Rheumatoid arthritis MTA - drugs for treatment after failure of a TNF inhibitor: UCB response to appraisal consultation document

Key point summary

- NICE's Appraisal Consultation Document (ACD) on treatments for rheumatoid arthritis (RA) after failure of a TNF inhibitor (i.e., second line treatment) recommends that TNF inhibitors be used in this line of treatment only in the context of research.
- This recommendation is driven by the level of uncertainty in the clinical effectiveness data, and on the high ICERs vs conventional DMARDs and vs rituximab, which in the Assessment Group model range from (depending on the anti-TNF):
  - £34,300/QALY to £38,800/QALY (ICER of anti-TNFs vs cDMARDs)
  - £131,000/QALY to dominated (ICER of anti-TNFs vs rituximab)
- In response to the ACD it is UCB's position that not all relevant evidence has been taken into account. No consideration has been given to a scenario whereby a TNF blocker is not paid for if a patient does not initially respond to treatment.
- Certolizumab pegol (CERTOLIZUMAB) has been approved by NICE as a first line biologic treatment for RA. Response to certolizumab can be determined by week 12 of treatment, at which point non-responders can be taken off certolizumab.
- Certolizumab is available with a patient access scheme (PAS). This provides the first 12 weeks (10 vials) for free. This combined with the 12 week decision time point ensures non-responders incur no drug acquisition cost to the NHS.
- Including CERTOLIZUMAB with the PAS as a second-line treatment option in the calculation of cost-effectiveness indicates that in this line of therapy CERTOLIZUMAB is a cost-effective alternative to conventional DMARDs, with ICERs lower than those for the other anti-TNFs (vs cDMARDs). The range demonstrates the variation of results depending on choice of 1st line anti-TNF therapy.
  - ICERs of certolizumab vs cDMARDs: £15,500 to £16,300/QALY
  - ICERs for other TNF blockers vs cDMARDs: £19,000 to £46,000
- The ICERs for CZP compared to rituximab are also more favourable than the ICERs of other anti-TNFs compared to rituximab. The range demonstrates the variation of results depending on choice of 1st line anti-TNF therapy.
  - ICERs of CERTOLIZUMAB vs rituximab: £31,000 to £35,000/QALY
  - ICERs for other anti-TNFs vs rituximab: £400,000 to dominated

Conclusion

With the PAS that is currently in place, CERTOLIZUMAB is a cost-effective option as a second-line treatment after the failure of a first anti-TNF. This appraisal of the other TNF blockers does not consider all the available costing information and as a result certolizumab is denied the opportunity to demonstrate that it is a viable treatment after the failure of a first TNF blocker

1.1 Context

NICE has produced draft guidance on using adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor in the NHS in England and Wales, in the form of an appraisal consultation document (ACD). A key conclusion in the ACD is that "The TNF inhibitors adalimumab, etanercept, and infliximab are recommended for the treatment of rheumatoid arthritis after the failure of a previous TNF inhibitor only in the context of research."

This decision is driven by two key factors:

1) The lack of clinical effectiveness data for the TNF inhibitors in this stage of the treatment pathway and the resulting uncertainty in the ICERs.
2) ICERs for the TNF inhibitors compared with rituximab that were either very high or dominated by rituximab.

This document serves to provide comments on the ACD, in particular a response to the question "Has all of the relevant evidence been taken into account?" While Certolizumab pegol (CERTOLIZUMAB®) is not included as an intervention in the ACD (due to licensing after the MTA scope had already been developed), it is UCB's position that the draft guidance does not take all the relevant evidence into account.

Specifically, the ACD does not account for the fact that the cost-effectiveness of anti-TNFs after failure of a previous anti-TNF is greatly improved by a situation where there is no drug acquisition cost to the NHS for non-responders to the given anti-TNF, as is the case with certolizumab. When the patient access scheme (PAS) currently in place for certolizumab is accounted for, the use of certolizumab as a second-line anti-TNF is cost-effective, and furthermore eliminates the financial impact of any uncertainty around clinical effectiveness because the NHS would not pay for non-responders to treatment.

1.2 NICE recommendation of certolizumab pegol

Certolizumab pegol (CERTOLIZUMAB®, CZP) was recommended for use in the NHS by NICE in February 2010 (TA 186) for the treatment of rheumatoid arthritis after inadequate response to conventional DMARDs (i.e., first-line biologic DMARD use). As an antibody against TNF-α, certolizumab is in the same therapeutic class as three of the other drugs considered in this appraisal, namely adalimumab (ADA), infliximab (IFX) and etanercept (ETA).

Response to certolizumab can be determined by week 12 of treatment, at which point non-responders can be taken off certolizumab.[1]

A novel patient access scheme (PAS) for Certolizumab was approved by the Department of health in September 2010 and is currently in place. Under this scheme the first 12 weeks (10 vials) are provided by UCB free of charge to the NHS.

Importantly, the PAS when combined with the 12 week clinical effectiveness decision time point results in non-reponders to certolizumab incurring **no drug acquisition cost** to the NHS.

1.3 Certolizumab in second-line use - economic modelling methodology

As certolizumab was not yet licensed at the time the scope of the current MTA was developed, it was not included as an intervention in the current MTA. In order to consider the impact the inclusion of certolizumab would have on the MTA findings, UCB has evaluated the cost-effectiveness of certolizumab in the second-line setting by adapting the certolizumab model submitted to NICE as part of the single technology appraisal process (TA 186). This model has been rigorously evaluated by NICE and formed a key part of the evidence which led to the approval of certolizumab for use on the NHS; we therefore consider this an appropriate model on which to base our analysis of the cost-effectiveness of certolizumab.

In the original model on which the positive NICE recommendation was based, patients discontinuing on first-line anti-TNF therapy moved on to a sequence of follow-up therapies, beginning with sulfasalazine. We have modified this model so that patients discontinuing on first-line anti-TNF therapy instead move on to a second anti-TNF.

1.4 Results of modelling certolizumab as a second-line biologic

The BRAM model evaluates a patient population in second line treatment and thus does not include consideration of first-line treatments. In contrast, the certolizumab model incorporates a choice of first-line treatments. Results of the cost-effectiveness of second-line treatment are therefore presented in four ways, each considering a different first-line anti-TNF: (etanercept (ETA), adalimumab (ADA), infliximab (IFX), and certolizumab (CZP).

Second line use of anti-TNFs vs. cDMARDs – table 1

The results in Table 1 below indicate that regardless of the first-line therapy used, in second line use the ICER for certolizumab vs cDMARDs (range: £15,500 to £16,300) is lower than the ICERs for all the other three anti-TNFs vs cDMARDs (range: £19,000 to £46,000).

It should be noted that the results from the CERTOLIZUMAB model differ in magnitude from the results presented in the independent Assessment Group model, however the order and pattern of results are the same, with infliximab being the least cost-effective second-line treatment and rituximab being the most cost-effective second-line treatment.

Table 1: Summary of cost-effectiveness results for TNF inhibitors in combination with MTX

Comparator 1 - conventional DMARDs			*Comparator 2 - biologic therapy*			
Second line treatment	**Costs**	**QALYs**	**Second line treatment**	**Costs**	**QALYs**	**ICER (£)**
With ETA as first line and TNF inhibitors or rituximab as follow on therapy						
cDMARDs	£103,484	4.955	ADA	£112,760	5.397	21,011
cDMARDs	£103,484	4.955	IFX	£122,389	5.436	39,305
cDMARDs	£103,484	4.955	RIT	£110,350	5.405	15,253
cDMARDs	£103,484	4.955	**CZP**	**£111,331**	**5.436**	**16,314**
With ADA as first line and TNF inhibitors or rituximab as follow on therapy						
cDMARDs	£108,752	4.853	ETA	£117,919	5.301	20,451
cDMARDs	£108,752	4.853	IFX	£126,949	5.301	40,596
cDMARDs	£108,752	4.853	RIT	£114,803	5.269	14,526
cDMARDs	£108,752	4.853	**CZP**	**£115,902**	**5.301**	**15,952**

With IFX as first line and TNF inhibitors or rituximab as follow on therapy						
cDMARDs	£114,513	4.825	ADA	£123,029	5.265	19,351
cDMARDs	£114,513	4.825	ETA	£123,029	5.265	19,351
cDMARDs	£114,513	4.825	RIT	£120,848	5.274	14,111
cDMARDs	£114,513	4.825	**CZP**	**£121,976**	**5.305**	**15,528**

Second line use of anti-TNFs vs. rituximab – table 2

Similarly, the results indicate that regardless of the first-line therapy used, in second line use the ICER for CZP vs rituximab (range: £31,000 – 35,000) is lower than the ICERs for all the other three anti-TNFs vs rituximab (range: £400,000 to dominated).

Comparator 1 - rituximab			*Comparator 2 - TNF inhibitor*			
Second line treatment	**Costs**	**QALYs**	**Second line treatment**	**Costs**	**QALYs**	**ICER (£)**
With ETA as first line						
RIT	£110,350	5.405	IFX	£122,389	5.436	390,552
RIT	£110,350	5.405	**CZP**	**£111,331**	**5.436**	**31,807**
With ADA as first line						
RIT	£114,803	5.269	ETA	£117,919	5.301	98,404
RIT	£114,803	5.269	IFX	£126,949	5.301	383,550
RIT	£114,803	5.269	**CZP**	**£115,902**	**5.301**	**34,712**
With IFX as first line						
RIT	£120,848	5.274	ADA	£123,029	5.265	-245,491
RIT	£120,848	5.274	ETA	£123,969	5.305	98,618
RIT	£120,848	5.274	**CZP**	**£121,976**	**5.305**	**35,642**

It should be noted that the results presented above only consider a 6-month stopping rule. If a 3-month stopping rule is employed with certolizumab rather than a 6-month stopping rule, non-responders to certolizumab would come off treatment earlier, making the results more favourable towards certolizumab than those presented above. As has been outlined, certolizumab efficacy can be assessed at 3 months (12 weeks) and so no patients would progress and then fail at 6 months. All the other TNFs have a 6-month initial review period.[1, 2]

These results have not been presented here as we have only modelled the PAS as a cost saving option over the first three months. This has been done to allow proper comparison between each TNF inhibitor option. If we had applied a 3-month stopping rule to certolizumab and a different 6-months stopping rule to the other TNF inhibitors, the QALY for certolizumab would improve, the cost base would reduce and the ICER for certolizumab against the other TNF inhibitors would be further improved.

1.5 Conclusions

1. There is limited clinical trial data investigating use of second-line biologic DMARD therapy after failure on first-line biologic therapy. As acknowledged within this appraisal, this lack of evidence leads to considerable uncertainty in decision-making.

2. However, as discussed by clinical specialists and acknowledged by the committee, the efficacy of follow-up conventional DMARD therapy after failure on a biologic is limited, and there is therefore an unmet need for effective therapy in this setting (4.3.10).

3. The economic evaluation performed by the Assessment Group indicated considerable uncertainty as to whether infliximab, etanercept and adlimumab were cost-effective, due to either to high ICERs, or to considerable uncertainty in the results.

4. The introduction of certolizumab with the associated patient access scheme (PAS) overcomes the concerns around cost-effectiveness of second-line usage. With the PAS, ICERs for the anti-TNFs were within recognised standards of cost-effectiveness. Furthermore, the ICERs for certolizumab were lower than those of the other anti-TNFs.

5. The PAS overcomes uncertainty in the clinical and economic data because patients who do not respond to second-line anti-TNF therapy with certolizumab by week 12 should discontinue treatment. This is included within the treatment period covered by the PAS, and means that the NHS will not pay for non-responders. The uncertainty over lack of trial data is mitigated by ensuring that failed patients have no drug acquisition cost to the NHS, allowing certolizumab to be considered a cost effective therapy as a follow on TNF inhibitor.

Appendix A: Modelling assumptions

Outline of model structure and inputs

The model is a cost-utility Markov model with a lifetime time horizon and the perspective of a third-party payer. As a patient-level simulation model, the Assessment Group model models improvement on treatment through multiplying baseline HAQ score by a HAQ multiplier sampled from an appropriate beta distribution based on treatment efficacy data (from Bombardieri 2007, Bingham 2009 and REFLEX trial). The certolizumab model is a cohort model, and improvement in HAQ on treatment is driven by ACR response rates. Thus there are clear differences in the structure of the economic model used here and the model used by the Assessment Group. However, our assumptions of the efficacy of second-line treatment are based on the same data sources as the Assessment Group model and therefore can be judged to be similar.

Baseline characteristics: The starting patient group is modelled on patients in the CZP trials – i.e. patients with moderate to severe RA who have failed on conventional DMARD therapy. Because the patients move through the Markov model and are transitioned on to second-line therapy after discontinuation from a primary anti-TNF, with associated changes in disease progression assumed, the characteristics of patients in the "second-line" part of the model should be relevant to those likely to receive second-line therapy with anti-TNFs.

Efficacy estimates: First line assumptions were those used in the STA submission for Certolizumab, based on a systematic review and indirect analysis. Because there are no trials of certolizumab in the second-line setting, we instead used efficacy estimates from the sources identified by the NICE MTA and utilised in the NICE Assessment Group model. ACR20, 50 and 70 response rates for adalimumab came from the Bombardieri 2007 study, for etanercept from Bingham 2009, and for rituximab from the REFLEX trial. Due to lack of appropriate data in the second-line setting, response rates for infliximab and for certolizumab were assumed to be the same as for etanercept. Discontinuation rates for second-line biologics were used from the same studies. The efficacy assumptions used in the model are summarised in Table 2.

Table 2: Efficacy assumptions for first and second line treatments (%)

Treatment	First line			Second line		
	ACR 20	ACR 50	ACR 70	ACR 20	ACR 50	ACR 70
Adalimumab + MTX	70.8	0.0	0.0	60.1	33.0	13.0
Certolizumab pegol + MTX	71.1	35.9	21.6	42.3	18.4	8.0
Etanercept + MTX	66.4	61.1	23.7	42.3	18.4	8.0
Infliximab + MTX	58.6	27.0	19.6	42.3	18.4	8.0
Rituximab + MTX	-	-	-	65.2	32.9	12.3

The quality of life assumptions used in the model are summarised in Table 3 and are designed to correspond with the assumptions used in the STA submission for Certolizumab. All assumptions relating to first or second line bDMARDs are taken from ANCOVA regression analyses from baseline to 3 months of the certolizumab pegol arms of the RAPID trials. Assumptions relating to cDMARDs, palliation and third or later line bDMARD use follow NICE's recommendations following TA126.

Table 3: UCB model assumptions relating to instant change in quality of life on initiation of treatment and annual absolute change in quality of life on continuation of treatment

	Initiation of treatment			Continuation of treatment	
	ACR	HAQ	EQ-5D	HAQ	EQ-5D
First or second line bDMARD	<20	-	+0.053	-0.1913	+0.0402
	20-50	-	+0.183	-0.1913	+0.0402
	50-70	-	+0.263	-0.1913	+0.0402
	>70	-	+0.358	-0.1913	+0.0402
Second or later line cDMARDs		-0.04	+0.008	+0.012	-0.0025

Palliation		-0.04	+0.008	+0.012	-0.0025

The BRAM modelling assumptions relating to changes of quality of life on treatment are described below.

Table 4: BRAM assumptions relating to instant change in quality of life on initiation of treatment and annual absolute change in quality of life on continuation of treatment

	Initiation of treatment			Continuation of treatment	
	ACR	HAQ	EQ-5D	HAQ	EQ-5D
First or second line bDMARD	<20	-	+0.053	0	0
	20-50	-	+0.183	0	0
	50-70	-	+0.263	0	0
	>70	-	+0.358	0	0
Second or later line cDMARDs		-0.04	+0.008	0.045	-0.0095
Palliation		-0.04	+0.008	0.06	-0.0126

Cost data: The same unit cost and resource use data in the original Certolizumab model was also used to estimate costs of second-line therapy.