TECHNOLOGY ASSESSMENT REPORT

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor: A systematic review and economic evaluation

Response from Bristol-Myers Squibb

12 January 2010

To: Jeremy Powell, Technology Appraisal Project Manager

RE: Technology Assessment Report: Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor

Dear Jeremy

Bristol-Myers Squibb welcomes the opportunity to comment on the Technology Assessment Report (TAR) developed by the West Midlands Group for the appraisal of adalimumab, etanercept, infliximab, rituximab and abatacept for rheumatoid arthritis after the failure of a TNF inhibitor. This letter sets out our comments in the following sections:

1: Executive summary

2: Detailed comments on the clinical and cost effectiveness summarized in the TAR

2.1 Long term disease-control should be a critical factor in assessing the effectiveness of RA therapy in the management of chronic rheumatoid arthritis

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1: Executive summary

Clinical Effectiveness

Conventional DMARDs do not offer further improvements in HAQ after the failure of previous TNF-α inhibitor therapy.

Abatacept is associated with ongoing improvements in HAQ whilst on treatment which guarantees good long term disease control, with sustained long term efficacy and high retention rates. The resulting incremental improvements in HAQ should be reflected in the BRAM.

Rituximab is associated with underlying disease progression which should be captured within the BRAM as a worsening HAQ score.

Longer intervals between rituximab treatments lead to flares in disease and worsening of HAQ scores. Therefore shorter re-treatment intervals for rituximab should be used within the BRAM.

Rituximab demonstrates lower efficacy in RF negative patients.

Cost Effectiveness

The BRAM is not transparent nor are the model outputs presented in the TAR reproducible.

The BRAM overestimates the mean survival times (time on treatment) for rituximab which is unrepresentative of clinical practice. Shorter and more representative survival times for rituximab should be used in the BRAM.

Cost assumptions within the model are inaccurate

- **IV administration costs should be more representative of infusion time and associated resource use i.e. lower for abatacept than for rituximab and infliximab**
- **The TAR also overestimates the average dose of abatacept per patient**

The concluding results from the BRAM conflict with those from the York Model for the ongoing Psoriatic Arthritis (PSA) appraisal, which uses a similar RA evidence base.

2: Detailed comments on the clinical and cost effectiveness summarized in the TAR

The TAR concludes that '*there is a lack of good evidence comparing the effectiveness of the five technologies together'* (page 22, Section 2.6). BMS concurs with this view. The analysis presented in the TAR, while conducted in an objective scientific spirit, must, as we argue in detail below, be open to challenges as the basis for future policy recommendations, for the following reasons:

2.1 Long-term disease-control should be a critical factor in assessing the effectiveness of RA therapy in the management of chronic rheumatoid arthritis

The importance of tight disease control within the management of rheumatoid arthritis is acknowledged within the TAR; '*Controlling symptoms of joint pain and stiffness, minimising loss of function, improving quality of life and reducing the risk of disability associated with joint damage and deformity are central objectives in the management of RA at all stages. These objectives are not met with drug therapy alone: patients often need advice and support from a multi-disciplinary team including specialist nurses, podiatrists, physiotherapists and occupational therapists…… Indeed a key element of a Scottish trial reporting excellent outcomes was frequent specialist review with a focus on tight disease control'* (page 29, Section 3.1.7). The goal of any RA treatment is therefore not only to rapidly achieve low disease activity status, but crucially to ensure that this is maintained in the long-term, thereby achieving stable disease control over time.

There are key differences between abatacept and rituximab in terms of proven long term efficacy and levels of evidence to demonstrate long term disease control:

- Abatacept, administered as a single intravenous infusion every 4 weeks, provides sustained disease control, as demonstrated by sustained clinically meaningful responses for up to 5 years in the target population.

- The rituximab re-treatment regimen is based on the recurrence of symptoms which, by allowing disease flare, exposes patients to potential disease progression. The long term clinical evidence for rituximab is very limited; reported for up to 5 repeated courses in a responder population and only assessed 6 months after each course.

- Importantly, a fluctuating DAS28 response as seen with rituximab, but not with abatacept, is shown to be as damaging as a constant high DAS28 score, and represents a prognostic factor for irreversible joint damage, disability and costs[i,ii, iii]. Patients presenting a fluctuating low DAS28 response present the same risk of joint damage progression as patients with constant high DAS28[ii].

BMS asks that these crucial differences in long term efficacy and impact on disease progression are addressed within the analyses.

2.2 The clinical effectiveness profile of abatacept is better than rituximab

The TAR states, in its conclusions, that '*adjusted indirect comparison suggests there is no significant difference in the effectiveness between rituximab and abatacept*' (page 22, Section 2.6) which BMS strongly challenges as misleading. BMS believes it is not appropriate to base an assessment of relative efficacy/safety solely on a MTC of 6 months, as this does not take into account clinical evidence relating to long term efficacy nor relative efficacy in RF negative sub-groups.

2.2.1 Indirect comparison at 6 months - Rates of withdrawal

The TAR reports the results of an indirect comparison of abatacept and rituximab using the ATTAIN and REFLEX trials (page 149, Section 5.6.2). The relative risk for withdrawals for any reason at 6 months from this analysis are presented below in Table 1.

Table 1: TAR Indirect comparison: withdrawal for any reason (Table 42 in the TAR, page 149)

COMPARISON	RR	LCI	UCI	COMMENT
RITUXIMAB v PLACEBO	0.389	0.294	0.515	favours rituximab
ABATACEPT v PLACEBO	0.531	0.348	0.810	favours abatacept
RITUXIMAB v ABATACEPT	0.733	0.441	1.217	favours rituximab, wide CIs

The TAR states '*that no indirect comparison approached statistical significance, however the indirect comparison point estimates slightly favoured rituximab for ….withdrawal for any reason'* (page 149, Section 5.6.2).

The indirect comparison presented in the BMS submission showing the relative odds ratios of withdrawals due to any reason at 6 months are presented below in Figure 1.

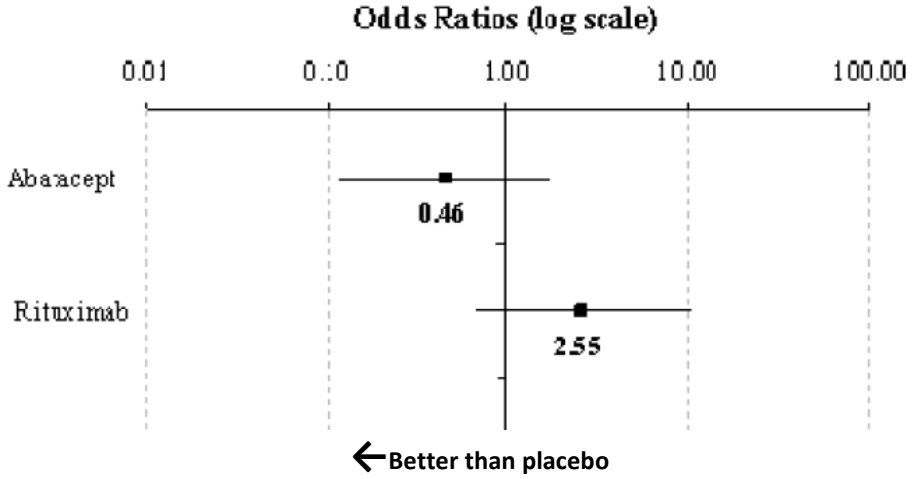


Figure 1: Results of Mixed Treatment Comparison - Relative odds ratios of withdrawals due to any reason at 6 months

According to the BMS analysis, both abatacept and rituximab were equivalent to placebo, but the comparison favoured abatacept as the least likely for withdrawal due to any reason.

It is important to note that both analyses concluded that there were no significant differences in withdrawal rates.

Importantly, over the longer term, the trend in favour of abatacept observed in the BMS indirect comparison is confirmed in the long term data set. Indeed, the TAR reports the withdrawal rates (for any reason) for rituximab of 63% at 12 months, (p102, Section 5.3.5.3), this compares to 30% for abatacept at 24 months (page 122, Section 5.3.6.3). Comparisons of post 12 month withdrawal/retention for rituximab are difficult to assess, because of the treatment regimen and the way data is reported by course and for responders only.

BMS believes that the indirect comparison of withdrawal rates presented in the TAR is not representative of the clinical evidence as it understates withdrawal rates for rituximab at 6 months and in the longer term. Therefore, more representative (higher) withdrawal rates should be used for rituximab, and lower ones for abatacept.

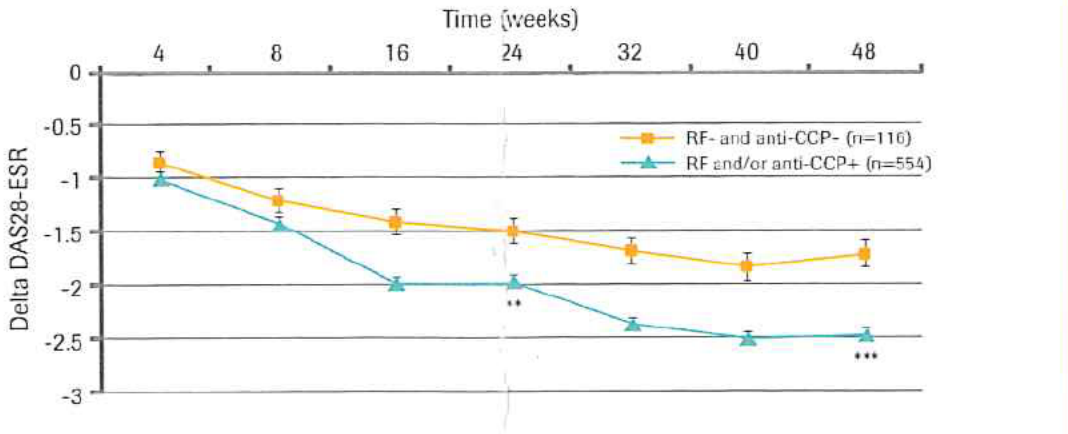
2.2.2 Efficacy in rheumatoid factor (RF) negative patients

The TAR states that '*Evidence from REFLEX trial suggested that the effectiveness of rituximab does not vary significantly according to the presence or absence of RF*.' (page 168, section 5.7.2). BMS would challenge this statement for the following reasons.

The statement contradicts the conclusions from this year's recently updated Consensus statement on biological agents for the treatment of rheumatic diseases[iv]. This reviewed evidence from two RA patient populations and concluded that '*More robust ACR responses were seen with rituximab in rheumatoid factor/anti-CCP-positive patients in DMARD non-responders and in TNF non-responders'*. Efficacy data presented for rituximab by RF subgroups in DMARD non-responders supported

this finding. Although not reviewed within the TAR, as it was out of scope, data presented within the BMS submission in DMARD non-responders (MIRROR and SERENE) showed a distinct difference in the response to rituximab in patients who were seropositive for rheumatoid factor and/or anti-CCP. The pooled data from the MIRROR and SERENE showed the clinical effect of rituximab is 2-3 times greater in seropositive patients, with a significantly greater change in DAS 28 (as derived by ESR) in the seropositive group[v] (see Figure 2).

Figure 2: Efficacy of rituximab in RF negative and positive subgroups (in DMARD non-responders)[v]



Data are represented as mean ± standard error of the mean. Significant differences between populations were compared by ANOVA fitting serotype as a covariate and using observed clinical data only (no imputation). **p<0.001, F=11.057; ***p<0.0001, F=20.36.

These data confirm the findings of the Evidence Review Group (ERG) Report appraising the NICE STA: Rituximab for Rheumatoid Arthritis (TA126). The report also recognised that there were statistically significant differences in efficacy (e.g. ACR response) between RF-positive and negative patients (Table 3-7, Rituximab ERG).

BMS believes that the conclusions reached within the TAR that there are no differences in efficacy between RF negative and RF positive subgroups is incorrect, and that there is evidence to show lower efficacy for rituximab in the RF negative subgroup, making up 25% of the target population. Therefore, this appraisal should address this issue.

2.2.3 Long term efficacy (at 1 year)

Long term data are summarised in the TAR for both abatacept and rituximab, however there are no conclusions regarding relative long term efficacy.

BMS acknowledges that the open-label design of long-term extension (LTE) studies prevents any formal indirect comparisons. Additionally, simple comparisons of these data are made difficult because of differences in how the LTE data are reported for rituximab (REFLEX LTE[vi]) and abatacept (ATTAINE LTE[vii, viii]), namely:

- REFLEX LTE only reports data for patients that have responded to the first and completed 3 courses of rituximab
- REFLEX LTE data are reported at 24 weeks after each course (up to 5

courses), whilst data for abatacept are reported monthly (up to 5 years).

For these reasons a post-hoc analysis of the ATTAIN data was presented in the BMS submission at one year, for responder/completer population, to allow comparison of similar patient populations, similar end points at comparable time points. Table 2 shows the cross study comparison of 1 year LTE outcomes between abatacept and rituximab.

The analyses showed abatacept to have superior clinical benefit over a single course of rituximab for all efficacy outcomes, most importantly for the clinically relevant outcomes of LDAS and DAS28-defined remission. LDAS rates at one year for abatacept were 29% compared to 24% for rituximab. DAS remission rates at one year for abatacept were 16% compared to 12% for rituximab. One year ACR20 responses for abatacept were 75% whereas for rituximab data reported for both one and two courses were 45% and 54% respectively.

Table 2: Cross study comparison of outcomes at year 1 using LTE data from ATTAIN and REFLEX (From BMS submission)

	ACR20 (%)	ACR50 (%)	ACR70 (%)	HAQ-DI (≥0.3) (%)	Mean DAS change	DAS Remission (%)	LDAS (%)
ATTAIN LTE	65.2	32.3	18.3	64.3	-2.33	13.9	24.2
ATTAIN LTE (Post hoc analysis)	73.75	40.00	25.00	NR	-2.59	15.71	28.6
REFLEX LTE (course 1)	51.0	34	14.0	55	-21	12	24
(course 2)	53.5%						

Source: Genovese et al 2008; Clinical Study Report Open Label IM101029, Cohen et al 2008
Post hoc analyses ACR20/50/70 (BMS data on file),
Post hoc analyses DAS/HAQ responses (BMS data on file)

BMS asks that these crucial differences between rituximab and abatacept long term efficacy and impact on disease progression are addressed within the analyses.

2.2.4 Unmet medical need

The TAR estimates that 27% of patients fail therapy with a first TNF-α inhibitor, which is the relevant patient population for this appraisal. The TAR also report that only 23% of this patient population are using rituximab (page 305, Section 10.11), despite it being the only recommended treatment option by NICE for this patient population. Despite the fact that sequential TNF-α inhibitor use is routine clinical practice, this very low uptake of rituximab indicates that rituximab is not suitable for all patients failing TNF-α inhibitors and highlights the need for abatacept in the RA treatment pathway.

BMS suggests that concerns regarding the relative efficacy and safety of rituximab may account for low uptake within the UK. BMS feels that the TAR does not fully explore the reasons that account for this observation. Further BMS asks the institute to take these concerns into account for its decision making.

2.3 Model inputs and outputs seem counter to expected clinical effectiveness

BMS believes that a number of assumptions, parameter choices and data inputs in the TAR are incorrect and bias the results, which appear counter-intuitive to expected clinical effectiveness. BMS were unable to explore the estimated impact of the specified parameters on the ICERs as the BRAM was not sufficiently transparent.

2.3.1 Comments on the BRAM

BMS is of the opinion that the model as delivered was not sufficiently transparent, e.g. assumptions used in the calculation of costs were not described. Therefore it is difficult to reproduce some of the findings in the assessment report such as the one way sensitivity analyses. Furthermore the concluding results from the BRAM conflict with those generated by the York Model in the ongoing appraisal of TNF-α inhibitors for PSA which uses a similar RA evidence base.

BMS asks the Institute to clarify how the industry-developed models and the York model can generate cost-effective results for sequential biologic use, whilst the BRAM does not.

2.3.2 Estimates of the efficacy of conventional DMARDs in late RA

There is a lack of evidence around the efficacy of conventional DMARDs in the targeted patient population, this is stated in the TAR (page 209, Section 6.3.1.2), and BMS also agree that this is the case. However in order to estimate an efficacy value of conventional DMARDs in late RA patients the independent group have taken the efficacy observed in conventional DMARDs derived from trials in early RA, and halved this value to obtain an efficacy value in late RA. This approach is fundamentally flawed, and should be treated as an assumption with a maximum amount of uncertainty.

In their response to NICE in February 2008, the BSR highlighted that data from the BSRBR abstract presented at EULAR 2007[ix] had not been considered in the appraisal leading to TA130. They highlighted that the evidence presented found that patients who stopped their TNF-α inhibitor and did not go onto another biologic had no change in their HAQ over one year. This group would have returned to non-biologic DMARDs, or pain-killers or some other palliative care, and showed no change. This is of importance as it reflects real world clinical practice with no placebo effect as seen in clinical trials. Patients who do not go onto another biological therapy have a HAQ that remains static over a year. The BSR also pointed out that that patients on DMARDs in the placebo arms of the abatacept and rituximab trials showed only a small HAQ improvement of 0.1 at 6 months, suggesting that they measure a placebo effect [x, xi].

BMS requests that data from the BSRBR be used to inform the effectiveness of conventional DMARDs in this appraisal.

2.3.3 Rituximab treatment intervals

The dosing regimen for rituximab is 1000mg by IV infusion followed by a second 1000mg infusion 2 weeks later. Subsequent infusions can be given at intervals of 16

weeks or greater (Rituximab SPC). The TAR model assumes a re-treatment interval of 8.7 months (page 213, Table 79) with the assumption that HAQ remains constant while on treatment.

The assumption that rituximab is administered every 8.7 months is unlikely to be the most optimal treatment regimen; with clinical practice in the UK recognising this issue and beginning to move towards 6 month re-treatment intervals. The greater the gap between infusions, the greater the probability of flares and disease progression: as seen in the clinical evidence for rituximab, which shows that between courses patients return to baseline HAQ levels[xii] . The maximum HAQ DI effect was seen at week 16, thereafter the HAQ value started to return to baseline. Based on this, re-treatment intervals could be potentially even shorter than 6 months.

It is notable that whilst the assessment of relative efficacy/safety for rituximab is based on MTC of 6 months efficacy, the model uses a re-treatment cycle of 8.7 months. Therefore the treatment cycles are not aligned with timing of the efficacy assessments.

While the TAR model has assumed that rituximab is administered every 8.7 months (i.e. assuming a flare-based regimen), it does not capture any change in HAQ resulting from the flares between treatments. As a consequence the efficacy of rituximab is over estimated.

BMS requests that the base case ICER reflects a 6 month retreatment interval in alignment with the clinical evidence and rituximab SPC. It is extremely important that the time between treatments is considered carefully. In addition it is important that the effect on HAQ change is captured in the BRAM in order to reflect what would actually occur in clinical practice. The TAR states '*Controlling symptoms of joint pain and stiffness, minimising loss of function, improving quality of life and reducing the risk of disability associated with joint damage and deformity are central objectives in the management of RA at all stages*' (page 29, Section 3.1.7). Disease management of patients on rituximab is likely to be most optimal with dosing intervals every 6 months.

BMS believes that the dosing interval of rituximab should be carefully considered with in the BRAM and requests the use of shorter 6 month dosing cycles in the base case with the view of avoiding disease flares.

2.3.4 Rituximab discontinuation

The probabilities for long term survival on treatment is estimated in the TAR model by fitting Weibull curves to available data. The estimated mean survival time ranges from 3.91 years for injectable gold (GST) to 15.53 years for azathioprine (AZA) (page 212, Table 77). The face validity of these estimates is questionable, and appear to over-estimate the probability of patients staying on therapy, particularly with regards to DMARDs and rituximab.

Specifically, the mean survival time for rituximab is estimated to be 11.31 years. This estimate is in contradiction with the observed withdrawal rate of 63% at week 48 in REFLEX RCT (page 101, Table 29). In addition, as the model assumes that the HAQ remains constant while a patient remains on rituximab therapy, the estimated 11 year mean time on rituximab would over-estimate the HAQ benefit received in rituximab treated patients.

BMS believes that the mean survival times presented in the TAR are not representative of clinical practice. Therefore, more representative, shorter, survival times (in line with the other biologics in this appraisal) should be applied for rituximab.

2.3.5 Cost assumptions

IV administration: The intravenous (IV) administration costs for all therapies is assumed to be the same. This assumption is not referenced or explained. The figure of £141.83 assumed for all IV administration was based on the cost for a half day infusion (page 212, Section 6.3.1.2). However the assumption that the cost for an infusion administration of abatacept, infliximab or rituximab are all equal is a mis-representation.

Abatacept is a short 30 minute infusion, with the cost of £141.83 per IV administration likely to be an overestimate. In addition the infusion times for rituximab and infliximab are 5 and 3 hours respectively, substantially longer than an abatacept infusion. This was noted in the ERG report for rituximab[xiii]. The price assumed for rituximab and infliximab IV administration should be reflective of their length. We propose that a cost of £284.73 would be a more appropriate cost[xiii].

BMS requests the length of IV administration should be considered within costs in order to accurately represent actual administration costs, and therefore higher administration costs should be applied for rituximab and infliximab.

Dosing of abatacept: The dose assumed for abatacept per patient in the TAR is 3 vials per patient. This figure is likely an over estimate of the number of vials required by the average patient.

Abatacept is a weight based drug:

Dose of ORENCIA		
Body Weight of Patient	Dose	Number of Vials
< 60kg	500mg	2
≥ 60kg ≤ 100kg	750mg	3
≥ 100kg	1000mg	4

The average dose per patient, based on GPRD weight distribution, is 2.85 vials (please see Table 3). The GPRD is a UK data base encompassing over 25,000 patients with rheumatoid arthritis.

Table 3: Weight (kg) of Patients with Rheumatoid Arthritis in the UK for calculation of abatacept vials.

Weight Range (kg)	Number of patients (N)	Percentage of patients	Vials	Mean number of vials of abatacept
60-100	17749	70%	3	2.09
< 60kg	5791	23%	2	0.45
>100kg	1947	7%	4	0.31
Total	25487			2.85

(General Practice Research Database (GPRD) Years 2000-2009. Inclusion criteria: Patients with mention of RA from 2000 on weight from 25kg-175kg at most recent measurement)

BMS believes that the TAR presents an overestimate of the cost of abatacept per patient, and therefore a reduced dose of abatacept should be used to inform the BRAM.

2.3.6 Infliximab dose increase

The TAR model does not include dose escalation for infliximab. According to the systematic review by Ariza-Ariza[xiv], the double blinded trial reported in Rahman[xv], and observational study of Agarwal[xvi] the majority of infliximab treated patients require dose escalation, either as dose increase and/or decreased treatment intervals. This will lead to increased infliximab drug costs.

BMS recommends that the impact of infliximab dose escalation should be explored within the BRAM.

2.3.7 Inclusion of toxicities

Toxicities as a consequence of drug therapy are associated with both higher costs and lower quality adjusted life years. We understand the technical issues associated with capturing adverse events/drug toxicities in the RA model. Each trial reports adverse events differently, they are difficult to compare and utility decrements are not easily available. However, NICE guidance recommends that adverse events be included, BMS is in agreement and therefore believes that toxicities should be captured within the base case ICER value.

BMS believes that the base case ICER should include adverse events and their associated disutilities.

2.4 References

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