- Light jogging
- Water aerobics
- Cycling
- Yoga
- Stretching

Adverse effects of drug

- **Corticosteroid-** steroids are very effective at alleviating symptoms rapidly, but cannot used at high doses for long periods of time because of their side effects.
- **Disease modifying antirheumatic drug-** best outcome are obtained treatment is started within 4 months of duration.

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Drug class	Adverse effects
Corticosteroid	Osteoporosis Avascular necrosis Hypertension Diabetes mellitus Infections Electrolyte abnormalities, Accelerated atherosclerosis, proximal myopathy, cataracts, glaucoma , Crushing's syndrome, neuropsychiatric, pancreatitis
DMARDS	
Methotrexate	Bone marrow suppression, hepatitis, liver fibrosis, lung fibrosis
Chloroquine	Retinopathy
Sulphasalazine	Bone marrow suppression, skin rashes
Leflunomide	Bone marrow suppression, diarrhea, rashes, headache, teratogenicity.

Recent drug development in RA

- Several Nobel RA therapies include interleukin receptor **sarilumab ,** approved in 2017. It is effective in RA , including patients with incomplete response to methotrexate and anti-tumor necrosis factor inhibitor, showing superior efficacy in higher dose to standard dose addlimab
- The two biosimilar drugs currently approved are **CT-PI3&SB2,** based on reference product Infliximab.
- Other drugs small targeted molecule filgotinib.
- **Emerging therapies-** IL-6 contrast to IL-6 inhibitor sirukumab is monoclonal antibody that binds to cytokine , rather than its receptor.
- **Biosimilars-** an important new class of drugs in rheumatologic armamentarium . There are two biosimilar product based on monoclonal antibody Infliximab now approved for RA treatment in U.S.
- First time to be approved was CT-PI3 in 2016. Across these studies no significant differences in efficacy , immunogenicity or safety in patients taking CT- PI3 . CT-PL3 demonstrate persistent efficacy and tolerability over time, through 102 weeks of observation.

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Conclusion

Rheumatoid arthritis is an enduring inflammatory diseases that is categorized by bumping off the joint and rigidity , bone, and cartilage devastation all above the joints. Many development have been made to treat disease and diagnosis of disease, surgery performed to remove cytokine. The requirements of additional new drugs is essential for successful treatment of Rheumatoid arthritis. An introduction of biologic DMARD has changed field of RA treatment.

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