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Contemporary Management of Rheumatoid Arthritis

- ☞ Rheumatoid arthritis (RA) is a chronic progressive autoimmune disease
- ☞ RA may cause joint destruction, extra-articular effects and premature death
- ☞ Early diagnosis and treatment with disease-modifying anti-rheumatic drugs (DMARDs) slows progression
- ☞ Biological DMARDs, targeting specific immune mechanisms have a significant role in selected RA patients

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic progressive systemic inflammatory autoimmune disorder that, if left untreated, leads to joint destruction, extra-articular manifestations and premature death.^{1,2} In addition, RA has a substantial societal impact in terms of cost, disability and lost productivity: up to half of all patients are unable to work within 10 years of diagnosis.^{3,4} RA is estimated to affect approximately 1% of the global population; certain ethnic groups (e.g. specific native American tribes) have higher prevalence rates, while populations in Sub-Saharan Africa have much lower rates.⁵ It is commoner in women (2-3:1) with peak onset occurring in the 4th-5th decades.^{5,6} Recent studies suggest that the incidence may be declining.⁶ Increased understanding of the immunogenic factors associated with RA has led to the development of newer treatment regimens.⁷ This bulletin will focus on the contemporary management of RA.

PATHOGENESIS

Although the cause of RA is not fully understood, there is considerable information on the possible cellular and molecular mechanisms involved. In RA, there is infiltration of inflammatory cells into the synovium and proliferation of synovial fibroblasts.^{1,8} Specific T-lymphocytes are involved in the induction of the immune response, caused by an unknown exogenous or endogenous antigen.⁷ These activated cells and fibroblasts produce cytokines, including tumour necrosis factor- α (TNF- α), interleukin-1 (IL-1) and interleukin-6 (IL-6), leading to an inflammatory cascade which results in damage to soft tissues and bones.^{2,7} These findings have aided the development of new therapies.⁷

Genetic factors are thought to play a role in the development of RA: disease prevalence in siblings of those with RA is 2-3%⁹ and monozygotic twins show higher disease concordance (15%) compared with dizygotic twins (4%).² The best-defined genetic association is with the human leucocyte antigen (HLA) complex: the presence of HLA DRB1*04 alleles is estimated to confer a 5-fold increase in relative risk for RA.^{2,9} However, it is likely that there are several other genetic factors involved.^{3,6} Environmental factors may influence the occurrence and expression of RA.¹⁰ Smoking has been implicated in the pathogenesis and progression of RA.¹¹ RA frequently goes into remission during pregnancy, but current evidence suggests that oral contraceptives have no effect on the risk of developing RA.⁶ Although infection may be involved, no infectious agent has been consistently cultured from synovial tissue, fluid or blood, suggesting an indirect triggering mechanism/cross-reactivity if infection is involved.¹⁰

In summary, it is thought that exposure to an unknown antigenic stimulus causes a chronic immune response in a genetically susceptible person, resulting in RA.²

CLINICAL PRESENTATION

Table 1 outlines the clinical features of RA.

Table 1: Clinical Features of Rheumatoid Arthritis^{3,6}

Symptoms	Joint swelling, pain/stiffness (especially in morning), deformity, fatigue, malaise, fever, weight loss, depression
Articular characteristics	Palpation tenderness, synovial thickening; effusion and/or erythema (in early phase). Decreased movement / ankylosis / subluxation (in later phase)
Distribution of affected joints	Symmetrical (especially later on in disease), distal joints > proximal joints (e.g. PIP, MCP/MTP, wrist/ankle)*
Extra-articular organ-specific features	Pericardial inflammation, valvular involvement, myocarditis; pulmonary fibrosis, pleural effusion; hepatitis; skin nodules; vasculitis; dry eye, iritis; oral (sicca symptoms); mononeuritis, nerve entrapment. Effects on blood cells; splenomegaly and thrombocytopenia (Felty's Syndrome)

*PIP=proximal interphalangeal joint; MCP=metacarpophalangeal joint; MTP= metatarsophalangeal joint

Clinically RA presents and behaves in various ways but disease onset is insidious in most cases.^{3,6} Initially, the predominant symptoms are pain, stiffness and swelling of peripheral joints but **up to 30% of patients may present with non-specific symptoms such as malaise, weight loss and myalgia, without obvious joint swelling.**⁵ Disease course is variable, however all studies show continuing progression of irreversible joint destruction.³ Joint erosion can be seen in the majority of cases with symptoms for ≥ 6 months.⁶ In addition, extra-articular features are common (see Table 1). The widespread inflammation seen in active RA is thought to be associated with the high incidence of cardiovascular disease (with increased mortality) in RA patients.¹² Since it is thought that extra-articular disease decreases with more aggressive treatment of RA from the outset, **early diagnosis and treatment is important to improve the long-term outcome in RA.**^{12,13}

Diagnosis of early RA is primarily clinical, where a suggestive history is combined with the presence of some or all of the clinical features in Table 1.¹³ **Formal diagnosis** is based on the presence of the American College of Rheumatology (ACR) diagnostic criteria outlined in Table 2.¹⁴ **A diagnosis of RA is made if at least 4 of the ACR criteria are present.**

Table 2: ACR Diagnostic Criteria for Rheumatoid Arthritis¹⁴

1. Morning stiffness in affected joints lasting at least one hour
2. Soft tissue swelling (arthritis) of at least 3 joint areas (observed)
3. Swelling (arthritis) of PIP, MCP, or wrist joints
4. Symmetrical swelling (arthritis)
5. Rheumatoid nodules
6. Presence of rheumatoid factor
7. Radiographic erosions with/without peri-articular osteopenia particularly in hand, wrist or feet joints

Note: Criteria 1-4 should be present for at least 6 weeks

In addition, patients should be evaluated for risk of rapidly progressive disease. **Poor prognostic factors** include high ESR or C-reactive protein levels, early erosive damage on x-rays, increasing number of affected joints, early disability, high titres of rheumatoid factor, presence of extra-articular features at diagnosis.³

MANAGEMENT OF RHEUMATOID ARTHRITIS

Management requires a multidisciplinary approach, involving pharmacological and non-pharmacological components, throughout the course of the disease.

Current guidelines recommend early diagnosis and early referral (ideally within 3 months of symptom onset) to a rheumatologist for the introduction of disease modifying anti-rheumatic drugs (DMARDs).¹⁵ These agents interfere with progression of the disease process (both joint destruction and the extra-articular disease).¹³ In addition, **patients require ongoing physiotherapy** (to maximise joint protection) and **occupational therapy** (to help with adaptation to disease-induced loss in function).⁵ Patients may also require access to chiropody and surgical services during the course of their disease.⁵

PHARMACOLOGICAL MANAGEMENT

The goals of pharmacotherapy are to achieve pain control and to control the disease progression.

Pain Control

Although DMARDs may be introduced at time of diagnosis, they have a slow onset of effect (weeks+) and therefore little or no impact on acute pain.¹ Most patients will require at least periodic courses of analgesics or non-steroidal anti-inflammatory drugs (NSAIDs).⁵ These agents have been profiled in previous NMIC bulletins (2005; Vol 11: 5, 6). The following points are relevant to their use in RA:

Paracetamol monotherapy is seldom sufficient to control acute pain in RA; however studies have shown that regular dosing of paracetamol potentiates the therapeutic effects of NSAIDs in RA.¹⁶ Paracetamol-NSAID combination therapy may allow a reduction of the NSAID dosage.¹⁶

Opioid analgesics may be used during acute attacks of RA, especially in elderly patients who may not be able to tolerate NSAIDs.¹⁷ Their continuous / long-term use is problematic due to the risk of addiction, cognitive decline, constipation and respiratory depression.¹⁷ Compound analgesics (such as paracetamol / opioid combinations) have been used in acute RA patients especially in those at risk of developing NSAID toxicity.¹⁸

Corticosteroids (CS) are useful in the management of acute pain and also have disease-modifying properties.¹³ Over the short-term they exert a profound effect on the symptoms of RA but their efficacy diminishes over time.^{13,19} The preferred method of administration of CS is intra-articular which produces rapid symptom relief; in acute polyarthritis where this is not possible, an intramuscular injection (e.g. 120mg methylprednisolone) may be given, while waiting for DMARDs to take effect.¹³ **Oral CS should only be used in conjunction with DMARDs until the latter take effect or intermittently to help control acute disease.**¹³ Long-term use of even low-dose CS may result in osteoporosis and other steroid-related adverse effects.^{15,19}

NSAIDs reduce swelling and stiffness in addition to providing pain relief, and they improve quality of life in the majority of cases with acute RA.¹⁶ However, because of their well-documented toxicity profile, including GI toxicity, renal dysfunction, fluid retention and skin reactions, and the recent evidence linking selective COX-2 inhibitors (and possibly all NSAIDs) to an increased risk of myocardial infarction,^{19,21} **long-term use should be avoided, especially in patients with known cardiovascular or GI risk and only one NSAID should be used at any one time.**^{5,19}

Control of Disease Progression

Table 3 outlines the most commonly used non-biological (conventional) DMARDs that are authorised for monotherapy. Similar efficacy has been reported for methotrexate, sulfasalazine and leflunomide in studies of up to 12 months.^{3,22}

Table 3: Most commonly used non-biological DMARD agents^{19,23-26}

Drug*	Dose Regimen	Adverse Effects	Monitoring / Precautions in Use
Methotrexate (immunomodulator)	7.5mg – 20mg once weekly** orally [IM or SC administration possible]	Nausea, stomatitis [may be relieved by folic acid 5mg 1-6 times weekly] rash, bone marrow suppression, pneumonitis, hepatotoxicity, alopecia	Regular FBC, LFTs, U&E (monthly initially) Ensure adequate contraception for up to 6 months after discontinuation (d/c) in females and males
Sulfasalazine (immunomodulator)	0.5g daily increasing weekly to max of 3g daily in divided doses	GI effects, leucopenia, bone marrow suppression, rash, hepatitis, reversible oligospermia, discolouration of urine / contact lens	Regular FBC, LFTs, U&E, especially in the first 3 months
Hydroxychloroquine (immunomodulator)	6.5mg/kg daily (max 400mg daily)	Visual disturbances, retinopathy, rash **Very toxic in overdose**	Baseline assessment of visual acuity and at least every 12 months thereafter
Leflunomide (immunomodulator)	100mg daily X 3 loading dose, then 10-20mg daily	Diarrhoea, rash, alopecia, hypertension, hepatotoxicity, bone marrow suppression. Teratogenicity and possible male-mediated foetal toxicity	Regular FBC, LFTs, U&E, BP monitoring, at 2 - 4 weeks for 6 months, then 2-monthly Ensure adequate contraception (females and males) for up to 2 years after d/c in females and 3 months after d/c in males

*Please check the Summary of Product Characteristics for complete information on each medicine, including potential drug interactions

**Patient safety information leaflet available from <http://www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/oral-methotrexate/>

Monotherapy: Low dose **weekly methotrexate** (MTX) is the most widely prescribed DMARD, both as monotherapy and as an anchor agent in combination therapy.³ It produces 50-80% clinical response relative to baseline, slows the rate of joint destruction (as seen on x-ray) and improves function and quality of life.³ Onset of action takes 6 - 12 weeks. Doses of up to 20mg weekly may be needed; parenteral administration (SC, IM, starting at 7.5-10mg weekly) may be considered in severe acute RA, if oral treatment is ineffective or in those unable to tolerate oral MTX.¹⁹ As most serious / fatal adverse effects reported with methotrexate are due to an absolute or relative overdosage, **patients should be given clear instructions on how to take the weekly MTX dosage regimen (strength and number of tablets, day of week to be taken).**¹⁹

Sulfasalazine has a slow onset of effect (1 - 3 months).²⁴ Patients may discontinue long-term treatment due to GI complaints.

Hydroxychloroquine takes several weeks to exert its effect.²⁵ It has been reported to be less effective than the other DMARDs but is well-tolerated; therefore it may be useful in mild disease or in combination therapy.¹ Because of its potential for dose-related retinal toxicity, regular ophthalmological review is required.²⁵

Leflunomide is effective within 6 - 12 weeks of treatment.²⁶ It can cause potentially life-threatening hepatotoxicity (usually within the first 6 months), therefore combination with methotrexate is not recommended.^{19,26} As it has a long persistence in the body, a specific washout procedure (using cholestyramine / activated powdered charcoal for 11 days) should be followed if a) hepatotoxicity occurs, b) before switching to another DMARD (especially methotrexate) or c) if the patient wishes to become pregnant.²⁶

Other agents: **Penicillamine** and **IM gold** have shown similar efficacy to methotrexate but they have been largely superseded by newer, less toxic and/or better-tolerated agents.^{19,22}

Azathioprine and **Ciclosporin** tend to be reserved for severe RA, when other DMARDs are ineffective or inappropriate.^{27,28}

Combination DMARD therapy: Studies evaluating combined conventional DMARDs (sulfasalazine and/or hydroxychloroquine plus methotrexate and tapering corticosteroids) have shown highly effective control of active disease with lower radiographic progression and no differences in discontinuation rates for ADRs compared with monotherapy regimens.^{15,29}

Biological Therapies

Biological agents target specific aspects of the inflammatory process of RA. Table 4 outlines the biological DMARDs currently authorised for use in RA. TNF- α and IL-1 (cytokines in the inflammatory process of RA), T-lymphocytes and B-lymphocytes have been targeted in the development of these agents.³⁰

In general, **use of biological agents is reserved for patients with moderate-severe active RA who have failed therapy with conventional DMARDs.**³¹⁻³⁶ They are usually used in combination with conventional DMARDs (see Table 4). Use should be initiated and supervised by specialists in RA.

TNF- α inhibitors have shown efficacy in a range of populations with RA.³⁷ Although there are no head-to-head trials, clinical experts do not consider there to be clinically significant differences between the currently authorised agents: **etanercept**, **adalimumab** or **infliximab** (see Table 4).³⁷ Use of TNF- α inhibitors should be discontinued, after 6 months, in the absence of a clinical response; within this timeframe, an alternative TNF- α inhibitor may be considered if treatment with one TNF- α inhibitor has been withdrawn due to toxicity.³⁸ The main **adverse effects** are injection site / infusion reactions and the risk of serious bacterial infections (see Table 4). Although there is a potential risk of malignancy (especially lymphoma), data from the British Society of Rheumatology Biologics Register have shown no overall increase, to date, in mortality, cancer or serious adverse events compared with patients not exposed to TNF- α inhibitors.³⁷

Other Biological Agents: **Abatacept** interferes with T-lymphocyte activation.³⁴ Studies have reported a modest anti-inflammatory effect in advanced RA; it seems to be effective in TNF- α inhibitor resistant RA.³⁹ It is authorised for combination therapy with methotrexate only in patients who have failed TNF- α treatment.³⁴ **Abatacept should not be used in combination with a TNF- α inhibitor due to the risk of serious infection.**³⁴

Rituximab acts by depletion of B cells and is used in the treatment of lymphoproliferative malignancies.³⁵ Its use in RA is restricted to severe RA patients who have failed therapy with (or were intolerant of) other DMARDs including one or more TNF- α inhibitors - so-called **salvage therapy**.^{35,40}

Anakinra in combination with methotrexate has been shown to be more effective compared with methotrexate alone in RA patients.^{5,8} It must be administered daily because of its short half-life.⁷ With the advent of newer biological agents, its use has declined.⁴¹ The main **adverse effects** are injection site reactions (>50% of patients) and neutropenia. **Anakinra should not be used in combination with TNF- α inhibitors because of the increased risk of serious infection.**³⁶

Table 4. Biological Agents authorised for use in Rheumatoid Arthritis³⁰⁻³⁸

Drug*	Dose Regimen	Adverse Effects	Precautions for Use
Etanercept (TNF- α inhibitor) Enbrel®	25mg SC injection twice weekly or 50mg SC injection weekly [combination therapy with MTX or as monotherapy if MTX not tolerated or inappropriate]	Injection site reactions; serious infections including reactivation of TB; potential for malignancy	Patients must be pre-screened and any infection (including TB) treated before start of therapy; stop therapy if infection occurs
Adalimumab (TNF- α inhibitor) Humira®	40mg SC injection every other week [combination therapy with MTX or as monotherapy if MTX not tolerated or inappropriate]	Injection site reactions; serious infections including reactivation of TB; potential for malignancy	Management of infection risk before and during treatment as for etanercept; contraindicated in moderate – severe heart failure
Infliximab (TNF- α inhibitor) Remicaide®	3mg/kg IV infusion at weeks 0,2,6 and 8-weekly thereafter; doses up to 7.5mg/kg may be used if insufficient response [combination therapy with MTX]	Infusion reactions; serious infections including reactivation of TB; potential for malignancy	Management of infection risk before and during treatment as for etanercept; contraindicated in moderate – severe heart failure
Abatacept (T-cell modulator) Orencia®	10mg/kg IV at weeks 0, 2 4 and then 4-weekly [combination therapy with MTX only in patients who have failed TNF- α treatment]	Infusion reactions; serious infections including reactivation of TB; potential for malignancy	Management of infection risk before and during treatment as for etanercept
Rituximab (B-cell modulator) MabThera®	2 X 1000mg IV infusion given 2 weeks apart [combination therapy with MTX only in severe RA patients, who have failed TNF- α treatment]	Infusion reactions; serious infections including reactivation of TB; potential for malignancy	Pre-treat with IV corticosteroids. Management of infection risk as per etanercept; contraindicated in severe heart failure
Anakinra (IL-1 antagonist) Kineret®	100mg daily by SC injection [combination therapy with MTX when no response to MTX monotherapy]	Injection site reactions; risk of serious infection; neutropenia	Regular check on FBC and renal function. Monitor closely for signs of infection and treat rapidly; contra-indicated in severe renal disease

*Please check the Summary of Product Characteristics for complete information on each medicine

MANAGEMENT OF RHEUMATOID ARTHRITIS IN CLINICAL PRACTICE

In current practice, most patients are treated initially with monotherapy using conventional DMARDs, usually **methotrexate**.¹⁵ Clinical response should be monitored at 1-3 monthly intervals (including use of composite scales such as the **Disease Activity Scores**) until remission is attained. Many patients on monotherapy have progressive disease and studies have reported drop-out rates of 20-30% due to poor tolerability.^{3,15} Therefore, it may be necessary to **“step up”** to combination DMARD therapy (which may include a biological DMARD, depending on the individual) in patients not responding to or intolerant of increasing doses of monotherapy in order to achieve remission.^{13,15} **Patients judged to be at risk for rapidly progressive disease at diagnosis should be considered for immediate combination DMARD therapy.**¹⁵ Once patients achieve remission, treatment may be reduced (so-called **“step down”** approach) in order to maintain remission with the least toxic DMARD regimen.¹⁵

The patient should be provided with a plan of care from time of diagnosis in order to optimise treatment compliance.¹⁸ Poor prognosis in RA is inversely proportional to educational status;⁴² targeted patient education, i.e. explaining the disease process and possible therapeutic options, has been shown to improve outcome.^{18,42} Specialist nurses and self-help patient groups are also valuable for ongoing patient education and counselling.^{18,42}

The availability of disease-modifying therapies has improved the outlook for RA patients. The best effects (in terms of reduced morbidity and improved survival) are achieved by early diagnosis and early access to specialist care for initiation of DMARD therapy and multidisciplinary management.^{5,43}

Management Plan for Rheumatoid Arthritis: Summary

1. Early diagnosis and early specialist referral for
 - Assessment of risk for rapidly progressive disease
 - Access to multidisciplinary care (physiotherapy etc) and patient education
2. Early conventional DMARD monotherapy (combination if poor prognosis) +/- acute pain relief +/- corticosteroids
3. Regular monitoring of disease response (1-3 monthly)
4. If disease activity persists, increase dose / change DMARD / start combination DMARDs

List of references available on request. Date of preparation: May 2008

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