2010 Annual Evidence Update on rheumatoid arthritis

Introduction

NHS Evidence - musculoskeletal have produced an Evidence Update on Rheumatoid Arthritis. Having searched the literature for high quality evidence that has accumulated within the last year, NHS Evidence - musculoskeletal have focused on guidance and systematic reviews published before March 2010. As in recent years the majority of publications relate to various aspects of drug treatments. Although this constitutes a proportion of the clinical activity in relation to this disease, other important developments and various aspects of rheumatoid disease management also feature prominently in our update. This Evidence Update should be of particular interest to all health professionals working in this field.

Acknowledgements

We would like to acknowledge and thank Dr Ray Armstrong, Lead Consultant Rheumatologist in Southampton University Hospitals NHS Trust and the Clinical Lead for NHS Evidence - musculoskeletal specialist collection, for providing the commentary and appraising the literature search which has enabled this Annual Evidence Update to be produced.

2010 Annual Evidence Update on rheumatoid arthritis - Methodology

The Annual Evidence Update (AEU) on rheumatoid arthritis for 2010 was produced by NHS Evidence - musculoskeletal. The aim was to identify all systematic reviews published in the past year.

- Total publications: 2211
- RCTs: 100
- Systematic Reviews after appraisal: 50

Search period

The final search was conducted on the 19 February 2009.

Databases and search strategies

- Ovid Medline using SIGN Medline filter. We searched “rheumat* AND arthriti**” and limited the search to records published in the last year, and English language.
- Ovid Embase using SIGN Embase filter. We searched “rheumat* AND arthriti**” and limited the search to records published in the last year, human and English language.
- PubMed clinical queries systematic review filter. We searched “rheumat* AND arthriti**” and limited the search to records published in the last year, human and English language.
- 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* AND arthriti**” (Ti/Ab). The search was limited to records published in the last year, human and English language.
- NHS Evidence - musculoskeletal. We searched “rheumatoid AND arthritis” as a free text search term.
- NHS Evidence - trauma and orthopaedics. We searched “rheumatoid AND arthritis” as a free text search term.
- Cochrane Library. Searching “rheumatoid AND 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 3 databases using systematic review filters, and 3 libraries using free text searching. All citations from database and NHS Evidence 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 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 and topic scoping of the identified systematic reviews was made by Dr Ray Armstrong FRCP, Clinical Lead for NHS Evidence - musculoskeletal and Lead Consultant Rheumatologist, Southampton General Hospital.

2010 Annual Evidence Update on rheumatoid arthritis - Results

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

- **Guidance** (9)
- **Diagnosis** (1)
- **Drug treatment**
- **DMARDs** (13)
- **Corticosteroids** (2)
- **Biologics** (16)
- **Complementary & alternative** (1)
- **Intra-articular hyaluronate** (1)
- **Physical interventions** (3)
- **Surgery** (2)
- **Complications** (3)
- **Risk** (5)
- **Trial methodology and reporting** (5)

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.

**Guidance**

BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. March 2010. [Link to guidelines - pdf]


EULAR/EFORT recommendations for the diagnosis and initial management of patients with acute or recent onset swelling of the knee. 11 December 2009. *Annals of the Rheumatic Diseases.* [Link to specialist collection]


**Diagnosis**


**Drug treatment**

**DMARDs**


Schipper LG, Fransen J, Barrera P, van Riel PL. Methotrexate in combination with sulfasalazine is more effective in rheumatoid arthritis patients who failed sulfasalazine than in patients naive to both drugs. *Rheumatology (Oxford)* 2009; 48(7):828-833. [Link to specialist collection]


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**Corticosteroids**

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**Biologics**

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**Complementary & alternative**


**Intra-articular hyaluronate**


**Physical interventions**


**Surgery**


**Complications**


**Risk**


**Trial methodology and reporting**


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**2010 Annual Evidence Update on rheumatoid arthritis - Commentary**

**Guidance**

The BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy are so named in anticipation of possible changes in NICE guidance on the use of these drugs especially with new agents becoming available. It is suggested that the threshold for treating rheumatoid disease with biological agents should be decreased from a DAS28 score of 5.1 to 3.2. The rationale for this change in guidance is discussed with reference to the relevant literature. From the same source comes the guidance for management of rheumatoid arthritis after the first 2 years. A recent addition to the therapeutic armamentarium for the treatment of rheumatoid disease is Certolizumab Pegol which has recently received approval from NICE for use in the NHS. Perhaps one of the more interesting features of this guidance is the patient access scheme. Please see the following for further discussion of this guidance - [click here](#)

From a primary care perspective, it is important that there should be clear guidance for management of both suspected and confirmed rheumatoid disease. This has been published within the last year as part of the Clinical Knowledge Summaries series. Other aspects of rheumatoid disease management have also received attention. EULAR has published recommendations for cardiovascular risk management in patients with rheumatoid disease and other forms of inflammatory arthritis and in addition, the Royal College of Ophthalmologists has up-dated its recommendations on screening patients for ocular toxicity when receiving treatment with hydroxychloroquine. It is acknowledged that the incidence of significant hydroxychloroquine retinopathy is very low indeed and that this would be rather more likely to occur with chloroquine, should this be used instead. Therefore, they recommend that hydroxychloroquine should always be used preferentially and the use of chloroquine would need to be discussed with the patient with respect to its risk of causing visual impairment. The early detection of hydroxychloroquine retinopathy is discussed. Various methods of screening are mentioned. The reviewing group concluded that the available evidence does not support the introduction of a programme of systematic screening for hydroxychloroquine toxicity at the present time because clinically significant maculopathy is very rare and there is currently no reliable test for detecting it at a reversible stage. Recommendations for good practice are listed including the advice that the maximum dosage should not exceed 6.5 mg/kilogram of lean bodyweight. If visual impairment is suspected, the patient should be advised to consult an optometrist in the first instance. Referral to an ophthalmologist is desirable if the patient has a visual impairment or eye disease detected at a baseline assessment and confirmed by an optometrist. Reduction or alteration of vision during treatment should also prompt consideration for referral. Recommendations are also given as to the nature of the examination to be undertaken by the ophthalmologist.

**Systematic Reviews**
As in previous years, a predominance of systematic reviews deals with therapeutic aspects of rheumatoid arthritis. There are not many publications in this update that will result in any significant change in practice but it is worth highlighting some of the conclusions.

**Conventional DMARDs:**
Methotrexate, and rightly so as the cornerstone of initial DMARD therapy, continues to receive much attention. The message continues to be (with appropriate monitoring of course) that methotrexate is safe and it is suggested that for patients in remission, it may be appropriate to extend the interval for methotrexate therapy [Bogas]. Interestingly, although we are encouraged to initiate combination therapy in early rheumatoid arthritis, Katchamart suggests that in DMARD naive patients, the balance of efficacy/toxicity favours methotrexate monotherapy. Another publication [Schipper] suggests that while adding methotrexate to sulfasalazine monotherapy may be effective, using methotrexate and sulfasalazine concurrently in DMARD naive patients has no added value.

Yet another publication [Loza] provides reassurance that in certain circumstances at least, it is safe to continue with methotrexate perioperatively. With regard to adverse effects of methotrexate, folic acid and folinic acid seem to be equally efficacious in reducing the risk of liver enzyme elevation [Prey]. However, there is no evidence for benefit with regard to other adverse effects although insufficient data make it difficult to know whether haematological side-effects are any different on this treatment. Clinicians recognise that liver enzyme elevations occur frequently and often transiently. Sometimes serially abnormal tests can be associated with liver pathology but cirrhosis is fairly rare [Visser]. However, what isn’t clear is how treatment should ideally be adjusted in these circumstances or indeed to what extent methotrexate independently contributes to liver toxicity.

**Corticosteroid:**
Modest doses of steroid seem to be fairly safe in the medium to long term [Ravindran] but in the literature, the risk of adverse effects seems to depend on study design and disease under consideration. There seems to be much variability in assessment and reporting of adverse events [Hoes].

**Biologic DMARDs:**
Nothing very startling has been reported within the last year. There is some ongoing uncertainty about the risk of malignancy with TNF inhibition but so far the evidence has been that the risk is minimal and in the study reported [Bongartz], this was not statistically significant. TNF inhibitors are generally safe in standard dosage but there is a twofold increase in risk of serious infections with high-dose anti-TNF therapy [Leambruno]. Indirect comparisons must always be treated with caution but in the study by Singh, the conclusions were that Anakinra was less effective than adalimumab and etanercept, and etanercept was safer than adalimumab, anakinra and infliximab which probably reinforces current impressions.

Given the significant primary and secondary non-response rate when using TNF inhibitors, it would be extremely helpful to have biomarkers to assist in selection of patients who are likely to benefit from this intervention. One particular candidate has been studied by two groups who have come to slightly different conclusions! [O'Reilly, Pavey].

**Other aspects of rheumatoid disease:**
It is reported that the 60% increase in cardiovascular death in rheumatoid patients compared to the general population has not changed recently so efforts to address risk factors need to be intensified [Meune]. In one study, it is reported that biologic DMARDs appear to be associated with an increase in lipid levels during treatment but the implications are not straightforward since the atherogenic index didn't significantly change. Studies that report effects on cholesterol seldom report on the whole lipid profile [Schimmel].

**Patient centred aspects:**
It seems that a self-report tender joint count correlates reasonably well with that undertaken by a trained assessor whereas in the case of swollen joint counts, the level of correlation is lower. The authors raise the possibility of incorporating self-report tender joint counts in assessment of disease activity [Barton].

Patient reported outcomes (PROs) have been stimulating increasing interest. However in recently published trials, there has been great variability in reporting these outcomes and some domains which
patients probably consider to be most important are often omitted (e.g. fatigue, coping and sleep disturbance). More work is required here [Kalyoncu].

And finally.....
Given our reliance upon reviews in the biomedical literature to inform clinical decision-making (as exemplified by what you are reading now) it is disappointing that we still need to be quite so cautious about believing and relying upon everything that comes to our attention. In one study, in excess of 90% of published reviews were found to be narrative and not systematic and frequently, conflicts of interest were inadequately reported [Roundtree]. Selection and reporting bias can seriously undermine the authority of a review.

2010 Annual Evidence Update on rheumatoid arthritis - Treatment uncertainties

The NHS Evidence - musculoskeletal project team have identified treatment uncertainties for rheumatoid arthritis. This involved critically appraising the systematic reviews identified in the Annual Evidence Update (AEU) regarding treatment options. The following treatment uncertainties were identified:

Drugs

- Abatacept for rheumatoid arthritis
- Biologics for rheumatoid arthritis
- Intra-articular hyaluronate for rheumatoid arthritis
- DMARDs for rheumatoid arthritis
- Methotrexate combination therapy with non-biologic disease modifying antirheumatic drugs for treating rheumatoid arthritis in adults

Physical interventions

- Assistive technology for rheumatoid arthritis
- Dynamic exercise programs (aerobic capacity and/or muscle strength training) in rheumatoid arthritis

2010 Annual Evidence Update on rheumatoid arthritis - Horizon scanning

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

National Institute for Health and Clinical excellence (NICE)

- Rheumatoid arthritis - tocilizumab (May 2010)
- Tocilizumab for the treatment of rheumatoid arthritis (June 2010)

SIGN
The following guideline is in the process of being updated:

- Management of early rheumatoid arthritis - selective update (Spring 2010)

HTA Projects (recent)
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

Rheumatoid arthritis - drugs for treatment after failure of a TNF inhibitor

Abatacept 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

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor

Certolizumab pegol (CIMZIA®) for the treatment of Rheumatoid Arthritis

Cochrane Library - protocols

- Rituximab for rheumatoid arthritis
- Tocilizumab for rheumatoid arthritis
- Comprehensive physiotherapy for rheumatoid arthritis
- Biologic interventions for fatigue in rheumatoid arthritis
- Home-based exercise therapy for rheumatoid arthritis
- Non-pharmacological interventions for fatigue in rheumatoid arthritis
- Opioid therapy for treating rheumatoid arthritis pain
- Erythropoietin for anemia in rheumatoid arthritis
- Certolizumab pegol (CDP870) for rheumatoid arthritis in adults
- Aquatic therapy exercise for treating rheumatoid arthritis
- Balance training (proprioceptive training) for patients with rheumatoid arthritis
- Hypolipidemic and antihypertensive drugs for prevention of cardiovascular complications in patients with rheumatoid arthritis
- Metal versus non-metal backing of the tibial component for total knee replacement for osteoarthritis and/or rheumatoid arthritis
- Exercise therapy for the rheumatoid hand

2010 Annual Evidence Update on rheumatoid arthritis - Additional reference material

The past year has seen a number of reports relating to rheumatoid arthritis published:

- ARMA 'Charter for work'. Arthritis and Musculoskeletal Alliance (ARMA). 02 March 2010. [Link to specialist collection]

- Services for people with rheumatoid arthritis. United Kingdom Parliament. 23 February 2010. [Link to specialist collection]
