

# Technology Assessment



**Technology  
Assessment Program**

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**APPENDICES TO –  
MODELING THE COST EFFECTIVENESS OF  
ETANERCEPT, ADALIMUMAB AND  
ANAKINRA COMPARED TO INFLIXIMAB IN  
THE TREATMENT OF PATIENTS WITH  
RHEUMATOID ARTHRITIS IN THE  
MEDICARE PROGRAM**

**APPENDIX 3**  
**REVIEW OF EFFICACY OF BIOLOGIC DMARDS IN COMBINATION WITH**  
**METHOTREXATE VERSUS METHOTREXATE ALONE IN PATIENTS WITH**  
**RHEUMATOID ARTHRITIS**

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# **1. Review of Effectiveness of Biologic DMARDs in Patients with Rheumatoid Arthritis – First Exposure to Biologic DMARD**

## **1.1 Background**

This report reviews evidence of effectiveness of the biologic response modifier drugs etanercept (Enbrel® - Wyeth), infliximab (Remicade® - Schering-Plough), anakinra (Kineret® - Amgen) and adalimumab (Humira® - Abbott).

Each of these drugs have been the subject of detailed systematic reviews undertaken by the University of Birmingham, UK, on behalf of the UK NHS National Institute for Health and Clinical Excellence {Burls 2003}{Jobanputra 2001}{Chen 2006}. This report draws on the reviews undertaken by Birmingham.

## **1.2 Methods for reviewing effectiveness**

### ***1.2.1 Search strategy***

The search aimed to update the review by the University of Birmingham for new trials in which etanercept, infliximab or anakinra have been studied, and to identify all trials for which adalimumab has been studied. The main searches were conducted in January 2004.

Five electronic bibliographies were searched, covering biomedical, science, social science and grey literature [Cochrane Library, MEDLINE, EMBASE, NHS Database of Reviews of Effectiveness (DARE)]. Proceedings from the ACR and European Congress of Rheumatology meetings were searched electronically for the years 2001 to 2004. Food and Drug Administration (FDA) submissions for new drug applications were searched. The reference lists of identified publications were reviewed to identify any additional studies and/or citations.

### ***1.2.2 Search terms***

A combination of free-text and thesaurus terms were used. ‘Population’ search terms (e.g. rheumatoid arthritis) were combined with ‘intervention’ terms (e.g. adalimumab, TNFa etc) which in turn were combined with ‘trial design’ terms (e.g. randomised or quasi-randomised controlled trials). A full list of search strategies is shown in Appendix A.

### ***1.2.3 Inclusion and exclusion criteria***

The University of Birmingham reviews had the objective of assessing the effectiveness and safety of the biologic agents. The objective of this review differs since we are interested in quantifying the effectiveness of biologic agents. Consequently we applied an additional filter layer to the inclusion/exclusion criteria.

The criteria used by Burls et al. were

#### Inclusion criteria

- Population: adults aged 18 years and above with rheumatoid arthritis
- Intervention: anakinra (Kineret®) alone or in combination with other drugs
- Comparator: Placebo, or other drug treatments for RA
- Publication: all data to be included irrespective of publication status.
- Study design: randomised or quasi-randomised controlled trials
- Outcomes: to include mortality, morbidity (e.g. disability/mobility, disease progression, joint damage, pain, adverse events), response rates and QoL.

#### Exclusion criteria

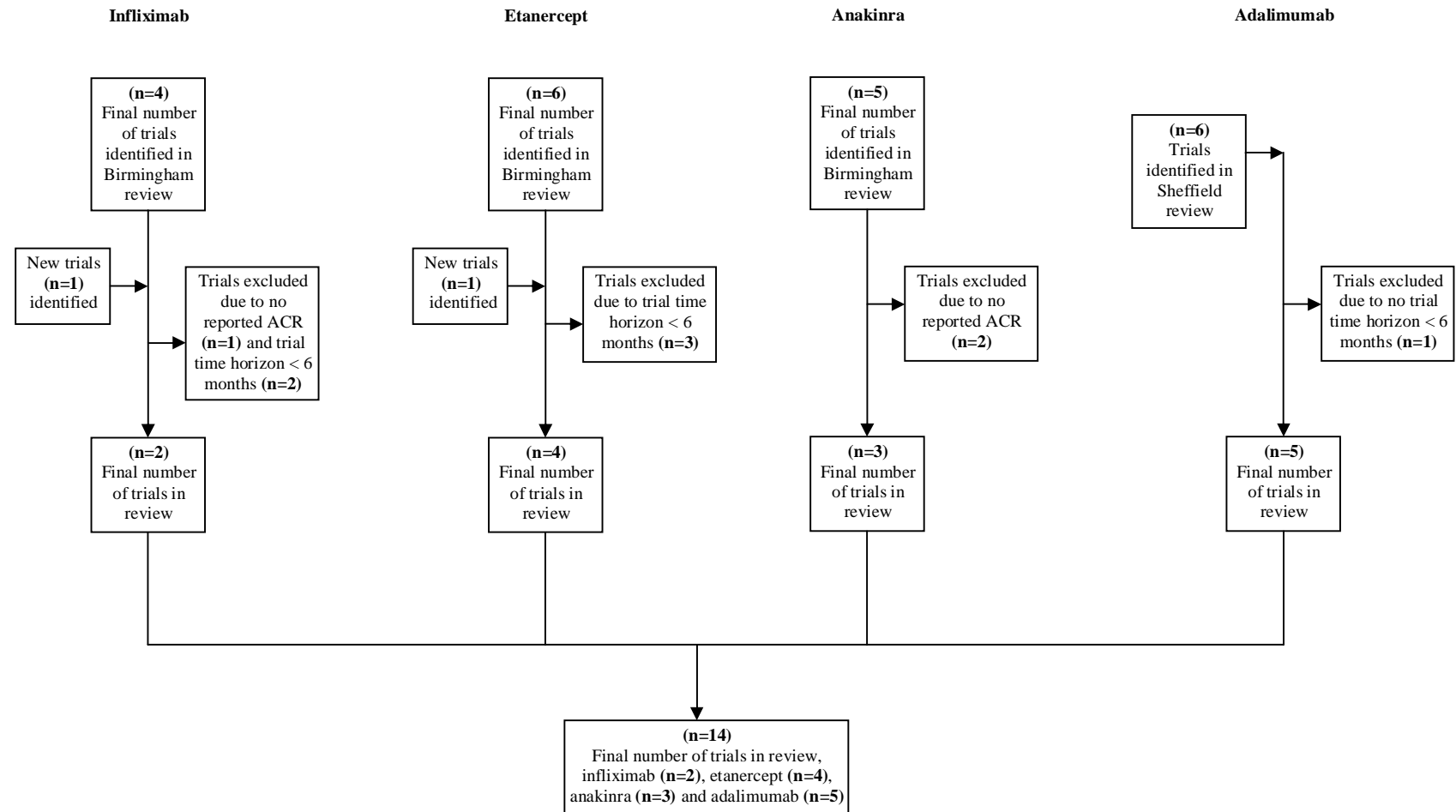
- Trials only recruiting children with juvenile idiopathic arthritis
- Trials with no comparator arm
- Trials that were not randomised
- Articles reporting solely on laboratory measures aimed at investigating disease or treatment mechanisms.

The additional exclusion criteria filter applied was

- Trial with duration less than 6 months (24 weeks) duration.
- Trials not reporting results using the ACR response criteria.

The justification for these additional filters is that the full potential of biologic therapy is reached by 6 months (whilst in a majority of patients the response to treatment is fast, trials have shown that only 70-80% of responders at 6 months have been responders at 3 months). To synthesise data on outcomes, the ACR response criteria is the primary measure of efficacy in randomised controlled trials. We therefore have chosen only to include studies that report ACR response. These search terms were applied to anakinra, etanercept, adalimumab and infliximab.

Table 1: Flow diagram for identified trials



### **1.2.3 Quality assessment**

Fourteen RCTs were included in total. Three of these were of anakinra, four of etanercept, two of infliximab and five of adalimumab.

Each study was assessed using the Jadad quality assessment score, {Jadad et al. 1996} which awards studies points from 0-5 (poor quality being <3, good quality 3-5). Scoring is based on the following criteria:

- was the study described as randomised?
- was the study described as double-blind?
- was there a description of withdrawals and drop outs?

A score of 1 point is given for each 'yes' and 0 for each 'no'. 1 additional point each is given if randomisation/blinding is appropriate, and 1 point each deducted if randomisation/blinding is inappropriate. It should be stressed that the JADAD score is not a direct indicator of study quality but rather an assessment of how well the study was reported.

### **1.2.4 Data extraction**

For each of the studies we provide study details, including patient baseline characteristics, American College of Rheumatology improvement criteria (ACR) and Health Assessment Questionnaire (HAQ) response.

## **1.3 Results**

### **1.3.1 Infliximab**

Two studies of infliximab were included (the ATTRACT and ASPIRE studies). Elliot et al (1994) and Kavanaugh et al. (2000) were excluded due to the short study duration (4 weeks and 12 weeks respectively) and Maini et al. (1998) was excluded since it reports PAULUS<sup>1</sup> response and not ACR.

The ATTRACT study scored 4/5 on the JADAD scale since it was felt there was no adequate description given of the methods of randomisation. Jobanputra et al. gave this study a score of 5. The ASPIRE study scored 5 on the JADAD scale.

#### ***ATTRACT (Maini et al. 1999, Lipsky et al. 2000)***

Maini et al. (1999) reports results up to 30 weeks. Lipsky et al. (2000) reports the results at 54 weeks.

A full review of this study is reported in Jobanputra et al.(2001). ATTRACT is a randomised controlled trial of infliximab versus placebo, details of which are reported in table 1. 428 patients were randomised to receive either placebo (saline or 0.1% albumin

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<sup>1</sup> The Paulus Criteria requires a 20 percent improvement in four of the following six parameters: tender and swollen joint count; global patient assessment; physician assessment of disease activity, patient assessment of disease activity, morning stiffness and erythrocyte sedimentation rate (ESR).

infusions) or infliximab at 3mg/kg every 8 weeks, 3 mg/kg every 4 weeks, 10 mg/kg every 8 weeks or 10 mg/kg every 4 weeks. All interventions were in addition to methotrexate 12.5 mg per week or more.

The trial was unblinded after 54 weeks for patients treated with placebo, for ethical reasons. No data from this trial are used after these participants were unblinded.

Improvements in ACR are reported in table 2 and figure 1. ACR20 response criteria was the primary efficacy measure, representing a 20% improvement from baseline. At 30 weeks, 53, 50, 58 and 52% of patients had achieved this response receiving 3mg/kg every 4 or 8 weeks or 10mg/kg every 4 or 8 weeks , respectively.

Figure 1 also shows HAQ improvement at 30 weeks follow up (54 weeks follow up is difficult to extract from the reported charts).

### ***ASPIRE (St Clair et al. 2004)***

The ASPIRE study is a well conducted and reported RCT (JADAD score =5) of infliximab in combination with methotrexate for patients with RA of less than three years duration.1449 patients were randomized in a ratio of 4:5:5 to receive either methotrexate in combination with placebo, methotrexate in combination with infliximab 3mg/kg or methotrexate in combination with infliximab 6mg/kg.

Trial duration was 54 weeks. ACR response over this period was the primary study endpoint. ACR20, ACR50, ACR70 and ACR90 were reported. Other outcomes include DAS score, Sharp score, SF36 and HAQ.

Intervention groups demonstrated significantly higher response rates in terms of ACR20, ACR50 and ACR70 than the placebo group. Similar differences were observed in terms of HAQ improvement. However, the method of reporting HAQ improvement makes comparisons with other studies difficult. The HAQ improvement was described as the mean and median decrease from baseline from weeks 30-54 averaged over time.

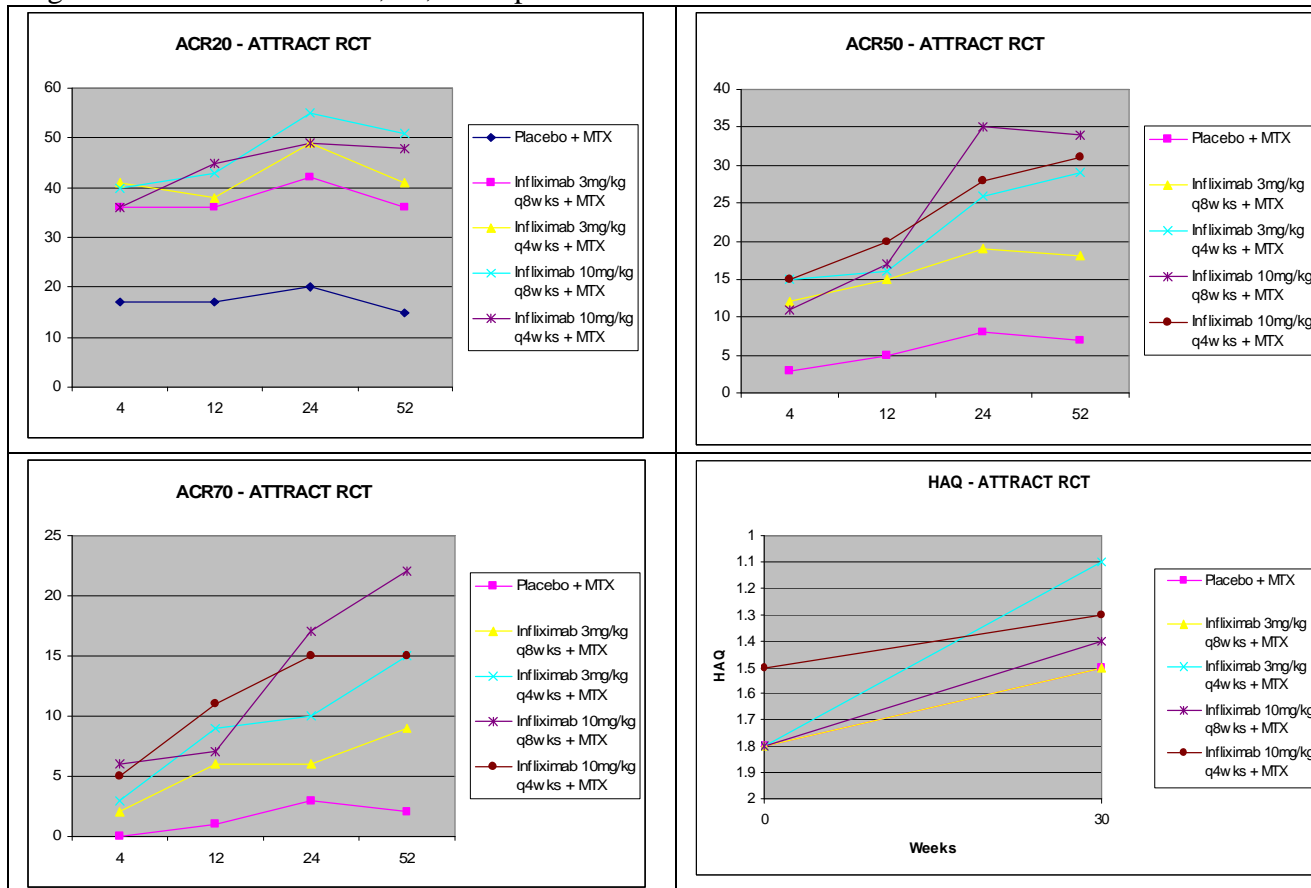
Table 1: Infliximab RCT study characteristics.

Baseline Characteristics							
Trial	Trial Design Arms	N	Mean Age (years)	Disease duration (mean years)	No previous DMARDs (mean)	Baseline HAQ	JADAD score
ATTRACT 1999	Placebo + MTX	88	51	11	2.5	1.8	4
	Infliximab 3mg/kg q8wks + MTX	86	54	10	2.8	1.8	
	Infliximab 3mg/kg q4wks + MTX	86	52	9	2.6	1.8	
	Infliximab 10mg/kg q8wks + MTX	87	54	11	2.5	1.8	
	Infliximab 10mg/kg q4wks + MTX	81	52	12	2.5	1.5	
ASPIRE 2004	MTX + placebo	298	50	0.9		1.5	5
	MTX + 3mg/kg Infliximab	373	51	0.8		1.5	
	MTX + 6mg/kg Infliximab	378	50	0.9		1.5	

Table 2: Infliximab ACR response.

Trial	Trial Design Arms	ACR20 (%)				ACR50 (%)				ACR70 (%)			
		4	12	24	52	4	12	24	52	4	12	24	52
ATTRACT 1999	Placebo + MTX	17	17	20	15	3	5	8	7	0	1	3	2
	Infliximab 3mg/kg q8wks + MTX	36	36	42	36	12	15	19	18	2	6	6	9
	Infliximab 3mg/kg q4wks + MTX	41	38	49	41	15	16	26	29	3	9	10	15
	Infliximab 10mg/kg q8wks + MTX	40	43	55	51	11	17	35	34	6	7	17	22
	Infliximab 10mg/kg q4wks + MTX	36	45	49	48	15	20	28	31	5	11	15	15
ASPIRE 2004	MTX + placebo				54				32				21
	MTX + 3mg/kg Infliximab				62				46				33
	MTX + 6mg/kg Infliximab				66				50				37

Figure 1: Infliximab ACR20, 50, 70 response.



### **1.3.2 Etanercept**

Four studies of etanercept were included in the review. Moreland et al. (1999), Weinblatt et al. (1999), Bathon et al. (2000), and Klareskog et al. (2004). It should be noted that the study by Bathon et al. (2000) scored only 2 on the JADAD scale, since no description of blinding was given or adequate description of randomisation. This was also the only study that did not report HAQ as an outcome measure.

Excluded were Moreland et al (1996), Moreland et al (1997) and Wadjula et al (2001) due to insufficient time horizons (4 weeks, 12 weeks and 3 months respectively).

Summaries of the included studies are presented in table 3.

#### **16.0009 (Moreland et al. 1999)**

A full review of this study is reported in Jobanputra et al.(2001).

Placebo controlled RCT etanercept 10mg (n=76) vs etanercept 25mg (n=78) vs placebo (n=80). The study lasted for 6 months and ACR20, ACR50, ACR70 and HAQ were all reported at 3 and 6 months follow up. Change in HAQ (along with SF36 quality of life data) is reported more fully in Mathias et al. (2000). This study scored 5 on the JADAD scale.

ACR20 responses at 6 months were 11% for placebo, 51% etanercept 10 mg, and 59% for etanercept 25 mg ( $p < 0.001$  etanercept versus placebo). ACR50 responses were 5%, 24% and 40% respectively ( $p < 0.001$  etanercept versus placebo). Swollen joint counts increased with placebo by 7% and decreased by 45% and 47% with increasing dose of etanercept ( $p < 0.001$ ).

Mean HAQ improvement at 6 months was 2% (placebo) vs. 34% (etanercept 10mg) vs 39% (etanercept 25mg).

Fifty-four patients (67%) on placebo withdrew, compared with 24 (32%) on etanercept 10mg and 19(24%) etanercept 25 mg. Lack of efficacy accounted for most withdrawals.

#### **16.0014 (Weinblatt et al. 1999)**

A full review of this study is reported in Jobanputra et al.(2001).

Methotrexate and placebo injections twice weekly (n=30) versus methotrexate and etanercept 25 mg injections twice weekly (n=59). This study scored 4 on the JADAD scale.

Study duration was 24 weeks and the primary measure of efficacy was ACR20. ACR50 and ACR70 responses are also reported as is HAQ score, at 12 and 24 weeks.

ACR20 response for placebo was 27% compared with 71% for etanercept.

Median HAQ improvement at 6 months was 0.4 (placebo) vs. 0.7 (etanercept).

Six placebo patients (20%) were withdrawn, four for lack of benefit, against 2 (3%) withdrawals with etanercept, none for lack of benefit. Injection-site reactions occurred in 7% of placebo patients, compared with 42% for etanercept ( $p < 0.001$ ). All were described mild and were similar to those described above and occurred with approximately 1 in 10 injections.

#### ***ERA (Bathon et al. 2000)***

The Etanercept Early Rheumatoid Arthritis (ERA) trial was included in Jobanputra et al.(2001).

We have assigned a JADAD score of 2 (poor quality) to this study since there was no description of blinding and insufficient detail of randomisation. Initially this study was designed to demonstrate superiority of etanercept over methotrexate but this goal was changed before unblinding to demonstrate equivalence of etanercept and methotrexate.

In total, 632 patients who had had RA for less than 3 years were randomised to receive either etanercept 10mg twice weekly and placebo tablets ( $n=208$ ) vs. etanercept 25mg twice weekly and placebo tablets ( $n=207$ ) or methotrexate plus placebo injections ( $n=217$ ). Median disease duration was 7 to 8 months.

ACR 20, 50 and 70 response scores were assessed at 2 weeks, 1 month, 6,8,10 and 12 months. This study did not include HAQ score as a measure of response.

ACR20 response for methotrexate was 65%, etanercept 10 mg 61%, and etanercept 25 mg 72% ( $p=0.16$  etanercept 25 mg versus methotrexate).

Withdrawal rates for any reason were 21% methotrexate, 20% etanercept 10 mg and 15% etanercept 25 mg. Withdrawal rates for adverse events were 10%, 4% and 5%, ( $p=0.016$ , methotrexate versus all etanercept patients) and for lack of efficacy 4%, 7%, and 5% respectively.

Withdrawal due to adverse events was more common with methotrexate ( $p=0.016$  versus etanercept groups): in particular nausea and mouth ulcers were more common. Rates for injection-site reactions were 7% methotrexate, 30% etanercept 10 mg and 37% etanercept 25 mg ( $p < 0.001$  compared with methotrexate).

#### ***TEMPO (Klareskog et al 2004)***

This study was not included by Jobanputra et al.

Double blind, randomised study of 686 RA patients allocated to etanercept 25mg twice weekly ( $n=223$ ), etanercept plus methotrexate ( $n = 231$ ) versus methotrexate alone ( $n = 228$ ). This study scored 5 on the JADAD scale.

ACR20, 50, 70 and HAQ over 1 year follow up.

At 52 weeks, 72% of patients on methotrexate alone met ACR20 response criteria compared to 78% (etanercept alone) and 81% (etanercept plus methotrexate).

Mean HAQ scores fell by 0.6, 0.8 and 1 in the methotrexate, etanercept and combined arms respectively.

Table 3: Etanercept RCTs baseline characteristics

Trial	Trial Design Arms	N	Baseline Characteristics				JADAD score
			Mean Age (years)	Disease duration (mean years)	No previous DMARDs (mean)	Baseline HAQ	
Moreland 1999	Placebo	80	51	12	3	1.7	5
	Etanercept 10 mg 2 x week	76	53	13	3.4	1.7	
	Etanercept 25 mg 2 x week	78	53	11	3.3	1.6	
Weinblatt 1999	Placebo + MTX	30	53	13	2.8	1.5	4
	Etanercept + MTX various	59	48	13	2.7	1.5	
ERA 2000 (Bathon et al. 2000)	Placebo + MTX	217	49	1	0.6	2	
	Etanercept 25 mg 2 x week	207	51	1	0.5		
	Etanercept 10 mg 2 x week	208	50	0.9	0.5		
TEMPO (Klareskog et al 2004)	Placebo + MTX	228	53	6.8	2.3	1.7	5
	Etanercept 25 mg 2 x week + MTX	231	52.5	6.8	2.3	1.8	
	Etanercept 25 mg 2 x week	223	53.2	6.3	2.3	1.8	

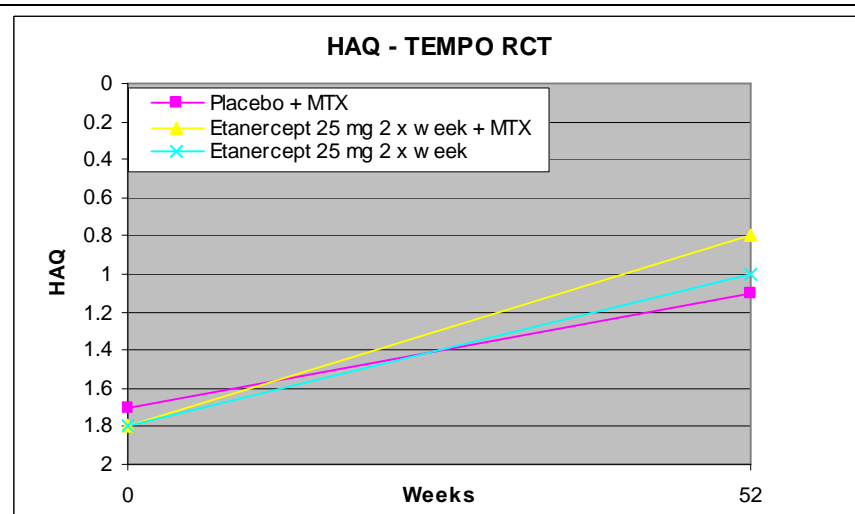
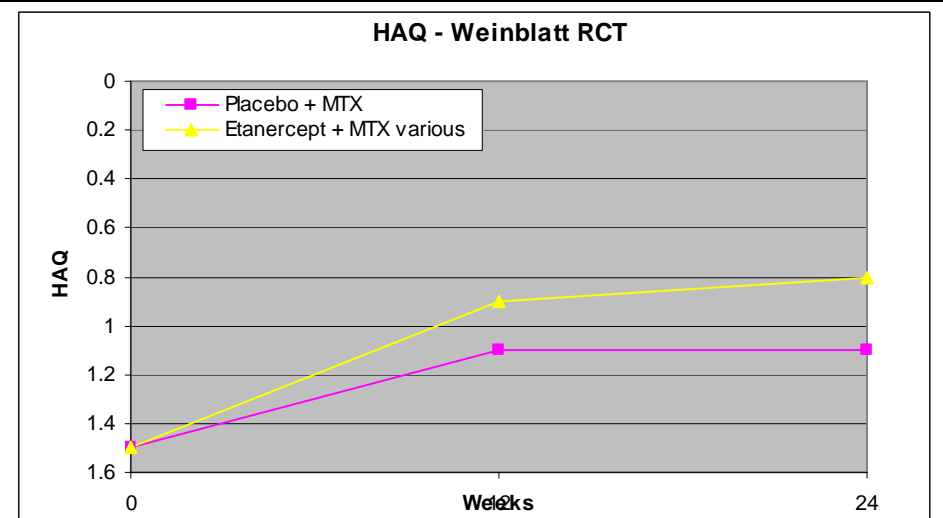
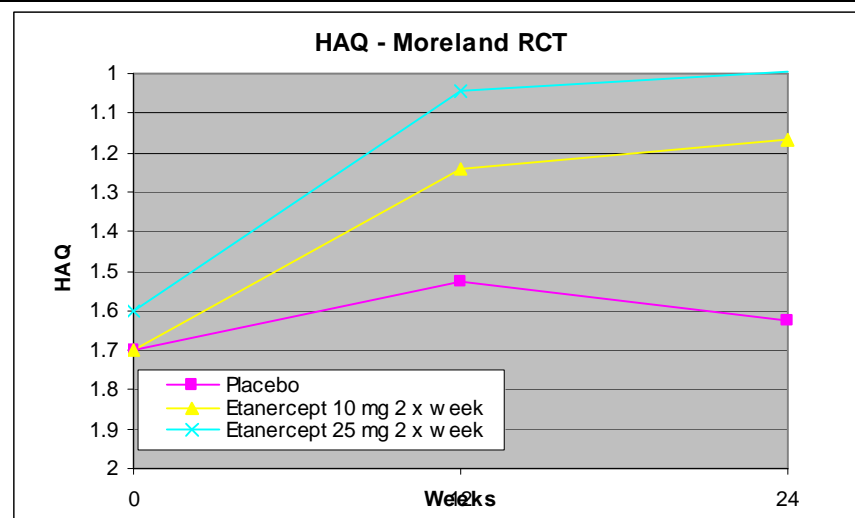
Table 4: Etanercept ACR Response

Trial	Trial Design Arms	ACR20 (%)				ACR50 (%)				ACR70 (%)			
		4	12	24	52	4	12	24	52	4	12	24	52
Moreland 1999	Placebo	1	23	11	-	0	8	5	-	0	4	1	-
	Etanercept 10 mg 2 x week	17	45	51	-	4	13	24	-	0	8	9	-
	Etanercept 25 mg 2 x week	32	62	59	-	6	41	40	-	1	15	15	-
Weinblatt 1999	Placebo + MTX	-	33	27	-	-	0	3	-	-	0	0	-
	Etanercept + MTX various	-	66	71	-	-	42	39	-	-	15	15	-
ERA 2000 (Bathon et al. 2000)	Placebo + MTX	19	56	59	66	3	24	31	40	0	6	13	19
	Etanercept 25 mg 2 x week	44	62	66	72	17	28	39	46	6	12	19	22
	Etanercept 10 mg 2 x week	43	53	62	62	12	28	33	30	4	8	12	13
TEMPO (Klareskog et al 2004)	Placebo + MTX	34	63	74	72	4	27	40	41	1	5	14	18
	Etanercept 25 mg 2 x week + MTX	57	74	79	81	19	41	58	67	6	21	33	41
	Etanercept 25 mg 2 x week	52	71	73	78	16	35	41	50	3	10	18	24

Table 5: HAQ response Etanercept Studies

Trial	Trial Design Arms	HAQ at week			
		0	12	24	52
Moreland 1999	Placebo	1.7	1.53	1.63	
	Etanercept 10 mg 2 x week	1.7	1.24	1.17	
	Etanercept 25 mg 2 x week	1.6	1.04	0.99	
Weinblatt 1999	Placebo + MTX	1.5	1.1	1.1	
	Etanercept + MTX various	1.5	0.9	0.8	
TEMPO (Klareskog et al 2004)	Placebo + MTX	1.7			1.1
	Etanercept 25 mg 2 x week + MTX	1.8			0.8
	Etanercept 25 mg 2 x week	1.8			1

Figure 2: HAQ response in etanercept studies.



### **1.3.2 Anakinra**

Three anakinra studies were included in the review (Cohen et al 2002, Breshinan 1998, Cohen 2004). Study 960182 was excluded since the trial time horizon was 12 weeks. Study 990757 (Fleischman et al) was excluded as no ACR results were reported. This study is perhaps the most controversial since it is the largest trial of anakinra (n=1116 treated patients) but the ACR results collected have never been reported (Burls and Jobanputra, 2004).

#### **960180 (Cohen et al. 2002)**

A full description of this study is provided in Burls et al. (2003).

419 patients were enrolled in this study in 36 centres in the US, Canada and Australia and randomised to receive either:

- Control (MTX alone) n=74, 12 weeks, n= 48, 24 weeks
- Anakinra 0.04mg/kg/day n= 63, 12 & 24 weeks
- Anakinra 0.1mg/kg/day n= 74 12 weeks, n= 46 ,24 weeks
- Anakinra 0.4mg/kg/day n= 77 12 weeks, n= 55 24 weeks
- Anakinra 1.0mg/kg/day n= 59 12 & 24 weeks
- Anakinra 2.0mg/kg/day n= 72 12 weeks, n= 46 24 weeks

Study drugs were all administered by subcutaneous injection once daily by the patient or caregiver. Initially this was designed as a 12 week study but was subsequently extended to 24 weeks.

Mean disease duration was 7.5 years.

Median HAQ scores for all groups were either 1.4 or 1.5 at baseline.

ACR 20 was the primary endpoint. ACR50 and ACR70 also reported, as was HAQ. ACR 20 response at 12 weeks was 19% with control and 25%, 35%, 25%, 46% and 38% with anakinra 0.04-2.0mg/kg/day respectively. A significant dose response was seen ( $p=0.001$ ) across the anakinra groups. The proportions of patients showing ACR20 responses were significantly greater for 0.1, 1.0 & 2.0mg/kg/day of anakinra compared with control ( $p=0.014$ , 0.001 & 0.007 respectively). Similar results were apparent for ACR20 at 24 weeks but a significantly improved response was only apparent with the 1.0mg/kg/day dosage group ( $p=0.018$  vs. control). ACR20 responses were evident from week 2 but statistically significant differences between active and control treatment did not appear before week 4.

A sustained ACR20 response (see above for definition) was seen more frequently for anakinra 0.1,1.0 & 2.0mg/kg/day compared to control (30%, 31%, 35% respectively vs 15% with control;  $p<0.05$  for all).

Withdrawals were due to lack of efficacy in 7%, 14%, 10%, 8%, 7% & 6% of patients respectively.

Across the dosage groups 4% patients on control, 3%, 1%, 7%, 14% and 15% patients on anakinra 0.04-2.0mg/kg/day withdrew from the study as a result of adverse events.



Table 6: Anakinra study characteristics

Trial	Trial Design Arms	N	Baseline Characteristics				JADAD score
			Mean Age (years)	Disease duration (mean years)	No previous DMARDs (mean)	Baseline HAQ	
Cohen 2002	Placebo + MTX alone	74	53	8	2	1.4	5
	Anakinra 0.04mg/kg/day + MTX	63	53	6	2	1.4	
	Anakinra 0.1mg/kg/day + MTX	74	53	9	2	1.5	
	Anakinra 0.4mg/kg/day + MTX	77	53	7	1	1.5	
	Anakinra 1.0mg/kg/day + MTX	59	49	7	2	1.3	
	Anakinra 2.0mg/kg/day + MTX	72	54	8	2	1.3	
Bresnihan 1998	Placebo	121	52	3.7	1.3	1.5	5
	Anakinra 30mg/day	119	53	4.3	1.3	1.5	
	Anakinra 75mg/day	116	53	4.2	1.3	1.6	
	Anakinra 150mg/day	116	54	3.9	1.2	1.6	
Cohen 2004	Placebo+ MTX	251	57	10	-	1.4	4
	Anakinra 100mg/day + MTX	250	56	11	-	1.4	
Study 960182101	Placebo	30	52	5	2	-	
	Anakinra 2.5mg/day	42	54	3	1	-	
	Anakinra 10mg/day	40	52	4	2	-	
	Anakinra 30mg/day	29	50	3	1	-	
Fleischman, 2001	Placebo + current DMARD regimen	283	56	11	-	-	
	Anakinra 100mg/day + current DMARD treatment	1116	55	10	-	-	

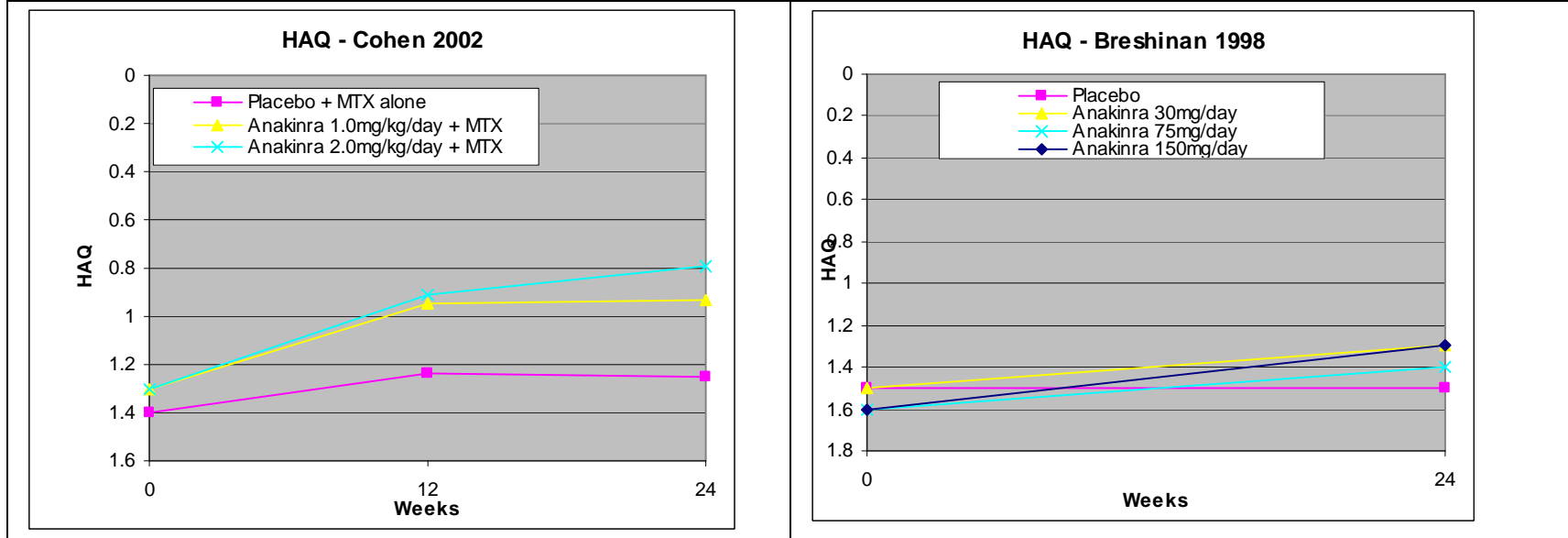
Table 7: Anakinra ACR response

Trial	Trial Design Arms	ACR20 (%)			ACR50 (%)			ACR70 (%)		
		4	12	24	4	12	24	4	12	24
Cohen 2002	Placebo + MTX alone	15	19	23	4	4		0	0	
	Anakinra 0.04mg/kg/day + MTX		25	19	5	13		2	5	
	Anakinra 0.1mg/kg/day + MTX		35	30	15	20		3	7	
	Anakinra 0.4mg/kg/day + MTX		25	36	5	10		3	3	
	Anakinra 1.0mg/kg/day + MTX	29	46	42	19	24		5	10	
	Anakinra 2.0mg/kg/day + MTX	29	38	35	24	17		11	7	
Bresnihan 1998	Placebo			27			8			0
	Anakinra 30mg/day			39			13			4
	Anakinra 75mg/day			34			10			0
	Anakinra 150mg/day			43			18			0
Cohen 2004	Placebo+ MTX	11	24	22			8			2
	Anakinra 100mg/day + MTX	22	34	38			17			6

Table 8: Anakinra HAQ response

Trial	Trial Design Arms	HAQ at week			
		0	12	24	52
Cohen 2002	Placebo + MTX alone	1.4	1.24	1.25	
	Anakinra 0.04mg/kg/day + MTX	1.4			
	Anakinra 0.1mg/kg/day + MTX	1.5			
	Anakinra 0.4mg/kg/day + MTX	1.5			
	Anakinra 1.0mg/kg/day + MTX	1.3	0.95	0.93	
	Anakinra 2.0mg/kg/day + MTX	1.3	0.91	0.79	
Bresnihan 1998	Placebo	1.5		1.5	
	Anakinra 30mg/day	1.5		1.3	
	Anakinra 75mg/day	1.6		1.4	
	Anakinra 150mg/day	1.6		1.3	
Cohen 2001	Placebo+ MTX	1.4		1.2	
	Anakinra 100mg/day + MTX	1.4		1.09	

Figure 3: HAQ response Anakinra



**0560 (Bresnihan et al. 1998)**

This study is included in Burls et al. (2003) and a full description is given there.

472 patients were recruited to this 24 week, double blind, randomised, placebo controlled study. Patients were allocated to placebo (n=121) or anakinra at a daily dose of 30mg (n=119), 75mg (n=116) or 150mg (n=116). All interventions were given as a single daily subcutaneous injection administered by the patient or caregiver.

Median disease duration was 3.3 years for placebo and 3.9 years for anakinra. At baseline notable differences across the treatment groups were fewer men, lower previous DMARD use and fewer erosions in the highest anakinra dose group.

The primary outcome measure was ACR composite score & Paulus criteria. The percentage of patients achieving ACR response at 24 weeks was 27%, 39%, 34% and 43% when treated with placebo and anakinra 30mg, 75mg, 150mg respectively (p=0.047, 0.276, 0.014 for each dose versus placebo).

ACR50 responses occurred in 8% of placebo patients, 13%, 10% and 18% with increasing doses of anakinra (LOCF method).

ACR70 responses occurred in less than 1% of cases except for the group treated with anakinra 30 mg (4%).

27 % of patients dropped out of this trial prior to the 6 month primary endpoint with the highest drop out occurring in the placebo group (26% placebo vs 20%, 19% & 24% anakinra 30mg, 75mg & 150mg respectively). Of the completers 37% of placebo patients achieved ACR20 response at 24 weeks compared with 49.5%, 42% and 52% with increasing doses of anakinra (p = 0.12, 0.56 and 0.04 respectively). One patient allocated to anakinra withdrew before receiving study medication. Of the remaining withdrawals 20% patients on placebo and 12% on anakinra (all doses) withdrew due to lack of efficacy and 4% vs. 9% respectively for adverse effects.

**990145 (Cohen et al. 2004)**

This study is included in Burls et al. (2003) and a full description is given there.

The analysis reports 506 patients randomized to anakinra (100mg/day) plus methotrexate or methotrexate and placebo. Patients were aged over 18yrs, had RA for greater than 6 months and radiographic evidence of bone erosion.

ACR20, ACR50 and ACR70 response was reported up to week 24 and it is reported that this trial forms part of a larger 52 week study. HAQ improvement was also reported.

ACR20 response rates were 38% vs. 22% (p<0.001) for the anakinra and placebo groups respectively. Greater proportions of patients achieved ACR50 and ACR70 in the anakinra group.

90% of anakinra patients experienced an adverse event compared to 81% in the placebo group. 8.4% of whom withdrew due to injection site reactions compared to 0.8% for the placebo group.

### **1.3.4 Adalimumab**

Five studies of adalimumab were included; ARMADA {Weinblatt et al. 2003}, van de Putte {van de Putte et al., 2004}, Keystone {Keystone et al. 2004}, PREMIER {Breedveld et al.} and STAR {Furst et al. 2004}. Key study details are reported in table 9.

The studies were of variable quality according to the JADAD quality score. The Armada study received a JADAD score of 3. Other studies scored over 3.

ACR response rates are reported in table 10 and HAQ response in table 11 and figure 4.

#### ***ARMADA (Weinblatt et al. 2003)***

This study received only 3 on the JADAD scale since insufficient details were given in relation to randomisation and blinding to be able to judge if this was done appropriately. 271 patients were randomised to receive either adalimumab 20mg, 40mg or 80mg or placebo every other week, in addition to methotrexate.

ACR20 at 24 weeks was the primary endpoint for the study. In addition, ACR50, ACR70 and HAQ are reported.

#### ***DE019 (Keystone et al. 2004).***

This study is a randomised, placebo-controlled multicentre trial over 52 weeks. 619 participants were randomised to receive either adalimumab 40mg every other week (n=207), adalimumab 20mg every week (n=212) or placebo (n=200). ACR20, 50 and 70 were recorded at weeks 2 and 4, then every 4 weeks from week 4 to week 24 and every 8 weeks from week 24 to week 48, plus a final time at week 52. HAQ was recorded at baseline, week 24 and week 52.

#### ***DE011 (van de Putte et al. 2004)***

26 week double blind, placebo controlled, randomised trial. 544 patients were randomised to either adalimumab 20mg (n=106) or 40 mg (n=113) every other week, or 20mg (n=112) or 40 mg (n=103) weekly or placebo (n=110). Patients were those with RA for whom previous DMARD treatment had failed.

ACR20 was the primary endpoint with ACR50 and ACR70 also reported over the 26 weeks of follow up. HAQ was an additional endpoint.

#### ***PREMIER (Breedveld et al. 2005)***

Currently only in abstract form so no quality scoring has been assigned.

This study is a two year, double blind, controlled study of methotrexate naïve adult patients with active early RA. Patients received either methotrexate alone, adalimumab alone (20mg/wk) or the two in combination. Results are reported a 1 and 2 year follow up. ACR20/50/70 and HAQ were reported although only partial results are available in abstract form.

***STAR (Furst et al. 2003)***

Double blind, randomised, placebo controlled trial involving 636 patients with RA randomly assigned to receive either adalimumab 40mg every other week (n=318) or placebo (n=318) in addition to standard antirheumatic therapy. This study scored 4 on the JADAD scoring system. Duration was 24 weeks. The study was primarily a safety study with efficacy in terms of ACR response the secondary endpoint. HAQ was not reported at follow up. Overall, patients treated with adalimumab had a higher ACR20 response rate (51.9% vs. 34.6%,  $p < 0.001$ ). Adverse events occurred in 86.5% of adalimumab-treated patients compared to 82.7% given placebo. This was not significantly different.

Table 9 Adalimumab study characteristics

Trial	Trial Design Arms	N	Baseline Characteristics				JADAD score
			Mean Age (years)	Disease duration (mean years)	No previous DMARDs (mean)	Baseline HAQ	
ARMADA 2003	Placebo + MTX	62	56	11.1	3	1.64	3
	Adalimumab 20mg + MTX	69	53.5	13.1	3	1.52	
	Adalimumab 40mg + MTX	67	57.2	12.2	2.9	1.55	
	Adalimumab 80mg + MTX	73	55.5	12.8	3.1	1.55	
Keystone 2004	Placebo + MTX	200	56.1	10.9	2.4	1.48	4
	Adalimumab 40mg + MTX	212	57.3	11	2.4	1.45	
	Adalimumab 20mg + MTX	207	56.1	11	2.4	1.44	
van de Putte 2004	Placebo	110	54	12	3.6	1.9	5
	Adalimumab 20mg eow	106	23	9	3.7	1.9	
	Adalimumab 20mg wkl	112	54	11	3.6	1.9	
	Adalimumab 40mg eow	113	53	11	3.8	1.8	
	Adalimumab 40mg wkl	103	52	12	3.8	1.8	
PREMIER (Breedveld et al.)	MTX	257	52	0.8	-	1.5	
	Adalimumab 40mg/wk	274	52	0.7	-	1.5	
	Adalimumab 40mg/wk +MTX	268	52	0.7	-	1.5	
Furst et al (STAR) 2003	Placebo + Current DMARD	318	56	11.5	-	1.43	4
	Adalimumab 40mg eow + Current DMARD	318	55	9.3	-	1.37	

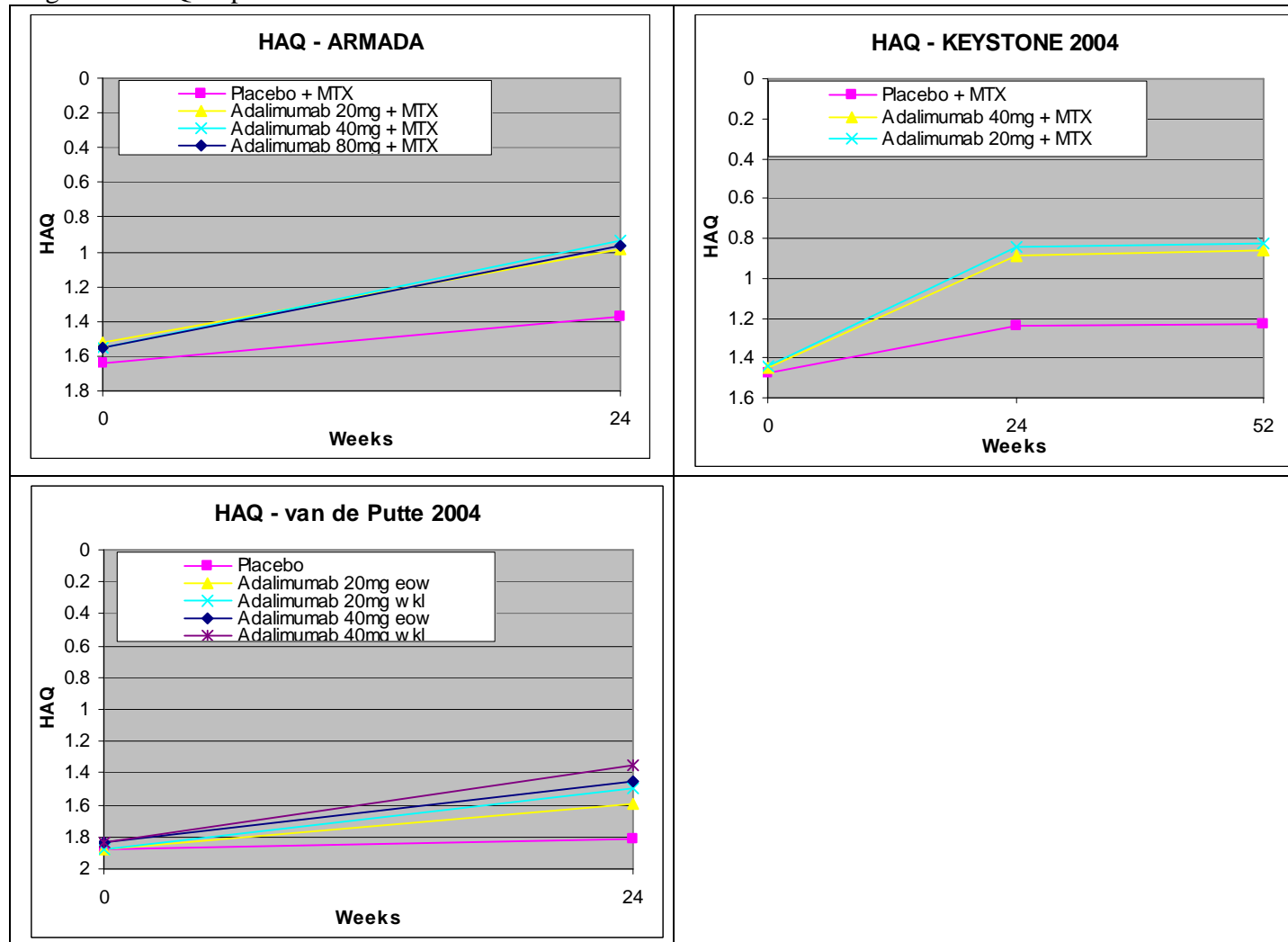
Table 10: Adalimumab ACR response

Trial	Trial Design Arms	ACR20 (%)				ACR50 (%)				ACR70 (%)			
		4	12	24	52	4	12	24	52	4	12	24	52
ARMADA 2003	Placebo + MTX	24	21	15		5	10	8		0	5	5	
	Adalimumab 20mg + MTX	42	52	48		16	26	32		7	12	10	
	Adalimumab 40mg + MTX	52	66	67		12	33	55		3	6	27	
	Adalimumab 80mg + MTX	49	70	66		16	26	42		5	15	19	
Keystone 2004	Placebo + MTX	22	24	30	24	5	9	10	10	2	3	3	5
	Adalimumab 40mg + MTX	50	53	61	55	15	31	41	38	5	11	17	21
	Adalimumab 20mg + MTX	45	58	63	59	19	31	39	42	4	11	21	23
van de Putte 2004	Placebo	13	17	19		1	4	8		0	2	2	
	Adalimumab 20mg eow	32	34	36		8	15	19		5	9	8	
	Adalimumab 20mg wkl	34	43	39		11	20	21		2	6	10	
	Adalimumab 40mg eow	42	46	46		15	24	22		6	12	12	
	Adalimumab 40mg wkl	35	52	53		13	25	35		1	5	18	
Furst et al (STAR) 2003	Placebo + Current DMARD	17	30	35		3	8	11		1	3	4	
	Adalimumab 40mg eow + Current DMARD	39	50	53		16	27	29		5	12	15	
PREMIER (Breedveld et al.)	MTX				63				46				28
	Adalimumab 40mg/wk				54				42				26
	Adalimumab 40mg/wk +MTX				73				61				46

Table 11: HAQ response Adalimumab Studies

Trial	Trial Design Arms	HAQ at week		
		0	24	52
ARMADA 2003	Placebo + MTX	1.64	1.37	
	Adalimumab 20mg + MTX	1.52	0.98	
	Adalimumab 40mg + MTX	1.55	0.93	
	Adalimumab 80mg + MTX	1.55	0.96	
Keystone 2004	Placebo + MTX	1.48	1.24	1.23
	Adalimumab 40mg + MTX	1.45	0.89	0.86
	Adalimumab 20mg + MTX	1.44	0.84	0.83
van de Putte 2004	Placebo	1.88	1.81	
	Adalimumab 20mg eow	1.88	1.59	
	Adalimumab 20mg wkl	1.88	1.49	
	Adalimumab 40mg eow	1.83	1.45	
	Adalimumab 40mg wkl	1.84	1.35	

Figure 4: HAQ response Adalimumab



## 1.4 Conclusion

- Fourteen studies in total were included in this review.
- Two studies of infliximab were included, comprising almost 1500 patients in total demonstrate that infliximab is an effective treatment for RA compared to placebo. Evidence suggests significant improvements in ACR20, ACR50, ACR70 and HAQ.
- Four studies of etanercept were included, comprising in excess of 1600 patients.
- ACR20, 50 and 70 response rates were higher in patients treated with etanercept compared to those treated with placebo and in those treated with etanercept and methotrexate versus methotrexate alone.
- Etanercept also demonstrates improvement in mean HAQ compared to placebo.
- Three studies of Anakinra demonstrate the efficacy of anakinra compared to placebo in 1400 patients.
- ACR and HAQ responses are relatively modest in relation to those observed in reported studies for other biologics.
- Five included studies of adalimumab consisted of almost 2900 patients.
- Compared to placebo adalimumab demonstrates significant improvements in HAQ and ACR response rates.

Table 12: Summary of all studies included

Study	Interventions	N	Mean Age (years)	Disease duration (mean years)	No previous DMARDs (mean)	Baseline HAQ	RF+ (%)	~24 Weeks			~52 Weeks		
								ACR20	ACR50	ACR70	ACR20	ACR50	ACR70
<b>Infliximab</b>													
ATTRACT 1999	Placebo + MTX	88	51	11	2.5	1.7	77	23	9	3	17	8	2
	Infliximab 3mg/kg q8wks + MTX	86	54	10	2.8	1.8	84	49	22	7	42	21	10
	Infliximab 3mg/kg q4wks + MTX	86	52	9	2.6	1.7	80	57	30	12	48	34	17
	Infliximab 10mg/kg q8wks + MTX	87	54	11	2.5	1.7	82	63	40	20	59	39	25
ASPIRE 2005	Infliximab 10mg/kg q4wks + MTX	81	52	12	2.5	1.7	82	60	35	19	59	38	19
	Placebo + MTX	282	50	0.9	-	1.5	71	-	-	-	54	32	21
	Infliximab 3mg/kg + MTX	359	51	0.8	-	1.5	71	-	-	-	62	46	33
	Infliximab 6mg/kg + MTX	363	50	0.9	-	1.5	73	-	-	-	66	50	37
<b>Etanercept</b>													
Moreland 1999	Placebo	80	51	12	3	1.7	79	11	5	1	-	-	-
	Etanercept 10mg 2xweek	76	53	13	3.4	1.7	82	51	24	9	-	-	-
	Etanercept 25mg 2xweek	78	53	11	3.3	1.6	79	59	40	15	-	-	-
Weinblatt 1999	Placebo + MTX	30	53	13	2.8	1.5	90	27	3	0	-	-	-
	Etanercept 25mg 2xweek + MTX	59	48	13	2.7	1.5	84	71	39	15	-	-	-
ERA 2000	Placebo + MTX	217	49	1.0	0.6	1.4	89	59	31	13	66	40	19
	Etanercept 25mg 2xweek	207	51	1.0	0.5	1.4	88	66	39	19	72	46	22
	Etanercept 10mg 2xweek	208	50	0.9	0.5	1.4	87	62	33	12	62	30	13
TEMPO 2004	Placebo + MTX	228	53	6.8	2.3	1.7	71	74	40	14	72	41	18
	Etanercept 25mg 2xweek + MTX	231	53	6.8	2.3	1.8	75	79	58	33	81	67	41
	Etanercept 25mg 2xweek	223	53	6.3	2.3	1.8	76	73	41	18	78	50	24
<b>Anakinra</b>													
Cohen 2002	Placebo + MTX	74	53	7.8	2	1.4	74	23	4	0	-	-	-
	Anakinra 0.04mg/kg/day + MTX	63	53	6.3	2	1.4	81	19	13	5	-	-	-
	Anakinra 0.1mg/kg/day + MTX	74	53	8.8	2	1.5	78	30	20	7	-	-	-
	Anakinra 0.4mg/kg/day + MTX	77	53	7.0	1	1.5	78	36	10	3	-	-	-
	Anakinra 1.0mg/kg/day + MTX	59	49	6.5	2	1.3	73	42	24	10	-	-	-
	Anakinra 2.0mg/kg/day + MTX	72	54	8.0	2	1.3	83	35	17	7	-	-	-
Bresnihan 1998	Placebo	121	52	3.7	1.3	1.5	69	26	8	1	-	-	-
	Anakinra 30mg/day	119	53	4.3	1.3	1.5	71	39	17	4	-	-	-
	Anakinra 75mg/day	116	53	4.2	1.3	1.6	69	34	11	1	-	-	-
	Anakinra 150mg/day	116	54	3.9	1.2	1.6	69	42	19	1	-	-	-
Cohen 2001	Placebo+ MTX	251	57	10.4	-	1.3	78	22	8	2	-	-	-
	Anakinra 100mg/day + MTX	250	56	11.1	-	1.4	76	38	17	6	-	-	-
<b>Adalimumab</b>													
ARMADA 2003	Placebo + MTX	62	56	11.1	3	1.6	79	15	8	5	-	-	-
	Adalimumab 20mg eow + MTX	69	54	13.1	3	1.5	81	48	32	10	-	-	-
	Adalimumab 40mg eow + MTX	67	57	12.2	2.9	1.6	80	67	55	27	-	-	-
	Adalimumab 60mg eow + MTX	73	56	12.8	3.1	1.6	80	66	42	19	-	-	-
STAR 2003	Placebo + DMARDs	318	56	12	-	1.4	62	35	11	4	-	-	-
	Adalimumab + DMARDs	318	55	9	-	1.4	63	53	29	15	-	-	-
Keystone 2004	Placebo + MTX	200	56	10.9	2.4	1.5	82	30	10	3	24	10	5
	Adalimumab 20mg eow + MTX	212	57	11.0	2.4	1.5	90	61	41	17	55	38	21
	Adalimumab 40mg eow + MTX	207	56	11.0	2.4	1.4	81	63	39	21	59	42	23
van de Putte 2004	Placebo	110	54	11.6	3.6	1.9	90	19	8	2	-	-	-
	Adalimumab 20mg eow	106	23	9.3	3.7	1.9	85	36	19	8	-	-	-
	Adalimumab 20mg wk1	112	54	11.3	3.6	1.9	94	39	21	10	-	-	-
	Adalimumab 40mg eow	113	53	10.6	3.8	1.8	90	46	22	12	-	-	-
	Adalimumab 40mg wk1	103	52	11.9	3.8	1.8	85	53	35	18	-	-	-
PREMIER 2005	MTX	257	52	0.8	-	1.5	83	-	-	-	63	46	28
	Adalimumab 40mg eow	274	52	0.7	-	1.5	83	-	-	-	54	42	26
	Adalimumab 40mg eow + MTX	268	52	0.7	-	1.5	83	-	-	-	73	61	46

## **2. Review of Sequential use of Biologic DMARDs**

### **2.1 Background**

The TNF- $\alpha$  antagonists adalimumab, etanercept and infliximab have been demonstrated to be similarly effective in randomised controlled trials. The IL-1 antagonist anakinra has also been shown to be an effective treatment in comparison to methotrexate. Since no head to head studies have demonstrated superiority of one treatment over the other, if one treatment does not work or gives an adverse event, clinicians frequently will either increase the dose of a treatment or switch to another biologic. Given the high cost of these treatments, the question posed is whether this dose escalation or switching is an effective management strategy. We reviewed the evidence for this.

### **2.2 Methods for reviewing effectiveness**

#### *Search strategy*

The search aimed to identify all literature relating to the clinical effectiveness of subsequent use of adalimumab, etanercept, infliximab or anakinra after the use of an initial biologic in patients with rheumatoid arthritis. The main searches were conducted in December 2004.

Five electronic bibliographies were searched, covering biomedical, science, social science and grey literature [Cochrane Library, MEDLINE, EMBASE, NHS Database of Reviews of Effectiveness (DARE)]. Proceedings from the ACR and European Congress of Rheumatology meetings were searched electronically for the years 2001 to 2004. Food and Drug Administration (FDA) submissions for new drug applications. The reference lists of identified publications were reviewed to identify any additional studies and/or citations.

#### *Search terms*

A combination of free-text and thesaurus terms were used. 'Population' search terms (e.g. rheumatoid arthritis) were combined with 'intervention' terms (e.g. adalimumab, TNFa etc) which in turn were combined with 'trial design' terms (e.g. sequential use, cross over study). A full list of search strategies is shown in Appendix A.

### **2.3 Results**

Titles were hand searched. Any study which included patients on biologic agents was included. No language restriction were included. The total number of independent titles identified by the search was 54 [Medline (44), Embase (52), NHS CRD databases

(DARE, HTA, EED) (5), Cochrane Database of Systematic Reviews (CDSR) (1), CENTRAL (5), Science and Social Sciences Citation Indexes (16) ]

After screening, 14 articles papers were identified as potentially relevant and were reviewed. These are shown in Table 1. Of these, 2 papers were reviews with no primary research reported (Combe *et al* and van Vollenhoven (c) *et al*). Also two papers reported the same study (Gomez-Puerta *et al* and Sanmarti *et al*).

**Table 1. Table of studies returned from the literature search**

<b>Author</b>	<b>Country</b>	<b>Notes</b>	<b>In review?</b>
Ang <i>et al</i>	US	Research article	Yes
Brocq <i>et al</i>	France	Research article - in French	Yes
Buch <i>et al</i>	UK	Research article	Yes
Combe <i>et al</i>	-	Editorial Review - no primary research	No
Favelli <i>et al</i>	Italy	Letter	Yes
Gomez-Puerta <i>et al</i>	Spain	Letter – same study as Sanmarti	Yes
Hansen <i>et al</i>	US	Research article	Yes
Haroui <i>et al</i>	Canada	Research article	Yes
Sanmarti <i>et al</i>	Spain	In Spanish – same as Gomez-Puerta	No
van Vollenhoven (a) <i>et al</i>	Sweden	Research article	Yes
van Vollenhoven (b) <i>et al</i>	Sweden	Research article	Yes
van Vollenhoven (c) <i>et al</i>	-	Review – no primary research	No
Wick <i>et al</i>	Sweden	Abstract only	Yes
Yazici <i>et al</i>	US	Letter	Yes

The review therefore focussed on the 11 independent studies. A majority of the articles focus on switches between two of the TNF- $\alpha$ , antagonists etanercept and infliximab. Single studies look at the subject of dose escalation in infliximab, switches to anakinra and switches to adalimumab. No studies look at dose escalation in etanercept, adalimumab or anakinra. Similarly no studies look at switches from adalimumab or anakinra to other biologic agents.;

**Table 2. Descriptions of studies in the review**

<b>Author</b>	<b>Number of patients in study</b>	<b>Treatment switched from (n)</b>	<b>Reason for Switching</b>	<b>Treatment switched to</b>	<b>Time beyond switch measurement made</b>	<b>Primary outcome variable</b>
Ang <i>et al</i>	29	INF (24) ETA (5)	Lack of efficacy/ Adverse event	ETA INF	Not reported	Joint count
Brocq <i>et al</i>	14	INF (8) ETA (6)	Miscellaneous	ETA INF	Not reported	Not reported
Buch <i>et al</i>	26	ETA (6) INF (11) ETA/INF (9)	Lack of efficacy	ANA ANA ANA	12 weeks	ACR20/50/70, DAS28
Favelli <i>et al</i>	15	INF (14) ETA (1)	Lack of efficacy/ Adverse event Lack of efficacy	ETA INF	6 months	ACR20, DAS28, HAQ
Gomez-Puerta <i>et al</i>	12	INF (12)	Lack of efficacy	ETA	6 months	DAS28
Hansen <i>et al</i>	20	ETA (20)	Lack of efficacy/ Adverse event	INF	Not reported	SWJ, TJC
Haroui <i>et al</i>	22	INF (22)	Lack of efficacy/ Adverse event	ETA	12 weeks	ACR20, HAQ
Van Vollenhoven <i>et al</i> (a)	31	ETA (18) INF (13)	Lack of efficacy Side effects	INF ETA	>8 weeks	DAS28, ACR-N
Van Vollenhoven <i>et al</i> (b)	44	INF (44) [3mg/kg]	Inefficacy	INF [5-7mg/kg]	>8 weeks	ACR, DAS28
Wick <i>et al</i>	23	INF (17) ETA (6)	Secondary loss of efficacy	ADA ADA	6 months	ACR20, DAS28
Yazici <i>et al</i>	21	ETA (21)	Miscellaneous	INF		

ETA= etanercept, INF = Infliximab, ANA = Anakinra, ADA = Adalimumab

### ***Etanercept to Infliximab***

Six studies looked at the efficacy of patients switching from etanercept to infliximab. A majority of these found that a similar number of patients responded to the infliximab as responded to etanercept. In van Vollenhoven *et al* (a) the mean DAS28 was 3.6 after the switch, significantly better than the DAS28 seen when patients were on etanercept. A similar result was seen using the ACR-N (during etanercept treatment the best ACR-N was 17.2 and during subsequent infliximab treatment this was 40.4). Hansen *et al* found contradictory results to Yazici *et al* when comparing the efficacy of patients who had made the switch, to patients who had not attempted prior etanercept. In Hansen *et al* infliximab was seen to be as effective in etanercept failures as in etanercept naïve patients. Yazici *et al* found that efficacy was in favour of etanercept naïve patients. However a number of concerns arise from these studies due to differences in patient group. In both, disease duration was longer for the etanercept failure group than the etanercept naïve group. Also, the dose of infliximab was much higher in the etanercept failure group (4.4mg/kg versus 3.2mg/kg). Brocq *et al* showed that 50% of the 6 patients had a favourable response whilst Ang *et al* found that the efficacy of the second agent was not predicted by that of the first.

### ***Infliximab to Etanercept***

In the converse switch, a similar story is seen. Again the few studies only looked at small patient numbers. van Vollenhoven *et al* (a) found that switching to etanercept from infliximab gave just equivalent efficacy (the best DAS28 value achieved during etanercept was 3.6 compared with 4.1 in the initial infliximab). In the largest study, Haroui *et al* showed that 14 of 22 patients (64%) achieved at least a 20% improvement in ACR criteria (ACR20). Also, some 13 (59%) experienced improvements in physical function that were considered clinically important ( $\geq 0.22$  point decrease in overall Health Assessment Questionnaire score). Response rates for Brocq *et al*, Favalli *et al* and Gomez-Puerta *et al* were 63% (type of response not reported), 87% (ACR20) and 67% (moderate DAS28 response). Favalli also reported that the 2 patients that failed to respond did not for the same reason as they discontinued the first treatment (adverse events).

### ***Etanercept or Infliximab to Adalimumab***

The only source of data on the switch to adalimumab comes from an abstract published by Wick *et al*. In this 17 patients had initially attempted infliximab, and 6 had tried etanercept. Adalimumab was found to be as effective as infliximab and etanercept had been initially (67% of patients were ACR20 responders). There was no difference between whether the patients had tried etanercept or infliximab first.

### ***Etanercept or Infliximab to Anakinra***

Buch *et al* reports on patients that had trialled etanercept, infliximab or both treatments initially before switching to anakinra. Of all the patients only 2 of the 26 patients (8%) achieved ACR20. None of the patients achieved an ACR50 or 70. In terms of DAS28 response, 33% were moderate responders whilst 0% were good responders.

### *Dose escalation*

Dose escalation is predominantly an issue in infliximab but has been seen in the other treatments. van Vollenhoven (b) *et al* looked at 44 patients that had increased their dose of infliximab. Following dose increase, disease activity showed modest but statistically significant improvements. The improvement achieved after dosage escalation was equal to, but not better than, the best values before dose escalation. The authors suggest that this finding could be interpreted as “recapturing” the previous response. However, similar improvements were seen in control groups of patients treated with infliximab but without dose increases, and patients given etanercept. They suggest that further research is necessary.

## 2.4 Conclusion

1. 11 studies were reviewed. All were made up of small patient groups (all under 44 patients with a mean of 23.) Consequently the quality of the studies is poor.
2. No studies looked at switches from adalimumab or anakinra to etanercept or infliximab. Also, no studies looked at dose escalation of drugs other than infliximab.
3. Studies used different measures for response so results are not directly comparable.
4. Results generally suggest that subsequent TNF- $\alpha$  inhibitor therapy is as effective as the initial therapy. Anakinra appears ineffective in patients that have attempted a previous TNF- $\alpha$  inhibitor. However, there are a number of issues which could confound these conclusions given the study designs.
5. Not analysed is whether response is dependent on why the patient switched. There is potentially a different outcome for patients that did respond to their first treatment initially, or who had an adverse event.

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## **APPENDIX 1A: SEARCH STRATEGIES EMPLOYED IN SEQUENTIAL SEARCH**

**EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2004> Cochrane Database of Systematic Reviews EMBASE**

- 1 (TNF\$ adj2 antagonist\$.ti.
- 2 exp \*Tumor Necrosis Factor/ai
- 3 (tumor necrosis factor\$ adj2 antagonist\$.ti.
- 4 (tumour necrosis factor\$ adj2 antagonist\$.ti.
- 5 etanercept.af.
- 6 [185243-69-0.rn.]
- 7 enbrel.af.
- 8 humira.af.
- 9 adalimumab.af.
- 10 infliximab.af.
- 11 remicade.af.
- 12 anakinra.af.
- 13 kineret.af.
- 14 anti-TNF\$.ti.
- 15 or/1-14
- 16 exp \*Arthritis, Rheumatoid/
- 17 arthrit\$.tw.
- 18 arthropath\$.tw.
- 19 or/16-18
- 20 15 and 19

## EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2004>

- 1 (TNF\$ adj2 antagonist\$.ti.
- 2 [exp \*Tumor Necrosis Factor/ai]
- 3 (tumor necrosis factor\$ adj2 antagonist\$.ti.
- 4 (tumour necrosis factor\$ adj2 antagonist\$.ti.
- 5 etanercept.af.
- 6 [185243-69-0.rn.]
- 7 enbrel.af.
- 8 humira.af.
- 9 adalimumab.af.
- 10 infliximab.af.
- 11 remicade.af.
- 12 anakinra.af.
- 13 kineret.af.
- 14 anti-TNF\$.ti.
- 15 or/1-14
- 16 [exp \*Arthritis, Rheumatoid/]
- 17 arthrit\$.tw.
- 18 arthropath\$.tw.
- 19 or/16-18
- 20 15 and 19

## **EMBASE**

- 1 (tnf\* and antagonist\*) in TI
- 2 (tnf\* and antagonist\*) in TI
- 3 (tumour necrosis factor\* or tumor necrosis factor\* or tnf\*) and antagonist\*
- 4 etanercept
- 5 185243-69-0
- 6 enbrel
- 7 humira
- 8 adalimumab
- 9 infliximab
- 10 remicade
- 11 anakinra
- 12 kineret
- 13 anti-tnf\*
- 14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
- 15 arthrit\*
- 16 arthropath\*
- 17 explode 'rheumatoid-arthritis' / all subheadings in DEM,DER,DRM,DRR
- 18 #15 or #16 or #17
- 19 #14 and #18

## MEDLINE

1 (TNF\$ adj2 antagonist\$.ti.  
2 exp \*Tumor Necrosis Factor/ai  
3 (tumor necrosis factor\$ adj2 antagonist\$.ti.  
4 (tumour necrosis factor\$ adj2 antagonist\$.ti.  
5 etanercept.af.  
6 185243-69-0.rn.  
7 enbrel.af.  
8 humira.af.  
9 adalimumab.af.  
10 infliximab.af.  
11 remicade.af.  
12 anakinra.af.  
13 kineret.af.  
14 anti-TNF\$.ti.  
15 or/1-14  
16 exp \*Arthritis, Rheumatoid/  
17 arthrit\$.tw.  
18 arthropath\$.tw.  
19 or/16-18  
20 15 and 19

## APPENDIX 2A: SEARCH STRATEGIES EMPLOYED IN SEQUENTIAL SEARCH

### EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2004>

- 1 (TNF\$ adj2 antagonist\$.ti.
- 2 exp \*Tumor Necrosis Factor/ai
- 3 (tumor necrosis factor\$ adj2 antagonist\$.ti.
- 4 (tumour necrosis factor\$ adj2 antagonist\$.ti.
- 5 etanercept.af.
- 6 [185243-69-0.rm.]
- 7 enbrel.af.
- 8 humira.af.
- 9 adalimumab.af.
- 10 infliximab.af.
- 11 remicade.af.
- 12 anakinra.af.
- 13 kineret.af.
- 14 anti-TNF\$.ti.
- 15 or/1-14
- 16 exp \*Arthritis, Rheumatoid/
- 17 arthrit\$.tw.
- 18 arthropath\$.tw.
- 19 or/16-18
- 20 15 and 19
- 21 switch\$.tw.
- 22 sequential\$.tw.
- 23 cross over\$.tw.
- 24 crossover\$.tw.
- 25 \*cross-over studies/
- 26 escalat\$.tw.
- 27 failed.ti.
- 28 failure\$.ti.
- 29 or/21-28
- 30 20 and 29

## EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2004>

- 1 (TNF\$ adj2 antagonist\$.ti.
- 2 [exp \*Tumor Necrosis Factor/ai]
- 3 (tumor necrosis factor\$ adj2 antagonist\$.ti.
- 4 (tumour necrosis factor\$ adj2 antagonist\$.ti.
- 5 etanercept.af.
- 6 [185243-69-0.rn.]
- 7 enbrel.af.
- 8 humira.af.
- 9 adalimumab.af.
- 10 infliximab.af.
- 11 remicade.af.
- 12 anakinra.af.
- 13 kineret.af.
- 14 anti-TNF\$.ti.
- 15 or/1-14
- 16 [exp \*Arthritis, Rheumatoid/]
- 17 arthrit\$.tw.
- 18 arthropath\$.tw.
- 19 or/16-18
- 20 15 and 19
- 21 switch\$.tw.
- 22 sequential\$.tw.
- 23 cross over\$.tw.
- 24 crossover\$.tw.
- 25 [\*cross-over studies/]
- 26 escalat\$.tw.
- 27 failed.ti.
- 28 failure\$.ti.
- 29 or/21-28
- 30 20 and 29

## EMBASE

- 1 (tnf\* and antagonist\*) in TI
- 2 (tnf\* and antagonist\*) in TI
- 3 (tumour necrosis factor\* or tumor necrosis factor\* or tnf\*) and antagonist\*
- 4 etanercept
- 5 185243-69-0
- 6 enbrel
- 7 humira
- 8 adalimumab
- 9 infliximab
- 10 remicade
- 11 anakinra
- 12 kineret
- 13 anti-tnf\*
- 14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
- 15 switch\*
- 16 sequential\*
- 17 cross over\*
- 18 crossover\*
- 19 escalat\*
- 20 (failed) in TI
- 21 (failure\*) in TI
- 22 'crossover-procedure' / all subheadings in DEM,DER,DRM,DRR
- 23 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
- 24 #14 and #23
- 25 arthrit\*
- 26 arthropath\*
- 27 explode 'rheumatoid-arthritis' / all subheadings in DEM,DER,DRM,DRR
- 28 #25 or #26 or #27
- 29 #24 and #28

## MEDLINE

1 (TNF\$ adj2 antagonist\$.ti.  
2 exp \*Tumor Necrosis Factor/ai  
3 (tumor necrosis factor\$ adj2 antagonist\$.ti.  
4 (tumour necrosis factor\$ adj2 antagonist\$.ti.  
5 etanercept.af.  
6 185243-69-0.rn.  
7 enbrel.af.  
8 humira.af.  
9 adalimumab.af.  
10 infliximab.af.  
11 remicade.af.  
12 anakinra.af.  
13 kineret.af.  
14 anti-TNF\$.ti.  
15 or/1-14  
16 exp \*Arthritis, Rheumatoid/  
17 arthrit\$.tw.  
18 arthropath\$.tw.  
19 or/16-18  
20 15 and 19  
21 switch\$.tw.  
22 sequential\$.tw.  
23 cross over\$.tw.  
24 crossover\$.tw.  
25 \*cross-over studies/  
26 escalat\$.tw.  
27 failed.ti.  
28 failure\$.ti.  
29 or/21-28  
30 20 and 29

## Appendix 4

# Using mixed treatment comparisons and meta-regression to estimate the efficacy of biologic treatments in rheumatoid arthritis

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Keywords: Meta-analysis, Mixed treatment comparisons, indirect comparisons, meta-regression, rheumatoid arthritis.

Short title: mixed treatment comparisons in rheumatoid arthritis

## Summary

Mixed treatment comparison is a generalisation of meta-analysis. Instead of the same treatment for a particular disease being tested in a number of studies, a number of different interventions are considered. Meta-regression is also a generalisation of meta-analysis where an attempt is made to explain the

heterogeneity between the treatment effects in the studies by regressing on study level covariables. Our focus is the circumstance where there are several treatments considered in a number of studies in a specific disease, but only one treatment in each study, and where differences in efficacy can be explained by differences in the study settings. We develop methods for simultaneously comparing several treatments and adjusting for study level covariables by combining ideas from mixed treatment comparisons and meta-regression.

We use a case study from rheumatoid arthritis where biologic therapies (TNF and IL-1 antagonists) have transformed the management of disease. We undertook a systematic review to identify relevant trials and extracted the variety of doses, comparators and patient baseline characteristics. Efficacy is measured using the log odds ratio of achieving ACR50 responder status at 6 months. A random-effects meta-regression model is fitted which adjusts the log odds ratio for study level prognostic factors of mean disease duration and baseline disability score. A different random effect distribution on the log odds ratios is allowed for each different biologic treatment to enable a log odds ratio for each treatment to be estimated. These prognostic factors explain 72% of the between-treatment heterogeneity. The odds ratio is found as a function of the prognostic factors for each treatment. The apparent differences in the randomised trials between TNF biologics are explained by differences in prognostic factors and the analysis suggest that these drugs as a class are not different from each other.

## **1. Introduction**

Meta-analysis attempts to combine the results from a number of studies that address a set of related research hypotheses. These studies may have been performed amongst different patient groups and with methodological differences, so heterogeneity between trials is expected with the true effects in each study not being identical. In a random-effects meta-analysis a random-effects distribution is placed on these effects sizes, and the mean used as the estimate of the overall mean.

We use a case study from rheumatoid arthritis (RA) The discovery that the inhibition of Tumor Necrosis Factor (TNF) alpha and Interleukin 1 (IL-1) may reduce the manifestations of RA, improving function and retarding radiological progression has led to the development of novel treatments [1]. Previously the early initiation of

disease modifying anti-rheumatic drugs (DMARDs) like the antimetabolite methotrexate (MTX), were considered the most successful strategy for delaying the progression in this chronic inflammatory disease [2]. We study the currently licensed treatments, the TNF antagonists adalimumab (Humira), infliximab (Remicade) and etanercept (Enbrel) along with the IL-1 inhibitor anakinra (Kineret). A number of systematic reviews of these so called 'biologic' therapies have confirmed their safety and efficacy in placebo controlled trials [3,4,5,6,7,8]. Efficacy in RA is determined using the American College of Rheumatology (ACR) improvement criteria, a measure which combines a core set of disease activity measures. An ACR50 requires a 50% reduction in the tender joint count, a 50% reduction in the swollen joint count, and a 50% reduction in 3 of 5 additional measures including patient global assessment, physician global assessment, pain, disability and an acute-phase reactant [9]. However, most trials have been performed on relatively small and diverse patient populations.

Mixed treatment comparison evidence synthesis is an extension of meta-analysis [10]. Instead of all studies comparing the same treatment with the same comparison, different comparisons are made. In our case four different biologic agents are studied. A special case of mixed treatment comparison is an indirect comparison. For example, no head-to-head study of etanercept and infliximab exists, but this could be estimated from studies comparing etanercept versus placebo and studies comparing infliximab versus placebo. Two further mixed treatment comparisons are applicable in this study. Firstly, MTX is sometimes used in both the placebo arm and in combination with a biologic in the treatment arm, sometimes it is only used in the control arm, and sometimes it is not used at all. Secondly, an unusual feature of this evidence synthesis is the multiple treatment arms are used in each of the studies, each using different doses and / or timing regimes.

A previous meta analysis compared the three therapies that target TNF alpha [4]. However this focussed on trials which were of a more similar design. Since then, the number of studies has doubled, and includes many in patient populations with early disease where the efficacy of the comparator arm is relatively high.

The objective of this paper is to combine standard meta-regression techniques and ideas from mixed treatment comparisons to find the odds ratio of an ACR50 event at six months if treated with a biologic in comparison to control. We examine how the

odds ratio varies with different important prognostic factors and compare the odds ratios between these treatments.

## **2. Methods**

### ***2.1. Literature search and data extraction***

A comprehensive and systematic literature search was performed. Reports of randomised controlled trials of biologic agents compared with placebo or methotrexate published between 1 January 1980 to 1 January 2005 were identified. Five electronic bibliographies were searched, covering biomedical, science, social science and grey literature [Cochrane Library, MEDLINE, EMBASE, DARE, Scientific Citation Index] The MeSH search used in Medline, Embase, and the NHS Database of Reviews of Effectiveness (DARE) consisted of three steps, each containing any possible MeSH relevant to the target condition [rheumatoid arthritis], study drug [biologic or TNF-a or IL-1 or etanercept, adalimumab, infliximab or anakinra], and study method [randomized controlled trial]. We searched the Scientific Citation Index and Cochrane Library with the keywords rheumatoid arthritis along with proceedings from the main rheumatology meetings and Food and Drug Administration (FDA) submissions.

The initial screen of the search results identified 107 reports which were potentially relevant. When we applied the filter that studies had to be randomised controlled trials comparing biologic agents to a placebo in patients with RA, only 60 reports remained. We applied a secondary filter to remove trials with a horizon less than 6 months (the point when the full potential of biologic therapy is generally reached), trials which did not report the primary measure of synthesis (the ACR response criteria) and trials that did not use a conventional comparison to methotrexate or placebo.

Thirteen RCTs (27 individual reports) were included in the final analysis. Four of these studied adalimumab[11,12,13,14], 3 studied anakinra [15,16,17], 4 studied etanercept[18,19,20,21] and 2 studied infliximab.[22,23] The average baseline disease duration varied from between 1 and 14 years and mean baseline Health Assessment Questionnaire Disability Index (HAQ-DI, the primary measure of disability in patients with RA) ranged from 1.3 to 1.9. Data are given in Table 1

## **2.2. Model development**

Figure 1 shows how the average disease duration of the patients in the studies relates to the log odds ratio of an ACR50 event. A weighted linear regression is fitted to this relationship. While this has many shortfalls; it ignores the heterogeneity between the studies and all the mixed treatment comparisons features described above, it does demonstrate the clear relationship between disease duration and effectiveness of treatment. Meta-regression attempts to explain the differences between studies by regressing the effect sizes from each study onto the study level characteristics. The effect sizes, adjusted for study level characteristics, will not be identical, as the regression will not completely explain the heterogeneity, so a random-effects distribution is placed on the adjusted effects sizes.

When a binary outcome is being explored in a meta-regression is it best to use the raw outcome counts as this avoids using an estimated standard error of the odds ratio [24]. There are many possible study and patient level covariates that could be used to explain the heterogeneity. With relatively few studies, multiple analyses using all study level covariables will have a high probability of finding a spurious explanatory variable, further there are insufficient degrees of freedom to sensibly model many covariables. We chose only covariables measured in all identified trials which are known to have prognostic value in determining the effect of treatment. These were disease duration (mean years),[25] and baseline HAQ-DI [26].

The studies used in the meta-regression are all randomised controlled trials. However, the meta-regression finds a relationship between the log odds ratio of the ACR50 outcome and study level characteristics. These characteristics have not been randomised and so the regression can be regarded as an observational relationship. Two of the studies have missing data for the six month ACR measure, and these studies use patients with newly diagnosed RA, which may be systematically different from the more common trials on patients with an established disease. This could lead to biased estimated treatment effects for infliximab and adalimumab. Meta-regression, adjusting for disease duration, may go some way to redress this bias, but it is unrealistic to suppose that it will fully adjust the analysis. Balance in the study designs between the different types of treatments is desirable to reduce the reliance on meta-regression to correct for this bias. Where the six-month ACR50 outcomes are missing they are replaced by the 12-months outcomes, in doing this surrogate

six-month data from studies on newly diagnosed RA patients treated with Infliximab and Adalimumab are available.

$i = 1 \dots 13$  denotes the study index;  $j = 0 \dots J_i$  the arm within the study, where 0 indexes the control group and  $J_i$  is the number of treatment regimes being tested in study  $i$ .  $n_{ij}$  denotes the number of patients in arm  $j$  of study  $i$ ;  $r_{ij}$  the number of patients achieving ACR50.  $m_{ij}$  is an indicator variable for treatment with MTX, and is 1 if MTX is given in arm  $j$  of study  $i$  and 0 otherwise. Two study-level covariates are also included:  $x_{1i}$  is the average disease duration, and  $x_{2i}$  the average baseline HAQ for each study. These are re-centred about their means across studies to aid model fitting.

### 2.2.1. Model 1 – Mixed treatment comparison model

Assume each patient in arm  $j$  of study  $i$  independently has a probability  $p_{ij}$  of achieving ACR50

$$r_{ij} \sim \text{Bi}(n_{ij}, p_{ij}) \quad (1)$$

$a_i$  is the log odds of ACR50 in the control arm of study  $i$ , these are fixed effects.  $q_{ij}$  is the log odds ratio of ACR50 for study  $i$  treatment  $j$ . This is written

$$\begin{aligned} \text{logit}(p_{i0}) &= a_i \\ \text{logit}(p_{ij}) &= a_i + q_{ij} \quad j = 1 \mathbf{K} J_i \end{aligned} \quad (2)$$

We assume each of these log odds ratios has been sampled from a normal distribution. This is assuming all the treatment effects are exchangeable both between studies and within studies.

$$q_{ij} \sim \text{N}(m_k, s^2) \quad (3)$$

$s^2$  is the heterogeneity between treatments, assumed common for all treatments, and  $m_k$  the overall log odds ratio of ACR50 given treatment with a biologic  $k$ .

$$q_{ij} \sim \begin{cases} \text{N}(m_1, s^2) & \text{for anakinra} \\ \text{N}(m_2, s^2) & \text{for etanercept} \\ \text{N}(m_3, s^2) & \text{for infliximab} \\ \text{N}(m_4, s^2) & \text{for adalimumab} \end{cases} \quad (4)$$

This is an example of an indirect comparison model. The model also allows for multiple treatment arms within a study, but makes no attempt to model the differences between these arms. To include the mixed treatments due to the MTX

given in combination with either placebo or treatment, two MTX covariables are included.

$$\begin{aligned}\text{logit}(p_{i0}) &= a_i + g_1 m_{i0} \\ \text{logit}(p_{ij}) &= a_i + q_{ij} + (g_1 + g_2) m_{ij}\end{aligned}\tag{5}$$

$g_1$  is the effect on the odds of an ACR50 event of treatment with MTX.  $g_2$  is a biologic treatment-MTX interaction, and is the additional affect of MTX if given in combination with a biologic compared to if given alone. The model given in equation (5) is referred to as model 1.

### 2.2.2. Model 2 – Include meta-regression coefficients

The average baseline disease duration and average baseline HAQ of patients are study level characteristics. They are included as treatment-disease duration and treatment-HAQ interaction effects to assess how they affect the log odds of ACR50 if treated compared to control.

$$\begin{aligned}\text{logit}(p_{i0}) &= a_i + g_1 m_{i0} \\ \text{logit}(p_{ij}) &= a_i + q_{ij} + b_1 x_{1i} + b_2 x_{2i} + (g_1 + g_2) m_{ij}\end{aligned}\tag{6}$$

This assumes that the  $b$  and  $g$  parameters are the same for all treatments.  $q_{ij}$  have been adjusted for study level covariates and treatment with MTX, so the interpretation of them is the log odds ratio at the mean value of the study level covariates and mono-therapy for the given treatment compared to placebo. The model given in equation (6) is referred to as model 2a with  $g_2$  included and model 2b with the  $g_2$  term dropped.

### 2.2.3. Model 3 – Include dose adjustment

The exchangeability assumption is strong. We would expect the log odds ratio for the same treatment and same dose to be more similar than for different treatments or doses. We model this by setting the adjusted log odds ratios  $q_{ij}$  from the same treatment and dose to be the same; this is shown explicitly in Table 2. Model 2b with this added structural assumption is referred to as model 3.

The model makes a fixed effect assumption for the same treatment/dose and a random effect assumption for different treatment/doses. Different biologic treatments,

and the inclusion of MTX in the control or intervention arm are accounted for by using mixed treatment comparison techniques. The effect of mean disease duration and mean baseline HAQ on the log odds ratio for patients in a study are included by using meta-regression techniques.

#### **2.2.4. Adding different random effects for TNF and IL-1 antagonists**

Instead of assuming a different random effect mean for each drug type, a different random effect mean could be included for each drug class: TNF antagonists and anakinra.

$$q_{ij} \sim \begin{cases} N(m_1, s^2) & \text{for anakinra} \\ N(m_2, s^2) & \text{for TNF antagonists} \end{cases} \quad (6)$$

Model 3 is also fitted with this random effects construction to make an indirect comparison between anakinra and all TNF antagonists.

#### **2.2.5. Model fitting**

All models were fitted by Markov chain Monte Carlo techniques (MCMC).[27]. Using the computer package WinBUGS.[28] Vague normal priors were placed on each  $a$ ,  $m$ ,  $b$  and  $g$ ; and a vague positive uniform prior was placed on  $s$ . All chains were run for 20 000 iterations after a burn in of 1000 iterations and demonstrated satisfactory convergence to their supporting posterior distributions. The code used to fit model 3 is given in the Appendix.

### **3. Results**

The results from the model fitting are shown in Table 3. This gives the median and the standard deviation of the posterior distribution of parameters, along with 95% credible intervals.

Model 1 is a mixed treatment comparison model. This estimates the log odds ratio of an ACR50 event for each biologic, along with adjustments for MTX as a main and an interaction effect. This model suggests that anakinra and infliximab have comparable effectiveness, which is worse than both etanercept and adalimumab. The estimate of the between-treatment variability is 0.416.

Model 2a augments model 1 by including study level characteristics of baseline disease duration and average baseline HAQ. This has a substantial effect on the estimated log odds ratio of an ACR50 event. The three TNF antagonists now appear to have comparable effectiveness, all better than anakinra. The between-treatment variability is reduced and we see that including these study covariables accounts for  $100\% \times (0.416^2 - 0.222^2) / 0.416^2 = 72\%$  of the between-treatment heterogeneity. The information used to estimate the MTX parameter  $g_1$  comes from situations where MTX is used in the control arm but not in the intervention arm, namely studies 6, 7 and 13. Information for  $g_2$  is given where MTX is not always used in the treatment arm within a study, namely studies 7 and 13. As only two treatment arms supply information on  $g_2$  it is not surprising it is imprecisely estimated. The negative value means the combined affect of treatment and MTX is less than the sum of the affect of treatment and MTX given separately. However, as the CI for this parameter includes 0 we drop this parameter from the analysis to give model 2b.

Model 2b includes study level characteristics of baseline disease duration and average baseline HAQ and a main effect for MTX. The CI for all of these does not include zero.

Model 3 adds structure to the random effects to acknowledge common doses used in the treatment arms. This is the model that is used for examining the effect of disease duration, HAQ and MTX on outcome. The disease duration parameter is estimated as 0.124. This means that a patient is expected to respond better to biologic drugs the longer they have been diagnosed with RA. The odds ratio of an ACR50 event for a patient with a disease duration one year longer than average will be  $\exp(0.124)=1.132$  times larger than for a patient with average disease duration. The HAQ parameter is estimated to be  $-2.255$ , so a patient is expected to respond worse the higher their baseline HAQ. The odds ratio of an ACR50 event for a patient with baseline HAQ 0.1 point higher than average will be  $\exp(-0.2255)=0.798$  that of a patient with average baseline HAQ. The MTX parameter is estimated as 0.734. This means that the average patient responds better in both the control and intervention arms if MTX is given with the placebo or drug respectively. As, in this model, the MTX-interaction term does not influence the log odds of treatment, MTX affects the response equally in both the placebo and treatment arms. MTX increased the odds of an ACR50 response by  $\exp(0.734)=2.083$  in both the placebo and intervention arms.

Figure 1 shows a plot of the observed log odds ratio of ACR50 at six months for all treatments plotted against the average disease duration for each comparison. A linear regression is fitted, weighted by the variance of the log odds ratio estimate. This has a gradient of 0.112, comparable with that found from the meta-regression in model 3.

Figure 3 shows the observed log odds ratios of ACR50 at six months for each trial arm as solid dots, and the log odds ratios the model predicts as open dots. These fitted values are estimated from the random effects, which have been shrunk towards the mean for that particular drug [29]. This figure shows which trials did better or worse than expected once the disease duration and MTX treatment have been accounted for. For example, 40 mg of adalimumab given weekly in study 12 did slightly better than expected, whereas 100mg of Anakinra given in combination with MTX daily in study 3 did slightly worse than expected.

Figure 4 shows how the predicted odds ratio of ACR50 at six months improves with the disease duration of the patient with average baseline HAQ of  $\bar{h}=1.557$ . The estimated mean log odds ratio of an ACR50 response given biologic mono-therapy compared to placebo is the same as that given biologic combination therapy compared to MTX (as  $g_2$  is zero) and is given by

$$m_k + b_1(d - \bar{d}) + b_2(h - \bar{h}) \quad (7)$$

where  $m_k$  is the random effects mean for the drug concerned,  $d$  is the disease duration,  $\bar{d}=7.789$  years is the average disease duration over all the studies and  $h$  is the baseline HAQ. This recentring is necessary as the disease duration data are recentred in the model fitting. For example, the odds ratio on an ACR50 response for etanercept given to a patient with a disease duration of three years and average baseline HAQ is estimated by  $\exp(1.383+0.124 \times (3-7.789))=2.20$ . As the estimate of  $b_1$  is positive then all the drugs become more effective if used to treat patients with longer disease duration. The CI for the effectiveness of anakinra includes zero if this drug is used to treat RA patients with disease duration up to five years (for patients with average baseline HAQ). However, anakinra is effective at treating patients with a longer disease duration. The TNF antagonists as a class are effective at achieving ACR 50 at six months for all disease durations (for patients with average baseline HAQ).

Figure 5 makes an indirect comparison between treatments by showing the ratio of the odds ratios of ACR50 at six months for each pair of TNF antagonists. This finds the odds ratio of ACR50 at six months when comparing each pair of TNF antagonists. Again this is the same odds ratio for mono-therapy compared to placebo as combination therapy compared to MTX. As  $b_1(d - \bar{d}) + b_2(h - \bar{h})$  is the same for any drug the difference in log odds ratios is modelled to be the same for any disease duration and baseline HAQ and is given by

$$m_{k1} - m_{k2} \tag{8}$$

where  $m_{k1}$  and  $m_{k2}$  are the random effect means for the numerator and denominator drugs respectively. For example, the odds ratio of ACR 50 at six months if treated with adalimumab compared to etanercept is  $\exp(1.402-1.383)=1.02$  95% CI (0.54,1.97).

## 4. Discussion

We identified 13 randomised controlled trials that tested biologic treatments for the management of RA. No head to head studies of these therapies has been performed. Each of the trials measured ACR50 as an outcome and may have used the active comparator MTX in the control arm and in combination with the biologic therapy in the treatment arm. Additionally, the differences study inclusion criteria meant disparity in the patient populations between the trials. In addition, these trials may have incorporated several treatment arms testing different dosing regimes.

We developed methods to deal with all these features. First, we used the techniques of mixed treatment comparisons by allowing different random effects for each treatment, and introducing a covariable for the possible inclusion of an active comparator in model 1. Second, ideas from meta-regression introduced study level covariables into model 2. Third, the multiple treatment arms are acknowledged by putting some structure on the random effects in model 3.

The results confirm the efficacy of TNF antagonists over control even for patients with very early disease. While each TNF antagonist has a slightly different mode of action or formulation, we found no statistical difference between their ability to induce an ACR50 response over placebo. We found that the IL-1 antagonist anakinra is also superior to control for patients with disease duration greater than 5 years. However, less data are available for the anakinra estimate compared to anti-TNF combined estimate so this leads to comparatively wider CI. This penalises anakinra, as longer

disease duration is then necessary for the CI of the estimated effectiveness to exclude zero.

There are a number of potential limitations to the study. First, the exchangeability assumption used on the random effects in model 2 is strong – the treatment effects both within a study and between studies are all exchangeable with each other. Model 3 goes some way to acknowledge this structure in the studies. However, within-study and between study components of variance could be separated by modelling the random effects by

$$\begin{aligned} q_{ij} &\sim N(q_i, s_w^2) \\ q_i &\sim N(m_k, s_b^2) \end{aligned} \tag{9}$$

where  $s_w^2$  is the within study variability (assumed the same for all studies) and  $s_b^2$  is the between study variability. This model was fitted but there was not sufficient data to achieve a reasonable model fit. The Markov chains did not converge and mix around the supporting distribution. The meta-regression element of the model would explain the between study heterogeneity and reduce this, but would not affect the within study heterogeneity.

Second, the within-study heterogeneity relates to the different dosing regimes, which is not directly modelled as the dose ordering is ignored. The model would be improved if some dose-response relationship could be included in the model, but it is not clear how 25mg of etanercept could be compared with 20mg of adalimumab, or even how 20mg of adalimumab administered every week could be compared with 40mg every other week.

Third, we estimated  $g_1$  from studies where MTX is used in the control are not in the intervention arm. Estimates of this parameter could have been improved by including trials of MTX vs. placebo, as these would have given a direct estimate of  $g_1$ . We decided to restrict the meta-analysis to studies for biologic treatment, as trials of MTX are very old and do not include the ACR50 measurement, and we believed the effect of MTX in such populations could be different than in other studies.

Fourth, an assumption of the models is that the study level and methotrexate parameters  $b$  and  $g$  are the same for all treatments. This is probably a reasonable

assumption for the TNF antagonists as they all have a similar mechanism of action, but maybe less reasonable for anakinra.

Fifth, the relationship of ACR50 at six months with average disease duration or baseline HAQ of patients across trials may not be the same as the relationship for patients within trials [24]. [Ref Thompson and Higgins? Which one?]. The relationship demonstrated here between the patient characteristics might be due to confounding with other study level variables that may not even have been measured, and there may not be a relationship between ACR50 at six months and disease duration or HAQ at a patient level. This is a generic problem with meta-regression and individual patient data is needed to find a relationship at this level. However, other studies have shown that disease duration and baseline HAQ are strong predictors of efficacy.[25,26]

Lastly, we were not able to address the concern of publication bias, which could lead to a spuriously elevated risk estimate. This could potentially be relevant for anakinra, which has not reported the ACR results from its largest randomised study [30]

We have compared multiple treatments for the same disease. This work has similarities with Lu and Ades.[10]. They define a method for mixed treatment comparison where several trials are combined which test different treatments for the same disease and which measure the same outcome. This method is used to strengthen the relative efficacy estimates that are directly measured in the trials and also to make indirect estimates of relative efficacies that are not directly measured. Their model has the greater flexibility in that it is able to cope with several treatments being tested within a study, whereas the method defined in this paper is only suitable for one treatment in a study. Multiple treatments being considered within a study required correlation between the treatment random effects as within trial treatment groups maybe correlated. In our case different treatments are never from the same study so all treatment groups are independent and independent random effects are sufficient.

The models defined in this paper differ from those of Lu and Ades in a number of ways. In some cases, there were several treatment arms within a study all applying that same treatment. The control arm may be a placebo or an active comparator, and the active comparator may also be used in combination with treatment, but possibly not for all treatment arms. Meta-regression techniques are employed so study level

variables are used to try and explain the variability between studies. The random effects have a structure placed on them to reflect an expected similar effect of the same dose of the same drug.

An advantage with using MCMC to fit these models is that it allows credible intervals to be sampled directly from statistics of interest, for example, the log odds ratio for a given disease duration and the difference between log odds ratios for different treatments. In this way all the correlations between the parameters that make up these statistics are dealt with appropriately. Models 1 and 2 could have been modelled using classical techniques, although they may not fit into the pre-programmed routines of a package. Model 3 would be difficult to fit in such a framework.

Until this analysis, it had been impossible to determine whether one TNF antagonist is superior to another. A direct head to head study is unlikely as there is no incentive for the existing pharmaceutical companies to fund such a study, and it would be difficult for a public body to justify the expense such a trial would consume. With the current evidence, we found no evidence to suspect that there are material differences between TNF antagonists, and therefore such a trial would not be necessary..

In conclusion, this paper defines and demonstrates an extension of standard meta-regression techniques by using ideas from multiple treatment comparisons. This allows different treatments for the same condition to be compared whilst adjusting for differences in the study populations.

## 5. Appendix

Bugs code for model 3.

```
model{
for(i in 1:N.c){ #N.c is the number of comparator arms
  r.acr.c[i] ~ dbin(p.c[i], n.c[i]) #n.c is the number of patients in the control arm
                                     #r.acr.c is the number of ACR50 events in the control arm
  logit(p.c[i]) <- mu[study.c[i]] + gamma1*mtx.c[i] #mtx.c is 1 if MTX is used, 0 o/w
}
}
```

```

for(i in 1:N.t){ #N.t is the number of treatment arms
  r.acr.t[i] ~ dbin(p.t[i], n.t[i]) #n.t, r.acr.t are as n.c and r.acr.c but for the treatment arm
  logit(p.t[i]) <- mu[study.t[i]] + gamma1*mtx.t[i]+lor[i]
  lor[i] <- theta[treat.t[i]]
    +beta1*(dur.s[study.t[i]]-dur.s.bar) #dur.s is the disease duration in a study
    +beta2*(haq.b.s[study.t[i]]-haq.b.s.bar) #haq.b.s is the baseline HAQ in a study
  fit.lor[i]<-lor[i]+gamma1*(mtx.t[i]-mtx.c[study.t[i]])
}

#random effect for all treatments
for(i in 1:N.t){
  re.mean[i] <- mu.theta[drug.t[i]]
}
tau.theta<-1/ss.theta
ss.theta<-s.theta*s.theta

#priors
for(i in 1:N.c){ mu[i] ~ dnorm(0, 1.0E-6)}
for(i in 1:4){mu.theta[i]~dnorm(0, 1.0E-6)}
s.theta~dunif(0.01, 10)

beta1 ~ dnorm(0, 1.0E-6) # duration
beta2 ~ dnorm(0, 1.0E-6) # haq
gamma1 ~ dnorm(0, 1.0E-6) # MTX affect

#transformed variables
for(i in 1:4){exp.mu.theta[i]<-exp(mu.theta[i])}

#adjusted mean lor for various durations and treated with MTX and biologic with average haq.
for(t in 1:4){ #treatment index
  for(d in 1:16){ #disease duration
    adj.lor[d,t]<-mu.theta[t]+beta1*(d-1-dur.s.bar)
    adj.or[d,t]<-exp(adj.lor[d,t])
  }
}
}

```

```

#difference in log OR between treatments. first-second
for(i in 1:3){
  i1[i]<-study.c[i]+1
  for(j in (i+1):4){
    df.lor[j,i]<-mu.theta[j]-mu.theta[i]
    df.or[j,i]<-exp(df.lor[j,i])
  }
}

```

```

#random effects structure
theta[14]<-theta[10]
theta[12]<-theta[11]
theta[13]<-theta[11]
theta[15]<-theta[11]
theta[16]<-theta[11]
theta[26]<-theta[23]
theta[28]<-theta[23]
theta[27]<-theta[24]
theta[30]<-theta[24]
theta[32]<-theta[24]
theta[33]<-theta[24]
theta[21]<-theta[17]
theta[1] ~ dnorm(re.mean[1], tau.theta)
theta[2] ~ dnorm(re.mean[2], tau.theta)
theta[3] ~ dnorm(re.mean[3], tau.theta)
theta[4] ~ dnorm(re.mean[4], tau.theta)
theta[5] ~ dnorm(re.mean[5], tau.theta)
theta[6] ~ dnorm(re.mean[6], tau.theta)
theta[7] ~ dnorm(re.mean[7], tau.theta)
theta[8] ~ dnorm(re.mean[8], tau.theta)
theta[9] ~ dnorm(re.mean[9], tau.theta)
theta[10] ~ dnorm(re.mean[10], tau.theta)
theta[11] ~ dnorm(re.mean[11], tau.theta)
theta[17] ~ dnorm(re.mean[17], tau.theta)
theta[18] ~ dnorm(re.mean[18], tau.theta)
theta[19] ~ dnorm(re.mean[19], tau.theta)
theta[20] ~ dnorm(re.mean[20], tau.theta)

```

```
theta[22] ~ dnorm(re.mean[22], tau.theta)
theta[23] ~ dnorm(re.mean[23], tau.theta)
theta[24] ~ dnorm(re.mean[24], tau.theta)
theta[25] ~ dnorm(re.mean[25], tau.theta)
theta[29] ~ dnorm(re.mean[29], tau.theta)
theta[31] ~ dnorm(re.mean[31], tau.theta)

#extra variables
dur.s.bar<-mean(dur.s[])
haq.b.s.bar<-mean(haq.b.s[])

}
```

## Tables and figures

Table 1 Data extracted from included phase three studies

Table 2 Structural assumptions on the random effects  $q_{ij}$ .  $i$  refers to the study and  $j$  the treatment within the study as given in Table 1

Table 3 Parameter estimates for models 1 to 3.

Figure 1 Observed log odds ratio of ACR 50 at six months in all treatment arms of studies compared to the control arm, by average disease duration. The linear regression weighted by the inverse of the variance of the log odds ratio estimate is also shown. The area of each circle is inversely proportional to the variance of the log relative risk estimate and the shading of the circle relates to the treatment used. The disease duration is the same for all arms within a study, and the study relating to the “column” of disease duration circles is given in the margin above the plot.

Figure 2 Plot of observed and fitted log odds ratios from model 3.

Figure 3 Odds ratio of ACR50 by treatment and disease duration compared to control predicted from model 3 fitted with both different random effects for each drug and different random effects for TNF antagonists and anakinra.

Figure 4 Odds ratios of ACR50 for all TNF antagonist treatment pairs predicted from model 3 fitted with different random effects for each drug. The Odds ratios and 95% CI are also shown.

**Table 1**

Study	Trial	Intervention	N	Mean Baseline Characteristics			6 Months
				Age (years)	Disease duration (years)	Baseline HAQ	ACR50
1	Cohen 2002	Placebo + MTX	74	53	7.5	1.4	4%
		Anakinra 0.04mg/kg/day + MTX	63				13%
		Anakinra 0.1mg/kg/day + MTX	74				20%
		Anakinra 0.4mg/kg/day + MTX	77				10%
		Anakinra 1.0mg/kg/day + MTX	59				24%
		Anakinra 2.0mg/kg/day + MTX	72				17%
2	Bresnihan 1998	Placebo	121	53	4.0	1.5	8%
		Anakinra 30mg/day	119				17%
		Anakinra 75mg/day	116				11%
		Anakinra 150mg/day	116				19%
3	Cohen 2001	Placebo+ MTX	251	57	10.7	1.3	8%
		Anakinra 100mg/day + MTX	250				17%
4	Moreland 1999	Placebo	80	52	12.0	1.7	5%
		Etanercept 10mg 2xweek	76				24%
		Etanercept 25mg 2xweek	78				40%
5	Weinblatt 1999	Placebo + MTX	30	50	13.0	1.5	3%
		Etanercept 25mg 2xweek + MTX	59				39%
6	ERA 2000	Placebo + MTX	217	50	1.0	1.4	31%
		Etanercept 25mg 2xweek	207				39%
		Etanercept 10mg 2xweek	208				33%
7	TEMPO 2004	Placebo + MTX	228	53	6.6	1.8	40%
		Etanercept 25mg 2xweek + MTX	231				58%
		Etanercept 25mg 2xweek	223				41%
8	ATTRACT 1999	Placebo + MTX	88	53	10.6	1.7	9%
		Infliximab 3mg/kg q8wks + MTX	86				22%
		Infliximab 3mg/kg q4wks + MTX	86				30%
		Infliximab 10mg/kg q8wks + MTX	87				40%
		Infliximab 10mg/kg q4wks + MTX	81				35%
9	ASPIRE 2005	MTX	282	50	0.9	1.5	32%*
		Infliximab 3mg/kg q8wks + MTX	359				46%*
		Infliximab 6mg/kg q8wks+ MTX	363				50%*
10	ARMADA 2003	Placebo + MTX	62	56	12.3	1.6	8%
		Adalimumab 20mg eow + MTX	69				32%
		Adalimumab 40mg eow + MTX	67				55%
		Adalimumab 80mg eow + MTX	73				42%
11	Keystone 2004	Placebo + MTX	200	57	11.0	1.5	10%
		Adalimumab 20mg eow + MTX	212				41%
		Adalimumab 40mg eow + MTX	207				39%
12	van de Putte 2004	Placebo	110	47	10.9	1.9	8%
		Adalimumab 20mg eow	106				19%
		Adalimumab 20mg wkl	112				21%
		Adalimumab 40mg eow	113				22%
		Adalimumab 40mg wkl	103				35%
13	PREMIER 2005	MTX	257	52	0.7	1.5	46%*
		Adalimumab 40mg eow	274				42%*
		Adalimumab 40mg eow + MTX	268				61%*

\* indicates the ACR50 at six months has been estimated by the ACR50 at 12 months.

eow=every other week, wkl=weekly.

Table 1

Study	Trial	Intervention	N	Mean Baseline Characteristics			6 Months
				Age (years)	Disease duration (years)	Baseline HAQ	ACR50
1	Cohen 2002	Placebo + MTX	74	53	8	1.4	4%
		Anakinra 0.04mg/kg/day + MTX	63	53	6	1.4	13%
		Anakinra 0.1mg/kg/day + MTX	74	53	9	1.5	20%
		Anakinra 0.4mg/kg/day + MTX	77	53	7	1.5	10%
		Anakinra 1.0mg/kg/day + MTX	59	49	7	1.3	24%
		Anakinra 2.0mg/kg/day + MTX	72	54	8	1.3	17%
2	Bresnihan 1998	Placebo	121	52	4	1.5	8%
		Anakinra 30mg/day	119	53	4	1.5	17%
		Anakinra 75mg/day	116	53	4	1.6	11%
		Anakinra 150mg/day	116	54	4	1.6	19%
3	Cohen 2001	Placebo+ MTX	251	57	10	1.3	8%
		Anakinra 100mg/day + MTX	250	56	11	1.4	17%
4	Moreland 1999	Placebo	80	51	12	1.7	5%
		Etanercept 10mg 2xweek	76	53	13	1.7	24%
		Etanercept 25mg 2xweek	78	53	11	1.6	40%
5	Weinblatt 1999	Placebo + MTX	30	53	13	1.5	3%
		Etanercept 25mg 2xweek + MTX	59	48	13	1.5	39%
6	ERA 2000	Placebo + MTX	217	49	1	1.4	31%
		Etanercept 25mg 2xweek	207	51	1	1.4	39%
		Etanercept 10mg 2xweek	208	50	1	1.4	33%
7	TEMPO 2004	Placebo + MTX	228	53	7	1.7	40%
		Etanercept 25mg 2xweek + MTX	231	52.5	7	1.8	58%
		Etanercept 25mg 2xweek	223	53.2	6	1.8	41%
8	ATTRACT 1999	Placebo + MTX	88	51	11	1.7	9%
		Infliximab 3mg/kg q8wks + MTX	86	54	10	1.8	22%
		Infliximab 3mg/kg q4wks + MTX	86	52	9	1.7	30%
		Infliximab 10mg/kg q8wks + MTX	87	54	11	1.7	40%
		Infliximab 10mg/kg q4wks + MTX	81	52	12	1.7	35%
9	ASPIRE 2005	MTX	282	50	1	1.5	32%*
		Infliximab 3mg/kg q8wks + MTX	359	51	1	1.5	46%*
		Infliximab 6mg/kg q8wks+ MTX	363	50	1	1.5	50%*
10	ARMADA 2003	Placebo + MTX	62	56	11	1.6	8%
		Adalimumab 20mg eow + MTX	69	54	13	1.5	32%
		Adalimumab 40mg eow + MTX	67	57	12	1.6	55%
		Adalimumab 60mg eow + MTX	73	56	13	1.6	42%
11	Keystone 2004	Placebo + MTX	200	56	11	1.5	10%
		Adalimumab 20mg eow + MTX	212	57	11	1.5	41%
		Adalimumab 40mg eow + MTX	207	56	11	1.4	39%
12	van de Putte 2004	Placebo	110	54	12	1.9	8%
		Adalimumab 20mg eow	106	23	9	1.9	19%
		Adalimumab 20mg wkl	112	54	11	1.9	21%
		Adalimumab 40mg eow	113	53	11	1.8	22%
		Adalimumab 40mg wkl	103	52	12	1.8	35%
13	PREMIER 2005	MTX	257	52	1	1.5	46%*
		Adalimumab 40mg eow	274	52	1	1.5	42%*
		Adalimumab 40mg eow + MTX	268	52	1	1.5	61%*

\* indicates the ACR50 at six months has been estimated by the ACR50 at 12 months.

eow=every other week, wkl=weekly.

Table 2

Drug	Dose	Constraints
Etanercept	10mg 2xweek	$q_{41} = q_{62}$
	25mg 2xweek	$q_{42} = q_{51} = q_{61} = q_{71} = q_{72}$
Infliximab	3mg/kg q8wks	$q_{81} = q_{91}$
Adalimumab	20mg eow	$q_{10,1} = q_{11,1} = q_{12,1}$
	40mg eow	$q_{10,2} = q_{11,2} = q_{12,3} = q_{13,1} = q_{13,2}$

**Table 3**

Model	Description	Parameter	Median	SD	95% CI	
1	Anakinra	$m_1$	0.940	0.353	(0.240	1.626)
	Etanercept	$m_2$	1.503	0.362	(0.815	2.239)
	Infliximab	$m_3$	0.921	0.412	(0.097	1.713)
	Adalimumab	$m_4$	1.381	0.316	(0.773	2.015)
	MTX	$g_1$	1.360	0.402	(0.615	2.140)
	MTX treatment interaction	$g_2$	0.069	0.330	(-0.571	0.734)
	Between treatment standard error	$s$	0.416	0.099	(0.251	0.636)
2a	Anakinra	$m_1$	1.029	0.291	(0.477	1.602)
	Etanercept	$m_2$	1.959	0.395	(1.236	2.797)
	Infliximab	$m_3$	1.948	0.427	(1.082	2.775)
	Adalimumab	$m_4$	1.817	0.326	(1.211	2.534)
	Baseline disease duration	$b_1$	0.122	0.026	(0.070	0.174)
	Baseline HAQ	$b_2$	-2.363	0.935	(-4.304	-0.561)
	MTX	$g_1$	1.269	0.379	(0.571	2.062)
	MTX treatment interaction	$g_2$	-0.518	0.341	(-1.208	0.161)
	Between treatment standard error	$s$	0.222	0.096	(0.026	0.409)
2b	Anakinra	$m_1$	0.8012	0.252	(0.336	1.329)
	Etanercept	$m_2$	1.468	0.238	(1.025	1.964)
	Infliximab	$m_3$	1.397	0.232	(0.957	1.866)
	Adalimumab	$m_4$	1.385	1.389	(1.058	1.385)
	Baseline disease duration	$b_1$	0.115	0.026	(0.065	0.169)
	Baseline HAQ	$b_2$	-1.671	0.781	(-3.203	-0.088)
	MTX	$g_1$	0.799	0.267	(0.290	1.353)
	Between treatment standard error	$s$	0.255	0.087	(0.094	0.443)
3	Anakinra	$m_1$	0.763	0.264	(0.251	1.309)
	Etanercept	$m_2$	1.383	0.265	(0.859	1.912)
	Infliximab	$m_3$	1.539	0.241	(1.094	2.051)

Adalimumab	$m_4$	1.402	0.208	(1.008	1.831)
Disease duration	$b_1$	0.124	0.021	(0.084	0.167)
Baseline HAQ	$b_2$	-2.255	0.652	(-3.555	-0.960)
MTX	$g_1$	0.734	0.122	(0.503	0.973)
Between treatment standard error	$s$	0.268	0.111	(0.085	0.521)

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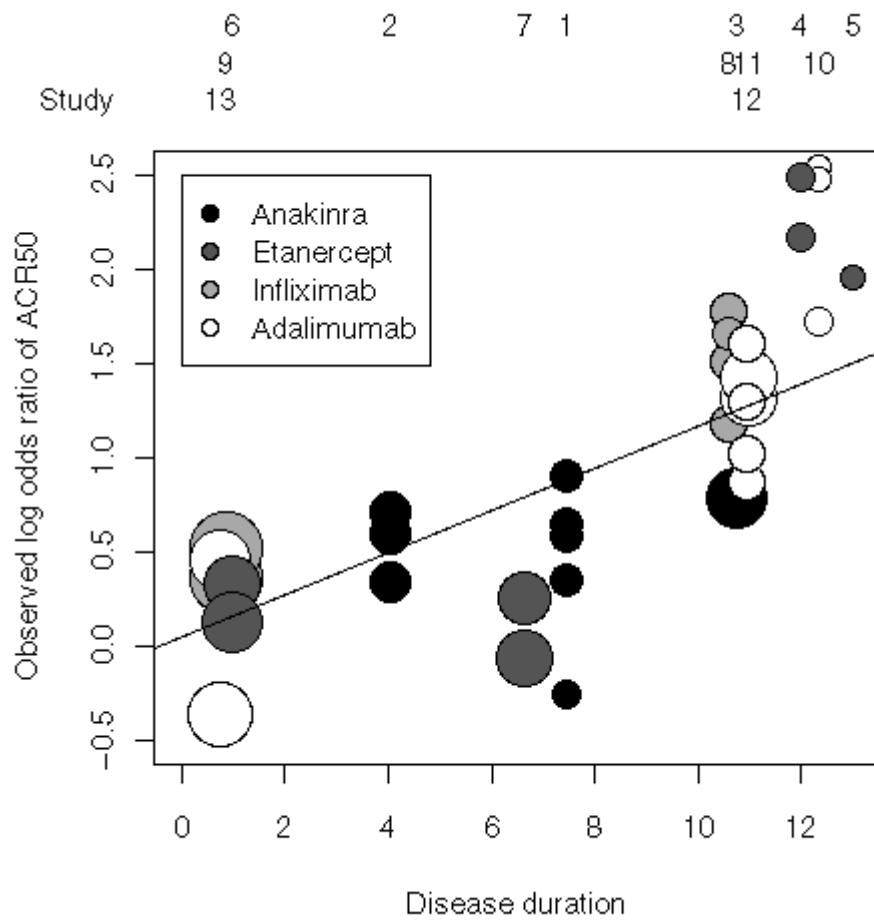


Figure 1

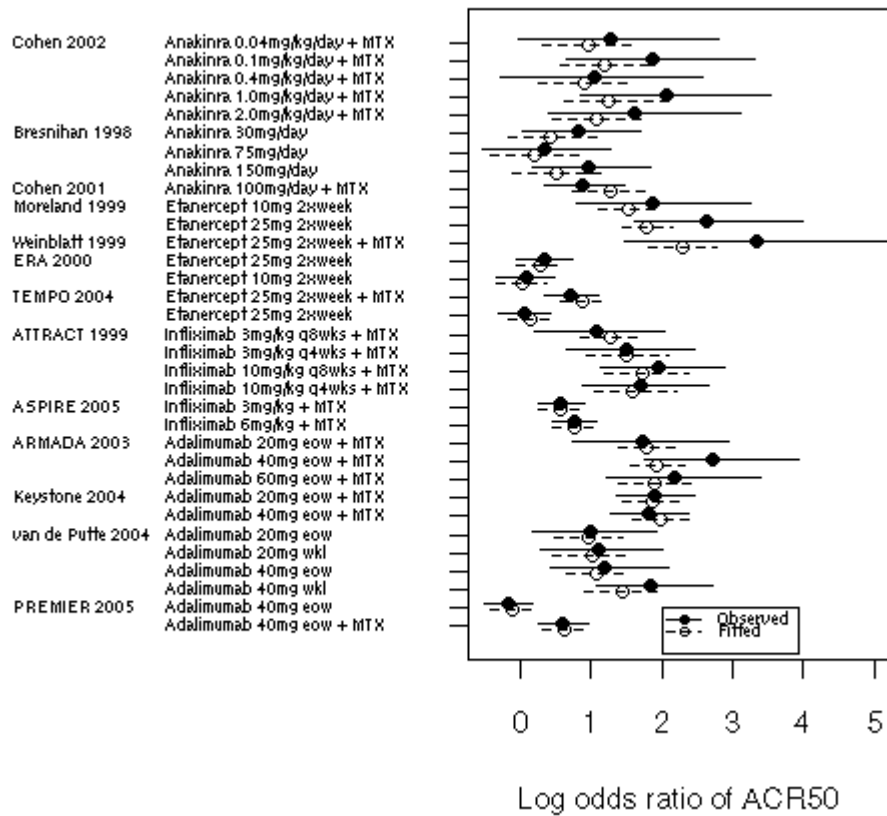
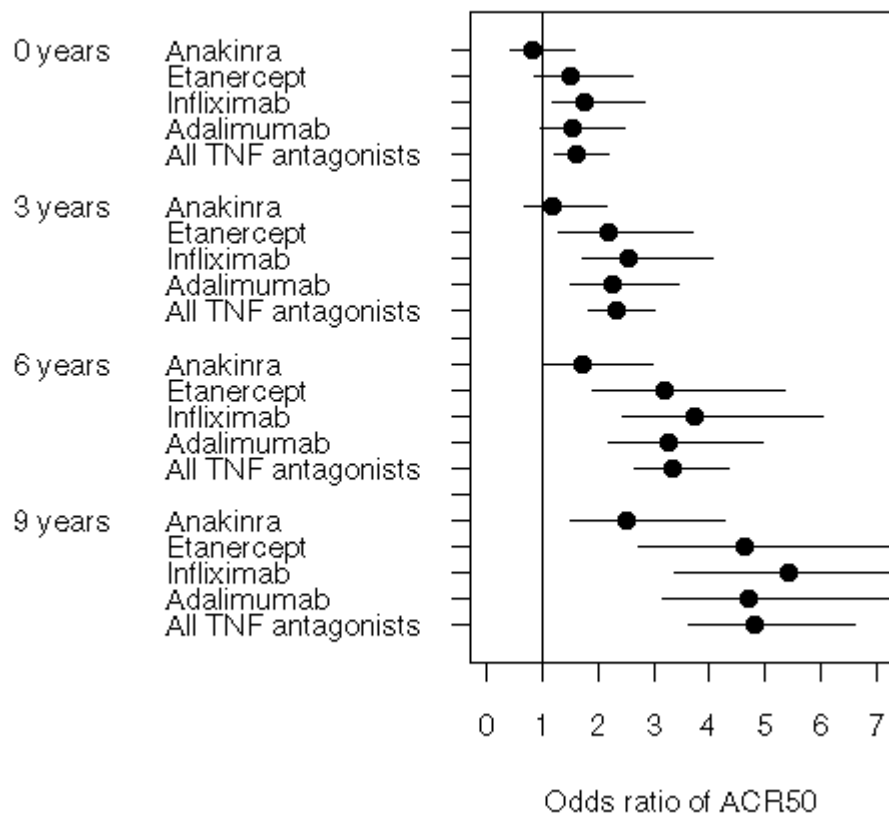
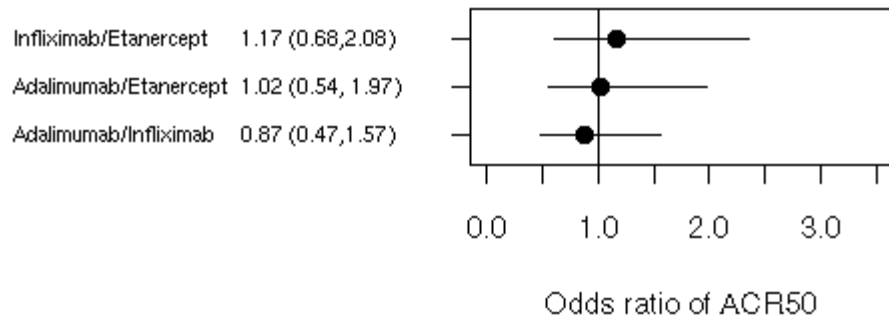


Figure 2



**Figure 3**



**Figure 4**

## 6. References

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