Early rheumatoid arthritis:
a literature review of recent evidence
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INTRODUCTION

Early inflammatory arthritis can be a self limiting disease, develop into rheumatoid arthritis (RA), or differentiate into another form of chronic arthritis. As is the case for other forms of arthritis, RA is thought to result from the combination of genetic susceptibility and exposure to an appropriate environmental trigger. It is the second most common form of arthritis and the most common autoimmune disease in Australia.[1] It is a chronic, inflammatory joint disease of unknown cause affecting approximately 2.5% of the Australian population, and is associated with substantial disability and economic losses.[2,3] It is more commonly diagnosed in women (57% in Australia).

Rheumatoid arthritis is characterised by persistent joint synovial tissue inflammation.[4,5] Joint damage in RA begins with the proliferation of synovial macrophages and fibroblasts after a triggering incident, possibly autoimmune or infectious.[6] Over time, bone erosion and irreversible joint damage can occur, leading to permanent disability.[7] Although most readily recognised by its articular manifestations, multiple organ systems may be affected and may result in shortened life expectancy, with increased deaths due to cardiovascular disease, infection, and cancer.[6] Systemic features may be associated with a poor prognosis, especially vasculitis, amyloidosis and pulmonary fibrosis.[8]

Early diagnosis and management of RA presents an important opportunity to alter the course of this progressive disease.

Objective

This literature review was conducted on behalf of The Royal Australian College of General Practitioners (RACGP) to inform the development of the evidence based *Clinical guideline for the diagnosis and management of early rheumatoid arthritis* (www.racgp.org.au/guidelines/rheumatoidarthritis) and *Recommendations for the diagnosis and management of early rheumatoid arthritis* (www.racgp.org.au/guidelines/rheumatoidarthritis/recommendations). The literature review cites four international guidelines that were used as the primary reference sources.

The objective of this review is to present the most recent evidence related to the diagnosis and management of RA to inform the development of evidence based recommendations for general practitioners working in the Australian health care setting. The questions of specific interest to this literature review were:

1. What diagnostic tests should be used in the assessment of early arthritis to support early recognition of RA, predict progression of undifferentiated inflammatory arthritis, and predict disease severity in patients 16 years and over?
2. What interventions should be used in primary care in the treatment of undifferentiated inflammatory arthritis and early RA in patients 16 years and over?

Commonly used abbreviations

ANA	antinuclear antibody
ACR	American College of Rheumatology
anti-CCP	anti-cyclic citrullinated peptide (antibody)
BMI	body mass index
BSR	British Society of Rheumatology
CI	confidence interval
CRP	C-reactive protein
DMARD	disease modifying antirheumatic drug
EORA	elderly onset rheumatoid arthritis
EPC	Enhanced Primary Care
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FBC	full blood count
GIT	gastrointestinal tract
GLA	gamma-linolenic acid
GP	general practitioner
HR	hazard ratio
LFT	liver function tests
MA	meta-analysis
MTX	methotrexate
NNH	number needed to harm
NNT	number needed to treat
NHMRC	National Health and Medical Research Council
NSAIDs	non-steroidal anti-inflammatory drugs
OR	odds ratio
OT	occupational therapy
PMR	polymyalgia rheumatica
RA	rheumatoid arthritis
RCT	randomised controlled trial
RhF	rheumatoid factor
RACGP	[The] Royal Australian College of General Practitioners
SMD	standardised mean difference
SIGN	Scottish Intercollegiate Guidelines Network
SR	systematic review
TENS	transcutaneous electrical nerve stimulation
TNF	tumour necrosis factor
WMD	weighted mean difference

METHOD

Selecting primary reference guidelines

This review built on a preliminary literature search, which identified four recent guidelines on which the guideline development was principally based:

- European League Against Rheumatism (EULAR). EULAR recommendations for the management of early arthritis: Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT).[9]

  The EULAR guideline was selected as a primary resource due to its high rigour of development and overall clarity.

- British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology Guideline for the management of rheumatoid arthritis (the first 2 years).[10]

  The BSR guideline was selected because of overall high scoring on the AGREE tool, and specifically for its strong GP focus, making this guideline particularly applicable to this project.

- Scottish Intercollegiate Guidelines Network (SIGN). Management of early rheumatoid arthritis.[3]

  The SIGN guideline was selected because of its high rigour of development, high scores, and overall clarity based on research published up to mid 2000.

- Emery P, Suarez-Almazor M. Rheumatoid arthritis. Clinical Evidence 2003;(9):1349-71.[5]

  Rheumatoid arthritis was selected as a primary source on medications as it provided a comprehensive review of the pharmacological management of RA based on research published up to 2002.

These guidelines were appraised for methodological quality and relevance using an appraisal instrument developed by the Appraisal of Guidelines for Research and Evaluation (AGREE) Collaboration.[11] This instrument consists of 23 appraisal questions covering six domains: scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability, and editorial independence as well as an overall assessment and recommendation regarding the use of the guideline. Reviewers' scores for each domain were used to calculate an overall percentage, indicating how well the paper addressed the considerations in each domain (*Table 1*).

Table 1. AGREE domain scores for selected primary reference guidelines

Guideline	Domain 1. Scope and purpose	Domain 2. Stakeholder involvement	Domain 3. Rigour of development	Domain 4. Clarity and presentation	Domain 5. Applicability	Domain 6. Editorial independence
EULAR, 2006	72%	25%	52%	71%	0%	0%
BSR, 2006	72%	67%	52%	75%	83%	92%
SIGN, 2000	61%	58%	40%	75%	17%	8%
Clinical Evidence, 2003	64%	8%	86%	58%	33%	66%

Each of the above guidelines grades its recommendations according to the volume and quality of evidence. The EULAR[9] and BSR[10] guidelines use the grading described in *Table 2*. The SIGN guideline[3] grades evidence according to the system outlined in *Table 3*.

Table 2. Evidence grading used by EULAR and BSR guidelines[12]

Level of evidence	Type of evidence	Grade of recommendation
Ia	Meta-analysis (MAs) of randomised controlled trials (RCTs)	**A**
Ib	At least one RCT	**A**
IIa	At least one well designed, controlled study, but without randomisation	**B**
IIb	At least one well designed quasi-experimental design	**B**
III	At least one non-experimental descriptive study (eg. comparative, correlation or case study)	**B**
IV	Expert committee reports, opinions and/or experience of respected authorities	**C**

Table 3. Key to evidence statements and grades of recommendations used by SIGN guideline[3]

STATEMENTS OF EVIDENCE

1^{++}	High quality MA, systematic reviews (SRs) of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted MAs, SRs, or RCTs with a low risk of bias
1^{-}	MAs, SRs, or RCTs with a high risk of bias
2^{++}	High quality SRs 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 RECOMMENDATIONS

A	At least one MA, SR, 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

Inclusion/exclusion criteria

Types of studies

For evidence related to the diagnosis and prognosis of RA, only studies comparing a diagnostic or screening test to a validated test or studies, or studies investigating prognostic indicators or SRs of such studies, were considered in the initial search for evidence. Due to the extensive volume of literature related to the management of RA, this literature review was limited to SRs or MAs and evidence based clinical guidelines or recommendations that related to the effectiveness and/or safety of interventions for RA. Studies providing evidence on the efficacy of an intervention compared to placebo, or compared to another intervention, were included.

Levels of evidence

Initial searches failed to identify many articles related to diagnosis of RA. The final search strategy sought to identify diagnostic studies of all levels of evidence. The intervention inclusion criteria limited this review to SRs and MAs, which were ranked as Level I evidence according to the National Health and Medical Research Council's (NHMRC) levels of evidence (*Table 4*).

Table 4. NHMRC levels of evidence[13]

Level	Intervention	Prognostic	Diagnostic
I	Evidence obtained from a SR of all relevant RCTs	A SR of Level II studies	A SR of Level II studies
II	Evidence obtained from at least one properly designed, RCT	A prospective cohort study	A study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation
III–1	Evidence obtained from well designed, pseudo-randomised, controlled trials (alternate allocation or some other method)	All or none All or none of the people with the risk factor(s) experience the outcome	A study of test accuracy with an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation
III–2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group	Analysis of prognostic factors among untreated control patients in a RCT	A comparison with reference standard that does not meet the criteria for Level II and III-1 evidence

III–3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group	A retrospective cohort study	Diagnostic case control study
IV	Evidence obtained from case series, either post-test or pre-test and post-test	Case series, or cohort study of patients at different stages of disease	Study of diagnostic yield (no reference standard)

Types of participants

Participants of interest to this literature review were people aged 16 years or over with a diagnosis of RA or undifferentiated inflammatory arthritis.

Types of interventions

Studies that investigated diagnosis and/or diagnostic tests were of interest to this literature review. Interventions included any therapies used to manage RA. Both pharmacological and non-pharmacological interventions were eligible for inclusion. Systematic reviews of RCTs that compared a single or combination intervention to placebo, sham intervention, no treatment or another active intervention were included.

Search strategy

The literature review was conducted in December 2006. Subsequently, the Working Group identified further research (spanning late 2006 and 2007) that was significant to the development of the guidelines, which have also been included in this review. Examples include: the use of disease modifying antirheumatic drug (DMARD) therapy in undifferentiated inflammatory arthritis; the use of low dose corticosteroids or omega-3 fatty acid supplements; and the cardiovascular effects of the non-steroidal anti-inflammatory drugs (NSAIDs). The Working Group acknowledges that such additional searches have been *ad hoc* and may not completely capture all literature relevant to this guideline. However, full effort has been made to identify and address any significant gaps.

The MEDLINE, EMBASE and CINAHL databases and the Cochrane Library (including CENTRAL Cochrane Controlled Trial Register) were searched to identify studies for inclusion. As this literature review intended to update a previous report, only papers published between January 2005 and December 2006 were included, and inclusion was limited to English language literature. The following search strategies were applied to the MEDLINE database and were adapted to apply to the other databases.

Search for evidence on diagnosis of RA

1. Arthritis, Rheumatoid/bl, cf, di, ra, ri, us [Blood, Synovial Fluid, Diagnosis, Radiography, Radionuclide Imaging, Ultrasonography] (13155)
2. Early Diagnosis/ or Diagnosis/ or Diagnosis, Differential/ (301051)
3. (sensitivity and specificity).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (202073)
4. sensitivity.tw. (302016)
5. specificity.tw. (198517)
6. (pre test or pre-test) adj probability).tw. (157)
7. (pre-test or pretest) adj probability).tw. (576)
8. predictive value$.tw. (12)

9. predictive value$.tw. (36002)
10. likelihood ratio$.tw. (3573)
11. 3 or 4 or 5 or 7 or 9 or 10 (545298)
12. 1 and 2 and 11 (111)
13. limit 12 to (humans and English language and yr='2005 - 2006') (21).

Search for evidence on management of RA

1. Arthritis, Rheumatoid/di, dh, pc, dt, ra, ri, rt, rh, su, th, us [Diagnosis, Diet Therapy, Prevention & Control, Drug Therapy, Radiography, Radionuclide Imaging, Radiotherapy, Rehabilitation, Surgery, Therapy,] (10573)
2. 'Practice Guideline [Publication Type]'/ (8111)
3. 'Review Literature'/or Meta-Analysis/ (6343)
4. 'Guideline [Publication Type]'/ (9399)
5. 2 or 3 or 4 (16730)
6. 1 and 5 (60)
7. limit 6 to (humans and English language and yr='2005 - 2006') (24)
8. from 7 keep 1-18 (18).

Critical appraisal

Critical appraisals were conducted for all studies that met the inclusion criteria, with the exception of Cochrane reviews, for which critical appraisal was not considered to be warranted (NHMRC advisor). Critical appraisals were conducted by two reviewers. Discrepancies in scoring were resolved by discussion until consensus was reached, with a third reviewer resolving minor discrepancies in scoring.

Appraisal of diagnostic studies

Methodological quality of diagnostic and screening tests was assessed using a version of the Cochrane Methods Working Group on Diagnostic and Screening Test modified by the NHMRC.[14] This assessment tool provided a method through which to assess key criteria such as method of patient selection, validity of reference tests, and methods of blinding and measurement. *Appendix 1* provides a tabulated summary of methodological appraisal of included diagnostic studies.

Appraisal of systematic reviews

Systematic reviews and MAs were appraised using a methodological checklist developed by the SIGN.[15] The SIGN checklist assesses description of aims and methodology; rigour of literature search; critical appraisal of included studies; appropriateness of methods of combining evidence; and an overall possibility of review bias, including conflict of interest. For this literature review, SRs and MAs were given a score from 0 to 12 based on the results of the SIGN methodological checklist (sections 1 and 2.1). Papers scored 2 for questions answered 'well addressed', 1 for questions answered 'adequately addressed' and '0' for questions answered as 'poorly addressed' or 'not addressed'. When a question was answered as 'not applicable' this question was removed from the overall score for that review. Throughout this literature review, papers that achieved a SIGN checklist score above 9 are referred to as good quality; those that scored between 5 and 9 are referred to as being of moderate quality; and reviews scoring below 5 are referred to as being of low quality. To achieve a grading of good quality, a review was required to provide a thorough outline of the aims and methods; use an appropriate search technique; include a description of an appropriate critical appraisal process; and pool studies in an appropriate manner. *Appendix 2* provides a tabulated summary of methodological appraisal of included SRs and MAs, together with their quality scores.

Appraisal of other evidence

Retrieved guidelines (other than the primary guidelines) and practice recommendations were appraised for methodological quality and relevance using an appraisal instrument developed by the AGREE Collaboration.[11] Additionally, literature identified in the *ad hoc* search was appraised using the appropriate assessment tool developed by SIGN.[15]

Data extraction

Diagnosis

The primary and secondary reviewers used a tabulated format to extract the relevant data. On combining data from the two reviewers, no discrepancies were found. *Appendix 3* provides a tabulated summary of the findings extracted from each included paper on RA diagnosis.

Management

The primary reviewer used the Joanna Briggs Institute data extraction tool for SRs[16] to extract data from the included studies in a systematic manner. The second reviewer checked and tabulated the data and no discrepancies were found. *Appendix 4* provides a tabulated summary of the findings extracted from each included paper on RA management.

SEARCH RESULTS

A range of evidence was found that addressed the review question regarding diagnosis and/or prediction of early RA in patients aged 16 years or over. There were 22 studies identified in the search for diagnostic evidence, conducted in December 2006. After review of the titles and abstracts by two reviewers, 12 studies were selected as meeting the inclusion criteria. Excluded studies related to diagnostic procedures not available within Australia, protocols for future research, and those related to other forms of arthritis. Five papers retrieved in full were excluded from this literature review because they were covered in other included SRs. Details of excluded studies are outlined in *Appendix 5.* An additional recent MA examining the use of anti-cyclic citrullinated peptide (anti-CCP) antibodies was also included as it was significant to the development of the guidelines.

From 24 studies that were identified in the search for evidence relating to management of RA, 18 studies were selected as meeting the inclusion criteria after review of the title and abstract by two reviewers. Fourteen of these references were SRs or MAs and four were recently published guidelines or recommendations. Following the critical appraisal process, 11 SRs or MAs (of which seven were Cochrane reviews) were included in this literature review. Seven papers retrieved in full were later excluded from this literature review. Three papers were opinion papers and therefore did not meet inclusion criteria, and one paper was a summary of a guideline already reviewed. Three guidelines were not recommended for use due to significant limitations in their methodological development. Details of excluded studies are outlined in *Appendix 5*. A number of more recent studies identified by the Working Group have also been included as they were judged to be significant to the development of the guidelines. This included studies that did not fit the original inclusion criteria (MAs or SRs).

EVIDENCE FOR THE DIAGNOSIS OF RA

Current guidelines[3,9,10] identify and describe the clinical features that support diagnosis of early inflammatory arthritis in terms of joint swelling, pain, stiffness and symmetrical involvement. These, together with the evidence presented in this review, support a recommendation for identifying early RA cases in primary care.

The EULAR[9] and BSR[10] guidelines make brief reference to newer diagnostic/prognostic techniques such as anti-CCP antibody testing, ultrasonography and magnetic resonance imaging (MRI). The EULAR[9] guideline recommends the inclusion of anti-CCP antibody test in the range of tests to

establish risk of persistent and erosive disease. The BSR[10] guideline also identifies the increased sensitivity of ultrasound and MRI in visualising early synovitis and erosions, which may not be evident in clinical examination or on plain radiographs. However, it makes no specific recommendations in this regard. MRI is generally not utilised in Australia for assessment of inflammatory arthritis.

The subsequent literature search has sought to update this data to more specifically inform recommendations for primary care, particularly in relation to recent tests such as anti-CCP antibody tests. No more up-to-date literature was found with respect to other recent diagnostic tools such as MRI and ultrasonography.

Role of anti-cyclic citrullinated antibodies

The search included five studies[17-21] that investigated the role of anti-CCP antibodies in the diagnosis of RA.

A good quality MA[19] of studies conducted between 1987 and September 2006 that involved a total of 30 235 participants compared the accuracy of anti-CCP antibody and rheumatoid factor (RhF) as markers in the diagnosis and prognosis of RA. Of the 302 reports identified, 86 studies (a third of which met more than 70% of the authors' quality criteria) involving the use of anti-CCP antibodies and/or RhF in the diagnosis or prognosis of known or suspected RA were analysed to assess:

- diagnostic accuracy of anti-CCP antibody and RhF
- diagnostic accuracy of anti-CCP1, anti-CCP2, and both anti-CCP antibodies and RhF
- prognostic value of anti-CCP antibody and RhF.

The pooled sensitivities of anti-CCP antibodies and immunoglobulin M (IgM) RhF were similar, being 67% (95% CI: 62–72%) for anti-CCP antibodies and 69% (95% CI: 65–73%) for IgM RhF. Pooled specificity was 95% (95% CI: 94–97%) for anti-CCP antibodies and 85% (95% CI: 82–88%) for IgM RhF. Positive likelihood ratios for anti-CCP antibodies and IgM RhF were 12.32 and 3.86, respectively. Negative likelihood ratios were 0.40 and 0.41, respectively.[19]

In terms of comparison of the diagnostic accuracy of anti-CCP1 and anti-CCP2, 29 studies (11 821 patients) assessed anti-CCP2, and five (2098 patients) assessed anti-CCP1. Anti-CCP2 was found to be a more sensitive marker than anti-CCP1. Summary positive likelihood ratios were 12.77 and 13.03 for anti-CCP1 and anti-CCP2, respectively. The negative likelihood ratios were 0.32 and 0.53, respectively.[19]

In terms of the prognostic value of anti-CCP antibodies and RhF, six studies reported that anti-CCP antibody positivity was a statistically significant risk factor for radiographic progression. Three of four studies found that the risk of radiographic progression was greater with anti-CCP antibody positivity than with IgM RhF positivity. Results of studies involving patients with early RA were similar to those from all studies. Likelihood ratios among IgM RhF, IgG RhF and IgA RhF were similar.[19]

The authors concluded that the presence of anti-CCP antibodies is more specific than RhF for diagnosing RA and early RA. They support inclusion of anti-CCP antibody positivity among the diagnostic criteria for these conditions. The conclusions suggest a role for anti-CCP antibody testing in the standard evaluation of early inflammatory polyarthrtitis to achieve early accurate diagnosis of RA, and in turn support early intervention with DMARD therapy. The authors offer discussion regarding the circumstances under which clinicians should measure anti-CCP antibodies alone or in combination with RhF. They suggest measuring anti-CCP antibodies alone in patients presenting with low probability of disease based on clinical findings to avoid false positives. Based on the increased sensitivity of the combined tests, they suggest measuring anti-

CCP antibodies and RhF in patients with a high probability of disease to avoid missing potentially treatable patients.[19]

A moderate quality SR[17] including literature published between 1999 and February 2006, evaluated the two generations of anti-CCP antibodies RA, both in healthy subjects and in patients with early undifferentiated arthritis. Data was collected on the sensitivity and specificity of the two generations of anti-CCP antibodies for diagnosing RA and predicting future development of the disease. Among 107 studies initially identified, 68 had interpretable data and were analysed. The quality of the studies was not reported.

Diagnostic properties were assessed in 58 studies involving 8206 patients with RA and 7380 controls. Mean sensitivities were 53 % (SD 10, range 41–68) for anti-CCP1; 68% (SD 15, range 39–94) for anti-CCP2; and 60% (range 25–95) for RhF. Mean specificities were 96% (SD 3, range 90–99) for anti-CCP1; 95% (SD 5, range 81–100) for anti-CCP2; and 79% (SD 15, range 31–95) for RhF. The predictive value of anti-CCP antibody testing in early undifferentiated arthritis was assessed in 11 studies involving 2877 patients. The mean odds ratio was 20 (95% CI: 14–31) for anti-CCP1 and 25 (95% CI: 18–35) for anti-CCP2.[17]

Three studies assessed the predictive value of anti-CCP antibody testing in healthy blood donors; however, numbers of subjects were small. The results pointed to a potential role of anti-CCP antibody testing in predicting the onset of RA in healthy subjects who may be at risk of developing RA. The authors also examined the prevalence of anti-CCP1 and anti-CCP2 in other rheumatic diseases, although again, patient numbers were small.[17]

The review confirmed the value of anti-CCP antibodies as a diagnostic and predictive marker of RA. Anti-CCP seems to represent a better serological marker than RhF, both for distinguishing between RA and other rheumatic diseases, and for predicting development of RA in patients with undifferentiated arthritis. The authors identified that anti-CCP antibody sensitivity is higher in established RA than in patients with recent onset RA. While the two generations of anti-CCP antibody tests have similar specificities, the anti-CCP2 test was shown to have a higher sensitivity than anti-CCP1, and therefore seems to have an advantage over anti-CCP1 in this regard.[17]

The authors concluded that consideration should be given to inclusion of anti-CCP antibody testing in the American College of Rheumatology (ACR) classification of RA. They also suggest there may be a role for anti-CCP as a screening test for RA in healthy people at risk (eg. due to genetic factors). The findings point to a potential for use of anti-CCP antibody tests in primary care, in order to support identification of those patients most likely to benefit from early management and referral to a rheumatologist. Cost, availability, and the identification of clear cut-off points to support decision making are issues for consideration.[17]

A small longitudinal study[21] (Level III–3 evidence) investigated the role of anti-CPP antibodies in predicting progression of palindromic rheumatism to RA. Stored sera, taken around the time of presentation from patients with palindromic arthritis, were assessed for anti-CCP antibodies and the results were correlated with subsequent clinical outcome. Twenty-nine of 61 patients had progressed to RA after a mean follow up of 5.4 years; 83% of these had had anti-CCP antibodies in their baseline sera. Sensitivity, specificity and likelihood ratios for anti-CCP antibodies were better than those for RhF in predicting progression of palindromic rheumatism to RA (*Table 5*). The best likelihood ratios were found using a combination requiring both a positive RhF and positive anti-CCP test, rather than either one or the other positive, although this reduced the sensitivity of the tests. A positive anti-CCP test in patients with palindromic rheumatism within the first year of presentation suggested these patients should be warned of the markedly increased likelihood of developing RA. The findings are relevant to establishing the likelihood of progression to RA in early rheumatic disease, and thus are relevant to the role of primary care.[21]

Table 5. Relative values of laboratory tests in predicting progression of palindromic rheumatism to RA[21]

	CCP	Rheumatoid factor	Both positive	Either positive	FANA
Sensitivity	83	67	77	83	70
Specificity	68	61	94	53	47
Positive predictive value	71	60	81	62	48
Negative predictive value	81	61	81	77	68
Positive likelihood ratio	2.6	1.7	4.8	1.8	1.30
Negative likelihood ratio	0.12	0.54	0.27	0.32	0.65

CCP = cyclic citrullinated peptide(antibody); FANA = fluorescent antinuclear antibody test

An observational study[20] (Level III–2 evidence) investigated the role of anti-CPP antibodies in patients with early inflammatory arthritis. One hundred and forty-three RhF negative patients with early inflammatory arthritis were investigated for anti-CCP antibodies, using the enzyme linked immunosorbent assay method (Euroimmune kit). After 3–6 months they were reviewed by a rheumatologist blinded to the results of the anti-CCP test. The sensitivity and specificity of anti-CCP antibody test was estimated in comparison to follow up and final clinical diagnosis. Thirty cases were positive for anti-CCP antibody of which 26 (86.7%) were diagnosed with RA. Overall, 41 cases were finally diagnosed with RA. The sensitivity of anti-CCP antibody testing for the diagnosis of RA in this group of patients was 63.4%, with 36.6% false negatives. The specificity was 96.1%, with 3.9% false positive cases. Both the positive predictive value of anti-CCP antibody and the negative predictive value were 86.7%. Anti-CPP positive patients were found to be 42.5 times more likely to have developed RA after 3–6 months. The study found a sensitivity and specificity of anti-CPP antibody testing for the diagnosis of early RA at a cut-off point of 5 units to be 63.4% and 96.1%, respectively. The authors concluded that the anti-CCP antibody test is a useful and highly specific test to detect RA and supplements RhF in the presence of a strong clinical suspicion.[20]

Another diagnostic study[18] (Level III–3 evidence) investigated the role of anti-CPP antibodies in the differential diagnosis of elderly onset rheumatoid arthritis (EORA) and polymyalgia rheumatica (PMR). There are clinical difficulties in differentiating EORA patients from those with PMR, especially when dealing with EORA-like PMR onset, seronegative EORA, and PMR with peripheral synovitis, which constitute the subgroups presenting the greatest difficulties. Serum samples were obtained from two groups of patients, one with EORA diagnosis (n=16) and another with a PMR diagnosis (n=15). Anti-CCP antibodies and RhF were determined. Of the 16 EORA patients, nine presented with anti-CCP antibodies, four of whom also tested positive for RhF. Of the 12 EORA patients who remained negative to RhF, five were positive for anti-CCP antibodies. Eight of the EORA patients started with polymyalgic symptoms. Three of these patients showed positive titres of anti-CCP antibodies with negative RhF. All 15 PMR patients presented negative anti-CCP antibodies, except one with weak positive titles, and all were negative for RhF. Seven PMR patients presented with oligoarticular synovitis at the onset. After a mean follow up of 3 months, two patients developed RA. When evaluating them for RhF and anti-CCP antibodies, one tested negative, while the other was positive for both antibodies. Using the PMR patients as a negative control group, anti-CCP antibodies showed a sensitivity of 56% and a specificity of 92%. The negative and positive predictive values were 63% and 90%, respectively.[18]

The researchers observed a tendency to higher values of anti-CCP antibodies in patients with extra-articular manifestations, radiological damage, and DMARDs. When compared to the PMR group, EORA patients presented more frequently with positive anti-CCP antibodies at the beginning of the disease to a statistically significant degree. One-third of the seronegative EORA patients presented positive anti-CCP antibodies at the onset. The authors concluded that the presence of anti-CCP in patients presenting with symptoms of PMR must be interpreted as highly suggestive of EORA.[18]

Role of hand radiographs

Radiography has an established role in the diagnosis and assessment of RA in detecting erosions or osteopenia, although erosions are rarely present in disease of less than 3 months duration.

A diagnostic study[22] (Level II–2 evidence) reported the performance of hand radiographs in predicting the diagnosis in patients with early inflammatory arthritis. Specifically, they evaluated the ability of baseline hand radiographs to predict the diagnosis 2 years later in a cohort of patients with early arthritis. The researchers evaluated 258 patients experiencing onset of arthritis within the previous year. All patients underwent a standardised evaluation including laboratory tests and radiographs. Hand radiographs were read by a blinded observer who used a standardised procedure for detecting features of crystal deposition diseases and RA. After 30 months (SD 11.3), the final diagnosis was established by a panel of rheumatologists. All radiographs were evaluated. At the end of follow up, 93 (36%) patients were given a diagnosis of RA.

Hand radiographs were able to predict RA, with sensitivities of 22.5%, a specificity of 87.5%, a negative predictive value of 66%, and a positive predictive value of 50%. The sensitivities of hand radiographs for diagnosing calcium pyrophosphate dihydrate (CPPD) arthritis or hydroxyapatite arthritis were high, ranging from 80–100%. Hand radiographs performed only moderately well for predicting RA at an early stage, which accords with reports that specific radiographic manifestations of RA appear later in the disease. However, the authors identified that hand radiographs may be useful in ruling out other causes of arthritis.[22]

Hand radiographs have a limited role in confirming the diagnosis of early RA. Negative X-rays should not rule out a diagnosis.

Table 6. Performance of baseline hand radiographs in predicting diagnosis established 2 years later[22]

	Diagnosis predicted at baseline based on hand radiographs			
Diagnosis made after 2 years by panel of rheumatologists	Sensitivity %	Specificity %	PPV %	NPV %
RA, chondrocalcinosis, or hydroxyapatite deposition disease	29 (31/108)	85 (119/140)	60 (31/52)	57.7 (119/206)

PPV = positive predictive value; NPV = negative predictive value

Implications for practice

A range of tests have an established role in the diagnosis and differential diagnosis of RA including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), full blood count (FBC), RhF, antinuclear antibody (ANA) and others.

A good quality SR[19] provided evidence to support the role of anti-CCP antibody testing in the diagnosis of early RA and in the prediction of progression to RA in patients with undifferentiated

inflammatory arthritis. The test demonstrated sensitivity similar to RhF, but considerably higher specificity. The anti-CCP test thus has a potential role in patients with a high probability of disease who would most benefit from early referral to a rheumatologist for commencement of DMARD therapy. Evidence supports the use of both RhF and anti-CCP testing as this provides better diagnostic information than either test alone.

Radiography remains a standard investigation for assessing and monitoring arthritis; however, the limitations in sensitivity should be recognised, particularly in early arthritis.

EVIDENCE FOR GENERAL CARE PRINCIPLES IN THE MANAGEMENT OF RA

The objectives of management of early RA include the control of synovitis, symptom control, physical and psychosocial functioning, and management/monitoring for complications associated with therapy and the disease. The four primary reference guidelines[3,5,9,10] used in this project address a range of management approaches in relation to early RA, including traditional pharmacological management, complementary medicines, exercise, other non-pharmacological therapies, and patient education. This review provides an update on the evidence included in those guidelines.

Multidisciplinary care and care planning

There is strong support from the existing guidelines[3,10] that the successful timely management of patients with RA depends on involvement of a range of health care professionals according to the individual patient's need. These health care professionals include, but are not limited to, GPs, rheumatologists, physiotherapists, occupational therapists, pharmacists, psychologists, dieticians and social workers.

The BSR guideline[10] emphasises the importance of ongoing involvement of both primary and secondary care in the long term management of patients with RA, particularly in view of the multisystem involvement of RA as the disease progresses. The guideline recommends primary care physicians remain closely involved in the care of these patients and be responsible for their general health, particularly with regard to cardiovascular risk. The role of the primary care physician also includes encouraging patients to exert more control over their disease and disease management (grade of recommendation B).

No further recent evidence regarding the involvement of the multidisciplinary team and care planning met inclusion criteria for this review.

Patient information and education

The EULAR, BSR and SIGN guidelines[3,9,10] identify patient information and education as important for arthritis patients. Information and education should aim to assist the patient in coping with pain and disability and encourage self management and problem solving (grade of recommendation B).[9,10]

The guidelines cite evidence of benefit for educational interventions, including intervention in early disease. The BSR[10] guideline cites a Cochrane review by Riemsma et al[23] which assessed the effectiveness of patient education interventions on health status (eg. pain, functional disability, psychological wellbeing and disease activity). They included 31 RCTs studies with relevant data and found that patient education had significant effects at first follow up for scores on disability, joint counts, patient global assessment, psychological status, and depression. A trend favouring patient education was found for scores on pain. Physician global assessment was not assessed in any of the included studies. The dimensions of anxiety and disease activity showed no significant effects. At final follow up (3–14 months), no significant effects of patient education were found,

although there was a trend favouring patient education for scores on disability. The BSR guideline[10] states that such programs can be effective, but it is important that they are ongoing and delivered at various times during the course of the disease. The BSR also recommends that education is offered early in the disease and tailored to individual need (grade of recommendation A). It identifies psychological issues as likely to be important in determining how receptive patients are to education opportunities about their disease and thus recommends a cognitive approach (grade of recommendation C).

The EULAR[9] guideline cites three RCTs which demonstrated that written information may increase knowledge about the disease. The guideline also cites one SR, four RCTs, and two controlled trials that showed self management programs result in improved short term clinical outcomes in patients with RA, but had no significant long term effects.

The BSR[10] guideline recommends that patients with RA should be helped to contact support organisations (grade of recommendation B). The SIGN[3] guideline also identifies the need to ensure consistency of health messages across the multidisciplinary team.

No further recent evidence specific to RA and meeting review criteria was found regarding patient information and education.

Psychosocial support

Given the potential for disability and reduction in quality of life, psychological and social support is considered an important aspect of the assessment and management of RA. Such support is required early in the disease in terms of coping with the diagnosis, and throughout disease progression as the impact of the disease becomes more evident. A considerable body of literature relating to chronic disease in general is relevant to this area but has not been reviewed in this literature review.

The BSR[10] guideline identifies a shared role for all members of the multidisciplinary team in providing guidance on coping with the disease and encouraging positive attitudes toward self management and adjustment to the diagnosis of RA. It recommends that individuals should have social and psychological support to help them to stay at work and participate in normal activities of living. This may be accessed through a range of means, including patient based support agencies. The BSR guideline[10] identifies evidence (although not high levels of evidence) of the effectiveness of support initiatives such as telephone help lines and the involvement of rheumatology nurses.

The BSR guideline[10] also makes a specific recommendation regarding the need to address sexuality and relationship issues with patients, identifying that health care professionals should provide opportunities to discuss these issues and refer patients for appropriate support (grade of recommendation C). Health professionals should be alert to issues such as the impact of pain, dysfunction, and dependence on relationships and self esteem.

Sleep patterns and fatigue

The BSR guideline[10] identifies sleep disturbance as a common feature of RA, particularly during disease flares. Fatigue is also found to be a significant problem.

The BSR recommends that the sleep patterns of patients with RA should be specifically assessed (grade of recommendation A). Early management of sleep disturbance may include tricyclic agents, behavioural therapy, and the use of exercise (grade of recommendation B). The guideline also recommends that health providers give consideration to the impact of fatigue on the quality of life in early RA. It cites a survey in which 40% of patients reported severe fatigue.

Disease monitoring and comorbidities

The EULAR[9] guideline includes a recommendation relating to disease activity monitoring, including tender and swollen joint count, patient and physician global assessments, monitoring of structural damage (eg. ESR, CRP, X-rays), and functional assessment (grade of recommendation A). The EULAR recommendation[9] is based on a number of RCTs, which showed significant improvement related to intensive treatment and monitoring strategy. Specific guidance regarding the role of the GP in monitoring is not included.

The BSR[10] guideline identifies a role for primary care in monitoring later complications of RA, but specific recommendations are not made in this regard. Such complications are beyond the scope of this literature review, which addresses management in the first 2 years only.

The BSR guideline[10] also addresses the specific management/monitoring of cardiovascular risk for RA patients. It recommends that, in light of the fact that RA is an independent risk factor for ischaemic heart disease, patients should be screened for cardiovascular risk factors. These factors should be actively addressed by primary care services. The guideline recommends that lifestyle advice should be given to all patients with RA to encourage smoking cessation, dietary modification, weight control and exercise. In addition, regular blood pressure monitoring and treatment of hypertension, diabetes screening and treatment, and screening and treatment of hyperlipidaemia are advised (grade of recommendation B).

No further evidence was found in relation to the role of the GP in monitoring RA and comorbidities.

EVIDENCE FOR PHARMACOLOGICAL INTERVENTIONS FOR THE MANAGEMENT OF RA

Simple analgesics

There is an accepted role for simple analgesics in managing pain in early RA, although the evidence supporting effectiveness is old and contains methodological flaws.[3,9,10] Furthermore, only a small number of patients with RA receive sufficient pain relief from simple analgesia alone.

Substantial evidence, including a Cochrane review in established RA (but not in early RA) indicates that both conventional NSAIDs and COX-2 inhibitors are more effective than simple analgesics in relieving the signs and symptoms of active disease.[3,9,10] However, this must be balanced against the potential gastrointestinal, renal, and cardiovascular side effects of NSAIDs and COX-2 inhibitors (see Section 3).

No further recent evidence was found regarding the use of simple analgesics for RA.

Fatty acid supplements

The EULAR[9] and BSR[10] guidelines do not make specific reference to omega-3 supplements. The SIGN[3] guideline identifies a benefit (based on a MA) in terms of a reduction in tender joints and duration of morning stiffness.

Recent evidence provides further support for the role of omega-3 fatty acids in the management of RA. A good quality MA[24] of the analgesic effects of omega-3 polyunsaturated fatty acids provided evidence for a role of this supplement in pain management in RA. Seventeen RCTs involving 823 patients were included. A MA of 16 of the studies at 3–4 months showed significant effects for four out of 6 pain outcome measures, including patient assessed pain (SMD -0.26, 95% CI: -0.49 to -0.03); morning stiffness (SMD -0.43, 95% CI: -0.72 to -0.15; p=0.003); number of painful and/or tender joints (SMD -0.29, 95% CI: -0.48 to -0.10; p=0.003); and NSAID consumption (SMD -0.40, 95% CI: -0.72 to -0.08; p=0.01). In contrast, significant effects were not detected for physician

assessed pain (SMD -0.14, 95% CI: -0.49 to 0.22; *p*=0.45) and the Ritchie articular index (SMD 0.15, 95% CI: -0.19 to 0.49; *p*=0.40). Eleven of the 16 studies used high doses (above 2.7 g omega-3 per day). Significant improvements were noted in patient assessed pain and morning stiffness among studies providing high dose, but not low dose omega-3. The results suggest a potential role for omega-3 supplements as adjunctive treatment for the pain and stiffness associated with RA. The results differ from previous MAs, showing a stronger effect than reported by Fortin et al[25] and a beneficial effect for patient assessed pain versus the lack of effect reported by Maclean et al.[26] The authors attribute the differences to the different outcomes measured, and to the inclusion of results from eight additional trials.[24]

In relation to the omega-6 supplement gamma-linolenic acid (GLA), The BSR[10] guideline cites a Cochrane review[27] in which the effectiveness of various complementary and alternative medicines in the treatment of RA was investigated. Of the 11 RCTs included seven compared GLA to placebo. All of these studies found some improvement in clinical outcomes. However, drawing conclusive results from these studies proved to be difficult due to the varied methodologies used and the quality of the studies. The better quality studies suggest potential relief of pain, morning stiffness and joint tenderness. Further studies are required to establish optimum dosage and duration of treatment. The BSR concludes that studies of GLA in the treatment of RA are promising and suggest that GLA may provide supplementary or alternative treatment to NSAIDs for some patients.

Traditional NSAIDs and COX-2 inhibitors

The primary guidelines[3,9,10] accept the role of NSAIDs and COX-2 inhibitors in managing symptoms in early RA, citing substantial evidence for their effect in relieving the signs and symptoms of active disease. The guidelines recommend caution in relation to the well established adverse effects of these drugs, including gastrointestinal tract (GIT), cardiovascular and renal effects. People at high risk should avoid NSAIDs and COX-2 inhibitors if possible (grade of recommendation B[10]).

Studies cited by the guidelines suggest that the risk of cardiovascular and GIT events is associated with the dose and duration of NSAID use. Thus, the guidelines advise the use of the lowest possible dose compatible with symptom relief (grade of recommendation A[10]; grade of recommendation B[3]). The guidelines further advise reduction or cessation of the dose once a good response from DMARD therapy has been achieved (grade of recommendation B[3]).

A poor quality MA[28] provides further evidence of the cardiovascular effects of NSAIDs. This MA included 138 RCTs (total of 145 373 participants) and investigated the safety of various selective COX-2 inhibitors (rofecoxib, eteriocoxib, lumiracoxib, celecoxib, valdecoxib) compared with a traditional NSAID or placebo. Among trials comparing the selective COX-2 inhibitors with placebo (n=121), allocation to a selective COX-2 inhibitor was associated with a 42% relative increase in the incidence of serious vascular events (1.2 vs. 0.9%/year; rate ratio 1.42; 95% CI: 1.13–1.78; *p*=0.003) with no significant heterogeneity among the different selective COX-2 inhibitors. This was mainly attributable to an increased risk of myocardial infarction (MI) by almost twofold (0.6 vs. 0.3%/year; rate ratio 1.86; 95% CI: 1.33–2.59; *p*=0.0003). There was no heterogeneity in the rate ratio for MI among individual selective COX-2 inhibitors. There was no significant difference in the incidence of a serious vascular event between groups in the overall analysis (1.0 vs. 0.9%/year; rate ratio 1.16; 95% CI: 0.97–1.38; *p*=0.10). However, there was a statistical heterogeneity between the trials of all selective COX-2 inhibitors investigated and naproxen. Overall, compared with naproxen, allocation to a selective COX-2 inhibitor was associated with a highly significant increase in the incidence of vascular events (rate ratio 1.57; 95% CI: 1.21–2.03; *p*=0.001), and a twofold increase in the risk of MI (rate ratio 2.04; 95% CI: 1.41–2.96; *p*=0.0002). Compared to non-naproxen NSAIDs versus investigated selective COX-2 inhibitor, there was no significant difference in the incidence of vascular events (rate ratio 0.88; 95% CI: 0.69–1.12; *p*=0.30). The rate ratio for vascular events for NSAIDs compared with placebo was 0.92 (95% CI: 0.67–1.26) for naproxen, 1.51 (95% CI: 0.96–2.37) for ibuprofen and 1.63 (95% CI: 1.21–2.37) for diclofenac.[28]

In consideration of GIT risk, the guidelines[3,9,10] advise prescription of gastro-protective agents (grade of recommendation B[3]) or use of selective COX-2 inhibitors. Additional evidence was provided by a good quality SR[29] that investigated the efficacy, tolerability and upper GIT safety of celecoxib (a selective COX-2 inhibitor) compared with placebo and other NSAIDs. Efficacy data was based on three RCTs of celecoxib in RA, and safety data was based on nine RCTs of celecoxib in RA. The review found that celecoxib was as effective as other NSAIDs in achieving an ACR 20 response and a reduction in painful and swollen joints when it was taken at the standard dose for up to 12 weeks by patients with active RA. Patients taking celecoxib were more likely to withdraw due to an adverse event, or specifically for a GIT adverse event, than those taking placebo. However, celecoxib had a more favourable tolerability profile than other NSAIDs. The rate of withdrawals due to adverse GIT events was 46% lower in celecoxib treated patients compared with those taking other NSAIDs at 3 months (95% CI: 29–58%; NNT 6). The incidence of ulcers detectable by endoscopy was 71% lower at 3 months (95% CI: 59–79%; NNT 6), and the incidence of symptoms of ulcers, perforations, bleeds and obstruction was 39% lower at 6 months (95% CI: 4–61%; NNT 208). There was insufficient evidence on the safety and efficacy of this medication beyond 12 weeks.[29]

Disease modifying antirheumatic drugs

Early commencement

The primary guidelines[3,5,9,10] support DMARD therapy as the mainstay of early intervention in RA and recommend commencement of DMARD therapy as soon as possible after diagnosis (grade of recommendation A[9]; B[3,10]). The guidelines support the concept of a 'window of opportunity' for effective treatment, which may be as short as 3–4 months.[10] The EULAR guideline[9] supports initiation of treatment in patients at risk of developing persistent and/or erosive arthritis, even if they do not fulfil established classification criteria for inflammatory rheumatological diseases (grade of recommendation A).

There is further recent evidence for commencement of DMARDs before confirmation of diagnosis in some patients. Results of a good quality RCT[30] provide evidence for a potential role for DMARDs in undifferentiated arthritis, in terms of postponing progression to RA and retarding radiographic joint damage. The authors compared methotrexate (MTX) treatment for 1 year with placebo in a double blind RCT. The delay in development of RA was seen particularly in anti-CCP antibody-positive patients. This result points to a possible role of early DMARD therapy in this group of patients who are considered to be at high risk of developing RA and in whom the risk of side effects may outweigh the benefits of treatment. Further research is required to confirm the results and to determine appropriate doses and duration of treatment.

Choice of a DMARD

Existing guidelines[3,5,9,10] identify clear evidence for the disease modifying effects of DMARDs including MTX, sulfasalazine, leflunomide, and intramuscular gold. They also indicate less compelling evidence, in terms of effect on reduction of erosions, for hydroxychloroquine, penicillamine, oral gold, cyclosporine and azathioprine.

The basis for first agent selection is the risk-benefit ratio. The SIGN guideline[3] provides a table of benefits and risks of various DMARDs to assist in selection. The EULAR and BSR guidelines[9,10] support MTX as a first line choice, particularly when the disease is judged to be moderate to severe or where there is a high risk of erosive disease (grade of recommendation A[9]; B[10]).

The EULAR guideline[9] identifies MTX as the 'anchor' drug that should be used first in patients at risk of developing persistent disease. This recommendation is based on a MA of studies conducted in patients with established RA. The MA showed a significantly lower discontinuation rate for MTX compared with other DMARDs (leflunomide and tumour necrosis factor [TNF] blockers were not evaluated). The recommendation is supported by several RCTs, which demonstrate the efficacy of MTX as well as a safer toxicity profile. In addition, the evidence base for MTX combined with

biological treatments leading to greater efficacy is well established. The EULAR guideline[9] recommends leflunomide, and to a lesser extent sulphasalazine, as the best alternatives when MTX may be contraindicated (grade of recommendation A).

The SIGN guideline[3] also identifies sulphasalazine and MTX as current DMARDs of choice due to their more favourable efficacy-toxicity profile. The BSR guideline[10] notes that MTX has displaced sulfasalazine as the most commonly used agent in the United Kingdom, based on evidence of long term safety and efficacy.

Combined therapies

Combinations of DMARDs are increasingly used to treat RA. Three of the base guidelines[5,9,10] cite a high level of evidence, including RCTs and a SR, for the greater benefit of combination therapy over monotherapy, particularly in patients with severe disease (grade of recommendation A[9]; grade of recommendation B[10]). The SIGN guideline[3] identifies insufficient evidence to support combination therapy in early RA (grade of recommendation B).

A good quality SR[31] provides additional evidence that combination DMARD therapy is more effective than monotherapy in RA. The review included papers published from 1975 to April 2004. Assessment criteria were based on whether the treatments were stopped because of lack of efficacy or because of adverse effects. The SR included 36 RCTs of DMARD therapy involving 1867 patients; nine RCTs with 548 patients in early RA; and 27 RCTs with 1319 patients in established RA. Twenty-five trials had a Jadad score of 3 or above. The analysis found that combination DMARD therapy has a reduced risk of withdrawals due to lack of efficacy (75%) compared with monotherapy, both overall and in step-up, parallel and step-down studies. This is balanced against an increased risk of withdrawals (37%) due to adverse effects. The benefits of combination therapy were evident for patients with an early diagnosis as well as those with established disease. The authors noted concurrence of their findings with three previous SRs, which all reported strong evidence for combining MTX with sulfasalazine and/or hydroxychloroquine in established RA. The MA also identified MTX and TNF inhibitors as an effective combination. The authors concluded that combination therapy should be considered for most patients early in the disease process.[31]

Biological DMARDs

There are a number of biological therapies now available in Australia, including TNF inhibitors (infliximab, etanercept and adalimumab); the interleukin 1 inhibitor, anakinra; and, most recently, the B-cell active biological, rituximab. These agents may only be prescribed by rheumatologists; thus the relevance to primary care is limited, other than for GPs to gain a broad understanding of the treatment options and the toxicity profile of these agents so they may be alert to signs and symptoms emerging in their patients. General practitioners need to be familiar with the side effects and implications of the use of these medications (and any advanced therapy) as they will be involved in ongoing monitoring as part of the multidisciplinary team activities.

The BSR[10] guideline cites the known increased risks of bacterial infection, tuberculosis and the induction of other autoimmune disease with these agents. It also identifies the potential for an increased risk of malignancies, including lymphoma. While the issue of increased cancer risk remains unresolved in light of rapidly changing information, concerns about toxicity are reflected in a good quality SR[32] of nine RCTs investigating the safety of the TNF inhibitors, infliximab or adalimumab, used for at least 12 weeks. The review assessed the extent to which anti-TNF therapies may increase the risk of serious infections and malignancies. The pooled odds ratio for malignancy was 3.3 (95% CI: 1.2–9.1), and for serious infection was 2.0 (95% CI: 1.3–3.1). This review provides evidence that anti-TNF antibody therapy for 6–12 months is related to an increased risk of serious infections and malignancies in patients with active RA. Malignancies were significantly more common in patients treated with higher doses. However, the review did not show an accumulation of malignancies with longer study duration. The authors concluded that these risks should be considered alongside the efficacy of anti-TNF therapy in patients with RA and the

limited therapeutic alternatives available for patients with active disease that is unresponsive to traditional DMARD therapy. Risks and benefits of this treatment must be considered for each individual.

Recent studies confirm the increased infection risks. Navarro-Sarabia et al[33] conducted a review of six RCTs investigating adalimumab alone or in combination with MTX. Patients taking adalimumab and MTX had a higher rate of serious infections (3.81%) compared with those taking MTX and placebo (0.5%; NNH=30).

A good quality SR investigating anakinra[34] found no significant increase in adverse effects compared with control groups. However, while the overall incidence of serious adverse effects was not significant, one of the RCTs involving 1414 patients did find that serious infections were more common in the group treated with anakinra (2.1 vs. 0.4%). The most common serious infections seen with anakinra were pneumonia (10 patients), cellulites (three patients) and osteomyelitis (three patients). A good quality SR[35] found no significant increase in serious adverse effects with infliximab or etanercept compared with control groups over 12 months.

Corticosteroids

Corticosteroids are used in RA for symptom control (reducing pain and swelling) and for their potential disease modifying action. The potential long term adverse effects need to be considered.

Systemic corticosteroids

Three of the four primary guidelines[5,9,10] recommend that systemic corticosteroids should be considered as short term therapy as part of a DMARD strategy (grade of recommendation A[9]; B[10]). The BSR[10] guideline specifically recommends that systemic steroid therapy may have an important early role in establishing control of synovitis or bridging disease control between different DMARD therapies (grade of recommendation B). The SIGN guideline[3] recommends that oral corticosteroids should not be used routinely due to the risk of toxicity (grade of recommendation B).

Recent evidence supports the use of short term, low dose corticosteroids as described below.

Symptom control

A Cochrane review,[36] which included 10 studies involving 320 patients, compared short term, oral, low doses (equivalent to 15 mg or less of prednisolone per day) with placebo or NSAIDs in RA. Prednisolone had a marked effect on joint tenderness compared to placebo (SMD 1.30; 95% CI: 0.7–1.83), as well as on pain (SMD1.75, 95% CI: 0.87–2.64) and grip strength (SMD 0.41, 95% CI: 0.13–0.69). Prednisolone also had a significantly greater effect than NSAIDs on joint tenderness (SMD 0.63, 95% CI: 0.11–1.16) and pain (SMD 1.25, 95% CI: 0.26–2.24). There was no significant difference between improvements in grip strength for the prednisolone and NSAID groups. Adverse effects were not well described. The authors concluded that prednisolone (<15 mg/day) may be used intermittently in patients with RA, particularly if the disease cannot be controlled by other means.[36]

Disease modification

Another Cochrane review[37] reported on the efficacy of corticosteroids in inhibiting the progression of radiological damage in adults with RA. The review included 15 RCTs using various daily and cumulative doses of oral corticosteroid and with a therapy duration ranging from 6 months to 2 years. Most of the studies were in patients with early RA and most participants were also prescribed DMARDs. Patients treated with corticosteroids had substantially less joint damage at 1–2 years follow up. The proportion of benefit gained in reducing the progression of erosions from an average of all studies was 67.2% over a 1 year period and 61.3% over 2 years. This benefit was over and above any benefit from DMARDs. The radiological benefit was demonstrated with all treatment combinations. The reviewers concluded that, for patients with active arthritis of less than 2 years duration who require treatment with DMARDs, there would be substantial reduction in joint

destruction with the addition of a suitable low dose or step-down corticosteroid regimen. The harmful events of treatment was not reported in this review.[37]

Intra-articular corticosteroid injections

There are few controlled trials on intra-articular steroid injections in RA, although this treatment is widely accepted for the short term relief of pain and swelling. Large cohort trials suggest that complications such as joint sepsis are rare, and that aspiration of synovial fluid at the time of joint injection reduces relapse rate. There is no evidence of the long term effect on radiological progression or disability for intra-articular steroids.

The EULAR guideline[9] recommends that intra-articular corticosteroid injections may be considered for the relief of local symptoms of inflammation (grade of recommendation A). The other primary guidelines do not provide specific recommendations in this regard.

Other complementary and alternative medicines

Other than the evidence relating to fatty acid supplements (see above), there is limited evidence of the effect of complementary/alternative medicines in RA. The primary guidelines report that studies are few and are generally of poor quality.[3 9,10]

Recent evidence includes a good quality SR[38] that investigated the effect and tolerability of Ayurvedic medicines on symptoms including pain, morning stiffness, joint swelling and general health questionnaire. Of the seven RCTs reviewed, only one was of good quality. This RCT showed Ayurvedic medicines had no effect above placebo in improving symptoms in patients who have had RA for at least 6 months. Minor adverse events were reported (rate not determinable).

A good quality SR[39] investigated the efficacy and safety of *Tripterygium wilfordii*, a Chinese herb with immunosuppressive effects and an established history of use in the treatment of RA. Based on findings from two RCTs of moderate to good quality, the authors concluded that *T. wilfordii* extract was effective in improving symptoms and functional outcomes in RA patients with active symptoms. However, it was associated with significantly higher rates of serious adverse events than placebo and its use could not be recommended.

There continues to be a need for more high quality research into the efficacy and safety of complementary medicines in RA.

EVIDENCE FOR NON-PHARMACOLOGICAL INTERVENTIONS FOR THE MANAGEMENT OF RA

Weight control

The SIGN guideline[3] highlights the importance of maintaining a health weight and body mass index (BMI) in the general management of patients with RA. Weight reduction in RA patients who are overweight or obese reduces the impact on weight bearing joints and reduces risk factors for cardiovascular disease. This guideline also cites several studies that suggest RA patients with a BMI below the healthy range have poorer functional status.[3] This highlights the importance of maintaining a BMI within the normal range. The EULAR and BSR[10] guidelines also identify weight control as an important aspect of general disease management.

There have been insufficient studies on the effectiveness of specific diets in managing RA, and studies that have investigated diet have not reported BMI as an outcome measure. The SIGN[3] and EULAR[9] guidelines report that small RCTs investigating a range of diets, including gluten free, vegetarian, vegan and fasting diets, found evidence of significant effect on the ACR 20 response and pain in patients with RA. However, long term compliance and nutritional deficiencies reduced the acceptability and practicality of many dietary interventions.

Exercise

Exercise therapy is well accepted as having a role in combating the adverse effects of RA on muscle strength, endurance and aerobic capacity. The effect of exercise has not been investigated in early inflammatory or RA and can only be extrapolated from results in established disease.

In recommending such interventions as treatment adjuncts in early arthritis (grade of recommendation B), the EULAR guideline[9] cites a number of RCTs and Cochrane reviews in support of dynamic exercise and hydrotherapy. The effect is generally on improved strength and physical functioning, but may also have symptom relieving effects.

Based on a Cochrane review,[40] the SIGN guideline[3] also identifies that dynamic exercise therapy (ie. exercises of low to moderate aerobic intensity) is effective in increasing aerobic capacity and muscle strength, with no adverse effects on disease activity or pain observed. A recent SR[41] draws on this Cochrane review,[40] but concludes that there is insufficient evidence to support or refute the effectiveness of exercise therapy for patients with RA.

The BSR guideline[10] recommends aerobic exercise should be encouraged while being mindful of minimising short term exacerbation of disease or joint destruction (grade of recommendation B). The guideline cites two recent studies including one RCT that show exercise can be undertaken without exacerbation of disease in the short term. Long term effects are still not known.

Some studies have looked specifically at tai chi and its role in RA. A Cochrane review[42] examined four trials involving 206 participants. The comparative studies measured improvements in ambulatory adults suffering from RA who participated in 8–10 week tai chi programs. In three studies, tai chi had no clinically important or statistically significant effect on most outcomes of disease activity, including activities of daily living, tender and swollen joints, and patient global overall rating. In one small study, the most notable results were a significantly increased range of motion in the ankle, hip and knee, and an increased enjoyment of exercise. No detrimental effects were reported. Preserving range of motion in affected joints is particularly important for RA sufferers to maintain functionality.

Despite some conflicting conclusions from a number of reviews, there is adequate evidence to support inclusion of exercise therapy as an adjunct to pharmaceutical therapy in patients with early RA. Specific exercise programs such as tai chi may be of benefit in terms of helping to maintain the range of joint movement.

Occupational therapy

The primary guidelines[3,9,10] support the role of occupational therapy (OT) in maintaining function for patients with RA while accepting there is an absence of evidence from RCTs. Occupational therapy interventions include motor function, skills training, instruction on joint protection and energy conservation, counselling, instruction about assistive devices, and provision of splints.

The SIGN[3] guidelines recommend that skilled OT should be available to those experiencing limitation in function (grade of recommendation C). The BSR[10] guideline also recommends that joint protection, energy conservation and problem solving skills should be taught early in the course of the disease (grade of recommendation B). It also specifically recommends a continuing OT role in maintaining hand function, utilising devices for assisting hand function, and with aiding alternative work methods (grade of recommendation C).

A moderate quality SR[43] identified three SRs of OT interventions in RA. The review concluded that OT improved functional ability in RA patients. However, its effect on other outcome measures was unclear.

Foot care

The value of appropriate foot care for RA is well recognised in practice but there is little evidence based research to support recommendations. Both the SIGN[3] and BSR[10] guidelines identify podiatry input and appropriate foot orthoses as important and effective interventions in RA (grade of recommendation B[10]).

No further evidence on foot care in RA was found.

Complementary and alternative physical therapies

Numerous other non-pharmacological interventions have been investigated for the management of RA. The EULAR guideline[9] describes a number of these, including acupuncture, laser therapy, compression gloves, transcutaneous electrical nerve stimulation (TENS), ultrasound, thermotherapy, and splints and orthoses. Given the lack of evidence, the EULAR guideline recommends that such interventions only be applied as adjuncts to pharmaceutical therapies in patients with early arthritis (grade of recommendation B[9]).

The BSR guideline[10] also refers to a range of alternative physical therapies, including massage and the Alexander technique. While some studies report short term pain relief for some of these interventions, there is no evidence for long lasting benefits; thus recommendations are for use of such interventions only as adjuncts to pharmaceutical therapies (grade of recommendation B[10]). This approach is also supported by the SIGN[3] guideline. The BSR guideline[10] concludes that, while evidence of benefit of such therapies including massage and aromatherapy is limited, some may help alleviate symptoms as well as improve sense of wellbeing. They can also play a role in encouraging positive changes in lifestyle and outlook.

More recent studies not included in the above mentioned guidelines do not alter this general recommendation. One Cochrane review[44] of five small RCTs (less than 50 participants) found 'silver level evidence' (grading system from Cochrane Musculoskeletal Group) that lower level laser therapy (LLLT) for up to 4 weeks has a clinically relevant effect in reducing pain and morning stiffness in patients with RA of the hand. However, it does not appear to have long lasting effects. There appears to be no significant difference between dosage, wavelength, and method of delivery.

A Cochrane review[45] evaluated the effectiveness of thermotherapy on objective and subjective measures of disease activity in RA. Seven studies in 328 participants were included. The review found no significant effect on objective measures (joint swelling, pain, pain medication intake, range of motion, grip strength or hand function) for hot or cold pack application, cryotherapy or faradic baths. There was also no difference in patient preference and no harmful effects were reported. The review concluded that thermotherapy may be used as palliative therapy.[45]

Another Cochrane review[46] sought to establish the effect of acupuncture and electro-acupuncture as adjunct therapy for the symptomatic treatment of RA. Two studies involving a total of 84 people were included; one used acupuncture while the other used electro-acupuncture. In the acupuncture study, there was no statistically significant improvement relative to non-treatment for ESR, CRP, patient global assessment on visual analogue scale, number of swollen joints and tender joints, general health questionnaire, modified disease activity scale, or for a decrease in analgesic intake. Pain in the treatment group improved more than in the placebo group, but the difference was not statistically significant. In the electro-acupuncture study, a significant decrease in knee pain was reported 24 hours post-treatment in the experimental group compared with the placebo group. A significant decrease was also found also at 4 months post-treatment. However, the trial was of poor quality and involved only a small number of patients. The reviewers concluded that, based on limited evidence, acupuncture does not appear to improve the symptoms of RA.[46]

DISCUSSION

Limitations of the literature review

Search limitations

The literature review builds on four existing international guidelines[3,5,9,10] and presents the best evidence available up to December 2006. The search strategy did not include a search for grey literature, for example conference proceedings, therefore publication bias may have occurred. However, experts in the field informed the methods of this review and identified any known recent research.

Interventions and studies included

Evidence on management of RA was restricted to NHMRC Level 1 evidence. The majority of SRs, Cochrane reviews and MAs included in this report restricted inclusion criteria to SRs and RCTs. Many additional interventions may have only been investigated in study designs that meet criteria for lower levels of evidence (eg. cohort studies, case control, observational) and therefore have not been considered for this literature review.

Some of the pharmacological studies included in this literature review (as well as RCTs reported in included SRs) were conducted or sponsored by pharmaceutical companies with interests in the intervention medication. This factor was considered in the critical appraisal process; however, potential bias in results cannot be excluded.

Implications for practice and research

The recommendations presented in the previously published guidelines[3,5,9,10] are generally supported by the most recent evidence available on the management of early RA. The recent evidence provides additional clarity around a number of issues relevant to primary care physicians.

The importance of early referral to specialist rheumatology services is highlighted by recent evidence of the positive effect of initiation of DMARD therapy in undifferentiated inflammatory arthritis, and the benefits of combination DMARD therapy in early disease. Recent evidence also highlights the potential toxicity associated with biological DMARDs to which GPs should be alert when taking a co-ordinating role in the care of patients with RA.

Of more direct relevance to primary care physicians is evidence relating to symptomatic management, including the use of NSAIDs and other pharmacological and non-pharmacological treatments. Recent evidence supports the established cautionary use of NSAIDs and COX-2 inhibitors, particularly with respect to GIT and cardiovascular toxicity.

Evidence of the benefit of high doses omega-3 in treating the symptoms of RA provides an alternative management strategy for patients in whom NSAIDs are contraindicated or who are at high risk of NSAID related adverse events.

Recent evidence, including two Cochrane reviews, supports a role for intermittent, low dose, systemic corticosteroids, particularly for bridging DMARD therapy in patients who have not responded to other therapy. While these reviews did not report on side effects, this remains a primary concern for long term therapy. The major risks appear to be a doubling of the already increased risk of osteoporosis; an increase in blood glucose, which is dependent on the dose and type of corticosteroid used; fat redistribution; and an increase in body weight.

A commentary[47] identifies that there are still many unanswered questions about the use of low dose corticosteroids in RA, including the optimal dose and duration of treatment, and the true risks of adverse effects over the longer term. People with RA are already at an increased risk of cardiovascular disease and osteoporosis as a result of their disease. If oral corticosteroids are to be used, other drugs that increase steroid induced GIT and cardiovascular toxicity such as NSAIDs

should be avoided. The difficulties in being able to withdraw even low dose corticosteroids in routine clinical practice, and the concomitant risks associated with longer than planned use, should not be underestimated. Furthermore, their value in long standing RA is unknown and benefits need to be carefully weighed against the potential for harm in patients with, or at risk for, obesity, osteoporosis, diabetes, hypertension, glaucoma and heart disease. In view of the many unresolved issues, the authors conclude that the use of low dose oral corticosteroids should be reserved for patients with severe active RA and restricted to short term use. The authors strongly advise consultation with a rheumatologist before commencement of oral corticosteroids.[47]

There is a lack of new evidence to further guide recommendations in relation to the role of exercise and OT interventions. However, these remain important aspects of the overall approach to management of RA.

In relation to other complementary medicinal therapies (aside from high dose omega-3 supplements) there is limited new evidence to guide recommendations. There is some evidence that GLA may be a useful adjunct to treatment for some patients. The study of the herbal remedy, *Tripterygium wilfordii,* highlights the need for vigilance with respect to the potential toxicity of herbal remedies and the need for primary care physicians to be alert to the herbal/complementary medicines that their patients may be taking.

There is no recent evidence to support a role for other complementary physical therapies other than for short term pain relief. Primary care physicians are likely to be involved in advising/monitoring such therapies as part of their coordinating role and should be alert to the range of therapies that might be accessed by patients.

Evidence specific to special populations (rural, Aboriginal people and Torres Strait Islanders, Muslim, and Vietnamese populations in Australia) was not found in the literature included in this review. Multidisciplinary teams trained in RA management are not widely available in Australia, particularly in rural and remote areas. In some cases, special populations may be disadvantaged because of lack of access to the interventions. However, in most cases, there is no reason to believe that they would respond differently.

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REFERENCES

1. Australian Institute of Health and Welfare (AIHW). Arthritis and musculoskeletal conditions in Australia. Canberra: AIHW, 2005.
2. National Health Priority Action Council. National service improvement framework for osteoarthritis, rheumatoid arthritis and osteoporosis. Canberra: Department of Health and Ageing, 2006.
3. SIGN. Management of early rheumatoid arthritis: A national clinical guideline. SIGN Publication No. 48, 2000.
4. Access Economics. Painful realities: The economic impact of arthritis in Australia in 2007. Arthritis Australia, 2007.
5. Emery P, Suarez-Almazor M. Rheumatoid arthritis. Clinical Evidence 2003;10:1454–76.
6. Rindfleisch JA, Muller D. Diagnosis and management of rheumatoid arthritis. Am Fam Physician 2005;72(6):1037–47.
7. Pincus T, Marcum SB, Callahan LF. Longterm drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. J Rheumatology 1992;19:1885–94.
8. Klippel JH, Dieppe PA. Rheumatology 2nd edn. London: Mosby, 1998.
9. Combe B, Landewé R, Lukas C, et al. EULAR recommendations for the management of early arthritis: Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Diseases 2007. 66(1) 34–45 (preview published online 2006).
10. Luqmani R, Hennell S, Estrach C, et al. British Society for Rheumatology and British Health Professionals in Rheumatology. Guideline for the management of rheumatoid arthritis (the first 2 years). Rheumatology 2006;1–16.
11. Scottish Intercollegiate Guidelines Network. The SIGN guide to the AGREE guideline appraisal instrument. 2005 Available at www.sign.ac.uk/methodology/agreeguide/index.html. [Accessed September 2006].
12. Royal College of Physicians. Concise guidance to good practice: A new series of evidence-based guidelines for clinical management. London: Regent's Park, 2003.
13. Coleman K, Norris S, Weston A, et al. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines: pilot program 2005-2007. Canberra: NHMRC, 2005.
14. NHMRC. How to review the evidence: Systematic identification and review of the scientific literature. Canberra: Commonwealth of Australia, 2000.
15. SIGN. Critical appraisal: Notes and checklists. Available at www.sign.ac.uk/methodology/checklists.html. [Accessed 2007 December 2007].
16. Joanna Briggs Institute. Data extraction Tool. Available at www.joannabriggs.edu.au/isearch/index.php. [Accessed 2007].
17. Avouac J, Gossec L, Dougados M. Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review. Ann Rheum Diseases 2006;65(7):845–51.
18. Ceccato F, Roverano S, Barrionuevo A, Rillo O, Paira S. The role of anti-cyclic citrullinated peptide antibodies in the differential diagnosis of elderly-onset rheumatoid arthritis and polymyalgia rheumatica. Clinical Rheumatology 2006;25(6):854–57.
19. Nishimura K, Sugiyama D, Kogata Y, et al. Meta analysis: Diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med 2007;146:797–808.
20. Panchagnula R, Rajiv SR, Prakash J, Chandrashekara S, Suresh KP. Role of anti-cyclic citrullinated peptide in the diagnosis of early rheumatoid factor-negative suspected rheumatoid arthritis: Is it worthwhile to order the test? J Clin Rheumatology 2006;12(4):172–75.
21. Russell AS, Devani A, Maksymowych WP. The role of anti-cyclic citrullinated peptide antibodies in predicting progression of palindromic rheumatism to rheumatoid arthritis. J Rheumatology 2006;33(7):1240–42.
22. Devauchelle-Pensec V, Berthelot JM, Jousse S, et al. Performance of hand radiographs in predicting the diagnosis in patients with early arthritis. J Rheumatology 2006;33(8):1511–15.

23. Riemsma RP, Kirwan JR, Taal E, Rasker JJ. Patient education for adults with rheumatoid arthritis. Cochrane Database Syst Rev 2003; Issue 2.
24. Goldberg RJ, Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. Pain 2007;129(1–2):210–23.
25. Fortin PR, Lew RA, Liang MH, Wright EA, Beckett LA, Chalmers TC, Sperling RI. Validation of a meta-analysis: The effects of fish oil in rheumatoid arthritis. J Clin Epidemiology 1995;48:1379–90.
26. MacLean C, Mojica WA, Morton SC, et al. Effects of omega-3 fatty acids on lipids and glycemic control in type II diabetes and the metabolic syndrome and on inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus, and osteoporosis. Evidence Report Technology Assessment 2004;1–4.
27. Little CV, Parsons T. Herbal therapy for treating rheumatoid arthritis. Cochrane Database Syst Rev 2000; Issue 4.
28. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 2006;332:1302–08.
29. Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: Systematic review of randomised controlled trials. BMJ 2002;325(7365):619–23.
30. van Dongen H, van Aken J, Lard LR, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheumatism 2007;56(5):1424–32.
31. Choy EHS, Smith C, Dore CJ, Scott DL. A meta-analysis of the efficacy and toxicity of combining disease-modifying anti-rheumatic drugs in rheumatoid arthritis based on patient withdrawal. Rheumatology 2005;44(11):1414–21.
32. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: Systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295(19):2275–85.
33. Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. Journal of Rheumatology 2006;33(6):1075–81.
34. Clark W, Jobanputra P, Barton P, Burls A. The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: A systematic review and economic analysis. Health Technology Assessment 2004;8(18):iii-75.
35. Jobanputra P, Barton P, Bryan S, Burls A. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. Health Technology Assessment 2002;6(21):1–110.
36. Gotzsche PC, Johansen HK. Short-term low dose corticosteroid vs placebo and non-steroidal antiinflammatory drugs in rheumatoid arthritis. Cochrane Database Syst Rev 2005; Issue 1.
37. Kirwan JR, Bijlsma JWJ, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev 2007; Issue 1.
38. Park J, Ernst E. Ayurvedic medicine for rheumatoid arthritis: A systematic review. Semin Arthritis Rheumatism 2005;34(5):705–13.
39. Canter PH, Lee HS, Ernst E. A systematic review of randomised clinical trials of Tripterygium wilfordii for rheumatoid arthritis. Phytomedicine 2006;13(5):371–77.
40. Van den Ende CHM, Vliet Vlieland TPM, Munneke M, Hazes JMW. Dynamic exercise therapy for treating rheumatoid arthritis. Cochrane Database Syst Rev 1998; Issue 4.
41. Smidt N, de Vet HCW, Bouter LM, et al. Effectiveness of exercise therapy: A best-evidence summary of systematic reviews. Australian Journal of Physiotherapy 2005;51(2):71-85.
42. Han A, Judd MG, Robinson VA, Taixiang W, Tugwell P, Well G. Tai chi for treating rheumatoid arthritis. Cochrane Database Syst Rev 2004; Issue 3.
43. Steultjens EMJ, Dekker J, Bouter LM, Leemrijse CJ, van den Ende CHM. Evidence of the efficacy of occupational therapy in different conditions: An overview of systematic reviews. Clinical Rehabilitation 2005;19(3):247–54.
44. Brosseau L, Robinson V, Wells G, et al. Low level laser therapy (Classes I, II and III) for treating rheumatoid arthritis. Cochrane Database Syst Rev 2005; Issue 4.

45. Robinson VA, Brosseau L, Casimiro L, Judd MG, Shea BJ, Tugwell P, Wells G. Thermotherapy for treating rheumatoid arthritis. Cochrane Database Syst Rev 2002; Issue 2.
46. Casimiro L, Barnsley L, Brosseau L, Milne S, Robinson VA, Tugwell P. Acupuncture and electroacupuncture for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev 2005; Issue 4.
47. Winzenberg T, Buchbinder R, Shaw K, Jones G. Musculoskeletal conditions - what's new from Cochrane and how might this affect your practice? Aust Fam Physician 2007;36(6):433–34.

APPENDIX 1. CRITICAL APPRAISAL OF RHEUMATOID ARTHRITIS DIAGNOSTIC STUDIES

Anti-cyclic citrullinated peptide antibodies

Study	Study design	Participant selection	Blinding	Comparisons made	Results	Comments	SIGN score
Nishimura et al, 2007[19]	Meta-analysis; 86 studies each involving at least 10 participants. Medline search 1987 to September 2006, hand search of references. Study quality assessed and reported. Many studies had methodological limitations.	37 studies of anti-CCP antibodies, 29 studies assessed anti-CCP2 and five assessed anti-CCP1. 50 studies of RhF. Participants had early RA (defined as <1 year).	Most studies did not explicitly mention blinding of investigators.	Diagnostic accuracy of anti-CCP antibody and RhF. Diagnostic accuracy of anti-CCP1, anti-CCP2 and both anti-CCP antibody and RhF. Prognostic value of anti-CCP and RhF.	**Diagnostic accuracy of IgM RhF, IgG RhF and IgA RhF** Similar likelihood ratios between all. Results from studies in early RA were similar to those from all studies. **Diagnostic accuracy of anti-CCP antibody and RhF** Anti-CCP antibody test pooled sensitivity 67% (95% CI: 62–72%); IgM RF pooled sensitivity 69% (CI 65-73%); anti-CCP antibody test pooled specificity 95% (CI: 94-97%); IgM RF pooled specificity 85% (CI: 82-88%); anti-CCP positive likelihood ratio 12.32; negative likelihood ratio 0.40; IgM positive likelihood ratio RF 3.86; negative likelihood ratio 0.41. **Diagnostic accuracy of anti-CCP1 and anti-CCP2** Anti-CCP2 a more sensitive marker than anti-CCP1. Anti-CCP2 positive likelihood ratio13.03; negative likelihood ratio 0.53. Anti-CCP1 positive likelihood ratio12.77; negative likelihood ratio 0.32. **Prognostic value of anti-CCP antibodies and RhF** Six studies reported anti-CCP positivity was a statistically significant risk factor for radiographic progression. Three of 4 studies found that the risk of radiographic progression was greater with anti-CCP antibody positivity than with IgM RF.	Possible publication bias for studies favourable to anti-CCP antibodies. Because RhF is incorporated into the current diagnostic criteria of RA, diagnostic studies of IgM RF might have some incorporation bias that could have increased the apparent sensitivity of this marker.	12/12

Study	Study design	Participant selection	Blinding	Comparisons made	Results	Comments	SIGN score
Avouac et al, 2006[17]	Systematic review; 107 studies, 68 useable for diagnostic data. Database search 1999 to February 2006 and hand search of references. Study quality not reported.	Diagnostic studies involved 8206 patients with RA plus control groups of healthy subjects or other rheumatic diseases. Predictive properties assessed in 14 studies.	Not applicable	Diagnostic accuracy (sensitivity and specificity) for anti-CCP1 and anti-CCP2 and RhF; and duration of disease. Predictive value of anti-CCP antibodies in early undifferentiated arthritis and in healthy blood donors.	**Diagnostic accuracy of anti-CCP1** Specificity 96% (SD 3%, range 90–99); sensitivity 53%. **Diagnostic accuracy of anti-CCP2** Specificity 95% (SD 5%, range 81–100); sensitivity 68%. Sensitivity of anti-CCP antibody test appears higher in established RA than in patients with recent disease onset. **Diagnostic accuracy of RhF** Specificity 79% (SD 15%, range 31–95); sensitivity 60%. **Prediction in undifferentiated arthritis** Anti-CCP antibodies are a valuable predictor of progression to RA in undifferentiated arthritis. Anti-CCP1 mean OR 20 (95% CI: 14–31). Anti-CCP2 mean OR 25 (95% CI: 18–35).	Studies reviewed did not include a specific comparison of levels of anti-CCP antibodies in RA and other rheumatic disease. No cut off score can therefore be defined to distinguish RA from other diseases. Differences were seen in the characteristics of the patients evaluated as well as for the cut off for a positive test. Variation was also noted for the cut off for CCP1 and CCP2.	8/12

Study	Study design	Participant selection	Blinding	Comparisons made	Results	Comments	SIGN score
Ceccato et al, 2006[18]	Cross sectional	Opportunistic at first consultation and then assessment according to criteria for EORA or PMR. 16 EORA patients, 15 PMR patients. Elderly patients with similar onset of symptoms including seronegative EORA and PMR with peripheral synovitis.	Not reported	RhF and anti-CCP antibodies in EORA and PMR.	**Sensitivity and specificity for patients with EORA** 9/16 patients presented anti-CCP antibodies, four who tested positive for RhF. 12 EORA patients remained negative to RhF, five were positive for anti-CCP antibodies. Eight of the EORA patients started with polymyalgic symptoms. Three of these patients showed positive titles of anti-CCP antibodies with negative RhF. EORA patients presented positive anti-CCP at the beginning of the disease in a statistically significant amount. One-third of the seronegative EORA patients presented positive anti-CCP antibodies at the onset. **Sensitivity and specificity for patients with PMR** All PMR patients presented negative anti-CCP antibodies, except one with weak positive titles, and all were negative for RhF.	Small number of patients. Also, there could be a representative bias since the patients were already diagnosed. The study is specific to elderly patients with similar symptom onset.	8/14

Study	Study design	Participant selection	Blinding	Comparisons made	Results	Comments	SIGN score
Russell et al, 2006[21]	Longitudinal	61 patients presenting with palindromic arthritis within previous 12 months. Followed up over 5.4 years. All patients had had at least three attacks of self limited pain and swelling in or around the joint and one episode was to be observed by the physician.	Not apparent. Serum is taken within the first year of presentation.	Sensitivity and specificity compared for anti-CCP antibodies, RhF and ANA.	29 of 61 patients progressed to RA after a mean of 5.4 years. **Sensitivity comparisons** Anti-CCP antibodies: 83% RhF: 67% ANA: 70%. **Specificity comparisons** Anti-CCP antibodies: 68% RhF: 61% ANA: 47%. The best likelihood ratios were found using a combination of both positive RhF and positive anti-CCP antibodies.	Patients with palindromic arthritis are a more homogenous group and this could inflate the sensitivity of estimations. The study had a small number of subjects.	10/14
Panchagnula et al, 2006[20]	Observational	143 patients with early stage, suspected RA; RhF negative. Mean age 47.1 years; 0.22: 1 male to female; Indian.	Clinicians blinded to the anti-CCP antibody results.	Anti-CCP positivity and subsequent diagnosis of RA.	**Sensitivity and specificity of anti-CCP** All cases were RhF negative. Thirty cases were positive for anti-CCP antibody of which 26 were diagnosed with RA at 3 or 6 month follow up. Sensitivity estimated at 63.4% and specificity 96.1%.	Indian patients.	12/14

Hand radiographs

Study	Study design	Participant selection	Blinding	Comparisons made	Results	Comments	SIGN score
Devauchelle-Pensec et al, 2006[22]	Longitudinal	Early arthritis. 258 patients with onset of arthritis within previous year.	Hand radiographs read by blinded observer who used a standardised procedure for detecting features.	Baseline evaluation, including laboratory tests and radiographs. After 30 months (SD 11.3) final diagnosis established by panel of rheumatologists.	**Hand radiographs** Sensitivity 22.5% Specificity 87.5% Negative predictive value of 66% Positive predictive value of 50%.	The sensitivities of hand radiographs for diagnosing calcium pyrophosphate dihydrate arthritis or hydroxyapatite arthritis were high, ranging from 80 to 100%. Hand radiographs performed only moderately well for predicting RA at an early stage, which accords with reports that specific radiographic manifestations of RA appear later in the disease.	13/14

APPENDIX 2. SUMMARY OF RHEUMATOID ARTHRITIS DIAGNOSTIC STUDIES

Anti-cyclic citrullinated peptide antibodies

Study	Participants	Diagnostic test	Reference standard	Sensitivity	Specificity	Conclusion of the article	Conclusions and relevance of outcomes
Meta-analysis Nishimura et al, 2007[19]	86 studies yielding 30 235 participants 29 studies assessed anti-CCP2 and five assessed anti-CCP1.	Anti-CCP RhF	ACR criteria	**Anti-CCP antibody and RhF** Anti-CCP antibodies pooled sensitivity 67%. IgM RF pooled sensitivity 69%. **Anti-CCP1 and anti-CCP2** Anti-CCP1 positive likelihood ratio 12.77. Anti-CCP2 positive likelihood ratio 13.03.	**Anti-CCP antibody and RF** Anti-CCP antibodies pooled specificity 95%. IgM RhF pooled specificity 85%. **Anti-CCP1 and anti-CCP2** Anti-CCP1 negative likelihood ratio 0.32. Anti-CCP2 negative likelihood ratio 0.53.	Anti-CCP antibody positivity seems to be more specific than IgM RF positivity for identifying patients with RA and may better predict erosive disease. Anti-CCP antibody positivity was a statistically significant risk factor for radiographic progression. Risk of radiographic progression was greater with anti-CCP antibody positivity than with IgM RhF.	There may be a potential role for the test in supporting early diagnosis of RA in primary care and in predicting patients most likely to progress to RA, and thus who may benefit from early referral to a rheumatologist and treatment with DMARDs.

Study	Participants	Diagnostic test	Reference standard	Sensitivity	Specificity	Conclusion of the article	Conclusions and relevance of outcomes
Systematic review Avouac et al, 2006[17]	Diagnostic properties assessed in 58 studies (involving 8206 RA patients; 7380 controls). Predictive properties assessed in 14 studies (2877 with undifferenti-ated arthritis, 162 health subjects).	Anti CCP antibodies. Anti CCP-1. Anti CCP-2 or both.	ACR criteria RhF	**Diagnostic properties** Anti-CCP1 mean sensitivity 53% (SD 10%, range 41–68). Anti-CCP2 mean sensitivity 68% (SD 15%, range 39–94). **Predictive properties** OR for predicting RA among patients with early undifferentiated RA: Anti-CCP1 OR 20 (95% CI: 14–31) Anti-CCP2 OR 25 (95% CI: 18–35). OR for predicting RA among healthy subjects: Anti-CCP1 OR 64.5 (95% CI: 8.5–48.9) Anti-CCP2 OR 28 (95% CI: 8–95).	**Diagnostic properties** Anti-CCP1 mean specificity 96% (SD 3%, range 90–99). Anti-CCP2 mean specificity 95% (SD 5%, range 81–100).	Anti-CCP2 has a similar sensitivity to RF in detecting RA. Anti-CCP antibodies (1&2) are more specific than RhF in distinguishing RA from other diseases. They also appear to be highly predictive of future development of RA in healthy subjects and those with undifferentiated arthritis.	There may be a potential role for the test in supporting early diagnosis of RA in primary care and for predicting progression of undifferentiated arthritis to RA, and thus supporting early treatment/referral as appropriate.

Study	Participants	Diagnostic test	Reference standard	Sensitivity	Specificity	Conclusion of the article	Conclusions and relevance of outcomes
Ceccato et al, 2006[18]	Six patients with EORA; 15 patients with PMR.	Anti-CCP antibodies	ACR criteria	**Differentiation** 56% using PMR as the negative control group. Negative predictive value 63%. Positive predictive value 90%.	**Differentiation** 92%	Anti-CCP antibodies appear to be useful in the differentiation of EORA from PMR, with EORA patients presenting anti-CCP positive statistically more often than PMR patients.	The presence of anti-CCP antibodies in patients presenting with symptoms of PMR should be interpreted as highly suggestive of EORA. The findings support a potential role for anti-CCP antibodies for differentiating rheumatic disease.
Russell et al, 2006[21]	61 patients with PA presenting in previous 12 months. Follow up over 5.4 years for progression to RA.	Anti-CCP antibodies	ACR criteria	**Progression to RA** Anti-CCP antibodies: 83% RhF: 67%.	**Progression to RA** Anti-CCP antibodies: 68% RhF: 61%.	The authors suggest that a positive anti-CCP antibody test in patients with PA within the first year indicates a marked increase in likelihood of progressing to RA. The best likelihood ratios were found using a combination requiring both a positive RhF and positive anti-CCP test, rather one or the other positive, although this reduced the sensitivity of the tests.	Anti-CCP antibodies had better sensitivity and specificity than RhF in predicting progression of PA to RA. The findings support a role for anti-CCP antibody tests in establishing prognosis in rheumatic disease. They may be relevant to primary care in terms of establishing a need for referral to a rheumatologist.

Study	Participants	Diagnostic test	Reference standard	Sensitivity	Specificity	Conclusion of the article	Conclusions and relevance of outcomes
Panchagnula et al, 2006[22]	143 patients with early stage suspected RA; RhF negative; Indian population.	Anti-CCP antibodies	ACR criteria	63.4% Positive predictive value 86.7%	96.1% Negative predictive value 86.7%	Anti-CCP antibodies are a highly specific test for detecting RA in patients presenting with suspected RA in the early stages when RhF is negative. It supplements RhF testing in the presence of a strong clinical suspicion.	The findings support a role for anti-CCP antibody tests in predicting RA in early arthritis.

Hand radiographs

Study	Participants	Diagnostic test	Reference standard	Sensitivity	Specificity	Conclusion of the article	Conclusions and relevance of outcomes
Devauchelle-Pensec et al, 2006[22]	Patients evaluated from 1995 to 1997 in seven Brittany hospitals for arthritis <1 year duration after referral from GP or rheumatol-ogist.	Hand radiographs of crystal deposition disease and RA.	ACR criteria	22.5% Positive predictive value: 50%	87.5% Negative predictive value: 66%	Hand radiographs were able to predict RA with modest success (144/216) and a (21/42). The sensitivities of hand radiographs for diagnosing calcium pyrophosphate dihydrate arthritis or hydroxyapatite arthritis were high, ranging from 80–100%. Hand radiographs may be useful in ruling out other causes of arthritis.	Modest sensitivity in detecting RA state 2 years after onset. Thus negative X-rays are not able to rule out RA as a diagnosis in early RA.

APPENDIX 3. CRITICAL APPRAISAL OF RHEUMATOID ARTHRITIS MANAGEMENT STUDIES

Fatty acid supplements

Review	Types of studies	Methodology	Outcomes measures	Analysis performed	Effect sizes and confidence intervals	Relevance of outcomes	SIGN score
Goldberg and Katz, 2007[24]	Meta analysis of 17 RCTs (823 patients) of **omega-3 polyunsaturated fatty acids to placebo.** 12 trials had Jadad scores of 3 or more.	Searched five major databases, hand search, reference lists, no search for grey literature. Critical appraisal using Jadad.	Pain relieving effects based on: – physician assessed pain – duration of morning stiffness – number of painful or tender joints – Ritchie articular index – NSAID consumption.	Narrative and tabulated summary	**Patient assessed pain** SMD -0.26, 95% CI: -0.49 to -0.03 **Morning stiffness** SMD -0.43, 95% CI: -0.72 to -0.15; *p*=0.003 **Number of painful and/or tender joints** SMD -0.29, 95% CI: -0.48 to -0.10; *p*=0.003 **NSAID consumption** SMD 0.40, 95% CI: -0.72 to -0.08; *p*=0.01 **Physician assessed pain** SMD -0.14, 95% CI: -0.49 to 0.22; *p*=0.45 **Ritchie Articular Index** SMD 0.15, 95% CI: -0.19 to 0.49; *p*=0.40. Significant improvements in patient assessed pain and morning stiffness among studies providing high dose (above 2.7 g omega-3 per day) but not low dose omega-3.	The results suggest a potential role for omega-3 supplements as adjunctive treatment for pain and stiffness associated with RA.	11/12

Non-steroidal anti-inflammatory drugs and COX-2 inhibitors

Review	Types of studies	Methodology	Outcomes measures	Analysis performed	Effect sizes and confidence intervals	Relevance of outcomes	SIGN score
Deeks et al, 2002[29]	Systematic review of three high quality RCTs of **celecoxib** in RA. Safety data is based on nine high quality RCTs.	Major database search and contact pharmaceutical agencies for research up to 2000; two reviewers; critical appraisal performed but not reported; standardised data extraction.	Disease severity ACR 20 criteria and/or improvement in number of painful and swollen joints. Tolerability/safety Withdrawal rates due to adverse events; withdrawal rates due to GIT events; incidence of ulcers detected by endoscopy.	Dichotomous data relative risks; difference in means for continuous data heterogeneity test.	**Celecoxib vs. any NSAIDs at 12 weeks (three RCTs)** ACR 20 Standard dose celecoxib 4% higher (95% CI: -20 to 36%). Number painful and swollen joints Number or painful joints: 9% more celecoxib patients showed improvement (95% CI: -10 to 32%). Number of swollen joints: 2% more celecoxib patients showed improvement (95% CI: -15 to 22%).	Good quality evidence that celecoxib is as effective as other NSAIDS in achieving a response on ACR 20 and a reduction in painful and swollen joints when taken for up to 12 weeks by patients with active RA. The difference in means were small and the CI included the null value therefore the clinical relevance is questionable. Review funded by manufacturer of celecoxib.	10/12
Kearney et al, 2006[28]	Systematic review of 138 RCTs on **COX-2 inhibitors.** Trials with short term follow up (<4 weeks) were excluded.	Search of three major databases and contact with pharmaceutical companies. Assessment of study methodology not reported.	Safety study Serious vascular events (defined as myocardial infarction, stroke, or vascular death).	Rate ratios and 95% CI for each of the pre-specified comparisons by using the Peto 'one step' approximation.	This was a safety trial reporting on adverse events. See summary table for findings related to adverse events.	Selective COX-2 inhibitors are associated with a moderate increase in the risk of vascular events, as are high dose regimens of ibuprofen and diclofenac, but high dose naproxen is not associated with such an excess. However, most trials were not to identify serious cardiovascular events associated with anti-inflammatory drug use.	4/12

Disease modifying antirheumatic drugs

Review	Types of studies	Methodology and critical appraisal	Outcomes measures	Analysis performed	Effect sizes and confidence intervals	Conclusions and relevance of outcomes	SIGN score
Bongartz et al, 2006[32]	Systematic review of nine RCTs investigating the safety of **infliximab or adalimumab** used for at least 12 weeks.	Search of three major databases to December 2005; hand search of EULAR and ACR conference proceedings; and contact with pharmacological agencies; two reviewers; critical appraisal.	Safety study Malignancies. Serious infections (ie. infections requiring antimicrobial therapy and/or hospitalisation).	Fixed effects model, OR and pooled estimate of two dose groups using a continuity correction relative to study size. NNH heterogeneity test.	This was a safety trial reporting on adverse events. See summary table for findings related to adverse events.	Included trials were heterogeneous in terms of disease duration, disease activity and previous/concomitant DMARD treatment. Evidence suggests that the risk rate for malignancy is dose dependent, increasing with higher anti-TNF antibody doses.	10/12

Review	Types of studies	Methodology and critical appraisal	Outcomes measures	Analysis performed	Effect sizes and confidence intervals	Conclusions and relevance of outcomes	SIGN score
Choy et al, 2005[31]	Systematic review of 36 RCTs of **combination DMARD therapy.** Nine RCTs in early RA; 27 RCTs in established RA. 2536 trials had a Jadad score ≥3.	Search of three major databases; no grey literature search; two independent reviewers; critical appraisal; and Jadad scoring.	Withdrawal rate; withdrawal due to adverse events; ACR 70 remissions; and/or ACR 20 responses; joint tenderness count.	Risk ratio based on random effects model for dichotomous outcomes. Heterogeneity test.	**Overall efficacy DMARD combination therapy vs. monotherapy (30 studies)** Favoured DMARD combination therapy RR=0.35, 95% CI: 0.28–0.45; *p*=0.00001 Methorexate(MTX) with anti-TNF inhibitors more effective than MTX alone (six RCTs) RR=0.22, 95% CI: 0.14–0.32; *p*=0.00001 MTX with sulphasalazine and/or antimalarials more effective than MTX alone (eight RCTs) RR=0.41, 95% CI: 0.24–0.7; *p*=0.00001. **Efficacy early RA DMARD combination therapy vs. monotherapy (nine studies)** Favoured DMARD combination therapy RR=0.56, 95% CI: 0.35–0.91; *p*=0.02. **Efficacy established RA DMARD combination therapy vs. monotherapy (22 studies)** Favoured DMARD combination therapy RR=0.31, 95% CI: 0.40–0.91; *p*=0.00001. Corticosteroids added to one DMARD not statistically more effective than monotherapy (seven RCTs) RR=0.48; 95% CI: 0.2–1.14; *p*=0.1. **Tolerability – withdrawal due to inefficacy** Favoured DMARD combination therapy 19 vs. 22%; RR=0.89, 95% CI: 0.80–0.99; *p*=0.033.	Good quality review providing evidence from moderate quality RCTs that combination DMARD therapy is more effective than monotherapy in RA. Combination therapy was more effective for both patients with an early diagnosis as well as those with established RA. More patients withdrew from DMARDs combination therapy due to side effects than those on monotherapy.	11/12

Review	Types of studies	Methodology and critical appraisal	Outcomes measures	Analysis performed	Effect sizes and confidence intervals	Conclusions and relevance of outcomes	SIGN score
Clark et al, 2004[34]	Systematic review of five RCTs on use of **anakinra** alone or in combination with MTX or other DMARDs in RA. (All RCTs Jadad score of 5).	Search up to 2002 of all major databases; hand searching of journals and conference proceedings; requests to relevant agencies for trial information; two reviewers; critical appraisal and Jadad scoring; systematic data extraction.	ACR 20/50/70 HAQ. Patient global assessment. Swollen joint counts.	Weighted mean difference (WMD). Fixed effects model. Heterogeneity test.	**Anakinra vs. placebo** ACR response improvement ACR 20: RR=1.6; NNT 7 (95% CI: 5–11) ACR 50: RR=2.3; NNT 11 (95% CI: 8–20) ACR 70: RR=3.1; NNT 33 (95% CI: 20–100) Health Assessment Questionnaire (0–3 scale) WMD: -0.18; 95% CI: -0.12 to -0.24 Patient global assessment (0–100 scale) WMD: -10.4; 95% CI: -6.3 to -14.4 Swollen join count Mean change from baseline -1.5; 95% CI: -0.38 to -1.68. **Anakinra in combination with MTX vs. placebo** ACR response improvement ACR 20: NNT 6 (95% CI not reported) ACR 50: NNT 9 (95% CI not reported) ACR 70: NNT 20 (95% CI not reported) HAQ (0–3 scale) WMD: -0.14; 95% CI: -0.07 to -0.22 Swollen join count Mean change from baseline: -1.2; 95% CI: 0.15 to -2.54. **Adjusted indirect comparison of anakinra vs. TNF inhibitors** Risk difference for ACR 20 response TNF inhibitor with MTX vs. MTX alone RD: 0.37; 95% CI: 0.28–0.45 Anakinra with MTX vs. MTX alone RD: 0.16; 95% CI: 0.09–0.23 Anakinra with MTX vs. TNF inhibitor with MTX RD: -0.21; 95% CI: -0.32 to -0.10.	The researchers note that efficacy data from one large trial remains withheld from the public and its results may influence these findings. Good quality evidence suggests that anakinra may be less effective than TNF inhibitors when used in combination with methotrexate.	12/12

Review	Types of studies	Methodology and critical appraisal	Outcomes measures	Analysis performed	Effect sizes and confidence intervals	Conclusions and relevance of outcomes	SIGN score
Jobanputra et al, 2002[35]	Systematic review of six RCTs investigating **etanercept** and four RCTs investigating infliximab. (All studies Jadad score of 5.)	Search of major databases; relevant conference proceedings; registered research databases; critical appraisal and Jadad scoring; two reviewers; systematic data extraction.	Physical disability health assessment questionnaire (HAQ); patient global assessment; swollen joint count. Overall effect ACR 20/50/70 criteria.	Pooled data for 1, 3, 6 and 12 months of therapy WMD or SMD.	**Anti-TNF antibodies vs. placebo** ACR 20/50/70 ACR 20: NNT 2 ACR 50: NNT 4 (*p*=significant but not reported) ACR 70: NNT 8 (*p*=significant but not reported) Health Assessment Questionnaire WMD: -0.40, 95% CI: -0.62 to -0.18 Patient global assessment WMD: -2.1 (95% CI: -2.7 to -1.6) Swollen joint count Reduced by 7.7, 95% CI: 4.2-11.4.	Good quality evidence that anti-TNF treatments have a clinically significant effect in adults with early and established RA with active disease that has been unresponsive to DMARDs. Anti-TNF is effective as a monotherapy or in combination with MTX.	12/12

Review	Types of studies	Methodology and critical appraisal	Outcomes measures	Analysis performed	Effect sizes and confidence intervals	Conclusions and relevance of outcomes	SIGN score
Navarro-Sarabia et al, 2006[33]	Systematic review of six RCTs of investigating **adalimumab** alone or in combination with MTX. (Studies had Jadad score of ≥3).	Major database search to 2004 with no language restriction; search of conference proceedings; request to relevant agencies for trials; four reviewers; standardised data extraction; critical appraisal and Jadad, grading of evidence.	Disease severity measured using ACR and EULAR criteria. Disease progression measured with Modified Sharp Index, erosion score and joint space index.	WMD. Absolute benefit and relative difference for continuous data. Relative risk (RR), weighted (WRD) or absolute risk difference (ARD) and NNT or NNH heterogeneity using Chi-square test.	**Adalimumab 40 mg weekly vs. placebo for 26 weeks** (one RCT) ACR response ACR 20: 53.39% adalimumab vs. 19.10% placebo ARD 0.34 (95% CI: 0.22–0.46); RR=2.80 (95% CI: 1.83–4.28); NNT 2.9 ACR 50: 34.95% adalimumab vs. 8.18% placebo ARD 0.27 (95% CI: 0.16–0.37); RR=4.27 (95% CI: 2.17–8.43); NNT 3.7 ACR 70: 18.44% adalimumab vs. 1.81% placebo ARD 0.17 (95% CI: 0.09–0.25); RR=10.15 (95% CI: 2.42–42.18); NNT 6.0 EULAR response 13.59% adalimumab vs. 3.63% of placebo ARD 0.10 (95% CI: 0.02–0.17); RR=3.74 (95% CI: 1.27–10.99); NNT=10. **Adalimumab 40 mg every other week vs. placebo for 24–26 weeks** (two RCTs) ACR response ACR 20: 47.05% adalimumab vs. 23.41% placebo WRD: 0.24 (95% CI: 0.14–0.34); RR=1.91 (95% CI: 1.17–3.10); NNT=5.0 ACR 50: 23.53% of adalimumab vs. 8.22% placebo. WRD: 0.15 (95% CI: 0.08–0.23); RR=2.84 (95% CI: 1.58–5.12); NNT=7.0 ACR 70: 14.11% adalimumab vs.1.89% placebo WRD: 0.12 (95% CI: 0.06–0.18); RR=7.33 (95% CI: 2.25–23.90); NNT 9.0 EULAR response 8.85% adalimumab vs. 3.63% placebo ARD 0.05 (95% CI: -0.01 to 0.12); RR=2.43 (95% CI: 0.79–7.53). **Adalimumab 40 mg plus MTX every other week vs. placebo for 24 weeks** (three RCTs) ACR response ACR 50: 36.44% adalimumab vs. 10.52% placebo. ARD 0.30 (95% CI: 0.16–0.45); RR=3.73 (95% CI: 2.21–6.29); NNT 4.0 (95% CI: 3.0–8.0) ACR 70: 18.31% adalimumab vs. 3.38% placebo ARD 0.16 (95% CI: 0.09–0.23); RR=5.14 (95% CI: 3.14–8.41); NNT 7.0 (95% CI: 5.0–13.0). *Continued….*	Good quality evidence that adalimumab 40 mg every week or every other week is effective in the management of RA, either in combination with methotrexate or as monotherapy. When used for 24–26 weeks NNT to achieve ACR 20/50/70 response ranged from 2.9–9.0.	12/12

Review	Types of studies	Methodology and critical appraisal	Outcomes measures	Analysis performed	Effect sizes and confidence intervals	Conclusions and relevance of outcomes	SIGN score
Navarro-Sarabia et al, 2006[33] *Cont…*	***Effect sizes and confidence intervals continued…*** **<u>Adalimumab 40 mg plus MTX every other week vs. placebo for 52 weeks (one RCT)</u>** <u>ACR response</u> ACR 20: 58.93% adalimumab vs. 24% placebo ARD 0.35 (95% CI: 0.26–0.44); RR=2.46 (95% CI: 1.87–3.22); NNT 2.9 ACR 50: 41.54% adalimumab vs. 9.5% placebo ARD 0.32 (95% CI: 0.24–0.40); RR=4.37 (95% CI: 2.77–6.91); NNT 3.1 ACR 70: 23.18% adalimumab vs. 4.5% placebo ARD 0.19 (95% CI: 0.12–0.25); RR=5.15(95% CI: 2.60–10.22); NNT 5.3 <u>Change in modified Sharp Index</u> Adalimumab 0.10 (SD 4.80) vs. placebo 2.70 (SD 6.80) WMD -2.60 (95% CI: -3.83 to -1.37); relative difference of 3.91% <u>Change in erosion score</u> Adalimumab 0.00 (SD 2.80) vs. placebo 1.60 (SD 4.40). WMD -1.60 (95% CI: -2.37 to -0.83); relative difference of 4.30% <u>Change in joint space index</u> Adalimumab 0.10 (SD 2.30) vs. placebo 1.00 (SD 3.00) WMD -0.90 (95% CI: -1.46 to -0.34); relative difference of 3.08%.					

Study	Random allocation	Follow up complete	Analysis by ITT	Comparable groups baseline	Comparable treatment beside intervention	Outcome measure blind	Effect size and confidence intervals (CI)	Comments	SIGN score
van Dongen et al, 2007[30]	Method not stated	5/55 in each group lost to follow up.	No, patients lost to follow up excluded from analysis.	Yes	Yes	Double blind	**MTX vs. placebo at 30 months total study population** MTX group: 22/55 (40%) progressed to RA; placebo group: 29/ 55 (53%) progressed to RA. HR 1.7 (95% CI: 0.99–3.01); *p*=0.04. **MTX vs. placebo at 30 months subgroup patients positive for anti-CCP** antibodies (n=27) HR 4.9 (95% CI: 1.88–12.79); *p*=0.001. **MTX vs. placebo at 30 months subgroup patients negative for anti-CCP antibodies** (n=83) HR 1.3 (95% CI: 0.61–2.63); *p*=0.51.	Moderate quality evidence that MTX therapy for 12 months can postpone, but not prevent, progression of undifferentiated arthritis to RA.	13/18 §

§ This RCT was critically appraised using the SIGN RCT checklist[15] that assesses quality of randomisation; blinding and concealment; between group differences at the commencement of, and throughout the trial; intention-to-treat analysis; and overall possibility of study bias, including conflict of interest.

Other complementary and alternative medicines

Review	Types of studies	Methodology and critical appraisal	Outcomes measures	Analysis performed	Effect sizes and confidence intervals	Conclusions and relevance of outcomes	SIGN score
Park and Ernst, 2005[38]	Systematic review of seven studies on Ayurvedic medicines (one good quality RCT and six low quality RCTs).	Major data base search; hand searching of relevant journals; no language restriction; standardised data extraction by two reviewers and Jadad scoring.	Pain measured on VAS; morning stiffness; joint swelling; HAQ.	Narrative summary	Effect sizes not reported. No significant differences found between Ayurvedic medicines and placebo on primary outcome measures of symptoms and global assessments.	Good quality evidence from one robust RCT that Ayurvedic medicines do not have an effect above placebo in improving symptoms in patients who have had RA for at least 6 months. Minor adverse events were reported (rate not determinable). There was insufficient evidence about this intervention.	11/12
Canter et al, 2006[39]	Systematic review of two RCTs that investigated ***Tripterygium wilfordii*.** (Jadad scores 3 and 5.)	Major data base search to February 2005, no language restriction; quality assessed using Jadad scores; multiple reviewers.	Physician rated joint tenderness and swollen joint count; duration of morning stiffness; ESR; RhF; ACR 20 and patient and physician rated global assessment.	Narrative summary	Effect sizes not reported. **ACR 20** High dose (360 mg/day) *T. wilfordii* vs. placebo (p=0.0001). Low dose (180 mg/day) *T. wilfordii* vs. placebo (p=0.029). Low dose vs. high dose (p=0.27).	Good quality review found there was limited evidence on the efficacy and safety of *T. wilfordii.* Although it appears effective in improving symptoms and functional outcomes in RA patients with active symptoms, it is associated with significantly higher rates of serious adverse events than placebo and its use cannot be recommended.	10/12

Exercise

Review	Types of studies	Methodology and critical appraisal	Outcomes measures	Analysis performed	Effect sizes and confidence intervals	Conclusions and relevance of outcomes	SIGN score
Smidt et al, 2005[41]	Systematic review of SRs reporting results of at least one RCT on effectiveness of **exercise interventions**, only two SRs met with RA patients' inclusion criteria, one of which was moderate quality.	Search of major data bases up to 2002; multiple reviewers; critical appraisal and inclusion of papers reaching at least reasonable quality; standardised data extraction form.	Specific clinical outcome measures not reported.	Narrative summary and panel review of conclusions.	Effect sizes and CI not reported. One SR of moderate quality concluded there was insufficient evidence on the effectiveness of exercise therapy.	Review concluded there was a paucity of evidence on the effectiveness of exercise interventions in RA.	11/12 10/12

Occupational therapy

Review	Types of studies	Methodology and critical appraisal	Outcomes measures	Analysis performed	Effect sizes and confidence intervals	Conclusions and relevance of outcomes	SIGN score
Steultjens et al, 2005[43]	Systematic review including three SRs of **OT** interventions.	Search of three databases to 2004; minimal assessment of quality; data extraction not described.	Functional ability, grip strength, range of motion, dexterity, pain.	Narrative summary	Effect sizes and CI not reported. Two SRs found evidence for the efficacy of OT in improving functional ability. One SR showed evidence of the efficacy of joint protection on functional outcomes. Two SRs had conflicting findings on the efficacy of hand splints in improving outcome measures including pain, dexterity, grip strength and range of motion.	Moderate quality evidence that OT, including joint protection, improves functional ability in RA patients.	9/12

APPENDIX 4. SUMMARY OF RHEUMATOID ARTHRITIS MANAGEMENT STUDIES

Patient information and education

Review	Participants	Interventions tested	Comparator(s)	Results	Adverse effects	Conclusions and relevance of outcomes
Riemsma et al, 2003[23]	Cochrane review of 31 RCTs.	Patient education interventions.	No intervention or symptom recording (eg. daily diary).	**Information only interventions** No significant effect on pain, disability, joint counts, patient global assessment, anxiety, depression or disease activity. **Education programs** At first follow up there were beneficial effects for patient education for pain (4%), disability (10%), joint counts (9%), patient global assessment (12%), psychological status (5%) and depression (12%). There were no significant effects for disease activity or anxiety. At final follow up (3–18 months) no significant effects were found, only a trend for scores on disability favouring patient education. **Counselling interventions** No significant effects on the above outcomes, although there was a positive trend for psychological status. **Behavioural treatment** Significant effects for scores on disability, patient global assessment and depression. At final follow up, trends favouring behavioural treatment were found for scores on disability and depression.	Not reported	Patient education had small short term effects on disability, joint counts, patient global assessment, psychological status and depression. There was no evidence of long term benefit. In all studies education was provided supplementary to standard medical care.

Fatty acid supplements

Review	Participants	Interventions tested	Comparator(s)	Results	Adverse effects	Comments
Goldberg and Katz, 2007[24]	Systematic review of 16 RCTs with 823 patients with RA or with joint pain secondary to bowel disease (one study) and dysmenorrhoea (one study).	Omega-3 polyunstaurated fatty acid supplementation.	Placebo, active treatments.	Meta-analysis showed significant effects at 3–4 months for pain outcome measures including patient assessed pain, morning stiffness, number of painful and/or tender joints and NSAID consumption. Significant effects were not detected for physician assessed pain and the Ritchie Articular Index. Eleven of the 16 studies used high doses (above 2.7 g omega-3 per day). Significant improvements were noted in patient assessed pain and morning stiffness among studies providing high dose, but not low dose, omega-3.	Not reported	This good quality MA of the analgesic effects of omega-3 polyunsaturated fatty acids provides good evidence for a role of this supplement in pain management in RA.

Review	Participants	Interventions tested	Comparator(s)	Results	Adverse effects	Comments
Little and Parsons, 2000[27]	Cochrane review of seven RCTs involving 286 patients with RA.	Herbal interventions, including GLA	Placebo	Patients treated with GLA showed significant improvement compared with placebo on pain VAS (WMD -32.834, 95% CI: -56.247 to 9.420; *p*>0.05); duration of morning stiffness (two studies, WMD -30.092, 95% CI: -70.190 to 10.006); joint swelling (WMD -14.433, 95% CI: -31.427 to 2.560; *p*>0.05) and joint tenderness (WMD -37.428, 95% CI: -55.729 to -19.126). In two studies, those taking GLA were able to reduce or stop NSAIDs, the combined RR for this outcome being 0.69 (95% CI: 0.47–1.03; *p*>0.05).	Studies reported that there was no increase in adverse effects related to GLA.	With the exception of one study, the review shows improvements in objective measures of effect of GLA. These included pain assessment, morning stiffness, joint assessment and NSAID use. The quality of studies and small patient numbers prevent firm conclusions being drawn about the role of GLA in the treatment of RA.

Traditional NSAIDs and COX-2 inhibitors

Review	Participants	Interventions tested	Comparator(s)	Results	Adverse effects	Comments
Deeks et al, 2002[29]	Systematic review of studies including RA patients with active disease.	**Celecoxib** at the licensed dose for at least 12 weeks of treatment.	Placebo; another NSAID at a standard dose (naproxen 500 mg twice daily or diclofenac 75 mg twice daily, or ibuprofen).	There was no statistically significant difference in the effect on any outcome measures between celecoxib and NSAIDs for all efficacy outcomes.	**Celecoxib vs. placebo at 12 weeks** Withdrawal due to adverse events Higher for patients taking celecoxib vs. placebo RR=1.49 (95% CI: 1.15–1.92) Withdrawal due to adverse GIT events Higher for patients taking celecoxib vs. placebo RR=1.68 (95% CI: 1.07–2.65) Ulcers/perforations Threefold increase in number of events detected on endoscopy in the celecoxib group vs. placebo; difference not significant. **Celecoxib vs. NSAIDs at 12 weeks** Withdrawal due to adverse events No statistical difference Withdrawal due to adverse GIT events No statistical difference for overall GIT events. More patients in the NSAIDs group withdrew due to dyspepsia and abdominal pain Ulcers/perforations Incidence rate in patients taking celecoxib was 71% lower (95% CI: 59–79%) than those taking NSAIDs (NNH=6).	Patients taking celecoxib were more likely to withdraw due to any adverse event or specifically a GIT adverse event than those taking placebo. However, celecoxib had a more favourable tolerability profile than other NSAIDs. There was insufficient evidence on the safety and efficacy of this medication beyond 12 weeks.

Review	Participants	Interventions tested	Comparator(s)	Results	Adverse effects	Comments
Kearney et al, 2006[28]	Systematic review of 138 RCTs involving 145 373 participants with various comorbidities including RA.	COX-2 inhibitors	Placebo; traditional NSAID.	This was a safety trial reporting on adverse events. **COX-2 inhibitors vs. placebo** Incidence of serious vascular events 42% relative increase (1.2 vs. 0.9%/year) RR=1.42 (95% CI: 1.13–1.78); *p*=0.003 No significant heterogeneity among different selective COX-2 inhibitors Incidence of MI Increased by almost twofold (0.6 vs. 0.3%/year) RR=1.86 (95% CI: 1.33–2.59); *p*=0.0003 No significant heterogeneity among different COX-2 inhibitors. **COX-2 inhibitors vs. NSAID** Incidence of serious vascular events No significant difference (1.0 vs. 0.9%/year) RR=1.16 (95% CI: 0.97–1.38); *p*=0.10 Statistical heterogeneity between trials of a selective COX-2 inhibitor and naproxen. **COX-2 inhibitors vs. naproxen** COX-2 inhibitors had significant increase in incidence of vascular events RR=1.57 (95% CI: 1.21–2.03); *p*=0.001) COX-2 inhibitors had twofold increase risk of myocardial infarction RR=2.04 (95% CI: 1.41–2.96); *p*=0.0002. **Non-naproxen NSAIDs vs. selective COX-2 inhibitor** Incidence of vascular events No significant difference RR=0.88 (95% CI: 0.69–1.12); *p*=0.3. **NSAID vs. placebo** Rate ratio for vascular events in comparison to placebo was 0.92 (95% CI: 0.67–1.26) for naproxen; 1.51 (95% CI: 0.96–2.37) for ibuprofen and 1.63 (95% CI: 1.21–2.37) for diclofenac.		Evidence that selective COX-2 inhibitors are associated with a moderate increase in the risk of vascular events, as are high dose regimens of ibuprofen and diclofenac. High dose naproxen was not associated with an increase in risk.

Disease modifying antirheumatic drugs

Study	Participants	Interventions tested	Comparator	Outcome measures	Results	Adverse effects	Comments
van Dongen et al, 2007[30]	110 patients aged over 18 years with undifferentiated arthritis of less than 2 years duration.	**MTX** for 1 year, commencing dose 15 mg/week.	Placebo	Diagnosis (RA, undifferentiated arthritis, remission or other) and radiographic progression.	The most beneficial outcomes were achieved in patients positive for anti-CCP antibodies. 24% of the placebo group achieved spontaneous remission, indicating that MTX may be over-treatment in a considerable proportion of patients. Optimal duration and intensity of treatment remain to be determined.	**Placebo group** 33% experienced one or more adverse events 25 adverse events 4 serious events. **Methotrexate group** 47% experienced one or more adverse event 44 adverse events 5 serious events.	Results showed that MTX treatment in undifferentiated arthritis can postpone progression to RA and can retard radiographic joint damage when compared with placebo.

Review	Participants	Interventions tested	Comparator(s)	Results	Adverse effects	Comments
Choy et al, 2005[31]	Patients with early RA or established RA being treated with DMARDs. Patients not necessarily diagnosed with RA according to ACR criteria.	**Combination therapy** with two or more DMARDs or one DMARD and one biological agent.	DMARD monotherapy	Results showed combination DMARDs associated with statistically significant reduction in disease severity compared to monotherapy. Combination DMARDs had a moderate effect size when measuring overall efficacy and joint tenderness count as well as withdrawal rate due to inefficacy. The most significant effects were seen in patients with established RA treated with combinations of MTX with anti-TNF, or with sulfasalazine-hydroxychloroquine after partially responding to DMARD monotherapy.	Combination DMARD therapy had a statistically significantly increased risk of withdrawals due to toxicity compared to monotherapy. RR=1.37 (95% CI: 1.16–1.62); *p*=0.0001.	Overall, there was a similar rate of withdrawals. However, there was a higher rate of withdrawal due to inefficacy in monotherapy patients and a higher withdrawal rate due to adverse events in those taking combination DMARD therapy.

Review	Participants	Interventions tested	Comparator(s)	Results	Adverse effects	Comments
Clark et al, 2004[34]	2932 adults 18+ years with RA (primarily established RA for more than 3 years).	**Anakinra (Kineret)** alone (two studies) or in combination with other drugs (three studies) for 12 weeks to 12 months in doses ranging from 2.5 mg/day to 100 mg/day.	Placebo; MTX; other DMARDs.	At the licensed dose (100 mg/day) anakinra showed a modest but significant reduction in clinical symptoms measured as response to ACR 2/50/70 and swollen and tender joint count. Benefit was evident both in monotherapy and in combination with MTX. An indirect comparison showed that anakinra and MTX may be significantly less effective than TNF inhibitors and MTX.	<u>Withdrawal due to adverse event</u> 10.1% of anakinra treated patients compared with 6.7% in the control group, primarily due to injection site reactions. <u>Serious adverse events</u> Not significant between anakinra and placebo. <u>Injection site reactions</u> 60% of patients on anakinra compared with <34% in the control groups. Generally mild-moderate in nature. <u>Malignancies and death</u> Not significant; 16 malignancies and 17 deaths reported in patients taking anakinra vs. six malignancies and one death in patients taking placebo.	Good quality evidence that anakinra 100 mg/day has a modest clinical effect on ACR response in patients with established RA. Evidence suggests that anakinra may be less effective than TNF inhibitors in combination with MTX.
Jobanputra et al, 2002[35]	Adults with RA with suboptimal response to DMARDs or (for infliximab trials) taking MTX for ≥3 months before recruitment.	**Infliximab** or **etanercept** in varying doses as monotherapy or in combination with MTX for 4 weeks to 12 months.	Placebo; or placebo combined with MTX.	Anti-TNF medications have a statistically significant and clinically important effect on all outcome measures compared to placebo.	Minor adverse events were common for both anti-TNF and placebo patients. No serious adverse events.	Good quality review providing evidence for the effect of infliximab or etancercept with or without MTX for adults with RA.

Review	Participants	Interventions tested	Comparator(s)	Results	Adverse effects	Comments
Navarro-Sarabia et al, 2006[33]	2390 randomised participants with clinically confirmed RA.	**Adalimumab** Subcutaneous (SC) 40 mg every week or adalimumab SC 40 mg in combination with MTX every other week for 4–52 weeks.	Placebo; placebo in combination with MTX.	Adalimumab alone or in combination with MTX every week or every other week was associated with a statistically significant reduction in disease severity as measured by response on ACR and EULAR at 24/26 and 52 weeks compared to placebo.	Data from studies was heterogeneous and data pooling on adverse events was not conducted. The only potentially serious adverse effect in one larger 52 week study of adalimumab with MTX was a significant increase in the frequency of serious infections compared to placebo combined with MTX (3.81 vs. 0.5%). NNH=30; RR=7.64 (95% CI: 1.02–57.18).	Evidence from a limited number of studies with methodological flaws on the effectiveness of adalimumab. Further research is required on the long term effectiveness of this intervention.
Bongartz et al, 2006[32]	5014 participants with clinically diagnosed RA, primarily with active disease non-responsive to DMARDs. In one of the nine included studies, patients had active, early (<3 years) RA.	**Infliximab** or **adalimumab** as monotherapy or in combination with MTX treatment for 12 weeks or more.	Placebo; placebo in combination with MTX.	This was a safety trial reporting on adverse events **Malignancies over treatment period of 6–12months** Anti-TNF (n=3493): 29 malignancies Control (n=1512): two malignancies NNH 154 (95% CI: 90–500) for one additional malignancy RCTs with at least one malignancy reported Pooled OR 3.3 (95% CI: 1.2–9.1) Low dose anti-TNF vs. high dose anti-TNF vs. placebo Significant difference between malignancy rate: Low dose anti-TNF OR 1.4 (95% CI: 0.3–5.7) High dose anti-TNF OR 4.3 (95% CI: 1.6–11.8) **Serious infections over treatment period of 6–12 months** Anti-TNF (n=3493): 493 serious infections Control (n=1512): 26 serious infections OR 2.0 (95% CI: 1.3–3.1) NNH 59 (95% CI: 39–125) Low dose anti-TNF vs. high dose anti-TNF vs placebo Significant difference between serious infection: Low dose anti-TNF OR 1.8 (95% CI: 1.1–3.2) High dose anti-TNF OR 2.3 (95% CI: 1.5–3.6).		Good quality evidence that anti-TNF therapy for 6–12 months is related to an increased risk of serious infections and malignancies in patients with active RA that is non-responsive to DMARDs.

Corticosteroids

Review	Participants	Interventions tested	Comparator(s)	Results	Adverse effects	Comments
Gotzsche and Johansen, 2005[36]	Cochrane review of 10 studies involving 320 patients with RA.	**Low dose corticosteroids** (<15 mg/day) used for short term (1 month).	Placebo; NSAIDs.	Compared to placebo, prednisolone had a marked effect on joint tenderness (SMD 1.30, 95% CI: 0.78–1.83) as well as on pain (SMD 1.75, 95% CI: 0.87–2.64) and grip strength (SMD 0.41, 95% CI: 0.13–0.69). Prednisolone also had a significantly greater effect than NSAIDs on joint tenderness (SMD 0.63, 95% CI: 0.11–1.16) and pain (SMD 1.25, 95% CI: 0.26–2.24), but not on grip strength.	Not reported	Evidence from a Cochrane review that low dose prednisolone (not exceeding 15 mg/day) may be used intermittently in patients with RA, particularly if the disease cannot be controlled by other means.
Kirwan et al, 2007[37]	Cochrane review of 15 studies involving 1414 patients. Most studies were conducted in patients with early RA (within 2 years).	Glucocorticoids	Placebo; active treatment.	For studies reporting 2 years of treatment, corticosteroids were beneficial compared with placebo in reducing disease progression for patients with early RA (SMD at 1 year 0.41, 95% CI: 0.29–0.66; SMD at 2 years 0.42, 95% CI: 0.30–0.55). The proportion of benefit calculated for corticosteroids over 1 year was 59.8% (95% CI: 45.4–74.1%) and over 2 years 61.3% (95% CI: 46.4–76.1%). Joint space narrowing was less in all corticosteroid treated patients compared with placebo, although for some studies (eg. <26 weeks of treatment) the difference was not always significant. The beneficial effects of corticosteroids were generally achieved when used in conjunction with other DMARD treatment.	Although not explicitly investigated in this SR, the authors reported that recent RCTs of low dose glucocorticoid treatment in RA suggest that adverse effects are modest, and often not statistically different from placebo. The most immediate concern is bone mineral density.	Evidence from a Cochrane review that, in patients with active RA of less than 2 years duration who require treatment with DMARDs, there would be a clinically effective reduction in joint destruction with the addition of a suitable low dose or step-down corticosteroid regimen.

Other complementary and alternative medicines

Review	Participants	Interventions tested	Comparator(s)	Results	Adverse effects	Comments
Little and Parsons, 2000[27]	Cochrane review of four RCTs on herbal interventions in patients with RA.	Herbal interventions: Feverfew *T. wilfordii* Capsaicin Reumalex.	Placebo	*T. wilfordii* (one RCT) was associated with significant improvements in joint tenderness, joint swelling, morning stiffness, grip strength and 15 metre walking time compared to placebo. In one small RCT, patients using capsaicin cream achieved improvements in pain compared to placebo. In one small RCT reumalex was associated with improvements in pain compared to placebo. In another small trial, patients treated with fever few had no significant difference in outcomes compared with placebo.	***T. wilfordii*** Adverse events were higher than placebo group and resulted in four withdrawals. One patient had a severe reaction (fever and aplastic anaemia). **Capsaicin** 44% treatment group experienced burning at application site.	The low quality and quantity of studies and small samples sizes prevent firm conclusions being drawn about the role of most herbal/alternative interventions in the treatment of RA. Severe adverse events associated with *T. wilfordii* suggest patients should be warned regarding the product's use.
Park and Ernst, 2005[38]	RA patients. In the most robust study, participants were over 18 years of age, were recruited from 'arthritis camps', had been diagnosed for at >6 months, and had at least three active symptoms.	**Ayurvedic medicine** (preparations made following the Hindu tradition of Ayurveda) administered orally or topically. Different formulations and dosing regimens were used in each study. Treatment for 16 weeks in most robust study.	Placebo; various different Ayurvedic medicine preparations.	In the most robust study, the Ayurvedic medicine group had significantly higher haemoglobin (p=0.02) and lower RhF factor (p=0.01) compared with placebo; however, there was no significant difference in clinical outcome measures between the groups. The other trials showed inconclusive results, or were difficult to interpret because of incomplete data, withdrawals or other flaws in the studies.	Rates of adverse events were not reported. However, a description of minor events (nausea, anorexia, headaches, diarrhoea, constipation, abdominal pain) lasting less than 5 days was provided for some studies.	One good quality trial showed no significant effect of the therapy and only minor adverse events; other trials were inconclusive.

Review	Participants	Interventions tested	Comparator(s)	Results	Adverse effects	Comments
Canter et al, 2006[39]	RA patients with adult onset RA for ≥6 months with active symptoms, which were non-responsive to NSAIDs following at least 2 months of treatment.	***T. wilfordii* extract** in doses of 60, 180, 360 mg/day for 4–26 weeks.	Placebo	Patients treated with *T. wilfordii* extract had significant clinical improvement measured as response to ACR 20 compared with placebo. The effect was greater with higher of *T. wilfordii*. 80% of high dose participants, 40% of low dose participants and 0% of placebo participants achieved improvement up to 26 weeks.	In both trials there were more drug related adverse events in the *T. wilfordii* groups compared to placebo. (eg. skin rash, diarrhoea, amenorrhoea, hair loss and nausea.)	There was limited evidence on the efficacy and safety of *T. wilfordii.* Based on findings from two RCTs of moderate to good quality, *T. wilfordii* extract is effective in improving symptoms and functional outcomes in RA patients with active symptoms but has a high rate of serious adverse events.

Exercise

Review	Participants	Interventions tested	Comparator(s)	Results	Adverse effects	Comments
Smidt et al, 2005[41]	Patients with RA	**Exercise programs** (various)	Controls not specified	Primary data was not reported. A moderate quality SR included in this review found insufficient RCTs on exercise interventions to determine effectiveness.	Not reported	There was insufficient evidence on the effectiveness of exercise interventions in RA.

Review	Participants	Interventions tested	Comparator(s)	Results	Adverse effects	Comments
Van den Ende et al, 1998[40]	Cochrane review of five RCTs in patients with RA, median n=32.	**Dynamic exercise therapy** only exercise programs with an intensity adequate to improve aerobic capacity were included.	Another form of exercise therapy or non-exercise.	Data pooling was not conducted due to wide range of outcome measures. Five RCTs reported a 4–33% increase in VO_{2max} compared to control -4 to 6% change, which was significant in three RCTs. Two RCTS reported significant improvement in muscle strength compared with controls. Small improvements in functional ability were seen in all studies No studies found a statistically significant improvement in pain. Two RCTs found a significant decrease in number of clinically active joints associated with exercise.	No evidence of deleterious effects on joint inflammation and disease progression for the short term exercise interventions.	Dynamic exercise therapy was effective in improving aerobic capacity, muscle strength and joint mobility, but less effect in improving functional ability or managing pain.

Review	Participants	Interventions tested	Comparator(s)	Results	Adverse effects	Comments
Han et al, 2004[42]	Cochrane review of four RCTS and controlled clinical trials including 202 participants with RA.	**Tai chi**	Non-exercise	Two studies found no significant difference in functional outcome measures for tai chi compared to control (WMD 0.01, 95% CI: -2.94 to 2.97). Two studies found a clinically significant reduction in tender joints (18 and 37%) but this was not significant compared with control (WMD -0.83, 95% CI: -3.30 to 1.64) and not accompanied by a reduction in swollen joints. Range of movement in some joints was significantly improved compared with control (ankle plantar flexion WMD 24.00°, 95% CI: 3.34–44.66; lower extremity flexion WMD 34.00°, 95% CI: 10.79–57.21). Range of motion in other joints were not statistically different. Participants in the tai chi groups were more likely to complete the intervention than controls and reported high levels of enjoyment.	In two RCTs, approximately 30% of patients complained of soreness in the knee, shoulder or lower back during the first 3 weeks of the intervention. This subsided and did not interfere with completion of the program, except in one patient.	This review of low quality studies found tai chi had a significant effect on some outcome measures (eg. range of motion in some joints). Although improvements on other measures (eg. functional assessment, tender/swollen joint count) were not significant, participants reported enjoyment of the activity.

Occupational therapy

Review	Participants	Interventions tested	Comparator	Results	Adverse effects	Comments
Steultjens et al, 2005[43]	Systematic review of three SRs with RA patients.	**Occupational therapy** interventions	Controls not specified	Two SRs found evidence for the efficacy of comprehensive OT in improving functional ability, and one review showed evidence of the efficacy of joint protection on functional outcomes. Two reviews had conflicting findings on the efficacy of hand splints in improving outcomes including pain, dexterity, grip strength and range of motion.	Not reported	Moderate quality evidence supporting the efficacy of OT in improving functional outcomes. However, its effect when measured using other outcomes is unclear.

Complementary and alternative physical therapies

Review	Participants	Interventions tested	Comparator (s)	Results	Adverse effects	Comments
Brosseau et al, 2005[44]	Cochrane review of five RCTs (median Jadad score 3) including 204 adults aged over 18 years with RA of the hand.	**Low level laser therapy (LLLT)** including wavelengths from 632–1064 nm. Two to three sessions/week for 3–4 weeks (one study duration was 10 weeks).	Placebo; treated vs. untreated limbs in same trial (18 patients).	Placebo controlled trials found statistically significant improvements in pain on VAS (WMD -1.10, 95% CI: -1.82 to -0.39), flexibility (tip to palm distance, difference 1.3 cm, 95% CI: 0.9–1.7 cm), and duration of morning stiffness (decrease 27 minutes, 95% CI: 3–52 minutes; RR=0.25, 95% CI; 0.03–2.09). Improvements were not sustained at 3 months follow up. In one RCT that used the opposite hand of the same individuals as the control, there were no significant improvements in the hands treated with lasers versus the controls. Subgroup analysis of trials showed a range of trends for various methods of laser application (wavelength, joint/nerve application, duration, dose).	Not reported	Good quality review found silver level evidence that LLLT for up to 4 weeks has a clinically relevant effect in reducing pain and morning stiffness in patients with RA of the hand; however, it does not appear to have long lasting effects. There was a range of different regimens used and there was insufficient data on any one regimen to make overall conclusions on the most effective LLLT.
Robinson et al, 2002[45]	Cochrane review of seven low quality RCTs including 328 adults with RA.	Thermotherapy	No treatment or active therapy (eg. ultrasound).	No significant effect of hot and ice packs applications, cryotherapy, and faradic baths on objective measures of disease activity including joint swelling, pain, medication intake, range of motion, grip strength, hand function compared with a no treatment or active control therapy. There is no significant difference between wax and therapeutic ultrasound, or between wax and faradic baths, combined compared with ultrasound alone. There was no difference in patient preference for all types of thermotherapy.	There were no adverse events reported by participants.	Conclusions were limited by methodological considerations such as the poor quality of trials. Patients achieved some relief with some forms of thermotherapy, although these were not significant on outcomes measured.

Casimiro et al, 2005[46]	Cochrane review of two RCTs involving 84 people with RA.	Acupuncture or electro-acupuncture.	Placebo	In one RCT on acupuncture there was no significant difference found for any outcome measures between the intervention and placebo. In one RCT on electro-acupuncture, the intervention was associated with significant decrease in knee pain 24 hours post-treatment when compared with placebo (WMD -2.0, 95% CI: -3.6 to -4.0). This was sustained at 4 months post-treatment (WMD -0.2, 95% CI: -0.36 to -0.04).	Not reported	Although the study using electro-acupuncture showed some benefit in terms of reduction in pain, the study was of poor quality and involved small numbers. The reviewers concluded that, based on limited evidence, acupuncture does not appear to improve the symptoms of RA.

APPENDIX 5. EXCLUDED STUDIES

Paper	Reason for exclusion
Nell VP, Machold KP, Stamm TA, Eberl G, Heinzl H, Uffmann M, Smolen JS, Steiner G. Autoantibody profiling as early diagnostic and prognostic tool for rheumatoid arthritis. Annals of the Rheumatic Diseases 2005;64(12):1731-36.	Included in another reviewed article
Rantapaa-Dahlqvist S. Diagnostic and prognostic significance of autoantibodies in early rheumatoid arthritis. Scandinavian Journal of Rheumatology 2005;34(2):83-96.	Included in another reviewed article
Sauerland U, Becker H, Seidel M, Schotte H, Willeke P, Schorat A, Schluter B, Domschke W, Gaubitz M. Clinical utility of the anti-CCP assay: Experiences with 700 patients. Annals of the New York Academy of Sciences 2005;1050:314-18.	Included in another reviewed article
Garcia-Berrocal B, Gonzalez C, Perez M, Navajo JA, Moreta I, Davila C, Gonzalez-Buitrago JM. Anti-cyclic citrullinated peptide autoantibodies in IgM rheumatoid factor-positive patients. Clinica Chimica Acta 2005;354(1-2):123-30.	Included in another reviewed article
Raza K, Breese M, Nightingale P, Kumar K, Potter T, Carruthers DM, Situnayake D, Gordon C, Buckley CD, Salmon M, Kitas GD. Predictive value of antibodies to cyclic citrullinated peptide in patients with very early inflammatory arthritis. Journal of Rheumatology 2005;32(2):231-38.	Included in another reviewed article
Matchaba P, Gitton X, Krammer G, Ehrsam E, Schorr Sloan V, Olson M, Mellein B, Hoexter G, Orloff J, Garaud JJ. Cardiovascular safety of lumiracoxib: A meta-analysis of all randomised controlled trials ≥1 week and up to 1 year in duration of patients with osteoarthritis and rheumatoid arthritis. Clinical Therapeutics 2005;27:1197-1214.	This low quality SR (2/12) does not present information for RA specific use of the medication data combined with that from trials in patients with OA. Due to the non-specific disease focus combined with low quality, this review has been excluded.
Plosker GL, Croom KF. Sulfasalazine. A review of its use in the management of rheumatoid arthritis. Drugs 2005;65(13):1825-49.	This is a literature review. There are no inclusion and exclusion criteria and no critical appraisal.
Stamp LK, James MJ, Cleland LG. Diet and rheumatoid arthritis: A review of the literature. Seminars in Arthritis Rheumatism 2005;35:77-94.	This is a literature review. There are no inclusion and exclusion criteria and no critical appraisal.
Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: A review. Rheumatology 2004;43:267-71.	This is a literature review. There are no inclusion and exclusion criteria and no critical appraisal.
Luqmani R, et al. British Society for Rheumatology and British Health Professionals in Rheumatology. Guideline for the management of rheumatoid arthritis (the first 2 years). Rheumatology 2006;45:1167–69.	This is a summary of the BSR guidelines, the full version of which has already been reviewed as part of this project.
Pham T, Gossec L, Fautrel B, Combe B, Flipo R-M, Goupille P, Le Loet X, Mariette X, Puechal X, Wendling D, Schaeverbeke T, Sibilia J, Sany J, Dougados M. Physical examination and laboratory tests in the management of patients with rheumatoid arthritis: development of recommendations for clinical practice based on published evidence and expert opinion. Joint, Bone, Spine: Revue du Rhumatisme 2005;72(3):222-28.	The level of evidence on which these recommendations is based is low and there was no critical appraisal process of the literature outlined. While studies were given a grade of evidence it is unknown whether the RCTs used a sound methodological process. In addition, for many of these recommendations, more than 30% of the expert panel did not agree or strongly agree with the recommendation and the reason for their disagreement is not outlined.

Gossec L, Fautrel B, Pham T, Combe B, Flipo R-M, Goupille P, Le Loet X, Mariette X, Puechal X, Wendling D, Schaeverbeke T, Sibilia J, Sany J, Dougados M. Structural evaluation in the management of patients with rheumatoid arthritis: Development of recommendations for clinical practice based on published evidence and expert opinion. Joint, Bone, Spine: Revue du Rhumatisme 2005;72(3):229-34.	There is very little detail in this paper to make a judgment. All recommendations were graded D, indicating a lack of clinical studies and reliance only on expert opinion. The level of evidence on which these recommendations is based is low and there was no critical appraisal process of the literature outlined. While studies were given a grade of evidence, it is unknown whether the RCTs used a sound methodological process. Although most of the recommendations received agreement from 95% of the experts, the reason for any disagreement is not outlined.
Kennedy T, McCabe C, Struthers G, Sinclair H, Chakravaty K, Bax D, Shipley M, Abernethy R, Palferman T, Hull R. BSR guidelines on standards of care for persons with rheumatoid arthritis. Rheumatology 2005;44(4):553-56.	This paper is largely a review of other guidelines and, as such, provides an overview of guidelines in the area of RA management. It does not provide any SR of evidence. There is no method outlined, and particularly the retrieval, review and appraisal of evidence on which these standards are based has not been discussed. Grades of recommendation are listed beside the 12 references; however, this scale is not outlined. These standards broadly summarise other guidelines.