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REVIEW

Rheumatoid Arthritis

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Abstract

Immune-mediated inflammatory disorders include a clinically diverse group of conditions sharing similar pathogenic mechanisms. Conditions such as rheumatoid arthritis, psoriasis, spondyloarthropathy, inflammatory bowel disease and connective tissue diseases are characterised by immune dysregulation and chronic inflammation. This review will focus immuno-pathogenic mechanisms, aspects of early disease, co-morbidity and therapy in rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA) is the archetype of an immune-mediated inflammatory disorder. Numerous advances have been made in the understanding of the pathogenic mechanisms at a molecular level, which have allowed for novel efficacious therapies. An understanding of these pathogenic mechanisms is imperative, as therapies targeting specific molecular and cellular components of the inflammatory response are being used successfully to treat a diverse group of other immune-mediated inflammatory diseases such as psoriasis, spondylo-arthropathy, inflammatory bowel disease, and connective tissue disorders.[1]

Pathogenesis of rheumatoid arthritis

A normal immune response requires the innate and adaptive immune responses working together to protect against foreign organisms. The innate immune system consists of cellular and molecular components such as macrophages, neutrophils and complement that interact with foreign antigens in an immediate and non-specific manner and also present the antigens to the adaptive immune response. The adaptive immune system acts in a more delayed but specific response to get rid of or neutralise effects of foreign antigens, not handled completely by the initial response. The adaptive response consists predominantly of T and B cells that effect a response depending on the inciting antigen, environmental and host factors. This usually results in an increase in anti-body formation and molecular mediators of inflammation called "cytokines". Cytokines enable cross talk between various components of the immuno-inflammatory response with a host of cytokines such as tumour necrosis factor (TNF), interleukin (IL) 1, IL 6 and IL 17 promoting inflammation, counter-balanced by cytokines such as interleukin IL 4 and IL 10[2] (Fig 1).

Immune dysregulation in RA results in a host of auto-antibodies such as rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA). The inciting antigen is unknown, with infective agents such as parvo-virus B19 and an organism causing gingivitis (porphyromonas gingivalis) having been implicated as possible triggers.[3] Smoking has recently received much interest in the possible initiation of a chemical change in lung tissue – a process called "citrullination". [4] Citrullination involves a chemical change in certain peptides containing the amino acid arginine to citrulline. This citrullinated peptide is now exposed to the immune system and in genetically predisposed individuals results in the generation of ACPA. Citrullination also occurs in the rheumatoid synovium and interaction with these anti-bodies may not only be the trigger of disease but might also account for disease persistence.

Genetic factors play an important role in disease susceptibility, with specific amino acid sequence on certain Human Leukocyte Antigens (HLA) found to be associated with RA. The HLA system is important for immune tolerance and response. For this reason certain specific genetically determined amino acid sequences may be associated with certain diseases.[5] In RA this sequence is termed the "shared epitope" and is found in around 80% of patients, particularly in those that are also ACPA positive. Presence of the shared epitope varies in different ethnic groups, with some studies showing a lower prevalence in African patients; however, a recent South African study found a similar percentage as that seen in Caucasians (83%).[6]

Once the immune system is activated disease persistence is maintained by as yet unexplained mechanisms. Phenotypic changes in synovial cells, particularly synovial fibroblasts, may play a critical role.[7] These cells act in an autonomous almost tumour-like fashion, generating pro-inflammatory cytokines, which result in synovial proliferation and consequent local and systemic effects.[8]

Early Rheumatoid Arthritis

Immunological and biochemical changes occur even before the clinical onset of disease with differing immuno-biology before disease onset, in early disease, and in established disease. Early disease represents a window of opportunity to get the best, most cost effective results. This window seems to be within the first 2-3 years of disease, with most authorities advocating aggressive therapy aimed at disease control within 3-6 months of symptom onset.

The initial challenge is early diagnosis. The previous classification criteria (1987 ARA criteria) proved to be very insensitive to the diagnosis of early RA. Incorporated in these criteria is the presence of rheumatoid nodules and radiographic changes but these features are not seen in most patients with early disease. To this end the new 2010 RA criteria allow for making a diagnosis earlier, including in patients with disease duration of less than 6 weeks[9] (Table 1). These criteria are more sensitive and care needs to be taken to exclude viral infections, conditions such as osteoarthritis, psoriatic arthropathy and early connective tissue disorders.

Clinical features suggestive of early RA include morning stiffness lasting more than 30 minutes affecting multiple joints, symmetrical joint involvement particularly of the hands (Fig 2) and feet (sparing the distal inter-phalangeal joints), associated soft tissue swelling ('boggyness'), decreased range of motion (unable to make a fist) and metacarpal/metatarsal tenderness (positive squeeze test). Characteristic deformities of RA are usually seen in patients with established, poorly controlled disease due to bone and soft tissue changes. Typical deformities in the hand include radial deviation at the wrist, ulnar deviation of the fingers, Z deformity of the thumb, finger swan neck and boutonniere deformities (Figs 3 and 4). Tendon rupture may occur in early or late disease and is related to tenosynovitis or attrition from adjacent bony deformities (Fig 5). In patients with disease duration of less than 6 weeks viral aetiologies such as hepatitis B, hepatitis C and human immunodeficiency viral infections need to be excluded. In the presence of distal inter-phalangeal (DIP) joint involvement, osteoarthris (OA) or psoriatic arthropathy should be considered. Typical joints involved in OA (Fig 6) are the DIP, proximal inter-phalangeal (PIP), first metacarpophalangeal (MCP) and first carpometacarpal joints of the hands, with associated bony swelling and morning stiffness of less than 10 minutes' duration. Patients with psoriatic arthritis may have inflammatory arthritis similar to RA often with DIP joint involvement. Systemic enquiry should include a family history of psoriasis and a search for characteristic nail and skin changes, noting that arthritic manifestations may precede skin involvement. Early connective tissue disorders (CTDs) such as systemic lupus erythematosus may have similar articular features to RA and a systematic review is essential to look for some suggestive manifestations such as malar or discoid rashes, photosensitivity, alopecia, recurrent oral ulceration, Raynauds phenomenon, serositis or major organ involvement.

Extra-articular manifestations are less common in early RA and usually portend a poorer prognosis. Rheumatoid nodules occur in about 1% of patients with early disease typically seen on the extensor surface of the forarm just distal to the elbow. Ocular involvement includes dry eye syndrome, episclerits and rarely scleritis and keratitis. Pulmonary fibrosis may occur from the disease or as a side effect of therapy. Neurologic involvement is usually related to entrapment, such as carpal tunnel syndrome and myelopathy from cervical spine subluxation.

Investigations

i) Full blood count

Anaemia of chronic disease is mediated by cytokines such as IL 6, inhibiting iron transport and utilization. Associated thrombocytosis may reflect an acute-phase response or gastrointestinal bleeding. A low white cell count may be seen in patients with a more severe form of RA, namely Felty's syndrome (RA, splenomegaly, chronic vasculitic leg ulcers and neutropenia).

ii) Urea and electrolytes

Direct renal involvement in RA is rare but it is important to monitor renal function at least yearly as drug dosages may need to be adjusted or avoided altogether.

iii) Liver function tests (LFT)

Evidence of chronic liver disease may be apparent but even if LFT is normal viral hepatitis serology needs to be reviewed before starting therapy. Drug-related hepatitis may occur therefore 3-4 monthly monitoring of aspartate transaminase/alanine transaminase is recommended.

iv) Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)

These non-specific measures of inflammation are usually, but not always, elevated in patients with active rheumatoid arthritis. Up to 40% of patients may have a normal ESR or CRP at presentation despite active disease.[10] The ESR may be affected by multiple factors such as age, anaemia and immunoglobulin concentration. The CRP may be more specific for inflammation but elevation may be related to smoking and associated insulin resistance.[11]

v) Rheumatoid factor, anti-citrullinated peptide and anti-nuclear factor antibodies (ANF)

Rheumatoid factor is an antibody to IgG immunoglobulins seen in 80%-90% of patients with established RA. It is seen in only 50%-60 % of patients with early RA. Patients with positive RF factor tend to have more aggressive disease and extra-articular manifestations. The test is used for diagnostic purposes only and has no role to play in monitoring response to therapy; hence if positive once there is no need to repeat. False positives may occur in the elderly and in numerous unrelated infective/ inflammatory conditions such as tuberculosis, hepatitis and interstitial lung disease.

ACPA has a specificity of around 98% for RA, but for RF it is seen in only around 50% of patients with early disease and used for diagnosis only. ACPA positivity is associated with radiographic progression and a poorer prognosis. Testing for ACPA is appropriate if RF is negative in a patient with suspected RA or if

a false positive RF is probable, for example, in the elderly and in patients with hepatitis C.

Antinuclear factor antibodies are directed to nuclear antigens seen in a host of connective tissue diseases (CTD), with up to 30% of patients having a positive ANF with no associated underlying CTD. In patients who have clinical features of RA and are sero-negative (RF/ACPA negative), the presence of ANF may be the clue to the presence of an early CTD. An ANF is considered positive if the titre is >1/160 and 5% of the normal population may have a positive test. The test should therefore be requested only in the presence of suggestive clinical features and not for non-specific arthralgia.

vi) Imaging

Plain radiographs of the hand and feet may reveal the presence of erosive disease and joint space narrowing. However, they are insensitive in early RA, as erosions are seen only after 1-2 years of disease. Newer imaging modalities such as ultrasound and MRI are able to detect synovitis and erosive disease very early in the course of the disease. Internationally, ultrasound is gradually being incorporated into routine rheumatological practice for diagnosis and sonar guided infiltrations, with lack of expertise limiting widespread use locally. MRI offers a more objective assessment of synovitis and bony involvement but cost and accessibility limits its use in routine clinical practice.

Co-morbidity of chronic inflammation

Uncontrolled chronic inflammation results in the obvious local effects of joint destruction, deformity and consequent disability. However, inflammation can have systemic effects, with RA having found to be associated with premature atherosclerosis, osteoporosis and depression.

Pro-inflammatory cytokine levels are elevated in the systemic circulation in patients with RA and this has several pro-atherogenic effects by affecting endothelial cell function, altering lipid metabolism and promoting insulin resistance. All of these effects results in RA being an independent risk factor for ischeamic heart disease comparable to the effect seen in type 2 diabetes.[12]

Synovitis results in erosive bony changes mediated by activated osteoclasts at the junction of bone and the proliferating synovium called the pannus. Normal bone turnover is a dynamic process maintaining homeostasis with a balance between bone resorbing (osteoclast) and bone-forming cells (osteoblasts). The pro-inflammatory cytokine milieu, both locally and systemically, enhances osteoclastic activity resulting in peri-articular and generalized osteopenia.[13]

Patients with RA have a much higher prevalence of depression than the general population. Depression in RA is associated with disease activity, increased work disability and poor compliance. The effect of chronic disease plays a significant role but abnormal pro-inflammatory cytokine profiles have also been demonstrated in patients with primary depression.[14]

Therapy

Key principles in the management of RA are disease control within 3-6 months, aiming for remission or at least a low disease-activity state. An important pitfall in the management of patients with early RA is 'reassurance' of disease control with pain management. Initially many patients' symptoms improve significantly with pain management, especially if combined with corticosteroids, but a comprehensive review often reveals ongoing disease activity. Ongoing disease activity is associated with joint damage, and studies in manual labourers with RA show loss of work ability within 2 years of disease onset. Measuring disease activity is thus paramount to guiding therapy so as to bring the disease under control within 3-6 months.

Measures of disease activity

Unfortunately no single measure has been shown to correlate well with disease activity and consequent disease progression. The ESR and CRP are used as measures of activity in many inflammatory disorders but have significant limitations, as individual parameters in patients with RA. Composite disease-activity measures have been validated to assess and monitor disease activity. These are various different scoring systems that incorporate: responses to patient questionnaires on function and pain; clinical assessment of the number of swollen tender joints; duration of morning stiffness; and ESR or CRP. A practical scoring system advocated by many for routine clinical use is the simplified disease activity index (SDAI). The SDAI is a summation of: i) the number of swollen and tender joints counts and the evaluation of bilateral shoulders, elbows, wrists, MCPs, PIPs and knees (28 joint count); ii) physician global assessment of activity noted on a scale of 0-10 with 0 low activity and 10 high; iii) patient global activity score also out of 10; and iv) the CRP in mg/dl. A score of >26 reflects high disease activity, >11 ≤26 moderate disease activity, >3 ≤11 low disease activity and ≤ 3.3 remission. Ongoing disease activity is associated with radiographic progression, disability, morbidity and premature mortality. The objective is to achieve at least a low disease-activity score, with remission being the desired goal. With recent advances in the pharmacological management of RA this target is certainly achievable in the majority of patients.

Pharmacological therapy

Recommendations for the management of RA in SA have been published, and include an algorithm with appropriate therapies and appropriate timelines.[15] Disease-modifying anti-rheumatic drugs (DMARDs) remain the cornerstone of RA management. There have been tremendous advances in this class of drugs that have not only revolutionised management of RA but also therapy across the spectrum of immune-mediated inflammatory disorders. Two sub-classes are now identified – synthetic(s) - or biologic (b) DMARDs.

Synthetic DMARDs, also sometimes referred to as "traditional DMARDs", include drugs such as choloroquine, salazopyrine, methotrexate and leflunomide. Methotrexate is the anchor drug in the management of patients with RA.

Methotrexate is a folic-acid antagonist-blocking purine and pyrimidine synthesis required for nucleotide formation. Inhib-

iting nucleotide formation results in the prevention of cellular proliferation in predominantly rapidly dividing cells, which include cellular components of the immuno-inflammatory response.[16] Inhibition of cellular proliferation also occurs in normal compartments such as the gastro-intestinal tract and bone marrow and accounts for some of the side effects seen, such as oral ulcers, diarrhoea and cytopaenias. Co-administration of folic acid 5mg daily decreases these side effects with only a minor impact on efficacy. Methotrexate exerts these effects only after undergoing an intracellular chemical change of polyglutamation. Polyglutamated methotrexate can remain active intracellularly for days despite the drug being cleared from the systemic circulation within a few hours, hence the reason for the recommended weekly dosage. The usual initiating dose is 10mg-15mg weekly, with a maximum dose of 25mg weekly. Side effects to monitor for include hepatitis, interstitial lung disease, mucositis, GI disturbances and bone marrow suppression. Methotrexate should be avoided in patients with renal dysfunction, liver or pulmonary disease and it is teratogenic. In patients with poor prognostic features, triple therapy combined with Chloroquine and Salazopyrin may be considered.

Chloroquine and salazopyrin may be used as monotherapy in mild disease or if methotrexate is contraindicated. In patients on chloroquine, it is important to monitor for retinal toxicity with yearly opthalmological assessments. Salazopyrine has a sulphur moiety and should be avoided in patients with a sulphur allergy.

Leflunomide is a pyrimidine antagonist, similar to methotrexate in blocking cellular proliferation and can be used as an alternative to methotrexate but is commonly used after methotrexate failure. It has a long half life and an enterohepatic circulation resulting in elevated serum levels months after the drug has been stopped. This is an important consideration in females planning a pregnancy as special washout regimens need to be followed.

Longer disease duration prior to starting sDMARD therapy is associated with a poorer response. However, with the appropriate use of DMARDs in early RA, 70%-80% of patients will have an acceptable response to therapy. Patients with an inadequate response will benefit from b DMARDs, albeit at a higher cost.

Biologic DMARDs have changed the landscape of RA therapy with marked improvement in up to 70% of patients that have failed the therapy referred to immediately above. These drugs target specific components of the immuno-inflammatory response. Currently available drugs in South Africa antagonise pro-inflammatory cytokines (TNF/IL 6), T-cell function and B-cell proliferation. B DMARDs are generally well tolerated with specific precautions and patient screening required to minimise side effects, most importantly infections including reactivation tuberculosis; therefore, use of these agents is restricted to specialist care.

Despite the fact that pain management does not modify disease progression, it still remains an integral component in RA management. Pain management includes prudent use of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), using the lowest dose required, combined with gastro-protective agents in patients at high risk of peptic ulcer disease. Avoid NSAIDs in patients with renal dysfunction and use with caution in patients with ischemic heart disease, particularly if patients are on aspirin. The protective effect of aspirin on ischaemia may be lost if combined with some NSAIDs, as they compete with the same binding sites on platelets. If it is considered necessary to use the combination then separate the dosage times by at least 3 hours. On initiating an NSAID, it is also essential to monitor for changes in blood pressure, as some patients may develop hypertension.

Corticosteroids have a dual role in RA management, with excellent relief of symptoms especially in early disease and modified disease progression to a limited extent. Corticosteroids are often given as a pulse either intramuscularly or orally. If orally then the lowest possible dose orally over a 6-month period, aiming to wean off completely thereafter. Corticosteroids used in early RA may mask ongoing disease and joint damage, as they have the potential to delay appropriate therapy because their symptomatic effect is so great that patients markedly improve functionally. Certainly there is no role for corticosteroids as mono-therapy for disease modification but they play rather an adjunctive role with other DMARDs.

Non-pharmacological therapy

A multidisciplinary approach to patients with RA is vital. Allied health disciplines such as physiotherapists, occupational therapists, podiatrists and nutritionists provide an important supportive role. Educating patients about their disease improves compliance and outcome. Specific counselling to deal with psycho-social matters and cessation of smoking should be incorporated in the management plan.

Challenges to the management of RA in South Africa

Early diagnosis and management of patients with early RA especially in the public sector is of concern. Hodkinson et al. in a recent study of 171 patients with early RA attending public sector rheumatology clinics demonstrated a high disease burden at presentation, with only 28% of patients achieving a low disease activity state at 12 months under routine care. Over 60% of patients in this study had substantial functional disability and suboptimal mental health after 1 year of therapy.[17] As shown in this and other studies, a low level of schooling was identified as one of the poor prognostic features.

Socio-economic factors and access to health services are obvious challenges affecting optimal management of RA. Biologic therapies are expensive and may also predispose to specific infections such as tuberculosis. The direct cost of biological therapies needs to be balanced with the potential for decreasing the social and economic burden passed onto the public health system. Guidelines have been established for the appropriate use of DMARDs including biological therapies in South Africa and their use is steadily becoming available in the public sector.

Conclusion

RA is a chronic inflammatory disorder with considerable morbidity. Monitoring of co-morbidity such as increased cardiovascular risk needs to be incorporated into management strategies. Early diagnosis and aggressive therapy have

improved the prognosis for most patients. The introduction of DMARD therapy early in the disease course with frequent follow up aiming for rapid and measurable disease control is not only inexpensive but also effective in most patients. The judicious use of biologic therapies has added hope to all patients with RA.

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Recommended resource

South African recommendations for the management of rheumatoid arthritis: an algorithm for the standard of care in 2013.[4]

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