

**THE EFFECTIVENESS OF NON BIOLOGIC DMARDS AFTER
ANTI TNF α INHIBITOR FAILURE**

DECISION SUPPORT UNIT

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1. INTRODUCTION

Estimates of the cost effectiveness of sequential use of the tumour necrosis factor alpha inhibitors (TNF- α inhibitors) etanercept, adalimumab and infliximab depend on a number of factors, *inter alia*, the effectiveness of the TNF- α inhibitors themselves in patients that have failed a previous TNF- α inhibitor and the effectiveness of the comparator i.e. non biologic disease modifying anti-rheumatic drugs (DMARDs) in the same population.

The independent assessment group model (BRAM) considers individual patients receiving different drugs in sequence but is limited by the absence of evidence which specifically relates to the drugs in the positions in which they are being modelled (Chen et al. 2006). Therefore, assumptions which relate the available evidence to the actual model are required. One approach is to assume that the effectiveness of each drug is not affected by its position in the sequence. However, since disease duration and the number of previous DMARDs have been shown to influence the probability of response in rheumatoid arthritis (Anderson et al. 2000; Drossaers-Baker et al. 2002), this may not be an appropriate assumption. The Appeal Panel specifically requested that the committee consider “an extended sensitivity analysis that considers a wider possible range of effectiveness for standard disease-modifying agents when used after anti TNF therapy” (point 140, NICE)

The purpose of this review is to identify and summarise evidence that relates to the effectiveness of non biologic DMARDs in patients that have previously failed a biologic and to provide other information that may be useful in the consideration of this issue. Specific aims are:

- 1) To update the review undertaken by the independent assessment group to identify:
 - a. Evidence of effectiveness of DMARDs in patients that have failed a TNF- α inhibitor
 - b. Evidence of effectiveness of DMARDs in patients that have late stage RA

2) Identification of other evidence which highlights the influence of disease duration and/or number of previous DMARDs failed on the effectiveness of DMARDs.

2. METHODS FOR REVIEWING EFFECTIVENESS

2.1. SEARCH STRATEGY

The primary purpose of the search was to identify all evidence relating to the clinical effectiveness of any DMARD used in the BRAM model, irrespective of its position in the sequence (methotrexate, sulfasalazine, leflunomide, gold, azathioprine, cyclosporin, penicillamine) or DMARDs as a class in patients that had failed a TNF- α inhibitor. The secondary aim was to assess the evidence in patients that had late RA.

The search terms used by the independent assessment group were run (Chen et al. 2006, Appendix 6; see Appendix 1 of this document) in an updated search covering the dates 2005 to November 2007. Medline, Cinahl, Embase, NHS EED and HEED were searched. Hand searches of reviews were also conducted.

2.1.1. Inclusion/exclusion criteria

Inclusion

- Any study which considers one or more of the DMARDs used in the Birmingham cost effectiveness model (methotrexate, sulfasalazine, leflunomide, gold, azathioprine, cyclosporin, penicillamine) or DMARDs as a class
- Any study type
- Primary effectiveness reported in terms of HAQ, ACR, DAS, EULAR or other recognised outcome measured in RA.
- Rheumatoid arthritis patients only or where mixed groups of patients are studied, the results are reported for RA patients alone.
- For part a) studies which identified patients that had previously withdrawn from a TNF- α inhibitor due to either lack or loss of efficacy.

Exclusion

- Studies that considered any of the biologic DMARDs unless they also consider the non biologic DMARDs listed above
- Studies that do not report relevant clinical outcomes.
- Studies of patients with juvenile arthritis, Crohn’s disease, psoriatic arthritis and other forms of spondyloarthritis, unless RA patients could be distinguished in the results.
- Studies not reported in English

3. RESULTS

3.1.NUMBER OF RELEVANT STUDIES

The updated searches identified 218 references. On inspection of the titles and abstracts where available, 26 papers were considered eligible for full review. These papers are reported in Table 1. Only three of these papers considered DMARDs in patients that had failed a TNF- α inhibitor (Cohen et al. 2006, Genovese et al 2006, Westhovens et al. 2006). These are studies which relate to clinical trials of abatacept and rituximab and are discussed in section 3.3.1 below. Four papers were identified that provided information on DMARDs in late RA (Lehman et al. 2005; Aletaha et al. 2008; Brennan et al. 2007; Van der Keijde et al. 2006). Brennan et al. (2007) is a cost effectiveness analysis which uses the BSRBR as the principle source of data for the model. The relevant element of this paper is described in section 3.3.2 below.

Table 1: Studies identified by the searches with reasons for exclusion from the final review

	REFERENCE	Reviewed or excluded? (DMARDs post anti TNF)	Reviewed or excluded? (DMARDs in late RA)
1	Abe et al. (2006)	Excluded: Anti-TNF study, not DMARD	Excluded: Anti-TNF study, not DMARD
2	Aletaha (2008)	Excluded: Not DMARDs post anti TNF failure	REVIEWED
3	Alten et al. (2006)	Excluded: In German	Excluded: In German
4	Arshad (2007)	Excluded: Review article	Excluded: Review article
5	Augustsson (2006)	Excluded: Patient population is early RA	Excluded: Patient population is early RA
6	Bathon et al. (2006)	Excluded: Anti-TNF study, not DMARD	Excluded: Anti-TNF study, not DMARD

7	Bongartz (2006)	Excluded: Anti-TNF study, not DMARD	Excluded: Anti-TNF study, not DMARD
8	Brennan (2007)	Excluded: Not DMARDs post anti TNF failure	REVIEWED
9	Buchbinder (2007)	Excluded: Not a formal study	Excluded: Not a formal study
10	Capell et al. (2007)	Excluded: Patient population is early RA	Excluded: Patient population is early RA
11	Chen et al. (2001)	Excluded: Anti-TNF study, not DMARD	Excluded: Anti-TNF study, not DMARD
12	Cohen (2006)	REVIEWED	
13	Doan (2005)	Excluded: Anti-TNF study, not DMARD	Excluded: Anti-TNF study, not DMARD
14	Genovese (2005)	REVIEWED	
15	Kawai (2006)	Excluded: Not DMARD therapies	Excluded: Not DMARD therapies
16	Khan (2007)	Excluded: Patient population is early RA	Excluded: Patient population is early RA
17	Lehman et al. (2005)	Excluded: Not DMARDs post anti TNF failure	REVIEWED
18	Maddison (2005)	Excluded: Patient population is early RA	Excluded: Patient population is early RA
19	Nixon et al. (2007)	Excluded: Not a formal study	Excluded: Not a formal study
20	Pieringer (2007)	Excluded: Not a study of DMARD discontinuation after a sub-optimal response or adverse event	Excluded: Not a study of DMARD discontinuation after a sub-optimal response or adverse event
21	Pincus et al. (2007)	Excluded: Review article	Excluded: Review article
22	Plosker (2005)	Excluded: Patient population is early RA	Excluded: Patient population is early RA
23	Summers et al. (2005)	Excluded: Anti-TNF study, not DMARD	Excluded: Anti-TNF study, not DMARD
24	Van der Keijde (2006)	Excluded: Not DMARDs post anti TNF failure	REVIEWED
25	van Der Heijde (2007)	Excluded: Patient population is early RA	Excluded: Patient population is early RA
26	Westhovens et al. (2006)	REVIEWED	

3.2. REVIEW OF STUDIES

Aletaha et al. (2008) identified all RCT data published between 1980 and 2005 that included information on mean duration of RA and HAQ change at either 6 or 12 months. Treatment arms within trials were classed as “non biologic DMARDs”, “biologic DMARDs” or “placebo”. Multiple regression was then used to estimate the relationship between HAQ effect (defined as [mean HAQ at 6 months – mean baseline HAQ]/SD of baseline HAQ) and disease duration and treatment as explanatory variables. The results claim to show that disease duration is associated with lower HAQ effect in studies of both biologics and traditional DMARDs (p.241). However, the main 6 month analysis shows a stable HAQ responsiveness as disease duration increases in the traditional DMARD studies. In both the 6 and 12 month analysis, there is no significant difference between DMARDs and biologics after approximately 7 years disease duration. However there are several limitations to the study.

The authors do not report the actual models fitted. Although a GLM model is fitted the link function used is not reported and the results appear to be no different to an OLS. More importantly, since neither the actual model fitted, or the coefficients on the explanatory variables are reported, it is difficult to assess the appropriateness of the statistical approach or the interpretation of the results. The method of reporting suggests that the modelling of the treatment covariate imposes restrictions that may not be appropriate, although there is insufficient detail on this issue.

It should also be noted that whilst the analysis is restricted to RCTs, arms of the trials are considered as separate and independent in the analysis. The limitation to RCTs in this situation may not be appropriate.

It is a limitation of the study that “number of previous DMARDs failed” is not considered since this is also likely to be an important determinant of treatment effect and be correlated with disease duration.

Finally, the authors report subgroup analyses which include consideration of just methotrexate trials. Since methotrexate is not one of the DMARDs under consideration for those that have failed a biologic, it is questionable how much of the data relates to other relevant DMARDs and whether the same results would be obtained.

Lehman et al (2005) consider 65 patients randomised to receive either intramuscular gold (n=38) or placebo (n=27) in addition to methotrexate. All patients had previously experienced a suboptimal response to methotrexate over at least 12 weeks of therapy. Although this study does not specifically consider patients with late RA, the baseline characteristics are not substantially different from the early RA study used currently in the Birmingham model to estimate the mean HAQ improvement for both gold and cyclosporine (Kvien et al. 2002). Table 2 shows that patients in the Lehman study have slightly later stage disease than those in the Kvien study, in terms of disease duration (3.4 yrs versus 1.02yrs) and HAQ (1.27 versus 1.1), although this is substantially different to the BSRBR cohort (mean 13.7 years at the start of first TNF inhibitor). Lehman includes the mean number of previous DMARDs failed in the description of baseline characteristics. Kvien report the proportion of patients that had failed at least one previous DMARD at baseline. Therefore, the study populations are not directly comparable on this criteria.

Table 2: Comparison of patient characteristics in Lehman and Kvien studies

	Gold arm (Lehman 2005)		Gold arm (Kvien 2002)	
	Mean	sd	Mean	sd
Disease duration (yrs)	3.4	2.5	1.02	0.86
Number of previous DMARDs failed	1.62	0.64		
HAQ-DI	1.27	0.6	1.1	0.6
Previous DMARDs			0.44	

Lehman (2005) reports ACR20 response rates of 58% versus 22% for gold versus placebo, 18% versus 0% for ACR50 and 4% versus 0% for ACR70 (see Table 3). HAQ changes are reported as a percentage change from baseline (38% versus 15%).

Table 3: Lehman (2005) efficacy results at 24 weeks

	Gold	Placebo
ACR20 (%)	58	22
ACR50 (%)	18	0
ACR70 (%)	4	0
HAQ (percentage reduction)	38	15

van der Keijde et al. (2006) is a long term follow up of a trial of etanercept plus methotrexate versus methotrexate alone in patients that had experienced an unsatisfactory response to at least one DMARD, but not methotrexate, and had not received any DMARD or corticosteroid for at least 4 weeks. The full details of this trial are reported in Klareskog et al. (2004) and since the one year results are also presented in this paper this review draws principally on Klareskog et al. (2004). Patients were randomised to receive either methotrexate plus placebo (n=228), etanercept plus methotrexate (n=231) or etanercept alone (n=223).

Baseline characteristics show that patients in this trial have a mean disease duration of 7 years, have failed 2.3 previous DMARDs and have a baseline HAQ of 1.8 (see Table 4).

Table 4: Baseline characteristics in TEMPO trial (from Klareskog et al. 2004)

	N	Age in years (sd)	Disease duration years (sd)	No previous DMARDs (sd)	Baseline HAQ
Placebo + MTX	228	53 (12.8)	6.8 (5.5)	2.3 (1.6)	1.7
Etanercept + MTX	231	52.5 (12.4)	6.8 (5.4)	2.3 (1.4)	1.8
Etanercept	223	53.2 13.8)	6.3 (5.1)	2.3 (1.4)	1.8

Response rates are shown in Table 5. 74% of patients in the methotrexate arm achieved an ACR20 response at 24 weeks, 40% achieved ACR50 and 14% achieved ACR70. HAQ changes are reported at 52 weeks only. A mean improvement of 0.6 was experienced by those in the methotrexate arm.

Table 5: Responses in TEMPO study (from Klareskog et al. 2004)

	ACR20	ACR50	ACR70	HAQ
	% at 24 wks			52 wks
Placebo + MTX	74	40	14	-0.6
Etanercept+ MTX	79	58	33	-1.0
Etanercept	73	41	18	-0.7

It should be noted that whilst the TEMPO study is on average a late RA population, the wide variation in disease duration means that a significant proportion of patients have early disease. Furthermore, the mean of 6.8 yrs is substantially less than the mean of the BSRBR population (13.7 years at the start of first TNF inhibitor). In addition, the study is restricted to methotrexate amongst the DMARDs. Since the licensing authorisation for etanercept, adalimumab and infliximab state that these should be given in combination with methotrexate, the study may be of limited usefulness.

Methotrexate is the first DMARD considered in the sequence of drugs in the BRAM and current NICE guidance recommends patients only receive TNF- α inhibitors after having failed methotrexate unless contraindicated.

3.3. OTHER RELEVANT EVIDENCE IDENTIFIED

3.3.1. Abatacept and rituximab studies

Abatacept (Orencia®, Bristol Myers Squibb) and Rituximab (Mabthera®, Roche) are both licensed for the treatment of patients with RA after failure of a TNF- α inhibitor. The pivotal trials of these treatments both include a control arm of patients who received treatment with traditional DMARDs. The start of DMARD treatment does not coincide with the baseline measures of the trial and therefore these are not trials of the effectiveness of DMARDs. Nevertheless, some potentially useful information may be provided in relation to the longer term effect of conventional DMARDs after TNF- α inhibitor failure.

Genovese et al. (2005) consider the use of abatacept versus placebo in patients that had withdrawn from either etanercept or infliximab due to lack of efficacy after at least three months of treatment. Adalimumab use was not widespread at the time of the study. All patients had to have been taking oral DMARDs or anakinra for at least 3 months (and a stable dose for 1 month). Changes in DMARD doses were not permitted within the study period except to avoid adverse events..

Cohen et al. (2006) consider the use of rituximab versus placebo in patients that had experienced an inadequate response or intolerance to at least one of the anti-TNF therapies. All patients had to have been taking methotrexate for at least 3 months (and a stable dose for at least 1 month) and methotrexate treatment was continued throughout the study period.

Therefore, whilst neither study provides direct evidence of initial response to conventional DMARDs in those that have withdrawn from a TNF- α inhibitor, there is some indication given as to the long term effect and may provide an indication of the lower bound of initial effect.

Considering the placebo arms of these two studies, similar improvements of 0.1 in mean HAQ score are reported at 6 months (see Table 6).

Table 6: Baseline and 6 month outcomes from abatacept and rituximab trials at 6 months.

	Genovese et al.					Cohen et al.				
	Placebo (n=133)		Abatacept (n=256)			Placebo (n=209)		Rituximab (n=298)		
		sd		sd	p		sd		sd	P
Baseline										
Age (yrs)	52.7	11.3	43.4	12.4		52.8	12.6	52.2	12.2	
Sex (% female)	79.7		77.1			81		81		
Disease Duration (yrs)	11.4	8.9	12.2	8.5		11.7	7.7	12.1	8.3	
HAQ	1.8	0.6	1.8	0.6		1.9	0.5	1.9	0.6	
No of previous DMARDS						2.4	1.8	2.6	1.8	
6 months										
HAQ	-0.11	0.46	-0.45	0.48	<0.001	-0.1	0.5	-0.4	0.6	<0.0001
ACR20 (%)	19.5		50.4		<0.001	18		51		<0.0001
ACR50 (%)	3.8		20.3		<0.001	5		27		<0.0001
ACR70 (%)	1.5		10.2		<0.001	1		12		<0.0001
EULAR Good (%)						2		15		
EULAR Moderate (%)						20		50		<0.0001*

* P-value for EULAR/Good Moderate responses combined

3.3.2. *British Society for Rheumatology Biologics Registry (BSRBR)*

An analysis of the cost effectiveness of the TNF- α inhibitors for RA was undertaken by Brennan et al. (2007) based on data from the BSRBR. As part of the cost effectiveness model developed for this work, a proportional odds cumulative logit model was estimated to predict the probability of achieving a good, moderate or poor EULAR response according to various covariates. Because this analysis is based on EULAR response, the results are not directly usable in the BRAM which is based on mean HAQ changes.

The data are drawn from patients treated with a first TNF- α antagonist (n=7083) and a control group treated with conventional DMARDs (n=870). The analysis does not specifically consider patients that have previously failed a biologic. Nevertheless, the regression provides a useful means of considering the possible impact the failure of an additional DMARD, ageing and disease duration might have on the probability of response to a further DMARD.

Table 7 shows the probability of non/moderate/good EULAR responses after 6 months for patients on conventional DMARD therapy. Using the mean characteristics of the BSRBR cohort that went on to receive a biologic, the probability of response to a conventional DMARD is 0.37/0.51/0.12 for no/moderate/good EULAR response respectively. The probability of response for patients that have failed a biologic may be estimated by increasing the mean age and disease duration by the mean duration of first biologics (we assume a mean duration of three years since it is not possible to calculate this figure directly for patients that withdraw due to loss or lack of efficacy) and increasing the number of previous DMARDs failed. Column 2 of the results shows that the probability of response is reduced by only a small degree. Columns 3 and 4 of the table show the estimated probability of EULAR responses if the mean number of DMARDs failed is two, as in the current NICE recommendations, rather than the mean of 5 in the BSRBR. Again, there is only a small reduction in the probability of achieving a moderate or good response.

Table 7: Probability of response to non biologic DMARDs using model based on BSRBR data

Probability of EULAR response	BSRBR cohort		NICE scenario (2 DMARDS failed)	
	As alternative to 1 st Anti-TNF	After failure of 1 st Anti-TNF	As alternative to 1 st Anti-TNF	After failure of 1 st Anti-TNF
None	0.37	0.39	0.33	0.35
Moderate	0.51	0.50	0.53	0.52
Good	0.12	0.11	0.14	0.13

3.3.3. *The BeST Study*

The Behandel-Strategieën (“treatment strategies”, BeST) study is a randomised controlled trial comprising four treatment arms for patients with very early RA (Goekoop-Ruiterman et al. 2005, Allaart et al. 2006). Each arm consists of a series of treatment strategies with three monthly therapy adjustments made in response to DAS measurements. One arm starts treatment with infliximab in combination with methotrexate. In this arm of the trial patients have increases in the dose of infliximab, followed by a sequence of non biologic DMARDs if inadequate response persists. This sequence is sulfasalazine, leflunomide, combined methotrexate, prednisone and cyclosporin, gold combined with methylprednisolone and finally azathioprine with prednisone. Those patients that achieved DAS44 2.4 had the dose of infliximab tapered. Other arms of the trial include sequential monotherapy with infliximab included in the sequence after failure of the first four DMARDs and combination therapy with infliximab included after failure of four DMARDs in combination. Patients were followed up for two years and outcomes reported included DAS and HAQ. The study therefore offers the potential to provide useful information about the response to non biologic DMARDs after failure of infliximab.

After 1 year, 102 (81%) of those that started on infliximab remained at the first treatment stage because they had a sustained DAS44 less than 2.4. In fact, 50% had been able to stop taking infliximab. At year 2, 22 (18%) of patients had not achieved a DAS \leq 2.4 in infliximab despite dose increases. Thus the number of patients that had progressed to a non biologic DMARDs were few. Those that had progressed beyond sulfasalazine were even fewer. In addition, results are not reported according to the individual treatments patients were receiving but rather by the treatment strategy to which they were allocated.

The value of the other arms of the trial, either in informing the effectiveness of traditional DMARDs after failing an anti TNF or after failing other DMARDs, is limited. There are only small numbers of patients switching to infliximab therapy and beyond in the sequences. The numbers of patients switching to sequential DMARDs is larger but since results are presented by treatment strategy group, the effectiveness of individual DMARDs is difficult to assess. Because the papers present the proportions of patients that are on each treatment within the strategies in three month blocks, inferences can be made about the proportions of patients that have failed to achieve a DAS28 response in the first 3 months. However, the effectiveness of individual DMARDs in those that have failed previous DMARDs are better assessed in the relevant clinical trials that are currently included in the BRAM model rather than by the very indirect approaches available in the BeST study.

4. SUMMARY OF FINDINGS

We have not identified any evidence that directly considers the effectiveness of non biologic DMARDs in the population of interest – patients that have failed treatment with a TNF- α inhibitor. Further evidence may be available from additional analyses of a large US patient registry that are being undertaken, it is hoped they will report shortly.

Evidence from the BSRBR using regression analysis with covariates for the number of previous DMARDs failed, disease duration and age, suggests that the response from a DMARD post TNF- α inhibitor failure may be only slightly different in terms of EULAR response rates to DMARDs prior to receiving TNF- α inhibitor treatment. It should be noted that this analysis does not specifically consider patients that failed a TNF- α inhibitor and that the covariate “previous DMARDs” does not distinguish the distinction between biologic and non biologic DMARDs. However, the availability of registry data from the same source as estimates of the effectiveness of second TNF- α inhibitors does offer advantages in terms of consistency, although the BRAM cost effectiveness model cannot directly use the existing analysis based on EULAR responses.

Alternative evidence from trials of abatacept and rituximab are consistent in terms of the degree of HAQ improvement in the placebo arms of these two trials. However, since patients started DMARD therapy 3 months prior to the baseline measures in the trials, the observed improvement is not equivalent to the initial effect of treatment required in the cost effectiveness model.

5. REFERENCES

- Abe T, Takeuchi T, Miyasaka N, Hashimoto H, Kondo H, Ichikawa Y, Nagaya I. 2006. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. *The Journal of rheumatology* 33:37-44.
- Allaart CF, Goekoop-Ruiterman YPM, de Vries- Bouwstra JK, Breedveld FC, Dijkmans BAC. Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeST study, *Clin Exp Rheumatol* 2006;24(supp. 43);s77-s82
- Alten R. 2006. [Long-term therapy with the selective costimulation modulator CTLA4lg in rheumatoid arthritis]. *Zeitschrift für Rheumatologie* 65:252-253.
- Anderson JJ, Wells G, Verhoeven AC, Felson DT. Factors predicting response to treatment in rheumatoid arthritis - the importance of disease duration. *Arthritis Rheum* 2000;43:22-9.
- Arshad AS. 2007. Optimizing the use of traditional DMARD in RA: Getting the most out of what we can afford! *APLAR Journal of Rheumatology* 10:3-8.
- Augustsson JJ. 2006. Infliximab in the treatment of rheumatoid arthritis. *Aging Health* 2:19-33.
- Bathon JM, Fleischmann RM, van der HD, Tesser JR, Peloso PM, Chon Y, White B. 2006. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. *The Journal of rheumatology* 33:234-243.
- Bongartz TS. 2006. 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. *Journal of the American Medical Association* 295:2275-2285.
- Brennan A, Bansback N, Nixon R, Madan J, Harrison M, et al. Modelling the cost effectiveness of TNF- α antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry, 2007, *Rheumatology*;46:1345-1354
- Buchbinder RM. 2007. Effect of treatment with biological agents for arthritis in Australia: The Australian Rheumatology Association Database. *Internal medicine journal* 37:591-600.
- Capell HA, Madhok R, Porter DR, Munro RA, McInnes IB, Hunter JA, Steven M, Zoma A, Morrison E, Sambrook M, Wui PF, Hampson R, McDonald F, Tierney A, Henderson N, Ford I. 2007. Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine: results from the double-blind placebo-controlled MASCOT study. *Annals of the Rheumatic Diseases* 66:235-241.
- Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al.* A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. *Health Technol Assess* 2006;10(42).
- Doan TM. 2005. Rituximab. *Drugs of Today* 41:785-797.
- Drossaers-Bakker KW, Zwinderman AH, Vlieland TPMV et al. Long-term outcome in rheumatoid arthritis: a simple algorithm of baseline parameters can predict radiographic damage, disability, and disease course at 12-year follow-up. *Arthritis Rheum-Arthritis Care Res* 2002;47:383-90.
- Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, et al. Clinical and Radiographic Outcomes of Four Different Treatment Strategies in Patients with Early Rheumatoid Arthritis (the BeST Study), *Arthritis and Rheumatism* 2005;52(11):3381-3390.

Kawai S, Hashimoto H, Kondo H, Murayama T, Kiuchi T, Abe T. 2006. Comparison of tacrolimus and mizoribine in a randomized, double-blind controlled study in patients with rheumatoid arthritis. *The Journal of rheumatology* 33:2153-2161.

Klareskog L, van der HD, de Jager JP, Gough A, Kalden J, Malaise M, *et al.* Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004; **363**(9410):675-681.

Kvien TK, Zeidler HK, Hannonen P, Wollheim FA, Forre O, Hafstrom I, *et al.* Long term efficacy and safety of cyclosporin versus parental gold in early rheumatoid arthritis: a three year study of radiographic progression, renal function, and arterial hypertension. *Ann Rheum Dis* 2002; **61**:511-516.

Lehman AJ, Esdaile JM, Klinkhoff A, V, Grant E, Fitzgerald A, Canvin J. 2005. A 48-week, randomized, double-blind, double-observer, placebo-controlled multicenter trial of combination methotrexate and intramuscular gold therapy in rheumatoid arthritis: results of the METGO study. *Arthritis and Rheumatism* 52:1360-1370.

Maddison PK. 2005. Leflunomide in rheumatoid arthritis: Recommendations through a process of consensus. *Rheumatology* 44:280-286.

National Institute for Health and Clinical Excellence. Advice on Advice on adalimumab, etanercept and infliximab for the treatment of Rheumatoid Arthritis. Decision of the Appeal Panel.

Nixon RMB. 2007. Using mixed treatment comparisons and meta-regression to perform indirect comparison to estimate the efficacy of biologic treatments in rheumatoid arthritis. *Statistics in Medicine* 26:1237-1254.

Pieringer HS. 2007. Patients with Rheumatoid Arthritis Undergoing Surgery: How Should We Deal with Antirheumatic Treatment? *Seminars in Arthritis and Rheumatism* 36:278-286.

Pincus TT. 2007. Shouldn't standard rheumatology clinical care be evidence-based rather than eminence-based, eloquence-based, or elegance-based? *Journal of Rheumatology* 34:1-4.

Plosker GLC. 2005. Sulfasalazine: A review of its use in the management of rheumatoid arthritis. *Drugs* 65:1825-1849.

Summers KM, Kockler DR. 2005. Rituximab treatment of refractory rheumatoid arthritis. *Annals of Pharmacotherapy* 39:2091-2095.

Van der Keijde, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, Tornero-Molina J, Wajdula J, Pedersen R, Fatenejad S, Tempo S, I. 2006. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis and Rheumatism* 54:1063-1074.

van Der Heijde, van AJ, Lard LR, Visser K, Roday HK, Hulsmans HM, Speyer I, Westedt ML, Peeters AJ, Allaart CF, Toes RE, Breedveld FC, Huizinga TW. 2007. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. *Arthritis and Rheumatism* 56:1424-1432.

Westhovens, R. Cole, J.C. Li, T. Martin, M. Maclean, R. Lin, P. Blaisdell, B. Wallenstein, G.V. Aranda, R. Sherrer, Y. "Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial." *Rheumatology (Oxford, England)* 45.10 (2006): 1238-46.

Appendix 1 – Search terms used

Source –Ovid MEDLINE(R)

- 1 arthritis rheumatoid/
- 2 (hydroxychloroquine or ciclosporine or gold or methotrexate or leflunomide or penicillamine or sulfasalazine or azathioprine).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 3 dmard\$.mp.
- 4 1 and (2 or 3)
- 5 (systematic adj review\$).mp.
- 6 (data adj synthesis).mp.
- 7 (published adj studies).ab.
- 8 (data adj extraction).ab.
- 9 meta-analysis/
- 10 meta-analysis.ti.
- 11 comment.pt.
- 12 letter.pt.
- 13 editorial.pt.
- 14 animals/
- 15 human/
- 16 14 not (14 and 15)
- 17 4 not (11 or 12 or 13 or 16)
- 18 or/5-10
- 19 17 and 18
- 20 limit 19 to yr=2001 - 2005
- 21 from 20 keep 5-6,9,12

Source - EMBASE (Ovid)

- 1 (systematic adj review\$).mp.
- 2 meta-analysis.ti.
- 3 meta-analysis/
- 4 arthritis rheumatoid/
- 5 (hydroxychloroquine or ciclosporine or gold or methotrexate or leflunomide or penicillamine or sulfasalazine or azathioprine).mp. [mp=title, abstract, subject

headings, drug trade name, original title, device manufacturer, drug manufacturer name]

6 dmard\$.mp.

7 or/1-3

8 4 and (5 or 6)

9 7 and 8

10 limit 9 to yr=2001 - 2005

11 from 10 keep 1,3,6,13,22,32,59

Source – Cochrane Library

#1 dmard* in All Fields in all products

#2 hydroxychloroquine OR ciclosporine OR gold OR methotrexate in All Fields in all products

#3 leflunomide OR penicillamine OR sulfasalazine OR azathioprine in All Fields in all products

#4 "rheumatoid arthritis" in All Fields in all products

#5 MeSH descriptor Arthritis, Rheumatoid, this term only in MeSH products

#6 (#1 OR #2 OR #3)

#7 (#4 OR #5)

#8 (#6 AND #7)