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Scottish Intercollegiate Guidelines Network
Part of NHS Quality Improvement Scotland

NHS
Quality
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Scotland

123

Management of early rheumatoid arthritis

A national clinical guideline

February 2011

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

GOOD PRACTICE POINTS

☑	Recommended best practice based on the clinical experience of the guideline development group

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ISBN 978 1 905813 70 4

Published February 2011

Citation text
Scottish Intercollegiate Guidelines Network (SIGN). Management of early rheumatoid arthritis. Edinburgh: SIGN; 2011. (SIGN publication no. 123). [cited February 2011]. Available from URL: http://www.sign.ac.uk

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Contents

1 Introduction

1.1 THE NEED FOR A GUIDELINE

Rheumatoid arthritis (RA) is an inflammatory disease which, though systemic, typically involves the small joints of the hands and feet, often symmetrically. It affects approximately 1% of the population and is more common in women. The course of RA is variable and unpredictable but for a significant number of patients it is a severe disease resulting in persistent pain and stiffness, progressive joint destruction, functional decline and premature mortality.[1-3] There is also the potential loss of social and financial independence[4] and the burden of care on direct (eg medical care) and indirect costs (eg effects on the individual's ability to work).[5, 6] The goal of early treatment for rheumatoid arthritis is to achieve clinical and radiological remission and reduce functional limitations and permanent joint damage.

1.1.1 UPDATING THE EVIDENCE

This guideline updates SIGN 48 to reflect the most recent evidence.

Where no new evidence was identified to support an update, text and recommendations are reproduced verbatim from SIGN 48. The original supporting evidence was not re-appraised by the current guideline development group.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline addresses the diagnosis of early RA, its pharmacological treatment including symptom relief and disease modification, and the role of the multidisciplinary team in improving the care of patients with RA. The guideline does not address the treatment of comorbidities (eg anaemia, osteoporosis), complications of drug therapy and their management, or treatment of extra-articular disease (eg vasculitis, ocular complications, amyloid).

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of particular interest to rheumatologists, general practitioners (GPs), rheumatology nurse specialists, physiotherapists, occupational therapists, dietitians, podiatrists and pharmacists.

1.2.3 SUMMARY OF UPDATES TO GUIDELINE BY SECTION

2	Key messages	New
3	Diagnosis	Major update
4	Principles of treatment	Partial update
5	Analgesics and non-steroidal anti-inflammatory drugs	Partial update
6	Disease modifying drugs	Major update
7	The role of the multidisciplinary team	Partial update

1.3 DEFINITIONS

At present there is no formal definition of 'early RA'. It is defined in this guideline as disease duration of ≤5 years from onset of symptoms. The guideline development group recognises that the interval between seeking advice and initiation of disease modifying anti-rheumatic drugs (DMARD) treatment has continued to narrow and patients should be advised to seek treatment as early as possible to reduce disease progression.

1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.4.1 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (product licence). This is known as 'off label' use. It is not unusual for medicines to be prescribed outwith their product licence and this can be necessary for a variety of reasons.

Generally the unlicensed use of medicines becomes necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience.[7]

Medicines may be prescribed outwith their product licence in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose.

"Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines."[7]

Any practitioner following a SIGN recommendation and prescribing a licensed medicine outwith the product licence needs to be aware that they are responsible for this decision, and in the event of adverse outcomes, may be required to justify the actions that they have taken.

Prior to prescribing, the licensing status of a medication should be checked in the current version of the British National Formulary (BNF).[7]

1.4.2 ADDITIONAL ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

NHS QIS processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice and NHS QIS validated NICE MTAs relevant to this guideline are summarised in section 9.4.

2 Key messages

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation. The grade of recommendation relates to the strength of the supporting evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

2.1 PRINCIPLES OF MANAGEMENT

☑ All patients with suspected inflammatory joint disease should be referred to a specialist as soon as possible to confirm the diagnosis and evaluate disease activity.

☑ The multidisciplinary team has been shown to be effective in optimising management of patients with RA. All patients should have access to such a range of professionals including general practitioner, rheumatologist, nurse specialist, physiotherapist, occupational therapist, dietitian, podiatrist, pharmacist and social worker.

B **Early initiation of treatment with DMARDs is recommended to control the symptoms and signs of RA as well as limiting radiological damage.**

B **Patients with moderate to severe disease activity should:**

- **be assessed for disease activity using a standardised scoring system such as DAS/DAS28**
- **be reviewed monthly until remission or a low disease activity score is achieved**
- **receive treatment with DMARDs, adjusted with the aim of achieving remission or a low DAS/DAS28 score.**

2.2 DISEASE MODIFYING ANTI-RHEUMATIC DRUGS

A **Methotrexate and sulfasalazine are the DMARDs of choice due to their more favourable efficacy and toxicity profiles.**

B **DMARD therapy should be sustained in patients with early RA to control the signs and symptoms of disease.**

A **A combination DMARD strategy, rather than sequential monotherapy, should be considered in patients with an inadequate response to initial DMARD therapy.**

2.3 BIOLOGIC RESPONSE MODIFIERS

Use of the TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.

3 Diagnosis of early rheumatoid arthritis

The diagnosis of early RA relies heavily on the accurate interpretation of medical history and clinical examination, and is informed by clinical investigations. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) 2010 criteria for the classification of RA illustrates this.[8] The evidence reviewed within this guideline uses the 1987 ACR criteria, as the studies predate the publication of the 2010 criteria.[9]

3.1 CLINICAL INDICATORS

3.1.1 ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES

Two meta-analyses concluded that in patients with a high clinical probability of RA, anti-cyclic citrullinated peptide antibodies (anti-CCP) may identify those with a higher probability of developing radiological damage.[10,11] Few studies included patients with early RA and neither review provided an estimate of the sensitivity and specificity of anti-CCP in early disease. | 2^{++}

A systematic review concluded that anti-CCP2 is useful in early RA diagnosis because of its greater specificity but it has similar sensitivity to rheumatoid factor (RF).[12] Of the eight cohort studies included, IgM RF had a specificity of 86% (95% CI 78 to 92) and anti-CCP2 had a specificity of 96% (95% CI 93 to 97). This review was limited by poor quality studies. | 2^{++}

No evidence was identified on the use of anti-CCP in guiding the management of patients with early RA.

B **Anti-CCP2 antibody may be used as part of the assessment of a patient suspected of an early inflammatory polyarthritis such as RA.**

3.1.2 IMAGING

The evidence for additional imaging at diagnosis to assess disease activity in early RA is limited and methodologically poor.[13,14] The evidence suggests that power Doppler ultrasound may be useful in assessing disease activity and may have predictive value on radiological outcome.[15] | 2^{-}

4 Principles of management

4.1 PATIENT EDUCATION

Patient-led self management education programmes are increasing in popularity but evidence for their effectiveness is limited.[30,31] Programmes such as The Expert Patient endorsed by the Department of Health aim to instill core self management skills: problem solving, decision making, resource utilisation, formation of a patient-professional partnership and taking action.[32] Evaluation of these programmes should be undertaken in Scotland if they are to be made available more widely.

4.2 MULTIDISCIPLINARY TEAM

A shared care approach between primary and secondary care physicians and the multidisciplinary team facilitates optimal monitoring of the efficacy and toxicity of drug therapy and the prompt identification of the complications of RA and its treatments (*see section 7*).[33,34]

4.3 EARLY TREATMENT

There is evidence that delays in initiating treatment with DMARDs is associated with more radiological damage and poorer functional status.[35-38] 1+

An audit based on SIGN 48: Management of early rheumatoid arthritis has shown that, in Scotland, there is a significant delay between symptom onset and first assessment by a physician, most occurring before referral from the GP.[39]

B **Early initiation of treatment with DMARDs is recommended to control the symptoms and signs of RA as well as limiting radiological damage.**

☑ All patients with suspected inflammatory joint disease should be referred to a specialist as soon as possible to confirm the diagnosis and evaluate disease activity.

4.4 ASSESSING DISEASE ACTIVITY

Quantifying disease activity and outcome is important in assessing, comparing and standardising treatment. Several composite measures of disease activity have been developed and validated for use in RA. One of the most commonly used is the 28 joint count disease activity score (DAS28). Scores of >5.1; >3.2 to ≤5.1 or ≤3.2 indicate the presence of high, moderate or low disease activity respectively. A score of <2.6 indicates remission.[40,41]

EULAR has suggested response criteria to treatment depending on the degree of improvement in the DAS28 (*see Table 1*).[42]

☑ Patients with early RA should have their disease activity quantified.

Table 1: EULAR response criteria

			Improvement in DAS/DAS 28 from baseline		
	DAS at endpoint	DAS28 at endpoint	>1.2	>0.6 to ≤1.2	≤0.6
Low	≤2.4	≤3.2	Good	Moderate	None
Moderate	>2.4 and ≤3.7	>3.2 and ≤5.1	Moderate	Moderate	None
High	>3.7	>5.1	Moderate	None	None

4.5 TREAT-TO -TARGET STRATEGIES

A single blind RCT (n = 110) compared routine treatment with an intensive outpatient treatment for 18 months in patients with high disease activity. The intensive treatment included monthly reviews, formal assessment of disease activity using DAS, use of parenteral (intra-articular or intramuscular) corticosteroid and escalation of DMARD therapy. For the intensive group, statistically significant improvements were seen in disease activity scores, and significant improvements in physical function, health-related quality of life and radiographic progression in comparison to routine group.[43] 1++

B **Patients with moderate to severe disease activity should:**

- **be assessed for disease activity using a standardised scoring system such as DAS/DAS28**
- **be reviewed monthly until remission or a low disease activity score is achieved**
- **receive treatment with DMARDs, adjusted with the aim of achieving remission or a low DAS/DAS28 score.**

5 Analgesics and non-steroidal anti-inflammatory drugs

5.1 ANALGESICS

Analgesics in early RA should only be used as an adjunct to non-steroidal anti-inflammatory drugs (NSAIDs) and DMARD therapy. There is evidence that both paracetamol and codeine are effective in reducing pain in RA.[44-48] These trials were carried out more than 25 years ago, are in small patient numbers and of short duration.

5.2 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs provide some relief of pain and stiffness in RA (but do not influence radiographic progression) by inhibiting cyclo-oxygenase (COX).[49,50] There are at least two COX isoforms and non-selective NSAIDs inhibit both COX-1 and COX-2 in differing ratios. Selective COX-2 inhibitors or coxibs were designed to avoid gastroduodenal ulceration which arises due to inhibition of COX-1 by NSAIDS.[51]

5.2.1 EFFICACY

There is no difference in the efficacy of non-selective NSAIDs. A health technology assessment concluded that selective COX-2 inhibitors have a similar efficacy to NSAIDs.[51] 1++

5.2.2 SIDE EFFECTS OF NSAIDS

Side effects of NSAIDs are dose and duration of therapy dependent.[52,53] The gastrointestinal (GI) and cardiovascular side effects are of particular concern. Other less common but equally serious side effects include renal disease and hypersensitivity (including asthma). 1+

Gastrointestinal side effects

Ulceration of the gastrointestinal tract, particularly of the stomach and duodenum, arises due to the systemic inhibition of prostaglandins. Symptoms correlate poorly with GI ulceration which can occur throughout the length of the GI tract. GI bleeding, perforation and gastric outlet obstruction are recognised complications of ulceration.[52,53] 1+

The risk of GI bleeding is the most frequent complication of GI ulceration and occurrence differs between NSAIDs. Although the frequency of gastroduodenal ulceration is less with selective COX-2 inhibitors compared to non-selective NSAIDs the case for reduced GI ulcer complication rates is unproven.[51] 1++

Table 2: Risk factors for NSAID-associated gastroduodenal ulcers

Definite risk factors	Possible lifestyle factors
▪ advanced age (linear increase in risk) ▪ history of ulcer ▪ higher doses of NSAIDs ▪ combination use of NSAIDs ▪ concomitant use of corticosteroids ▪ comorbidity	▪ cigarette smoking ▪ alcohol consumption

Cardiovascular side effects

An increased risk of arterial thrombotic events such as acute myocardial infarction or stroke has been noted with some selective COX-2 inhibitors and the non-selective NSAIDs, although the overall risk is small.[51] This risk applies to all NSAID users and not just those at risk of cardiovascular events and occurrence increases with duration of treatment as well as being dose dependent. Differences are shown between NSAIDs: diclofenac (150 mg daily) and ibuprofen (2.4 g daily) are associated with an increased risk but naproxen (1 g daily) and lower doses of ibuprofen (1.2 g daily or less) are not.[54] Data on other NSAIDs are, as yet, inconclusive.[54] NSAIDs and COX-2 inhibitors should therefore be avoided in patients with ischaemic heart disease, cerebrovascular disease, peripheral arterial disease and moderate to severe heart failure.[7,55] 1++ 4

5.2.3 SUMMARY OF STRATEGIES TO MINIMISE THE RISK OF NSAID SIDE EFFECTS

B
- **The lowest NSAID dose compatible with symptom relief should be prescribed.**
- **NSAID dose should be reduced and if possible withdrawn when a good response to DMARDs is achieved.**

B **Gastroprotection should be introduced for patients with RA at risk of NSAID-associated gastroduodenal ulcers.**

☑ Only one NSAID should be prescribed at a time.

☑ Long term NSAID use should be reviewed periodically.

☑ NSAIDs least likely to cause GI and/or cardiovascular effects should be prescribed.

6 Disease modifying drugs

Disease modifying drugs are the most effective means of improving the signs and symptoms of RA as well as reducing radiological progression.[56] Agents in this class fall into two categories:

- non-biologics - disease modifying anti-rheumatic drugs such as methotrexate (MTX), sulfasalazine (SASP), and leflunomide (LEF). For the purpose of this guideline systemic corticosteroids are included in this category.
- biologics, such as anti-TNF-α antagonists.

6.1 SYSTEMIC CORTICOSTEROIDS – ORAL AND PARENTERAL

6.1.1 EFFICACY

Systemic corticosteroid therapy has been shown to improve RA symptoms and reduce radiological damage.[55,57] A Cochrane review of 11 RCTS concluded that low-dose oral corticosteroids (not exceeding 15 mg of prednisolone daily) in comparison to NSAIDs are effective for the short term relief of signs and symptoms. In the medium to long term their use can minimise radiological damage.[55] In a second Cochrane review corticosteroids, given in addition to DMARD therapy, were found to reduce the rate of progression of erosion in patients with active RA of less than two years duration.[57] 1++

A **Low-dose oral corticosteroids can be used in combination with DMARD therapy for short term relief of signs and symptoms, and in the medium to long term to minimise radiological damage.**

6.1.2 LONG TERM SIDE EFFECTS

A meta-analysis concluded that low-dose corticosteroid use in patients with RA reduces bone mineral density.[58] An RCT concluded that prednisolone 10 mg once daily also increased the risk of fractures.[59] 1++

Two case controlled studies show increased side effects in corticosteroid treated patients with RA, including cataracts, infections, gastrointestinal bleeds, avascular necrosis and fractures (the Medicines and Healthcare Products Regulatory Agency has drawn attention to the additional risks of chickenpox exposure in patients not previously infected).[54,55] Increased mortality has also been reported in RA patients on corticosteroids.[60]

☑ Consideration should be given to the risk benefit ratio of corticosteroids, particularly the long term side effects. Patients should be informed of the risks prior to prescription and issued with a steroid warning card.

☑ Guidelines for managing osteoporosis in patients taking oral corticosteroids should be followed.

6.1.3 INTRA-ARTICULAR CORTICOSTEROIDS

Intra-articular corticosteroid injections are widely used to provide rapid, and sometimes sustained, symptomatic relief in 'target' joints.

Intra-articular corticosteroid injections:

- provide symptomatic relief pending the onset of DMARD effect
- alleviate symptoms in particularly troublesome joints where the overall disease control is good
- deal with mono-/oligoarthritis in instances when DMARDs are deemed inappropriate.

There are few controlled trials in this area and there is no evidence on the long term effect on disability or radiological progression. Data from large cohorts suggest that complications such as joint sepsis are very rare.[61] Synovial fluid aspiration at time of joint injection has been shown to reduce relapse rate.[62]

Post-injection rest (24 hours) improves the symptomatic benefits as well as increasing walking times.[63]

☑ Intra-articular injections can be used for rapid, and sometimes sustained, symptomatic relief in 'target' joints.

☑ Intra-articular injections to any one joint should not be given more than three to four times in one year.

☑ When administering intra-articular injections:
- use sterile technique
- advise patients how to seek help if the joint fails to settle after an injection
- always consider possible septic arthritis in the differential diagnosis of mono-oligo flare in RA.

6.2 DISEASE MODIFYING ANTI-RHEUMATIC DRUGS

6.2.1 INTRODUCTION

DMARDs reduce the signs and symptoms of RA, improve physical function and laboratory markers of disease activity, and reduce radiographic progression.[64] The DMARDs for use in RA include ciclosporin A, hydroxycholoroquine (HCQ), leflunomide (LEF), methotrexate (MTX), intramuscular gold, penicillamine and sulfasalazine (SASP).[7] 1++

6.2.2 EFFICACY AND TOXICITY

The efficacy of MTX, intramuscular gold, LEF, penicillamine and SASP, is similar.[64] HCQ is less effective.[65] Intramuscular gold has the highest toxicity and therefore increased treatment drop-out rates compared to SASP, HCQ and MTX.[66] 1++ 1+

A systematic review found LEF, MTX and SASP to have comparable efficacy.[56] MTX has the most favourable efficacy/toxicity trade-off. SASP scored close to MTX and had more adverse events initially. HCQ had a relatively low rate of toxicity. 1++

In two randomised placebo controlled studies relapse in symptoms and signs occurred on withdrawal of DMARDS demonstrating that sustained use is necessary.[67,68] 1+

A **Methotrexate and sulfasalazine are the DMARDs of choice due to their more favourable efficacy and toxicity profiles.**

B **DMARD therapy should be sustained in patients with early RA to control the signs and symptoms of disease.**

6.2.3 TREATMENT STRATEGIES

DMARDs in combination can be used in a step-up approach, where a second drug is introduced after maximum but suboptimal benefit from the first DMARD, step-down where several drugs are introduced followed by protocol-driven sequential tapering and withdrawal of one or more drugs, or in parallel where combinations are introduced at the same time and maintained.

A systematic review of three randomised controlled trials concluded that combination therapy is more effective than sequential monotherapy in improving the symptoms and signs, physical function, and reducing radiographic progression.[56] Most combinations use MTX as an anchor drug. 1++

There is no consistent evidence that any combination strategy (step-up, step-down or parallel treatment) is superior to another.[56,69-71] No recommendations can be made on a specific combination strategy. The use of DMARDs with biologic response modifiers is discussed in section 6.3. 1++ 1+

Within the context of an intensive management programme (*see section 4.5*), step-up, and parallel DMARD strategies are equally effective in controlling symptoms, signs and physical function.[71] Within a less intensive treat-to-target strategy, the addition of high-dose oral steroids or anti-TNF-α led to more rapid but ultimately no greater improvement in disease activity.[70] 1++

A **A combination DMARD strategy, rather than sequential monotherapy, should be considered in patients with an inadequate response to initial DMARD therapy.**

☑ Where parallel or step-down strategies are employed, DMARDs should be carefully and slowly withdrawn in patients who are in remission.

6.2.4 PRACTICAL PRESCRIBING OF DMARDS

☑ The choice of the initial DMARD should take into account patient preferences and existing comorbidities.

☑ Patients should be informed of the potential benefits, risks and monitoring requirements of DMARDs.

☑ Monitoring of toxicity should follow the recommendations of the British National Formularly and the manufacturers' data sheets.

☑ Effective liaison between primary and secondary care is essential. Rheumatology nurse specialists have an important role in this aspect of care.

6.3 BIOLOGIC RESPONSE MODIFIERS

6.3.1 AGENTS AVAILABLE

There are a number of biologic response modifiers available for the treatment of RA (*see Table 3*).

Table 3: Licensed biologic agents available for rheumatoid arthritis

TNF-α blockers	Interleukin-1 receptor antagonist	Interleukin-6 antagonist	T-cell co-stimulation Modulator	B-cell depleting
Adalimumab	Anakinra	Tocilizumab	Abatacept	Rituximab
Certolizumab				
Etanercept				
Infliximab				

6.3.2 EFFICACY

A meta-analysis of seven RCTs involving 2,673 patients compared combination therapy with MTX and biologic (1,248 patients) to MTX alone (1,152). The biologics studied were infliximab, adalimumab, etanercept, and abatacept. The authors concluded that remission rates at one year were greater in the combination therapy groups, than MTX monotherapy. In the combination group significantly more achieved clinical remission but there was only a modest benefit on radiological non-progression. All of the biologic agents had a similar efficacy for clinical remission.[72] 1++

In an RCT of a TNF-α inhibitor in patients with early moderate to severe RA (DAS28 ≥3.2), the addition of infliximab to those with an inadequate response (DAS28 ≥3.2) to MTX was found to achieve a good EULAR response in more patients than the addition of HCQ and SASP to MTX.[73] This has yet to be shown to be cost effective.[74] 1++

Use of TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX or other DMARDs is not recommended.[74] 1++

6.3.3 TOXICITY OF TNF- α BLOCKERS

The adverse effects of infliximab and adalimumab were analysed in a recent systematic review of nine RCTs. RA patients receiving anti-TNF-α therapy had a significantly higher incidence of serious infection. The risk of malignancy was also increased and was found to be dose dependent.[75] 1++

7 The role of the multidisciplinary team

The multidisciplinary team has been shown to be effective in optimising management of patients with RA.[34]

☑ All patients should have access to a range of professionals, including general practitioner, rheumatologist, nurse specialist, physiotherapist, occupational therapist, dietitian, podiatrist, pharmacist, and social worker.

7.1 OCCUPATIONAL THERAPY

In everyday practice, the benefits of skilled occupational therapy (OT) intervention on quality of life for patients with RA is clear. Unfortunately, relatively few studies have been carried out and evidence from RCTs is absent. The OT approach is multifaceted and includes:

7.1.1 ACTIVITIES OF DAILY LIVING

Facilitation of the activities of daily living (eg washing, toileting, dressing, cooking, eating, working), sometimes with the provision of equipment and adaptations, is fundamental to the management of RA.[76] Effective OT advice is crucial in helping patients to maximise function and improve their level of independence. 1+

C **Skilled occupational therapy advice should be available to those experiencing limitations in function.**

7.1.2 JOINT PROTECTION

Joint protection aims to reduce pain and stress on joints whilst carrying out everyday activities.[77] 4

A range of strategies are employed including adapting movement patterns of affected joints to reduce strain, assistive devices, rest regimens, energy conservation techniques, exercise and splinting. These interventions are difficult to evaluate and formal studies are limited. Studies in patients with longer disease duration have shown encouraging results.

7.2 PHYSIOTHERAPY

The role of the physiotherapist in assessing and treating patients with RA is well established in clinical practice. Physiotherapy management has been shown to be effective in improving self efficacy, knowledge and morning stiffness.[78] Well conducted studies evaluating the effectiveness of intervention are lacking and the evidence base is limited.

7.2.1 EXERCISE THERAPY

Exercise therapy is prescribed in an attempt to overcome the adverse effects of RA on muscle strength, endurance and aerobic capacity. Dynamic exercise therapy (ie exercises of low to moderate aerobic intensity) is effective in increasing aerobic capacity and muscle strength. No adverse effects on disease activity or pain are observed.[79] Limited evidence indicates that specific strength training programmes can reduce impairment.[80] 1++

Two high quality reviews of T'ai Chi for patients with RA found little effect on disease activity and symptoms including activities of daily living, tender and swollen joints and patient overall rating.[81,82] There was a significant benefit from enjoyment in the participation of a T'ai Chi programme.[81] 2++

Low-intensity exercise programmes favour reduction in pain and an improved functional status compared with a high intensity programme which may exacerbate the inflammatory process and risk damage to the joints.[83] A further systematic review concluded that exercise from low to high intensity (including cycling, aquatic exercise, dancing or aerobic exercise) is effective in improving disease-related characteristics and functional ability.[84] These conclusions should be viewed with caution as they are based mainly on studies of poor methodological quality and a mixture of study designs. 2+

There is insufficient evidence to determine the effectiveness, or evidence of harm, of any type of exercise or dose (frequency, duration) on disease activity, symptoms and quality of life in people with early RA.

B **Patients should be encouraged to undertake simple dynamic exercises.**

☑ Exercise should be prescribed under the guidance of a qualified practitioner commencing with low-intensity exercise. Due care should be taken to monitor disease activity to avoid exacerbations of symptoms.

7.2.2 HYDROTHERAPY

Hydrotherapy is one of the oldest forms of treatment for patients with arthritis. Despite this, evidence showing benefit is sparse. Limited evidence suggests that hydrotherapy can effect and maintain an improvement in self efficacy in addition to some clinical and psychological gain.[85,86] A recent systematic review of balneotherapy (ie hydrotherapy or spa therapy) noted that no conclusion could be provided from the reviewed studies due to poor methodology.[87]

7.2.3 OTHER PHYSICAL THERAPIES

Evidence for other therapies such as the application of ice or heat,[88] transcutaneous electrical nerve stimulation or laser therapy[89-92] is conflicting or is insufficient to support their routine use. There is limited evidence showing symptomatic benefit from ultrasound.[93]

7.2.4 SPLINTING

Good evidence to support the use of resting hand splinting is sparse although two studies did report a significant reduction in pain when splints were applied.[94,95] Working wrist splints have been shown to decrease pain on activity[96,97] but do not improve function, grip strength or dexterity.[98,99] 1+

C **Resting and working splints can be used to provide pain relief.**

7.3 PODIATRY

The importance of appropriate footwear provision for comfort, mobility and stability is well recognised in clinical practice but there is little evidence based research to support such observations in patients with early RA.

There is some evidence regarding the efficacy of foot orthoses in terms of both comfort level and stride speed and length.[100]

☑ Podiatry referral should be offered to all patients.

7.4 DIETETICS

Nutritional advice plays an important part in the management of a patient with RA. Enquiries about diet are amongst those most commonly received from patients.

7.4.1 WEIGHT MANAGEMENT

Weight reduction in obese individuals is important particularly when weight-bearing joints are involved.

Cachexia may occur in those with severe active RA. The aetiology is likely to be multifactorial. Several studies have shown that patients with RA and low body mass index (BMI) do less well and have poorer functional status.[101,102] Whilst it is not clear whether dietary intervention improves outcome, for general health reasons, an adequate BMI should be maintained. Some patients will require diet supplements in addition to dietary advice.

7.4.2 DIET AS THERAPY

Few studies have assessed the potential benefits of diet therapy on disease activity in RA.[103] Fasting has been shown to be of benefit in some patients.[104] Practical difficulties have also been encountered in implementing and maintaining strict dietary changes. The evidence regarding food exclusion is inconclusive.

7.4.3 DIET SUPPLEMENTS

A meta-analysis of clinical trials of fish oil supplementation in RA concluded that there was a significant reduction in the number of tender joints and in duration of morning stiffness after three months of therapy. However, no effect was seen on indices of disease activity or progression of RA.[105]

The effect of other oils such as evening primrose oil and blackcurrant seed oil on disease activity in RA remains uncertain.[106,107]

7.5 COMPLEMENTARY AND ALTERNATIVE THERAPIES

The lack of adequate research studies precludes firm conclusions on the effectiveness of complementary medicine for treatment of patients with RA. Patients have a perception that because these treatments are ‘natural’ they are without side effects but this is not the case.[108]

Further research is needed to define benefits as well as harms.

8 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by healthcare professionals when discussing arthritis with patients and carers and in guiding the production of locally produced information materials.

8.1 SOURCES OF FURTHER INFORMATION

Arthritic Association
One Upperton Gardens, Eastbourne
East Sussex BN21 2AA
Freephone: 0800 652 3188 • Tel: 01323 416550 • Fax: 01323 639793
Email: info@arthriticassociation.org.uk
Website: www.arthriticassociation.org.uk

The Arthritic Association is a registered charity which aims to relieve the pain of arthritis by treating it through natural methods.

Arthritis and Musculoskeletal Alliance
Bride House, 18-20 Bride Lane
London EC4Y 8EE
Tel: 0207 842 0910/11 • Fax: 0207 842 0901
Email: info@arma.uk.net
Website: www.arma.uk.net

ARMA is the umbrella body providing a collective voice for the arthritis and musculoskeletal community in the UK.

Arthritis Care in Scotland
Unit 25A, Anniesland Business Park
Glasgow G13 1EU
Tel: 0141 954 7776 • Fax: 0141 954 6171
Email: Scotland@arthritiscare.org.uk
Website: www.arthritiscare.org.uk/InyourArea/Scotland/

Arthritis Care in Scotland supports people with arthritis through support groups, information provision, self management courses and campaigning on issues and services for people with the condition.

Arthritis Research UK
Copeman House, St Mary's Gate, Chesterfield
Derbyshire S41 7TD
Tel: 01246 558033 • Fax: 01246 558007
Email: enquiries@arthritisresearchuk.org
Website: www.arthritisresearchuk.org

Arthritis Research UK raises funds to promote medical research into the cause, treatment and cure of arthritic conditions; to educate medical students, doctors and allied healthcare professionals about arthritis; and provides information to the general public.

National Rheumatoid Arthritis Society
Unit B4, Westacott Business Centre
Maidenhead Office Park, Westacott Way, Littlewick Green
Maidenhead SL6 3RT
Tel: (helpline): 0800 298 7650 • Tel: (general): 01628 823524 • Fax: 0845 458 3971
Email: enquiries@nras.org.uk
Website: www.rheumatoid.org.uk

The National Rheumatoid Arthritis Society provides support and information for people with rheumatoid arthritis and juvenile idiopathic arthritis, their families, friends and carers, and health professionals with an interest in rheumatoid arthritis.

8.2 CHECKLIST FOR PROVISION OF INFORMATION

This section explains what information patients/carers can reasonably expect to be provided with at the key stages of the patient journey and how assessments and interventions should usually be organised. The checklist was designed by members of the guideline development group based on their clinical experience and their understanding of the evidence base.

These key messages are not intended for direct dissemination to patients, but are provided for possible use by clinicians in discussing treatment options with patients who have RA. They may be incorporated into local patient information materials.

- In RA joints become inflamed making them painful, swollen and stiff.
- The cause of RA is unknown.
- There is no single test to diagnose RA.
- RA cannot be cured at present, but in many cases it can be controlled.
- The progression of RA is different in each person.
- RA can be treated; reducing pain, stiffness, swelling, and damage to joints.
- The earlier treatment starts, the better, resulting in less damage in the joints, meaning less restriction in carrying out normal activities.
- Treatment with DMARDs should begin as soon as possible after diagnosis.
- DMARDs take several weeks to start working and should be continued indefinitely.
- The treatment of RA requires input from a range of healthcare professionals.
- People living with RA can achieve a good quality of life with support and skills training to manage their condition effectively. There are organisations set up to provide these skills and peer support (*see section 8.1 for details of relevant organisations*).

9 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

9.1 IMPLEMENTATION

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by SIGN.

9.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations are considered likely to reach the £5 million threshold which warrants full cost impact analysis.

9.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

- time from GP referral to rheumatology specialist
- number of patients with moderate to severe activity:
  - assessed for disease activity using tools such as DAS/DAS 28
  - reviewed on a monthly basis until remission or low disease activity score achieved
  - treated with DMARDs, adjusted with the aim of achieving remission or a low DAS/DAS 28 score
- time from symptom onset to introduction of DMARD therapy
- access to multidisciplinary team.

9.4 ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

NHS Quality Improvement Scotland advises that the recommendations in the following NICE technology appraisals are as valid for Scotland as for England and Wales:

- NICE Technology Appraisal Guidance No.130 – Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (October 2007).[74]
- NICE (Multiple) Technology Appraisal Guidance No. 195 - Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010).[109]

The Scottish Medicines Consortium has published guidance on the use of adalimumab, etanercept, rituximab, abatacept, tocilizumab and certilzumab pegol for the treatment of patients with rheumatoid arthritis in NHSScotland. Further information is available from the SMC website www.scottishmedicines.org.uk.

10 The evidence base

10.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer in collaboration with members of the guideline development group.

For the 2011 update the Cochrane Library, Medline and Embase were used to identify studies relating to the key questions listed in Annex 1. For the initial update searches the date range covered was 2003–2009. Additional searches were carried out on key questions 2a and 8 following peer review with a date range of 2003-May 2010. The search results were supplemented by material identified by individual members of the guideline development group.

10.1.1 PATIENT SEARCH

At the start of the guideline development process, a SIGN Information Officer conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to the management of early rheumatoid arthritis. Databases searched include Medline, Embase, CINAHL and PsycINFO, and the results were summarised and presented to the guideline development group. A copy of the Medline version of the patient search strategy is available on the SIGN website.

10.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline. The following areas for further research have been identified:

- defining the specificity and sensitivity of anti-CCP2 in diagnosing early RA
- investigating the cost and benefit of new imaging modalities
- the effect of anti-TNF therapy on the ability of people with RA to remain in employment
- the use of CCP in guiding the management of patients with early RA.

10.3 REVIEW AND UPDATING

This guideline was issued in 2011 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**.

11 Development of the guideline

11.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in SIGN 50: A Guideline Developer's Handbook, available at **www.sign.ac.uk**

11.2 THE GUIDELINE DEVELOPMENT GROUP

Dr Rajan Madhok *(Chair)*	*Consultant Rheumatologist, Glasgow Royal Infirmary*
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Miss Ann Tierney	*Research and Business Systems Manager, Glasgow Royal Infirmary*
Dr Debbie Turner	*Senior Lecturer in Podiatry, Glasgow Caledonian University*

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive.

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive. All members of the SIGN Executive make yearly declarations of interest and further details of these are available on request.

Ms Mary Deas	*Distribution and Office Coordinator*
Mrs Karen Graham	*Patient Involvement Officer*
Mrs Lesley Forsyth	*Events Coordinator*
Mr Stuart Neville	*Publications Designer*
Miss Gaynor Rattray	*Senior Guideline Coordinator*

11.2.1 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the guideline development group responsible for the development of SIGN 48: Management of rheumatoid arthritis, on which this guideline is based.

11.3 CONSULTATION AND PEER REVIEW

11.3.1 PUBLIC CONSULTATION

The draft guideline was available on the SIGN website for a month to allow all interested parties to comment. All contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

11.3.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Mrs Fran Bowen	*Clinical Specialist Physiotherapist, Ross Memorial Hospital, Dingwall*
Mr Gary Cook	*Principal Clinical Pharmacist, Perth Royal Infirmary*
Ms Debbie Crerar	*Team Lead Physiotherapist, Tollcross Health Centre, Edinburgh*
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11.3.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows:

Dr Keith Brown	*Chair of SIGN; Co-Editor*
Dr Roberta James	*Acting SIGN Programme Director; Co-Editor*
Ms Fiona McMillan	*Royal Pharmaceutical Society of Great Britain*
Dr Graeme Simpson	*Royal College of Physicians of Edinburgh*
Dr Derek Stewart	*Royal Pharmaceutical Society of Great Britain*
Dr Sara Twaddle	*Director of SIGN; Co-Editor*

All members of the SIGN Editorial group make yearly declarations of interest and further details of these are available on request from the SIGN Executive.

Abbreviations

ACR	American College of Rheumatology
BMI	body mass index
BNF	British National Formulary
BSR	British Society for Rheumatology
CCP	cyclic citrullinated peptide
COX	cyclo-oxygenase
CRP	C-reactive protein
DAS	disease activity score
DMARD	disease modifying anti-rheumatic drug
EULAR	European League Against Rheumatism
GI	gastrointestinal
GP	general practitioner
HCQ	hydroxychloroquine
LEF	leflunomide
LFT	liver function test
MTA	multiple technology appraisal
MTX	methotrexate
NHS QIS	NHS Quality Improvement Scotland
NICE	National Institute for Health and Clinical Excellence
NSAID	non-steroidal anti-inflammatory drug
OT	occupational therapy
RA	rheumatoid arthritis
RCT	randomised controlled trial
RF	rheumatoid factor
SASP	sulfasalazine
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
TNF	tumour necrosis factor

Annex 1

Key questions addressed for the selective update

The update of this guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

ASSESSMENT AND DIAGNOSIS	
Key question	**See guideline section**
1. In patients with undifferentiated or early polyarthitis does testing for cyclic citrullinated peptide (CCP) in addition to (or instead of) rheumatoid factor confer any benefit in the diagnosis and management of early RA?	10.2
2. In patients with RA does testing for cyclic citrullinated peptide: a. predict occurrence of laboratory markers of inflammation, radiological outcome and disability? b. aid management of patients with early RA?	3.1.1
3. Does additional imaging (MRI, CT, ultrasound) help in diagnosing early RA or the assessment of disease activity compared to clinical assessment and/or clinician observation?	3.1.2
TREATMENT	
4. In patients with early RA does intensive treatment improve symptoms, functional capacity, radiological progression and disability?	4.5
5. In patients with early RA what are the advantages of non-selective COX inhibitors/NSAIDs compared to selective COX-2 inhibitors in relieving symptoms and reducing toxicity?	5.2
6. When used with disease modifying therapy are oral corticosteroids effective in symptomatic relief in patients with early RA? Consider: laboratory markers of inflammation, radiological outcome and side effects	6.1.1
7. In patients with early RA is there any difference between sulfasalazine and methotrexate in symptomatic relief? Consider: laboratory markers of inflammation and radiological outcome and disability, side effects	6.2.2
8. In patients with early RA is combination therapy better than single therapy for first line symptomatic control and radiological progression in symptomatic relief? Consider: laboratory markers of inflammation and radiological outcome and disability; side effects; combination of DMARD therapy; methotrexate, sulfasalazine and hydroxychlorquine.	6.2.3
9. In patients with early RA whose initial DMARD is unsuccessful, is adding an additional DMARD more effective than changing to a different DMARD in symptomatic relief? Consider: laboratory markers of inflammation and radiological outcome, side effects.	6.2.3
10. Is anti-TNF therapy as monotherapy or in combination with disease modifying therapies effective in symptomatic relief in patients with early RA? Consider: laboratory markers of inflammation and radiological outcome, side effects.	6.3
11. In patients with early RA is exercise (weight-bearing and non-weight-bearing) beneficial in improving symptoms and quality of life?	7.2.1

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ISBN 978 1 905813 70 4

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