THE SEQUENTIAL USE OF TNF-α INHIBITORS.

UPDATE TO A REPORT BY THE DECISION SUPPORT UNIT

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CONTENTS

1. INTRODUCTION

The tumour necrosis factor alpha inhibitors (TNF-α inhibitors) etanercept, adalimumab and infliximab have been demonstrated to be similarly effective in clinical trials (Nixon et al. 2006). In clinical practice, patients that withdraw from one anti-TNF due to adverse events, lack of efficacy or loss of response, may be switched to another anti-TNF. Current NICE guidance recommends that such switching occur only in the event of withdrawal due to adverse events. The purpose of this report is to inform the Institute's considerations of the anti-TNFs in relation to patients that may switch due to either lack of efficacy or loss of response.

This report is an update to a review conducted by the Decision Support Unit (DSU) (Wailoo and Bansback, 2006) which in turn included an update to previous work (Wailoo et al. 2006). The aim of this report is to provide a systematic review of studies considering the clinical effectiveness of sequential use of the anti-TNFs.

2. METHODS FOR REVIEWING EFFECTIVENESS

2.1. SEARCH STRATEGY

The purpose of the search was to identify all evidence relating to the clinical effectiveness of either infliximab, adalimumab or etanercept in patients that had failed a previous anti-TNF. Updates of previously performed searches of electronic bibliographies were performed together with hand searching of two recently published reviews (Suarez Almor, 2007 and Aletaha, 2007).

2.1.1. 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 1. for the updated searches, terms relating to anakinra were excluded.

2.1.2. Inclusion/exclusion criteria

Inclusion

- Patients that have withdrawn from either infliximab and/or etanercept and/or adalimumab (but not all three) and have been switched to a different TNF-α inhibitor
- Published studies, conference abstracts and published letters
- Primary effectiveness reported in terms of HAQ, ACR, DAS, EULAR or other recognised outcome measured in RA.
- Rheumatoid arthritis patients only or where mixed groups of patients are studied, the results are reported for RA patients alone.

Exclusion

- Studies that considered anakinra, ritixumab or abatacept without also considering at least one of the anti-TNFs.
- Studies that only reported either duration of treatment or dose changes rather than primary response.
- Studies that do not report relevant clinical outcomes.
- If primary effectiveness after switching was not reported studies were excluded.
- Studies of patients with juvenile arthritis, Crohn's disease, psoriatic arthritis and other forms of spondyloarthritis, unless RA patients could be distinguished in the results.
- Studies not reported in English

3. RESULTS

3.1. NUMBER OF RELEVANT STUDIES

The updated searches identified 86 references. On inspection of the titles and abstracts where available, 20 papers were considered eligible for full review. These papers are reported in Table 1. Ten of these papers were included in the final review. Of the 10 which were excluded at this stage, three did not consider patients switching to a different anti-TNF, three did not report response data, one focussed on switchers to etanercept due to adverse events, one focussed on the third rather than second anti-

TNF, one was a review and another considered those who were switched from infliximab despite a good clinical response.

In the previous review of studies identified prior to 2007, 20 studies were included. In the current searches, Bombardieri et al. (2007) is the full publication that supersedes Bombardieri et al. (2006) which was a conference abstract. Additional information is included in the published paper. A total of 29 studies are therefore included in the review. Three of these studies are reported as letters (Gomez Puerta, 2004, Favelli et al. 2004, Yazicki 2004).

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

	Author	Country	Included /reason for exclusion
1	Allaart et al. (2006)	Netherlands	No – does not consider switching TNFs
2	Bennett et al. (2005)	UK	Yes
3	Bombardieri et al (2007)	Europe and Australia	Yes - replaces Bombardieri et al. (2006)
4	Buch et al. (2007)	UK	Yes
5	Di Poi et al (2007)	Italy	Yes
6	Finckh et al (2006)	Switzerland	No / does not consider switching
7	Finckh, Cuirea (2007)	Switzerland	Yes
8	Furst et al. (2007)	US	Yes
9	Gibofsky et al. (2006)	US	No / no data on response
10	Goekoop-Ruiterman	Netherlands	No / early RA and not switching
11	Gomez-Reino (2006)	Spain	No / no data on response
12	Hjardem et al (2007)	Denmark	Yes
13	Hyrich et al (2007)	UK	No / no data on response
14	Iannone et al (2007)	Italy	No / switchers due to adverse events
15	Kafka et al (2005)	US	Yes
16	Keystone et al (2004)	Not stated	Yes
17	Solau-Gervais (2006)	France	No / focus is on third biologic and only limited outcomes data (DAS28)
18	Suarez Almazor (2007)	Canada	No / no primary data
19	van der Bijl et al (2005)	Not stated	Yes
20	Walsh (2007)	Ireland	No / patients were switched despite response to IXB

Table 2: Studies included in the review and their key features

Author	Number of patients in study	Treatment switched from (n)	Reason for Switching	Treatment switched to	Time beyond switch measurement made	Primary outcome variable
Ang et al. (2003)	29	IXB (24) ETP (5)	Lack of efficacy/ Adverse event	ETP IXB	Not reported	Joint count
Atzeni et al. (2006)	15	IXB followed by ETP or vice versa	Non response or adverse events for first switch, switch to ALB on basis of DAS28>5.1	ALB	At the time of stopping 2nd biologic and then every 6 months	Unclear. HAQ, DAS.
Bennett et al. (2005)	26	IXB, ETP, AKA	No response (27%), loss of efficacy (45%), adverse events (21%,	ALB	4,8,16,26,52 weeks	DAS28, HAQ, EULAR
Bombardieri et al. (2007)	899	ETP or IXB	Mixture - no response, loss of efficacy, intolerance.	ALB	12 weeks	ACR, DAS28
Brulhart et al. (2006)	20	At least one TNF alpha	"failure" according to patient's rheumatologist	RXB (10), another tnf alpha (10)	3, 6 months	DAS, HAQ
Buch et al. 2005 (a)	34	IXB	Non response and a) never achieved a 20% improvement in CRP (n=10) and b) achieved a temporary improvement in CRP (n=15)	ETP	12 weeks	ACR
Buch et al. (2005b)	59	IXB	Non response (32%), loss of efficacy (51%) and toxicity (18%)	ALB	12weeks	EULAR and DAS28
Buch et al. (2007)	95	IXB	Non response (36%),	ETP	12 weeks	EULAR and DAS28

			Loss of efficacy (40%), and toxicity (24%)			
Brocq et al. (2002)	14	IXB (8)	Miscellaneous	ETP	Not reported	Not reported
		ETP (6)		IXB		
Brocq et al. (2004)	18	ETP(8), ETP followed by IXB (10)	Mixed	ALB	2-8 months	Not stated
Cantini et al. (2005)	22	IXB (15), ALB (7)	Inefficacy (68%), adverse event (32%)	ETP	Baseline, 4,12, 24 weeks	ACR, DAS28
Cohen et al. (2005)	38	IXB (24), ETP (14)	Non response (29), adverse events (9)	IXB, ETP	3 months	DAS28
Di Poi et al (2007)	18	IXB	Non response (61%) Loss of efficacy (39%)	ETP	2 weeks, 3 months, every 3 months until last follow – up (not defined)	EULAR, DAS28
Favelli et al. (2004)	15	IXB (14)	Lack of efficacy/ Adverse event	ETP	6 months	ACR20, DAS28, HAQ
		ETP (1)	Lack of efficacy	IXB		
Finckh (2007)	116	ETP or IXB or ALB	Any	Any	another tnf alpha (66) RXB (50)	DAS28
Furst et al. (2007)	28	ETP		IXB	16 weeks	ACR, DAS28, HAQ,
Gomez-Puerta et al. (2004)	12	IXB (12)	Lack of efficacy	ETP	6 months	DAS28, EULAR
Hansen et al. (2004)	20	ETP (20)	Lack of efficacy/ Adverse event	IXB	Not reported	SWJ, TJC
Haroui et al. (2004)	22	IXB (22)	Lack of efficacy/ Adverse event	ETP	12 weeks	ACR20. HAQ
Hjardem et al (2007)	235	IXB (178) ETP (18) ALB (39)	"lack of efficacy" (46%) adverse events (31%)	all	3,6 months	DAS28, EULAR

Kafka et al. (2005)	191	Any anti tnf alpha	MD choice (46%), adverse events (18%), lack of efficacy (17%)	Any	3 months	DAS
Keystone et al (2004)	155	IXB (83), ETP (72)	Lack of efficacy	ETP, IXB	6 months	HAQ
Kristensen et al. (2006)	404	Any anti tnf alpha	Any	ETP (239), ALB (165)	3,6,12,24,36 months (12 for ALB)	ACR20
Naumann et al. (2006)	31	Any anti tnf alpha	severe adverse event (7) ineffectiveness (22) incompliance (2)	IXB, ETP or ALB	3yrs max	DAS
Nikas et al. (2006)	24	IXB	Lack of efficacy/ Adverse event	ALB	12 months	ACR, DAS28
Van der Bijl et al (2005)	37	IXB	Loss of efficacy (19), lack of response (13), adverse events (5)	ALB	16 weeks	ACR, DAS28, EULAR
Van Vollenhoven et al (a) (2003)	31	ETP (18)	Lack of efficacy	IXB	>8 weeks	DAS28, ACR-N
		IXB (13)	Adverse event	ETP		
Wick et el. (2005)	36	IXB (27), ETP (9)	Secondary loss of efficacy	ALB	3,6 months	DAS28
Yazici et al. (2004)	21	ETP (21)	Miscellaneous	IXB		

ETP= etanercept, IXB = Infliximab, ALB = Adalimumab, RXB = Rituximab, CRP= C-Reactive Protein, DAS=Disease Activity Score, EULAR= European League Against Rheumatism, ACR=American College of Rheumatology, TJC=Total Joint Count, SWJ = Swollen Joint

3.2. STUDY CHARACTERISTICS

3.2.1. Size of studies

It should be noted that many of the included studies are very small scale. Twenty studies have samples of less than 50 patients. Earlier studies in particular tend to be smallest.

Bombardieri et al. (2007) is the largest study (n=899). Other substantial studies are Kristensen et al. (2006) (n=404), and Hjardem et al. (2007) (n=235).
Five studies include over 50 switchers to a second anti-TNF: Buch et al. (2005b), Buch et al. (2007), Keystone et al (2004), Kafka et al (2005) and Finckh et al. (2007).

3.2.2. Types of studies

Only one of the identified studies is a randomized, controlled trials (Furst et al. 2007) and this is an open-label, pilot study (n=28). Most of the studies have no comparator group and even where given, comparisons must be treated with caution due to the observational nature of the studies. Some studies make comparisons with other cohorts of patients taking a first anti-TNF and who may or may not include the group that subsequently switched (e.g. Kristensen et al. (2006), Bombardieri et al. (2007)), and two others make comparisons with patients that switched to rituximab (Finckh et al. (2007), Brulhart et al. (2006)).

3.2.3. Variability of the studies

The studies identified use a variety of outcome measures and follow up timings making comparisons across studies difficult to make.

Five studies report ACR response criteria at 3 months (Buch 2005a, Buch 2007, Bombardieri 2007, Furst 2007, Kristensen 2006), although one of these only reports ACR20 (Kristensen 2006). Two studies report ACR responses at 6 months (Cantini 2006, Kristensen 2006) (of which one also reports 3 month data), two studies report

ACR at 12 months (Kristensen 2006, Nikas 2006)(of which one also reports 6 and 3 month data).

Eights studies report DAS improvements over 3 months (Wick 2005, Brulhart 2006, Bombardieri 2007, Buch 2005b, Buch 2007, Furst 2007, Finckh 2007, Hjardem 2007), seven report DAS improvements at 6 months (Favelli, 2004, Gomez Puerta 2004, Wick 2005, Atzeni 2006, Brulhart 2006, Cantini 2005, Finck 2007) of which three also report the 3 month data) (Wick 2005, Brulhart 2006, Finck 2007), and one study reports DAS improvements at 12 months (Nikas 2006).

EULAR responses are reported by three studies at 3 months (Buch 2005b, Buch 2007 and Hjardem, 2007), and by one study at 6 months (Gomez Puerta 2004) and by one study at 12 months (Nikas 2006). Bennett et al. report DAS and EULAR responses at various time points up to one year/

HAQ is a less reported outcome measure and the manner of reporting is not consistent. For example some studies report the proportion of patients achieving an improvement in HAQ of at least 0.22 or 0.4 (for example, Furst et al, 2007). Bombardieri (2007) and Haroui (2004) report mean HAQ improvement at 3 months and Favelli (2004) and Keystone et al (2004) report mean HAQ improvement at 6 months.

There is also variability on the reporting of outcome measures such as number of tender joints, number of swollen joints, erythrocyte sedimentation rate, and global disease activity.

Studies also vary in terms of which of the anti-TNFs patients have failed and the reasons why they have failed (the three greatest reasons are adverse events, lack of response or loss of efficacy) and which of the anti-TNFs patients switch to. Where feasible we report results by drug switched to and excluding patients that withdrew from the previous anti-TNF due to adverse events.

3.3. OUTCOMES

3.3.1. Switches to etanercept

Six studies considered only switches to etanercept (Gomez-Puerta et al. 2004, Haroui et al. 2004, Buch et al 2005a, Buch 2007, Cantini et al. 2005, Di Poi 2007) and a further eight considered switches to etanercept as well as other switches but reported outcomes from the etanercept group separately (Ang et al. 2003, Brocq et al. 2002, van Vollenhoven et al 2003, Keystone et al 2004, Cohen et al 2005, Naumann et al 2006, Kristensen et al 2006, Hjardem 2007).

Earlier studies tended to examine the effect of switching from infliximab to etanercept and more recent studies have included the switch from adalimumab to etanercept. A summary of results are shown in Table 3.

The largest study (Kristensen et al. 2006) comprised 239 patients switched to etanercept and compared them with a group of patients that took etanercept prior to any other biologic (n=442). ACR20 response rates were lower in the group that had previously failed a biologic than biologic naïve patients treated with etanercept at each of the five time points reported: 3 months (61% vs 52%), 6 months (63% vs 59%), 12 months (67% vs 63%), 24 months (64% vs 39% - p=0.028), and 36 months (63% vs 40%). Whilst comparisons are made at five time points up to 36 months of follow up, statistical tests are reported only for the greatest difference between the groups (at 24 months). The numbers of patients included at each time point are not reported in this abstract.

Buch et al. (2007) found that in 95 switchers to etanercept, 38% achieved an ACR20 at 12 weeks, with 24% and 15% achieving ACR50 and ACR70 responses respectively. Responses were slightly higher in those that had withdrawn from the previous anti-TNF (infliximab) due to primary non response rather than secondary non response.

Three other studies reporting ACR responses are based on relatively small numbers of patients (Cantini et al. 2005, Buch et al. 2005a and Haroui et al. 2004). Haroui et al. (2004) is based on 22 patients that switched from infliximab to etanercept. 18 did so

due to lack of efficacy. ACR20/50/70 response rates of 64%/23%/5% are reported an no comparator group is reported.

Cantini et al. (2005) reports ACR20/50/70 response rates of 90%/33%/10% (n=22). No comparisons are made.

Buch(2005a) reports ACR20/50/70 response rates of 66%/66%/33% for group A, those that were non responders to infliximab (n=12), and 71%/57%/14% for those that were non responders to infliximab and had a temporary CRP response (n=22). Details of a comparator group, those that remained on infliximab therapy despite no ACR 20 response at 12 weeks but CRP improvement, are provided (n=58). ACR20/50/70 responses at 24 weeks are 59%/35%/6% respectively. The ACR 20 response rate is slightly lower than for the two switcher groups and ACR50 and ACR70 responses are substantially lower.

Favelli (2004), although reporting ACR20 at 24 weeks, only does so for a combined RA and juvenile RA population.

The largest study reporting EULAR response rates is Buch (2007) who finds that 73% of switchers to etanercept achieve a good or moderate EULAR response (n=95).

Hjardem et al (2007) finds that for those switching to etanercept from infliximab for any reason, 53% achieve a good or moderate EULAR response (n=57), compared to 66% of those switching from adalimumab (n=17) although this latter group is relatively small. Comparisons are made with the responses achieved by these same patients on the first anti TNF. Good or moderate EULAR responses were seen in 59% of those that were originally on infliximab (p=0.29) and 62% for those originally on adalimumab. No statistically significant differences were observed between DAS28 improvements on first and second drugs in either of these switching groups. It should be noted that the results are not reported by subgroups of patients categorised according to both the drugs switched to/from AND the reason for switching. The results for the subgroups according to the reason for switching are reported in Section 3.3.4 below.

van Vollenhoven et al (2003) 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). However, 11 of the 13 patients that made this switch did so due to adverse events. Therefore, these results are of limited relevance.

Gomez Puerta et al. (2004) consider 12 patients who switched from infliximab to etanercept due to inefficacy (4 never achieved a response). 83% achieved good or moderate EULAR responses to etanercept at 6 months. Comparisons in terms of DAS are made between the same patients whilst they were on infliximab. However, since this is a subgroup of treatment failures and the time points at which comparisons are made, these figures are not useful.

Di Poi et al. (2007) reports that EULAR good or moderate responses were identified in 7/11(64%) of patients that had no response to infliximab, and that 6/7 (86%) of those that lost response to infliximab achieved good or moderate EULAR responses to etanercept. However, the time point at which response was assessed is not clear in the paper.

HAQ improvements after 6 months of etanercept treatment are reported by Keystone et al (2004) in a group of patients that had switched from infliximab due to lack of efficacy. It is not stated whether failures were primary or secondary lack of efficacy. The mean improvement in HAQ was 0.41 (sd 0.25). Other outcome measures such as tender joint counts, swollen joint counts showed that patients benefited from switching. 33% of patients achieved a modified ACR20 response. Interestingly, this group are compared with a group of patients that made the opposite switch (etanercept to infliximab – reported in section below) and were similar at baseline. The group that switched to etanercept had better outcomes on all the measures reported.

Table 3: Summary of results from studies considering switchers to etanercept

Study	*n*	*Comparator*	*Week*	*%*			*DAS28*	*EULAR %*			*HAQ*
				ACR20	*ACR50*	*ACR70*		*None*	*Moderate*	*Good*	
Cantini (2005)	15	None	24	90	33	10	-2.43				
Kristensen (2006)	239 442	First biologic	26*	59 63							
Cohen (2005)	24	none	12				-1.5	26	16	58	
Buch (2005a) - Group A	12		12	66	66	33					
Buch (2005a) - Group B	22		12	71	57	14					
	58	Continue infliximab**		59	35	6					
Gomez Puerta (2004)	12	Same patients first biologic	26				-1.33 not comparable	17	67	17	
Haroui (2004)	22	None	12	64	23	5					-0.45
Buch (2007)	95	None	12	38	24	15	-1.47	27	61	12	
Di Poi (2007)	18	None					-2.0	28	33	39	
Hjardem (2007) from IXB	57	Same patients first biologic	12				-1.2	46 41	30 39	23 20	
Hjardem (2007) from ALB	17	Same patients first biologic	12				-1.6	33 38	33 31	33 31	
van Vollenhoven (2003)	13										
Naumann (2006)	31										
Keystone (2004)	83	Patients switched to IXB	26								-0.41

* Note: data to 36 months are reported, ** Patients continued with infliximab despite not achieving ACR20 at 12 weeks but CRP improvement

3.3.2. Switches to infliximab

Only two studies report exclusively changes to infliximab (Hansen et al 2004 and Yazici et al 2004) and neither of these studies report either HAQ, ACR or EULAR outcome measures.

A further seven studies consider switchers to infliximab as well as other switches but report the results in a disaggregated manner (Ang et al 2003, Brocq et al 2002, van Vollenhoven et al 2003, Keystone et al 2004, Cohen et al 2005, Furst 2007, Hjardem et al 2007). In all cases, the first biologic was etanercept except for Hjardem et al (2007) who includes 5 patients that switched from adalimumab. Hjardem et al. (2007) consider only 9 switchers in total. Results are shown in Table 4.

It should be noted that most of the studies which report useful outcome data comprise small samples.

Keystone et al (2004) is the largest study with data reported for 67 respondents that switched from etanercept due to lack of efficacy. A modest improvement in HAQ at 6 months was reported (0.13, sd 0.13) from a baseline of 1.57. Other measures are reported which demonstrate that patients improve. For example, 21% of patients achieved a modified ACR20 response. However, the improvements are less than those reported for a group that switched from infliximab to etanercept (see previous section).

Furst et al. (2007) report a pilot study (n=28) which compares patients with an inadequate response to etanercept who were randomised to switch to infliximab (n=14) or continue with etanercept (n=14). The results show higher response rates in terms of ACR20/50 (62%/31% for switchers vs 29%/15% for those continuing with etanercept) and DAS28 improvement (-2.2 vs -1.3) at week 16 in the group that were switched, although no tests of statistical significance are reported. The small numbers are obviously a severe limitation.

Several studies found that a similar number of patients responded to infliximab as responded to etanercept. van Vollenhoven et al (2003) considers 18 patients that switched from etanercept to infliximab in a Swedish registry, of whom 14 switched due to lack of efficacy. The mean best DAS28 was 3.6 (sd 0.6) after the switch, significantly better than the mean best DAS28 of 4.8 (sd 0.6) seen when patients were on etanercept ($p<0.05$). 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 (2004) found contradictory results to Yazici et al (2004) when comparing the efficacy of patients who had made the switch, to patients who had not attempted prior etanercept. In Hansen et al (2004) infliximab was seen to be as effective in etanercept failures as in etanercept naïve patients. Yazici et al (2004) 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 (2002) showed that 50% of the 6 patients had a favourable response whilst Ang et al (2003) found that the efficacy of the second agent was not predicted by that of the first.

Cohen et al (2005) found that 12/14 patients responded to infliximab despite not responding to etanercept.

Table 4: Summary of results from studies considering switchers to infliximab

Study	*n*	*comparator*	*Week*	*%*			*DAS28*	*EULAR %*			*HAQ*
				ACR20	*ACR50*	*ACR70*		*None*	*Moderate*	*Good*	
Cohen (2005)	14	none	12				-1.7	33	33	33	
van Vollenhoven (2003)	18	same patients on first biologic	24	67			-1.6 Not reported				
Furst (2007)	14 14	Continue etanercept	16	61.5 29	30.7 15		-2.2 -1.3				
Hjardem (2007) from ETP	4	Same patients first biologic	12				-1.4 0.2	25 100	50 0	25 0	
Hjardem (2007) from ALB	5	Same patients first biologic	12				-0.9 -0.7	25 50	75 50	0 0	
Hansen (2004)	20										
Yazicki (2004)	37										
Ang (2003)	29										
Brocq (2002)	14										
Keystone (2004)	67	None	26								-0.13

3.3.3. Switches to adalimumab

Eight studies considered only patients that switched to adalimumab (Nikas et al 2006, Wick et al 2005, Bennett et al 2005, Brocq et al 2004, Atzeni et al 2006, Bombardieri et al 2007, van der Bijl et al 2005 and Buch et al 2005b) whilst two others also considered adalimumab switchers and reported the results of this subgroup separately (Kristensen et al 2006, Hjardem et al 2007). A summary of the findings of these studies is reported in Table 5.

The largest study, Bombardieri et al (2007), considered 899 switchers and found a lower response rate to adalimumab in those that had failed a previous anti TNF compared to adalimumab as a first biologic (n=5711). For example, the percentage of patients achieving an ACR20 response at 12 weeks was 60% compared to 70%. The mean HAQ reduction was 0.48 compared to 0.55. Results are presented for subgroups defined according to the previous anti-TNF and the reason for switching and indicate substantial variability between groups.

The lowest response rates were seen in those that had withdrawn from etanercept due to lack of response (n=63). 41% of this group achieved ACR20 response. The mean HAQ improvement was 0.33. The best responses amongst switchers were in those that had withdrawn from the previous anti-TNF due to adverse events and there were no significant differences between etanercept and infliximab switchers. In those that withdrew due to loss of efficacy, a slightly lower response in etanercept switchers compared to infliximab switchers was reported in terms of HAQ improvement.

When considering the comparisons made in this study, it should be noted that patients that switched had failed a greater number of DMARDs (5.1 (sd 1.9) versus 2.7 (sd 1.6)) and had a worse HAQ (1.6 ((sd 0.68)versus 1.91 (sd 0.63)).

Kristensen et al (2006) also considered a relatively large number of switchers to adalimumab (n=165) and found lower ACR20 response rates in patients that switched to adalimumab versus those that took adalimumab as a first TNF-α inhibitor. The rates were particularly different at 3 months (62% response in biologic naïve patients versus 33% in switchers) and 12 months (61% vs. 36%). At 6 months the difference

was 62% versus 52%. The only test of statistical significance reported is at 3 months (p=0.0015). Interestingly, the ACR20 responses in the group that switched to adalimumab were substantially lower than those reported for those that switched to etanercept.

Hjardem (2007) considers 73 patients that switch from infliximab to adalimumab for any reason. 63% achieve a EULAR good or moderate response 12 weeks after switching. Compared to the responses seen to infliximab in the same group of patients 61% achieved a EULAR good or moderate response (p=0.46). Only 5 patients were included in this study that switched to adalimumab from etanercept.

Consistent with Bombardieri et al (2007), Buch et al (2005b) illustrates that primary non response to infliximab was associated with a poorer response to adalimumab compared to those that withdrew from infliximab due to loss of response. Using patients from a UK biologics database, patients treated with adalimumab either as first anti-TNF α (n=30), primary non response to infliximab (n= 19) or loss of response to infliximab (n=30) were included. EULAR good or moderate responses at 12 weeks are reported in 43% of primary non responders compared to 68% of those that had an initial response to infliximab but later withdrew due to loss of that response. 50% of patients in the group that received adalimumab as first treatment achieved EULAR good or moderate responses. DAS28 improvements were similar in all three groups.

Smaller studies such as Wick et al (2005), Nikas et al (2006) found no difference between responses to adalimumab in switchers versus biologic naïve patients. Wick et al (2005) compared patients in a Swedish TNF-α registry who received adalimumab after secondary loss of efficacy to infliximab (n=27), or etanercept (n=9) with a group of patients who started treatment with adalimumab as their first anti TNF- α (n=26). Similar ACR20 responses were seen in all groups although DAS28 improvements were greater, though not statistically significant, in the anti-TNF- α naive group.

Atzeni et al (2006) consider patients switching to adalimumab after failing both etanercept and infliximab due to inefficacy (n=15).

Bennett et al (2004) consider a group of patients taking adalimumab in clinical practice. Of 70 patients in total, 26 had previously been treated with a biologic. Whilst response rates in terms of HAQ, DAS28 and EULAR are reported, these are considered according to the mean time on treatment for the patient groups rather than a defined time from treatment initiation. Therefore, comparisons with other studies are difficult to make. However, the study identifies that those that switched had a better DAS28 and HAQ improvement on adalimumab compared to their previous biologic, but that there was no significant difference between this group and those that were biologic naive.

Van der Bijl et al (2005) report 16 week outcomes for 41 patients that switched from infliximab either due to no response (n=13), loss of response (n=19) or intolerance (n=5). ACR20/50, DAS28 and EULAR responses are reported. Although no statistical tests are performed on the differences between the groups, it is clear that those that switched from infliximab due to a lack of response achieve worse outcomes than switchers due to loss of response or adverse events.

Table 5: Summary of results from studies considering switchers to adalimumab

Study	*n*	*comparator*	*Weeks*	*%*			*DAS28*	*EULAR (%)*			*HAQ*
				ACR20	*ACR50*	*ACR70*		*None*	*Moderate*	*Good*	
Nikas (2006) - all	24		52	75	50	33	-2.4		71**		
- loss/lack of effect	24	First time ALB	52	89	56	33	-2.1		78**		
	25	users		76	56	36	-2.6		72**		
Wick (2005) from IXB	27		26	70			-1.3				
Wick (2005) from ETP	9	First time ALB	26	78			-1.9				
	26	users		70			-2.1				
Atzeni (2006)	15	None	26				-2.7				
Bombardieri (2007) - all	899		12	60	33	13	-1.9	24	53	23	-0.48
– no response	173		12	52	25	8	-1.9	26	55	19	-0.44
– loss of response	306		12	67	37	13	-2.0	21	57	22	-0.51
	5711	First biologic		70	41	19	-2.2	16	35	49	-0.55
Buch (2005b) - non response	19		12				-1.3	57	36	7	
Buch (2005b) - loss of response	30		12				-1.4	32	61	7	
	30	First biologic						50	40	10	
Kristensen (2006)	165		26*	52							
	90	First biologic		62							
Hjardem (2007) from IXB	73	Same patients	12				-0.9	36	46	17	
		first biologic					-1.3	39	39	22	
Hjardem (2007) from ETP	5	Same patients	12				-1	25	50	25	
		first biologic					-1.5	40	20	40	
Bennett (2005)	26	Fist biologic	varied				-1.7	19	46	35	-0.31

	44					-2.4	15	30	55	-0.31
Brocq (2004)	18	No useable info								
van der Bijl (2005) – all	41	None	16	49	26	-1.6		65		
- Loss of efficacy	19			61	39	-2.1		74		
- lack of response	13			33	8	-1		46		
- adverse events	5			40	20	-1.4		80		

* 12 month data also reported, ** EULAR good/moderate

3.3.4. Non specific switches

Six studies were identified that considered switches to anti-TNFs considered as a class (Brulhart et al, 2006; Favelli et al, 2004; Finckh et al, 2007; Naumann et al, 2006; Hjardem et al, 2007). Results from these studies are shown in Table 6.

The largest of these studies is Hjardem et al. (2007) which reports results for those that have switched according to the reason for switching. It should be noted that subgroups of patients categorised according to the sequence of drugs are reported in previous sections. All patients switched within a year of starting the first anti-TNF and the category "lack of efficacy" may therefore comprise both primary and secondary lack of response. We combine patients that have failed for "lack of efficacy" with those that have switched for other reasons (n=109). Therefore, those that have switched due to adverse events are excluded from the analysis. At 12 weeks, 72% of patients have achieved a good or moderate EULAR response. Comparisons are made with the same patients response to the first biologic. Considering only those patients categorised as switching due to lack of efficacy, 67% achieved a good or moderate EULAR response to the first treatment (p=0.02). Median DAS28 improvements at 3 months for this subgroup are 1.1 for the first biologic and 1.6 for the second treatment (p=0.09).

Finckh et al. (2007) considers 66 patients that switched to a second anti TNF and compared them with a group that switched to rituximab (n=50) in a longitudinal cohort study. At 6 months, the mean decrease in the DAS28 was -1.61 (95% confidence interval [95% CI] -1.97, -1.25) among patients receiving rituximab and -0.98 (95% CI -1.33, -0.62) among those receiving subsequent anti-TNF therapy. 3 and 9 month improvements were also greater in the rituximab group.

The three other studies are small, with a maximum of 20 patients switching.

Brulhart et al. (2006) report a case control study set in Switzerland where patients received rituximab (n=10) or a second or third anti TNF-α (n=10). The two groups were similar at baseline. At three months, decrease in DAS28 was -1.84 (95% CI -

2.45; -1.22) with rituximab and -0.8 (95% CI -1.38; -0.23) for the anti-TNF α switchers. At six months, decrease in DAS28 was -1.8 (95% CI: -2.65; -0.87) with rituximab and -1.07 (95% CI: -1.94; -0.19) with anti-TNF α. Given the patient populations, it is possible that this study considers a subgroup of patients reported in Finckh et al. (2007).

Favelli et al. (2004) report the experience of 15 patients that discontinued etanercept or infliximab therapy due to either loss of response or adverse events and switched to the other anti-tnf α (adalimumab was not available at this time). Of these only 8 had RA and 7 had juvenile RA. Improvements in DAS28 and HAQ after 6 months of treatment are reported.

Kafka et al (2005) report on 191 patients switched to at least one anti-TNF recruited in the CORRONA database in the US. Only data on DAS change after 3 months are reported (mean of -0.84 improvement). However, most patients were not switched from the original anti TNF for either lack of loss of efficacy.

Table 6: Summary of results from studies considering switchers to anti-TNFs as a group

Study	*n*	*comparator*	*weeks*	*%*			*DAS28*	*EULAR %*			*HAQ*
				ACR20	*ACR50*	*ACR70*		*None*	*Moderate*	*Good*	
Brulhart (2006)	20 10	 rituximab	12*				-0.8 -1.48				
Favelli (2004)	8	none	24				-1.42				-0.34
Finckh (2007)	66 50	 rituximab	12*				-0.8 -1.28				
Naumann (2006)	18	no useful information									
Hjardem (2007) - loss/lack of efficacy	109	Same patients first biologic	12				-1.41 -1.1	28 33	48 48	24 19	
Kafka (2005)	191	None	12				-0.8				

* 24 week data also reported

3.4. SUMMARY OF FINDINGS

The number of studies, and the sizes of those studies, is rapidly growing as clinical experience of anti-TNFs develops. In many cases, the data described come from registries. None of the data comes from randomized controlled trials and therefore many of the comparisons between groups must be treated with caution. These comparisons vary – some studies consider different patients that have not switched, others consider the responses seen to first treatments in the patients that subsequently switched. In some cases the response to first biologic is from a mixed population of patients that includes those that have not yet switched and those that have. This second In particular, there is now relatively good data in relation to switchers to adalimumab whilst the evidence in relation to infliximab is more limited.

It should be noted that data in relation to HAQ changes in response to a second anti-TNF are extremely limited.

In general, there is evidence that patients can receive a good response to a second anti-TNF having failed a previous anti-TNF. However, the probability of achieving a good response is lower than for a first anti-TNF.

For adalimumab, there is good evidence to illustrate that the probability of response varies according to the previous anti-TNF and the reason for switching from the previous anti-TNF. In particular, those switching from infliximab experience superior outcomes to those switching from etanercept. In addition, those switching for lack of response have a lower probability of response to adalimumab than those that withdrew from the first anti-TNF because of adverse events.

Consideration should be given to the generalisability of results for adalimumab to the other two anti-TNFs.

The largest study, Bombardieri et al. (2007), not only provides good evidence of the effect of switching to adalimumab, but does so in terms of HAQ changes (in addition to ACR and EULAR) and also reports baseline HAQ and the associated standard

deviations. Therefore, the study results are compatible with the BRAM model. Of the other studies that report HAQ, only two are published studies (Bennett et al. 2005 and Haroui et al 2004) which include only small numbers of patients (21 and 22 respectively). In addition, Bennett et al do not report outcomes at set times from baseline. Of the other two studies which report HAQ outcomes, Favelli et al (2004) is a letter that reports outcomes for only 8 patients. Keystone et al (2004) is a conference abstract that reports baseline HAQ but not its standard deviation. It should also be noted that the HAQ change in the Bombardieri study is the largest of any of the other studies reporting HAQ effects.

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Appendix 1: Search Terms for sequential anti-TNFs

EBM Reviews - Cochrane Central Register of Controlled Trials

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

EBM Reviews - Cochrane Database of Systematic Reviews

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 2: Glossary of response measures

ACR20	Defined as a twenty percent improvement in the counts of the number of tender and swollen joints and at least 3 items from the following: observer evaluation of overall disease activity; patient evaluation of overall disease activity; patient evaluation of pain; a score of physical disability; and improvements in blood acute phase responses.
ACR50	Defined as a fifty percent improvement in the parameters described above.
ACR70	Defined as a seventy percent improvement in the parameters described above.
CRP	C-reactive protein
DAS	Disease Activity Score. The DAS is calculated using a formula which includes counts for tender (53 joints) and swollen joints (44 joints), an evaluation by the patient of general health, and blood acute phase response. Scale 0 (best) to 10 (most active disease).
DAS28	Disease Activity Score 28, similar to DAS above but using only 28 joints for assessment only. Scale 0 (best) to 10 (most active disease).
HAQ	The Health Assessment Questionnaire is designed to assess the physical function of patients. Scores range from 0 (no functional impairment) to 3 (most impaired).
EULAR	A means of measuring efficacy of treatment using DAS and DAS28

The EULAR response criteria

	DAS28		
Change in DAS28	>5.1	≤5.1 and >3.2	≤3.2
>1.2	Moderate	Moderate	Good
>0.6 and ≥ 1.2	None	Moderate	Moderate
≤0.6	None	None	None