Review Article – Rheumatoid Arthritis, Diagnosis and Treatment

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Abstract— This review article will focus on Etio-pathogenesis, Clinical features, Diagnosis and treatment of Rheumatoid arthritis (RA).Quick review of salient features on RA will help Rheumatologists and PCPs to diagnose RA at the initial visit and start a therapeutic regimen that could prevent disability in future.

Index Terms— Rheumatoid arthritis (RA), Etio-pathogenesis, Clinical features, Diagnosis and treatment, arthritis, inflammatory disease, swelling and stiffness.

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic condition with systemic involvement .RA has both articular symptoms and extraarticular manifestations. RA is an inflammatory disease of the joints [1].Predominant articular symptoms are pain, swelling and stiffness. RA is marked by flares and remission .It shows varied disease activity

Still its etiology is unknown.Genetic background, environmental factors [2] ,immune dysregulation are considered as possible causative factors for the occurrence of the disease .It affects 0.5-1.0% of the general population.Hallmark feature of RA is symmetric, erosive synovitis.Uncontrolled synovitis leads to joint and cartilage damage, significant disability, and reduction in quality of life. Advances in therapeutic interventions have revolutionized the clinical management of patients. Biologic agents in combination with conventional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX) control disease activity,clinical manifestations and the target goal is disease remission.Early aggressive treatment is highly recommended to reduce future complications. Timely diagnoses, monitoring disease activity and therapeutic response are the keys.

Current approach that is a mainstay of rheumatology is to rely on clinical examination, laboratory parameters, and conventional radiography (CR) for patient evaluation. Till date no cure has been found for RA, but the goal of management plan is to suppress diseases activity, retard the progression of disease, adequate management of comorbidities.

This review article will focus on Etio-pathogenesis, Clinical features, Diagnosis and treatment of Rheumatoid arthritis (RA).Quick review of salient features on RA will help Rheumatologists and PCPs to diagnose RA at the initial visit and start a therapeutic regimen that could prevent disability in future.

2. DISCUSSION

2.1. Epidemiology

RA affects it affects 0.5-1.0% of the general population3 and is more common in females 4 .The prevalence varies in all parts of the world .Prevalence is low in South Africa and Nigeria .This prevalence rate suggests association of RA with luxurious life style of developed countries. Onset is triggered by interaction of genetic background, environmental factors and lifestyle factors all together.

3. GENETIC FACTORS

RA causation has a genetic basis .Studies have concluded that the prevalence of RA is more in first degree relatives of RA patients .[5,6].Disease concordance in identical twins is 15 % as compared to non identical twins which is 4 % ,12 MHC II ,Alleles of major histocompatibility complex class II have been identified as risk

alleles for RA [7],Amongst all genes Human Leukocyte Antigen (HLA DRB1) gene [8].Shared epitope hypothesis emphasizes on the concept of rheumatoid epitope i.e conserved amino acid sequence that is shared by multiple risk alleles of the HLA –DRB1 genes and RA susceptibility relies on these alleles .Non MHC alleles ,recently identified include PTPN22 ,[9] ,STAT4 [10] and TRAF 1-C5 [11].Contribution of MHC alleles is 30 % and non MHC alleles is 3-5% .PTPN22,pose the strongest risk in European population .16.HLA-DRB1 and PTPN22 risk alleles show strong association with most severe disease forms of RA .[12,13.]This could be used to stratify RA patients depending on their disease severity

4. HORMONAL FACTORS

Females are 2-3 times more prone for RA then men [4] .Nulliparous women has more risk while pregnancy has a beneficial effect on RA. [14]. During pregnancy alloantibodies develop against paternal HLA 28 and inhibit the function of HLA –DR alleles and reduce the disease severity .This helps us to conclude the role of hormones in development of RA by interaction with genetic factors.

5. INFECTIOUS AGENTS

Many infectious agents role have been investigated in the pathogenesis of RA and most important of consideration is the Epstein –Barr virus, [15] .This virus shares the same HLA –DRB epitopes with type II collagen found in the cartilage of the joints .Immunological response triggered on exposure to EBV, also triggers response in the joints due to similarities of the virus to type II collagen and causes synovial inflammation .[16] High prevalence of RA are found in in population inflicted by EBV.[17]

5.1. Smoking

Smoking is a key environmental factor of consideration in the etiology of RA.[18,19] and it has also been found smoking interacts with HLA –DR SE in RA patients[20].Protein citrullination plays vital role[21].In protein citrullination ,there is post –transcriptional modification of arginine into citrulline which cause major alterations in the structure and function of various proteins[22].Antibodies to citrullinated proteins ,such as anti –cyclic citrullinated peptide (anti-CCP) antibody are the biomarkers that are used for definitive diagnosis of RA patients since they represent protein citrullination and precede the development of RA[23-25.]This protein citrullination has also been considered a cause of RA[26].Smoking increases the conversion of arginine to citrulline by increasing the activity of peptidylarginine deiminases in the alveolar tissue of smokers..Smoking in HLA –DR SE genes patients is associated with higher risk of developing of anti –CCP positive RA[21].HLA –DR SE genes smokers give more pronounced autoimmune response by facliltating protein citrullination in the lungs .Silica is also a risk factor for causation of anti-CCP positive RA .Silica and smoking play synergistic role and give more stronger effect . This shows environmental factors via inhalation are an important pathway in the pathogenesis of RA through protein citrullination in alveolar tissue.

5.2. Pathogenesis

RA is an autoimmune disease in which autoantibodies come into play and cause joint degradation and destruction .Antigen presenting cells (APC s) like macrophages, dendritic cells and B cells form complexes with MHC II proteins which engulf antigens, digest them and display the fragments of the antigen on the groove on their surface .T cell receptors on CD4+ T cells recognize the antigens bound to MHC II proteins and CD4+ T cell become activated [27]

CD4+ T cells stimulate the production of pro-inflammatory cytokines TNF-ALPHA,IL-1,IL-6,IL-17[27].There is recruitment of inflammatory cells which is facilated by IL-8,monocyte chemoattractant protein -1 and macrophage inflammatory protein –alpha [29] .The next step is the leukocyte and endothelial interactions [30] .Complement factors C3a and C5 attract CD4 + T cells ,B cells and macrophages to the endothelium

and then E selectin facilitate slow rolling of leukocytes along the endothelium until firm adhesions are established .[31] Adhesion molecules allow transmigration of leukocytes to the site of inflammation .[31] Proinflammatory cytokines increase the expression of adhesion molecules and play active role in leukocyte-endothelial interactions.[32] The resultant effect of these mechanisms is angiogenesis ,synovitis and pannus formation .[27].This cause articular symptoms of pain and swelling of the joints .[30].Pannus has a high concentration of macrophages ,T cells ,B cells and is a hallmark of RA. Macrophages in pannus further release proinflammatory cytokines which in turn stimulate synovial fibroblasts ,osteoclasts and chondrocytes to cause cartilage and bone erosion [33]. Main culprits are TNF-alpha,IL-1 and IL-6 and perpetuate joint destruction.Continued activation of CD4+ T cells by APC s is the underlying cause for chronic inflammatory nature of RA .Bcells are the most prominent APC s in the synovium .Activated T cells stimulate the conversion of B cells to plasma cells and antibody production .1.RF is the best example of this sequale and is responsible for severe articular disease .RF is also responsible for extraarticular manifestations such as CVD in RA patients which is a MCC of mortality in RA patients .[34]Thus in RA patients both T cells and Bcells play vital role and contribute to chronic inflammation .

6. CLINICAL FEATURES OF RHEUMATOID ARTHRITIS

Joint symptoms are predominant in RA and mainly consist of pain ,swelling and stiffness .The disease has varied presentations with slow and gradual onset to very rapid onset .The MC joints affected are the MCP,PIP,MTP joints and the wrists .Other joints affected in some of the patients are the shoulders ,elbows,knees and ankles .Affected Joints display cardinal signs of inflammation such as redness,tenderness ,swelling and warmth .MCP is the earliest joint affected .[36].RA is known to cause physical deformities and disability[37].Irreversible deformities caused are pes planus ,hammer and claw toes ,joint subluxations [36].

Extraarticular manifestations are common in RA patients with high disease activity .Table 1.Hence comorbid conditions should be treated adequately in the management plan of RA patients.

7. DIAGNOSIS

Diagnosis of RA rests on patient's history, physical examination, clinical symptoms and signs, laboratory and radiological features [36]

The 1987 revised criteria for the classification of RA by the ACR (Table 1)[44]

Table No -1

ACR/EULAR (2010) Classification Criteria for RA

ACR/EULAR (2009) Classification Criteria for Rheumatoid Arthritis [44]

Symptom Duration (as reported by patient)	**Points**
▪ < 6 weeks	0
▪ > 6 weeks	1

Joint Distribution	**Points**
▪ 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

Serology	**Points**

- RF- and CCP-

0

- Low RF+ or CCP+

2

- High RF+ or CCP+

3

Acute Phase Reactants

Points

- Normal ESR or CRP

0

- Abnormal ESR or CRP

1

RF: rheumatoid factor. CCP: anti-citrullinated citric peptide. ESR: erythrocyte sedimentation rate. CRP: C-reactive protein. Low: < 3 x upper limit of normal (ULN). High: > 3 x ULN

Requirements: patients who have at least 1 swollen joint and not better explained by another diseaseto be applied. A score ≥ 6 points is required for classification as definite RA.

Patients are diagnosed with RA when they meet 4 out 7 of the criteria, with 1-4 being present for atleast 6 weeks

8. IMAGING

Newer imaging modalities are used to diagnose RA patients such as ultrasonography,MRI,CT.These imaging methods detect synovitis ,effusion ,joint subluxation and erosions .Ultrasound is also used performing joint aspirations and injecting steroids into the affected joints .

9. ASSESSMENT OF DISEASE ACTIVITY

Till date there is no cure for RA Hence the goal of management is control the disease activity and monitor the progression of the disease.MC assessment tool used to monitor the disease activity is the DAS 28.Response to treatment is monitored by ACR and European League against Rheumatism (EULAR) response criteria .Table 1 [44]

HAQ is used to assess the effects of disease severity on the patient's functional ability .HAQ scores are inversely proportional to functional abilities of the patients.

10. TREATMENT OF RA

Careful selection of drugs for treatment of RA patients is vital and it rests on disease severity, symptoms .The goal of treatment is to reduce inflammation and stop the destruction of the joints and bones .Its highly stressed on early aggressive treatment to reduce disability percentage.

NSAIDS-Most commonly used as the first line of treatment till investigations are awaited .MC used are aspirin and ibuprofen. Their target is to reduce the inflammation but they were unable to reduce RA disease progression .Mechanism of action of NSAIDS is inhibition of cyclooxygenase pathways.76.Most common side effect is gastric bleeding .COX -2 inhibitors have limited GI side effects and increased risk of cardiac events.This effect of COX 2 inhibitors is more pronounced in RA patients in whom inflammatory burden increases the risk of CVD events in RA patients.

11. DMARDS

NSAIDS reduce inflammation but DMARDS greatly reduce and suppress disease progression 88.DMARDS effect takes a little longer time hence NSAIDS are prescribed to reduce inflammation and for symptomatic relief .Radiological damage occurs early in RA hence early start of DMARDS is highly recommended to reduce the chances of disability in RA patients..Henceitsadviced to prescribe DMARDS in early RA stage itself to reduce the complications.

There are 2 approaches either step up approach ,where u begin with one DMARD and then add more later on .The advantage of this approach is limited side effect but at the same time compromising at the control of disease activity

.Other approach is the Reverse pyramid approach where we start with combination DMARDS and then reduce one as the disease is adequately controlled .In this approach ,there are more side effects but the disease progression is halted early .MC ,DMARDS used are methotrexate,sulphasalazine and leflunomide .MTX inhibits the production of cytokines and hence controls the disease progression .

12. BIOLOGICAL DRUGS

The MC biological drug used to treat RA is anti-TNF –ALPHA ,which inhibits the cytokine TNF-Alpha 96.TNF-alpha ,synthesizes other proinflammatory cytokines IL-6,IL-1 GCSF and synthesize adhesion molecules .Adalumimab ,human anti TNF –alpha monoclonal antibody inhibits activity of the TNF –alpha cytokine ,etanercept ,fusion protein which inhibits TNF –alpha receptors ,Infliximab,chimeric anti TNF-Alpha antibody ,certolizumabpegol ,recombinant humanized Fab fragment inhibits TNF –alpha activity ,golimumab ,human monoclonal antibody inhibits TNF –Alpha activity .These drugs work up well with the traditional DMARDs such as MTX also ,they have rapid onset of action and also reduce disease activity.National Institute of Health and Clinical Excellence(NICE),recommends their use in severe diseases who have inadequate response to atleast 2 DMARDS ,one of which must be MTX.

Recently ,newer types of biologic drugs have made their way including rituximab (anti –CD20 agent),abatacept,selective costimulation of T cells modulator ,IL-1 receptor anakinra and IL 6 receptor tocilizumab need further research on their effectiveness and safety profile [35,38-40]

13. GLUCOCORTICOIDS

Glucocorticoids effectively control inflammatory symptoms of RA as well as halt disease progression[41].They have systemic effects .Most common effects are osteoporosis, weight gain, muscle weakness, alopecia, cataract and hypertension[42-43].Glucocorticoids are used on short term basis to curtail the flare ups during active periods of the disease.

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15. CONCLUSION

RA is a chronic inflammatory autoimmune disease which if not adequately controlled leads to disability and decline in quality of life .Various immune cells come into play and initiate inflammation and cause joint damage .Aim of the treatment is to reduce inflammation ,prevent radiological damage to the bones and cartilage .Early aggressive treatment helps in reducing disability .RA patients have greater manifestation of extra articular symptoms ,CVD as the MCC of morbidity and mortality in RA patients [45-47]