Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Assessment Report Guide

Title: Golimumab for the treatment of rheumatoid arthritis after failure of previous disease-modifying antirheumatic drugs: A Single Technology Appraisal

Produced by ScHARR, University of Sheffield

Authors Jon Tosh, Research Associate, ScHARR

Abdullah Pandor, Research Fellow, ScHARR

Matt Stevenson, Reader in Health Technology Assessment and Technical Director of ScHARR Technology Assessment Group

Correspondence to Jon Tosh

Research Associate

ScHARR

University of Sheffield

Regent Court

30 Regent Street

Sheffield

S1 4DA

Tel: +44 (0) 114 2220830

Email: j.tosh@sheffield.ac.uk

Date completed March 2011

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 08/118/01.

Declared competing interests of the clinical advisor: Professor David L. Scott. None declared

Report by the ERG for the third committee meeting

March 2011

BACKGROUND

Following the second NICE appraisal committee meeting (November 2010), the appraisal process for golimumab was suspended and the manufacturer (MSD) was given the opportunity by NICE to provide further clinical evidence and updated economic models. The ERGs critique of the evidence submitted is contained within this report. The ERG also consulted with a clinical expert regarding specific clinical issues.

MANUFACTURER'S SUBMISSION

In January 2011, NICE asked MSD to provide:

1. Radiographic outcomes data supporting the licence extension regarding golimumab reducing the rate of progression of joint damage
2. Revised economic model and results incorporating ACR70 for the DMARD-experienced population
3. Provide SF-36 data from GO-FORWARD and perform a sensitivity analysis in which these data are included in the economic model using SF-6D and/or mapping approaches to EQ-5D
4. Economic model and clinical and cost-effectiveness results for the TNF inhibitor-experienced population for golimumab compared with tocilizumab including a description of the methods used
5. Data supporting the level and frequency of dosing with golimumab
6. Any further long term outcomes data such as maintenance of HAQ improvement, or maintenance of ACR response for the DMARD experienced population
7. Update on the patient access scheme
8. Update on recently reported longer term safety data.

The ERG are satisfied that in the manufacturer's response (dated 28th Jan 2011) that they have looked to address each of these points.

1. RADIOGRAPHIC OUTCOMES DATA SUPPORTING THE LICENCE EXTENSION REGARDING GOLIMUMAB REDUCING THE RATE OF PROGRESSION OF JOINT DAMAGE

The manufacturer has used the van der Heijde modified Sharp (vdH-S) score as a measure of joint damage and progression. The ERG and their clinical adviser agree that this is an acceptable and appropriate measure of structural damage in patients with RA.

Additional data from the GO-BEFORE (DMARD-naïve) and GO-FORWARD (DMARD-experienced/TNF-α inhibitor naïve) trials were provided by the manufacturer (dated 3rd March 2011) following an ERG request. This data (including a critique) is summarised below.

DMARD-naïve patients - GO-BEFORE trial

A summary of the data provided by the manufacturer is provided in Table 1. This data appears to show that golimumab+methotrexate (MTX) may halt the progression of structural damage in patients who are DMARD-naïve. It further supports the Committee for Medicinal Products for Human Use's (CMHP) revision of the golimumab+MTX license to include use in patients with severe active RA who have not previously been treated with MTX. Although the ERG and their clinical advisor have no reasons to dispute these findings, the ERG note that the data provided in Table 1 does not correspond to the data provided in Appendix 1 (data summarised in Table 2) of the manufacturer's response (3rd March 2011) to the ERG's clarification letter (24th February 2011).

Table 1: GO-BEFORE radiographic data at week 52 (Table 1 of MS: 28th January 2011)

	MTX	50mg GOL+MTX	p-value
Reduction in rate of progression of structural damage			
Mean change from baseline in vdH-S score - All subjects at week 52	1.37 ±4.555	0.74 ±5.233	0.015
Subjects at week 52 with abnormal (>1.0mg/dL) at baseline	2.16 ±5.642	1.29 ±6.991	0.010
All subjects (from baseline at week 28)	1.11 ±3.875	0.71 ±3.771	0.065
All subjects (from week 28 to week 52)	0.26 ±1.707	0.04 ±2.615	0.034
Subjects with change in the total vdH-S score ≤ 0 at week 52	76 (53.9%)	100 (71.4%)	0.003
Mean change from baseline in vdH-S erosion score (hands and feet)	0.74 ±2.818	0.48 ±2.079	0.344
Mean change from baseline in vdH-S JSN score (hands and feet)	0.58 ±2.258	0.23 ±1.992	0.044
Prevention of structural damage			
Subjects with no new erosions at week 52 in the joints with 0 score at baseline	76 (53.9%)	100 (71.4%)	0.003
Subjects with no new JSN at week 52 in the joints with 0 score at baseline	117 (83%)	126 (90%)	0.091

Table 2: GO-BEFORE radiographic data at week 52 and week 104 (summarised from MS: 3rd March 2011)

	MTX	GOL+MTX	
		50mg	100mg
Randomised subjects			
Baseline			
n			
Mean ±SD			
Week 52			
n			
Mean ±SD			
Week 104			
n			
Mean ±SD			
Change from baseline at week 52			
n			
Mean ±SD			
Change from baseline at week 104			
n			
Mean ±SD			

DMARD-experienced patients - GO-FORWARD trial

Week 24 data from the GO-FORWARD trial was presented in the original ERG report and has been reproduced below in Table 3. The manufacturer states that the data shows minimal progression in structural damage across all active golimumab and control groups. The ERG and their clinical advisor believe that the manufacturer's summary of this week 24 evidence is appropriate. The data does suggest that for many patients receiving active treatment, structural damage may stop.

Table 3: NCT00771251 efficacy results through week 24 (Table 17 of ERG report)

Assessment	Placebo + MTX	Golimumab 50 mg + MTX	Golimumab 100 mg + MTX
Patients treated (n)			
ACR20			
ACR50			
ACR70			
Mean change from baseline in vdH-S (TSS) (SD, range)			
Median change from baseline in vdH-S (TSS) (IQ range)			
Mean change from baseline in Joint			

Space Narrowing Score (SD, range)	[redacted]	[redacted]	[redacted]
Median change from baseline in Joint Space Narrowing Score (IQ range)	[redacted]	[redacted]	[redacted]
Mean change from baseline in Bone Erosion Score (SD, range)	[redacted]	[redacted]	[redacted]
Median change from baseline in Bone Erosion Score (IQ range)	[redacted]	[redacted]	[redacted]

[redacted]In appendix 2 of the manufacturer's latest clarification document (3rd March 2011), the manufacturer provides 104 week radiographic data for the GO-FORWARD trial. The data is summarised below in Table 4. The manufacturer claims in their submission (28th January 2011) that these data support the CMHP's statement that long-term golimumab+MTX treatment *"continues to support a positive effect on progression of structural damage"*. The ERG's interpretation of the data is limited by the fact that patients 'crossed over' between treatments.

[redacted]However these data contain patients who are receiving 100mg golimumab+MTX, but in the 100mg golimumab+MTX it appears patients do not cross-over, and so a comparison between these two groups would be inappropriate. Also these data cannot be compared to the placebo arm because some patients in this group are receiving active treatment. The ERG therefore believes that firm conclusions regarding the long-term effectiveness of golimumab+MTX in halting/reducing structural damage in DMARD-experienced patients cannot be drawn.

Table 4: GO-FORWARD radiographic data at week 52 and week 104 (summarised from MS: 3rd March 2011)

	Placebo+MTX[a]	GOL+MTX	
		50mg[b]	100mg
Randomised subjects	[redacted]	[redacted]	[redacted]
Change from baseline at week 52			
n	[redacted]	[redacted]	[redacted]
Mean ±SD	[redacted]	[redacted]	[redacted]
Change from baseline at week 104			
n	[redacted]	[redacted]	[redacted]
Mean ±SD	[redacted]	[redacted]	[redacted]

a – Includes subjects who early escaped at week 16 or crossed over at week 24 to receive 50mg gol+mtx or dose escalated after week 52 database lock to receive 100mg gol+mtx

b – Includes subjects who early escaped at week 16 or dose escalated after week 52 database lock to receive 100mg gol+mtx

The manufacturer highlights particular factors of the study design which may account for the minimal progression rates seen across treatment and control arms in the GO-FORWARD study design. These include radiographic progression being a secondary outcome, a short placebo-controlled time period, and low baseline disease activity. The ERG are not convinced the reasons expounded fully explain the progression in structural damage in patients receiving golimumab+MTX. The clinical advisor did not identify anything inappropriate in the manufacturer's interpretation of the analysis, although comments that positive findings have been emphasised.

2. REVISED ECONOMIC MODEL AND RESULTS INCORPORATING ACR70 FOR THE DMARD-EXPERIENCED POPULATION

The results in MSD's latest submission (28th January 2011: Table 2 of document) are consistent with the output of the electronic models provided. The results were deterministic and no incremental results have been provided. The PSA has been run by the ERG and incremental results for the model are provided below in Table 5.

Table 5 - Basecase latest MSD PSA results: DMARD experienced population

Technology	Total Costs (£)	Total QALYs	Incremental Analysis – comparison made to next least effective non-dominated strategy ICER (£/QALY)	ICER (£/QALY) versus Methotrexate§
Methotrexate	38,586	6.038	-	-
Infliximab	68,648	7.215	Extendedly dominated by certolizumab	25,541
Golimumab	71,646	7.221	Extendedly dominated by certolizumab	27,946
Adalimumab	74,840	7.435	Extendedly dominated by certolizumab	25,951
Etanercept	82,644	7.662	Dominated by certolizumab	27,129
Certolizumab	82,111	7.956	22,693	22,693

§ Indicates cost-effectiveness when all other biologics contraindicated

The ERG requested a full list of changes that the manufacturer made to the model, which has subsequently been provided by MSD (3rd March 2011). The ERG can confirm that each change appears to have been implemented appropriately. The model was tested for internal consistency within the markov sheets. The errors previously identified have been corrected and no new errors were found. The changes detailed by the manufacturer were reversed to ensure that the results matched those contained within the previous submission. The ERG were unable to fully replicate results, however the results were very similar. Due to time and resource constraints the ERG were unable to completely validate the submitted model, however the ERG are confident that no other changes to the model have occurred which will have significantly altered the results.

3. PROVIDE SF-36 DATA FROM GO-FORWARD AND PERFORM A SENSITIVITY ANALYSIS IN WHICH THESE DATA ARE INCLUDED IN THE ECONOMIC MODEL USING SF-6D AND/OR MAPPING APPROACHES TO EQ-5D

As noted in the previous ERG critique post-ACD (November 2010), the SF-36 data reported in the GO-FORWARD trial suggests that golimumab+MTX has a significant impact on the physical component of HRQoL in DMARD-experienced RA patients. The manufacturer presents a sensitivity analysis using the SF-36 values mapped to SF-6D using the Sheffield algorithm (Kharroubi *et al.* 2007). The manufacturer derives SF-6D values for the methotrexate arm by estimating the ratio of HAQ scores between the two arms and then applying this ratio to the golimumab SF-6D values. The ERG are unclear as to why the manufacturer has chosen this method, rather than estimating the values directly from the trial.

The manufacturer presents two economic models, one using a normal distribution for the utility values (bounded at 1 to stop approximately 2% of draws sampling values being greater than one) and one using a beta distribution, which is bounded at zero and one. There are only slight differences in the PSA. The beta distribution PSA was run and the results are presented below in Table 6.

Table 6 – MSD SF-6D (Beta distribution) Sensitivity Analysis PSA results: DMARD experienced population

Technology	Total Costs (£)	Total QALYs	Incremental Analysis – comparison made to next least effective non-dominated strategy ICER (£/QALY)	ICER (£/QALY) versus Methotrexate§
Methotrexate	36,829	6.482	-	-
Infliximab	66,266	7.497	Extendedly dominated by certolizumab	28,990
Golimumab	69,602	7.525	Extendedly dominated by certolizumab	31,420
Adalimumab	72,577	7.668	Extendedly dominated by certolizumab	30,129
Etanercept	80,799	7.928	Dominated by certolizumab	30,412
Certolizumab	79,600	8.055	27,182	27,182

§ Indicates cost-effectiveness when all other biologics contraindicated

The results are generally robust to this sensitivity analysis; however the ranking of treatments should not be compared because golimumab utility values are used for each TNF-α inhibitor comparator. To allow this comparison the manufacturer should have derived utility values for each comparison directly, however the ERG are unsure of the availability of HRQoL evidence for all biologic comparators and it may not have been possible.

4. ECONOMIC MODEL AND CLINICAL AND COST-EFFECTIVENESS RESULTS FOR THE TNF INHIBITOR-EXPERIENCED POPULATION FOR GOLIMUMAB COMPARED WITH TOCILIZUMAB INCLUDING A DESCRIPTION OF THE METHODS USED

The ERG has checked the TNF-α inhibitor model with tocilizumab and abatacept added as comparators, and believe that the manufacturer has implemented these changes appropriately. The manufacturer's assumptions regarding the dosing and administration of tocilizumab and abatacept appear to be appropriate. The ERG cross-referenced the effectiveness estimates regarding tocilizumab (Emery *et al.* 2008) and abatacept (Genovese *et al.* 2005) and the values in the economic model match these. The ERG cross-checked with the relevant NICE Technology Appraisals (Tocilizumab TA198, Abatacept TA195), and these two trials selected by the manufacturer appear to

be the only relevant trials in this population. A full validation of the economic model was not possible; however the model maintained internal consistency and the incumbent comparators (methotrexate, rituximab and golimumab) have results that match the previous submission. Table 7 provides an incremental analysis of the PSA results from the manufacturer's basecase analysis.

Table 7 – Baseline latest MSD PSA results: TNF-experienced population

Technology	Total Costs (£)	Total QALYs	Incremental Analysis – comparison made to next least effective non-dominated strategy ICER (£/QALY)	ICER (£/QALY) versus Methotrexate§
Methotrexate	37,170	3.936	-	-
Rituximab	52,112	4.153	Extendedly dominated by golimumab	68,663
Golimumab	53,832	4.441	32,979	32,979
Abatacept	69,999	4.897	35,457	34,155
Tocilizumab	71,031	4.913	63,610	34,644

§ Indicates cost-effectiveness when all other biologics contraindicated

These results include the revised assumption that HAQ progression while on palliative care is 0.06 per year. However it maintains the assumptions that rituximab has a HAQ progression of 0.045 per year, and is re-administered every 6 months. When the model is run with the ERGs preferred estimates of a zero HAQ progression rate for rituximab and a re-administration every 9 months, the results change substantially (see Table 8).

Table 8 – ERG PSA results: TNF-experienced population

Technology	Total Costs (£)	Total QALYs	Incremental Analysis – comparison made to next least effective non-dominated strategy ICER (£/QALY)	ICER (£/QALY) versus Methotrexate§
Methotrexate	37,257	3.929	-	-
Golimumab	53,749	4.430	Dominated by rituximab	32,903
Rituximab	44,139	4.493	12,196	12,196
Abatacept	70,020	4.887	65,734	34,198
Tocilizumab	70,853	4.898	80,008	34,691

§ Indicates cost-effectiveness when all other biologics contraindicated

5. DATA SUPPORTING THE LEVEL AND FREQUENCY OF DOSING WITH GOLIMUMAB

The ERG and their clinical advisor agree with the manufacturer that the results of the dose finding phase II trial (Kay *et al.*) suggest that the lowest dosage regimen (50mg every 4 weeks) represents the minimum effective dose from those evaluated. The ACR response rates across the 4 dosing regimens assessed are presented below in Figure 1, and suggest broadly similar results with no regimen consistently appearing better or worse than the remaining regimens.

Figure 1: Kay *et al.* dose finding results

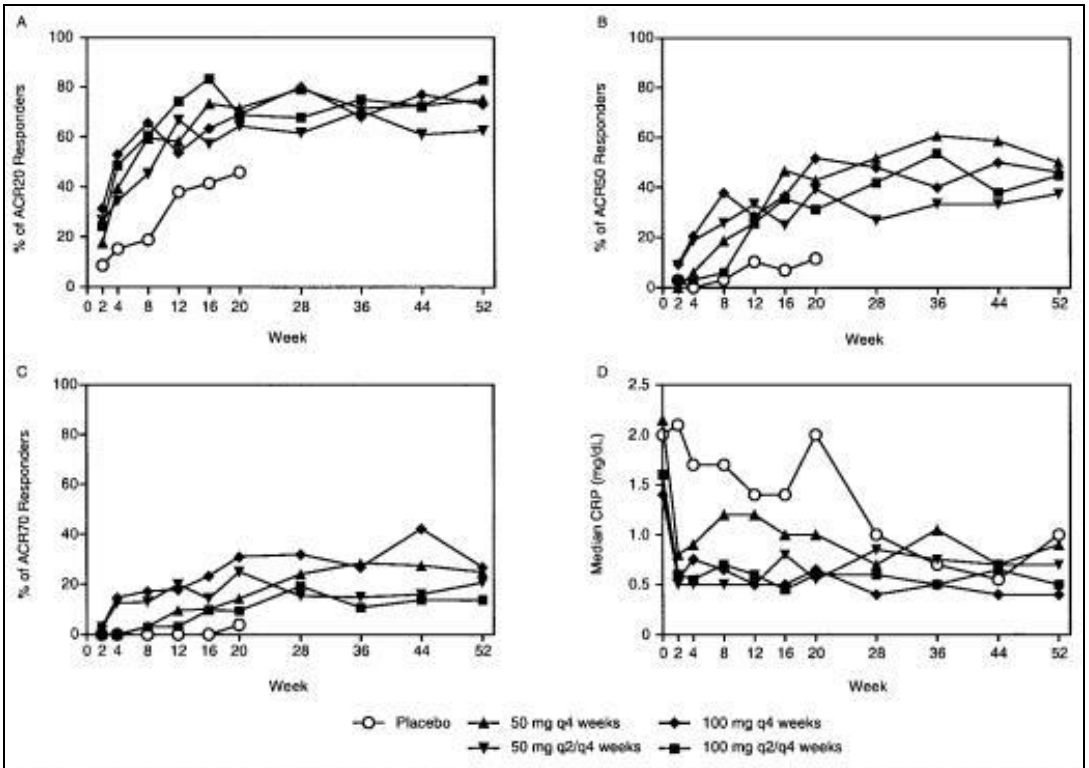

Figure 2. Percentage of patients meeting the American College of Rheumatology 20% improvement criteria (ACR20 responders) (A), percentage of ACR50 responders (B), percentage of ACR70 responders (C), and median C-reactive protein (CRP) level (D) through week 52. q4 weeks = every 4 weeks.

While these results provide evidence regarding golimumab+MTX 50mg monthly in terms of disease activity/symptomology, they do not provide evidence regarding the comparative effectiveness of alternative golimumab+MTX dosing strategies to halt radiographic progression (see Question 1).

6. ANY FURTHER LONG TERM OUTCOMES DATA SUCH AS MAINTENANCE OF HAQ IMPROVEMENT, OR MAINTENANCE OF ACR RESPONSE FOR THE DMARD EXPERIENCED POPULATION

The ERG has no particular concerns regarding the evidence provided by the manufacturer regarding HAQ and ACR response. As stated by the manufacturer (28th January 2011), they seem to suggest that the week 52 ACR response is maintained at week 104. The HAQ response data presented in Table 9 of the manufacturer's latest submission (28th January 2011) appears to show maintained efficacy, although the data is muddied by responder bias and patient cross-over.

7. UPDATE ON THE PATIENT ACCESS SCHEME

The manufacturer states that final advice document is pending; however, at the time of writing, the ERG has not received any confirmation regarding the manufacturer's application for a PAS scheme.

8. UPDATE ON RECENTLY REPORTED LONGER TERM SAFETY DATA.

The manufacturer provides an aggregated summary of safety data from phase III trials of golimumab in patients with RA, psoriatic arthritis and ankylosing spondylitis. Five trials are pooled, of which three are in RA patients (GO-BEFORE (104 week), GO-FORWARD (104 week) and GO-AFTER (100 week)). A justification for pooling different patient populations is not given, and the clinical advisor states that although there is no particular concern, it may be conceivable that RA patients may have slightly different underlying risks for infections.

Firm conclusions regarding the safety of golimumab cannot be drawn. There is a recognised concern regarding serious infections caused by biologic agents in patients with RA (Galloway *et al.* 2011), however trial data is a suboptimal method for providing this evidence. It is the belief of the ERG and the clinical advisor that prospective safety data for golimumab should be routinely collected in the British Society for Rheumatology Biologics Registry.

REFERENCES

Emery P, Keystone E, Tony H-P, Cantagrel A, Vollenhoven R, Sanchez A, Alecock E, Lee J & Kremer J. IL-6 Receptor inhibition with tocilizumab improvements treatment outcomes in patients with rheumatoid arthritis refractory to anti-TNF biologics: results from a 24-week multicentre randomised placebo controlled trial. Ann Rheum Dis. 2008; 68: 296-313

Galloway J. B, Hyrich K. L, Mercer L. K, Dixon W. G, Fu B, Ustianowski A. P, Watson K. D, Lunt M, BSRBR Control Centre Consortium, Deborah P. M. Symmons, and on behalf of the British Society for Rheumatology Biologics Register. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (2011) 50(1): 124-131

Genovese M, Becker J, Schiff M, Luggen M, Sherrer Y, Kremer J, Birbara C, Box J, Natarajan K, Nuamah I, Li T, Aranda R, Hagerty D, Dougados M. Abatacept for Rheumatoid Arthritis Refractory to Tumor Necrosis Factor α Inhibition. The New England Journal of Medicine. 2005 353(11): 1114-1123

Kharroubi S. A, Brazier J. E, Roberts J. O'Hagan A. Modelling SF-6D health state preference data using a nonparametric Bayesian method. Journal of Health Economics (2007) 26(3): 597-612