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Treatment of Rheumatoid Arthritis — State-of-the-Art

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INTRODUCTION

Treatment of Rheumatoid arthritis (RA) has always been a challenge. Understanding different facets of disease, major changes and advancements in treatment of RA and on the other hand removal of different perceptions and myths about the disease from the mind of the patients is equally important for the treating physician. It is not only scientific education and learning about different available modalities of treatment and drugs but art of proper, timely and appropriate strategic execution of these modalities that is more important for a successful outcome.

Readers are encouraged to be familiar with the clinical course and complications of disease, details of available drug therapy, proper indication, use and toxicity. A treatment plan appreciating the stage and severity of the disease in an individual patient is the hallmark of successful outcome. Articular and extraarticular manifestations are equally to be evaluated as they both add on to considerable mortality and morbidity. Functional health status declines as early as 1 year and moderate to severe functional loss by 6 years. Work disability is estimated to occur in 25% of RA patients at 6.4 years[1,2]. Role of progression of radiographic scores is rapid and early in disease and if left untreated leads to irreversible destruction.[3] Mortality rate has been shown to rise over 5-20 years; with as high as 35% by 20 years.[4] Further data support that patient with very poor function experience direct medical cost 2.55 to 6.97 times higher than patients with relatively good function[5]. This alarming physical, social and economic burden in RA with a prevalence of 0.65-1%[6,7], is preventable to a greater extent with an approach aimed at early identification of disease and aggressive treatment with available medical therapy.

The goals of treatment of RA: Relief of pain, maintenance of joint function, prevention/correction of joint deformities and disease modification—*induction of remission*—absence of following: fatigue, joint pain by history, synovial swelling, joint tenderness and normal ESR, morning stiffness less than 15 minutes. Patients must meet 5 of these criteria to be classified as being in remission[8] and or DAS28 less than 2.6.[9] The above goals can be achieved by appropriate use of pharmacological and non-pharmacological measures.

Pharmacological Treatment

Nonsteroidal anti-inflammatory drugs: NSAIDs are the most often used and perhaps the most effective adjunctive therapy in RA, providing both analgesic and anti-inflammatory benefits. Their efficacy is superior to that of placebo[10]. Nonspecific NSAIDs or COX-2 specific NSAIDs show comparable efficacy[11]. However, they do not cure or alter the course of the disease and articular cartilage damage may continue despite symptomatic relief[12]. NSAIDs combination should be best avoided. Long acting NSAIDs may be added at night for those patients who have significant morning stiffness. At times an analgesic like acetaminophen is a useful adjunct.

Long term use of non-specific NSAIDs is a known risk factor for gastrointestinal toxicity. Such patients may require additional PPI co-therapy[13]. COX-2 inhibitors although have a lower risk of development of gastro-intestinal bleeding but recent reports indicate increased risk of cardiovascular related deaths with refocoxib, celocoxib and thrombo-embolic events with parecoxib and valdecoxib. This has created sense of insecurity among prescribers and among consumers[14-16]. A significant association for both selective and nonselective NSAIDs with acute renal failure also has been suggested

recently[17]. Thus, NSAIDs should be prescribed in smallest possible dose for a minimum period keeping co-morbid conditions in mind.

Glucocorticoid (GC) therapy:[18-20] Evidence is in favor that low dose daily glucocorticoid produces more clinical improvement and reduces the rate of radiographically detected progression of disease. Though, not recommended as a single therapy for treatment of RA, they can be very useful as bridge therapy to control symptoms of the disease, especially disease flares and to improve patient's quality of life until the effects of DMARDs are achieved. In contrast to NSAIDs, they have effects on preventing the onset of erosions as well as their progression. In patients with significant renal insufficiency in whom the NSAIDs are contraindicated, as is methotrexate, small doses of corticosteroids can make the difference. In pregnancy, prednisolone is a preferred drug[21]. The high dose GC/pulse therapy is used in systemic vasculitis and major end organ damage. Whereas, intra-articular or intralesional injection therapy is preferred in patients with monoarthritis, oligoarthritis or isolated soft tissue lesions. Osteoporosis is a frequent serious complication of long term GC therapy. Calcium, Vitamin D and if there is any significant bone loss, addition of anti-resorptive agents like bisphosphonates should be considered.

Disease Modification therapy:[22-26] DMARDs therapy is paramount in the treatment and should be offered to all patients of RA. They should be started at an early stage of the disease, ideally within the first 2-4 months since early therapy reduces or prevents joint damage, delays or minimizes functional deterioration and occupational disability. There are many DMARDs available for modifying rheumatoid process favorably. *Commonly used are* methotrexate (MTX), hydroxychloroquine (HCQ), sulfasalazine (SSZ) and leflunomide. *Less commonly used are* gold salts, D-penicillamine, minocycline, cytotoxic drugs (Azathioprine, Cyclosporine, Cyclophosphamide and Tacrolimus) (Table 1).

Table 1: Commonly used DMARDs[24]

Drug	*Dose*	*Adverse effects*	*Onset of action*	*Monitoring*	*Interval*
Methotrexate	7.5-25 mg once weekly orally, SC or IM	Bone marrow toxicity, megaloblastic anemia, liver toxicity, pneumonitis, rarely lymphomas and infections	1-2 months	FBC LFT	Every 4 weeks for 3 months then once in 2- 3 months
Hydroxychloroquine	200 mg twice daily x 3 months then once daily	Skin pigmentation, retinopathy, nausea, psychosis, myopathy	2-4 months	Visual fields	6 monthly
Sulfasalazine	2 gm daily orally	Rash, myelosuppression	1-2 months	FBC LFT	Every month for 3 months then every 2-3 months
Leflunamide	Loading 100 mg daily	Abnormal liver function,	1-2 months	LFT FBC CVS monitoring	Monthly first 6 months and then every 2 months
D-penicillamine	500-1000 mg orally daily	Rash, cytopenias, proteinuria	3-6 months	FBC, Urine	Fortnightly, then every 1-3 months
Gold	Inj-10-50 mg weekly IM Oral-3 mg bd orally	Rash, stomatitis, nephropathy	3-6 months	FBC, Urine	Prior to each injection
Azathioprine	50-150 mg orally	GI side effects, myelosuppression, infection	3-6 months	FBC	Monthly first 3 months and then every 1-3 months
Cyclosporine	3-5 mg/kg/day	Nephrotoxic, hypertension	3-4 months	- Creatinine, BP - FBC, LFT, K^+	Monthly - Periodically
Cyclophosphamide	50-150 mg orally	Myelosuppression, infection, gonadal toxicity	3-6 months	FBC, LFT	Every Month

Methotrexate is considered as DMARD of choice for majority of cases. Co-administration of folic acid (5 mg weekly) is usually recommended. *Leflunomide* can be considered along with *sulphasalazine* as treatment options, especially when MTX is contraindicated or has provided inadequate response. *Hydroxychloroquine* may be considered only for milder and non-erosive disease and for combination therapy with other DMARDs. Toxic drugs like cyclophosphamide and with low response rates like auranofin should not be usually used for the treatment of RA. Cyclophosphamide can be given in severe rheumatoid vasculitis. *Azathioprine* has demonstrated efficacy in the treatment of RA, but its use has been limited by toxicity and risk benefit considerations. *D-penicillamine* and intramuscular gold are less frequently used and preferred these days. *Cyclosporin A* has been recommended for patients with refractory disease, when MTX has failed. Tacrolimus has been tried in patients where cyclosporine is inappropriate or who fail to treatment with MTX[22].

Combination therapy with DMARDs:[24] Lot of interest is being generated about the use of DMARDs in combination. Various protocols include: Step up approach, step down approach, saw tooth approach and parallel approach. Combinations are effective if they include methotrexate as an anchor drug. Combination of methotrexate with leflunamide acts as synergistic as methotrexate act on purine pathway and leflunamide on pyrimidine pathway. DMARDs in combination are best reserved for use in patients with aggressive or refractory disease. Various possible combinations are: Mtx + SSZ; Mtx + HCQ; Mtx + SSZ + HCQ; Mtx + leflunomide or anakinra or etanercept or infliximab.

Biologicals or biological response modifiers: 20-30% of patients of RA do not improve sufficiently with DMARDs[23]. Overcoming this challenge, biologics are the result of newer insights into the pathogenesis of RA and represent a greatest advance in the treatment of RA in the last decade (Table 2)[27-29]. They are significantly better

Table 2: Commonly used biologics[27-29]

Drugs	*Binding target*	*Dose*	*Adverse drug reaction*
TNF blockers			
Etanercept Recombinant human soluble receptor-Fc construct *FDA- approved*	TNF-α and lymphotoxin-α	25 mg SC twice weekly or 50 mg once weekly	Erythema, pain, swelling and itching
Infliximab Chimeric (25% mouse and 75% human) monoclonal antibody *FDA- approved*	TNF-α	3 mg/kg IV every 4 to 8 weeks	Infections, tuberculosis, SLE like syndrome, nausea, headache, sinusitis, rash and cough
Adalimumab Human-derived antibody *FDA- approved*	TNF-α	20-80 mg S/C weekly	Serious infection, neurologic effects and certain malignancies of the lymphoid system
IL-1 Blocking Agent			
Anakinra Recombinant-Human nonglycosylated receptor antagonist *FDA- approved*	Interleukin-1 receptor	1-2 mg/kg/day S/C	Neutropenia, cardiopulmonary arrest, influenza like symptoms, production of antibodies, serious infections
B-Cell Directed therapy			
Rituximab Genetically engineered human-mouse chimeric monoclonal antibody against the CD20 antigen. *FDA approved*	Binds to the CD20 antigen on the surface of B-cell	Slow infusion for several hours 1 gm every 2 weeks	Infusion reactions
Other Targeted Therapies			
Abatacept a recombinant fusion *FDA -approved*	Selectively modulates the CD80 or CD86-CD28 co-stimulatory signal required for full T-cell activation	10 mg/kg IV every 2 weekly for 3 doses followed by 4 weekly	–

in reducing disease activity, sign and symptoms in early and aggressive RA, improve functional disability and retard radiographic progression. They produce significantly more response rate than the MTX and control group. When combined with traditional DMARDs, etanercept, infliximab and adalimumab appear to offer similar protection against progressive structural joint damage and combination therapy with either of these agents appear to be more effective than alone. Etanercept and adalimumab can be given in patients intolerant to MTX. Infliximab and etanercepts can be interchanged in case of failure to one of the therapy. In active RA resistant to DMARDs or refractory RA to other biologics—rituximab and abatacept are considered effective. However, 20-40% of RA exhibits an incomplete or no response at all. Cost is a big constrain for their use in developing countries.

Safety concerns with TNF blockers: The potential risk of *reactivation of TB* infection with the use of TNF inhibitors e.g. infliximab is a serious cause of concern in countries like India, thus patients should be carefully evaluated for tuberculosis before, during and after the therapy. If inactive (latent) TB diagnosed, prophylactic anti-tuberculosis therapy must be started before initiating anti-TNF therapy[30]. *Other infections* like upper respiratory infections, *malignancies*, *worsening congestive heart failure (CHF)* particularly in RA patients with NYHA Class III–IV CHF have been reported. Rarely autoimmune-like syndromes, neurological diseases, hepatitis, antigenicity, hematological disorders also have been reported[31]. There is insufficient data to advise continuation or starting of anti-TNF therapy or IL-1 inhibitor in pregnant women[21]. Hence, TNF-α blockers should be instituted as per the British Society for Rheumatology Guidelines[32].

Other modalities: Minocycline shows moderate improvement in clinical parameters in patients with early synovitis[22]. Recently, few clinical trials have strongly suggested statins to possess an important role in RA mainly mediated by their anti-inflammatory and immunumodulatory properties[33]. Interleukin-10; MRA anti-interleukin-6 (IL-6) receptor antibody; AMG714 human monoclonal antibody to interleukin-15; anti-interleukin 12 and 17 antibodies and protein-A immuno absorption column and AlphaV Beta 3 Integrin[34] are some other modalities under trial. Gene therapy in RA at present remains experimental. Early phase human clinical trials have been conducted successfully and others are in progress[35].

Non-Pharmacological Management

Diet: Consumption of cooked vegetables, olive oil, omega-3 or omega 6-fatty acid is inversely and independently associated with risk of RA[36]. Free radicals may perpetuate tissue damage. Thus, preventive and an adjuvant role of antioxidant supplementation or intake of natural dietary antioxidants in RA patients have been suggested[37].

Cigarette smoking, coffee and alcohol:[38-39,40] Cigarette smoking and coffee intake are associated with increased disease activity and severity despite appropriate therapy, whereas alcohol intake can complicate the treatment of RA. Hence, they should be avoided.

Exercise and physiotherapy: 'Physician add years to life whereas, physiotherapist adds life to years'. Various modalities like SWD, ultrasound, TENS may help in relieving pain, improving joint function[26]. Exercise more than 3 times a week, for at least 20 minutes, and for more than 6-consecutive months after being diagnosed with RA, has advantages for patients with RA to decrease fatigue and disability[41].

Education: A low formal education level is a behavioral risk factor predisposing to etiology and poor outcome in RA. Thus educating patients about their disease can make a big difference[42]. Appropriate sexual, psychosocial and vocational counseling should also be imparted to all patients.

Surgery: May be supplemented to medical treatment in conditions like carpel tunnel syndrome, rupture of tendons, atlantoaxial dislocation and joint replacement[26].

Co-morbidities: Co-morbidities like heart disease, hypertension, diabetes and osteoporosis should be evaluated at the disease onset. Special attention should be given to evaluation of atherosclerosis as these patients have altered lipid profile, vascular inflammation, and endothelial dysfunctions which can increase mortality among RA patients.

Conclusion: RA leads to substantial morbidity and mortality if left untreated. Early and aggressive institution of DMARDs is the hallmark of the treatment along with supportive NSAIDs and corticosteroids therapy. Biologics should be considered in DMARDs resistant RA. However, cost may be a limiting factor in their liberal use. Early diagnosis, education about the disease, change in the lifestyle, proper selection, skill and state of art of institution of available modalities (Fig. 1) at proper and appropriate time is very important to achieve a complete remission and in turn high quality of life.

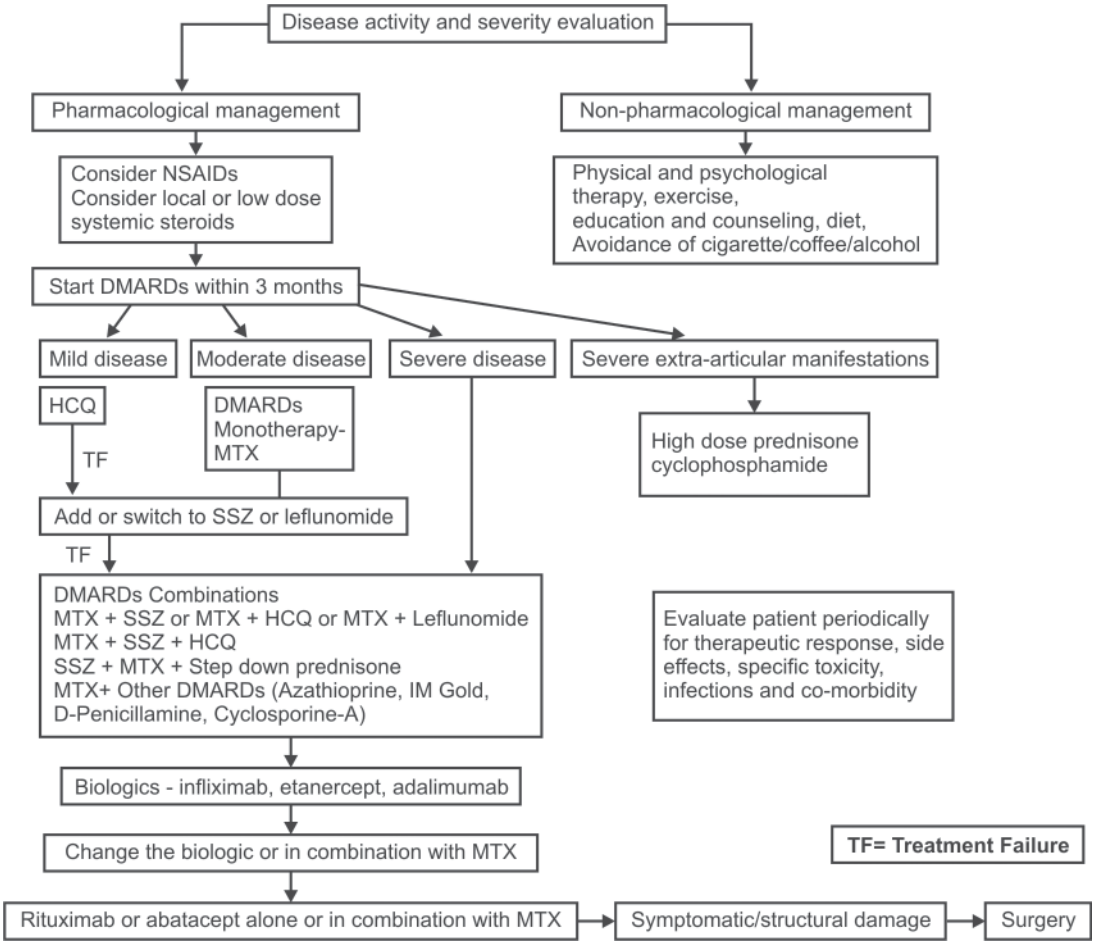

Fig. 1: Prescribing drugs in RA[43]

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