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RHEUMATOID ARTHRITIS – A CONCISED REVIEW

Rheumatology

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ABSTRACT

"Rheumatoid arthritis (RA) is a common autoimmune disease that is associated with progressive disability, systemic complications, early death, and socioeconomic costs". RA is an inflammatory disease chronic in nature with lining inflammation involving, T and B lymphocytes, fibroblasts, dendritic cells, macrophages and chondrocytes which subsequently cause destruction of the adjacent bone and cartilage. The disease affects primarily the synovial joints, causing pain, deformity and eventually limitation of function leading to substantial morbidity and accelerated mortality. It is basically a multifactorial disease which happens when other risk factors occurs simultaneously. RA requires life-long medications and treatments. The radiological damage occurs even before diagnosis. "Disease modifying anti-rheumatic drugs (DMARDs)" is biological - response modifying drugs which have been proved to reduce the disease progression. Combination therapy is more effective than monotherapy. Inadequately treated RA is allied with rise in death.

KEYWORDS

INTRODUCTION:

"Rheumatoid arthritis (RA) is a chronic inflammatory, autoimmune disorder characterised by a persistent joint inflammation leading to cartilage and bone damage, disability and eventually, to systemic complications including cardiovascular and pulmonary disorders". It is a disease of inflammatory origin mostly affecting the synovial joints which has a lining called synovium, a particular tissue in-charge of safeguarding the joint lubrication and nourishment. The pattern by which the synovial joints are involved is characteristic. The small joints of the upper and lower extremities are disturbed regularly, and more often observed bilaterally with a symmetrical appropriation, but whichever synovial joint could be included. The long-lasting and dynamic condition shows involvement of most joints according to the duration.

ETIOLOGY:

Similar to other autoimmune diseases, multiple factors are involved in etiology of RA. The monozygotic twin studies along with familial clustering studies shows that 50% of risk to develop RA is attributed by the genetic factors.(1) The shared epitope including DRB1, Human Leukocyte Antigen-DR45(HLA- DR45) and different other alleles are genetically associated with RA.(2) CD40 locus and STAT4 gene has shown high risk for RA in studies regarding genome association.(3) Smoking is the most important environmental cause for patients having a genetic risk for RA.—(4) Infections might retrieve an autoimmune response, but no specific pathogen is confirmed to cause RA.(5)

PATHOGENESIS:

The underlying trigger for RA is obscure. Literature proposes variations in the immune system can prompt progress of irregular inflammatory and immune responses, especially in joints lined by synovium. The inflammation could start few years afore the beginning of symptoms of RA.

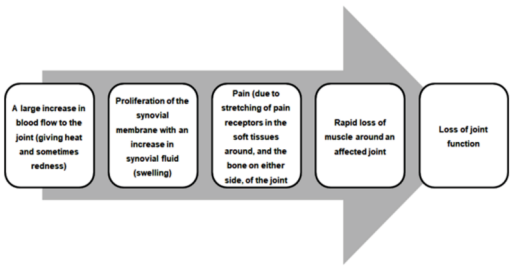

Figure 1: Progression of RA

If the inflammation cannot be controlled, cumulative damage may be caused to the joint due to the enzymes secreted by immune cells which can degrade proteins and can lead to pannus formation (hyperplastic inflammatory change of the synovial layer) which can invade the soft tissues and bone around the joint. The duration and amount of inflammation contributes to the severity of the disease. Progressive distortion, incapacity and loss of function occur as a result of the joint damage. Structures such as tendon sheaths with similar synovial lining might also undergo inflammation that may lead to breach in the ligament. Hence the control of inflammation in the initial stages of the condition may improve the prognosis.

Other than being an arthroidal disease, RA likewise has systemic manifestations. In these patients, proteins of the inflammatory process, for example, "Tumour Necrosis Factor-α (TNF-α)" are released in substantial amounts bringing about tiredness, fever, weight reduction and sweats. In addition, different systems of the body may likewise be influenced because of the inflammation bringing about hyposecretion of tears and salivation (Sjogren's syndrome) and nodules or swellings on the extensor surfaces, for example, backside of the elbow are involved in one thirds of the patients.

Inflammatory pathways leading to pannus formation are characteristic of RA. Erosion of the surrounding bone and destruction of cartilage occurs due to consequent pannus formation which is hastened by pro-inflammatory cytokines overproduction.(6) Family history of RA, elder age and female sex are the factors with high risk of RA.(7) Both current cigarette smoking and its history also shows higher risk for RA.(8)

Immunologic tolerance in Pregnancy leads to RA remission.(9) Parity have an impact on the risk of developing in the following manner; lesser risk of RA in parous women and breast feeding mother whereas irregular menstrual cycles and early menarche cause increase in risk for RA.(10) Oral contraceptive pills or vitamin E has no effect on RA risk.(11)

CLINICAL FEATURES:

Pain and stiffness in many joints are the typical presentation in RA. The metacarpo-phalangeal joints, proximal interphalangeal joints and wrists are the mostly involved joints. Morning stiffness with duration lasting for more than an hour is suggestive of an inflammatory etiology. Palpable synovial thickening on joint examination or visible boggy swelling owing to synovitis may be evident. Before the onset of clinically evident swelling, asymptomatic arthralgia may be present. Systemic symptoms such as low-grade fever, weight loss, and fatigue occurs in accordance with the active disease.(12)

Major inflammatory indicators may lead to severe problems, such as pulmonary fibrosis, pleural and pericardial effusions, or inflammation of the blood vessels. Vasculitis leads to inflammation of internal lining of the blood vessels which might cause plausible disturbing effects for the organs which are supplied by these vessels. Examples of inflammation of the blood vessels are scleritis of the eye and peripheral neuropathy (irreversible damage of nerve).Arthroidal Inflammation affecting the neck may be life threatening as it may cause unstable articulations which can exert pressure on the spinal cord leading to inadequate blood supply and neurological consequences affecting the extremities, bladder and intestinal function and/or the respiratory muscles and the respiratory control centres in the brain stem, which can potentially result in death.(13)

DIAGNOSTIC CRITERIA:

1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour
2. Arthritis of ≥3 joints	The qualified areas are PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hand joints	At least 1 area swollen in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas on both sides of the body
5. Rheumatoid nodules	Subcutaneous nodules over bony prominences, extensor surfaces, or around joints
6. Rheumatoid factor	Positive rheumatoid factor
7. Radiographic changes	Including erosions or periarticular demineralization

Table 1: "1987 ACR/EULAR Classification criteria for Rheu ma toid Arthritis"

The criteria mentioned in table 1 was providing a benchmark in defining the disease; however had a significant limitation that it was derived to distinguish established RA patients from the patients with other rheumatologic diagnoses and was not helpful in early diagnosis of the disease.

Therefore a working group of "The ACR and the European League Against Rheumatism (EULAR)" was formed in order to develop a different method of classifying the disease. The classification criteria were used as an aid in diagnosis but these criteria were not developed in order to be used as a referral tool in diagnosing RA for the physicians. Hence this joint group of ACR and EULAR was in charge of developing criteria which can act as an early diagnostic tool which resulted in framing the "2010 ACR/EULAR classification criteria" for RA.

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D;	
a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)#	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

Table 2: "2010 ACR/EULAR classification criteria for Rheum atoid Arthritis"

The new classification criterion redefines the older model of RA by means of focusing on the symptoms of earlier stages of RA which is also in accordance with persistent and/or erosive RA. The attention is refocused on the essential necessity for earlier diagnosis and establishment of efficient "disease-suppressing therapy" to prevent or reduce the incidence of adverse sequelae of the current pattern of RA.(15)

OTHER DIAGNOSTIC METHODS:

Autoantibodies are the characteristic feature of autoimmune diseases including RA.

- "Rheumatoid factor" (RF) is not a definite marker for RA as it could be seen in hepatitis C patients and even in normal healthy individuals.
- "Anti-citrullinated protein antibody" (ACPA) remains comparatively specific for Rheumatoid Arthritis and might perform a vital role in RA pathogenesis.(2) Approximately 50 to 80% of individuals with RA have RF, ACPA, or both.
- Antinuclear antibody (ANA) test may be positive in RA patients, which is of prognostic importance in juvenile cases. –(16)
- "Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)" levels are frequently elevated in active form of RA, and these level are now a part of the new criteria for RA.(15)
- ESR aids to track the disease activity along with reaction to the given medication.

FOLLOW UP DIAGNOSTICS:

- Complete blood count including differential count
- Kidney and liver function tests helps in deciding the treatment options, for example in case of renal insufficiency NSAIDs are avoided and methotrexate is not prescribed for individuals with hepatic disease.
- In chronic disease, mild anemia has been reported in 33 to 60% of RA patients,(17) even though before prescribing NSAIDs and corticosteroids, gastrointestinal bleeding have to be considered.
- Negative tuberculin test is needed or the latent tuberculosis should be treated before prescribing Biologic therapy, like a TNF inhibitor; this treatment may even cause Hepatitis-B react ivation.(18)
- Radiographic examination of extremities must be done to estimate specific erosive changes around the articular surfaces, which could be suggestive of aggressive subtype of RA.(6)

TREATMENT:

Once the disease is diagnosed and preliminary evaluation is performed, treatment must be started. For the management of RA guidelines has be developed recently,(19) on the other hand patient predilection similarly plays an important role. Women of motherhood age should be given special considerations since various drugs may show harmful effects over pregnancy. Minimising the pain and swelling and avoiding the loss of function, managing the quality of living and controlling the radiographic erosion changes and the systemic manifestations remains main objectives of the treatment. "Disease-modifying anti-rheumatic drugs (DMARDs)" forms the basis of RA therapy.

ACR Guidelines for Treatment of Rheumatoid Arthritis:

1. Regardless of disease activity level, use a treat-to-target strategy rather than a non-targeted approach
2. If the disease activity is low, in patients who have never taken a DMARD: • use DMARD monotherapy (MTX preferred) over double therapy • use DMARD monotherapy (MTX preferred) over triple therapy
3. If the disease activity is moderate or high, in patients who have never taken a DMARD: • use DMARD monotherapy over double therapy • use DMARD monotherapy over triple therapy
4. If disease activity remains moderate or high despite DMARD monotherapy (with or without glucocorticoids), use combination DMARDs or a TNFi a non-TNF biologic (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone.
5. If disease activity remains moderate or high despite DMARDs: • use a TNFi monotherapy over tofacitinib monotherapy • use a TNFi + MTX over tofacitinib + MTX.
6. If disease activity remains moderate or high despite DMARD or biologic therapies, add low-dose glucocorticoids.
7. If disease flares, add short-term glucocorticoids at the lowest possible dose and for the shortest possible duration.

Table 3: 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

Disease-modifying anti-rheumatic drugs (DMARDs):

DMARDs can be biologic or non-biologic.(12) The recombinant receptors as well as monoclonal antibodies to block the pro-inflammatory cytokines which are liable for the disease symptoms. Methotrexate is the primary treatment choice recommended in individuals through active form of RA, if not tolerated or not contraindicated,(19)[18]Leflunomide could be used instead of methotrexate, even though deleterious outcomes on gastrointestinal

system is comparatively common. "Sulfasalazine" or else "hydroxychloroquine" could be suggested as monotherapy for better prognosis patients.(19)[18]

Combination therapy is comparatively efficient than monotherapy; yet greater adverse effects might be present. If RA is resistant to a "non-biologic DMARD", a biologic DMARD must be introduced which might be a TNF inhibitor which are the first line drug of this category.(19)[18] If they are also ineffective, other biologic treatments could be taken into consideration. Due to increased rate of adverse effects not more than one biologic therapy is done simultaneously.(19) Drug therapy in RA involves NSAIDs and corticosteroids in various routes like intra-articular, oral and intramuscular to control inflammation and pain for a short interval and DMARDs remains the preferred treatment of choice.(19)[18]

OTHER TREATMENTS:

Dietary interventions, was studied in treating RA but no convincing evidence was derived.(20)[21]Despite certain positive effects, lack of substantiation was seen for the effectiveness of acupuncture in patients with RA.(22)[23] Therapeutic ultrasound and thermotherapy for RA ought to be studied adequately.(24)[25] A detailed review about the role of herbal managements for RA by Cochrane group established that gamma-linolenic acid and *Tripterygium wilfordii* have prospective benefits but serious adverse effects of this treatment should be informed to the patients.(26)

Physical exercise to develop muscular strength and value of life in patients with RA has been supported by Randomised Controlled Trial (RCT) studies,(27) however such exercise programs have not shown any decrease in the disease activity, radiographic damage or the pain scores.(28) Ankle range of motion has been improved by Tai chi technique even though further studies are mandatory to confirm its benefit.(29)

Remission is attainable in 10 to 50% of RA patients, which is more to be expected in males, individuals below 40 years of age, non-smokers, patients by way of delayed beginning of disease, disease of shorter duration, with trivial activity of disease, without raised acute phase reactants and without positive RF and ACPA findings.(30)

Once the disease is organised, the dosages of the medicines must be carefully reduced to the minimal necessary dosage. Frequent monitoring of patients is required to make sure steady symptoms, with rapid raise in the dosage of medicine is suggested for sudden aggravation in the disease.(18)

In cases with severe joint damage and not responding to medications, joint replacement is suggested. Longstanding results are good; with 4 to 13% of "large joint replacements" needs review before 10 years. Hip joints and knee joints are the frequently replaced joints.

COMPLICATIONS IN RA:

Even though RA is considered to be an arthroidal disease, it can also act as a systemic disease adept of involving many organ systems. RA patients have

- A two-fold greater risk for lymphoma that is supposed to be triggered by the core inflammatory progression.
- A higher risk of coronary heart disease. TNF inhibitors are contraindicated in Class III or IV "congestive heart failure" (CHF), as it could aggravate CHF outcomes.
- In RA patients with malignancy, precaution should be taken not to use DMARDs continuously, specifically TNF inhibitors. In patients with active viral, fungal and bacterial infections, certain therapies such as leflunomide, methotrexate and Biologic DMARDs must not be prescribed.(19)
- RA patients survive 3 to 12 years lesser when compared with general population.
- Higher mortality rate in RA patients is chiefly because of accelerated heart diseases, mainly in persons with chronic inflammation and higher disease activity.

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