SEQUENTIAL USE OF TNF-α INHIBITORS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS. REPORT BY THE NICE DECISION SUPPORT UNIT.

Health Economics and Decision Science, ScHARR
MRC Biostatistics Unit, Cambridge

24 August 2006

1. INTRODUCTION

This report provides a commentary on additional work undertaken as part of the NICE Health Technology Appraisal into adalimumab, etanercept and infliximab for treatment of rheumatoid arthritis. The additional work focuses on the use of these Tumour Necrosis Factor alpha inhibitors (TNF-α) in patients that have previously withdrawn from a TNF-α inhibitor. The British Society for Rheumatology Biologics Registry (BSRBR) at the University of Manchester have undertaken several analyses in order to inform the cost effectiveness model (Birmingham Rheumatoid Arthritis Model – BRAM) used in this appraisal. These analyses are described and their potential use in the BRAM described. In addition, we have updated an existing review of sequential biologics (Appendix A).

The DSU has not had access to any data held by the BSR. Nor has a review of the BRAM been undertaken.

In the Appraisal Consultation Document (ACD) issued by NICE in February 2006, the sequential use of TNF-α inhibitors was only recommended where withdrawal from an agent is due to toxicity. Sequential use in the case of lack of initial response or loss of efficacy was not recommended outside study settings since there was deemed to be insufficient evidence to warrant routine sequential use.

The British Society for Rheumatology (BSR) supports a registry, the BSRBR, that has collected data on biologics use in the UK since October 2001 and now holds sufficient data on patients that have switched TNF-α inhibitor to make a valuable contribution to modelling the cost effectiveness of such strategies. The purpose of this document is to describe the analyses undertaken by the BSRBR in order to generate updated estimates of cost effectiveness using the BRAM.

In the appraisal report, the BRAM was used to estimate the cost effectiveness of strategies using two or three TNF-α inhibitors. However, none of the parameters used in that analysis were based on evidence specifically relating to sequential TNF-α inhibitor use. In addition, the analyses did not distinguish between patients according to the reasons why they withdraw from a first TNF-α inhibitor. There are several reasons why patients withdraw from TNF-α inhibitor treatment including adverse events, lack of response or loss of efficacy. The BRAM does include separate estimates for withdrawal

at different points for different reasons and this part of the model design could therefore be used.

2. PARAMETER REQUIREMENTS FOR THE BRAM

There are two key parameters used in the BRAM that determine the cost effectiveness of a second TNF-α inhibitor. The initial treatment response to a second TNF-α inhibitor and the duration of that treatment. The issue of dose increase may also be important in estimating the cost effectiveness of TNF-α inhibitors, particularly in relation to infliximab. However, no analysis of dose has been included here since this was not included in the original estimates of cost effectiveness in relation to first TNF-α inhibitor and there is likely to be insufficient follow up of patients on second TNF-α inhibitor.

2.1 Treatment response to second TNF-α inhibitor

In the BRAM, initial treatment response is defined in terms of Health Assessment Questionnaire (HAQ). A HAQ multiplier is derived for each TNF-α inhibitor (and traditional DMARD) separately from the mean baseline HAQ and mean HAQ improvement in randomised controlled trials. In order to estimate a HAQ multiplier from the BSRBR, the same two pieces of information are required. The mean (standard deviation) HAQ at the time of withdrawal from first TNF-α inhibitor and the mean (standard deviation) HAQ improvement after twelve months.

An additional complication associated with the registry data is that observations are made at six month intervals. The time of withdrawal from first TNF-α inhibitor and the time of starting a second TNF-α inhibitor may not coincide with the time at which data are collected from patients. This issue does not apply to first TNF-α inhibitor in the BSRBR since data are collected at the time of treatment initiation.

The analysis undertaken by the BSRBR provides estimates of change in HAQ between baseline (defined as the time when a patient withdraws from first TNF-α inhibitor) and approximately twelve months later. Patients included in the analysis are non responders to the first TNF-α inhibitor with a HAQ measurement within 90 days of the date at which they were deemed to be response failures and a further HAQ measurement 12 months later. Patients that stopped treatments due to adverse events are not included.

Three groups are defined.

Group 1: Continue group – who remain on the first TNF-α inhibitor treatment.
Group 2: Stopped group – who stop taking the first TNF-α inhibitor.
Group 3: Changed group – who stop taking the first TNF-α inhibitor and switch to a second.

Sensitivity analyses are done by:

1) Restricting the data set to patients who have HAQ measured before failure to respond. This ensures that the baseline is not biased by patients that have started a second treatment and already had some response.

2) Define group 3b to be patients who stop taking the first TNF-α inhibitor and switch to a second, but who also take the second TNF-α inhibitor for a minimum of 6 months.

Summary statistics (Table 1 of the BSR analysis) indicate that HAQ decreases in the three groups. From worse to best these are group 2, group 1, group 3 and group 3b. The mean baseline HAQ for all three groups is shown in table 3 of the BSR analysis. For each of the group 3 sub categories, the baseline HAQ is approximately 2.1 which is equal to the mean baseline HAQ for patients treated with a first TNF-α inhibitor [1].

A number of covariates are adjusted for: age, disease duration, sex, DAS and HAQ at baseline. Two analyses where performed: regression models for change in HAQ, and an inverse probability of treatment weighting (IPTW) model was used to adjust for DAS as a time varying covariate.

The IPTW model shows that DAS at six months after baseline does not predict changes in treatment, so the results of this analysis are not used.

The analysis that will feed the model therefore is from the regression model.
The model fitted is

$$\Delta HAQ = \alpha + \beta \text{group} + \gamma^T \text{covariates} \quad (1)$$

Group 2 is used as the reference group. Table 4 of the BSR analysis document gives the results of this analysis. Four models have been fitted in all combinations of:
With and without adjustment for confounders.
Full data set, and data set restricted to HAQ measured before failure.

The base case analysis should use the HAQ improvement for the group that have had at least 6 months treatment on second TNF-α inhibitor, with baseline HAQ measured before first treatment failure and with adjustment for confounders. This gives a mean HAQ improvement of 0.21 (sd=0.068).

This compares to a mean HAQ improvement of 0.4 for first TNF-α inhibitor in the BSRBR in those that remain on the drug at 12 months (see Table 5.8 of the original BSR NICE submission).

Appendix A provides details of other identified evidence in relation to sequential TNF-α inhibitor use. In general this evidence does seem to support the BSRBR findings that TNF-α inhibitors are effective in patients that have failed a previous anti-TNF α but that the magnitude of this benefit may not be as great as for anti TNF-α naïve patients.

2.2 Duration of second TNF-α inhibitor treatment

The estimation of duration of second TNF-α inhibitor is complicated by the fact that patients who receive a second treatment in the registry are those who had a shorter first treatment time. These patients may therefore have a propensity for a shorter second

treatment time than the average patient in the data set. The shared frailty model is used to try and account for this.

Three models are fitted
1) Weibull models in the first and second treatment spell with common shape.
2) Frailty models with common shape but independent random effects.
3) Shared frailty models with common shape and common random effects.

The simple Weibull models show that survival is shorter on the second treatment than the first (which could be due to the bias explained above). The Frailty model also gives the same pattern, but with far longer mean survival times than from the simple Weibull. The shared frailty model shows that survival is much longer of the second treatment.

A simple summary of the results is as follows:
If a patient has a short duration of first treatment, then a) they have a short second duration of treatment, and b) the second duration is longer than the first.

Adjusting for bias in the data is assuming that the model used is correct. There is not inference robustness to the choice of model, with results being highly sensitive to different reasonable models being used. More follow-up data is required before a clear picture of the time on a second TNF-α inhibitor can be confidently assessed. For the cost-effectiveness model, the simplest choice of parameters for the time on a second TNF-α inhibitor are the parameters for the time on first TNF-α inhibitor (i.e. the estimates described in the appraisal report). However, the BSR data is representative for patients who fail their first treatment within a year, so the shared frailty model could potentially be used in this context. But this would lead to a discontinuity in the cost-effectiveness model between patients treated from less than one year and more than one year .

3. MODELLING ISSUES

The data that the BSRBR are able to provide relates specifically to those that have withdrawn from first TNF-α inhibitor because of lack of response. The primary analysis should therefore address the following question:

> *What is the cost effectiveness of a second TNF-α inhibitor compared to traditional DMARD treatment in patients with late RA that are withdrawn from a first TNF-α inhibitor due to inadequate response?*

A secondary question might be:

> *What is the cost effectiveness of a second TNF-α inhibitor compared to traditional DMARD treatment in patients with late RA who have failed a first TNF-α inhibitor for any reason?*

However, results of such modelling must be interpreted with more caution since the BSRBR do not have data at this point which relate to this group of patients.

Issues relating to the current construction of the BRAM and the new BSRBR data:

- Caution must be exercised in combining evidence from different data sources which relate to different patient groups. For example, the traditional DMARD HAQ multipliers in Table 38 of the TAR indicate that the BRAM allocates improvements in HAQ to patients at the start of each traditional DMARD left in the sequence. These improvements are greater than the improvements observed in the BSRBR even for first TNF-α inhibitor. This is partly because these data relate to RCTs of patients with early RA. For example, the mean disease duration for patients in the RCT of leflunomide is 3.7yrs and the mean number of failed DMARDs is 1.1[2]. In the BSRBR the mean duration of disease at the time of starting a first TNF-α inhibitor is 13.7yrs and the mean number of failed DMARDs is 4.

- The BRAM does not model current UK guidance with respect to withdrawals for inadequate response. The ACD states: "Treatment with TNF-α inhibitors should be withdrawn if there is an inadequate response at 3 months or in the event of severe drug-related toxicity. Inadequate response is defined as a lack of improvement by at least 1.2 points in the DAS28." The model does include a separate estimate of withdrawal between weeks 6 and 24 for inefficacy but these data are based on a Swedish study and do not relate to the UK criteria.

- The estimates of mean HAQ change from the registry are for all patients that take a second TNF-α inhibitor. In fact, HAQ change will differ according to whether patients are poor/moderate/good DAS responders (as is the case for first TNF-α inhibitor). Patients that achieve only a poor DAS response should be withdrawn whereas those that continue treatment can be expected to have achieved a better than mean HAQ response.

- The Weibull drug survival is also based on non UK data and the estimates are markedly different for etanercept compared to adalimumab and infliximab. Consideration should be given as to how to estimate duration of second TNF-α inhibitor where the analysis is undertaken for TNF-α inhibitors as a class.

- Treatment multipliers are very different between the TNF-α inhibitors in the BRAM. This is not consistent with the treatment responses seen in the BSRBR to first TNF-α inhibitor. Nor is it consistent with recently published meta regression analysis of RCT data[3]. The BSRBR has only supplied HAQ improvement data for TNF-α inhibitors combined in relation to sequential use. Again, this is not consistent with the estimates used in the TAR which warrants discussion on the part of the authors.

4. LIMITATIONS

The issue of dose increase is not addressed. This is well documented for infliximab[4,5]. In addition, if TNF-α inhibitor switching is recommended, patients may be less likely to remain on a treatment and increase the dose trying to gain or regain response than they would do in the event that switching were not recommended.

There is no distinction made between the TNF-α inhibitors: either which drug has already been withdrawn or which is being switched to. The process may not be memoryless and should be monitored in future research.

There is no distinction made between the effectiveness of second TNF-α inhibitors and the reason why withdrawal took place originally. This may also true for the duration of second treatment[6].

---

[1] Hyrich K, Dixon W, Watson K, Griffiths I, Silman A, Symmons D. Anti-TNFα agents in rheumatoid arthritis. Report to NICE from BSR. June 2005.

[2] Emery P, Breedveld FC, Lemmel EM, Kaltwasser JP, Dawes PT, Gomor B, et al. " A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis", Rheumatology, 2000; 39; 655-665.

[3] Nixon RM, Bansback N, Brennan A. Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. Statistics in Medicine, 2006, Early view [http://www3.interscience.wiley.com/cgi-bin/abstract/112736820/ABSTRACT]

[4] Stern R, Wolfe F. Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. Journal of Rheumatology 2004:31:1538-45.

[5] van Vollenhoven RF, Brannemark S, Klareskog L. Dose escalation of infliximab in clinical practice: improvements seen may be explained by a regression-like effect. Annals of the Rheumatic Diseases 2004; 63:426-430

[6] ACR 2005 poster presentation. Influence of Response and Adverse Event Rates to First Anti-TNF Agent on Outcome to Second Agent: Results from British Society of Rheumatology Biologics Register

APPENDIX A: REVIEW OF SEQUENTIAL USE OF TNF-α INHIBITORS. REPORT BY THE NICE DECISION SUPPORT UNIT.

Health Economics and Decision Science, ScHARR
Centre for Health Evaluation and Outcome Sciences, University of British Columbia, Canada

18 August 2006

1. BACKGROUND

The TNF-α inhibitors adalimumab, etanercept and infliximab have been demonstrated to be similarly effective in randomised controlled trials [Nixon et al. 2006]. Since no head to head studies have demonstrated superiority of one treatment over the other, if one treatment does not work or leads to an adverse event, clinicians frequently will switch patients to another TNF-α inhibitor. Given the high cost of these treatments, it is questionable whether switching strategies is an effective management strategy.

We previously conducted a review of evidence for all biologics, including the interleukin-1 receptor antagonist (IL-1Ra), anakinra.[Wailoo et al. 2006] The purpose of this report is to update that review.

2. METHODS FOR REVIEWING EFFECTIVENESS

Search strategy
The original 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 were also searched. The reference lists of identified publications were reviewed to identify any additional studies and/or citations.

We have updated the electronic bibliography searches to 2006 and also searched the abstracts for the EULAR and ACR conferences. We have excluded studies that considered switches to anakinra.

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 at the end of this document.

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

- We excluded studies that considered anakinra, ritixumab or abatacept.
- 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.

3. RESULTS

Titles were hand searched. Any study which included patients on TNF-α inhibitors was included. No language restrictions were included. The total number of independent titles identified by the original 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)]. The following additional titles were identified in the update to these searches [Cochrane (4) Medline (29), EMBASE (36)].

After screening, 27 articles papers were identified as potentially relevant and were reviewed. These are shown in Table 1. Of these, 7 papers were excluded either because they were reviews with no primary research reported (Combe et al. 2004and van Vollenhoven (c) et al. 2004), because their content was replicated in other studies (Sanmarti et al. 2004 in Gomez-Puerta et al. 2004, Bombardieri et al. 2005 in Bombardieri et al. 2006*),* Wick et al. 2004 in Wick et al. 2005), because they reported dose increase rather than drug switching (van Vollenhoven et al. (c) 2004) or because they mixed rheumatoid arthritis and psoriatic arthritis patients (Chalmeta-Verdejo et al. 2006).

Table 1. Table of studies returned from the literature search

Author	Country	Notes	In review?
Ang *et al. (2003)*	US	Research article	Yes
Brocq *et al. (2002)*	France	Research article - in French	Yes
Combe *et al. (2004)*	-	Editorial Review - no primary research	No
Favalli *et al. (2004)*	Italy	Letter	Yes
Gomez-Puerta *et al. (2004)*	Spain	Letter – same study as Sanmarti	Yes
Hansen *et al. (2004)*	US	Research article	Yes
Haroui *et al. (2004)*	Canada	Research article	Yes
Sanmarti *et al. (2004)*	Spain	In Spanish – same as Gomez-Puerta	No
van Vollenhoven (a) *et al. (2003)*	Sweden	Research article	Yes
van Vollenhoven (b) *et al. (2004)*	Sweden	Research article – Dose increase	No
van Vollenhoven (c) *et al. (2004)*	-	Review – no primary research	No
Wick *et al. (2004)*	Sweden	Abstract only – same as Wick et al. (2005)	No
Yazici *et al. (2004)*	US	Letter	Yes
Nikas et al. (2006)	Greece	Research article	Yes
Cohen et al. (2005)	France	Research article	Yes
Wick et el. (2005)	Sweden	Research article	Yes
Buch et al. (2005a)	UK	Research article	Yes
Brocq et al. (2004)	France	Letter	Yes
Atzeni et al. (2006)	Italy	Abstract	Yes
Brulhart et al. (2006)	Switzerland	Abstract	Yes
Naumann et al. (2006)	Germany	Abstract	Yes
Kristensen et al. (2006)	Sweden	Abstract	Yes
Bombardieri et al. (2006)	Various	Abstract- updated from Bombardieri 2005	Yes
Chalmeta-Verdejo et al. (2006)	Spain	Abstract – mixed RA and PA	No
Cantini et al. (2005)	Italy	Abstract	Yes
Bombardieri et al. (2005)	Various	Abstract – older version of Bombardieri 2006	No
Buch et al. (2005b)		Abstract	Yes

The review therefore focussed on the 20 independent studies. A majority of the articles focus on switches between two of the TNF-α, antagonists etanercept and infliximab.

Table 2. Descriptions of studies in the review

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)	Lack of efficacy/ Adverse event	EPT	Not reported	Joint count
		EPT (5)		IXB		
Brocq et al. (2002)	14	IXB (8)	Miscellaneous	EPT	Not reported	Not reported
		EPT (6)		IXB		
Favelli et al. (2004)	15	IXB (14)	Lack of efficacy/ Adverse event	EPT	6 months	ACR20, DAS28, HAQ
		EPT (1)	Lack of efficacy	IXB		
Gomez-Puerta et al. (2004)	12	IXB (12)	Lack of efficacy	EPT	6 months	DAS28
Hansen et al. (2004)	20	EPT (20)	Lack of efficacy/ Adverse event	IXB	Not reported	SWJ, TJC
Haroui et al. (2004)	22	IXB (22)	Lack of efficacy/ Adverse event	EPT	12 weeks	ACR20. HAQ
Van Vollenhoven et al (a) (2003)	31	EPT (18)	Lack of efficacy	IXB	>8 weeks	DAS28, ACR-N
		IXB (13)	Adverse event	EPT		
Yazici et al. (2004)	21	EPT (21)	Miscellaneous	IXB		
Nikas et al. (2006)	24	IXB	Lack of efficacy/ Adverse event	ALB	12 months	ACR, DAS28
Cohen et al. (2005)	38	IXB (24), EPT (14)	Non response (29), adverse events (9)	IXB, EPT	3 months	DAS28
Wick et el. (2005)	36	IXB (27), EPT (9)	Secondary loss of efficacy	ALB	3,6 months	DAS28
Buch et al. 2005 (a)	34	IXB	Non response and a) never achieved a 20% improvement in CRP	EPT	12 weeks	ACR

			(n=10) and b) achieved a temporary improvement in CRP (n=15)			
Brocq et al. (2004)	18	EPT(8), EPT followed by IXB (10)	Mixed	ALB	2-8 months	Not stated
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.
Brulhart et al. (2006)	20	At least one TNF alpha	"failure" according to patient's rheumatologist	Ritixumab (10), another tnf alpha (10)	3, 6 months	DAS, HAQ
Naumann et al. (2006)	31	Any anti tnf alpha	severe adverse event (7) ineffectiveness (22) incompliance (2)	IXB, EPT or ALB	3yrs max	DAS
Kristensen et al. (2006)	404	Any anti tnf alpha	Any	EPT (239), ALB (165)	3,6,12,24,36 months (12 for ALB)	ACR20
Bombardieri et al. (2006)	899	EPT or IXB	Mixture - no response, loss of efficacy, intolerance.	ALB	12 weeks	ACR, DAS28
Cantini et al. (2005)	22	IXB (15), ALB (7)	Inefficacy (68%), adverse event (32%)	EPT	Baseline, 4,12, 24 weeks	ACR, DAS28
Buch et al. (2005b)	59	IXB	Non response (32%), loss of efficacy (51%) and toxicity (18%)	ALB	12weeks	EULAR and DAS

EPT= etanercept, IXB = Infliximab, AKA = Anakinra, ALB = Adalimumab, 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

Switches to etanercept

Four studies considered only switches to etanercept (Gomez-Puerta et al. 2004, Haroui et al. 2004, Buch et al 2005a, Cantini et al. 2005) and a further seven considered switches to etanercept as well as other switches (Ang et al. 2003, Brocq et al. 2002, Favelli et al 2004, van Vollenhoven et al 2003, Cohen et al 2005, Naumann et al 2006, Kristensen et al 2006.)

Earlier studies examined the effect of switching from infliximab to etanercept and more recent studies have included the switch from adalimumab to etanercept.

The largest study (Kristensen et al. 2006) comprised 239 patients switched to etanercept. ACR20 response rates were lower in this group than biologic naïve patients treated with etanercept (61% vs 52% at 3 months, 64% vs 39% at 24 months).

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). Haroui et al (2004) 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 (≥ 0.22 point decrease in overall Health Assessment Questionnaire score). Response rates for Brocq et al (2002), Favalli et al (2004) and Gomez-Puerta et al (2004) were 63% (type of response not reported), 87% (ACR20) and 67% (moderate DAS28 response). Favalli et al (2004) also reported that the 2 patients that failed to respond did not for the same reason as they discontinued the first treatment (adverse events).

Switches to adalimumab

Six studies considered only patients that switched to adalimumab (Nikas et al 2006, Wick et al 2005, Brocq et al 2004, Atzeni et al 2006, Bombardieri et al 2006 and Buch et al 2005b) whilst 2 others also considered adalimumab switchers (Kristensen et al 2006 and Naumann et al 2006).

The largest study, Bombardieri et al (2006), considered 899 switchers and found a lower response rate to adalimumab in those that had failed a previous TNF- α inhibitor compared to adalimumab as a first biologic. The lowest response rates were seen in those that had not responded to the first TNF-α inhibitor and this was not substantially different between infliximab and etanercept failures.

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%).

Buch et al (2005b) illustrates that primary non response to infliximab was associated with a poorer response to adalimumab and suggests a central failure to TNF-targeted treatment.

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.

Switches to infliximab

Only two studies report exclusively changes to infliximab (Hansen et al 2004 and Yazici et al 2004) and a further five include infliximab switchers as well as other

switchers (Ang et al 2003, Brocq et al 2002, Favelli et al 2004, van Vollenhoven et al 2003, Cohen et al 2005). Favelli et al (2004) however only includes one infliximab switcher and other studies were relatively small. In all cases, the first biologic was etanercept.

Several studies found that a similar number of patients responded to infliximab as responded to etanercept. In van Vollenhoven et al (2003) 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 (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.

4. CONCLUSION

There are an increasing number of studies that address the issue of switching between biologics but the majority of studies include only a small number of patients and there are not controlled trials. As patient and clinical experience of TNF-α inhibitors has grown, larger numbers of patients have been included in studies. In addition, as the most recent TNF-α inhibitor there has been greater opportunity for adalimumab to be used in patients that have already failed etanercept or infliximab. Several studies are currently available in abstract form only and it is therefore difficult to assess their quality.

An additional difficulty is that different comparisons can be made when assessing response to sequential TNF-α inhibitors. Some studies report the response to first and second TNF-α in the same group of patients, whereas others compare switchers with patients using the same anti TNF-α at first use. Given that studies allow include patients that have switched for varying reasons, the interpretation of these different comparisons is not straightforward.

There is evidence that patients that switch from one TNF-α inhibitor have a high probability of response. This is the case for patients that have failed to respond to the first biologic and those that have withdrawn due to adverse events.

It is less clear whether responses to a second TNF-α inhibitor is as good as seen in biologic naïve patients.

For adalimumab, the evidence seems strongest and suggests that switchers do not respond as well as anti TNF-α naïve patients and that response is poorest in non responders to the previous drug.

Sequential use of etanercept is also less effective than etanercept in anti TNF-α naïve patients in the largest study. Smaller studies report similar responses to etanercept as the same patients achieved to first anti TNF-α.

For infliximab the data are not sufficient to make more detailed claims.

REFERENCES

Ang HT, Helfgott S. Do the clinical responses and complications following etanercept or infliximab predict similar outcomes with other tumour necrosis factor alpha antagonists in patients with rheumatoid arthritis? J Rheumatology 2003; 30:2315-8

Atzeni F, Sarzi-Puttini P, Antivalle M, Turiel M, Carrabba M. Adalimumab in severe rheumatoid arthritis after failure of two anti-tnf agents: a prospective 1-year follow-up study of 15 patients. EULAR 2006

Bombardieri S, Tzioufas AG, McKenna F, Özer Ü, Kupper H. Adalimumab (Humira®) is effective in treating patients with rheumatoid arthritis who previously failed etanercept and/or infliximab in real-life clinical settings. ACR 2005

Bombardieri S, McKenna F, Drosos AA, Michel BA, Hartz D, Oezer U, Kupper H. Efficacy and safety of adalimumab (Humira®) in 899 patients with rheumatoid arthritis (RA) who previously failed etanercept and/or infliximab in clinical practice. EULAR 2006

Brocq O, Plubel Y, Breuil V *et al*. Etanercept-infliximab switch in rheumatoid arthritis. 14 out of 131 patients treated with anti TNF alpha. Presse Med 2002; 31:1836-9

Brocq O, Albert C, Roux C, Gerard D, Breuil V, Euller Ziegler L. Adalimumab in rheumatoid arthritis after failed infliximab and/or etanercept therapy: experience with 18 patients. Joint Bone Spine. 2004. 71:601-603.

Brulhart L, Finckh A, Ciurea A, Notter A, Waldburger J, Kyburz D, Gabbay C. Rheumatoid arthritis patients who have failed to anti-tnf agents. Is b-cells depletion more effective than switching to an alternative anti-tnf agent? EULAR 2006

Buch MH, Bingham SJ, Bryer D, Emery P. Type of previous infliximab non-response in rheumatoid arthritis determines subsequent response to adalimumab. ACR 2005 (b)

Buch MH, Seto Y, Bingham SJ, Bejarano V, Bryer D, White J, Emery P. C-Reactive Protein as a Predictor of Infliximab Treatment Outcome in Patients With Rheumatoid Arthritis. Defining Subtypes of Nonresponse and Subsequent Response to Etanercept. Arthritis Rheumatism. 2005(a). 52(1):42-48.

Cantina F, Niccoli L, Porciello G, Storri L, Chindamo D, Nannini C, et al. Switching from Infliximab or Adalimumab to Etanercept 50 Mg/Once Weekly in Resistant or Intolerant Patients with Rheumatoid Arthritis: 24-Week Results. ACR 2005

Chalmeta-Verdejo C, Hortal-Alonso R, Abad-Franch L, Fernandez-Llanio Comella N, Ojeda F, Ivorra-Cortes J, et al. Failure with tnf alfa blocker treatment in chronic arthritis. is it useful a second antagonist? EULAR 2006

Cohen G, Courvoisier N, Cohen JD, Zaltni S, Sany J, Combe B. The efficiency of switching from infliximab to etanercept and vice-versa in patients with rheumatoid arthritis. Clinical & Experimental Rheumatology. 2005: 23(6):795-800

Combe B. Switching between anti-TNF agents: what is the evidence? Joint Bone Spine. 2004;71(3) 169-255

Favalli EG, Arreghini M, Arnoldi C, Panni B, Marchesoni A, Tosi S, Pontikaki I. Anti-tumor necrosis factor switching in rheumatoid arthritis and juvenile chronic arthritis. Arthritis Rheumatism 2004;51: 301-2 (letter)

Gómez-Puerta JA, Sanmartí R, Rodríguez-Cros JR, Cañete JD. Etanercept is effective in patients with rheumatoid arthritis with no response to infliximab therapy. Ann. Rheum. Dis, Jul 2004; 63: 896.

Hansen KE, Hildebrand JP, Genovese MC *et al*. Etanercept is effective in patients with rheumatoid arthritis with no response to infliximab therapy. J Rheumatology. 2004;31:1098-102

Haraoui B, Keystone EC, Thorne JC, Pope JE, Chen I, Asare CG, Leff JA. Clinical outcomes of patients with Rheumatoid Arthritis after switching from Infliximab to Etanercept. J Rheumatology. 2004;31:2356-9

Kristensen LE, Saxne T, Geborek P. Switching between anti-tnf therapies does not affect level of adherence to therapy in rheumatoid arthritis but response rates seem to decline. EULAR 2006

Naumann L, Detert J, Buttgereit F, Burmester G. A second anti-tnfa therapy after treatment failure of the first anti-tnfa therapy results in a significant decrease of concomitant glucocorticoid treatment in patients with rheumatoid arthritis. EULAR 2006

Nikas SN, Voulgari PV, Alamanos Y, Papadopoulos CG, Venetsanopoulou AI, Georgiadis AN and Drosos AA. Efficacy and safety of switching from infliximab to adalimumab: a comparative controlled study. Ann Rheum Dis 2006;65;257-260;

Nixon RM, Bansback N, Brennan A. Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. Statistics in Medicine, 2006, Early view [http://www3.interscience.wiley.com/cgi-bin/abstract/112736820/ABSTRACT]

Sanmartí R, Gómez-Puerta JA, Rodríguez-Cros JR, Albaladejo C, Munoz-Gomez J, Canete JD. Etanercpet in rheumatoid arthritis patients with a poor theraputic response to infliximab. Med Clin 2004; 122: 321-4

van Vollenhoven RF (a), Harju, A, Bran-Newark S, Klareskog L. treatment with infliximab when etanercept has fialed or visa versa: data from the STURE registry showing that swithcing tumour necrosis factor alpha blockers can make sense. Ann Rheum Dis 2003; 62: 1195-8

van Vollenhoven RF (b), Brannemark S, Klareskog L. Dose escalation of infliximab in clinical practice: improvements seen may be explained by a regression-like effectAnn. Rheum. Dis, 2004; 63: 426 - 430.

van Vollenhoven RF (c), Switching between biological agents. Clinical Experimental Rheumatology. 2004;22 (suppl 35) S115-S121

Wailoo A, Brennan A, Bansback N, Nixon R, Michaud K, and Wolfe F. Modeling the cost effectiveness of etanercept, adalimumab and anakinra compared to infliximab in the treatment of patients with rheumatoid arthritis in the Medicare program. Agency for Healthcare Research and Quality, Technology Assessment Report 2006.

Wick MC, Lindblad S, Klareskog L, Van Vollenhoven RF. Adalimumab restores clinical response in patients who have lost response to infliximab or etanercept: data from the STURE registry. EULAR 2004

Wick MC, Lindblad S, Klareskog L, Van Vollenhoven RF. Adalimumab (Humira) restores clinical response in patients with secondary loss of efficacy from infliximab (Remicade) or etanercept (Enbrel): results from the STURE registry at Karolinska University Hospital. Scandinavian Journal of Rheumatology. 2005;34(5):353-8.

Yazici Y, Erkan D. Do etanercept-naive patients with rheumatoid arthritis respond better to infliximab than patients for whom etanercept has failed? Ann. Rheum. Dis, 2004; 63: 607 - 608.

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$).ti.
5 etanercept.af.
6 [185243-69-0.rn.]
7 enbrel.af.
8 humira.af.
9 adalimumab.af.
10 infliximab.af.
11 remicade.af.
12 anakinra.af.
13 kineret.af.
14 anti-TNF$.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 <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