2009 Annual Evidence Update on rheumatoid arthritis (RA)

Introduction

The team responsible for NHS Evidence - musculoskeletal (formerly the National Library for Health Musculoskeletal Specialist Library) has searched the literature for high quality evidence that has accumulated within the last year. We have focused on guidance and systematic reviews published before March 2009. As in recent years the majority of publications relate to various aspects of treatment with biologics. Although this constitutes an increasing proportion of the clinical activity in relation to this disease, we should not lose sight of other important developments and various aspects of rheumatoid disease management feature prominently in our update. It might seem obvious that patients should be able to expect the same high standard of care from the NHS wherever they are located in the UK but the fact that their experience varies greatly has been highlighted in a report from the Kings Fund [1]. This would be justifiable if there was no evidence to guide practice but this is far from being the case. Perhaps the most important publication during the year has been the NICE Guideline on rheumatoid arthritis [2]. The widespread implementation of this guidance has the potential to greatly improve the lives and outlook of very many patients with this devastating disease. However, adherence to the guidance will have important resource implications for many providers which may be a challenge in these straitened times.

1. Perceptions of patients and professionals on rheumatoid arthritis care. The Kings Fund January 2009. [Direct document link - PDF] [Link to specialist collection]


Acknowledgements

The NHS Evidence - musculoskeletal project team would like to thank all those involved with this Annual Evidence Update, in particular Dr Ray Armstrong, the Clinical Lead; Dr Chris Deighton for his editorial on the new NICE guidance on the management of RA in adults; Dr Peter Fisher for his editorial on complementary therapies for RA and Mark Fenton for helping with the treatment uncertainties.

2009 Annual Evidence Update on rheumatoid arthritis (RA) - Results

The results of the search have been reviewed and grouped into the following topics:

- **Guidance / Management** (5)
- **Drugs**
  - Biologics (12)
  - DMARDs (4)
  - Corticosteroids (2)
  - NSAIDs and COX-II (1)
- **Other drugs** (1)
- **Complementary / Alternative** (8)
- **Drugs - adherence** (1)
- **Risk**
  - Aetiology (5)
  - Cardiovascular disease (3)
  - Malignancy (3)
Please note that the inclusion of citations in this list does not imply endorsements. NHS Evidence - musculoskeletal does not accept responsibility for the content or quality of the included or excluded studies.


Standards of Care for people with musculoskeletal foot health problems. Podiatry Rheumatic Care Association. April 2008. [Link to specialist collection]

**Biologicals**


Shergy, W. J. Selective Costimulation Modulation with Abatacept: A Look at Quality-of-Life Outcomes


**DMARDs**


**Corticosteroids**


**NSAIIDs and COX-II**


Ernst, E. Frankincense: systematic review. *BMJ.* 2008;337:a2813. [Link to specialist collection]


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**Aetiology**


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**Cardiovascular disease**


**Malignancy**


2009 Annual Evidence Update on rheumatoid arthritis (RA) - Commentary

This commentary on the 2009 Annual Evidence Update on rheumatoid arthritis has been written by Dr Ray Armstrong, Clinical Lead of NHS Evidence - musculoskeletal.

Guidance

The main topic of interest here is of course the new NICE Guidance on the management of Rheumatoid Arthritis and we recommend that you read Dr Chris Deighton’s editorial about this topic which also refers to the King’s Fund report which was published during the year. NICE also conducted an appraisal of abatacept, a novel agent for the treatment of RA after TNF blockade has failed. It was not found to be cost-effective and was therefore not recommended for use in the NHS at the present time.

The Clinical Knowledge Summaries (CKS) section on DMARDs was updated last year and replaces the previous Prodigy guidance. The evidence-base has been reviewed in detail, and recommendations are more clearly justified and transparently linked to the supporting evidence. This resource provides quickly and easily accessible information for the clinician at the point of care. More detailed information is available in the BSR/BHPR publication which was produced in consultation with our Dermatological colleagues.

We are used to hearing that care of the rheumatoid foot is a ‘Cinderella’ topic. There has been improved recognition over the years of the needs of rheumatoid sufferers with regard to foot disease, but there is room for improvement. The Standards of Care for People with Musculoskeletal Foot Health Problems, funded by the Arthritis Research Campaign, should lead to further improvement and this document contains links which provide access to audit tools.

Systematic Reviews

As usual, we have concentrated our attention on systematic reviews, these being acknowledged to be of generally greater value than individual studies. Please note that these systematic reviews have not been critically appraised.

First, how do we diagnose early RA? – Not very well by using the ACR 1987 revised criteria according to Banal et al. Their value is only really apparent when considering established RA.

Therapy of rheumatoid arthritis - biologics

On the therapeutic front, most attention as in recent years has focused on the biological agents or ‘biologics’. The efficacy of these drugs is now well established and a study indicating that anakinra is less effective than other biologics (Mertens) comes as no surprise. A review of a new agent, a humanised monoclonal antibody directed against IL-6 receptor, tocilizumab, describes it as ‘promising’ and its arrival on the market is anticipated in the not too distant future (Plushner).

A number of reviews have examined a variety of aspects of biological therapy and in the absence of direct comparisons; it is difficult to discern any major differences between these drugs. Perhaps unsurprisingly, the treatment response to combined anti-TNF and MTX is better following failed MTX treatment than if the patient had previously responded well to MTX monotherapy (Alonso) and the combination is more efficacious than monotherapy (Lee). The therapeutic effects of the 3 drugs were similar in the Alonso review although drop-out rates differed whereas in the Lee review, indirect...
comparisons seemed to suggest that etanercept wasn’t quite as effective. Venkateshan confirmed that all biologics are efficacious in both MTX-naive and refractory patients. In terms of differential efficacy, Zintzaras reported that infliximab worked better at higher doses and in more severe RA and those benefits became more apparent with length of follow-up. This benefit was accentuated by the addition of low dose steroid.

Zintzaras also found that increasing the dose of infliximab was not associated with a higher incidence of adverse reactions and adverse reactions continue to be the focus of some reviews. Leombruno found that when using recommended doses of TNF blockers there is no increase in serious adverse reactions but that higher doses results in a doubling of the incidence. Salliot reports an increased risk in serious infection with higher dose anakinra but not with rituximab and abatacept but the comment is made that larger studies are necessary to be confident about this. Bongartz looked at etanercept with respect to the risk of malignancy. A higher rate in the etanercept treated patients was not statistically significant and wide confidence intervals mean that there is continuing uncertainty, at least from the results of this review. Finally, a review of abatacept demonstrated that this drug improves the Quality of Life in individuals who have an inadequate response to DMARDs and TNF blockers and while such results address one of the patients’ main concerns, this drug has not so far proved sufficiently cost effective to persuade NICE to recommend that it be available on the NHS (Shergy).

A couple of the publications warn us that we should not accept everything we read about anti-TNF drug treatment uncritically. The Lopez-Olivo and Roundtree reviews warn us firstly that not all guidelines and consensus statements are equal and secondly that reports of primary research may be open to criticism.

**Other drugs and aspects of RA therapy**

Reference has been made already to the risk of malignancy. Additional reviews by Kaiser and Smitten reinforce the existing view that the increased risk of lymphoma in RA is down to the disease rather than treatment. The second of these papers also refers to the increased risk of lung cancer and a reduced incidence of colorectal and breast cancer in rheumatoid patients. Methotrexate continues to receive attention. Katchamart suggests that efficacy/toxicity data don’t support combination DMARD therapy in preference to MTX monotherapy in MTX naive patients and in those with an inadequate response to a DMARD, more research is needed to compare MTX and combinations. The value of folic acid supplementation is confirmed by Prey’s review (it’s cheaper than folinic acid which is also effective) and Salliot has found that low dose MTX is safe in the longer term with some caveats about the low dose in studies and lack of data. Visser sets out what appears to be an optimal MTX dosing regime based on a systematic review of the literature.

Even low dose corticosteroid has consequences for bone density (Hoes) and curiously, adverse effects of corticosteroid seem to be reported less frequently in treatment of RA than inflammatory bowel disease but this may relate to some extent to duration of therapy and some differences in dosage.

The review by Chen highlights what we know about COX 2 drugs compared to standard NSAIDs and suggests that with the fall in price of PPIs, future research should pitch COX 2 drugs against an NSAID plus PPI.

One review (Perrot) examines the role of antidepressants and suggests that in chronic inflammatory conditions they have a role in managing fatigue and sleep disorders but not pain. Existing evidence suggests that adherence with therapy is likely to be a problem but this has not been studied systematically in chronic inflammatory rheumatoid conditions. (Harrold)

The reviews by Hawke and van der Leeden highlight the need for more research relating to the management of foot pain in RA.

There are only 2 systematic reviews dealing with surgery in relation to RA. One suggests that it would be premature to abandon wrist arthrodesis for arthroplasty (Cavaliere) and the other tells us that currently we have very little good evidence on which to base decisions about post operative management after MCP arthroplasty (Massy-Westropp).

Avina-Zubieta, Levy and Metsios deal with cardiovascular risk in RA patients and the now familiar messages about increased risk are reinforced (RA National Knowledge Week 2007 and 2008 - Why is cardiovascular disease so common in RA and what can we do about it?). The last of these reviews highlights the fact that there are no studies examining the role of exercise in mitigating these effects.

**Measurement**

Disease activity and outcome measures have been examined by Bentley, Kalyoncu and Karontisch. New instruments will require more work before they could be fully adopted. The importance of Patient Reported Outcomes is increasingly being recognised but reporting is variable – more work is needed here also. At least the ACR and EULAR have reached some agreement about reporting disease activity in trials based on a combination of evidence and expert opinion.
**Ethical and social considerations**

Moving away from directly clinical topics, Caplan reports that consideration of ethical issues is conspicuously absent from the rheumatology literature. Reported research also often treats study populations as being fairly homogeneous. McIlvane and Tugwell’s reviews draw attention to the fact that minority groups may not be properly represented and also that health inequalities are often not considered. The Cochrane Health Equity Field has been established to deal with this.

**2009 Annual Evidence Update on rheumatoid arthritis (RA) - Treatment uncertainties**

The NHS Evidence - musculoskeletal project team held a workshop with Mark Fenton of the UK Database of Uncertainties about the Effects of Treatments (DUETs) on 6 April 2009. The aim of the workshop was to identify treatment uncertainties for rheumatoid arthritis (RA). This involved critically appraising the identified Annual Evidence Update (AEU) systematic reviews regarding treatment options. The following treatment uncertainties were identified:

**Drugs - Biologicals**

- **Anakinra compared to other biological therapies for rheumatoid arthritis** (Mertens, M. and Singh, J. A. Anakinra for rheumatoid arthritis. Cochrane Database Syst Rev. 2009, Issue 1. [Link to specialist collection])

**Drugs - DMARDs**

- **Methotrexate combination therapy with non-biologic disease modifying antirheumatic drugs for rheumatoid arthritis in adults** (Katchamart, W., Trudeau, J., Phumethum, V., and Bombardier, C. The efficacy and toxicity of Methotrexate (MTX) monotherapy vs. MTX combination therapy with non-biologic disease-modifying anti-rheumatic drugs in rheumatoid arthritis: A systematic review and metaanalysis. Ann Rheum Dis. 2008. [Link to specialist collection])
- **Does methotrexate monotherapy increase the risk of malignancy in rheumatoid arthritis?** (Salliot, C. and van der Heijde, D. Long term safety of Methotrexate monotherapy in rheumatoid arthritis patients: A systematic literature research. Ann Rheum Dis. 2008. [Link to specialist collection])

**Other drugs**

Complementary / Alternative


Risk - cardiovascular


Risk - malignancy


Surgery


2009 Annual Evidence Update on rheumatoid arthritis (RA) - Methodology
The Annual Evidence Update (AEU) on rheumatoid arthritis for 2009 was produced by NHS Evidence - musculoskeletal. The aim was to identify all systematic reviews published in the past year.

- Total publications: 2205
- RCTs: 91
- Systematic Reviews after appraisal: 50

**Search period**
The final search was conducted on the 01 March 2009.

**Databases and search strategies**
**NHS search 2.0 (including AMED, British Nursing Index, CINAHL, EMBASE, MEDLINE and PsychINFO).** The library searched for "systematic* AND (review* OR overview*)" OR "meta*" AND "rheumat* arthritis"(Title / Abstract). The search was limited to human, English language and publication year 2008-2009. 41 records retrieved.

**PubMed clinical queries systematic review filter.** The library searched "rheumat* arthritis" as a free text search term, limiting the search to records published in the last year, human and English language. 97 records retrieved.

**PubMed using the SIGN systematic review filter.** The SIGN systematic review filter was selected because it emphasises specificity rather than sensitivity. The filter was combined with a search for "rheumat* arthritis" (Title / Abstract). The search was limited to records published in the last year, human and English language. 230 records retrieved.

**NHS Evidence - musculoskeletal**
The library searched "rheumat* arthritis" as a free text search term.

**Cochrane Library**
The library searched "rheumat* arthritis" as a free text search term

**Systematic review identification criteria**
Our aim was to identify all systematic reviews published on rheumatoid arthritis for the last year. To achieve this we searched 7 databases and 2 libraries listed above. All citations from database searches were imported into a bibliographic database and duplicates removed. The search results were then scanned by the information specialist. This involved scanning the titles, abstracts and full texts where available to identify potential systematic reviews.

To identify systematic reviews the definition used by [Glossary of Cochrane Collaboration Terms](http://www.cochrane.org/terms) was used:

“A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.”

The final decision on whether to include a citation as being a valid systematic review was made by Dr Ray Armstrong FRCP, Clinical Lead for NHS Evidence - musculoskeletal and Lead Consultant Rheumatologist, Southampton General Hospital.

**NICE guidance: The management of rheumatoid arthritis in adults**
[Link to 2009 Annual Evidence Update Rheumatoid Arthritis Contents](http://www.nice.org.uk/)

*This editorial was written by Dr Chris Deighton to accompany the 2009 Annual Evidence Update (AEU) on Rheumatoid Arthritis (RA). Dr Deighton was Clinical Advisor to the Guideline Development*
The NICE Guidelines on RA management were published in February 2009 [1]. The best available evidence has been interpreted by a Guideline Development Group (GDG) consisting of rheumatologists, patients, GPs, nurse specialists, and allied health professionals. This series of systematic reviews resulted in forty-six recommendations. This article focuses on some key recommendations, and contrasts them with the results of the recently published King’s Fund Report “Perceptions of patients and professionals on rheumatoid arthritis care”, commissioned by the Rheumatology Futures Group [2].

**Key recommendation 1:**
Refer for specialist opinion any person with suspected persistent synovitis of undetermined cause. Refer urgently if any of the following apply:

- the small joints of the hands or feet are affected
- more than one joint is affected
- there has been a delay of 3 months or longer between onset of symptoms and seeking medical advice.

The concept of a “window of opportunity” has emerged in early inflammatory arthritis, where prompt intervention can exert a profound impact on long-term outcomes [3]. By contrast, delays in presentation to specialist care and commencing disease modifying anti-rheumatic drugs (DMARDs), can lead to irreversible joint damage, and resultant disability that may never be recovered. Although there are classification criteria for RA [4], these were not designed for diagnosis in a recent onset of inflammatory arthritis [5], and any persistent inflammation in a joint requires a specialist opinion. However, the classical features of RA carry a particularly poor prognosis, such as disease affecting many joints, and particularly small joints of the hands and feet [3, 6]. Such patients therefore need to be referred urgently. The window of opportunity to exert an impact on long-term outcomes probably only lasts for about three months [1]. Therefore patients delaying seeing their GP should also be referred urgently. Recent research has highlighted that this delay from symptom onset to seeing the GP makes the greatest contribution to the overall delay to going onto DMARDs [7, 8]. The King’s Fund report highlighted the desire of patients to have first contact with a knowledgeable GP who can promptly recognise the signs and symptoms of inflammatory arthritis, and rapidly refer to specialist care [2]. 48.7% had to visit their GP more than 4 times before being referred, and 8.9% more than ten times. The delay from GP to specialist was less than 6 months in 71.6% of respondents. However, this is still too long for influencing disease outcomes, particularly if there was a further delay before the patient saw their GP.

What should happen to implement this recommendation? There is a need for public awareness of the importance of attending GPs early with symptoms and signs of synovitis. GPs require education with regular reminders on identifying early inflammatory arthritis, and to understand the justification for prompt referral to specialist care. The King’s Fund report recommended the use of referral criteria, structured local pathways, and access to service summaries which would assist GPs in raising awareness about local services available to RA patients, the preferred process for accessing the service, and the goals of treatment. Commissioning pathways need to ensure integration between primary and specialist care, so that rapid referral is encouraged and facilitated. Key performance indicators could be introduced to encourage early identification of inflammatory arthritis and prompt referral.

**Key Recommendation 2:**
In people with newly diagnosed active RA, offer a combination of disease-modifying anti-rheumatic drugs (DMARDs) (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment as soon as possible, ideally within 3 months of the onset of persistent symptoms.

There has been controversy about how best to treat early RA. Traditionally the approach was conservative, with symptom controlling medication followed by single DMARDs in those whose RA progressed. In recent years, trials of combinations of DMARDs have shown remarkable results in recent onset RA, with high rates of remission that are equivalent to those seen with biological therapies [9, 10]. A health economic analysis of various DMARD strategies in early RA conducted for
the NICE guidelines showed that aggressive use of combinations of DMARDs was more cost effective than any other strategy [11]. These trials have also tended to use steroids in some form or another, either orally, intramuscularly or intra-articularly. In addition, these studies have all been conducted in patients who fulfill the ARA classification criteria for RA, and usually in patients with “active” disease (albeit defined in different ways in different trials). In other words, this recommendation only applies to active polyarthritis that is symmetrical and peripheral. It is not known how best to treat more benign inflammatory arthritis. The NICE RA Guidelines highlight this as a recommendation for further research [1].

The King’s Fund report suggests a priority for improving services would be better awareness of RA treatment among GPs. If GPs witnessed a rapid service provided to patients with a acute synovitis, and the aggressive management where appropriate from disease onset, this would highlight the urgency of the situation, and the need for specialist management. However, there are barriers to combination therapies being prescribed for newly diagnosed active RA. In spite of the evidence to support this approach, rheumatologists may still be reluctant to use combination therapies [12, 13]. This may be due to concerns over toxicity, and problems convincing patients that this is the appropriate approach, thus jeopardizing adherence to regimens [13]. The evidence base for combination therapies in active RA needs to be reinforced to the rheumatology community to encourage change in current practice. Patients need to be provided with information so that they can make appropriate informed decisions on the treatment of their recently diagnosed RA.

**Key recommendation 3:**

In people with recent-onset active RA, measure C-reactive protein (CRP) and key components of disease activity (using a composite score such as DAS28) monthly until treatment has controlled the disease to a level previously agreed with the person with RA.

Traditionally patients with recent onset RA have been followed up at a time and frequency revolving around clinic appointment availability, rather than the needs of the patient. Assessment of disease has focused on physician and patient perceptions, rather than more objective indices of disease activity. Although the DAS28 has limitations [14], it is preferable to relying on physician and patient perceptions alone. The GDG was impressed by studies that demonstrated substantial improvements in disease control when patients were seen on a monthly basis, an index of disease activity was recorded, and action taken if inflammatory control was not satisfactory [9, 15, 16]. Benefits from this approach led to remission and disease control rates equivalent to those seen for biological therapies, but at considerably lower cost.

Resources issues are the barrier to implementing this recommendation, with more nurse specialists needed to see patients intensively from the start of active disease, and formally measure disease activity, with protocols to drive action for unsatisfactorily controlled disease. However, once the disease has come under control, follow ups could then be more relaxed, with prompt access for disease flares. Loading more resources into the acute aspects of the disease may decrease the need for expensive interventions in later disease, as well as keeping people in employment and other social roles that they fulfilled prior to the onset of RA.

**Key recommendation 4:**

People with RA should have access to a named member of the multidisciplinary team (for example, the specialist nurse) who is responsible for coordinating their care. The King’s Fund report highlighted the need for more consistent provision of multi-disciplinary team care, as the variation in access is stark across the UK. The report also emphasized the frequent delay in access to services when a flare of disease occurred, often waiting several weeks before being seen. The GDG recognized the value of the specialist nurse in the multidisciplinary team, the role they could have in coordinating care, acting as a contact point for patients, and helping them to steer through the sometimes confusing care pathways. The GDG made further recommendations for established RA, including the need for an annual review, where a structured approach could be taken to the musculoskeletal problems, as well as the impact of the disease on other organ systems (e.g. cardiovascular risk, osteoporosis, etc). This approach would help to identify the stoics who are gradually declining but not complaining, as well as the hidden consequences of RA.

In conclusion, the NICE RA Management Guidelines highlight evidence based recommendations for providing a high quality service. The King’s Fund report demonstrates that the provision of this service
is at best patchy and at worst non-existent. The Department of Health is developing a Commissioning Pathway on Inflammatory Arthritis that will be populated with the recommendations from the NICE guidelines, and with resource implications delineated. This will give an opportunity for commissioners to implement the NICE guidelines. It is to be hoped that if the King’s Fund report is repeated in five years time, then a greater quality and uniformity of care would be demonstrated, when compared with their bleak assessment in 2009.

References

2. Perceptions of patients and professionals on rheumatoid arthritis care. The Kings Fund, January 2009. [Direct document link - PDF] [Link to specialist collection]
8. Sandhu RS, et al. Comment on: Delay in presentation to primary care physicians is the main reason why patients with rheumatoid arthritis are seen late by rheumatologists. Rheumatology (Oxford) 2008; 47:559-560; author reply 560. [Link to journal full-text]
Acupuncture
A systematic review looked at acupuncture for pain and other parameters in RA. Eight randomized clinical trials (RCTs) including a total of 536 subjects were included: 4 placebo-controlled and 4 active-controlled trials. Average study duration was 11 weeks. Six studies reported a decrease in pain for acupuncture versus controls; the mean or median decrease in Tender Joint Count ranged from 1.5 to 6.5. Some studies also reported reduced inflammatory markers, but only one showed a significant difference for both ESR and CRP. The authors concluded that there are some favourable results in active-controlled trials, but placebo-controlled trials the evidence is conflicting. (Wang C, et al. Acupuncture for pain relief in patients with rheumatoid arthritis: a systematic review. Arthritis Rheum. 2008;59:1249-1256. [Link to specialist collection])

A systematic review of acupuncture for RA by another team of authors identified eight RCTs. Of these, four compared manual or electro-acupuncture with penetrating or non-penetrating sham acupuncture and did not show specific effects of acupuncture on pain. One compared manual acupuncture with indomethacin and suggested favourable effects of acupuncture in terms of total response rate. Three RCTs compared acupuncture and moxibustion with conventional drugs and did not show it superior to these. The authors concluded that RCTs of acupuncture controlled against penetrating or non-penetrating sham acupuncture did not show specific effects of acupuncture for pain control in patients with RA. (Lee MS, et al. Acupuncture for rheumatoid arthritis: a systematic review. Rheumatology (Oxford). 2008;47:1747-1753. [Link to specialist collection])

A systematic review by the same group looked at Bee venom acupuncture (BVA) for musculoskeletal pain. This involves injecting diluted bee venom at acupoints. The review included one trial in RA, controlled against disease-modifying anti-rheumatic drugs. This study and nearly all the other 10 studies included reported positive results. The authors considered that there is suggestive evidence for the effectiveness of BVA in musculoskeletal pain, but that definitive conclusions cannot be drawn because of the small number of studies and small sample size. (Lee MS, et al. Bee venom acupuncture for musculoskeletal pain: a review. J Pain. 2008;9:289-297. [Link to specialist collection])

All 3 reviews called for more rigorous research.

Diet and Nutrition
A Cochrane Review examined randomised controlled and controlled clinical trials (CCTs) of dietary manipulation for RA. Studies of nutritional supplements were excluded. 14 RCTs and one CCT, involving 837 patients, were included. Due to heterogeneity of interventions and outcomes, baseline imbalance and inadequate reporting, no overall effects could be calculated. A single trial with a moderate risk of bias found that fasting, followed by 13 months on a vegetarian diet, may reduce pain mean difference (MD) on a 0 to 10 scale -1.89, 95% CI -3.62 to -0.16, but not physical function or morning stiffness. Another single trial with moderate risk of bias found that a 12-week Cretan Mediterranean diet may reduce pain (MD on a 0 to 100 scale -14.00, 95% CI -23.6 to -4.37), but not physical function or morning stiffness. Two trials comparing a 4-week elemental diet with normal diet reported no significant differences. Due to inadequate reporting, the effects of vegan and elimination diets are uncertain. There was significantly higher total drop-out of (10%) and higher treatment-related drop-out of (5%) and a significantly more weight loss (weighted mean difference 3.23kg) comparing any dietary manipulation with normal diet. The authors’ conclude that the effects of dietary manipulation, including vegetarian, Mediterranean, elemental and elimination diets, on rheumatoid arthritis are uncertain because the studies are small, single trials with moderate to high risk of bias. Higher drop-out rates and weight loss with dietary manipulation that potential adverse effects should not be ignored. (Hagen KB, et al. Dietary interventions for rheumatoid arthritis. Cochrane Database Syst Rev. 2009, Issue 1. [Link to specialist collection])

A Cochrane review of antioxidant supplements for prevention of mortality found 67 randomised trials with 232,550 participants and concluded that there is no evidence to support antioxidant supplements for primary or secondary prevention; Vitamin A, beta-carotene, and that vitamin E may even increase mortality. Five of these trials were in RA, but there were no deaths in any of these. The review did not look at the effects of antioxidants on RA per se. (Bjelakovic G, et al. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst Rev. 2008, Issue 2. [Link to specialist collection])

Herbal medicines
A meta-analysis compared Sinomenine, an alkaloid derived from the plant Caulis sinomenii, used in Traditional Chinese Medicine, with non-steroidal anti-inflammatory drugs (NSAIDs) in terms of efficacy and safety in rheumatoid arthritis. 10 clinical trials involving 1185 patients, all conducted in China, met
the inclusion criteria. Significantly more patients improved and became rheumatoid factor negative after treatment with Sinomenine than with NSAIDs (p<0.00001 and p = 0.008). Sinomenine was more effective in terms of morning stiffness (p<0.00001), painful joints, and erythrocyte sedimentation rate. There was no significant difference between the two treatments in swollen joints, grip strength, and C-reactive protein. Adverse events occurred less frequently in the digestive system with Sinomenine but more frequently in the dermatomucosal system. The authors conclude that Sinomenine may be of value in RA but more high-quality trials are required. (Xu M, et al. Sinomenine versus NSAIDs for the treatment of rheumatoid arthritis: a systematic review and meta-analysis. *Planta Med.* 2008;74:1423-1429. [Link to specialist collection])

A systematic review of the effectiveness of willow bark for musculoskeletal pain found one study in RA. No significant effect was detected but the study was grossly underpowered. Positive results were found for low back pain. Ethanolic extracts in daily doses up to 240 mg salicin for six weeks were used. Minor adverse events only occurred. The authors conclude that further studies are required to determine if RA responds to higher doses. (Vlachojannis JE, et al. A systematic review on the effectiveness of willow bark for musculoskeletal pain. *Phytother Res.* 2009 Jan 12. [Epub ahead of print] [Link to PubMed abstract])

A comprehensive review of the literature summarised the pharmacological and clinical effects of rose hip (fruit of Rosa canina L.). Preparations of rose hip, and rose hip and seed are known to have antioxidative and anti-inflammatory effects. The proprietary rose hip preparation Litozin® has been associated with positive results in small scale studies in conditions including RA. However, the size of the clinical effects needs to be clarified to confirm clinical significance. Rose hip also has smooth muscle-relaxing actions, lipid-lowering, anti-obesity and anti-ulcerogenic effects. Further research is needed to verify these claims. (Chrubasik C, et al. A systematic review on the Rosa canina effect and efficacy profiles. *Phytother Res.* 2008 Jun;22(6):725-33. [Link to specialist collection])

### 2009 Annual Evidence Update on rheumatoid arthritis (RA) - Horizon scanning

The NHS Evidence - musculoskeletal Project Team have identified forthcoming guidelines, projects and reviews concerning rheumatoid arthritis. These establish evidence which will be published on rheumatoid arthritis in the future.

**National Institute for Health and Clinical Excellence (NICE)**

- [Rheumatoid arthritis - tocilizumab](https://www.nice.org.uk/guidance/cg136/guidance) (Oct 2009)
- [Golimumab for the treatment of methotrexate-naive rheumatoid arthritis](https://www.nice.org.uk/guidance/cg137/guidance) (Jan 2010)
- [Rheumatoid arthritis - certolizumab pegol](https://www.nice.org.uk/guidance/cg138/guidance) (Feb 2010)
- [Rheumatoid arthritis (methotrexate-naive) - golimumab](https://www.nice.org.uk/guidance/cg137/guidance) (Jan 2010)

**Cochrane Library - Protocols**

- Abatacept for rheumatoid arthritis
- Aquatic therapy exercise for treating rheumatoid arthritis
- Assistive technology for rheumatoid arthritis
- Balance training (proprioceptive training) for patients with rheumatoid arthritis
- Biologics for rheumatoid arthritis: an overview of Cochrane reviews
- Certolizumab pegol (CDP870) for rheumatoid arthritis in adults
- Comprehensive physiotherapy for rheumatoid arthritis
- Dynamic exercise therapy in patients with rheumatoid arthritis
- Erythropoietin for anemia in rheumatoid arthritis
- Exercise therapy for the rheumatoid hand
- Home-based exercise therapy for rheumatoid arthritis
- Hypolipidemic and antihypertensive drugs for prevention of cardiovascular complications in patients with rheumatoid arthritis
- Mobile bearing vs fixed bearing prostheses for total knee arthroplasty for post-operative functional status in patients with osteoarthritis and rheumatoid arthritis
- Opioid therapy for treating rheumatoid arthritis pain
- Rituximab for rheumatoid arthritis

**SIGN**
The following [forthcoming guidelines](#) are in development or in the process of being updated:


**HTA Projects (recent)**

- [Tocilizumab for the treatment of rheumatoid arthritis](#)
- [SARAH: Strengthening And stretching for people with Rheumatoid Arthritis of the Hands: The clinical and cost-effectiveness of an exercise programme over and above usual care](#)
- [Abatacept for the treatment of refractory rheumatoid arthritis](#)
- [Rituximab for the treatment of refractory rheumatoid arthritis](#)
- [Randomised controlled trial of tumour-necrosis-factor inhibitors against combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis: the TACIT trial](#)