Introduction:
Rheumatoid arthritis is a chronic systemic inflammatory disease whose major manifestation is synovitis of multiple joints. The hallmark of rheumatoid arthritis is symmetrical synovial proliferation and tenderness of multiple joints, particularly the small joints of hands and feet. When the disease is unchecked, it leads to substantial disability and premature death. It affects approximately 0.8 percent of adults worldwide and is more common in women (by a ratio of 3 to 1) and has an earlier onset in women, frequently beginning in the childbearing years. Recent advances in understanding the cytokine networks that are responsible for the ongoing inflammatory response in rheumatoid arthritis have led to the successful use of therapies that target tumor necrosis factor α (TNF-α) and interleukin-1. During the past 10 years, improved understanding of the pathophysiology of rheumatoid arthritis has led to several key changes in the approach to therapy. First, early diagnosis and treatment are important; second the use of disease modifying anti rheumatic drugs (DMARDs) in combination is highly effective. Third, the use of agents that target cytokines, such as (TNF-α) and interleukin-1 is an effective strategy. And fourth, recognition is growing that the assessment of treatment outcomes should include an analysis of important coexisting illnesses (particularly cardiovascular disease and osteoporosis). In this article, I will discuss the clinical application of these principles, which has resulted in marked improvement in clinical outcomes.

Early Diagnosis and Treatment
Joint damage occurs early in the course of rheumatoid arthritis; 30 percent of patients have radiographic evidence of bony erosions at the time of diagnosis, and this proportion increases to 60 percent by two years. Unfortunately, bony erosions and deformities are largely irreversible. Initiation of therapy with DMARDs within three months after the diagnosis of rheumatoid arthritis is crucial; a delay of as little as three months in the introduction of these medications results in substantially more radiographic damage at five years. Therefore, early diagnosis, although challenging, is critical. The diagnosis of rheumatoid arthritis cannot be established by a single laboratory test or procedure but is made with four or more of the diagnostic criteria. The diagnostic criteria are the presence of morning stiffness (more than 1 hour), arthritis of three or more joint areas, arthritis of the hand joints, symmetrical arthritis, rheumatoid nodules, elevated levels of serum rheumatoid factor, radiographic changes and duration of 6 weeks or more. Many other syndromes, including self-limiting viral conditions lasting several weeks, mimic rheumatoid arthritis. Antibodies to cyclic citrullinated peptides (CCPs) appear to have a high specificity (90 to 98 percent) and thus may prove useful in early diagnosis even though the sensitivity of the test for them is approximately 50 to 60 percentages at presentation. Interestingly, these antibodies may appear in the serum years before the onset of clinical disease.

General Therapeutic Principles
Guidelines concerning therapy for rheumatoid arthritis have been published recently by the American college of Rheumatology. No treatment cures rheumatoid arthritis; therefore, the therapeutic goals are a remission of joint symptoms, a return of full function, and the maintenance of remission with DMARD therapy. A useful intermediate goal is to have all patients evaluated by a rheumatologist within three months after the onset of symptoms, So that essentially all patients will be receiving DMARDs by the time they have had symptoms for three months.
To evaluate the success of intervention, investigators have used a number of clinical measures. They include the number of joints that are tender and swollen, markers of inflammation (including the erythrocyte sedimentation rate and c-reactive protein level), and patients’ responses to questions about their pain, their global assessment of disease activity, and their physical function. The American College of Rheumatology criteria for improvement can be used by clinicians to quantify patients’ improvement after treatment (Table 1)\(^\text{12}\). Most clinical studies have required a benchmark of 20 percent improvement in these criteria, a result that is known as ACR 20; now that better treatments are being initiated earlier in the course of the disease, 50 percent improvement (ACR 50) is becoming a more frequent target.

**Medications**

Medications that are used to treat rheumatoid arthritis are divided into three main classes: nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids and DMARDs (both synthetic and biologic).

**NSAIDs**

NSAIDs are particularly helpful during the first few weeks in which a patient has symptoms, because the drugs provide partial relief of pain and stiffness until a definitive diagnosis of rheumatoid arthritis can be established. NSAIDs have not been shown to slow the progression of the disease; therefore, in long-term care, NSAIDs should be used together with DMARDs\(^\text{11}\). Although both these classes of medications are well tolerated for short periods, long-term administration may result in gastrointestinal ulcer, perforation, and hemorrhage. Every year 1.5 percent of patients with rheumatoid arthritis are hospitalized with gastrointestinal problems\(^\text{13}\). The risk of these complications increases with older age, corticosteroid use, and a history of peptic ulcer disease.

Recently cyclooxygenase-2 (COX-2) inhibitors, which decrease the incidence of gastric and duodenal ulcers by approximately 50 percent as compared with traditional NSAIDs, have been introduced\(^\text{14,15}\). To a similar degree, the addition of proton-pump inhibitors to therapy with NSAIDs also decreases the incidence of bleeding ulcers associated with traditional NSAIDs\(^\text{15}\). The efficacy of the COX-2 inhibitors is no better than of the older and less expensive NSAIDs\(^\text{14}\). Both traditional NSAIDs and COX-2 inhibitors have associated with increased fluid retention, exacerbation of hypertension, and impairment of renal function in susceptible patients\(^\text{14}\). Thrombotic events have been reported in patients who are taking COX-2 inhibitors and may occur more frequently than with traditional NSAIDs\(^\text{16}\).

**Corticosteroids**

Corticosteroids are potent suppressors of the inflammatory response in rheumatoid arthritis and in

<table>
<thead>
<tr>
<th>Measure of Disease Activity</th>
<th>Requirement</th>
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<tr>
<td>Tender-joint count</td>
<td>&gt;20% Improvement</td>
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<tr>
<td>Swollen-joint count</td>
<td>&gt;20% Improvement</td>
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<td>Patient’s assessment of pain</td>
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<tr>
<td>Patient’s global assessment of disease activity</td>
<td>&gt;20% Improvement in three of the five measures</td>
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<td>Physician’s global assessment of disease activity</td>
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<tr>
<td>Patient’s assessment of physical function</td>
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<td>Markers of inflammation</td>
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\(^{12}\) American College of Rheumatology preliminary Definition of 20 percent Improvement in Rheumatoid Arthritis (ACR 20).
many other diseases. Unfortunately, their dose-dependent side effects are familiar to all clinicians. Studies conducted more recently 17,18 have corroborated findings from older trials by clearly establishing that corticosteroids decrease the progression of rheumatoid arthritis as detected radiographically. Corticosteroids in low doses (e.g. <10mg of prednisone per day) are used to treat 30 to 60 percent of patients 17. Table II presents some useful guidelines for corticosteroid use in patients with rheumatoid arthritis. Predictable side effects of corticosteroid drugs include thinning of the skin, cataracts, osteoporosis, hypertension, and hyperlipidemia 18. The latter three conditions may be preventable with aggressive management of osteoporosis and cardiovascular risk factors. Essentially, all patients taking corticosteroids should receive supplemental calcium (1to 1.5g per day) and vitamin D (800 IU per day) 19. Bisphosphonates appear to be very effective in reducing vertebral fractures is patients taking corticosteroids 19 (offering a reported 70 percent reduction in incidence) and should be prescribed for patients who have low bone density (e.g. a T score of -2 or lower). Recent evidence suggests that inflammation plays a major role in atherosclerosis 20; the ability of corticosteroids to decrease inflammation rapidly may offset some of the potentially detrimental effects of the drugs on the vascular endothelium 20.

**Synthetic Dmards**

Optimal management of rheumatoid arthritis requires rapid and sustained suppression of inflammation with DMARDs, which are defined as medications that retard or halt the progression of disease. Disease modification is most convincingly demonstrated by the ability of the medications to decrease radiographic progression. A metaanaylsis of blinded clinical trials has suggested that the relative efficacy of methotrexate, sulfasalazine, intramusculat gold and penicillamine is similar 21. Antimalarial drugs (e.g. chloroquine and hydroxychloroquine) are less effective. Penicillamine, because of concern about its toxicity, and oral gold, because of its marginal efficacy are rarely used today 21.

<table>
<thead>
<tr>
<th>Table-II</th>
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<tbody>
<tr>
<td><strong>Keys to Optimizing the Outcome of Treatment</strong></td>
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<tr>
<td>Make an early diagnosis</td>
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<tr>
<td>Start DMARD therapy as early as possible (within three months after onset of symptoms)</td>
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<tr>
<td>Strive for remission (no joint symptoms) in all patients Use corticosteroids as bridge to effective DMARD therapy</td>
</tr>
<tr>
<td>Prednisone at doses &gt;10mg/day is rarely indicated for joint disease</td>
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<tr>
<td>Avoid using corticosteroids without DMARDS</td>
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<tr>
<td>Minimize duration and dose by tapering to the lowest dose that controls the disease</td>
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<tr>
<td>Always consider prophylaxis to avert osteoporosis</td>
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<tr>
<td>Recognize and treat coexisting illnesses</td>
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<tr>
<td>Facilitate communication between primary care physician and rheumatologist</td>
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</tbody>
</table>

Since observational trials have clearly identified methotrexate as the synthetic DMARD that is most likely to induce a long-term response, it is most often selected for initial therapy 21. It has demonstrated efficacy and durability, a long-term track record of acceptable toxicity, and low cost 22. An important observational study has shown that patients with rheumatoid arthritis who have been treated with methotrexate have significantly lower mortality (odds ratio for death, 0.4) than patients who have not been treated with methotrexate 23. Due to its marked efficacy, safety, tolerability and sustainable effect, most clinical trials have listed active disease despite methotrexate therapy as an inclusion criterion and have tested the safety and efficacy of new drugs in comparison with methotrexate 22. Concomitant administration of folic acid (1 to 3 mg per day) or folinic acid (2.5 to 5 mg given 12 to 24 hours after methotrexate) significantly decreases many toxic effects without a measurable decrease in efficacy and has improved the tolerability of methotrexate 24.
finding that has permitted clinicians to administer 20 to 30 mg of methotrexate per week when necessary. Most data suggest that methotrexate is most effective at a dose of 7.5 to 30 mg per week\textsuperscript{25} but that oral adsorption may be highly variable. Therefore, if oral methotrexate produces a suboptimal response, a trial of subcutaneous or intramuscular methotrexate is indicated\textsuperscript{11}.

**Leflunomide**, a new synthetic DMARD, has an efficacy similar to that of sulfasalazine or moderate dose methotrexate\textsuperscript{26, 27}. Leflunomide is given orally as a loading dose of 100 mg daily for 3 days followed by a daily dose of 20 mg. Leflunomide is an alternative to MTX as a first-line DMARD in patients intolerant of MTX or with renal insufficiency.

**Hydroxychloroquine** (200-400 mg/day), considered the least potent but best tolerated of the DMARDs \textsuperscript{21} is the DMARD that is most commonly combined with methotrexate. Hydroxychloroquine may be used by itself in an early and mild RA. **Sulfasalazine** was the first DMARD that was developed specifically to treat rheumatoid arthritis and has an efficacy similar to that of methotrexate\textsuperscript{21}. It is often a first-choice agent for rheumatoid arthritis; starting with one tablet (500mg) daily and building up to the full dose of 2-3 gm daily over two weeks. Sulfasalazine is most commonly used in the United States as part of combination DMARD therapy\textsuperscript{21}. Intramuscular **gold** (500mg/month) provide significant clinical improvement in up to 30% of patients with rheumatoid arthritis and prolonged complete remission have been observed\textsuperscript{28}. Its cumbersome administration and toxicity have limited its use\textsuperscript{21}. Safe administration of DMARDs requires critical and careful monitoring (table III)\textsuperscript{29}. Detailed monitoring guidelines have been published to help avert damage to the liver\textsuperscript{30}, which was a major concern when use of the drug for rheumatoid arthritis became popular in the mid-1980s. These guidelines include measuring serum albumin and aminotransferase levels every four to eight weeks. Doses of methotrexate should be decreased when aminotransferase levels are elevated above the upper limit of normal, and treatment should be stopped if the elevation persists. Obtaining complete blood counts and measuring serum creatinine are also recommended\textsuperscript{29} since a decrease in renal function may precipitate toxic effects in a patient in previously stable condition who is taking methotrexate.

Both methotrexate and leflunomide have a substantial potential for teratogenesis\textsuperscript{30}. So women of childbearing potential who require these medications should be using reliable birth control. Subacute pneumonitis is rare with methotrexate (51 cases have been reported worldwide) but may be life-threatening\textsuperscript{32}. If pneumonitis is suspected on the basis of clinical findings or a chest radiograph, methotrexate should be promptly discontinued and not reintroduced. As the best tolerated of all the DMARDs, hydroxychloroquine is used at doses below 6.5 mg per kilogram of lean body mass per day, requires only yearly visits to the ophthalmologist to prevent the rare occurrence of retinal toxic effects\textsuperscript{33}.

Four double blind, controlled trials have now shown that minocycline is effective in treating rheumatoid arthritis\textsuperscript{34, 35}. Minocycline that was used as initial therapy in patients who tested positive for rheumatoid factor was superior to placebo (response rate 65 percent, as compared with 13 percent for placebo)\textsuperscript{34} and superior to hydroxychloroquine (60 percent vs. 33 percent)\textsuperscript{35} when measuring ACR 50. The mechanism by which minocycline works is incompletely understood but probably involves immunomodulation, suppression of matrix metalloproteinases and suppression of nonspecific infections that would otherwise stimulate inflammatory cytokine production\textsuperscript{35}. Reversible hyperpigmentation is seen in up to 30 percent of patients who are receiving long-term minocycline therapy.
Three biologic products that inhibit the actions of TNF-α (infliximab, etanercept, and adalimumab), one that inhibits the action of interleukin-1 (anakinra) and an anti CD20 monoclonal antibody are now available to treat rheumatoid arthritis. Infliximab is a chimeric human-murine anti TNF-α monoclonal antibody, which is administered by intravenous infusion, 3mg/kg at 0, 2 and 6 weeks and then every 1-2 month. Etanercept is a synthetic human TNF receptor-Fc protein, administered subcutaneously 25mg twice weekly or 50 mg weekly. Adalimumab is a human monoclonal antibody to TNF-α administered subcutaneously 40 mg every 1-2 week. Anakinra, a recombinant form of human interleukin-1 receptor antagonist, 100mg daily by subcutaneous injection may be useful in patients who have no response to or unable to tolerate methotrexate, leflunomide or TNF-α antagonist.

Rituximab is a chimeric (humanized mouse) anti CD20 monoclonal antibody that depletes CD20 positive B cells. It has been approved by the FDA in 2006 and has demonstrated clinical efficacy and safety in of rheumatoid arthritis with incomplete response to methotrexate. In a randomized, double-blind controlled clinical study of 161 patients who had active rheumatoid arthritis despite methotrexate treatment, a single course of two infusions of rituximab (1000mg on days 1 and 15) alone or in combination with either cyclophosphamide(750 mg on days 3 and 17) or continued methotrexate(≥10mg/week), provided significant improvement in disease symptoms at both weeks 24 and 48.
These drugs are more effective than standard DMARDs (with faster onset of action, greater clinical efficacy and sustained benefit) but because of their cost many countries have set restrictive guidelines for their use. Current UK recommendations are that they should be initiated only in active RA when an adequate trial of at least two other DMARDs (including methotrexate) has failed.

**Combination Therapy with DMARDS**

One of the first randomized studies that directly compared combination DMARD therapy with methotrexate was a two-year, double-blind trial in which patients were assigned to three groups: those who took methotrexate alone (at 17.5 mg per week), those who took a combination of sulfasalazine (at 1 g per day) and hydroxychloroquine (at 400 mg per day), and those who took all three medications. At two years, the end point of 50 percent improvement in composite symptoms of arthritis was reached by 77 percent of patients who were treated with all three drugs but by only 33 percent of patients who were treated with methotrexate alone. Patients who received combination therapy did not have more side effects than those who received methotrexate alone. In another study, the triple combination of methotrexate (at 17.5 mg per week), sulfasalazine (at 2 g per day), and hydroxychloroquine (at 400 mg per day) was superior to either the combination of methotrexate and sulfasalazine or the combination of methotrexate and hydroxychloroquine.

In patients who have early disease, three critical trials have all shown that initial combination therapy is superior to therapy with a single DMARD. The Combination therapy Bij Rheumatoid Arthritis (COBRA) trial compared sulfasalazine alone with the combination of sulfasalazine, low-dose methotrexate (which was stopped at 40 weeks), and prednisolone (which was given initially at 60 mg per day but tapered off by 28 weeks). Patients in the combination group had a more rapid response to treatment, fewer withdrawals from the study because of toxicity, and most important, less radiographic evidence of progression at five years. Other trials involving patients with early disease have demonstrated the superiority of triple therapy (methotrexate, sulfasalazine, and hydroxychloroquine) over sulfasalazine alone, double therapy (methotrexate and sulfasalazine or methotrexate and hydroxychloroquine), and monotherapy.

**Initial Treatment**

Establishing a diagnosis as early as possible and then starting DMARD therapy is the foundation for successful treatment of patients with rheumatoid arthritis. Most rheumatologists select methotrexate as the initial therapy for most patients. The characteristics and personal choices of patients influence this decision. Methotrexate should not be used in patients who have underlying liver or renal disease, who consume alcohol, who plan to become pregnant in the near future, or who do not want to undergo regular laboratory monitoring. Whether to start a course of low-dose corticosteroids initially along with the chosen DMARD is controversial, many clinicians start treatment with prednisone at 5 to 7.5 mg per day as bridge therapy until the slower-acting DMARDs have a chance to work. Once the DMARD begins working, corticosteroids should be tapered.

Methotrexate is started at a dose of 10 mg, given orally once weekly. If patients continue to have active disease (as indicated by swollen and tender joints), as most do, the dose should be increased in 5 mg increments after two weeks interval up to 30 mg per week. If patients continue to have active disease, consideration should be given to switching to subcutaneous administration of equivalent dose of methotrexate. If active disease persists despite optimal methotrexate therapy for 2-3 months, other DMARDs should be added. The Early Rheumatoid Arthritis (ERA) trial is an important study that compared methotrexate (at a dose that escalated to 20 mg per week) with etanercept in patients with disease diagnosed within the preceding three years. Both treatments were very effective in controlling the disease at one year, but etanercept (administered at 25 mg subcutaneously twice a week) was more effective in rapidly suppressing disease activity. In both the ERA and COBRA trials, markers of inflammation (including the erythrocyte sedimentation rate and the C-reactive protein level) were dramatically reduced after two weeks of therapy. If, in fact, it is important to control disease in days, rather than in weeks or months, then corticosteroids and TNF inhibitors (both...
of which appear to be capable of stopping active
disease) should be examined in trials to test the
concept of induction therapy (i.e., medication that is
administered initially and then withdrawn).

**Therapy for Established Rheumatoid Arthritis**

If patients continue to have active disease after two to
three months of methotrexate at a dose of 20 to 30 mg
per week, or if they cannot tolerate higher doses of
methotrexate despite folate replacement, the current
standard practice is to add another DMARD to
methotrexate. The most economical initial choice for
the patient who has active disease despite taking
methotrexate is the addition of sulfasalazine,
hydroxychloroquine, or both. If active disease
(manifested by swollen and tender joints) persists
after three months of these DMARD combinations,
leflunomide or a TNF inhibitor should be added to
methotrexate.

If DMARD therapy is started within three months
after the onset of symptoms and escalated with the
goal of achieving remission, the majority of patients
will have their disease well controlled within a year
while taking conventional single or combination
DMARD therapy. If inflammatory disease is
inadequately controlled, therapy with TNF inhibitors
should be started.

**Coexisting Illnesses**

The long-term prognosis for patients with rheumatoid
arthritis depends not only on how well their joint
disease is treated but also on how well their
coeexisting illnesses are addressed. The three
coeexisting conditions that have the greatest effect on
morbidity and mortality in rheumatoid arthritis are
infection (particularly pulmonary infection),
osteoporosis, and cardiovascular disease.

Rheumatoid arthritis is associated with approximately
doubling of the risk of infection, as compared with
the risk in age-matched controls, and the degree of
increase in the risk correlates with the severity of the
disease. Although some studies suggest that
corticosteroids may increase the risk of infection,
controversy exists about whether such an increase is
due to the use of corticosteroids itself or to the fact
that patients who are at higher risk are more likely to
use corticosteroids. Whether the new TNF inhibitors
increase the risk of infection is a matter for debate
since the drugs have been associated with a change in
the spectrum of infections specifically, increase
tuberculosis, histoplasmosis, and listeria.

The clinician who is caring for patients with
rheumatoid arthritis should be aware of the risk of
infection. All patients should have yearly influenza
vaccinations and should receive the pneumococcal
vaccine at appropriate intervals. Since patients may
have a better immunologic response to vaccination
before taking methotrexate, it seems prudent to
vaccinate before starting DMARD treatment, when
possible. Live vaccines should be avoided in patients
who are receiving immunosuppressive medications.

When considering TNF inhibitors, clinicians should
recommend that all patients be tested for prior
exposure to tuberculosis. Both clinicians and patients
with rheumatoid arthritis should be vigilant with
regard to avoiding infections and treating them early
and aggressively. Stopping or withdrawing drug
treatment during infections is critical.

The incidence of osteoporosis is doubled in patients
with rheumatoid arthritis and baseline bone-density
studies should be performed in all patients,
particularly those who will receive corticosteroids. If
osteoporosis is present, bisphosphonate therapy,
which is reported to decrease the risk of fracture by
70 percent despite the co administration of
corticosteroids should be used.

Cardiovascular disease accounts for most of the
excess mortality associated with rheumatoid
disease. The newer concepts of the pathogenesis of
atherosclerosis suggest that inflammation is a key
factor in causing vascular endothelial damage. It
has been hypothesized that the systemic inflammation
that characterizes rheumatoid arthritis may play a key
role in the excess atherosclerosis seen in patients
with this disease. Risk factors for atherosclerosis
should be aggressively sought and addressed. In
particular, smoking cessation may be fruitful, since
smoking has been associated with increased severity
of arthritis. Current trials of statin therapy in
patients with rheumatoid arthritis may address the
risk of cardiovascular disease, since statins should
decrease atherosclerosis and inflammation.

Many of the new therapies are expensive, with initial
costs that may exceed $1,500 per month. However,
these upfront costs may be justified in the long term by savings that result from an improved quality of life and enhanced productivity.

The treatment of rheumatoid arthritis has improved dramatically in the past decade. Thanks to early diagnosis and the availability of DMARDs. Physicians can now have the goal of eradicating active disease and aggressively intervening to address coexisting illnesses. Remission in patients who are receiving therapy is now a realistic goal.

Summary and Conclusion:
The treatment of rheumatoid arthritis has changed dramatically in the past decade due to improved understanding of its pathophysiology and the availability of DMARDs. Initiation of treatment very early in the disease (within three months), the use of combinations of DMARDs and emergences of a number of new drugs (TNF-α antagonists, IL-1 antagonist, anti CD20 antibody) that have novel mechanism of action have made it possible to achieve control of synovitis and improvement in the quality of life in the majority of rheumatoid arthritis patients. Many of the new therapy are expensive, with initial costs that may exceed £1500 per month. However, these upfront costs may be justified in the long term by savings that result from an improved quality of life and enhanced productivity. Indeed, emerging clinical and epidemiological data suggest that excellent long term control of synovitis will result in significant reduction in rate of unemployment, joint surgeries, disability and mortality in rheumatoid arthritis patients. Complete remission of disease (on therapy) should be the goal of treatment, even if not achievable, in all RA patients.

Reference:


