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Rheumatoid Arthrities: Etiology Pathophysiology and Modern Treatments

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease that affects the joints. Age, gender, genetics, and environmental exposure are all factors (cigarette smoking, air pollutants, and occupational). If untreated, felty syndrome, rheumatoid vasculitis, and irreversible joint damage might occur, necessitating splenectomy. Because there is no cure for RA, treatment seeks to reduce pain and prevent further damage.

To develop effective RA treatments, researchers must first understand how the disease advances in people and how pathogenic pathways influence this progression. Modern pharmacologic therapy have made tremendous progress in obtaining illness remission without joint deformity (including conventional and biological treatments as well as novel potential small-molecule disease-modifying drugs). Despite this, many RA patients do not respond well to conventional treatments, necessitating the development of novel drugs. This comprehensive review of current advancements covers RA causation, disease-modifying drugs, and prospective RA therapeutics. This section summarises the various RA-related therapies available in the past and now.

Keywords- Rheumatoid arthritis, Pathogenesis, Etiology, Modern treatment.

I. INTRODUCTION

Females are more likely than males to be diagnosed with rheumatoid arthritis (RA). In 2002, the prevalence rate varied from 0.5 to 1% of the population. Rheumatoid arthritis is a common cause of disability and death among the elderly (RA). Synchronous joint involvement can cause edoema, redness, and possibly range of motion limits[1].

Early diagnosis is the essential improvement metric for the most ideal outcomes (i.e. reduced joint destruction, less radiologic progression, no functional disability, and DMARD-free remission). A comprehensive history and physical examination are used to make an early diagnosis, which is then confirmed by blood testing and imaging studies. In terms of why a RA diagnosis takes longer than expected, both the patient and the clinician appear to be responsible[2,3]. Involvement of patients, delay to adequate treatment following beginning of symptoms, and doctor's diagnostic ability all impact RA treatment and outcome. Poorly controlled or severe illness can cause extraarticular symptoms such granulomas on the lung, pericarditis/pleuritis, and small vessel vasculitis.

Despite the lack of a cure for RA, the treatment plan aims to speed up diagnosis and reduce disease activity (LDAS). The Disease Activity Score (DAS-28), Simplified Disease Activity Assessment Index (SDAI), and Clinical Efficacy Index (CEI) are all composite scales (CDAI). To achieve complete remission (clinical remission), rheumatologists must regularly evaluate disease activity[4].

NSAIDs and corticosteroids have been demonstrated to relieve stiffness and pain, but not to impede the progression of the disorder. The efficacy of DMARDs has been studied extensively over the last two decades due to its capacity to successfully reduce disease activity and joint deformity[5].

Conventional synthetic medications, biological DMARDs, and new prospective small molecules are all included in this class of therapy possibilities. These drugs are rarely utilised in modern therapy. There are now many bioactive antirheumatic drugs on the market. Anti-TNF (Amjevita), anti-CD20 (Truxima), anti-IL-6 receptor (Kevzara), anti-RANKL (Pralia), and a JAK inhibitor (Olumiant). Many patients do not achieve long-term remission despite new drugs and treatment regimens, necessitating new therapeutic options[6-9].

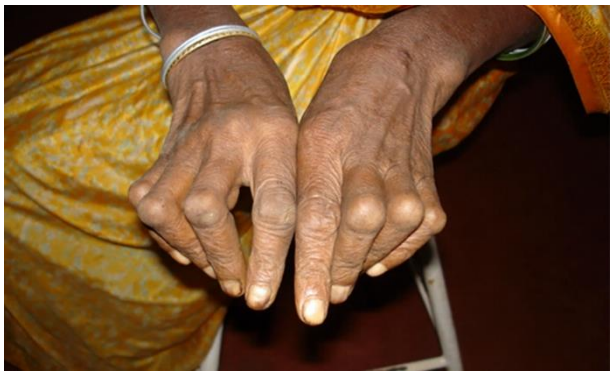

Fig 1: A classic example of joint deformities associated with rheumatoid arthritis.

II. ETIOLOGY

RA's cause is unknown. It's thought to be a genetic-environmental product. The overall MZ concordance rate was 15% and the dizygotic concordance rate was 5% among 91 monozygotic and 112 dizygotic British twin pairs[10]. Seropositive rheumatoid arthritis has a heritability of 40-65%, while seronegative has a heritability of 20%. The HLA-DRB1*04, *01, and *10 alleles have been related to an elevated risk of rheumatoid arthritis. These HLA-DRB1 alleles contain a common epitope (SE) and conserved five amino acid sequences in the third hypervariable region of their DRB1 chain[11-14]. The STAT-4 and IL-10 genes, which encode signal transducers and transcription activators, may also contribute to RA vulnerability. SNPs in PSORS1C1, PTPN2, and MIR146A genes link severe disease.

Heritable modifications without altering DNA sequence are epigenetic. Changes in DNA and chromatin may be to blame. Other mechanisms exist besides DNA methylation and non-coding RNA regulation. The tyrosine phosphatase SHP-2 (coded by PTPN11) enhances the invasiveness of RA-FLS. This led to altered epigenetic regulation of the PTPN11 gene and altered RA-ability FLS response[15]. The most common environmental risk factor for rheumatoid arthritis is cigarette smoking. Anti-citrullinated protein antibody (ACPA) positive people are more prone to RA due to genetics and smoking[16]. Changes in the gut microbiome have been associated to rheumatoid arthritis. Patients with RA (dysbiosis) have reduced gut microbial variety than healthy patients, resulting in altered gut microbiome composition. These microorganisms are on the rise. Collinsella alters gut mucosal permeability, increasing rheumatoid arthritis severity[17-20].

III. PATHOGENESIS OF RHEUMATOID ARTHRITIS

These antibodies target two of the most frequent kinds of RA (ACPAs). The calcium-dependent enzyme peptidyl-arginine-deiminase converts a positively charged arginine into a polar but neutral citrulline (PAD). ACPAs can help patients with early undifferentiated arthritis determine if they will become RA, as they are found in approximately 67 percent of RA patients[21]. The ACPA-positive subset of RA is more aggressive than the ACPA-negative subset. The immune cell responses to citrullinated antigens are different in ACPA-negative RA than in ACPA-positive RA[22-25]The ACPA-negative fraction responded less well to MTX and rituximab. Future studies should examine the pathophysiology of these two subgroups. For this review, RA will be divided into stages, with an emphasis on the ACPA-positive subset. These stages might occur consecutively or simultaneously.

IV. TREATMENT OF RHEUMATOID ARTHRITIS

- ***First-Line Management:***

NSAIDS and Corticosteroids

First-line treatment targets pain and inflammation. NSAIDs including aspirin, naproxen, ibuprofen (Advil and Motrin), and etodolac act quickly (Lodine). Aspirin is a good anti-inflammatory for RA because it inhibits prostaglandins. It's one of the oldest NSAIDs for joint pain. High doses of aspirin can cause tinnitus, hearing loss, and gastrointestinal discomfort. Since the debut of aspirin, other NSAIDs have appeared on the market, all proving to be effective. These drugs also require fewer daily doses[26]. NSAIDs block cyclo-oxygenase, preventing prostaglandin, prostacyclin, and thromboxane formation. Among the most common side effects include stomach pain, ulcers, and intestinal haemorrhage. Symptoms can be reduced with meals, antacids, proton pump inhibitors, or misoprostol (Cytotec), Celecoxib (Celebrex), a newer NSAID, with fewer GI side effects than celecoxib (Celebrex)[27-30].

However, corticosteroids are more potent anti-inflammatory medications than NSAIDs. Anti-inflammatory medications are used to treat RA flares and exacerbations. Intra-articular corticosteroid injections can help relieve local inflammation. Limit phospholipid release and minimise eosinophil activity. These drugs can weaken bones and promote weight gain, as well as diabetes and immunosuppression[31]. Advise patients to take calcium and vitamin D supplements regularly to reduce bone loss. As a patient's condition improves, gradually lessen the dosage. The HPA can be reduced by abruptly stopping injectable or oral corticosteroids. This can cause RA flares[32-34].

NSAID classification and pharmacology

Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally categorised by their chemical structure; plasma half-life; and COX-1 versus COX-2 selectivity (Table 1). Low pH areas are more likely to be inflamed, hence the low pK values of most NSAIDs make them more likely to accumulate at these

locations[35]. This link is usually a clear correlation between the short half-life of low-pK compounds and the low pK of nonacidic compounds such as Nabumetone. Classifying NSAIDs based on plasma half-life may be challenging because these medications tend to collect in synovial fluid, where the concentration of drug may remain more constant than in the plasma[36]. NSAIDs with a short half-life could theoretically be given less frequently than their plasma half-life indicates. It takes longer for NSAIDs with longer half-lives to reach steady-state plasma concentrations. After a few days to many weeks (depending on the exact half-life), plasma levels of drugs having a half-life of more than 12 hours tend to remain stable between doses. Because synovial fluid contains less albumin than plasma, the total bound and unbound drug levels in synovial fluid are often lower than in plasma with NSAIDs with longer half-lives. There may be an increased risk of side effects with NSAIDs with longer half-lives or extended release formulations[37-40]. It is anticipated that COX-isozyme selectivity will play a major role in defining the relative risk of gastrointestinal and cardiovascular complications for each NSAID.

Table 1: Classification of Common NSAIDs [41-45]

Class	Subclass	Drugs
Carboxylic acids	Salicyclic acids	Acetylsalicyclic acid Trisalicyliate Salsalate
	Acetic acids	Diclofenac Sulindac Tolmetin Ketorolac Indomethacin
	Propionic acis	Ketoprofen Ibuprofen Naproxen Fenoprofen
Enolic acids	Pyrazolones Oxicams	Piroxicam Meloxicam
COX-2 selective	Sulfonamide Nonacid	Celecoxib Lumaricoxib

Therapeutic effects of NSAIDS in rheumatic diseases

As first-line medications for the treatment of many different inflammatory disorders, NSAIDs are routinely used. In double-blind, randomised clinical trials of inflammatory arthritis, NSAIDs have been compared with placebo, aspirin, and each other[46]. Clinical studies of NSAID efficacy in RA and OA most typically adopt a design whereby the current NSAID is withdrawn and the patient must show an increase in symptoms or flare to enter the research. The American College of Rheumatology-20 is the most commonly used primary outcome measure, but there is significant heterogeneity[47]. In individuals with active RA who are not using corticosteroids or other anti-inflammatory medicines, NSAIDs show greater efficacy over placebo within one to two weeks [48]. Traditional NSAIDs and COX-2-selective NSAIDs are almost always equivalent in efficacy when doses are acceptable. In spite of the fact that NSAIDs relieve pain and stiffness, they rarely alter radiographic progression or acute-phase reactants. Ankylosing spondylitis, ankylosing spondylitis, gout, and systemic lupus erythematosus have all been shown to benefit from NSAID anti-inflammatory properties[49-51]. As a result, their efficacy in the treatment of reactive arthritis and psoriatic arthritis, as well as acute and chronic bursts and tendinitis, is well recognised.

Analgesic effects of NSAIDs can be achieved at lower doses than those required to control inflammation. NSAIDs work as analgesics by inhibiting the production of PG in peripheral tissues and the brain. When it comes to the peripheral nervous system, PGs don't actually cause pain, but they do make nociceptors more sensitive to the effects of mediators like bradykinin and histamine [52]. For example, the activation threshold for tetrodotoxin-resistant sodium channels on sensory neurons is reduced following inflammation or severe damage. Aside from NSAIDs and acetaminophen, PGs also play a key role in neuronal sensitization in the central nervous system. The dorsal horn of the spinal cord expresses COX-2 by default, and this expression rises in response to inflammation [53]. Neuropathic pain is a result of spinal neurons and microglia being activated by centrally produced PGE2 [54-56]. Experimental pain reductions in mice lacking in either COX-1 or COX-2 show that both COX-1 and COX-2 play a role.

Opioid Analgesics

The usage of opioid analgesics for RA patients was examined by Whittle et al. Codeine, dextropropoxyphene, and tramadol may be useful in the short-term management of RA pain, but the side effects exceed the benefits. To begin with, they urge that different analgesics be tried out[57].

- ***Second-Line Management:***

Disease-Modifying Antirheumatic Drugs

A second-line therapeutic approach aims to slow or stop joint deterioration and deformity. Slow-acting drugs take weeks or months to work. DMARDs can help reduce the risk of developing lymphoma from RA[58].

Second-line treatment commonly includes methotrexate (MTX) (also considered an anchor drug). Folic acid analogue prevents dihydrofolic acid (FH2) from attaching to folinic acid-converting enzymes (FH4). Purine and pyrimidine metabolism is hampered, as is amino acid and polyamine synthesis. Because MTX is an immunosuppressive drug that might cause liver and bone marrow damage, regular blood tests are required. Folic acid pills can lessen side effects. It's a fantastic DMARD choice because it's effective, has few side effects, and can be dosed as needed[59]. Until date, there was no proof that combining MTX with typical synthetic

DMARDs was preferable to MTX alone. Biological and synthetic DMARDs are believed to be superior than MTX, while having more adverse effects and costing more.

Plaquenil (Hydroxychloroqyine) is an antimalarial that can be used long-term to treat RA (RA). This drug reduces monocyte-derived cytokines. GI, skin, and CNS are among the most prevalent side effects. High doses of this drug may cause eye damage. Patients taking this medication must see an ophthalmologist regularly[60].

DMARD sulfasalazine (Azulfidine) is often used to treat IBS. Anti-inflammatory medicines can be used with this DMARD to treat the illness. Researchers have yet to discover this drug's mechanism of action in treating RA. After treatment, sulfapyridine, a reduced version of the drug, may suppress IL-8 and MCP secretion (MCP)[61-64]. The drug's side effects include rashes, gastrointestinal and nervous system issues. If you are allergic to sulfa or salicylates, avoid this product.

Gold salts, such as aurothioglucose, auranofin, gold sodium thiomalate, D-penicillamine, are frequently used to treat RA (such as Solganal and Ridaura). They require regular blood and urine testing to check the bone marrow and kidneys[65]. They are less frequently used since that MTX is more effective. In addition to azathioprine (Imuran), cyclophsphamide (Cytoxin), chlorambucil (Leukeran), and cyclosporine (Sandimmune) may be used to suppress the immune system.

- ***Newer Medications***

To inhibit ribonucleotide uridine monophosphate pyrimidine production, leflunomide is converted to malononitrilamide, a strong inhibitor. It reduces RA symptoms and inhibits its progression[66]. It works best when paired with MTX, although it can also be used alone if MTX doesn't work. Side effects include ILD, neuropathy, dermatitis, and bone marrow loss. Side effects include hypertension.

Biological DMARDs, or biologics, can slow the deterioration of joints caused by RA. This style of therapy is associated with a "direct, defined, and targeted" approach. However, the risks of biologics, such as increased infection risk, must be recognised. MS and lymphoma are two more serious side effects[67-70].

TNF, a messenger protein, causes joint inflammation (TNF). Adalimumab, golimumab, and certolizumab pegol (Cimzia) are all TNF inhibitors that work by preventing the recruitment of pro-inflammatory cells[71]. This is why these medications work. If they don't work, further medicines are suggested. They are expensive and their efficacy in treating RA patients at various stages of the disease and with varying mechanisms of action is constantly being researched. They are widely used with other DMARDs besides MTX. Congestive heart failure and demyelinating diseases should avoid TNF inhibitors. Biologic drugs can be given in several ways[72-75].

Anakinra (Kineret) is injected daily. This substance binds to IL-1, the chemical messenger of inflammation. It is not used as often as it could be due to its low response rate compared to other biologics. Rituximab can reduce B cells responsible for inflammation and abnormal antibody production (Rituxan)[76]. When TNF inhibitors fail in RA, this drug can be used as a backup. Rituximab is also beneficial in treating RA comorbidities such vasculitis and cryoglobulinemia. It is given as an intravenous infusion in two doses every six months. Abatacept (Orencia), a biologic, inhibits T cell activation. Patients get an intravenous infusion once a month and a subcutaneous injection every week. This drug is given to patients who have failed to respond to other DMARDs[77].

Tocilizumab, a biopharmaceutical, inhibits IL-6 (Actemra). Weekly or monthly intravenous infusions deliver it. Patients who have not responded to other DMARDs can also benefit from this medication. And lastly, tofacitinib (Xeljanz) works by blocking Janus kinases, which are inflammation-related enzymes. So it's a JAK inhibitor. This drug is used to treat MTX resistance. Tofacitinib is used orally once or twice daily, alone or with MTX. It shouldn't be taken with other immune suppressants such biologics.

- ***Other therapies***

Contrary to prior recommendations, RA patients should not avoid any foods. The idea that a person's symptoms could be exacerbated by diet is no longer accepted. Home treatments for RA are beneficial, though not as effective as DMARDs. Taking fish oils and omega-3 supplements can help relieve the symptoms of RA[78]. Cumin's anti-inflammatory properties may help patients with Crohn's disease. Calcium and vitamin D pills can help prevent osteoporosis. Conversely, folic acid may help reduce MTX side effects.

Physical and occupational therapy can help RA sufferers. They should exercise regularly to keep their joints functioning and muscles strong[79]. Yoga, tai chi, and swimming are all good joint-friendly exercises. Heat and cold packs can help relieve discomfort before and after exercise. Researchers are studying numerous kinds of connective tissue collagen to better understand and treat rheumatoid arthritis. Finally, new medicines based on molecular pathway understanding are predicted in the not too distant future[80].

V. CONCLUSION

There is no recognised cure for RA. The best method to treat this problem is with an interprofessional team. To be effective, nurses, pharmacists, and primary care physicians must educate patients. The nurse should educate the patient on various organ system symptoms and when to seek medical assistance. Exercise can help restore joint function. An occupational therapy consultation may help someone better manage their daily activities. The pharmacist should explain the side effects

of rheumatoid arthritis drugs with the patient. Patients should be educated on good lifestyle choices such as stopping smoking, maintaining a healthy weight, getting needed immunizations, and eating a balanced diet. As a social worker, you should ensure that the patient's home is habitable and that they have enough support systems. The patient should be encouraged to join support groups. It is common for people to get depressed due to their condition and the mental health services they receive. A diverse team of healthcare specialists can help RA patients. Rheumatoid arthritis is a severe chronic inflammatory disease that can cause joint damage and disability. Early identification and treatment can avert serious injury and loss of vital body functions. The treating physician should consider T2T recommendations, which suggest setting goals and implementing processes to achieve and evaluate them. Early referral to an expert can also help. Because of advances in molecular medicine, we now know more about disease pathways, which can help produce more effective treatments. New therapeutic techniques have been created. Genome array analysis can help predict which patients will respond best to certain drugs. Personalized treatment reduces the risk of disease development during the research phase. Gene array analysis is utilised to determine patient risk for more aggressive RA. The treatment of RA is predicted to improve significantly in the near future.

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