Indian Rheumatology Association consensus statement on the management of adults with rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory arthritides that causes disability. Community studies point to a prevalence of 0.5% to 0.75%, in our country.1,2 The first Indian guidelines on management of RA were published in 2002.3 Since then there has been a paradigm shift in the management of RA which now aims at induction of remission and maintenance of tight control through use of conventional and biological disease modifying antirheumatoid drugs (DMARDs). The latter are more expensive and beyond the reach of majority of patients. These developments have actually posed new challenges to those practising rheumatology in a resource poor country like ours. Indian Rheumatology Association recognised the need to develop a consensus statement at this time based on expert opinion and published literature. This consensus is intended to guide the practising physicians, rheumatologists and clinical immunologists managing patients with RA. It is expected to ensure uniformity in the assessment and treatment of Indian patients with RA. However, treatment of a particular patient may need to be individualized.

Diagnosis

The diagnosis of patients with established RA is generally not difficult based upon symmetrical polyarthritis characteristically involving small joints of the hands with/without deformities, subcutaneous nodules, radiological changes (cartilage loss, juxtrarticular osteopenia, erosions) and the presence of rheumatoid factor. The diagnosis is predominantly clinical and is supported by imaging and laboratory investigations. Although the American College of Rheumatology (ACR)4 classification criteria is not intended to be used for bedside diagnosis, majority of patients will fulfill these criteria.

Definition of Early RA: Early rheumatoid arthritis is an important concept that has been developed recently to aggressively treat the patient within the therapeutic window of opportunity. This is variable, but IRA’s consensus was:
• Early RA: < 24 months
• Established disease: > 24 months
• Late disease: > 5 years

The diagnosis of RA in early disease may be difficult. The following, if present would favour RA
• Persistent inflammatory arthritis of more than 4 joints.
• Many active joints
• High ESR and/or CRP
• Positive IgM RF or anti-CCP2 (Antibody to CCP is more specific than RF)
• Radiographic changes of juxtaarticular osteopenia, erosions and joint space narrowing.

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 monthly 6 and radiology yearly to assess damage.

A. Clinical

Assessment of pain: Pain is assessed on VAS (visual analogue scale) (Appendix I). Briefly, this consists of a 10 cms 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 physician’s ‘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.

Duration of early morning stiffness: Patients should be asked about the time of waking and the time by which the stiffness is maximally improved. This time interval should be recorded in minutes.

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 and 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 (Appendix II).

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.

Serology: It is preferable to do both IgM-RF and anti-CCP. However, in most patients a semiquantitative test for IgM RF by latex agglutination, nephelometry or turbidimetry is sufficient.

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 (Appendix III). DAS28 calculator can be downloaded from the IRA website. If special calculators or softwares on computers and acute phase reactants (APR) at the time of calculation are not available, ‘simplified disease activity index (SDAI)’ and ‘clinical disease activity index (CDAI)’ (Appendix IV) can be used. The 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 recording of joint space narrowing, erosions and subluxation of the affected joints. For research, detailed scoring systems are available (‘Larsen score’ and ‘van der Heijde’s modification of Sharp’s score’ (Appendix V).

Disability assessment

RA is a disabling disease, the disability being contributed both by disease activity and damage. Disability is usually measured by measuring ‘disability component of HAQ’
IRA consensus statement on the management of adults with rheumatoid arthritis

(HAQ-DI). Two Indian HAQ-DI versions are available for use—a concise one and a more detailed one.

**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, interstitial lung fibrosis, vasculitis, bony erosions, IgM RF and antibodies to CCP.

**Treatment**

**Education and counseling**

Successful management of patients with RA depends upon empowering the patients with the knowledge about the chronic and fluctuating course of the disease, side effects and costs of the drugs and the rigorous and continuous need of physiotherapy. The level of communication will depend upon the patient's educational and social background and may require several sessions. More the time spent in counseling, more the chances that patient comes to terms with the chronic nature of the disease and adheres to treatment. Patients are likely to follow up with the same doctor/hospital if they have been counseled well. Patient’s anxiety regarding various diets, climatic conditions and other personal habits should be addressed. Smokers should discontinue smoking as it adversely affects the course of the disease and alcohol intake should be restricted in view of the hepatotoxicity of drugs used in RA. The positive aspect of therapy has to be spelt out that patients with drug therapy can hope to live a better quality of life.

The goals of treatment are to relieve pain and swelling of the joints so that 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.

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**

Pharmacotherapy of RA consists of the following:

1. Antiinflammatory drugs: Non steroidal antiinflammatory drugs (NSAIDs) and corticosteroids
2. Analgesics
3. Conventional disease modifying antirheumatoid drugs (DMARDs)
4. Biologics DMARDs

**Non steroidal antiinflammatory drugs**

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 pharmacological benefit but may potentiate adverse events. The overall aim should be to minimize their use when disease control is achieved with DMARDs.

**Gastrointestinal toxicity of NSAIDs:** The Food and Drug Administration (FDA) has published a general risk of 2% to 4% per year for non selective NSAIDs-induced gastroduodenal ulcer, its ensuing complications, or both. The risk factors for an NSAIDs-induced GI event are given in Table 1.

**Preventing gastrointestinal toxicity due to NSAIDs:** The risk of NSAIDs-induced gastric and duodenal ulcers (detected on endoscopy) can be reduced by the use of proton pump inhibitors such as omeprazole and lansoprazole, misoprostol, a prostaglandin analogue, and histamine-2 receptor antagonists (H2RAs) in double doses (equivalent to ranitidine 300 mg twice daily).

**Table 1 Risk factors for NSAIDs-induced gastrointestinal events**

- Age more than 65 years
- History of peptic ulcer disease or bleeding from the GI tract
- Concomitant use of glucocorticoids which may increase the risk for peptic ulcer disease by 4 fold
- Comorbid illness, such as significant cardiovascular disease
- Patients with more extensive or severe rheumatoid arthritis
- Increasing dose of specific and singular NSAIDs
- Combinations of NSAIDs
Cardiovascular (CV) toxicity of NSAIDs: Increased incidence of serious CV events has been observed in patients treated with Cox-2 inhibitors in various studies.\textsuperscript{11–13} Non-selective NSAIDs may also be associated with CV events, which have not been delineated. Following contraindications and precautions are applicable while prescribing Cox-2 selective NSAIDs:\textsuperscript{14}

- Established ischaemic heart disease, cerebrovascular disease and peripheral arterial disease.
- Caution in patients with risk factors for heart disease, such as hypertension, hyperlipidaemia, diabetes and smoking.

Renal toxicity of NSAIDs: NSAIDs may cause oedema, hypertension and renal failure and exacerbate heart failure in susceptible individuals. Both Cox-1 and Cox-2 are important in regulating renal blood flow and Cox-2 selective NSAIDs do not have any advantages over non-selective agents in terms of renal toxicity or hypertension. Care is needed with NSAIDs of all classes in patients on antihypertensive, the elderly and others at risk of renal diseases.\textsuperscript{15}

Other adverse effects: A variety of other adverse effects such as skin rashes, transient elevation of liver enzymes, photosensitivity, allergic reactions, mouth ulcers, headaches and tinnitus may occur with NSAIDs. In about 10% of cases, asthma may be aggravated by NSAIDs and aspirin. Reports suggest that Cox-2 selective NSAIDs may be safer than nonselective NSAIDs in aspirin-sensitive asthmatics. Hypersensitivity reactions and rare, but serious and sometimes fatal skin reactions can occur with all Cox-2 selective NSAIDs. In the majority of cases these occur in the first month of use. Caution should be exercised in patients with a history of drug allergies.

Corticosteroids

Corticosteroids have potent antiinflammatory effects and hence are effective for symptomatic relief.

Low dose oral prednisolone (5–10 mg/day): Selective use for short duration is beneficial in RA of <2 years duration with high disease activity\textsuperscript{16} under expert supervision. It has a role in symptomatic relief in RA not controlled with optimal therapy with DMARDs.

Note: Till date, there is no evidence to suggest the superiority of any of the synthetic analogues (methylprednisolone or deflazacort) over prednisolone in preventing side effects. Recently, a modified release preparation of prednisolone was found to be better than standard morning dose prednisolone in relieving symptoms in RA.\textsuperscript{17}

Intrarticular corticosteroids are indicated if a single joint or only few joints are inflamed. The drug of choice is triamcinolone hexacetonide; however hexacetonide salt is not available in our country and triamcinolone acetate has similar efficacy. Injection into the same joint should not be repeated before 3 months. No more than 3 injections per joint is advisable in a year. Contraindications for joint injections are: infected joints or surrounding periartritic infections, prosthetic joint, unstable joint and coagulopathies.

High dose steroid (prednisolone 0.5–1 mg/kg/day) is indicated in
1. Interstitial lung disease
2. Vasculitis – ulcers, neuropathy
3. Eye complications – scleritis, uveitis

Precautions

1. Patients on corticosteroids with additional risk factors (e.g. osteoporosis, obesity, 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.
2. 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.
3. Patients who are on long-term steroids, will need supplemental corticosteroids before surgery to prevent the development of Addisonian crisis.

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. Given within the specified dose limits, these are safer than NSAIDs with regard to GI, renal and cardiovascular toxicity.

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.\textsuperscript{18}

\textbf{Note:} The initiation of DMARDs therapy should not be delayed beyond 3 months in whom, in spite of adequate treatment with NSAIDs, there is ongoing joint pain, significant morning stiffness or fatigue, active synovitis, or persistent elevation of the ESR or CRP level.\textsuperscript{19–21}

\textbf{Choice of initial DMARDs}

- Methotrexate is the ‘anchor’ drug that should be used first in patients at risk of developing persistent disease.
- Leflunomide and Sulphasalazine\textsuperscript{18} are best alternative agents when methotrexate is contraindicated.

\textbf{Combination DMARDs vs Monotherapy}

Various RCT, meta-analysis and review articles\textsuperscript{18–22} have shown that combination DMARDs are better than monotherapy, particularly in patients with moderate to severe disease. This is balanced against an increased risk of withdrawals (37\%) due to adverse effects.

In combination, methotrexate with sulfasalazine and/or hydroxychloroquine, methotrexate and TNF inhibitors, are the most effective combinations. Methotrexate with Leflunomide is also very effective combination particularly in severe disease but requires careful monitoring for hepatotoxicity.

\textbf{Contraception}

For women of childbearing age, effective contraception is generally required when DMARDs are prescribed. The drug regimen will need modification if the patient is or wishes to become pregnant, or if breastfeeding is contemplated as discussed later.

\textbf{Duration of DMARDs treatment}

It is indefinite, probably life long. Once remission is achieved and maintained for a year, then drugs may be decreased or dose may be reduced. A minimum maintenance dose will be required for indefinite period.

\textbf{Biological DMARDs}

In the last decade, biological agents targeting molecules/cells involved in perpetuating persistent synovitis and causing 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. Some of them like infliximab, etanercept and rituximab are available in our country and more are likely to arrive in the near future (tocilizumab, abatacept and golimumab are undergoing Phase III/IV trials). At the present time, these drugs are expensive and can be afforded by a minority of patients. The Indian experience is limited.\textsuperscript{23} Besides the cost, flare up of latent tuberculosis has been a major concern in patients receiving TNF inhibitors. A thorough screening for TB prior to its use has resulted in lesser occurrence of TB from a country like Spain. Infliximab, a monoclonal antibody to soluble and membrane bound TNF is a chimeric antibody (partly murine and partly human); induces antibodies to itself (human anti-chimeric antibodies or HACA) that potentially reduce its effectiveness on continued use. Methotrexate is co-administered with it to suppress the development of HACA. Patient should be counseled before starting biological therapy that biological DMARDs are for control of disease and have to be continued life-long. There is no advantage of administering a few doses as invariably the disease will relapse after some time. Biological DMARDs are to be prescribed by experienced rheumatologists only and include:

a. TNF inhibitors
   1. Infliximab (mouse monoclonal antibodies to human TNF)
   2. Etanercept (soluble TNF receptors)
   3. Adalimumab (humanized anti TNF antibodies)
b. Rituximab (antibody against CD20 on B cells)
c. Abatacept (CTLA4-Ig)

\textbf{Indications for treatment with TNF inhibitors}

These indications are taken from BSR guidelines which were updated in 2005.\textsuperscript{24} Patient should
1. Fulfill the 1987 ACR classification criteria for RA.\textsuperscript{4}
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.
<table>
<thead>
<tr>
<th>DMARDs</th>
<th>Dosage</th>
<th>Time to benefit</th>
<th>Adverse effects</th>
<th>Monitoring</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine</td>
<td>200 to 400 mg orally per day.</td>
<td>2–6 months</td>
<td>Nausea, headaches, diarrhoea, rash, depigmentation, tinnitus. Rare: abdominal pain, myopathy, retinal toxicity.</td>
<td>Eye examinations (funduscopy and perimetry) every 12 months. Baseline over 60 years of age and pts with renal impairment.</td>
<td>Total daily dose should be kept below 6.5 mg/kg and should be used with caution in elderly and with renal impairment.</td>
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<tr>
<td>Methotrexate (MTX)</td>
<td>7.5 to 25 mg (0.2 to 0.4 mg/kg) orally, IM, or SC per week. When the dose is &gt;15 mg/week, parenteral route is preferable.</td>
<td>1–3 months</td>
<td>Nausea, diarrhoea, fatigue, mouth ulcers, rash, alopecia, abnormal LFTs. Rare: low WBC and platelets, pneumonitis, sepsis, liver disease, lymphoma, nodulosis.</td>
<td>Baseline: AST, ALT, ALP, albumin, bilirubin, hepatitis B and C serology, CBC, creatinine, and chest X-ray. MTX is contraindicated in alcoholics. Avoid MTX if there is baseline persistent AST elevation. Folic acid supplementation 5 mg/week, dose may be increased if side effects continue. CBC, creatinine, LFTs monthly for 3–6 months, then every 3 months, repeat AST/ALT in 2–4 weeks if initially elevated, and adjust dose as needed; liver biopsy if no resolution on discontinuation.</td>
<td>Leflunomide is eliminated from system with folinic acid 5 mg/week taken 8–24 hours after MTX. Folic acid dose may be increased if side effect continues.</td>
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<tr>
<td>Leflunomide</td>
<td>100 mg orally per 3 days, then 10 to 20 mg/day.</td>
<td>4–12 weeks</td>
<td>Nausea, diarrhoea, rash, alopecia, highly teratogenic, even after discontinuation. Rare: leukopenia, hepatitis, thrombocytopenia.</td>
<td>CBC and LFT after 2 weeks, and then 8 weekly, blood pressure monthly for the first 6 months and then 8 weekly. Leflunomide is contraindicated in pregnant women.</td>
<td>Precaution: Should not be used in young females of child bearing age group. It can be eliminated from system with folinic acid 5 mg/week taken 8–24 hours after MTX.</td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage</td>
<td>Duration</td>
<td>Side Effects</td>
<td>Monitoring</td>
<td>Side Effects</td>
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<tr>
<td>Sulfasalazine</td>
<td>2 to 3 g orally per day</td>
<td>1–3 months</td>
<td>Nausea, diarrhoea, headache, mouth ulcers, rash, alopecia, contact lens staining, reversible oligospermia, abnormal LFTs.</td>
<td>CBC every 2–4 weeks and LFT 6 weekly, for 3 months, then every 3 months.</td>
<td>Gradual increase in dose and if necessary use prochlorperazine for central nausea, reduces side-effect withdrawals.</td>
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<tr>
<td>Cyclosporine</td>
<td>2.5 to 4 mg/kg orally per day</td>
<td>2–4 months</td>
<td>Nausea, paresthesia, tremor, headaches, gingival hypertrophy, hypertrichosis. Rare: hypertension, renal disease, sepsis.</td>
<td>Serum creatinine and BP fortnightly until the dose has been stable for 3 months and thereafter monthly. CBC, LFT monthly until dose is stable for 3 months and then 3-monthly, serum lipids 6-monthly.</td>
<td>Base line: CBC, LFT and RFT. BP should be normal on two separate occasions prior to treatment, if creatinine rises by 30%, there is hyperkalaemia, new hypertension or significant rise in lipids, withhold drug.</td>
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<tr>
<td>Azathioprine</td>
<td>2.5 mg/kg/day orally</td>
<td>2–3 months</td>
<td>Nausea. Rare: leukopenia, sepsis, lymphoma.</td>
<td>CBC every 1–2 weeks until dose is stable, then every 1–3 months, AST, ALT monthly till dose stable, than every 3 months.</td>
<td>Use lower doses if there is significant renal or hepatic impairment. If allopurinol is co-prescribed the dose of azathioprine must be cut to 25% of the original dose.</td>
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</table>
Exclusion criteria

1. Women who are pregnant or breast-feeding.
2. Active infection including HIV, HBV (caution with hepatitis C).
3. Septic arthritis of a native joint or prosthetic joint within the last 12 months or indefinitely if the prosthetic joint remains in situ.
4. New York Heart Association (NYHA) grade 3 or 4 congestive cardiac failure (CCF).
5. History of demyelinating disease.
6. Caution is required if patients have pulmonary fibrosis.

Criteria for withdrawal of therapy

1. Inefficacy as indicated by failure of the DAS28 score to improve by > 1.2 or to reduce to a score of < 3.2 after 3 months of therapy. However, if other changes in therapy have occurred within the first 3 months (e.g. the treatment has allowed a reduction in steroid dose), treatment may be continued for a further 3 months, but should not be maintained for > 6 months if the DAS28 responses are not achieved (this statement is based on opinion rather than evidence).
2. Development of drug-related toxicity.
3. Severe intercurrent infection (temporary withdrawal).

Dosage, route and frequency of administration

**Infliximab:** 3 mg/kg IV infusion with dextrose or dextrose saline at 0, 2, and 8 weeks and at interval of 8 weeks. If there is relapse, the dose may be increased to 5 mg/kg. The infusion has to be given slowly over 4 hours under direct medical supervision. Since it is a foreign protein allergic and anaphylactic reactions are likely.

**Etanercept:** 25 mg twice a week or 50 mg once a week subcutaneously. The first dose needs to be administered under medical supervision in out patient department. Subsequent doses are self administered by patient at home.

Investigations before administering TNF inhibitors

Patients are to be screened for any infections particularly for active or latent tuberculosis. These tests include haematology, biochemistry to include liver and renal function tests, hepatitis B and C serology, routine urine and microscopy, chest x-ray and Mantoux test.

Note

1. There is no evidence to suggest that one type of anti-TNF therapy is more efficacious than the others.25
2. Infliximab can be useful when etanercept has failed, and vice versa. There is also evidence for adalimumab substitution.26
3. Methotrexate has to be co-administered with infliximab. Although it is not necessary to co-prescribe methotrexate with etanercept, in patients with inadequate response to etanercept, the addition of methotrexate is a useful option, and vice versa.27 Similarly, adalimumab may be administered with methotrexate.28
4. Treatment with TNF inhibitors may be withheld for 2–4 weeks prior to major surgery and restarted post operatively.
5. If live vaccines are required they should ideally be given 4 weeks prior to commencing treatment or 6 months after the last infusion of infliximab (or potentially earlier if risks from not vaccinating are high) or 2–3 weeks after the last dose of etanercept.29

Guidelines for potential adverse effects related to anti-TNF therapy

**Screening for tuberculosis**

It is recommended that all patients about to commence biologics be screened for the presence of active/latent TB. Screening should include a detailed history of prior TB, antituberculous treatment received, if any, and compliance to treatment. This should be supplemented with a thorough physical examination and a chest radiograph.30 It was agreed that the Mantoux test or the gamma interferon assay is not reliable indicator for latent TB. The prophylaxis issue is a controversial one. INH prophylaxis for 9 months has protected occurrence of reactivation in systemic lupus erythematosus.31 Hence the physician may consider using INH prophylaxis in patients being planned for anti-TNF therapy and if a nationwide biological register is maintained we will be able to assess the usefulness of this prophylaxis step. Active TB needs to be adequately treated for 9 months before anti-TNF therapy can be started.

- All patients with a positive Mantoux test, past history of TB, or abnormal chest X-ray suggestive of TB should receive prophylactic anti-TB therapy.
- All patients commenced on anti-TNF therapies need to be closely monitored for TB. This needs to be continued for 6 months after discontinuing infliximab treatment due to the prolonged elimination phase of infliximab.
- Patients on anti-TNF therapy who develop symptoms suggestive of TB should receive full anti-TB chemotherapy, and discontinue anti-TNF therapy.
**Systemic lupus erythematosus and autoimmunity**

- If symptoms of an SLE-like syndrome develop whilst on anti-TNF therapies:
  a. anti-TNF treatment should be discontinued,
  b. appropriate treatment should be initiated for the clinical symptoms and signs.

**Anti B-cell (rituximab) therapy**

The advantage of rituximab therapy in India is that there is no increased risk for TB.

**Indications**

- Active RA (DAS28 > 5.1) with inadequate response to multiple DMARDs.
- Active RA (DAS28 > 5.1) with contra-indication to TNF-inhibitors and inadequate response to (or intolerance of) at least 2 DMARDs one of which should be methotrexate.

**Contraindications**

Allergy to rituximab or any of the excipients of this product or to murine proteins, any active infection (acute or chronic), pregnancy or breast feeding, hepatitis B or C infection, patients prone to recurrent infections (chronic leg ulcers, persistent or recurrent chest infections, indwelling urinary catheters), hypogammaglobulinemia, NYHA grade 4 cardiac failure, severe uncontrolled cardiac disease, clinically significant comorbidities (e.g. chronic renal failure).

**Pre-treatment screening**

- History and physical examination.
- Laboratory testing: FBC, U&Es, LFTs.
- Immunoglobulin levels: IgG, IgA, IgM.
- Hepatitis B and C serology.

Etanercept should be stopped 4 weeks and infliximab and adalimumab for 8 weeks prior to instituting rituximab therapy. Vaccines such as pneumococcal, influenza and hepatitis B should be considered prior to therapy with rituximab. All live vaccines should be avoided after rituximab infusion.

**Treatment dose and co-medication**: Two 1000 mg IV rituximab infusions separated by 2 weeks. Methotrexate should be continued along with rituximab.

**Repeat treatment**: Should be considered in responders after week 24 with either
- Residual active disease (DAS28 > 3.2), or
- Reactivation of disease from low disease activity (increase in DAS28 > 0.6).

**Indications for withdrawal of therapy**

- Severe infusion reactions or any drug related toxicity.
- If there is no response by 16 weeks after the first infusion.
- Severe infections attributable to Rituximab therapy.
- Pregnancy (temporary withdrawal).

**Assessing change in disease activity**

Conventionally, ACR 20/50/70 improvement criteria have been used (appendix). However, the EULAR criteria based on DAS are also a well validated tool (appendix). Both DAS28-ESR and DAS28-CRP have been found to perform equally well in assessing change in disease activity. Regular assessment of patients with either of these is recommended.

**Summary of recommendations**

Conventional DMARDs, methotrexate (MTX), sulphasalazine (SSZ), leflunomide (LEF) and hydroxychloroquine (HCQS) are recommended to be used singly or in combination depending upon the categorization of patient as mentioned below:

<table>
<thead>
<tr>
<th>Disease activity</th>
<th>Duration of disease &lt; 2 years</th>
<th>Duration of disease &gt; 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>MTX</td>
<td>MTX/LEF/SSZ/MTX + HCQS</td>
</tr>
<tr>
<td>Moderate</td>
<td>MTX/LEF/SSZ/MTX + HCQS</td>
<td>MTX + HCQS/</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td>MTX + LEF/</td>
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<tr>
<td></td>
<td></td>
<td>MTX + SSZ/MTX + SSZ + HCQS</td>
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</table>
Management of rheumatoid arthritis in special situations

Pregnancy and lactation

In general, the disease is quiescent during pregnancy with a flare up in postpartum period. There is an inherent inadequacy in safety data on medications during pregnancy because pregnant women as a group are excluded from all premarketing clinical trials and safety studies for ethical reasons. The United States Food and Drugs Administration (FDA) category classification (Table 4) to describe risk and safety of individual medications during pregnancy is an important resource for physicians, being almost exclusively based on animal reproductive data is limited in its ability to precisely predict the human risk. Table 5 summarizes the safety of the different drugs during pregnancy and lactation.

Hepatitis C, Hepatitis B co-infection

NSAIDs should be used with caution being potentially hepatotoxic and should not be used in patients with cirrhosis as they can induce variceal bleed. The risk of elevated transaminases seems to be higher with diclofenac and rofecoxib as compared to other agents. Corticosteroids are not inherently hepatotoxic but have a theoretic risk of compromising immune response to HCV infection. Data in favour or against the use of these agents are insufficient. In the largest cohort study of RA with HBV co-infection majority of patients on antivirals developed reactivation with prednisolone use irrespective of dosage.

Data on the safety of HCQ are limited. Good tolerability and response was noted in a small case series while another series of arthritis associated with chronic viral hepatitis (HBV or HCV) noted liver function worsening in 53% cases. Being potentially hepatotoxic ACR has recommended caution against MTX use in patients with concomitant HBV and HCV infection. There have been reports of viral reactivation and hence routine use of MTX is not currently recommended.

There is limited data on anti-TNF therapy in HBV infection; reactivation has been reported with infliximab but not etanercept or adalimimab. Cyclosporine A has been shown to inhibit HCV replication in vivo and in vitro. Hence its use in HCV associated arthritis seems biologically plausible. Though limited, the available data has indicated promising results. Studies on anti-HCV therapy with interferon and ribavirin have yielded differing results. Antiviral treatment can potentially worsen autoimmune disorder it has been suggested that therapy with IFNα and ribavirin is indicated when required by hepatic or systemic involvement. Arthritis associated with cryoglobulinemia usually responds to antiviral treatment.

Elderly

Elderly-onset RA has more acute onset, marked elevation of ESR, disabling early morning stiffness, particularly of upper limb joints (especially shoulders). Elderly RA patients have a higher incidence of comorbidities, polypharmacy, non-compliance, dosage errors and adverse events to commonly used drugs. The elimination half-life correlates more strongly with creatinine clearance than age. Hence, it is recommended that MTX dose is adjusted as per
the creatinine clearance especially in elderly. No specific dose modifications are required for SSZ. A recent study has suggested that leflunomide induced pancytopenia is more common in elderly and with concomitant use of MTX.

Elderly patients are at a higher risk of NSAIDs toxicity particularly upper GI bleed, renal insufficiency and CNS dysfunction (especially with indomethacin). Selective Cox-2 inhibitors have a lesser incidence of GI side effects but effect on renal function & blood pressure is comparable. There has been evidence recently, suggesting increased risk of thrombotic events with these agents. Hence, careful patient selection is important. It has been recommended that NSAIDs should be initiated at lowest recommended dose especially in low weight individuals because higher plasma levels may occur.

Corticosteroids were previously recommended as second line agents in elderly because of their rapid onset of action and propensity of EORA to rapid functional deterioration. Majority of EORA respond to low dose corticosteroids but they are at a higher risk of adverse effects including osteoporosis, hyperglycemia, hypertension, infection. Recent data suggest that risk of osteoporosis outweighs the benefits of long-term corticosteroid therapy.

### Renal failure

Renal failure in RA poses two specific issues: first, the etiology of renal failure and second, the drug selection & dose adjustment for control of joint inflammation. Renal failure in RA could be attributed to drugs (e.g. NSAIDs, d-penicillamine, and gold etc.) in which case discontinuation of the offending drug is warranted. RA itself could lead to renal damage (e.g. glomerulonephritis, amyloidosis etc.) in which case specific therapy depending on the cause has to be initiated.

Management of joint inflammation in the setting of established renal insufficiency poses special issues because certain drugs are contraindicated (e.g. NSAIDs) while dose adjustment is required for various other drugs. Table 6 summarizes the use of DMARDs in renal failure. Methotrexate itself generally does not cause renal toxicity but being primarily excreted by kidneys the risk of serious toxicities is increased in patients with renal failure and hence should be avoided. Azathioprine can be used but dose reduction to

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### Table 5 Safety of the drugs used in RA in pregnancy and lactation

<table>
<thead>
<tr>
<th>Agent</th>
<th>US FDA Category</th>
<th>Adverse events</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>C</td>
<td>Oral clefts, dose related intrauterine growth retardation, pregnancy induced hypertension, gestational diabetes</td>
<td>Minimal risk</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>B (Diclofenac, celecoxib, ketorolac, piroxicam category C)</td>
<td>Gastrochisis (ibuprofen, Acetyl Salicylic acid), spontaneous abortion, renal dysgenesis, oligohydramios, fetal &amp; post partum haemorrhage, premature closure patent ductus arteriosus with 3rd trimester use</td>
<td>Minimal risk following first trimester exposure, contraindicated following 32nd week gestation</td>
</tr>
<tr>
<td>HCQ</td>
<td>C</td>
<td>Increased risk malformations not documented</td>
<td>Considered safe</td>
</tr>
<tr>
<td>MTX</td>
<td>X</td>
<td>Dose related fetal abnormalities documented</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>B</td>
<td>Substantial teratogenic risk unlikely</td>
<td>Considered safe in pregnancy, report of bloody diarrhea during lactation</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>X</td>
<td>Embryotoxic in animal studies, human teratogenic risk not established, no reports of structural defects</td>
<td>Undetermined</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>D</td>
<td>No documented risk</td>
<td>Data limited, substantial risk unlikely</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>C</td>
<td>No documented increased risk</td>
<td>Data limited, substantial risk unlikely</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>B</td>
<td>Minimal data, no documented risk</td>
<td>Data limited</td>
</tr>
<tr>
<td>Rituximab</td>
<td>C</td>
<td>Case reports indicate nor risk</td>
<td>Undetermined</td>
</tr>
</tbody>
</table>
50% is required if GFR is less than 10%. Haemodialysis (HD) effectively eliminates azathioprine and the drug could be effectively maintained in patients on regular HD. Renal failure increases the incidence of myopathy, neuropathy and cardiac myotoxicity of HCQ and the dose should be decreased by 50%. Cyclosporin and leflunomide can be given at normal doses to patients on regular haemodialysis. Recent reports have shown infliximab to be a safe and effective treatment option for patients on haemodialysis and in secondary amyloidosis.

**Diabetes**

The prevalence of diabetes in RA patients is not increased. However, the coexistence of these two disorders might pose a higher risk of atherosclerotic disease, nephrotoxicity of certain drugs (e.g. NSAIDs) and hyperglycaemia with systemic corticosteroids. The issue of drug management of RA with coexisting diabetes has not been specifically addressed. Two significant recent reports are noteworthy. In a recent report on patients with RA on HCQ for more than 4 years the risk of diabetes was decreased by 77%. The risk reduction was related to the duration of HCQ exposure; in patients with diabetes the requirement of oral hypoglycaemic drugs was lower. The effect could be attributed to beneficial effect on glucose metabolism and insulin sensitivity. Favorable effect of HCQ on dyslipidemia might be of benefit in decreasing atherosclerosis risk. and social well-being through manual therapy, therapeutic exercise and electro-physical modalities.

**Physical activity**

- Leisure time physical activity should be encouraged from initiation of treatment and should be considered as a preventive measure.
- Any daily physical activity e.g. walking, biking, gardening, or swimming might be beneficial if performed at a moderate level, at least 10 minutes at a time accumulated to 30 minutes a day for at least 5 days a week.

**Exercise:** Exercise is central to the management of patients with RA. The most important objectives of exercise therapy in RA are to preserve joint mobility and maintain muscle strength.

**Physical modalities and manual techniques:** Hydrotherapy is frequently used in the management of patients with RA. There is less conclusive evidence for the effectiveness of electrotherapeutic modalities, or electrotherapy, as part of the management of RA. Whilst there is reasonably high level evidence that therapeutic ultrasound has a positive effect on grip strength, research evidence has not demonstrated that heat or cold (thermotherapy) or faradic baths have any effect on objective outcomes in patients with RA. There may be a role for thermotherapy as palliative therapy or as an adjunct therapy combined with exercises as indicated clinically. Evidence supporting the use of transcutaneous electrical nerve stimulation (TENS) for RA patients is equivocal. Acupuncture-like TENS resulted in a decrease in pain and joint tenderness compared to placebo, but no benefit on grip pain, while patients who received conventional TENS reported a greater decrease in disease activity compared to patients who received acupuncture-like TENS.
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REFERENCES


Appendix I  Visual analogue scale for assessment of pain

<table>
<thead>
<tr>
<th>No pain</th>
<th>................................................................................................................................</th>
<th>Very severe pain</th>
</tr>
</thead>
</table>

How severe is your pain today? Place a vertical mark on the line below to indicate how bad you feel is your pain today.

The patient places a mark on the line to indicate his/her level of pain. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point marked by the patient.

Appendix II  Mannequin for recording tender and swollen joints
Appendix III  Simplified and clinical disease activity indices

SDAI = TJC + SJC + PGA + MDGA + CRP
CDAI = TJC + SJC + PGA + MDGA

SDAI – Simplified Disease Activity Score, CDAI – Clinical Disease Activity Index, TJC – Tender Joint Count (based on 28 joint assessments), SJC – Swollen Joint Count (based on 28 joint assessments), PGA – Patient Global Assessment of disease activity (on a visual analogue scale of 0–10 cm), MDGA – Physician Global Assessment of Disease activity (on a visual analogue scale of 0–10 cm), CRP – C-Reactive Protein (in mg/dL).

Appendix IV  EULAR criteria for improvement in disease activity

<table>
<thead>
<tr>
<th>DAS28 at endpoint</th>
<th>Improvement in DAS28 from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.2</td>
<td>Good</td>
</tr>
<tr>
<td>&gt; 0.6 and ≤ 1.2</td>
<td>Moderate</td>
</tr>
<tr>
<td>≤ 0.6</td>
<td>None</td>
</tr>
</tbody>
</table>

Appendix V  Radiological score

A. van der Heijde modification of Sharp’s method
- Scoring includes 2-features: Erosions AND Joint space narrowing
- Erosions are scored as – (16 areas from each hand and wrist, 10 metata MTPs and 2 interphalangeal joints of the big toes from feet are evaluated)
  0 = Normal,
  1 = Discrete erosions,
  2 to 3 = Larger erosions according to surface area involved,
  4 = Erosions extending over middle of the bone, and
  5 = Complete collapse.
- Joint space narrowing – (15 areas from the hands and wrists and 6 areas from the feet)
  0 = Normal,
  1 = Focal narrowing,
  2 = Reduction of less than 50% of joint space,
  3 = Reduction of greater than 50% of joint space, and
  4 = Ankylosis.
- The maximum erosion score is 160 for hands and wrists and 120 for feet. The maximum joint space narrowing score is 120 for hands and wrists and 48 for feet. Therefore, the total van der Heijde radiographic score ranges from 0 to 448.

B. Larsen method
- Includes both erosions and joint space narrowing in each joint as a single score
  0 = Intact bony outlines and normal joint space,
  1 = Erosion less than 1 mm in diameter or joint space narrowing,
  2 = One or several small erosions, diameter more than 1 mm,
  3 = Marked erosions,
  4 = Severe erosions, where there is usually no joint space left, and the original bony outlines are partly preserved,
  5 = Mutilating changes, where the original bony outlines have been destroyed.
- All synovial joints can be included in the Larsen score, and joints that are scored should, therefore, be listed, as well as the maximum score applied.