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RHEUMATOID ARTHRITIS: A REVIEW OF DIAGNOSIS AND TREATMENT

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory systemic autoimmune disease that affects the joints differently in different persons. RA primarily affects the synovial joint lining and is associated with progressive disability, premature death, and significant socioeconomic burdens. Age, gender, genetics, and environmental exposure are all risk factors (cigarette smoking, air pollutants and occupational).

A greater knowledge of how pathogenic mechanisms cause the worsening of RA progression in individuals is critically needed in order to create medicines that will successfully treat patients at each stage of disease progression. We examine the etiology and pathophysiology at four stages: (i) triggering, (ii) maturation, (iii) targeting, and (iv) fulminant stage, which is accompanied by hyperplastic synovium, cartilage destruction, bone erosion, and systemic effects. Modern pharmacologic therapies (including conventional, biological, and alternative remedies).

Novel prospective small molecule disease-modifying anti-rheumatic medicines) continue to be the mainstay of RA treatment, and there has been significant progress. Significant progress has been made toward disease remission without joint deformity. As there is no cure for RA, thetreatment goals are to reduce the pain and stop/slow the further damage.

Here we present a brief summary of various past and present treatment modalities to address complications associated with rheumatoid arthritis. This review discusses recent advances of our understanding of RA pathogenesis, disease modifying drugs and provides perspectives on next generation therapeutics for RA.

Keywords: Rheumatoid arthritis (RA), Novel prospective, diagnosis, treatment.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that affects women more than men and is most common in the elderly.It begins with tiny joints and progresses to larger joints before affecting the skin, eyes, heart, kidneys, and lungs. Joint bone and cartilage are frequently damaged, and tendons and ligaments become weak.

Rheumatoid arthritis symptoms include morning stiffness of the affected joints for more than 30 minutes, weariness, fever, weight loss, sensitive, swollen, and heated joints, and rheumatoid nodules under the skin. This condition usually appears between the ages of 35 and 60, with periods of remission and exacerbation. It can also affect young children before the age of 16, and is known as juvenile rheumatoid arthritis (JRA), which is similar to RA except that no rheumatoid factor is present. The prevalence of RA in the West is estimated to be 1-2%, with a global prevalence of 1%.Treatment for RA aims to minimise joint inflammation and pain, improve joint function, and avoid joint deterioration and deformity. Treatment approaches include a combination of medications, weight-bearing exercise, illness education, and rest.

Clinically, rheumatoid arthritis (RA) can be distinguished from osteoarthritis (OA) because the afflicted sites in RA are the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) (MP). In contrast to osteoarthritis, which primarily affects the distal interphalangeal (DIP) joints the most prevalent type of arthritis is osteoarthritis, which is caused by wear and tear rather than an injury. Autoimmune disease it is not harmful to the lungs, heart, or immune system. In addition, osteoarthritis, In contrast to rheumatoid arthritis, which is symmetrical, normally affects only one side of the body. Another distinguishing feature is that the patient has continuous morning stiffness, for at least one hour, preferably longer Morning stiffness is common with osteoarthritis, but it usually goes away or falls within 20-30 minutes.

Epidemiology

The goal is to use population-based studies to quantify the global population prevalence of rheumatoid arthritis (RA) and to examine factors that influence RA prevalence estimates. With a 95% prediction interval, the global RA prevalence estimate was 0.46% (95% CI 0.39-0.54; I2 = 99.9%). (0.06 - 1.27).

Between 1986 and 2014, the RA point-prevalence was 0.45% (95% CI 0.38-0.53%), whereas the pooled period-prevalence was 0.46% (95% CI 0.36% and 0.57%) from 1955 to 2015. The linked data source studies had the highest RA pooled prevalence (0.69%; 95% CI 0.47-0.95).

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Pathophysiology

T-lymphocytes, B cells, and monocytes infiltrate the synovial membrane in many joints, causing RA. This process is preceded by endothelial cell activation; neovascularization(the formation of new blood vessels) is another feature of RA synovitis. Synovial fibroblast-like and macrophage-like cell expansion results in a hyperplastic synovial lining layer.

According to the presence or lack of anti-citrullinated protein antibodies, there are two primary subtypes of RA (ACPAs). Citrullination Peptidylarginine-dependent enzyme catalyses this reaction & PAD, which converts a positively charged arginine as a result of a post-translational modification to a polar but neutral citrulline modification. ACPAs are seen in roughly 67% of RA patients.

Patients and act as a valuable diagnostic resource for patients accompany early, unexplained arthritis and offer evidence of the condition is most likely progressing to RA.

The ACPA- favourable.A subset of RA has a more aggressive clinical profile as compared to others. To the ACPA-negative subset of RA According to reports, ACPA-negative Different genetic association patterns exist for RA, and these patterns differ. Reactions of immune cell to citrullinated antigens from those a subpopulation of ACPA-positive individuals.

Molecules such as receptor activator of nuclear factor κB ligand(RANKL), prostaglandins, and matrix metalloproteinase areinduced by pro-inflammatory cytokines, including tumor necrosisfactor (TNF) and interleukin (IL)-6, and mediate signs and symptomsof the disease, including pain and swelling, and degradationof cartilage and bone.6 Stimulation by RANKL, TNF, and IL-6 generates osteoclasts within the synovial membrane and promotes bony damage. These molecular and cellular events result in the clinicaldisease expression. Progression of joint damage is intrinsicallyassociated with joint swelling.

The cause of RA is unknown. However, both hereditary and environmental factors contribute to RA. There are numerous gene loci that are linked. with RA (Box) related with RA.

Auto antibodies form before signs and symptoms appear. This stage is known as "pre-RA" and can last anywhere from one to ten years. The autoantibody profile influences the time it takes for RA symptoms to manifest. Individuals who solely express ACPAs acquire symptoms 5 to 10 years after the development of the autoantibody, but persons who develop ACPAs, RF, and high C-reactive protein (CRP) levels show symptoms within a few months of the presence of the third of these variables. Subtle inflammatory alterations in the synovium have been observed in certain pre-RA patients. Overt inflammatory alterations observed by histology in established RA are not usually accompanied by clinical signs and symptoms. 28 Early signs of RA range from mild arthritis with few affected joints to severe polyarticular disease, with autoantibodies ranging from negative to multiple positive. Early illness does not show structural damage, however later stages show erosive disease or joint space narrowing as an evidence of cartilage degradation. If not properly managed, RA develops into a more homogenous, devastating disease.

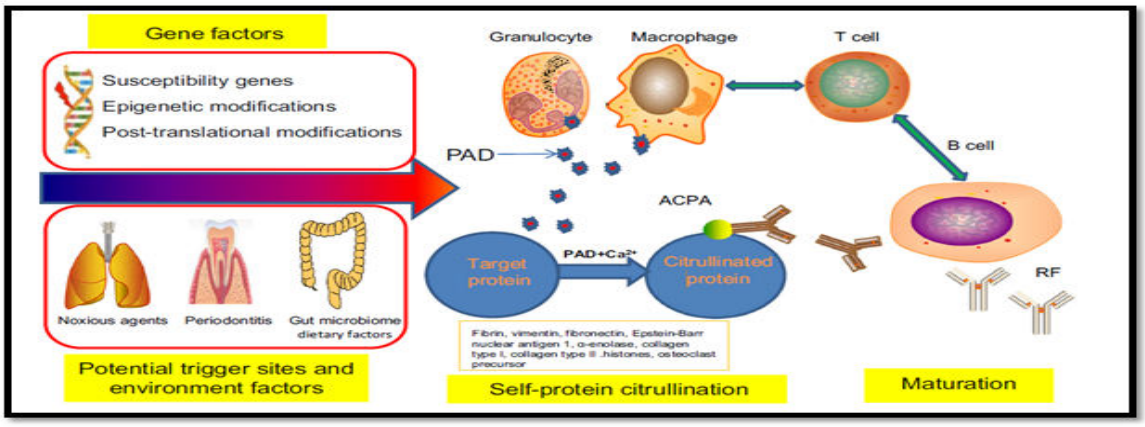

Fig: 1 Pathogenesis of RA.

Clinical Display

RA is a polyarticular symmetric illness that affects several joints on both sides. Pain and swelling in the joints of the hands and feet are characteristic symptoms of RA. Wrists, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joints are the most swollen. This is accompanied with morning joint stiffness that lasts longer than 30 minutes and can last for many hours. Because to synovitis and effusion, the swelling is often "soft," as opposed to the "hard" (bony) swellings of osteoarthritis.

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When the fingers are affected, the swelling is centred around the joint (fusiform) rather than encompassing the entire digit ("sausage digit"), as observed in psoriatic arthritis. Although the distal interphalangeal joints are rarely impacted, both small and big joints can be affected.If RA is insufficiently treated, extra-articular manifestations maydevelop. The most frequent are rheumatoid nodules (firm subcutaneous lumps near bony prominences such as the elbow).

A more serious manifestation is rheumatoid vacuities, a necrotizing inflammation of small or medium-sized arteries, mostly involving the skin, vasa nervorum, and occasionally arteries in other organs. Patients with RA may be affected by multiple comorbidities. Cardiovascular disease is a common consequence of chronic inflammation and the primary cause of death in people with RA. In patients with RA, cardiovascular disease is more closely associated with disease activity than with traditional cardiovascularrisk factors. Extra-articular symptoms may occur if RA is not well treated. Rheumatoid nodules (hard subcutaneous lumps around bony prominences such as the elbow) are the most common. Rheumatoid vasculitis, a necrotizing inflammation of small or medium-sized arteries, primarily involving the skin, vasa nervorum, and occasionally arteries in other organs, is a more significant symptom.

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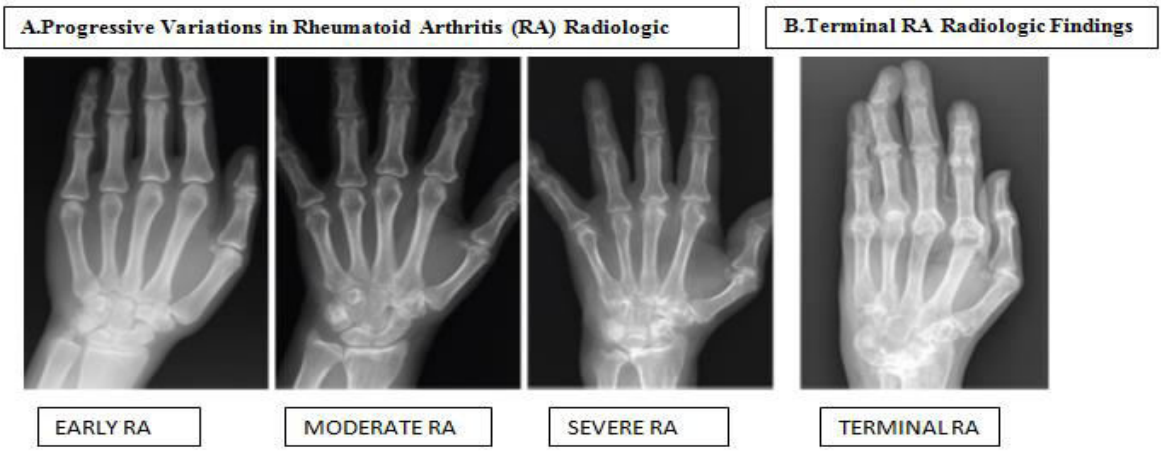

Figure 2: Structural Phenotypes of Rheumatoid Arthritis:

Diagnosis and Assessment

In early disease, RA may involve just 1 or a few joints. Simultaneouslyor even earlier, tendon inflammation (tenosynovitis) develops Thepresence of tenosynovitis, eg. at the flexor carpiulnaris tendon, and subclinical synovial inflammation can be detected by imaging withcolor Doppler sonography or gadolinium-enhanced magnetic resonanceimaging, which demonstrate expansion of intra-articular soft tissue or hypervascularization of the synovial membrane. No diagnostic criteria exist for RA. However, the 2010 classificationcriteria, although primarily developed for identification ofhomogenous patient populations in clinical studies of RA, may help physicians establish a diagnosis; differences between classification and diagnosis have been summarized in a recent report.

Physical examination or ultrasound or magnetic resonance imaging imaging of the joint adds up to 5 points; elevated levels of RF, ACPAs, or both contribute 2 points (or 3 points with levels >3 times the upper limit of normal); and length of symptoms (6 weeks) contribute 1 point each. These 2010 criteria have an 82% sensitivity and a 61% specificity. When compared to the 1987 criteria, the new classification criteria had an 11% higher sensitivity and a 4% lower specificity. Initial assessment requires examination of the joints as wellas serologic testing for autoantibodies and APRs. For follow-up, joint assessment, evaluation of APRs, and evaluation of patient reportedoutcomes such as patient global assessment of diseaseactivity and evaluation of physical function are important.

Compositemeasures that include joint counts, i.e. number of tender and swollen joints, constitute the best way to evaluate RA disease activity in practice (and in trials), since they capture the mostimportant disease aspects in a single score. These scores, namely the clinical disease activity index (CDAI), the disease activity scoreusing 28 joint counts (DAS28), or the simplified disease activityindex (SDAI), correlate with outcomes such as damage progressionand functional impairment. These measures allow quantificationof disease activity, and disease activity states based onspecific cut points of these indices have been defined to helpguide treatment.

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TREATMENT

Nsaids and Corticosteroids are used as first-Line Treatments

The primary goals of first-line treatment are to alleviate pain and reduce inflammation. Non-steroidal anti-inflammatory medications (NSAIDs) such as acetylsalicylate (Aspirin), naproxen (Naprosyn), ibuprofen (Advil and Motrin), and etodolac are examples of fast-acting pharmaceuticals (Lodine). Because of the suppression of prostaglandins, aspirin is an effective anti-inflammatory for rheumatoid arthritis when given at higher doses.

This is one of the first NSAIDs to be used to treat joint pain. Tinnitus, hearing loss, and gastrointestinal intolerance are all side effects of aspirin at high doses.

Other NSAIDs that are newer on the market than aspirin yet equally effective furthermore, these medications necessitate fewer dosages every day.

NSAIDs prevent the formation of prostaglandins, prostacyclin, and thromboxanes by inhibiting cyclooxygenase. Nausea, abdominal pain, ulcers, and gastrointestinal (GI) bleeding are common adverse effects. These symptoms can be alleviated by taking the medication with meals or with antacids, proton pump inhibitors, or misoprostol (Cytotec) Celecoxib (Celebrex), a more recent NSAID, is a selective Cox-2 inhibitor with a lower risk of GI side effects.

Corticosteroids are more potent anti-inflammatory drugs than NSAIDs, but they have more negative effects. As a result, they are only prescribed at modest doses for a brief length of time during rheumatoid arthritis exacerbations or flares. Corticosteroid injections intra-articular (IA) can be utilised to treat local inflammatory symptoms. They function by limiting phospholipid release and decreasing eosinophil activity, hence reducing inflammation.

Side effects of these medications include bone weakening, weight gain, diabetes, and immunosuppressant. Advising the patient to take calcium and vitamin D supplements can help avoid bone weakening. Side effects can be decreased by progressively reducing doses as the patient improves. It is critical not to abruptly quit injectable or oral corticosteroids because this can result in hypothalamic-pituitary-adrenal axis suppression (HPA) or rheumatoid arthritis flares.

Opoid Analgesics

Whittle et al. investigated the usage of opioid analgesics in patients suffering from rheumatoid arthritis discomfort. According to their findings, mild opioids such as codeine, dextropropoxyphene, and tramadol may be beneficial in the short term management of pain caused by rheumatoid arthritis, but the risks exceed the benefits. They advise that other analgesics be tried first.

Second-Line Therapy Includes Disease-Modifying Anti-Rheumatic Drugs (Dmards)

Second-line therapy aims to promote remission by slowing or preventing the progression of joint deterioration and deformity. These medications are classified as slow acting because they take weeks or months to become effective. DMARDs can also lower the risk of getting lymphoma, which is linked to rheumatoid arthritis.

Methotrexate (MTX) is the first-line treatment (also considered as an anchor drug). It is a folic acid analogue that inhibits the binding of dihydrofolic acid (FH2) to the enzyme responsible for converting FH2 to folinic acid (FH4). Purine and pyrimidine metabolism is hampered in the absence of FH4, and amino acid and polyamine production is impaired. Because of the side effects of liver issues, cirrhosis, and bone marrow degradation, MTX is an immunosuppressive medicine that requires regular blood tests.

Side effects can be reduced by taking folic acid supplements. It is an effective DMARD with a lower frequency of side effects than other DMARDs and dose flexibility, which means dosages can be modified as needed .Until present, there is no convincing evidence demonstrating the advantages of combining conventional synthetic DMARDs (csDMARDs) over MTX monotherapy. However, biological DMARDs (bDMARDs) paired with csDMARDs are said to be better than MTX but have more side effects and are more expensive.

Hydroxychloroqyine (Plaquenil) is an antimalarial medication that can be used long-term to treat rheumatoid arthritis. This medication reduces the release of proinflammatory cytokines from monocytes. Common adverse effects include gastrointestinal, cutaneous, and central nervous system issues. When used in greater doses, it can have an effect on the eye in particular. Patients taking this drug must see an ophthalmologist on a regular basis.

Sulfasalazine (Azulfidine) is a DMARD that is commonly used to treat irritable bowel syndrome. This DMARD, when combined with anti-inflammatory medicines, can be used to treat rheumatoid arthritis. This drug's mechanism of action in the treatment of rheumatoid arthritis has not been determined. Sulfapyridine, a decreased version of the medicine after delivery, is hypothesised to inhibit interleukin 8 (IL-8) and monocyte chemoattractant protein secretions (MCP). This medication has gastrointestinal and central nervous system adverse effects, as well as a rash.

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It is generally well tolerated by patients, however it should be avoided by those who have sulfa allergies because it includes sulfa and salicylate chemicals.

Aurothioglucose (Solganal), auranofin (Ridaura), gold sodium thiomalate (Myochrysine), and D-penicillamine (Depen, Cuprimine) have all been used to treat rheumatoid arthritis. Due to bone marrow and kidney damage, many DMARDs necessitate periodic blood and urine tests. Because of more effective therapies, particularly methotrexate, these drugs have not been utilised recently. Other immunosuppressive drugs, such as azathioprine (Imuran), cyclophsphamide (Cytoxan), chlorambucil (Leukeran), and cyclosporine (Sandimmune), can be used, but are normally reserved for individuals with highly active rheumatoid arthritis or illness consequences.

Novel Pharmaceuticals

Leflunomide is an oral drug that is metabolised to malononitrilamide, which inhibits ribonucleotide uridine monophosphate pyrimidine production (rUMP). It alleviates symptoms while slowing the course of rheumatoid arthritis. It is usually used in conjunction with methotrexate, but it can be used alone if patients do not respond to methotrexate. Hypertension, gastrointestinal disturbance, liver damage, leukopenia, interstitial lung disease, neuropathy, dermatitis, and bone marrow destruction are all possible side effects.

Biologics, also known as biological disease-modifying anti-rheumatic medicines (bDMARDs), are highly effective in slowing the course of rheumatoid arthritis-related joint deterioration. They are thought to offer a more "direct, defined, and targeted" therapy strategy. Nonetheless, biologics can have substantial side effects, such as an increased risk of infection. Other common side effects include multiple sclerosis-like neurologic illness and lymphoma. Tumor necrosis factor (TNF) is a messenger protein that causes joint inflammation. Etanercept (Enbrel), infliximab (Remicade), and adalimumab are examples of biologic drugs (Humira),

TNF inhibitors include golimumab (Simponi) and certolizumabpegol (Cimzia). These inhibitors block the recruitment of inflammatory cells, resulting in quick symptom alleviation. If other second-line drugs are ineffective, they are recommended. Unfortunately, these drugs are quite expensive, and their significance in treating individuals at various stages of rheumatoid arthritis, as well as their mechanism of action, is still being researched. These drugs are frequently used in conjunction with other DMARDs, particularly methotrexate. TNF inhibitors are not recommended for people suffering from congestive heart failure or demyelinating disorders.

Other Treatments

Contrary to prior ideas, it has been discovered that there are no specific foods that patients with rheumatoid arthritis should avoid. The notion that nutrition might "exacerbate" symptoms is no longer supported. Although not as efficient as DMARDs, home treatments have been shown to be beneficial for patients suffering with rheumatoid arthritis. Fish oils and omega-3 fatty acid supplements have been shown to help with rheumatoid arthritis symptoms in the short run.

Cumin has been proven to have anti-inflammatory properties in patients suffering from this condition. Calcium and vitamin D supplements may be beneficial in the prevention of osteoporosis. Finally, folic acid can help prevent methotrexate adverse effects.

Physical and occupational therapy are also beneficial to rheumatoid arthritis patients. Patients should exercise on a regular basis to keep their joints mobile and to strengthen the muscles around their joints. Swimming and other joint-friendly movement routines that improve muscle strength include: Yoga, and tai chi are examples of movement exercises that are gentler on the joints while increasing muscle strength. Applying heat and cold packs before and after exercise helps to reduce pain, symptoms. Different forms of connective tissue collagen are being studied in attempt to better understand and minimise the activity of the rheumatoid arthritis condition. Finally, in terms of science, newer and better molecular mechanisms, improvements and improved understanding of molecular mechanisms In the near future, treatment alternatives will be available.

CONCLUSION

Rheumatoid arthritis is a crippling chronic inflammatory disease that can cause joint damage and long-term disability. Early detection and intervention are critical for avoiding serious injury and the loss of vital physiological functions. The treating physician might consider following T2T recommendations by first identifying the goals and then implementing protocols for achieving and assessing them. Additionally, early referral to a professional can assist ensure better treatment outcomes. We now have a greater knowledge of disease pathways because to breakthroughs in molecular medicine, which aids in the development of more effective medicines. Old therapeutic modalities have been improved, while new ones have been developed. Gene array analysis is becoming useful in determining which patients will be more responsive to specific medications.

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