REVIEW ARTICLE

Rheumatoid Arthritis

Approach in the new millennium

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Rheumatoid Arthritis (RA) affects nearly 1% of the Indian population. While osteoarthritis is the commonest arthropathy encountered by a clinician, RA has the distinction of being the most frequent 'inflammatory' joint disease seen in clinical practice. It is an autoimmune disorder of unknown etiology characterized by erosions and joint destruction. The disease follows a chronic course, and if not treated adequately, progressive joint deformities and eventual joint loss are common. RA not only interferes with activities of daily living but also leads to shortened life expectancy. This realization, that RA is not the benign disease it was once thought to be, has led to a sea change in the treatment paradigm of RA. Passive treatment has now given way to active intervention. There has been a widespread acceptance of the early and aggressive use of disease modifying anti-rheumatic drugs (DMARDS) during the last two decades. The current focus is on the use of biological response modifiers in the treatment of RA, especially cytokine inhibitors like TNF alpha antagonists. The present article outlines the approach to RA at the turn of the millennium.

Clinical recognition of RA

Early recognition is the key to effective management. It needs to be reiterated that RA is primarily a clinical diagnosis. The first task of the clinician is to differentiate inflammatory joint disease from non-inflammatory joint disease (Table 1). RA is an inflammatory polyarthritis (5 or more than 5 joints involved) while osteoarthritis (OA) is the prototype non-inflammatory joint disease. In some patients both RA and OA may co-exist. RA is a diagnosis which should be considered in patients presenting with bilateral, symmetrical, inflammatory polyarthritis affecting hand joints, and where the duration of symptoms exceeds 6 weeks. Careful attention to this definition helps the clinician to avoid mistakes. Duration exceeding 6 weeks enables exclusion of viral arthritides which are self limited. In absence of clinical involvement of small joints of hands, one should be extremely reluctant to make a diagnosis of RA. In Table 2

Table 1

Differentiation between inflammatory and non-inflammatory joint disease

	Inflammatory	Non-inflammatory
Prototype disease	Rheumatoid Arthritis	Osteoarthritis
Morning stiffness	Marked	Mild or absent
Symptoms after		
Rest	Worsen	Improve
Activity	Improve	Worsen
Spontaneous ups & downs	++	–
Constitutional symptoms	++	–
ESR & other acute phase reactants	↑↑↑	Normal or mild ↑

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Table 2

Clinical Recognition of RA: Key points

- RA is entirely a clinical diagnosis. One can confidently make a diagnosis of RA on clinical grounds even if RF is absent. In fact, only 80-85% of the individuals are seropositive (that is, +ve for rheumatoid factor).
- RA is typically bilaterally symmetrical. Asymmetrical or unilateral involvement should arouse suspicion of other arthritides like psoriatic or seronegative spondyloarthropathy.
- RA is a polyarthritis. Never diagnose RA in a patient with monoarthritis
- Do not diagnose RA unless hands are involved.
- Distal interphalangeal joint involvement is exceedingly uncommon in RA. If DIP joints are involved suspect psoriatic arthropathy or osteoarthritis.
- Lumbar spine is not involved in RA. The presence of inflammatory low back ache with mono or oligoarticular involvement especially in lower limbs should arouse suspicion of seronegative spondyloarthropathy.

the important points have been outlined which a physician needs to keep in mind while diagnosing RA.

Laboratory investigation in RA

Laboratory workup in RA includes 2 groups of investigations:

1. Investigations which aid in diagnosis
2. Investigations to monitor treatment and complications

Investigations which aid in diagnosis

(a) Rheumatoid factor (RF)

Rheumatoid factor is one of the most frequently ordered tests in the work up of a patient with joint symptoms. The key points about rheumatoid factor are listed in Table 3. It needs to be emphasized that RF performs poorly as a screening test for rheumatoid arthritis due to the high frequency of false-positive results.

Table 3

Rheumatoid Factor : Key points

- Mere presence of rheumatoid factor in blood is not enough to make a diagnosis of RA.
- Only 80-85% patients with RA exhibit RF in their blood, while as many as 15-20% patients are seronegative.
- Once RF is positive in a given patient, it need not be repeated since it correlates poorly with clinical response to treatment.
- Titers of RF do not help in monitoring treatment efficacy.
- A negative RF needs to be repeated 4-6 monthly for the first 2 years of disease, since some patients may take 18-24 months to become seropositive.

(b) Acute phase reactants like ESR, CRP

These help a clinician in differentiating inflammatory from non inflammatory disease. Apart from ESR and CRP, platelets and serum alkaline phosphatase may also be raised as part of acute phase response.

(c) Radiographs

For radiographic diagnosis of RA, the most informative and single best x-ray to ask for is PA view of both hands including wrists. This again underscores the fact that RA affects hands predominantly. RA is characterized by periarticular osteopenia and erosions. In contrast, OA does not exhibit osteopenia or erosions; while osteophytes are common. Also OA typically involves distal interphalangeal (DIP) joints while these are spared in RA. X-rays of other joints like knee, shoulder etc. should be ordered only if the joint is clinically involved. They don't help much in diagnosis.

Investigations to monitor treatment and complications

These include Hb, TLC, DLC, Platelet counts, ESR. Normocytic normochromic anemia is common in an inflammatory condition like RA. ESR and platelets are frequently increased due to acute phase response. Baseline liver and renal function tests including

urinalysis are obtained to monitor subsequent drug side effects e. g. the use of methotrexate mandates regular LFT, the use of gold mandates regular blood counts and urinalysis. Stool for occult blood may be needed in patients of RA with microcytic hypochromic anaemia to exclude GI blood loss due to NSAID use. Patients on chloroquine require biannual perimetry to monitor ocular toxicity.

Goals of treating rheumatoid arthritis

The treatment of RA has to take into account that there is no known cure for RA. Early diagnosis and timely introduction of DMARDs are crucial. In this context, it is important to keep in mind that patients with seropositive, active disease often develop erosions within the first few months of disease. Hence DMARD therapy should be initiated as soon as the diagnosis is firmly established. This is analogous to the concept of 'window period' for administration of streptokinase therapy in acute myocardial infarction.

Treatment modalities for RA

The various agents used for treatment of RA include :

(1) NSAIDs
(2) DMARDs
(3) Steroids
(4) Biological therapies
(5) Surgery

Physiotherapy occupies a central and important role in the management of RA.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are an integral part of management of RA. NSAIDS, in equivalent doses, do not differ in efficacy. Only the side effects may differ. Combining two or more NSAIDs should be avoided since it does not increase efficacy but increases the incidence of side effects. Commonly used NSAIDs include ibuprofen, diclofenac, ketoprofen, naproxen, mefenamic acid, flurbiprofen and piroxicam. The use of a particular NSAID is more a matter of choice and patient tolerance than anything else.

GI side effects and renal insufficiency are common with prolonged use of NSAIDS. Administration after meals may reduce the propensity to cause peptic ulceration. H2 blockers protect only against duodenal ulcers and not gastric ulcers in patients taking NSAIDS. Since most ulcers due to NSAIDs are gastric rather than duodenal, co-administration of H2 blockers with NSAIDs in routine is not recommended. Prophylaxis with anti-ulcer agents is needed in high risk patients like the elderly or those with previous history of GI bleed. In this context, misoprostol is superior to H2 blockers for prevention of gastric ulcers and as effective for prevention of duodenal ulcers. Omeprazole has also been recently shown to be very useful in prevention and treatment of NSAID associated ulcers. Selective cyclo-oxygenase (COX-2) inhibitors like meloxicam, celecoxib and rofecoxib which have less GI effects have been developed. All these drugs are now available in India. NSAIDs cause GI side effects irrespective of the route. In this context, it is pointed out that injectable NSAIDs or even NSAID suppositories have as much potential for GI side effects as oral formulations. This is because the side effects are mainly due to prostaglandin inhibition and not so much due to topical effects.

Disease modifying anti-rheumatic drugs (DMARDs)

Early and judicious use of DMARDs is the cornerstone of current treatment strategies. DMARDs have the potential to reduce or prevent joint damage thereby, protecting joint integrity and function. The various DMARDs include:

* Chloroquine & Hydroxychloroquine
* Gold salts (oral & parenteral)
* Methotrexate
* Sulfasalazine
* D-penicillamine
* Cyclosporine A

* Levamisole
* Minocycline
* Azathioprine
* Cyclophosphamide
* Chlorambucil

Newer agents which are being tried out include:

* Bucillamine
* Leflunomide
* Mycofenolate mofetil
* Amiprilose hydrochloride

Indications of DMARDs

Disease modifiers or DMARDs are indicated in all patients with RA who continue to have active disease (in the form of significant morning stiffness, joint pains, elevated ESR) even after 3 months of NSAIDs use. This period of 3 months is arbitrary and has been chosen since a small percentage of patients may experience spontananeous remission. The vast majority, however, need DMARDs and many rheumatologists start DMARDs from Day 1.

Choice of DMARD

There are no strict guidelines to about which DMARD to choose first in an individual. Patient tolerance, cost considerations and physician's choice determine the selection of a disease modifier.

Patients tend to tolerate methotrexate much better than other agents. The effects of methotrexate and sulphasalazine become apparent with in 1-2 months of treatment, while chloroquine and injectable gold take 3-6 months to produce results. (Table 4). In terms of cost,

Table 4 – DMARDs in RA

NAME	DOSE	COMMON SIDE EFFECTS	MONITORING	ONSET OF ACTION
Chloroquine	250mg daily x 3 months, then alternate days	Skin pigmentation, retinopathy, nausea, psychosis, myopathy	Fundoscopy & Perimetery 6 monthly	2-4 months
Methotrexate (MTX)	7.5-15 mg once a week orally, s/c or i/m	Bone marrow suppression, hepatotoxicity, pulmonary fibrosis, mucositis, nausea	Blood counts, LFT 6-8 weekly, Chest x-ray annually, Urea/creatinine 3 monthly	1-2 months
Sulphasalazine	2 gm daily p.o	Rash, myelosuppression	Blood counts, LFT 6-8 weekly	1-2 months
D-penicillamine	250-500 mg p.o daily	Rash, cytopenias, proteinuria, autoimmune disease	Blood counts, Urinalysis	3-6 months
Gold inj.	10-50 mg weekly i.m.	Rash, stomatitis, cytopenias, nephropathy	- do -	3-6 months
Auranofin (Oral gold)	3mg bd orally	- do - GI effects more common	- do -	3-6 months
Azathioprine	50-150 mg orally	GI side effects, myelo-suppression, infection	Blood counts	3-6 months
Cyclosporin A	3-5 mg/kg/day	Nephrotoxic, Hypertension, hyperkalemia	Blood counts, creat, B.P., potassium	3-4 rnonths
Leflunomide	Loading 100 mg daily for 3days, Then 20 mg/day orally	Diarrhea, transaminitis, alopecia, rash. Do not use during pregnancy.	Blood counts, LFT	2 months
Cyclophospha-mide	50-150 mg orally	Myelo-suppression, infection, gonadal toxicity, hemorrhagic cystitis, bladder cancer	Blood counts, urinalysis	3-6 months

methotrexate therapy is the cheapest costing less than Rs 50 per month, while the monthly cost of therapy with injectable gold and sulphasalazine approximates Rs. 1,000. Also methotrexate enjoys the ease of once weekly oral administration. In contrast parenteral gold requires weekly intramuscular injections and sulphasalazine needs to be taken orally twice daily. All this combine to make methotrexate the most widely prescribed DMARD in the world. Methotrexate should not be used in patients with preexisting liver disease or alcoholics. LFT need to be monitored 6-8 weekly and a rise in SGOT/SGPT necessitates a dose reduction or even cessation of the drug. The mucositis associated with methotrexate can be taken care of by the concomitant administration of folic acid (5 mg per week). Nausea may require the use of antiemetics like ondansetron.

Combination Therapy with DMARDs

A lot of interest is being generated about the use of DMARDs in combination, very much akin to combination chemotherapy in malignancy. Since single DMARD therapy (in conjunction with NSAIDs) is often only modestly effective in treatment of RA, combination therapy has an inherent appeal. DMARD combinations appear to be especially effective if they include methotrexate. Cyclosporine and MTX is an exciting combination for refractory RA, although synergistic toxicity remains a major concern. DMARDs in combination are best reserved for use in refractory patients.

How to monitor treatment in RA

The disease activity is assessed by several parameters which include duration of morning stiffness, tender joint count, swollen joint count, observer global assessment, patient global assessment, visual analogue scale for pain, health assessment questionnaire for activities of daily living, and ESR. A detailed discussion of these is beyond the scope of the present write up.

How long should treatment be continued

Patients on MTX show clinical improvement in 6-8 weeks. Most other DMARDs take 3-6 months to produce beneficial effect. Therefore patient should be observed for 6 months before declaring a DMARDs ineffective. For MTX, 3 months trial is adequate to judge the response in an individual. Once remission is achieved, treatment with maintenance doses for long periods of time is recommended. Relapse occurs in 3-5 months (1-2 months in case of MTX) if drug is discontinued. DMARDs are discontinued by patients because of toxicity or secondary failure. Slip outs (secondary failure) are common after 1-2 years and patient might have to shift over to different DMARDs over 5-10 years. Regular follow up of these patients to detect DMARD toxicity is mandatory.

Corticosteroids in RA

Corticosteroids, both systemic and intra articular, are important adjuncts in the management of RA. The indications for oral corticosteroids are listed below :

(a) As 'bridge therapy' for 6-8 weeks before the actions of DMARDs begin.

(b) For treatment of rheumatoid flares.

(c) For rheumatoid vasculitis and interstitial lung disease.

(d) Maintenance doses of 10 mg or less of prednisolone daily in patients with active RA inspite of NSAIDs and DMARDS.

Intraarticular corticosteroids are the sheet anchor of managing one or more recalcitrant joints which continue to show active clinical synovitis inspite of systemic therapy. Joint infection should always be ruled out prior to local steroid injections.

Newer modalities of treating RA

The subspeciality of Rheumatology is at momentous crossroads as we prepare for the new millennium. Better understanding of the pathogenesis of several rheumatic diseases has enabled scientists to develop more specific interventions which integrate molecular biology with bedside medicine. The current treatment model of rheumatoid arthritis envisages early use of disease modifying drugs (DMARDs) like methotrexate (Fig. 1). However, DMARDs have 3 major shortcomings: only partial remission is induced in many cases, substantial toxicity which requires careful monitoring, and tendency of DMARDs to lose effectiveness with time — "slip out". It has been estimated that only 5-15% of the RA patients who have responded initially to a DMARD will continue to derive benefit from the same DMARD after 5 years. These drawbacks have made researchers look for alternative treatment strategies for RA. The thrust has been on immunointerventions in RA. The clinically important ones are tabulated in (Table 5). TNF blockade has shown very promising results. Recently gene therapy of RA has entered clinical trial stage.

Fig. 1. : Treatment paradigms of Rheumatoid Arthritis

PAST — Traditional pyramidal approach Go slow, go slow

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PRESENT — Early, aggressive use of DMARDs in combination

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FUTURE — DMARDs + Biologic agents (Immuno-interventions)

↓

Induction : DMARDs + Cytokine antagonists

Consolidation : TCR vaccine, Gene Therapy &
Maintenance Tolerance induction

Table 5
Immunointerventions in RA

1. Anticytokine therapy
   – TNF α neutralization
2. Oral tolerance therapy
3. Rheumatoid vaccine (TCR peptide vaccine)
4. Gene therapy
5. Stem cell transplantation

Anticytokine Therapy in RA

Cytokines have been the major target of therapeutic manipulations in RA. Rheumatoid arthritis is a T helper 1 (Th1) predominant state where proinflammatory cytokines like IL-1, IL-6 and TNF-α predominate. Therapeutic efforts revolve around down regulation of these proinflammatory cytokines or up regulation of Th2 cytokines like IL-10. Of the various cytokines, TNF-α neutralization has attracted maximum attention. Two different approaches are available to decrease TNF-α activity : treatment with anti-TNF-α antibodies (such as infliximab) or administration of soluble TNF receptors (such as etanercept). In the former approach there is direct neutralization of TNF-α while in the latter approach soluble receptors mop up the circulating cytokine, thereby preventing its attachment to the cellular receptor and thus its action. Infliximab (Remicade) are chimeric monoclonal antibodies to TNF-α and have a long half life necessitating intravenous administration once in 2 months. The drawback is generation of human antichimeric antibodies (HACA) which blunt the therapeutic advantage. This drawback is obviated by the concomitant use of methotrexate and this is the subject of an ongoing trial - the ATTRACT trial (Antitumour necrosis factor therapy in RA with concomitant treatment with methotrexate) - the preliminary results of which are very encouraging. The new century may well see combined treatment with biologicals and methotrexate become the standard of care for RA. The second therapeutic strategy involves use of soluble TNF-α receptors. The actions of TNF-α are mediated by binding to two different receptors (p55 & p75). Etanercept or Enbrel is a fusion protein of p75 soluble TNF receptor with Fc portion of human IgG1. Fusion with human IgG1 increases the half life and improves bioavailability. This biological agent is administered subcutaneously twice a week. The yearly costs work out to US $ 10,000

approximately. Anti TNF-α agents, have been approved by United States FDA for use in refractory rheumatoid arthritis. The coming decade shall provide answers to issues which are not yet resolved, namely, whether these agents be used early in RA or late in the course of disease and whether these should be used in combination with DMARDs. Other cytokines which are being targeted are IL-1 and IL-6. Recombinant IL-10 is being used to down regulate the inflammatory response.

Surgical intervention in RA

Minor or major surgical interventions are often needed simultaneously with the drug treatment. The most successful surgical procedures for RA are carpal tunnel release,resection of metatarsal heads, and total hip and knee arthroplasty. Synovectomy of joints which continue to have active synovitis inspite of local steroid injections may prevent erosions. Outcome of surgery and complication rates are related to timing and volume of surgery. A detailed discussion on the role of surgery in RA is beyond the scope of the present article.

Conclusions

RA is a chronic progressive polyarthritis associated with substantial disability. The traditional pyramidal approach which envisaged the sequential use of rest, physiotherapy and NSAIDs, with DMARD use being reserved for refractory cases has been abandoned. Current treatment protocols advocate early use of DMARDs before erosions develop. Combinations of methotrexate and anti-cytokines (like TNF alpha) may well become the standard norm of treatment in the new millennium. The treatment model for RA in the 21st century is likely to involve a combination of therapies. While DMARDS and cytokine antagonists would be employed for induction, rheumatoid vaccine, gene therapy and oral tolerance induction are going to find an increasing use in consolidation and maintenance therapy for RA. The need of the hour is to strike a balance between efficacy, toxicity and cost. The new millennium may well see rheumatologists talking not about symptomatic relief but potential cure in arthritis.

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