Review Article

Management of Rheumatoid Arthritis and Monitoring of Drug Therapy: A Review

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Accepted on: 16-08-2014; **Finalized on:** 31-10-2014.

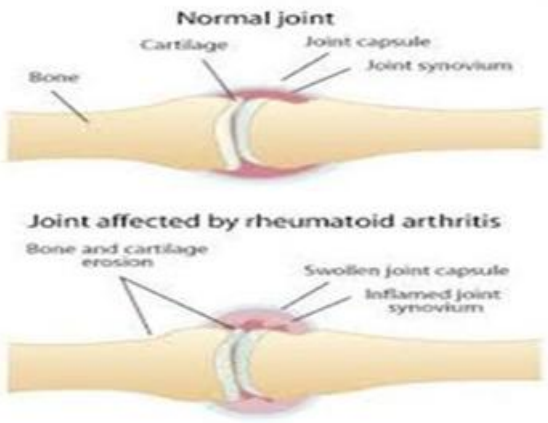
ABSTRACT

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease with multiple joints involvement. The disease involves inflammation of the synovial membrane, which releases inflammatory cytokines that cause damage to joint components, cartilage and bone, and thus leads to progressive joint destruction. The etiology of RA remains unknown, recent advances in molecular technology have made it possible to identify distinct cell subsets, cell surface markers, and cell products that contribute to the immune-mediated inflammatory responses associated with the disease. The traditional principles of the treatment of RA are empirical. The use of analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) for the control of pain and inflammation is combined with therapy using disease modifying anti rheumatic drugs (DMARDs) to slow the processes that result in joint destruction in RA, which are demonstrated by radiological changes, anatomical deformities, and joint dysfunction. The conventional mainstays of DMARD treatment include the antimalarial drugs, sulfasalazine, and methotrexate (MTX).[5] 50% of the risk for development of rheumatoid arthritis is attributable to genetic factors. This enhanced understanding of the immune-pathogenesis of RA provides opportunities to specifically target the immune response pathways using therapies that are more specific. The present article deals with the management of the rheumatoid arthritis.

Keywords: DMARDs, Inflammation, NSAIDs, Rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis is an inflammatory disease that affects joints of the entire body. The main complaints include joint pain and swelling. It is known that structural joint damage progresses as the disease evolves. Although it is very important for disease modifying antirheumatic drugs to inhibit the progression of joint damage.[1] Pain is a designation for a spectrum of sensations of highly divergent character and intensity ranging from unpleasant to intolerable.[2] Methotrexate is sometimes referred to as the anchor drug in the treatment of RA.[3] Rheumatoid arthritis (RA) is characterized by the inflammation and destruction of multiple joints. It can not only disturb quality of life but also shorten the lifespan of affected patients by causing comorbidities such as cardiovascular diseases.[4] The traditional principles of the treatment of RA are empirical. The use of analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) for the control of pain and inflammation is combined with therapy using disease modifying antirheumatic drugs (DMARDs) to slow the processes that result in joint destruction in RA, which are demonstrated by radiological changes, anatomical deformities, and joint dysfunction. The conventional mainstays of DMARD treatment include the antimalarial drugs, sulfasalazine, and methotrexate (MTX).[5] 50% of the risk for development of rheumatoid arthritis is attributable to genetic factors. Smoking is the main environmental risk. In industrialized countries, rheumatoid arthritis affects 0·5–1·0% of adults, with 5–50 per 100 000 new cases annually. The disorder is most typical in women and elderly people. Uncontrolled active rheumatoid arthritis causes joint damage, disability, decreased quality of life, and cardiovascular and other comorbidities. Disease-modifying anti rheumatic drugs (DMARDs), the key therapeutic agents, reduce synovitis and systemic inflammation and improve function. The leading DMARD is methotrexate, which can be combined with other drugs of this type. Biological agents are used when arthritis is uncontrolled or toxic effects arise with DMARDs. Tumour necrosis factor inhibitors were the first biological agents, followed by abatacept, rituximab, and tocilizumab. Infections and high costs restrict prescription of biological agents. Long-term remission induced by intensive, short-term treatment selected by biomarker profiles is the ultimate goal.[6]



Treatment of Rheumatoid Arthritis

The treatments of the rheumatoid arthritis mostly involve the chemical agents that are given in table 1 below;

Table 1: The various agents used for the treatment of RA

S. No.	Agents used for the treatment of Rhumatoid Arthritis
1	Non-steroidal anti-inflammatory drugs (NSAIDs)
2	Disease-modifying antirheumatic drugs (DMARDs)
3	Corticosteroids
4	Biological response modifiers.

Non-Steroidal Anti-Inflammatory Drugs

NSAIDs are an integral part of the management of RA. However, they are 'adjuncts to' and not 'substitutes for' DMARDs. Both agents are started together. DMARDs take several weeks to act and during this time NSAIDs are invaluable in reducing pain and inflammation. Once the disease has been brought into clinical quiescence by the use of DMARDs, NSAIDs can be stopped altogether or used intermittently on an 'as needed' basis, while DMARDs are continued long term. NSAIDs are also useful in treating rheumatoid flares. Various NSAIDs, in equivalent doses, do not differ in efficacy; only the side-effects may differ. The use of a particular agent is more a matter of choice and patient tolerance than anything else. Combining two or more NSAIDs is counterproductive since this increases the incidence of side-effects without increasing efficacy. The major adverse effects of NSAIDs are gastrointestinal (GI) and renal toxicity. GI injury is due to topical irritant actions that disrupt the epithelial barrier, as well as the inhibition of cyclo-oxygenase (COX), predominantly the COX-1 iso form in the mucosa.[7] NSAIDs cause GI side-effects irrespective of the route of administration (oral, parenteral or rectal). This is because the side-effects are mainly due to prostaglandin inhibition and not so much due to the topical effects. Selective COX-2 inhibitors such as celecoxib, rofecoxib, valdecoxib and etoricoxib have a lesser propensity to cause GI side-effects. They are cost-effective in patients who are at high risk for GI events such as elderly patients with cardiopulmonary disease or patients on concomitant steroids. However, they are as likely to cause renal injury as conventional NSAIDs.[2,8]

Disease-Modifying Anti rheumatic Drugs

Disease-modifying anti rheumatic drugs (DMARDs) are a heterogeneous collection of agents grouped together by use and convention. They are the mainstay of treatment for rheumatoid arthritis.[9] Their diverse mechanisms of action are incompletely understood. They reduce joint swelling and pain, decrease acute-phase markers, limit progressive joint damage, and improve function. Methotrexate is the dominant DMARD. Sulfasalazine and leflunomide are also widely used. Their efficacy has been established in placebo-controlled trials.[10] Hydroxychloroquine and chloroquine have DMARD-like properties. Gold (rINN sodium aurothiomalate) and ciclosporin are additional DMARDs; their use is limited by toxic effects. DMARDs are sometimes combined, and several combinations of DMARDs have proven efficacy.[11] An example is methotrexate, sulfasalazine, and hydroxychloroquine termed triple therapy. Use of DMARD combinations varies across different countries; in some regions they are used rarely. Adverse effects of DMARDs include those that are minor (eg, nausea) and serious (eg, hepatotoxicity, blood dyscrasias, and interstitial lung disease).[12-13] Monitoring of adverse effects requires pretreatment screening and subsequent safety recording of blood counts and liver function tests.[14]

DMARDs can be instituted in various ways as shown in table 2.

Table 2: Approaches for DMRDs.[15]

Approach	Description
Step-up approach	Therapy is started with a single DMARD, other agents are added one by one till response is achieved.
Step-down approach	Several DMARDs are started together till remission; one agent is then continued and others withdrawn.
Saw-tooth approach	Therapy is started with a single DMARD which is substituted by another agent in case of toxicity or when it ceases to be effective—'slip-out'.
Parallel approach	Several DMARDs are started simultaneously and continued.

Corticosteroids

Corticosteroids, both systemic and intra-articular, are important adjuncts in the management of RA. They effectively relieve synovitis. Low doses of glucocorticoid substantially retard the rate of joint destruction as seen on X-rays and have a disease modifying potential. However, they are double-edged weapons. The serious adverse effects such as weight gain, hypertension, osteoporosis, cataract, hyperglycaemia, accelerated atherosclerosis, etc. preclude their use as disease-modifying agents in RA. Though long term, low dose glucocorticoid therapy probably increases the risk of serious adverse effects, an evidence-based case can be made for the limited use of low dose glucocorticoid treatment in early disease. The indications for systemic corticosteroids in RA may be summarized as follows:

1. as 'bridge therapy' for 8–12 weeks before the onset of action of DMARDs;
2. for the treatment of rheumatoid flares;
3. for extra-articular RA such as rheumatoid vasculitis and interstitial lung disease;
4. maintenance doses <10 mg of prednisolone daily in patients where RA is active despite NSAIDs and DMARDs; and
5. in pregnancy when other DMARDs cannot be used.

Intra-articular corticosteroids are used to manage one or more 'recalcitrant' joints that continue to show active clinical synovitis in spite of systemic therapy. Joint

infection should always be ruled out before local steroid injections are given.[15-16]

Biological Response Modifiers

Biological response modifiers (BRMs) refer to genetically engineered treatments such as monoclonal antibodies and receptor– immunoglobulin fusion proteins. These are designed to modulate a specific aspect of the underlying autoimmune process while avoiding generalized immune suppression. The need for BRMs has arisen because conventional DMARDs have several shortcomings such as slow onset of action, partial remission in many cases, substantial toxicity that requires careful monitoring, and tendency to lose effectiveness with time—'slip-out'. Better understanding of the pathogenesis of RA has enabled the development of interventions that integrate molecular biology with bedside medicine. The biological therapies in RA include cytokine antagonists, costimulation blockers, anti-B cell therapies (rituximab), oral tolerance therapy, rheumatoid vaccine (TCR peptide vaccine), etc. Currently, the major thrust is on cytokine antagonists, especially tumor necrosis factor (TNF)-a antagonists.[17]

Table 3: Approaches for DMRDs.[15]

Study	Subjects	Therapy	Results	Comment
Tugwell *et al.*, 1995 [44]	148 patients with active RA on MTX	MTX + Cyclosporine (CSA) *vs* MTX + placebo	6 month ACR 20: MTX + CSA (48%) MTX + Placebo (16%)	Patients on CSA did have elevations in serum creatinine ($P = 0.02$)
O'Dell *et al.*, 1996 [7]	102 patients with active RA despite monotherapy	MTX *vs* HCQ + SSZ *vs* MTX + SSZ + HCQ	2 yr Paulus 50: MTX (33%) HCQ + SSZ (40%) MTX + SSZ + HCQ (77%)	No increased toxicity in triple therapy
Boers *et al.*, 1997 [9] COBRA Trial	155 early RA patients	SSZ *vs* SSZ + Prednisolone (high dose off by week 28) + MTX (off by week 40)	1 year pooled index (5 disease activity measures): triple did better to week 28 then they were the same 1 year Sharp/Van der Heijde radiographic damage score: significant and lasting improvement in triple therapy group	Suggests that induction may be effective
Calgurneri *et al.*, 1999 [8]	180 early RA patients	Monotherapy: MTX, SSZ, HCQ *vs* double therapy: MTX + HCQ MTX + SSZ *vs* triple therapy: MTX + SSZ + HCQ	2 year 50% modified Paulus criteria: Triple (88%) Double (73%) Mono (49%)	
Mottonen *et al.*, 1999 [10] Fin RA Trial	199 early RA patients	SSZ ± prednisolone *vs* MTX + SSZ + HCQ + prednisolone	2 year remission: OR for remission was 2.7 for receiving triple therapy early	
Bathon *et al.*, 2000 [51] ERA Trial	632 early RA patients	MTX (mean 19 mg/week) *vs* etanercept 10 mg *vs* etanercept 25 mg	1 year ACR 20: etanercept 25 mg (72%) MTX (65%) $P = 0.16$ 1 year increase in total Sharp score: etanercept 25 mg (0.57) MTX (1.06) $P = 0.001$	
Lipsky *et al.*, 2000 [50]	428 RA patients with active disease on MTX	MTX + placebo MTX + Infliximab	54 week ACR 20/50/70: MTX + placebo (17/8/2%) MTX + Infliximab (3 mg/kg Q8 weeks) (42/21/10%) 54 week increase in radiographic score: MTX + placebo = 7.2 MTX + Infliximab = 1.1 ± 4.7	All patients had suboptimal response to MTX as entry criteria, so cannot directly compare the two.
O'Dell *et al.*, 2001 [38]	60 patients with early RA (DMARD naive)	Minocycline *vs* HCQ (both with low dose prednisone)	2 year ACR 50: Minocycline (60%) HCQ (33%)	
O'Dell *et al.*, 2002 [46]	171 RA patients never treated with combination therapy	MTX + SSZ *vs* MTX + HCQ *vs* MTX + SSZ + HCQ	2 yr ACR 20/50: MTX + SSZ (49%/29%); MTX + HCQ (60%/40%); MTX + SSZ + HCQ (78%/55%)	

This table reviews relevant trials using conventional DMARDs and/or biologic therapies with their results.
ACR, American College of Rheumatology; MTX, methotrexate; HCQ, hydroxychloroquine; RA, rheumatoid arthritis; SSZ, sulfasalazine; DMARD, disease modifying antirheumatic drugs.

Future Perspectives: Pain is a designation for a spectrum of sensations of highly divergent character and intensity ranging from unpleasant to intolerable. Although many unresolved difficulties exist for people with rheumatoid arthritis, continuing introduction of innovative treatments can overcome many of them. One key need is definition of disease subsets in individuals with early arthritis so that intensive treatment regimens can be targeted at patients who most need them and are likely to respond. We also need to move beyond long term suppressive treatment towards short intensive therapeutic courses that result in remission. This progression requires improved drugs and biomarkers that accurately predict patients' status, using pathological information.[2,13-15]

CONCLUSION

Rheumatoid arthritis (RA) is characterized by the inflammation and destruction of multiple joints. The various methods or agents for the treatment of rheumatoid arthritis are used that are shortly described in this review.

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Source of Support: Nil, **Conflict of Interest:** None.