CLINICAL PRACTICE GUIDELINES

Management of Rheumatoid Arthritis

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1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology characterized by symmetric, erosive synovitis and, in some cases, extra-articular involvement. RA affects about 1% of the adult population.

Evidence is now accumulating that early and more aggressive intervention can improve long-term disease outcome. New classes of therapeutic agents have also been introduced.

These recommendations are based on best practices and a consensus of the committee. Several international RA guidelines were studied in preparation of these guidelines[1,2,3,4]. We hope it will prove useful to those who face the difficult task of making decisions about diagnosis and different courses of treatment and that, in the final analysis, it will result in better outcomes for patients with RA.

2. Diagnosis

Recommendation

1. Early diagnosis is important for better outcome.
2. Early diagnosis should rely on the history and clinical examination and less on investigations.

A. CLINICAL FEATURES

A typical patient with early RA will describe pain and stiffness in more than three joints that is worse in the morning and after inactivity lasting at least one hour.

Usual joints involved are small joints of the hands and feet and wrists (and to a variable extent the larger joints). Systemic flu like symptoms are not uncommon.

Examination reveals symmetrical involvement with tenderness and the presence of synovitis. (i.e. soft tissue swelling or fluid in relation to a joint). Rheumatoid nodules (subcutaneous nodules over bony prominences or extensor surfaces or in juxta-articular regions) may be found.

Atypical presentation of RA includes patients with mainly girdle joint involvement mimicking Polymyalgia rheumatica and those with persistent monoarthritis.

Assessing a patient presenting with inflammatory arthritis

History	Examination
Pain worse in morning	Affected joints - distribution
Stiffness after inactivity over 1 hour	Synovitis vs. bony swelling
Joint swelling	Range of movement
Fatigue	Extra-articular features

The American College of Rheumatology (ACR) criteria5 is primarily a research tool and is less useful in the diagnosis of early RA. The disease has to be well established to apply the ACR criteria.

The above findings are not however exclusive for early RA and may occur in a number of other inflammatory arthropathies. In early disease, therefore differential diagnosis should always be considered.

Differential diagnosis of early RA

- Viral arthritis –(eg. Parvovirus, rubella)
- Reactive arthritis (post infective, throat, gut, sexually acquired)
- Seronegative spondyloarthropathy (e.g. psoriatic, Ankylosing spondylitis, inflammatory bowel disease)
- Connective tissue disease (e.g. SLE, systemic sclerosis)
- Polymyalgia rheumatica
- Fibromyalgia
- Medical conditions presenting with arthropathy (e.g. Sarcoidosis, thyroid disease, infective endocarditis, haemochromatosis, diabetic cheiroarthropathy, paraneoplastic syndromes, multiple myeloma)

B. INVESTIGATIONS

Recommendation

Initial Investigations helpful in the diagnosis

1. ESR - raised
2. C- reactive protein (CRP) - raised
3. Full blood count - anaemia and thrombocytosis
4. Rheumatoid factor – higher titers are more significant
5. X-ray of hands AP view Radiographic evidence in the hands or wrists of articular erosions or osteopenia in or around the affected joints.

Investigations useful for differential Diagnosis

1. Serum uric acid
2. Antinuclear antibodies

Investigations to detect complications

1. Chest X-ray
2. Lung function tests

Investigations for follow up and treatment

1. ESR
2. Full blood count
3. Serum Creatinine
4. Liver enzymes
5. Chest X-ray

Investigations helpful in borderline patients

1. Anti--cyclic citrullinated peptide (anti-CCP)
2. MRI and ultrasonography of joints are highly sensitive to detect early inflammatory and destructive changes in RA joints.

There is no single diagnostic test for RA. Investigations are used largely to support the clinical diagnosis and negative results do not exclude the diagnosis of RA. False positive results may also occur with any of above investigations.

3. Evaluation

A. PROGNOSTIC FEATURES IN RA

Predicting outcome in RA in individual patients at disease outset is difficult. Improved understanding of prognostic features would help to identify patients with serious disease who require aggressive therapy and protect those with mild disease from exposure to potentially toxic treatment. Indicators for poor outcome are

- Many active joints
- High ESR or CRP at outset
- High rheumatoid factor titer
- Early radiological erosions
- Poorer scores of function (e.g. HAQ) at outset.
- Adverse socio-economic circumstances and lower educational level.

B. ASSESSMENT OF RESPONSE TO TREATMENT

Many approaches to assess clinical improvement have been described, most of them focusing on the application to clinical trials.

Following are recorded serially starting with baseline evaluation.

Clinical measures	Laboratory measures
Tender joint count (Appendix 1)	ESR
Swollen joint count. (Appendix 1)	CRP
Pain as evaluated on visual analogue scale (VAS) by the patient	Anaemia of chronic disease
Duration/severity of stiffness after inactivity.	Radiological progression
Patient's global assessment of disease activity	
Physician's global assessment.	
Functional ability(eg.HAQ score-Appendix 2)	

C. REMISSION

A patient is in remission if any five of the following six criteria 5 are absent for at least two months.

1. Morning stiffness for more than 15 minutes duration.
2. Fatigue, i.e. inability to carry out activities of daily living without a need for extra rest or feeling of tiredness.
3. Symptoms of active inflammatory joint pain
4. Joint tenderness or pain on motion
5. Soft tissue swelling in joints or tendon sheaths
6. Elevated ESR (ESR>30mm in first hour in females,>20mm in first hour in males.)

** Presence of Pericarditis, Pleuritis, Vasculitis, unexplained fever and weight loss negates the diagnosis of remission.

4. TREATMENT

Recommendation

1. Treatment including disease modifying anti-rheumatoid drugs (DMARD's) should be started as soon as the diagnosis is made.
2. Consultation with a rheumatologist is recommended prior to deciding on DMARDs.
3. Multidisciplinary approach should be adopted.

The objective of treatment is to induce complete disease remission and when this is not possible, to minimize disease activity. Treatment should be aimed at controlling inflammation, minimizing joint destruction and radiographic progression while preserving functional and work capabilities, and improving quality of life.

Early therapy delays or minimizes the functional deterioration and occupational disability. Management of rheumatoid arthritis needs a multidisciplinary approach. Rheumatologist / Physician should play the main role and be the coordinator. Other members of the team are Medical officers, Nurses, Physiotherapist, Occupational therapist and Social worker etc. Modes of treatment used are patient education, pharmacological and physical treatment.

A. PATIENT EDUCATION

Recommendation

This is an important part of management. Patient and family should be educated about

- Nature of the disease.
- Natural course of the disease.
- Prognosis.
- Drug treatment and benefits /adverse effects.

B. PHARMACOLOGICAL MANAGEMENT

Recommendation

1. DMARDs should be introduced early in all patients with RA.
2. Simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are used for symptomatic relief of pain and stiffness.
3. If possible simple analgesics should be used in place of NSAIDs.

(i) ANALGESICS IN RA

Analgesics (e.g. paracetamol and codeine) in RA are used as an adjunct to NSAID and DMARD therapy. There are effective in reducing pain in RA[6].

(ii) NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN RA

There is abundant evidence that NSAIDs are effective and provide symptomatic relief of pain and stiffness without influencing the progression of the disease[7]. The choice of short, medium or long acting preparations can be tailored to fit a patient's particular lifestyle. Toxicity is a major limiting factor and side effects are related to dose and duration of therapy.

Adverse effects of NSAIDs

Common	Uncommon-serious	Uncommon non-serious
Gastrointestinal	Renal disease	Headaches
Fluid retention	Hypersensitivity	Dizziness
Hypertension	Asthma	Tinnitus
		Rash
		Abnormal liver function tests

- **Gastrointestinal toxicity of NSAID's**

  Dyspepsia, gastric erosion, peptic ulceration, small bowel inflammation and bleeding, perforation, haematemesis or malaena and occult GI blood loss and anaemia occur to a varying extent with all preparations and all routes of administration.

Risk factors for NSAID's associated GI toxicity[8]

Definite risk factors	Possible life style
factors	
Advance age (linear increase in risk) History of ulcer consumption Higher dose of NSAIDs Combination use of NSAIDs Combination use of corticosteroids Co-morbidity	Cigarette smoking Alcohol
Note: Concomitant administration of anticoagulants will increase the risk of GI haemorrhage	

Every possible strategy should be employed to minimize risk of GI toxicity. e.g. smoking cessation, and alcohol reduction. Eradication of Helicobacter pylori in NSAID-associated peptic ulcers has not been shown to be of value.

Surveillance and endoscopic studies have confirmed that the incidence of GI mucosal injury is low with Cox2 inhibitors, nabumetone and meloxicam. Mefenamic acid and piroxicam are considered unacceptably toxic for long-term use in RA.[9] If NSAID use is unavoidable, gastro-protective agents may be used, as summarized below.

Summary of gastro-protective agents to use with NSAID's

· Proton pump inhibitors(PPIs)	most effective
· Prostaglandin analogues	effective, but less well tolerated compared to PPIs and a problem in premenapausal women
· Histamine H2 receptor-Antagonists	less effective than PPIs
· Mucosal protective agents	less effective than PPIs

It is important to note that the use of an enteric coated, parenteral or rectal NSAID preparation is not protective. The systemic effects of NSAIDs are the predominant cause of gastric mucosal damage.

· **Renal toxicity of NSAID's**

Use of NSAIDs under conditions where renal blood flow may be reduced (e.g. dehydration or blood loss, cardiac failure, chronic renal failure, diuretic use, or hypertension) may further impair the renal blood flow contributing to renal impairment (or overt renal failure), hyperkalaemia, oedema and hypertension. These are particularly likely in the elderly. Intestinal nephritis is an uncommon, idiosyncratic side effect, unrelated to the above pharmacological action of NSAIDs.

No currently available NSAID including selective COX-2 inhibitors has a completely safe renal profile.

· Usual dosage and frequency of administration of NSAIDs.

DRUG	TOTAL DOSE (mg/24h)	FREQUENCY OF ADMINISTRATION
Aspirin	3,000 - 6,000	6 - 8 h
Ibuprofen	1,200 - 2,400	8 h
Mefenemic acid	750 - 1,500	8 h
Diflunisal	500 - 1,000	12 h
Naproxen	500 - 1,000	12 h
Diclofenac Diclofenac retard	150 - 200 100	8 - 12 h 24 h
Indomethacin	75 - 150	8 h
Piroxicam	20	24 h
Meloxicam	7.5 - 15	24 h
Nabumetone	1,000 - 2,000	12 - 24 h
Celecoxib	200 - 400	24 h

Points to remember while using NSAID's in RA

- NSAIDs are analgesics as well as anti-inflammatory. The analgesic effect is prompt but anti inflammatory effect may take 1-2 weeks. Therefore NSAID should not be changed without an adequate trial period.
- In equivalent doses all NSAIDs are equally effective. Side effect profile however, varies. The lowest NSAID dose compatible with symptom relief should be prescribed.
- Consider intra-articular steroids, particularly when disease is localized.(Less than 3 joints)
- NSAIDs should not be combined. Combinations are no more effective but may have additive side effects. When a short acting NSAID is prescribed, a slow release formulation of the same NSAID at dinner time to combat early morning stiffness can be used.
- For additional analgesia, NSAIDs can be combined with simple analgesics like paracetamol and codeine.

- During remission simple analgesics should be used in place of NSAIDs. They may be used 'as needed' basis.
- Introduce gastro-protection in RA patients >65 years and those with a past history of peptic ulcer when using NSAID's.
- NSAIDs should be avoided in patients taking anticoagulants or corticosteroids.

(iii) DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)

Treatment with DMARDs is the only way to ensure the most favourable evolution for the patient and to improve the quality of life by retarding the disease progression, as well as providing symptomatic benefit. Onset of benefit is slow (4 to 16 weeks). Patients should be informed of the potential benefits, risks and monitoring requirements of these drugs.

COMPARISON OF DMARDs

Methotrexate, sulphasalazine, leflunamide and IM gold are equally effective DMARDs.

The best DMARDS for the treatment of RA are those that provide the most efficacies with the least toxicity over the long term. Data available suggests similar efficacy of methotrexate, sulphasalazine, lefIunomide and IM gold1[0-12]. Drugs of reduced efficacy from open RCTs include chloroquine/ hydroxychloroquine and oral gold (auranofin)[13]. There are no data from adequate studies with respect to azathioprine. A beneficial effect on radiological progression of RA has been shown with all DMARDs except hydroxychloroquine[14].

· **DMARD PROFILES** [2,3]

DRUG	DOSE	DOSE INCREMENT	ADVANDAGE OF THIS DRUG
METHOTREXATE **Administer folic acid (5-10 mg/week)24 hours after methotrexate.**	7.5-10 mg / week, by mouth	Increase 2.5-5 mg/week every 4 weeks up to 20 mg/week. In case of inefficacy or gastrointestinal toxicity, consider parenteral administration.	Rapid onset action (6-10 weeks) Can use when uncertain of diagnosis (e.g. RA, psoriatic, connective tissue disease) Can be given orally, IM or SC Weekly administration
SULPHASALAZINE	2-3 g/day, by mouth		Rapid onset action (8-12 weeks) Can use when uncertain of diagnosis (e.g. reactive/ psoriatic/ RA) Relatively safe in thrombocytopenia
LEFLUNOMIDE	20 mg/ day, by mouth		Remain to be established (recently introduced)
ORAL GOLD	6 mg/ day by mouth		Oral use
INJECTABLE GOLD	50 mg / week IM	Increasing doses of 10, 25 and 50 mg/week, maintaining the dose (from 6 to 24 months) or adjusting it depending on clinical response or adverse effects. Stop at cumulative dose of 3g.	Patient preference Ensures compliance

CHLOROQUINE	250 mg/ day, by mouth	Do not exceed 4 mg/kg/day	No blood monitoring required. Can use when uncertain of diagnosis (e.g. inflammatory arthritis, connective tissue disease) Can use despite leucopenia or thrombocytopenia
HYDROXY-CHLOROQUINE	400 mg/ day, by mouth	Do not exceed 6.5 mg/kg/day	
AZATHIOPRINE	1.5 - 2.5 mg/kg/ day, by mouth	Begin with low dose of around 1mg/kg/day and increase in 4-6 weeks to maintenance dose of 100-150 mg/day.	Can use in patients with renal disease
CYCLOSPORIN	2.5 -5.0 mg/kg/ day, by mouth	The initial dose can be increased by 0.5mg/kg/ day every 2 weeks up to 5mg/ kg/day.	
CYCLOPHOSPHAMIDE	1.5 -2.5 mg/kg/ day, by mouth	Begin with 50 mg/ day and increase dose every 4-6 weeks until a response is obtained, without exceeding 2.5 mg/kg/day.	

TOXICITY OF DMARDs

Toxicity assessment in a meta-analysis of 71 clinical trials that contained 129 treatment groups has shown that over a year almost one third of the patients stopped therapy. Half of these did so because of drug toxicity[15].

· Toxicity assessment of DMARD's [15]

DRUG	Assessment
Methotrexate	Most favourable efficacy/toxicity trade off. Folic or folinic acid supplementation of 5 mg folic acid weekly is useful in reducing mucosal and gastrointestinal side effects
Sulphasalazine	Slightly more toxic than methotrexate
Injectable gold	Had higher toxicity rates and higher total dropout rates than the other drugs
Anti-malarials	Had the lowest toxicity rate of all those studied, but efficacy was only moderate

· DMARDs adverse effects and monitoring1,2

DMARDs	Common/ minor adverse events	Rare/ severe adverse events	Monitoring requirements
METHOTREXATE	Nausea Diarrhoea Mouth ulcers Rash Alopecia Abnormal LFTs	Leucopenia Thrombo cytopenia Pneumonitis Sepsis Liver disease-late Nodulosis Epstein-Barr virus associated - lymphoma	Advise to restrict alcohol FBC, Creatinine, LFTs monthly for the first 6 months, every 1-2 months thereafter.**For <2 fold Upper Limit of Normal (ULN) elevations in AST or ALT**, repeat testing in 2-4 weeks. **For >2 to <3 fold ULN elevations in AST or ALT**, closely monitor, with LFTs every 2-4 weeks and dosage reduction as necessary. **For persistent elevations in AST or ALT >2 or >3-fold ULN increase** discontinue MTX and perform liver biopsy, if necessary to continue.
HYDROXY-CHLOROQUINE & CHLOROQUINE	Nausea, Headache	Retinal toxicity	Vision changes, funduscopy and visual fields every 12 months by ophthalmologist. Reduce dose if renal impairment

SULPHASALAZINE	Nausea Diarrhoea Headache Mouth ulcers Rash Oligospermia (reversible) Staining of soft contact lenses Abnormal LFTs	Leucopenia	FBC Liver and renal function Urinalysis every 2–4 weeks for first 3 months, then every 3 months thereafter
IM GOLD	Mouth ulcers, Rash Nitritoid reactions - vasomotor symptoms post-injection — a feature seen early in treatment which usually resolves if treatment is continued	Thrombo cytopenia Leucopenia Proteinuria Colitis	FBC Liver and renal function Urinalysis every 1–2 weeks for first 20 weeks, then at the time of each (or every other) injection
A U R A N O F I N (ORAL GOLD) Not available in Sri Lanka	Diarrhoea	Leucopenia	FBC Renal function Urinalysis every 4–12 weeks
LEFLUNOMIDE	Alopecia Diarrhoea Nausea Rash	Leucopenia Thrombo cytopenia Hepatitis	FBC Liver and renal function BP monitoring monthly for the first 6 months; every 1–2 months thereafter. **For elevations in AST or ALT <2-fold ULN**, repeat testing in 2–4 weeks. **For elevations in AST or ALT >2-**

			fold but <3- fold ULN closely monitor, with LFTs every 2–4 weeks and dosage reduction. **For persistent elevations of AST or ALT >2- or >3- foldULN increase**, discontinue leflunomide and eliminate with cholestyramine therapyPatients also taking MTX should have LFTs at least monthly.
AZATHIOPRINE	Nausea	Leucopenia Sepsis Lymphoma (late)	FBC, Liver function every 1–2 weeks with changes in dosage, and every 1–3 months thereafter
CYCLOSPORIN	Paraesthesia, Tremor Headache Hypertricho sis Gingival hypertrophy Nausea	Hypertension Renal disease Sepsis	Liver and renal function BP monitoring every 2 weeks until dosage is stable, then monthly

CHOICE OF DMARD

Recommendation

1. Because of its efficacy and toxicity profile, methotrexate is the recommended initial treatment in all patients who have not previously received DMARD treatment.
2. Nevertheless, initial treatment with Sulphasalazine, Leflunomide and Injectable gold is considered acceptable

Many factors influence the choice of DMARD for the individual patient (Table below). Patients and their physicians must select the initial DMARDs based on these. Because of these many considerations, input from a rheumatologist is an essential component of the overall management plan when initiating DMARD therapy.

The advantages of methotrexate over other DMARDs with similar short-term efficacy are a well-known toxicity profile, easy management, and a lower rate of withdrawal from treatment in the medium and long term. For all these reasons, it is recommended as the drug of choice in this guideline. Sulphasalazine, Leflunomide and Injectable gold are alternatives.

- **Factors influencing the choice of DMARD for an individual patient[1]**

Drug	Patient	Physician
Relative efficacy	Likelihood of compliance	Confidence in administering
Convenience of administration	Comorbid diseases	Confidence in monitoring
Requirements of the monitoring	Severity of the patient's disease	
Costs of the drug and monitoring	prognosis of the patient's disease	
Time until expected benefit	Patient's preference	
Frequency and seriousness of adverse reactions		

TIMING OF DMARD TREATMENT IN RA

Recommendation

Early DMARD therapy in RA is important to maintain function and reduce later disability.

The time between first symptoms and initiation of DMARD treatment is one of the few variables that the physician can modify. Early commencement of treatment is associated with a higher probability of favourable response and a lower probability of functional and radiological deterioration.

SUSTAINED DMARD THERAPY

Recommendation

DMARD therapy should be sustained in rheumatoid arthritis in order to maintain disease suppression. Withdrawal of treatment is seldom appropriate.

A sustained treatment is vital if disease suppression is to be maintained16,17. Remission is the goal but is seldom achieved. Equally 'cure' is not attained, thus withdrawal of treatment is seldom appropriate.
Sustained use of DMARDs has been shown to be safe after 10-15 years 18. Uncontrolled disease activity can cause late harm to the patient and this must be weighed against concerns about cumulative or late toxicity when selecting the most appropriate DMARD.

COMBINATION DMARD THERAPY

Combination DMARD therapy in RA is being increasingly used by rheumatologists. Over the last several years, combination DMARD therapy has played a significant role in improving our ability to control RA. The role of combination DMARD therapy continues to evolve[1].

Benefit of a combination of methotrexate, sulphasalazine and hydroxychloroqune has been shown but was not studied in early disease[19]. The addition of cyclosporin to methotrexate in patients with established RA has been shown to be of benefit[20]. A recent controlled study of iv infiximab in patients with partial response to methotrexate provided additional clinical benefit and prevented further radiological damage[21].

CHANGES IN TREATMENT

Recommendation

1. After initiating any treatment, it is necessary to evaluate the response and to monitor its toxicity.
2. Treatment failure or toxicity should be evaluated within a maximum of 3 months with a rheumatologist and consequent change in treatment should be considered.

If a satisfactory response is not obtained within 3 months, or if there is evidence of DMARD-related toxicity, consideration should be given to the possibility of a change in treatment by adding a new drug or modifying the dosage using simplified clinical clasification.

- **Alternative treatment for unsatisfactory response** (modified from ref. 2)

Simplified clinical classification of RA		First-choice treatment used	Alternative treatment in unsatisfactory response, in order of preference
No erosions	< 6 swollen joints	Methotrexate	Leflunomide
		Sulphasalazine	Methotrexate Leflunomide
	> 6 swollen joints	Methotrexate	Leflunomide Methotrexate + chloroquine + sulphasalazine
		Injectable gold	Methotrexate Leflunomide
Erosions present	< 6 swollen joints	Methotrexate	Leflunomide
	> 6 swollen joints	Methotrexate	Leflunomide Anti-TNF Methotrexate + anti-TNF Methotrexate + chloroquine + sulphasalazine
		Leflunomide	Methotrexate Anti-TNF Methotrexate+ anti-TNF

(iv) BIOLOGICALS IN RHEUMATOID ARTHRITIS

Recommendation

Anti-TNFα therapy can be used when remission is not achieved by using combination of conventional DMARD's which included methotrexate.

The development of genetically engineered biologic agents that selectively block cytokines (anti-cytokine therapy) in the short term represents a major advance in the treatment of RA. The most clinically effective anti-cytokine agents studied to date are antagonists to TNFα an essential mediator of the cytokine inflammatory cascade in RA.

- **Anti-tumor necrosis factor α (anti-TNFα) therapy**

Two anti-TNFα agents commonly used are etanercept, a recombinant soluble TNF-Fc fusion protein; and infliximab, a chimeric (mouse–human) anti-TNF monoclonal antibody.

Both etanercept[22] and infliximab[21] have been shown to be beneficial when used in combination with methotrexate in patients with ongoing active RA despite adequate doses of methtrexate alone. Infliximab is currently recommended for use only with concomitant MTX therapy. In these trials of etanercept and infliximab, many patients improved rapidly, even during the first 2 weeks of treatment.

Although data from randomized trials have not shown an increased frequency of serious adverse effects, such as serious infections or malignancies, for either anti-TNFα agent, concerns about the short-term and long-term safety of these agents continue. Anti-TNFα agents should therefore be used with caution in patients with any susceptibility to infection or a history of tuberculosis, should be avoided in patients with significant chronic infections, and should be discontinued temporarily in all patients with acute infection.

Post-marketing surveillance has yielded reports of sepsis, tuberculosis, atypical mycobacterial infections, fungal infections, other opportunistic infections, demyelinating disorders, and aplastic anemia.

Risk of latent tuberculosis should be assessed prior to initiation of a TNFα antagonist.

At this time, there appears to be no need for routine laboratory monitoring with the anti-TNFα agents, but patients should be alerted to report any signs or symptoms of infection.

At present these are not commonly available in Sri Lanka.

ETANERCEPT

25 mg, reconstituted in 1 ml water, in subcutaneous injection, twice a week at intervals of 72-96 hours
One dose of 25 mg administered once a week offers a slower response and may be less effective.

INFLIXIMAB

3 mg/kg intravenous perfusion for 2 hours. Then administer additional doses of 3 mg/kg in perfusion at weeks 2 and 6 following the first week, and one dose every 8 weeks thereafter.

Dose may be increased to 5 mg/kg if ineffective or in case of relapse. Some patients require a shorter interval of infusion every 4-6 weeks. Infliximab should be administered together with methotrexate.

(V) CORTICO STEROIDS IN RA

INTRA-ARTICULAR CORTICOSTEROIDS IN RA

Recommendation

1. Intra-articular injections can be used for rapid, and sometimes sustained, symptomatic relief in 'target' joints.
2. Intra-articular injections to any one joint should not be given more than three times in one year.
3. When administering intra-articular injections :
    a. Use sterile technique
    b. Aspirate synovial fluid at time of the joint injection
    c. Advise post-injection rest (24 hours)

d. Advise patients how to seek help if joint fails to settle after injection

4. Always consider possible septic arthritis in differential diagnosis of mono/oligo-articular flare in RA

Intra-articular corticosteroid injections:

- Allow local treatment of inflamed joints whilst minimizing undesirable systemic effects.
- Provide symptomatic relief pending the onset of DMARD effect.
- Treat particularly troublesome joints where the overall disease control is good.

However there are no evidence on the long-term effect on disability or radiological progression. Synovial fluid aspiration at time of joint injection has been shown to reduce relapse rate.[23]

SYSTEMIC CORTICOSTEROIDS IN RA – ORAL & PARENTERAL

Recommendation

1. Routine use of oral corticosteroids cannot be recommended.
2. It may be used as short term bridge therapy at onset or with flare-up of the disease.
3. It may be used in specific situations where there are strong contraindications to NSAIDs prescription, or difficulties in using DMARDs.
4. Oral corticosteroids should be withdrawn slowly to avoid rebound flare of symptoms.
5. The lowest possible dose of corticosteroid should be used for the shortest possible time.
6. Be alert to the possibility of diabetes, cataract and infection.
7. Ensure adequate prophylaxis and treatment of osteoporosis in patients taking oral corticosteroids.

- **Symptomatic benefit**

The symptom relieving anti-inflammatory effects of corticosteroids are well established Recent randomized controlled studies have shown that this benefit is not sustained beyond nine months[24,25].

Bridge corticosteroids, usually IM monthly or oral the dose ranging from 5 -10 mg/ day (maximum 15 mg/day) for 8-12 weeks are an option to provide symptomatic relief until DMARDs become effective.

- **Functional response**

Although some benefit in function from corticosteroids was reported, no objective long term benefit was discerned[26].

- **Radiological response**

  A number of early studies suggested that oral corticosteroids may inhibit radiological damage and recent randomized controlled trials confirm this finding.[25]

- **Toxicity of paranteral steroids in RA**

  Increased adverse events in corticosteroid treated rheumatoid arthritis patients, including cataracts, infections, gastrointestinal bleeds, avascular necrosis and fractures were seen. Increased mortality has also been reported.[27]

C. NON-PHARMACOLOGICAL TREATMENT

Recommendation

The multidisciplinary approach with nurses, physiotherapists, orthotists, occupational therapists, podiatrists. dieticians, social workers, the patient and the family of the patient. Plays an important part in the non-pharmacological management of rheumatoid arthritis.

PHYSIOTHERAPY

Recommendation

Formulating and implementing a programme of physiotherapy helps to relieve pain, improve joint mobility and strengthen the surrounding muscles and ligaments of RA patients.

Exercise therapy helps to improve muscle strength, endurance and aerobic capacity. Hydrotherapy is a form of physiotherapy which plays a role in mobilising joints and restoring muscle tone and power.

Other forms of physical treatment that are used to reduce joint pain and muscle spasm but with insufficient evidence of their benefits are, heat therapy, ice therapy and wax therapy, ultrasound, transcutaneous electrical nerve stimulation (TENS) and laser therapy.

OCCUPATIONAL THERAPY

Recommendation

The occupational therapist should assess the patient's degree of disability and formulat a programme to maximize the function and make the patient independent in activities of daily living (ADL).

The training in ADL, such as washing, toileting, dressing, cooking, feeding and working sometimes need provision of equipment and adaptations. Joint protection, which employs a range of strategies such as adapting movement patterns to reduce strain, providing assisting devices, rest regimens, energy conservation techniques, exercises and splinting are other forms of occupational therapy used in the management of patients.

PODIATRY

Provision of appropriate footwear for comfort, mobility and stability is a recognised form of management in rheumatoid arthritis affecting the feet.

5. SPECIAL SITUATIONS

A. RA DURING PREGNANCY AND LACTATION

- There is no evidence that RA has a negative effect on pregnancy outcome.
- However, treatment with DMARDs can have negative consequences on pregnancy, the fetus, and breastfeeding3. Thus, women of childbearing age should know the risk so they can act accordingly (contraceptive method, planning pregnancy after remission, choice of DMARD)
- Pregnancy itself seems to be associated with a reduced risk of newly developing RA, whereas the risk is increased in the 12 months after delivery28.
- The symptoms of RA disappear during pregnancy in 70% of cases, to reappear early in the postpartum period3.

NSAIDs:

Recommendation

1. NSAIDs should be avoided in the first and last trimester.
2. Since only trace amounts of NSAIDs appear in breast milk, breast-feeding is recommended to be compatible with NSAID use.

Teratogenic effects in the early weeks of pregnancy have been observed in animals receiving larger than pharmacological doses of NSAIDs. In both humans and animals, premature closure of the ductus arteriosus has also been observed in the last trimester. During breastfeeding, NSAIDs should be taken while the baby is feeding to avoid elevated concentrations in the milk. There is a lack of data on the new COX-2 selective inhibitors in pregnancy and their use in pregnant or lactating, hence should be avoided.

Corticosteroids

Recommendation

Low dose of prednisone is considered safe in pregnancy for both mother and child

There is no evidence that the corticosteroids produce serious adverse effects at average doses (upto 15mg/day) during pregnancy, except for promoting glucose intolerance, fluid retention, and hypertension[29].

DMARD's

Recommendations

1. The decision to withdraw continuous treatment during pregnancy should be made on an individual drug and patient basis.
2. If the disease is aggressive, it is preferable not to withdraw the DMARD (unless it has been shown to affect the embryo, fetus, or infant) and to leave it at the minimum effective dose.

- In RA no adverse effects on the child have been found with the use of **hydroxychloroquine**. Although it is considered compatible with breast-feeding, the slow elimination rate and the potential accumulation of a toxic amount of hydroxychloroquine in the infant, breast-feeding should be undertaken with caution.
- **Sulfasalazine** can be safely used prior to and during all stages of pregnancy. Males who wish to produce offspring should stop the drug because of its adverse effect on spermatozoa. This effect is reversible after discontinuation of the drug. Breast-feeding is compatible with sulfasalazine treatment though should be advised with caution because of the rare event that the mother is a slow acetylator.

- **Methotrexate** is contra-indicated in the treatment of the rheumatic diseases during pregnancy. Strict contraception is needed when a patient is on methotrexate. Women and men who wish to conceive have to stop methotrexate treatment 4–6 months prior to conception. Continuation of folate supplementation is advised to prevent adverse outcome due to folic deficiency. Breast-feeding is contra-indicated because of excretion of methotrexate in breast milk.

- **Gold** seems to have risk of foetal malformation, and should not be used in pregnancy. Gold therapy is compatible with breast-feeding.

- Women with severe rheumatic diseases that are otherwise hard to control may use **azathioprine** during pregnancy. Breast-feeding is not recommended.

- Exposure to **cyclophosphamide** during the first trimester of pregnancy leads to congenital malformation and should be avoided. Treatment with cyclophosphamide during the second half of pregnancy may be considered in case of severe, life threatening disease of the mother. Breast-feeding is contra-indicated.

- It is generally advised not to use **cyclosporine** during pregnancy unless the severity of the maternal disease urges to do so. Breast-feeding should be discouraged in women using cyclosporine.

- **Leflunomide** is contra-indicated during pregnancy. Breast-feeding is considered unsafe.

B. LUNG DISEASE AND RHEUMATOID ARTHRITIS

- The appearance of pleuritic pain, shortness of breath (either progressive or of recent onset), or hemoptysis suggests pulmonary disease in RA patients. Lung complications may include pleural disease, rheumatoid nodules, interstitial fibrosis, or bronchiolitis obliterans with organizing pneumonia (BOOP).

- **Pleural effusions** are the most common manifestation, mostly occurring in male patients with nodular RA during active disease. Usually, pleural effusions are small and asymptomatic; sometimes it is the beginning of clinically significant extra-articular disease[28].

- Intrapulmonary **rheumatoid nodules** usually remain asymptomatic, except when they cavitate, in which case they may become superinfected or produce hemoptysis. All pulmonary nodules should be biopsied to rule out neoplasia. Histologicaly proven rheumatoid nodules do not require treatment in the absence of complications[3].

- **Diffuse interstitial fibrosis** affects 10% of patients with RA. In all RA patients with pulmonary findings on the physical examination (fine basal crepitations) or on the radiography (reticular or reticulo-nodular pattern), the physician should request blood gas analysis and respiratory function tests (diffusion test). High-resolution tomography (HRCT) is a highly specific and sensitive technique for the diagnosis of pulmonary interstitial fibrosis. Interstitial disease of recent onset (acute) is an indication for prednisolone therapy (1-1.5 mg/kg/day). Patients who do not respond can be treated with cyclophosphamide or azathioprine, although there is no evidence that these agents reduce the progression of fibrosis[3].

- **BOOP** is a rare pulmonary disease that has been related with RA. It presents with cough and severe shortness of breath of recent onset. Chest X-ray shows bilateral opacities of the pulmonary parenchyma without loss of volume. High-resolution tomography reveals patchy areas in the pulmonary parenchyma, which are usually peripheral. A definitive diagnosis requires thoracoscopic lung biopsy, with the observation of intraluminal plugs in the bronchioles. The condition responds to Oral prednisolone (1.5 mg/kg/day) in a single daily dose for 4-6 weeks, then slowly tapering off until discontinuing the drug in 4-6 months.

- Many drugs used to treat rheumatoid arthritis, such as methotrexate, leflunamide, gold, penicillamine, and cyclophosphamide, can cause interstitial lung disease. Pneumonitis due to MTX can occur at any time during a course of therapy and at any dosage.

C. VASCULITIS IN **RA**

- Rheumatoid vasculitis is an infrequent extra-articular manifestation of RA. It appears in RA of long evolution, often with little or no joint inflammation. Risk factors for rheumatoid vasculitis are male gender, positive RF, the presence of other extra-articular manifestation of RA, and time of disease evolution[28]. A large number of extra-articular features have been reported in Rheumatoid vasculitis, as a result of involvement of many organs in the body.

- Generally Rheumatoid vasculitis is understood to be a set of vascular processes (periungual splinter hemorrhages, palpable purpura, polyarteritis nodosa) with variable prognosis and treatment[3].

- **Palpable purpura** is diagnosed clinically. Recently prescribed drugs should be reviewed to identify a possible pharmacological cause of the palpable purpura. Generally disappears spontaneously. The most important factor in treatment is rest. If it does not disappear, palpable purpura should be treated with full doses of NSAIDs and medium to low doses of prednisone, beginning with 15 to 30 mg/day and progressively reducing the dosage depending on disease evolution.

- **Polyarteritis nodosa-type rheumatoid** vasculitis is the most severe form of rheumatoid vasculitis and is life threatening in many patients Histopathological confirmation is recommended whenever possible, since treatment of this form of vasculitis is frequently accompanied by severe adverse effects. The condition needs aggressive treatment in the form of IV pulses (boluses) of methylprednisolone (500-1000 mg

OD IV for 3-5 days), followed by IV pulse (bolus) of cyclophosphamide (500-1000mg), repeated every 3 weeks or so, along with 1 mg/kg/day of oral prednisolone. On resolution the patient need to be on a DMARD, usually azathioprine and a reducing dose of prednisolone[29].

D. JOINT INFECTIONS AND RHEUMATOID ARTHRITIS

- Use of corticosteroids, cytotoxic drugs, and impaired host defences predispose patients with rheumatoid arthritis to infection as well as masking of symptoms and signs of sepsis. Septic arthritis in these patients can also be insidious, fewer than one-half of rheumatoid patients with joint infections present with fever and even fewer develop a leucocytosis[30].

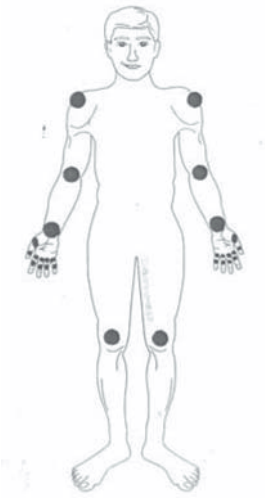
- Both infection and exacerbation of the rheumatoid condition can be monarticular or polyarticular (about 30 per cent of cases)[31].

- Whenever one of these clinical states is present, synovial fluid should be obtained, Gram stained, and cultured before considering any treatment.

- The treatment consists of drainage, antibiotics as appropriate, and initial joint immobilisation for pain relief. Joint aspiration and surgical drainage are probably equally effective and the decision is best individualised.

6. APPENDIX

1. Swollen and Tender 28 Joint Count



Tenderness and swelling are assessed separately in each joint.

The joint are scored on 0-1 scale
0 = No Tenderness / Swelling
1 = Tenderness / Swelling

The individual joint scores are summed for tenderness and swelling.

2. Health Assessment Questionnaire

Items	No. of questions
Dressing & grooming	2
Arising	2
Eating	3
Walking	2
Hygiene	3
Reach	2
Grip	3
Activities	3

Possible answers	Disability index
0 = without any difficulty 1 = with SOME difficulty 2 = with MUCH difficulty 3 = unable to do	The maximum scores per item are added and divided by the number of items answered (at least 6)
In case of 'aids or devices' or 'help from another person' given score is 2	