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RHEUMATOID ARTHRITIS DIAGNOSIS AND TREATMENT

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ABSTRACT:

Rheumatoid arthritis (RA) is a prevalent, systemic chronic autoimmune pathology characterized by progressive, symmetric synovial joint inflammation and diverse extra-articular manifestations affecting cardiovascular, pulmonary, and nervous systems. Driven by an intersection of environmental triggers and genetic factors,RA involves an intricate immune cascade where hyperactive T and B cells flood tissues with destructive master cytokines, including TNF-α, IL-6, and IL-1. This process leads to chronic synovitis, aggressive pannus formation, and structural bone and cartilage erosion. Secondary neuroendocrine imbalances and hormonal deficiencies also contribute to this pathology.Diagnosis centers on localized small-joint swelling and prolonged morning stiffness lasting greater than six weeks, supported by elevated inflammatory markers (CRP, ESR) and highly specific serological markers like anti-cyclic citrullinated peptide and rheumatoid factor (RF). Early structural changes are monitored using ultrasound, MRI, and X-ray imaging.Management requires an early, aggressive, and multi-tiered pharmacological approach paired with physical therapy. While NSAIDs and glucocorticoids offer rapid, symptomatic pain and inflammation relief, systemic disease control relies on conventional non-biologic disease-modifying antirheumatic drugs (DMARDs)—anchored by Methotrexate. Patients refractory to standard therapies are escalated to targeted biologic DMARDs—which directly neutralize specific cytokines or immune cell signals (e.g., TNF-α inhibitors, rituximab, abatacept, tocilizumab)—or targeted synthetic JAK inhibitors. Timely, targeted therapeutic intervention remains vital to preventing permanent joint destruction and long-term disability.

INTRODUCTION

Reumatoid arthritis is the most common inflammatory arthritis and is a major cause of disability[1].Rheumatoid arthritis (RA) is defined as a systemic autoimmune pathology associated with a chronic inflammatory process, which can damage both joints and extra-articular organs, including the heart, kidney, lung, digestive system, eye, skin and nervous system[2,3].Numerous types of arthritis have been investigated and described in order to classify them into non-inflammatory arthritis (osteoarthritis) and inflammatory arthritis caused by crystal deposition (gout), by bacterial and viral infections (Neisseria gonorrhea, or by autoimmune processes[4].

RA is a systemic chronic inflammatory condition that might affect numerous organs and tissues in a human body, but mainly it attacks the synovial joints. These methods result in the inflammatory synovitis response[5]

ETIOLOGY

The precise cause, definitive cure, and ultimate prevention of RA are as yet unknown, Genetic determinants of RA have been identified, and smoking is now established as an environmental risk factor. Autoantibodies to citrulline-containing proteins(ACPA) targets proteins modified from arginine to citrulline. These antibodies, which are highly specific to RA, is important in inflammation and destruction of joints. triggering a mix of immune and joint cells that causes inflammation and bone destruction. Pro-inflammatory cytokines play key roles in coordinating and amplifying these processes[6].

Three specific factors combine to cause joint damage in compromised immune systems:

1. Mild Cortisol Deficiency: Lacking enough natural cortisol, which is vital for immunity despite its bad reputation from high-dose medical misuse.
2. DHEA Deficiency: Lacking the main, understudied androgen hormone produced by the adrenal cortex.
3. Low-Virulence Infection: Infection by hard-to-detect organisms like mycoplasma that directly inflame and destroy joint tissues[7].

Clinical manifestations

Periarticular and articular manifestations:

Include severe mobility limitation, morning stiffness, joint swelling, and soreness in the affected joints.

Extra-articular Symptoms:

Nervous (numbness, tingling, or nerve damage from inflamed blood vessels), reticuloendothelial (enlarged spleen, swollen lymph nodes, and low white blood cell counts), cardiovascular (heart attacks, inflammation of heart sacs), and pulmonary (inflammation or accumulation of fluid around lungs)[8].

Cutaneous, hematological, neurological, pulmonary, cardiac, renal, and ophthalmic symptoms are examples of RA's extra-articular manifestations[9].

Risk parameters

Numerous environmental and genetic factors have been linked to either a higher or lower chance of developing RA.

GENETIC AND FAMILIAL RISK FACTORS FOR RA

Risk factors for RA that are genetic and familial

Among these characteristics is the overall higher incidence of RA in families, which results in estimates of familial risk with first-degree relatives exhibiting the highest risks.

RA has been linked to a number of dietary, behavioral, and environmental variables. Exposure to tobacco has the highest correlation with RA among a number of environmental variables[10].

Host related factors

1. Genetic elements

Having a close family member with RA raises your risk of getting the disease. First-degree relatives have an relative risk of RA that ranges from 2 to 5 and is comparable in men and women.

Your risk of acquiring rheumatoid arthritis is increased if you have a parent with an autoimmune condition like lupus ankylosing spondylitis.

Three primary epigenetic modifications

1. DNA methylation: The addition of chemical tags to DNA that usually cause genes to become inactive.

2. Post-Translational Histone Modifications: Modifications to the structural proteins (histones) that encircle DNA, changing the accessibility of genes.

3. Non-Coding RNAs: RNA molecules that aid in controlling gene expression but do not produce proteins.

Hormonal and Neuroendocrine Reproductive Factors

Estrogens are frequently pro-inflammatory, meaning they can either create or worsen inflammation in the body, in contrast to progesterone and androgens.

The Hormone Drop: Important anti-inflammatory, protective hormones including progesterone and androgens are reduced in both male and female RA patients.

As an essential endocrine mediator that regulates the immune system, vitamin D has immunomodulatory properties.

Mental illness:RA, depression, allergies, lung inflammation, chronic obstructive pulmonary disease, and chronic respiratory diseases are all associated with post-traumatic stress disorder.

Environmental Aspects:

Airborne exposures: inhaling toxic substances; infections; diet: food and beverages; socioeconomic factors: exposure at work[11].

Pathophysiology

Rheumatoid arthritis is a long-term, systemic autoimmune disease triggered by a mix of genetics, like the HLA-DRB1 shared epitope, and environmental factors like smoking. This interaction causes immune cells—specifically T cells and B cells—to become overactive and flood the body with inflammatory chemicals, most notably the master regulators TNF-alpha, IL-6, and IL-1. The disease cascade accelerates via the intracellular JAK-STAT signaling pathway when activated CD4+ T cells differentiate into Th17 cells to produce a powerful inflammatory protein called IL-17, while B cells release harmful autoantibodies, specifically Rheumatoid Factor and ACPAs, that worsen the attack. This coordinated assault forces a rush of mononuclear inflammatory cells into the joint lining, causing a painful swelling called synovitis and triggering the growth of abnormal new blood vessels. Over time, this swollen joint lining thickens into an aggressive, tumor-like tissue mass called a pannus. This pannus utilizes the RANK/RANKL pathway to activate bone-destroying osteoclasts that eat away at the bone structure, while local joint cells—specifically fibroblast-like synoviocytes and chondrocytes—release destructive matrix metalloproteinase enzymes that melt the surrounding protective cartilage[12].

Diagnosis

Affected Joints: Rather than the bigger distal interphalangeal (DIP) joints closest to the fingertips, the diagnosis mostly concentrates on the swelling and soreness of tiny joints (such as knuckles and wrists).

Symmetry: RA usually manifests symmetrically, impacting the same joints on both sides of the body.

Duration: To rule out transient viral or reactive arthritis, joint pain and swelling must persist for at least six weeks.

Blood Examinations (Serology)Although there isn't a single test that can definitively diagnose RA, blood tests can help determine the severity of the condition and confirm the diagnosis:

Anti-cyclic citrullinated peptide, or anti-CCP, is an extremely specific RA antibody. Increased levels are a clear sign of the illness.

About 70–80% of RA cases have rheumatoid factor (RF), while it can also show up in other inflammatory diseases.

Elevated CRP (C-Reactive Protein) and ESR (Erythrocyte Sedimentation Rate) are indicators of systemic inflammation in the body.

Imaging Studies: Imaging tests assist medical professionals in confirming joint injury and searching for early inflammation.

MRI and ultrasound are frequently used to identify early indicators of synovitis, or inflammation of the joint lining, before erosions are seen on X-rays.

X-rays: Although they could seem normal in the early stages, they are very helpful for tracking the long-term course of the disease and excluding other possible reasons of joint discomfort.

Morning Stiffness: One of the main symptoms of RA is prolonged joint stiffness (lasting longer than an hour), which usually gets better with exercise[13].

Treatment

Physical and occupational therapy, medication, and patient education make comprise a complete strategy to controlling rheumatoid arthritis. To preserve joint function and postpone disability, patients should be informed about the condition and sent to these auxiliary specialists. Nonsteroidal anti-inflammatory medications and low-dose oral or intra-articular glucocorticoids; disease-modifying antirheumatic medications; and, for patients who do not experience remission with standard therapy, consideration of biologic response modifiers (biologics) or targeted synthetic DMARDs (JAK inhibitors).

Options for pharmacotherapy in RA

Analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), Glucocorticoids, and Biologic and Non-biologic disease-modifying antirheumatic medications (DMARDs) are the five primary pharmacological types now in use. These treatments are often combined.

1. **Analgesics and Nsaids**

Short Acting-Ibuprofen, diclofenac, ketoprofen, and indomethacin.

Long Acting-Meloxicam, naproxen, celecoxib, nabumetone, and piroxicam.

Mechanism of action of NSAIDs:-

In Rheumatoid Arthritis, NSAIDs act as rapid-acting anti-inflammatory and analgesic agents by inhibiting COX-2 to halt joint-damaging prostaglandin synthesis, lowering peripheral and central pain sensitivity, and utilizing secondary G-protein or LOX pathways to dampen local immune activation.

COX-2 Blockage: Halt the production of inflammatory prostaglandins that cause joint heat and swelling.

Dual Pain Control: Lower pain sensitivity locally in the joints (peripheral) and globally in the brain/spinal cord (central).Use secondary mechanisms LOX and G-protein pathwaysto slow down local immune cells. Rapid Relief: Act quickly to reduce severe joint pain, swelling, and morning stiffness.

Key Limitation: Control daily symptoms effectively but do not stop permanent, underlying joint destruction[14].

When treating RA, analgesics and NSAIDs are typically taken temporarily until the DMARDs take effect.Acetaminophen is the most often used analgesic because to its minimal side effects.

The most common adverse effects include dyspepsia, peptic ulcers, bleeding, tinnitus, and cardiovascular disease.

Less common side effects include bromnospasm, aseptic meningitis, renal impairment, and abnormal electrolyte levels.

1. Glucocorticoids

Oral glucocorticoids (prednisolone),

Parentral glucocorticoids (methyl prednisolone)

Mechanism of action:

Glucocorticoids provide rapid symptom relief in rheumatoid arthritis (RA) by exerting potent anti-inflammatory and immunosuppressive effects. They act by freely crossing cell membranes to bind with glucocorticoid receptors, which then regulate gene transcription, inhibit pro-inflammatory cytokines, and rapidly alter cell signaling pathways to reduce joint swelling and pain**.**

Osteoporosis and skeletal fractures, gastrointestinal bleeding, peptic ulcer disease, diabetes mellitus, infections, cataracts, and compromised hypothalamic-pituitary-adrenal axis response are among the side effects.

Systemic effects, acute synovitis, osteonecrosis, tendon rupture, and septic arthritis.

2. Non biologic DMARDs

Methotrexate(MTX),sulfasalazine(SSZ),leflunomide,hydroxychloroquine(HCQ),

Methotrexate.

Mechanism of action

They work by broadly suppressing hyperactive immune responses. By doing so, these medications mitigate joint inflammation, reduce pain, and slow down or prevent structural damage and bone erosion.

7.5–10 mg per week is the starting dosage.The weekly dose is increased to 20–25 mg.

MTX is mostly eliminated via the kidneys, with the majority remaining unaltered in the urine.

MTX disrupts cell division and DNA synthesis.

Common side effects include rash, mouth ulcers, reversible baldness, increased rheumatoid nodule growth, and nausea the day following dosage.

Bone marrow suppression, liver cirrhosis (which is exacerbated by alcohol use), and pulmonary infiltrates/allergic pneumonitis are less common side effects.

Patients with immunodeficiency, severe hepatic problems, active viral diseases, or pre-existing bone marrow aplasia or cytopenias should not use MTX. Additionally, concurrent use of hepatotoxic medications or alcohol is not advised.MTX is obviously not advised for women who are pregnant or of childbearing age due to the danger of teratogenicity.

Sulfasalazine(SSZ)

30–50 mg/kg per day is the starting dose.Titrated up to 2.0–3.0 g daily.

Patients who are hypersensitive to sulfonamide derivatives or salicylates should not be administered SSZ. Additionally, patients with hepatic, renal, or hematological problems should not use it. It is safe to use SSZ when pregnant.

Common adverse effects include skin rash, pruritus, and gastrointestinal problems (nausea, vomiting, appetite loss, diarrhea).Males may also experience neurological symptoms such as headache, vertigo, or depression, as well as oligospermia with reduced motility.

Hepatitis, hemolytic anemia in individuals with glucose-6-phosphated hydroginase deficiency, leucopenia, bone marrow depression, and abdominal pain are uncommon side effects.

Hydroxychloroquine: Adults should start taking 400 mg daily. reduced to 300 mg daily after three months.

Typical adverse effects:

alopecia, skin rashes, diarrhea, nausea, bloating, and burning in the stomach.psoriasis and hyperpigmentation in places exposed to the sun.

Leflunomide

Loading dose of 100 mg daily for three days, then 10–20 mg daily after that.

Common adverse effects include skin rash, nausea, diarrhea, and reversible alopecia.

Rare side effects include persistent impaired liver function, infections, and severe bone marrow suppression.

3. Biologic DMARDs

Biologic therapies include the tumor necrosis factor (TNF) alpha inhibitors, anti-B cell therapy, T-cell co-stimulation blocker, anti-Interleukin 6 (IL-6), anti-Interleukin 1 (IL-1), and protein kinase inhibitors.

Mechanism of action:

Biologic DMARDs treat rheumatoid arthritis by directly neutralizing specific extracellular proteins, cytokines, or immune cells driving inflammation. By blocking these exact targets, they stop the immune system from attacking joint linings, thereby reducing pain, preventing structural damage, and halting disease progression

Patients with RA have high levels of TNF, a cytokine involved in systemic inflammation, in their serum and synovial fluid.

For instance, golimumab, certolizumab, adalimumab, etanercept, and infliximab.

Etanercept dosage: 25 mg twice a week or 50 mg once a week.

3 mg/kg of infliximab at 0, 2, and 6 weeks, then 3 mg/kg every 8 weeks.

50–100 mg of golimumab per month.

Common side effects:

headache, vomiting, diarrhea, rash, injection site reaction, bleeding, bruising, itching, cellulitis, respiratory tract infection, positive antibodies against double-stranded DNA, positive ANA (11%), and reactivation of latent tuberculosis (TB). Infliximab and adalimumab have a greater risk of reactivating Mycobacterium tuberculosis infection than etanercept.Anti-TNFs Patients with a history of demyelination, active infections like leg ulcers or long-term urinary catheters, and heart failure should not take anti-TNF.

Anti-B cell treatment

B cells are crucial to the pathophysiology of RA. Antibodies against the pan-B-cell surface marker CD-20 are used to target these cells. Anti-CD 19 and other targets are presently being assessed. Currently, the only approved anti-B cell treatment for RA is rituximab.

Rituximab

Rituximab is a monoclonal antibody that targets B-lymphocytes' CD20 antigen. rituximab binds to both human Fc receptors and the antigen on the cell surface, triggering complement-dependent B-cell cytotoxicity and cell death via antibody-dependent cellular toxicity.

1 g is delivered as an intravenous infusion on days 1 and 15 in conjunction with MTX; following courses may be given every 24–52 weeks if necessary, they may be repeated earlier, but no sooner than every 16 weeks**.**

T-Lymphocyte Co-Stimulation Blocker

For T-cells to be completely activated, they need two signals. The major histocompatibility complex (MHC) on the APCs and the T-cell receptor exchange the first signal. CD28 on T-cells and CD80/CD86 on APCs provide the second co-stimulatory signal. Although it has been identified, the inducible co-stimulator, another co-stimulatory receptor in T-cells, has not yet been investigated as a potential therapeutic target.

Abatacept

By attaching to CD80 and CD86 on APCs and preventing the necessary CD28 interaction between APCs and T-cells, abatacept, a selective co-stimulation modulator, prevents T-cell (T-lymphocyte) activation. Abatacept can be injected subcutaneously or intravenously. This

IV dose depends on your weight: people under 60 kg get 500 mg, those from 60 to 100 kg get 750 mg, and those over 100 kg get 1000 mg. After the first infusion, this dose is repeated every two and four weeks, then every four weeks after that. Every week, 125 mg is administered subcutaneously.

Anti-Interleukin-6

The inflammation and proliferation of synovial cells that define RA joint degradation are largely driven by IL-6. The only anti-IL-6 medication currently on the market is tocilizumab.

Tocilizumab

Tocilizumab is an IL-6 receptor antagonist. Once a month, it is administered intravenously at a dose of 8 mg/kg. Inflammatory stimuli cause endogenous IL-6, which promotes a range of immune responses. The production of cytokines and acute phase reactants is decreased when tocilizumab inhibits IL-6 receptors. Patients who have not responded well to MTX alone or to MTX + anti-TNF can benefit from using tocilizumab in addition to MTX.

Anti-Interleukin-1

Another significant pro-inflammatory cytokine in the aetiology of RA is IL-1. rheumatoid disease activity is correlated with higher IL-1 concentrations in plasma and synovial fluid. The only anti-IL-1 medication used to treat RA is anakinra.

Anakinra

Anakinra is an IL-1 receptor antagonist.

Anakinra is administered subcutaneously at a daily dose of 100 mg.

Patients with moderate to severe RA responded well to the addition of anakinra to a steady dosage of MTX.

Protein Kinase inhibitors

Protein kinases are tiny intracellular chemical enzymes that bind phosphate groups to other proteins to alter their function. There are more than 160 known kinases. The majority of kinases work on tyrosine, serine, or threonine. Four types of Janus kinase (JAK), a tyrosine kinase, have been identified: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2)

Jak Inhibitors

Kinase inhibitors specifically block JAKs, which mediate the signaling of growth factors and cytokines involved in immunological response and hematopoiesis.5 mg twice daily in

individuals with moderately to highly active RA who have not responded well to or are intolerant of MTX[15].

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