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Review Article

CURRENT CLINICAL STRATEGIES IN RHEUMATOID ARTHRITIS: A REVIEW

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ABSTRACT

Rheumatoid arthritis [RA] is one of the most common and severe autoimmune rheumatic diseases, diagnosed primarily according to clinical manifestations and radiological reports. For many years, laboratory diagnosis of rheumatoid arthritis has relied on the detection of rheumatoid factor [RF], as established by the ACR criteria. A recent test to detect antibodies towards citrullinated peptides, called the anti-CCP assay, showed a similar sensitivity but a more elevated specificity than the RF test. The direction of current therapies is to treat RA aggressively with early use of sequential or disease modifying anti rheumatic drugs (DMARDs). Here an attempt is made to review the existing physical and clinical methods to diagonise RA, therapeutical methods available and their drawbacks.

Keywords: Rheumatoid arthritis (RA), American college of rheumatology (ACR), Rheumatoid factor (RF), Anti-cyclic citrullinated peptide (Anti-CCP), Disease modifying anti rheumatic drugs (DMARDs).

INTRODUCTION

Rheumatoid arthritis [RA] a connective tissue disease manifested by autoimmunity. RA accompanied by systemic amyloidoisis is an important complication that leads towards achieving the highest possible level of arthritis disease activity, maximum joint damage, reducing physical function and quality of life. The goal of treatment is to keep patients in remission while controlling pain, reducing inflammation and preventing progression of joint erosion. The direction of current therapies is to treat RA aggressively with early use of sequential or disease modifying anti rheumatic drugs (DMARDs). However studies have determined that patients seldom continue therapy for more than 5 years with current DMARDS because of loss of efficacy or intolerable side effects.[1,2]

EPIDEMOLOGY AND ETIOLOGY

RA is one of the many chronic auto immune diseases affecting 0.5-1% of world's population that predominates in women. The female to male ratio is 2-4:1.The basis of gender difference is not known but presumably is related to effects of the hormonal milieu on immune function. The incidence of RA rises dramatically during adulthood and peaks in individual aged 40-60 years.[3,4,5] Possible etiology of the disease is still under dark side despite many years of intensive research going on worldwide but auto immunity plays a main role in its chronicity and progression. Environmental factors such as infections, vaccines inoculations and emotional trauma also plays a role in RA.[6,7]

PATHOPHYSIOLOGY

The key pieces of evidence relating to pathogenesis are: A genetic link with HLA-DR4 and related allotypes of MHC Class II and the T cell-associated protein PTPN22,blockade of the cytokine TNF (alpha), depletion of B lymphocytes, but no comparable response to depletion of T lymphocytes, the presence of auto antibodies to IgG Fc, known as rheumatoid factors (RF), and anti-citrullinated peptides to antibodies (ACPA).

The literature reviews data suggest that the disease involves abnormal B cell - T cell interaction, with presentation of antigens by B cells to T cells via HLA-DR eliciting T cell help and consequent production of RF and ACPA.[8,9]

ABNORMAL IMMUNE RESPONSE

The factors that allow an abnormal immune response, once initiated, to become permanent and chronic, are becoming more clearly understood. The genetic association with HLA-DR4, as well as the newly discovered associations with the gene PTPN22 and with two additional genes, all implicate altered thresholds in regulation of the adaptive immune response. Exactly how altered regulatory thresholds allow the triggering of a specific autoimmune response remains uncertain. However, one possibility is that negative feedback mechanisms that normally maintain tolerance of self are overtaken by aberrant positive feedback mechanisms for certain antigens such as IgG Fc (bound by RF) and citrullinated fibrinogen (bound by ACPA).[10]

PHYSICAL EXAMINATION

The joints involved most often are the: proximal interphalangeal (PIP), metacarpophalangeal (MCP), joints of the hands, the wrists (particularly at the ulnar-styloid articulation), shoulders elbows, knees, ankle, and metatarsophalangeal (MTP) joints. The distal interphalangeal (DIP) joints are generally spared. The spine except the atlanto-axial articulation in late disease is never affected.

Morning stiffness, persisting more than one hour but often lasting several hours, may be a feature of inflammatory arthritis but is especially characteristic of rheumatoid arthritis. Its duration is a useful gauge of the inflammatory activity of the disease. Similar stiffness can occur after long periods of sitting or inactivity (gel phenomenon). In contrast, patients with degenerative arthritis complain of stiffness lasting but a few minutes.

Nonspecific systemic symptoms primarily fatigue, malaise ,depression, fever occasionally occurs and is almost always low grade (37° to 38°C), patients complain of severe fatigue 4 to 6 hours after wakening.

Typical features of RA patients are their symptoms wax and wane. Atypical features of RA patients are intermittent joint inflammation that can be confused with gout or pseudogout, proximal muscle pain, tenderness mimicking polymyalgia rheumatica or diffuse musculoskeletal pain seen in fibromyalgia.[8,11]

CLINICAL EXAMINATION

Assessment of disease activity and damage

Disease activity parameters both clinical and investigational (blood and X-rays) are to be documented at baseline and at follow up. The frequency of follow up on an average is monthly 3. The haematology and biochemistry are needed at follow up visits, but tests for RF and antibodies to CCP are to be done only at the baseline. Disability assessment should be done once in 6 months and radiology yearly to assess damage.

A. Clinical

Assessment of pain*:* Pain is assessed on VAS (visual analogue scale). Briefly; this consists of a 10 cm horizontal line with '0' at one end (indicative of no pain) and '100' at the other end (indicative of the worst possible pain). Patient is asked to place a mark on this scale to indicate his level of pain.

Patient's and Physician's global assessment*:* These indicate the patient's and physicians 'overall assessment' of disease activity. These may be done on each visit on a VAS of 0–10 cm, with '0' at one end indicating very well and '100' at the other end indicating worst condition.

Number of tender and swollen joints*:* The '28 joint count' is the preferred one. Assessment for tenderness and swelling in the following 28-joints is done: 10 proximal interphalangeal joints (PIP), 10 metacarpo-phalangeal joints (MCP), 2 wrists, 2 elbows, 2 shoulders, 2 knees. Additional involved joints should also be recorded for further follow up. While assessing swollen joints, the swelling must be attributable to synovial hypertrophy and/or effusion and not bone overgrowth. A 'mannequin' is a good and easy way to keep a record of joint counts.[6]

B. Laboratory

Erythrocyte sedimentation rate (ESR) should be done by Westergren's method.

Full blood counts: Haemoglobin, Total and differential leukocyte count, Platelet count.

Biochemistry: AST/ALT (SGOT/SGPT), serum albumin, creatinine.Serology for hepatitis B and C is to be done if there is elevation of AST/ALT and serum albumin level is low. A clinician can order other tests based on his clinical judgment.

Radiology: Plain radiographs of the hands (AP view) and feet (AP view) is to be done in each patient. Additional radiographs of the affected joints may be done if indicated. A baseline chest radiograph is recommended in all patients. Newer imaging modalities like MRI and ultrasonography are established to correlate well with disease parameters; but currently these are not recommended for regular use in assessment of RA patients. However, in an individual patient where the objectives of ordering these tests are well defined, they may be considered.[11,12]

Quantification of current disease activity

Disease activity score (DAS) is currently the most popular tool to assess disease activity. Among the various modifications, the simplest one which is most commonly used is DAS28 which is based on 28-joint count. Apart from DAS quantification (SDAI) 'simplified disease activity index (SDAI) and 'clinical disease activity index' (CDAI) can be used. But same instrument should be used in subsequent follow up and they are not interchangeable.

Damage assessment

Damage should be assessed clinically by noting the presence of deformities and limitation of joint movement. Radiological assessment is preferred with cording of joint space narrowing, erosions and subluxation of the affected joints.[13]

Categorization of patients

Based on DAS28 score and presence/absence of poor prognostic factors, the patients are to be categorized for the purpose of deciding the line of treatment. Details are as follows:

Disease activity

- ✓ Low (DAS< 3.2 or CDAI ≤ 10)
- ✓ Moderate (DAS 3.2–5.1, CDAI 10–22)
- ✓ High (DAS> 5.1 or CDAI > 22)

Poor Prognostic factors: Subcutaneous nodules, secondary Sjogren's, interstial lung fibrosis, vasculitis, bone erosions, IgM RF and antibodies to CCP.[14,15]

Treatment

Joints i.e., cartilage and bone loss are minimized with improvement in functional quality of life. In terms of disease activity, the aim would be to bring DAS28 below 3.2 with monitoring for side effects of drugs. This is to be done by judicious use of DMARDs. Therapy is to be individualized in each patient to ensure sustained tight control of inflammation for better long-term outcome. At a given time, depending upon the disease burden, a particular patient will have features of both disease activity and damage (the later accruing with progress of time). Drug therapy will help to resolve activity while rehabilitation including surgery is required to restore functionality.[16] Treatment of RA involves a multidisciplinary approach. Drug therapy is advised by the internists/rheumatologists, physiotherapy and rehabilitation by trained physiatrists and surgical care by the orthopedic surgeons when necessary. Pharmacotherapy of RA consists of the following: Antiinflammatory drugs: Non steroidal antiinflammatory drugs (NSAIDs) and corticosteroids, analgesics, conventional disease modifying antirheumatoid drugs (DMARDs), biologicals DMARDs.

NSAIDs are one of the most commonly prescribed drugs for RA. NSAIDs are only for symptom relief. Careful monitoring for adverse effects is necessary for long term use of NSAIDs. Combination of more than one NSAIDs is not recommended. It has been clearly shown to have no additional pharmaceutical benefit but may potentiate adverse events. The overall aim should be to minimize their use when disease control is achieved with DMARDs. Gastrointestinal toxicity, renal toxicity, CVS toxicity are common.

Corticosteroids have potent antiinflammatory effects and hence are effective for symptomatic relief: Patients on corticosteroids with additional risk factors (e.g. osteoporosis, obesity, and hypertension, family history of diabetes or glaucoma) need monitoring for side effects especially blood sugar, lipid profile, hypertension, coronary artery disease and BMD measurements by DEXA scan. All patients on long-term steroids should be given calcium (1500 mg) and vitamin D (400-800 IU). Patients likely to receive steroids for > 3 months, especially in the postmenopausal group and others with a BMD ≤ 2.5 value should also receive bisphosphonates. Patients who are on long-term steroids, will need supplemental corticosteroids before surgery to prevent the development of Addisonian crisis. [12] Analgesics for pain relief, particularly during active phase of the disease, analgesics like paracetamol or tramadol can be used to supplement the NSAIDs. In patients who develop GI side effects, due to NSAIDs, these are a useful option.

Conventional disease modifying antirheumatoid drugs (DMARDs)

Indications

- All patients fulfilling ACR criteria for RA
- Patients who don't fulfill ACR criteria for RA, but have inflammatory persistent polyarthritis of rheumatoid distribution or oligoarthritis with high acute phase reactants,
- RF and anti-CCP positivity predictive of persistent synovitis or erosive disease.

Biological DMARDs

In the last decade, biological agents targeting molecules/cells cartilage or bone loss have made a significant positive impact in the treatment of patients who continued to have active disease despite trial of multiple DMARDs involved in perpetuating persistent synovitis .

Biological DMARDs are to be prescribed by experienced rheumatologists only and include:

a. TNF inhibitors

- ✓ Infliximab (mouse monoclonal antibodies to human TNF)
- ✓ Etanercept (soluble TNF receptors)
- ✓ Adalimumab (humanized anti TNF antibodies)

b. Rituximab (antibody against CD20 on B cells)

c. Abatacept (CTLA4-Ig)

Indications for treatment with TNF inhibitors

These indications are taken from BSR guidelines which were updated in 2005.24 Patient should:

1. Fulfill the 1987 ACR classification criteria for RA.
2. Have active RA (DAS28 score > 5.1 at two time points, 1 month apart.
3. Have failed standard therapy as defined by failure to respond or tolerate adequate therapeutic trials of at least two standard DMARDs. One of the failed or not tolerated therapies must be methotrexate. Adequate therapeutic trial is defined as:

a. Treatment for ≥ 6 months, with at least 2 months at a standard target dose unless significant toxicity limited the dose tolerated.

b. Treatment for < 6 months where treatment was withdrawn because of drug intolerance or toxicity, but normally after ≥ 2 months at therapeutic doses.[9,17]

DISCUSSION

Current therapeutic protocols in RA utilises as early as possible more aggressive drugs, which aim to control disease activity and give rapid exact diagnosis. Stratification of early RA into benign, moderate and severe prognosis is important in order to propose a tailormade therapy. So, there is a clear need to improve the diagnostic specificity of commercial RF test kits and on the other hand, to discover new serological markers with high specificity for RA.

To this purpose, anti-CCP antibodies can be considered a high specificity marker of RA, since they are detectable in very early stages of disease and several studies confirm the important role of citrullinated antigens in the diagnosis, prognosis and therapeutic management of RA.[18]

Several authors suggest that, to ensure a higher diagnostic effectiveness, RF test should be used together with anti- cyclic citrullinated peptide(CCP)antibodies in the diagnosis of early RA. In particular, it has been suggested that the combination of RF latex test plus anti-CCP antibody can be used as an effective screening strategy for RA in primary care. The combined test in primary care for suspected RA patients and also in making differential diagnosis in false positive patients for RF test is beneficial.[19]

Prolonged use of multiple drug therapy for RA should provide answers to critical questions about the safety of drugs conceive the overall safety profile, the effect of multiple causes of therapy, the impact of several beta-cell depletion during repeated courses. The impact of prolonged decreased IgG and IgM levels following repeat therapy, the effect of continued peripheral B-cell depletion and the incidence of serious infections when nontribal patients are treated with multiple causes over the years, along with the incidence of development of malignancies other than lymphoma plays a crucial role in multiple drug therapy in RA.[13,20]

PROGNOSIS

RA prognosis based on the presence or absence of different prognostic factors that have been identified from longitudinal studies. Some of the factors are interobserver, independent, where as others are subjective and variable. It is of importance to develop criteria that are applicable in routine clinical practice to distinguish those patients who are likely to develop severe erosive disease and who require biological agents from those with benign or moderate destructive potential and who require conventional DMARDs. It may therefore be more appropriate to consider markers at the onset of disease as predictors of response to individual treatment as opposed to prognosis.[21,22]

SUMMARY

The problems with defining early RA means that it is difficult to have useful definitions of established disease. Imaging advances suggest that in the future it may be possible using modern technology to combine an approach which gives diagnosis, prognosis and evidence of monitoring outcome. Radiological damage and disability are the two main complications of RA. The most reliable prognostic factors of radiological damage are ESR and CRP. Several predictive models for early RA have been developed but not validated. The research trust area can be the revision of ACR criteria, the combined test(multiplex cytoflourimetric RF assay plus anti-CCP antibody test)is the most efficient tool for early RA diagnosis, further long-term studies are required to validate the effect of modern treatment strategies on the natural history of RA.

In conclusion, clinical evidence supports the effectiveness of multiple drug therapies; however in the absence of long term data, predictive models for early RA have been developed but not validated. The purpose of this article is to provide an overview of different clinical approaches, and highlight some of the important issues surrounding the choice of drugs to be used in RA. It is hoped that the review will enable relative advantages of the various techniques, drugs used for treating RA and to evaluate the treatments of RA.

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