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A Review on Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily affect the lining of the synovial joints. Rheumatoid arthritis is characterized by synovial inflammation and hyperplasia (swelling), autoantibody production, cartilage and bone destruction (deformity).

The cause of rheumatoid arthritis is unknown. The disease occurs more frequently in females than males, being observed in the elderly. The risk factors include age, gender, genetics, and environmental exposure such as cigarette smoking, air pollutants etc.

Modern pharmacological therapies including conventional, biological, and disease modifying anti-rheumatoid drugs (DMARDs) remain the mainstay of RA treatment and there has been significant progress towards achieving disease remission without joint deformity. As there is no cure for RA, the treatment goals are to reduce the pain and stop or slow further damage. In this article describe about the ethiology, pathophysiology, diagnosis, treatment associated with rheumatoid arthritis.

KEYWORDS: -Autoimmune, hyperplasia, synovitis, rheumatoid factor, Bone erosion

I.INTRODUCTION

[3]Rheumatoid arthritis is a chronic inflammatory autoimmune disease that initially affect the small joints, progressing to larger joints, eventually to the eyes, skin, heart, kidneys and lungs. often the bones and cartilage of joints are destroyed, and tendons and ligaments weaken.

All this damage to the joints causes deformities and bone erosion, usually very painful for a patient. Common symptoms of RA include morning stiffness of the affected joints for >30 min, fatigue, weight loss, swollen and warm, and rheumatoid nodules under the skin.

Rheumatoid arthritis is most commonly occurred in women, because of hormonal imbalance or hormonal changes. Patient with RA have an increased prevalence of other serious illness. The predominant condition leading to this increased co-morbidity and mortality include infection, renal impairment, cardiovascular disease and lymphomas.

Treatment should start early and aggressively to prevent functional limitations and structural damages. Innovations in treatment and monitoring have resulted in patients achieving early and sustained clinical and radiographic remission. Researches shown that exercise is an essential tool in managing arthritis. mainly exercise reduces joint pain and increases flexibility and endurance. With advances in the field of molecular medicine, we have a better understanding of disease mechanisms which can aid in the designing of more effective treatments.

[1]Rheumatoid arthritis is commonly occurred due to some inflammatory cells secrete lysosomal enzymes which damage cartilage and erode bone, while prostaglandins produced in the process cause vasodilation and pain. NSAIDs are the first line drugs which afford symptomatic relief in pain, swelling, morning stiffness, immobility, but do not arrest the disease process. Today, the standard of care is early treatment with disease modifying anti-rheumatic drugs (DMARDs). The disease if not treated early, it will lead to progressive joint deformity and increased morbidity and mortality.

II.ETHIOLOGY

- The cause of rheumatoid arthritis is remained unclear, but genes,

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environmental factors, and hormones may be involved in its autoimmune disease and progression.

- Genetic factors contribute 53-65% of the risk of developing this

disease.

- [1]Certain risk factors appear to increase the risk of RA including old age (highest incidence in people aged 60 years); gender (higher incidence in women); genetics (especially human leukocyte antigen [HLA]class 2genotypes, such as HLA DRB1); smoking (tobacco, cigarettes); history of live birth (higher RA risk with nulliparity); early life exposure (if mother smoked, child has greater risk of RA); and obesity (higher risk with increasing body weight).
- [4]Cigarette smoking is the strongest environmental risk factors associated with rheumatoid arthritis. Studies have shown in ACPA (anti-citrullinated protein antibody) positive individual; there is an interaction between genes and smoking increases the risk factors.
- Collinsella is a genus of actinobacteria, these alters the gut mucosal permeability and has been related with increased rheumatoid arthritis disease severity.

Figure.1.: Deformities of rheumatoid arthritis.

III.PATHOPHYSIOLOGY

- The synovitis, Swelling and joint damage that characterize RA are the end result of complex autoimmune and inflammatory process that involve component of both innate and adaptive immune system.
- Chronic inflammation of the synovial tissue lining the joint results in the proliferation of this tissue. The inflamed, proliferating synovium in rheumatoid arthritis is called pannus.
- The pannus invades the cartilage and eventually the bone surface, producing erosion of bone and cartilage resulting in destruction of the joints.
- In a susceptible individual, the interaction of environment and genes results in a loss of tolerance of self-proteins that contain a citrulline residue. These proteins are generated via post translational modification of arginine residues to citrulline residues by the enzyme peptidyl arginine deiminase.
- Anti-citrullinated protein antibodies (ACPAs) can be detected in approximately 67% of RA patient and serve as a useful diagnostic reference for Patients with RA. Synovitis occurs as a consequence of leukocyte infiltration into the synovium.
- The joint swelling in RA is usually synovial membrane inflammation, with cytokine and

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chemokine involvement.

- The most relevant component in the inflamed space includes tumour necrosis factor (TNF), interleukin-6(IL-6), and granulocyte macrophage colony stimulating factors. Cytokines and chemokines induce or aggravate the inflammatory response by activating endothelial cells and promoting immune system cell accumulation within the synovial compartment.
- [5]Activated fibroblasts, B-cells, T-cells, monocyte and macrophage can eventually trigger osteoclast generation via receptor activator of nuclear factor kappa-B ligand (RANKL), which is expressed on B cells, T cells, and fibroblasts.
- In addition, the cartilage matrix within joints is eventually degraded by metalloproteinase and other enzymes.

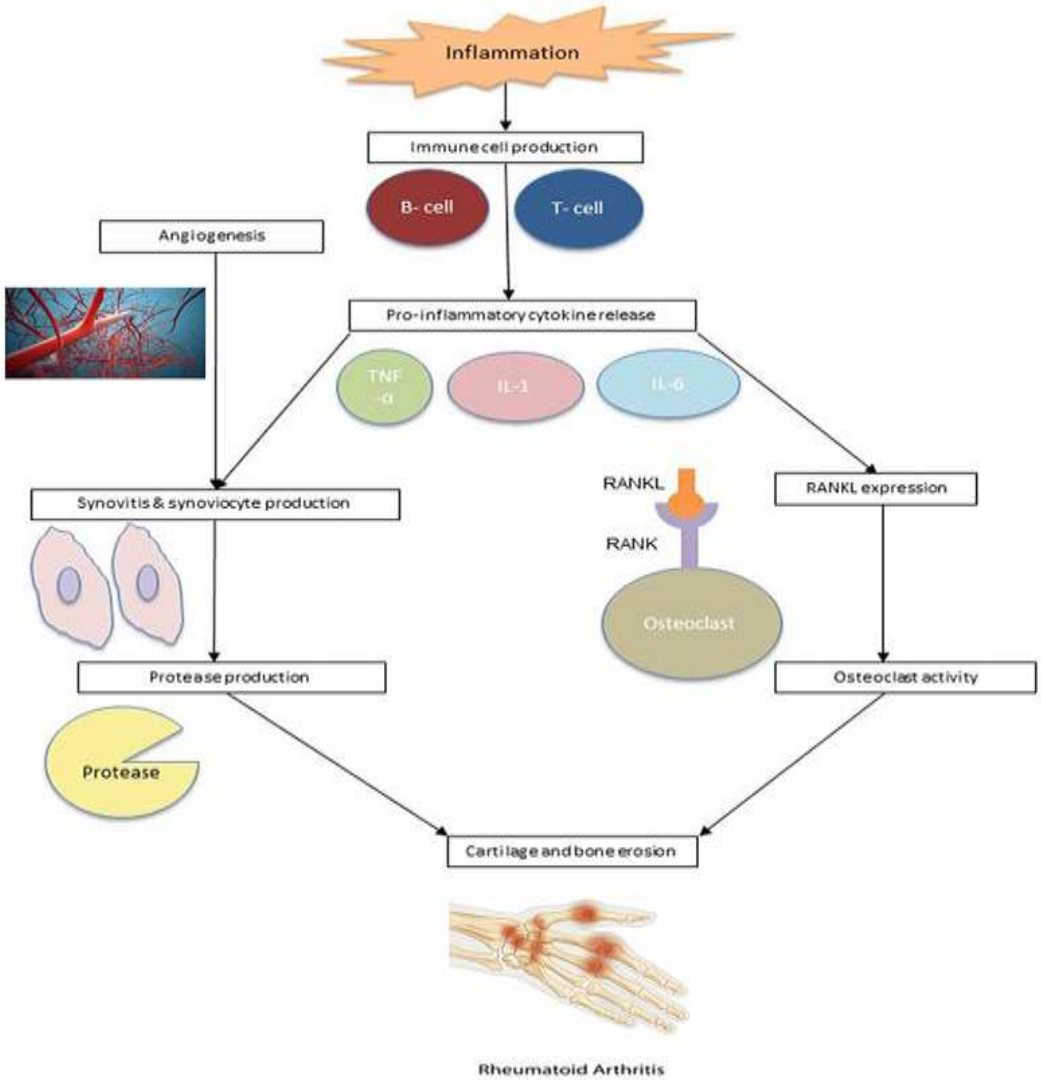

Fig:2. Pathophysiology of rheumatoid arthritis

IV.DIAGNOSIS

Clinical diagnosis of rheumatoid arthritis Made based on the patient history, presenting symptoms and clinical findings. Patient with rheumatoid arthritis generally complain of multiarticular pain/ aching morning stiffness, tenderness/swelling, and bilateral or symmetrical joint Involvement (e.g., both hands, both

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knees).Patient may present with weight loss, fever, fatigue, and or weakness. In addition to physical symptoms, the laboratory diagnosis (measurable sign) of RA has improved with the identification of highly specific biomarker.

History is useful, as well as investigations including blood test, ultrasound for the presence of synovitis and x-rays. The latter is used to demonstrate join destruction which indicates late manifestation of the disease. Emphasis on early diagnosis and treatment is extremely important to prevent disease activity, duration and ultimately joint destruction.

The American Rheumatism Association (ARA) criteria were principally designed for disease classification in patient with established disease and are not sensitive for patients in the early stages of rheumatoid arthritis.

Fig:3 Summary of disease activity score (DAS28) criteria for rheumatoid arthritis.

SUMMARY OF DAS28 (DISEASE ACTIVITY SCORE USING 28 JOINTS)

DAS28 is a composite formula. Four parameters are used to calculate a disease severity score:

1.Number of swollen joints out of a total of 28 specified joints

2.Number of tender joints out of a total of 28 specified joints

3. Erythrocyte sedimentation rate

4.. Patient's interpretation of wellbeing, with 0 being at there be stand 100 their worst.

Programmed calculators are used to determine the final DAS28.

DAS28 does not take into account other features of a patient's

disease, such as synovitis and other clinical symptoms.

High disease activity: of >5.1 DAS28

Moderate disease activity: DAS28 of >3.2 to 5.1

Low disease activity: DAS28 of 2.6–3.2

Remission: DAS28 of <2.6 in the assessment of rheumatoid arthritis

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Criteria	Definition
1.Morning stiffness	Morning stiffness in and around the joints lasting at least 1 hour before maximal improvement.
2.Arthritis of three or more joint areas	At least three joint areas simultaneously have soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible joint areas are (right or left): PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3.Arthritis of hand joints	At least one joint area swollen as above in wrist, MCP, or PIP joint.
4.symmetric arthritis	Simultaneous involvement of the same joint areas (as in 2) on both sides of the body (bilateral involvement of PIP, MCP, or MTP joints is acceptable without absolute symmetry).
5.Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta articular regions, observed by a physician.
6.Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method that has been positive in less than 5% of normal control subjects.
7.Radiographic changes	Radiographic changes typical of rheumatoid arthritis on postero anterior hand and wrist x-rays, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

Table:1 The American Rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis.

[2]For classification purposes, a patient is said to have rheumatoid arthritis if he or she has satisfied at least four of these seven criteria. Criteria 1 through 4 must be present for at least 6 weeks. Patients with two clinical diagnoses are not excluded.

V.TREATMENT:

Reversal of inflammation is the typical goal of therapy for RA, and without adequate treatment, patient can develop irreversible disabilities. There are four primary goals in the treatment of rheumatoid arthritis.

- Symptom relief including pain control
- Slowing or prevention of joint damage
- Preserving and improving functional ability
- Achieving and maintaining disease remission

The aim of therapy is to minimize joint destruction and to preserve function.

- Treatment regimen consist of combination of Pharmaceuticals, weight bearing exercise, educating patient about the disease, and rest. There are four main categories of drugs employed in the management of rheumatoid arthritis.
- non-steroidal anti-inflammatory drugs (NSAIDs)including cyclooxygenase Cox 2 inhibitors, glucocorticoids, DMARDs (Disease modifying anti rheumatic drugs) and biological therapies.
- Simple analgesia also has a small role to play in basic symptom relief and include paracetamol, codeine, and paracetamol and opiate combination. These analgesics do not

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have any anti-inflammatory effect and will not aid disease modification.

CLASSIFICATION OF DRUGS

- NSAIDs (Non-steroidal anti-inflammatory drugs)
  - Aspirin
  - Diclofenac
  - Indomethacin
  - Meloxicam

- DMARDs (Disease modifying anti rheumatoid drugs):

They are mainly divided into two Non biological drugs and biological drugs.

Non biological drugs

IMMUNOSUPPRESSANT: -

- Methotrexate
- Azathioprine
- Cyclosporine

IMMUNO-MODULATORS: -

- Sulfasalazine
- Hydroxychloroquine/chloroquine
- Leflunomide
- Tofacitinib

BIOLOGICAL AGENTS

TNF A-INHIBITORS: -

- Etanercept
- Infliximab
- Adalimumab

OTHER BIOLOGICALS: -

- Anakinra
- Abatacept
- Rituximab

ADJUVANT DRUGS

- Prednisolone
- Glucocorticoids

NON-PHARMACOLOGICAL APPROACH.

[12]Adequate rest, weight reduction if obese, occupational therapy, physical therapy, and use of assistive devices may improve symptoms and help Maintain joint function. Patients with severe disease may benefit from surgical procedures such as synovectomy, tendon repair, and joint replacements. Patient education about the disease and the benefits and limitations of Drug therapy is important.

PHARMACOLOGICAL APPROACH

General Approach

[1]• A disease-modifying antirheumatic drug (DMARD) should be started Within the first 3 months of symptom onset. DMARDs should be Used in all patients except those with limited disease. Early use of DMARDs Results in a more favourable outcome and can reduce mortality.

• First-line DMARDs include methotrexate (MTX), hydroxychloroquine, sulfasalazine, and leflunomide. The order of agent selection is not clearly defined, But MTX is often chosen initially because long-term data suggest superior Outcomes compared with other DMARDs and lower cost than biologic agents. Leflunomide appears to have long-term efficacy similar to MTX.

• Biologic agents with disease-modifying activity include the anti-TNF Agents (etanercept, infliximab, adalimumab), the IL-1 receptor antagonist anakinra, and rituximab, which depletes peripheral B cells. Biologic Agents are effective for patients who fail treatment with other DMARDs.

• DMARDs that are less frequently used include azathioprine, penicillamine, gold salts (including auranofin), minocycline, cyclosporine, and Cyclophosphamide. These agents have either less efficacy or higher toxicity, or both.

• Combination therapy with two or more DMARDs may be effective when Single-DMARD treatment is unsuccessful. Combinations that are particularly effective include (1) MTX plus cyclosporine, and (2) MTX plus Sulfasalazine and hydroxychloroquine.

• Nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids maybe used for symptomatic relief if needed. They provide relatively rapid Improvement compared with DMARDs, which may take weeks to months Before benefit is seen. However, NSAIDs have no impact on disease progression, and corticosteroids have the potential for long-term complications.

DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)

Joint damage is known to occur early in rheumatoid arthritis and is largely irreversible. The need for early intervention with DMARDs as part of an aggressive approach to minimize diseases progression has become standard practice and is associated with better patient outcome. Early introduction of DMARDs also results in fewer adverse reactions and withdrawal from therapy.

METHOTREXATE**: [**8**]** MTX inhibits cytokine production and purine biosynthesis, which may be Responsible for its anti-inflammatory properties. It is given as a once Weekly dose and can be given orally or parenterally via the Intramuscular or subcutaneous routes.

Dose: It is usually administered orally in 15-25mg doses once weekly

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Methotrexate tablets are available as 2.5-mg and 10-mg strengths; most pharmacies will dispense the 2.5-mg strength only for non-chemotherapy indications such as rheumatoid arthritis.

Adverse drug reaction: -diarrhoea, nausea, vomiting, thrombocytopenia, pulmonary fibrosis, hepatic cirrhosis may rare.

LEFLUNOMIDE: Leflunomide (Arava) inhibits pyrimidine synthesis, which reduces lymphocyte proliferation and modulation of inflammation. Its efficacy for RA Is similar to that of methotrexate.

Dose: - A loading dose of 100mg/day for the first 3 days may result in a therapeutic response within the first month. The usual maintenance dose of20mg/day may be lowered to 10mg/day in case of GI intolerance or another dose related toxicity.

ADR: - liver toxicity, it may cause bone marrow toxicity, it is teratogenic so avoid in pregnancy.

HYDROXYCHLOROQUINE**:**

[6]Hydroxychloroquine lacks the myelosuppressive, hepatic, and renal toxicities seen with some other DMARDs and itis also a antimalarial drug.which simplifies monitoring. Its onset may be delayed for up to 6 weeks, but the drug should not be considered a therapeutic failure until after 6 months of therapy with no response.

Dose: - orally 200-300mg twice daily, after 1 to 2 months may decrease to 2mg once or twice daily.

SULFASALAZINE: Sulfasalazine use is often limited by adverse effects. Antirheumatic effects Should be seen in 2 months. Blood Dyscrasias usually occur within the first 3–6months of treatment, therefore necessitating close monitoring in the initiation Period.

Patients should also be counselled to report warning Symptoms of unexplained bleeding, bruising, purpura, sore Throat, fever or malaise. Enteric-coated tablets are available to Minimize gastro-intestinal side effects.

Dose: -500mg twice daily orally

BIOLOGICAL THERAPIES

These are genetically engineered mono-clonal antibodies which selectively target different part of the inflammatory pathways. Activated T cells release pro-inflammatory cytokines including TNF-α, interleukin 1 and interleukin 6.

Adalimumab, etanercept, infliximab target TNF-α. Anakinra and tocilizumab target the interleukins, whilst abatacept and rituximab, act on T- cells and B-cells, respectively.

In current practice, biologics are used after a patient has failed DMARDs, although there is emerging evidence to suggest they should be used earlier in the disease.

[7]Infliximab: - It was the first anti-TNF-α agent studied for the treatment of RA but was first approved for treatment of Crohn's disease. Infliximab is the only anti-TNF agent which is given by intravenous infusion and must be given concomitantly with methotrexate.

Adalimumab is a recombinant human monoclonal antibody that binds to and neutralizes TNF-α. Etanercept is a human TNF fusion protein that binds to TNF cell surface receptors, thereby inhibiting interaction of TNF-α with its receptors.

BIOLOGICAL AGENTS USED IN TREATMENT OF RA

DRUG	USUALDOSE	ROUTE
Adalimumab	40 mg every 2 weeks	Subcutaneous
Etanercept	25mg twice weekly or 50mg weekly	Subcutaneous
Infliximab	3mg/kg at week 0, 2 and 6, then every 8weeks thereafter	Intravenous infusion
Rituximab	1g then 1g 2weeks later Max 2courses/year	Intravenous infusion
Abatacept	750 mg at week 0, 2 and 4, then every 4weeks thereafter	Intravenous infusion
Anakinra	100 mg daily	Subcutaneous

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Tocilizumab	8mg /kg every 4 weeks	Intravenous Infusion

Table:3 Biological agents used in the treatment of rheumatoid

VI.PATIENT COUNSELLING

Education and counselling can help you to better understand the nature of RA and cope with the challenges of your condition.

Your doctor will work with you to help ease your symptoms with medicine and other treatments. But you have the power to help yourself manage your RA every day.

TAKE CARE OF YOURSELF: Taking care of yourself and staying on top of the disease is a big part of RA treatment. Take your medicine as directed. Try not to skip a dose. Tell your doctor about any side effects. Talk to them or your pharmacist if you have questions.

EXERCISE: When you have joint pain and stiffness, you may not want to move around. But you should try to stay as active as possible. It actually helps ease your symptoms and prevent long-term problems. Exercise for rheumatoid arthritis usually includes:

[9]Stretching: Stretch when you get started to warm up. Stretch when you're done to cool down.

Low-impact aerobic exercise: These are exercises that keep your heart strong without hurting your joints. Walking, riding a bike, and swimming are good choices for people with RA.

Strengthening: These exercises help keep your muscles strong. You might use resistance bands that gently strengthen your muscles. You can also use light weights.

Keep a healthy diet – [10] Getting to a healthier weight can lead to fewer complications and a better chance of remission.

Lower Stress**:** Dealing with RA can be stressful, but there are many ways to lower your stress level**.** Talk with your doctor or nurse**.** Take time to rest during the day. Try to relax**.** Learn special technique like yoga and meditation.

Healthful eating:[11] Eat to maintain a normal weight. Being underweight or overweight can affect RA. Healthy diet includes,

Fish and other sources of omega 3-fats like olive oil.

Fresh fruits and vegetables.

Little or no saturated fat, especially fatty meats.

Low amount of salt and sugar.

The daily recommended amount of nutrients and minerals.

MEDICATIONS –

The best medication(s) and dose(s) for you will depend upon individual factors as well as potential drug side effects.

If you take medications for RA, you will need to see your health care provider regularly for examinations and blood tests to monitor for complications.

If you do experience side effects, they can often be minimized or eliminated by reducing the dose or switching to a different drug .

[8]DMARDs: - Disease-modifying antirheumatic drugs (DMARDs) can substantially reduce the inflammation of RA, reduce or prevent joint damage, preserve joint structure and function.

HYDROXYCHLOROQUINE (PLAQUENIL) AND SULFASALAZINE (AZULFIDINE) are used for mild rheumatoidarthritis. They are not as powerful as other DMARDs, but they usually cause fewer side effects. In rare cases, Plaquenil can adversely affect the eyes, and patients taking this medicine should be seen by an ophthalmologist at least once a year.

[8]Methotrexate: -Like other DMARDs, methotrexate has side effects; it can cause rash and stomach upset, can be toxic to the liver or bone marrow, and can cause birth defects. In rare cases, it can also cause shortness of breath. Regular blood work is necessary when taking methotrexate. Taking folic acid helps reduce some of the side effects. Methotrexate's biggest advantage could be that it has been shown to be safe to take for long periods of time and can even be used in children.

VII.CONCLUSION

Rheumatoid arthritis is a chronic inflammatory disease, capable of causing joint damage as well as long term disability. Early diagnosis and intervention are essential for the prevention of serious damage and loss of essential bodily functions. Excessive body weight and diet that include animal products (e.g., dairy, red meat) exacerbate the RA symptoms likely due to their pro-inflammatory effects. Old Treatment modalities have been optimized and new ones can be produced. Gene array analysis is proving beneficial in finding out which patient will be more responsive to specific medication. We need to understand the factors that leads to loss of tolerance and that cause localization of inflammation in the joint. we need to find ways to promote

immunological resolution or homeostasis and repair of damaged joints.

Treatment should start early and aggressively to prevent functional limitations and structural damages. Innovations in treatment and monitoring have resulted in patients achieving early and sustained clinical and radiographic remission. Researches shown that exercise is an essential tool in managing arthritis. mainly exercise reduces joint pain and increases flexibility and endurance. With advances in the field of molecular medicine, we have a better understanding of disease mechanisms which can aid in the designing of more effective treatments.

The majority of RA cases are diagnosed and treated on an outpatient basis. Pharmacists in ambulatory care settings (e.g., clinics, community pharmacies) have pivotal opportunities to counsel patients and ensure that RA drugs are administered appropriately. An example of such a drug is MTX, which should be taken once weekly, along with folic acid supplementation.

A healthy diet, nutrients and exercise reduce the risk of RA, and should avoid the use of red meat and dairy products fried food and fast food, alcohol and omega 6 fatty acid containing food such as soybeans, corn, meat, fish etc.

Rheumatoid arthritis patients today can live a healthy and productive life. Today's medicines used can relive pain and swelling and, in some cases, put the disease in remission, preventing bone damage or deformity.

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