

Rituximab in Combination with Corticosteroids for the Treatment of Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: A NICE Single Technology Appraisal

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Abstract As part of its single technology appraisal (STA) process, the National Institute for Health and Care Excellence (NICE) invited the manufacturer of rituximab (Roche Products) to submit evidence of the clinical and cost effectiveness of rituximab in combination with corticosteroids for treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). The School of Health and Related Research Technology Appraisal Group at the University of Sheffield was commissioned to act as the independent Evidence Review Group (ERG). The ERG produced a critical review of the evidence for the clinical and cost effectiveness of the technology, based upon the manufacturer's submission to NICE. The evidence was derived mainly from a double-blind, phase III, placebo-controlled trial of rituximab in patients with new or relapsed 'severe' AAV, which

compared a rituximab treatment regimen with an oral cyclophosphamide treatment regimen. Intravenous cyclophosphamide is also commonly used but was not included in the pivotal trial. The evidence showed that rituximab is noninferior to oral cyclophosphamide in terms of induction of remission in adults with AAV and de novo disease, and is superior to oral cyclophosphamide in terms of remission in adults who have relapsed once on cyclophosphamide. The ERG concluded that the results of the manufacturer's economic evaluation could not be considered robust, because of errors and because the full range of relevant treatment sequences were not modelled. The ERG amended the manufacturer's model and demonstrated that rituximab was likely to represent a cost-effective addition to the treatment sequence if given after cyclophosphamide treatment.

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Key Points

Rituximab given at a dose of $4 \times 375 \text{ mg/m}^2$ has an effectiveness profile similar to that of oral cyclophosphamide in terms of induction of remission in adults with anti-neutrophil cytoplasmic antibody-associated vasculitis and de novo disease, and it appears to be more effective than oral cyclophosphamide in terms of inducing remission in adults who have relapsed once on cyclophosphamide

Rituximab appears to represent a cost-effective addition to the treatment sequence at a cost-effectiveness threshold of £20,000 per quality-adjusted life-year gained, provided it is received only by patients who have exhausted their use of cyclophosphamide

The National Institute for Health and Care Excellence (NICE) Appraisal Committee recommended rituximab within its licensed indication. However, the recommendation was not as first-line treatment, except in patients who could not have cyclophosphamide

The evidence was restricted to adults with generalized, 'severe' anti-neutrophil cytoplasmic antibody-associated vasculitis, and longer-term data on safety are required

1 Introduction

Health technologies must be shown to be clinically effective and to represent a cost-effective use of National Health Service (NHS) resources to be recommended for use within the NHS in England and Wales. The National Institute for Health and Care Excellence (NICE) is an independent organization responsible for providing national guidance on promoting good health and preventing and treating ill health in priority areas with significant impact. The NICE single technology appraisal (STA) process usually covers new technologies soon after they have received UK marketing authorization and is specifically designed for appraisal of a single health technology within a single indication [1]. Within the STA process, the manufacturer provides NICE with a written submission, alongside a mathematical model that summarizes the manufacturer's estimates of the clinical and cost effectiveness of the technology. This submission is reviewed by the Evidence Review Group (ERG), an external academic organization

independent of NICE, with advice from clinical specialists, and an ERG report is produced. After consideration of the manufacturer's submission, the ERG report and testimony from experts and other stakeholders, the NICE Appraisal Committee formulates the preliminary guidance, the appraisal consultation document (ACD), which indicates the initial decision of the Appraisal Committee regarding the recommendation (or not) of the intervention. Stakeholders are then invited to comment on the submitted evidence and the ACD, after which a subsequent ACD may be produced or a final appraisal determination (FAD) is issued, which is open to appeal. An ACD is not produced when the intervention is recommended without restriction; in that instance, a FAD is produced directly.

This paper presents a summary of the ERG report [2] for the STA of rituximab (RTX) in combination with corticosteroids for the treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), and the subsequent development of the NICE guidance for the use of this drug in England and Wales. This is one in a series of STA summaries [3–25] being published in *Pharmacoeconomics*. Full details of all relevant appraisal documents (including the appraisal scope, ERG report, manufacturer and consultee submissions, FAD and comments from consultees) can be found on the NICE website [26].

2 The Decision Problem

RTX in combination with glucocorticoids is licensed for induction of remission in adults with severe, active granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis [WG]) and microscopic polyangiitis (MPA). GPA and MPA are the two major forms of AAV, a multisystem disorder characterized by inflammation and necrosis of small blood vessels and medium arteries [27]. GPA and MPA have comparable clinical features: left untreated, the natural history is that of a rapidly progressive, usually fatal disease [27]. In early studies of GPA, a mean survival of 5 months was observed, with 82 % of patients dying within 1 year [28].

AAV can manifest in many different ways, and patients may report different symptoms over time [29]. Common symptoms are often flu-like and include ear, nose and throat problems, such as hearing loss, otalgia, rhinorrhoea, otorrhoea, sinusitis, nasal crusting and recurrent otitis media [29]. The lungs and kidneys are often affected, as are the eyes and the nervous system [29]. Without treatment, AAV may rapidly lead to multiple organ failure and death, mainly caused by progressive renal failure and respiratory failure [28, 29]. However, modern treatment has significantly improved the prognosis of patients with AAV, and the disease is now typically chronic, with relapsing and

remitting phases. Despite this, the mortality rates remain approximately 2.6 times higher than those of an age-matched population [30]. The precise aetiology of AAV is unknown.

Disease onset usually occurs at 65–74 years of age, although it can occur at any age [31]. The combined average annual incidence of GPA and MPA in Norfolk, UK, between 1988 and 2010 was 17.2 per million people, and the prevalence at the end of 2008 was estimated to be 209 per million people [32]. The prevalence is generally higher in men, but the disease more commonly develops at a younger age in women [33].

It is important to note that RTX in combination with glucocorticoids is licensed for use in patients with severe GPA and MPA. In the manufacturer's submission, it was estimated that one third of patients have severe disease, but the definition of severity is not clear cut. The European Vasculitis Study Group and British Society for Rheumatology guidelines categorize severe AAV as disease including renal or other vital organ failure, with a serum creatinine level of greater than 500 $\mu\text{mol/L}$ (5.6 mg/dL) [27, 34]. However, the pivotal trial of RTX in combination with glucocorticoids, the Rituximab in ANCA-Associated Vasculitis (RAVE) trial, excluded patients with severe disease who required mechanical ventilation because of alveolar haemorrhage and patients with a serum creatinine level of greater than 4.0 mg/dL attributed to underlying AAV disease [35]. Under these guidelines, the RAVE definition of severe disease appears closer to what is classified as 'generalized' disease, where vital organ function is threatened and the serum creatinine level is less than 500 $\mu\text{mol/L}$ (5.6 mg/dL). Because patients with a serum creatinine level of greater than 500 $\mu\text{mol/L}$ were excluded from the RAVE trial, conclusions could not be reached regarding the effectiveness of RTX in that group. The ERG referred to the population included in the RAVE trial as those with generalized, 'severe' disease but recognized that according to other definitions, this population may be classed as having generalized disease, and that patients with the most severe disease were excluded from this definition.

2.1 Current Treatment

Cyclophosphamide (CYC) in combination with glucocorticoids (usually prednisolone) represents the mainstay of remission induction treatment for generalized and severe AAV [34]. There is currently no universal agreement as to whether treatment should be with oral CYC (2 mg/kg per day, for up to 6 months) or intravenous pulses following the CYCLOPS regimen (15 mg/kg every 2 weeks for three pulses, followed by the same dose administered at 3-week intervals, for up to 6 months). Typically, treatment with intravenous pulses is thought to lead to a lower risk of side

effects but may lead to a higher risk of relapse [34]. While CYC represents the standard of care for patients with moderate or severe AAV, other treatments, such as mycophenolate mofetil or methotrexate, may be used in patients who are intolerant of CYC or who do not wish to receive it. Those treatments have been investigated in generally less severely affected AAV patients [36, 37], and their effectiveness in patients with severe AAV is unknown.

Once patients have been induced into remission, they generally receive remission maintenance therapy with a combination of low-dose glucocorticoid therapy and azathioprine (2 mg/kg per day for at least 24 months) [34]. Leflunomide (20–30 mg per day) or methotrexate (20–25 mg/kg per week) are also sometimes used for remission maintenance [34].

The introduction of CYC treatment in the 1970s resulted in a significant reduction in mortality associated with the disease. However, considerable morbidity associated with both the disease and the treatment remains. In patients who are successfully induced into remission, up to 50 % will relapse within 5 years, and each relapse carries a risk of subsequent critical organ damage [27, 28]. Therapies used to treat AAV are themselves also associated with substantial toxicities, which frequently result in severe and permanent patient morbidity and mortality [38]. In particular, treating AAV with CYC can lead to opportunistic infections, bone marrow suppression, hemorrhagic cystitis, infertility and cancer—particularly haematopoietic and bladder malignancies [39, 40]. There are also substantial morbidities associated with a repeated and prolonged course of glucocorticoids. Infections are a well-known complication of glucocorticoids, especially in the treatment of vasculitis [41]. Other known complications of steroid therapy include new-onset diabetes, osteoporosis, avascular necrosis, peptic ulcers and cataracts [42].

RTX, a genetically engineered chimeric mouse/human monoclonal antibody, received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use in March 2013 for the indications of GPA and MPA [43]. The indicated RTX dose is 375 mg/ m^2 , administered as an intravenous infusion once per week for 4 weeks, although a $2 \times 1,000$ mg dose administered on day 1 and day 15 of the treatment cycle is widely used off-label in the UK for AAV. RTX should be combined with glucocorticoid treatment [44].

NICE issued a final scope to appraise the clinical effectiveness and cost effectiveness of RTX for treatment of patients with AAV. The decision problem addressed in the manufacturer's submission differed slightly from the NICE scope, because of the slightly more restrictive nature of the drug's indication. The appraisal considered treatment with RTX in combination with corticosteroids for

induction of remission in patients with severe AAV (MPA or GPA), compared with alternative treatment strategies. The outcome measures that were included were mortality, the remission rate and the duration of remission, relapse rates, the cumulative dose of immunosuppressants, adverse events (AEs) and health-related quality of life (HRQoL). An economic evaluation expressing the cost effectiveness of RTX in terms of an incremental cost per quality-adjusted life-year (QALY) gained was submitted to NICE by the manufacturer.

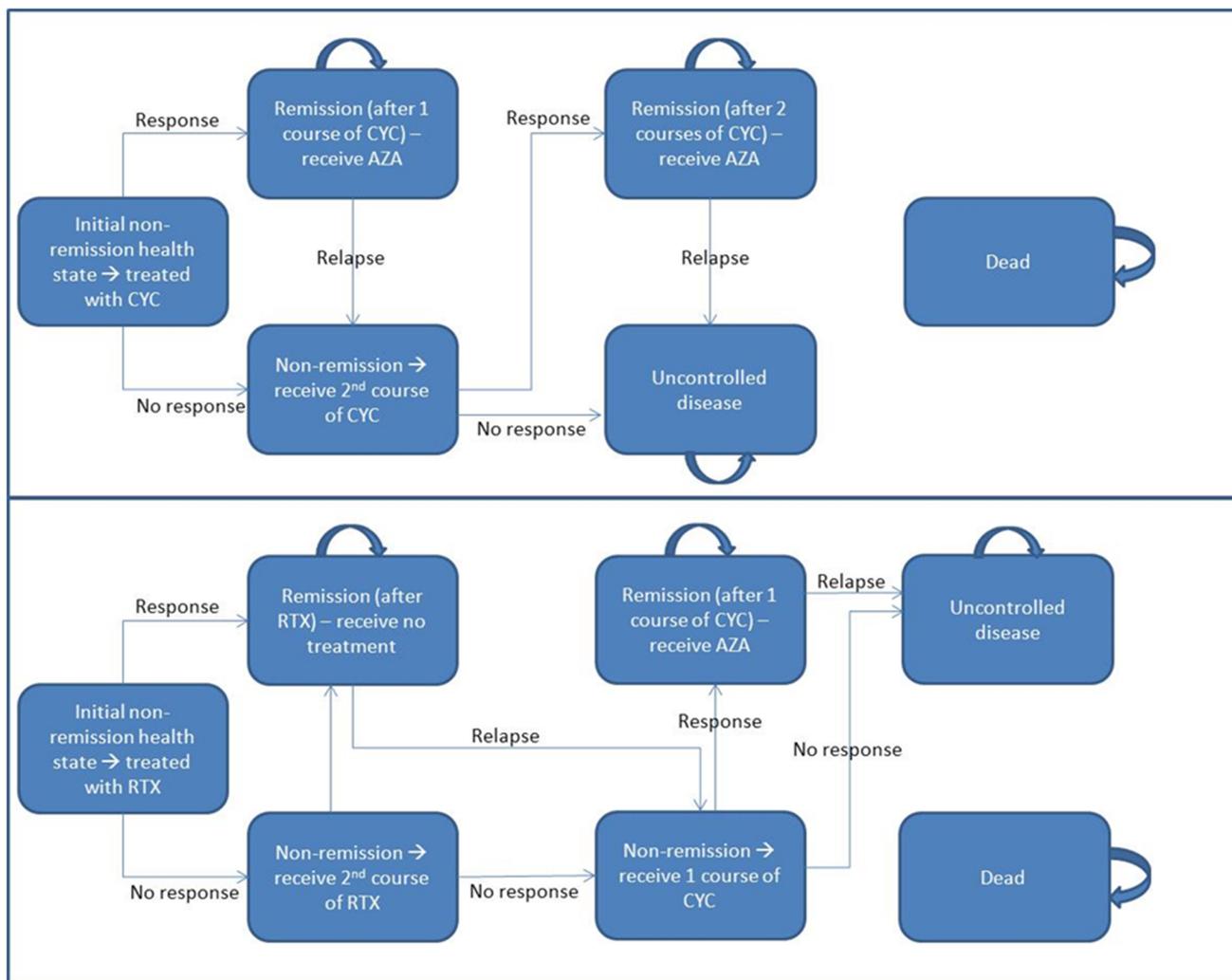
3 The Independent Evidence Review Group Review

The ERG report comprised a critical review of the clinical and cost-effectiveness evidence presented in the manufacturer’s submission, assessing the appropriateness of the manufacturer’s interpretation and analysis of the evidence.

In accordance with the process for STAs, the ERG had the opportunity to seek clarification on specific points in the manufacturer’s submission, which resulted in the manufacturer providing additional information. The ERG also modified the manufacturer’s model to examine the impact of altering certain key assumptions on the model results.

3.1 Clinical Evidence Provided By the Manufacturer

The clinical effectiveness evidence in the submission was based predominantly on data from two randomized, controlled trials. RAVE was a multicentre, randomized, placebo-controlled, double-blind, double-dummy, noninferiority trial, which compared RTX (375 mg/m² per week for 4 weeks) and CYC (2 mg/kg per day) for induction of remission in 197 patients with new or relapsed severe MPA or GPA [35]. The Randomized Trial of Rituximab



Note: transition to death can occur from any state.

Fig. 1 Manufacturer’s model structure (drawn by the Evidence Review Group). AZA azathioprine, CYC cyclophosphamide, RTX rituximab

Versus Cyclophosphamide in ANCA-Associated Vasculitis (RITUXVAS) was a phase II, open-label, randomized, controlled, prospective study, which evaluated RTX (375 mg/m² per week for 4 weeks) combined with two intravenous doses of CYC (15 mg/kg given with the first and third RTX doses), compared with the CYCLOPS intravenous CYC regimen (15 mg/kg for 3–6 months, 6–10 doses in total) in 44 patients with newly diagnosed severe AAV [45]. In both studies, patients in the CYC control group received azathioprine as remission maintenance therapy, whereas patients in the RTX group received no remission maintenance therapy. The manufacturer gave precedence to data from the RAVE trial because this reflected the regimen sanctioned in the market authorization, presenting data from RITUXVAS as supporting evidence.

In RAVE, the primary endpoint was remission of disease without use of prednisone at 6 months; glucocorticoids were tapered off, such that all patients who had remission without disease flares had discontinued glucocorticoids by 5 months. Remission was signified by a Birmingham Vasculitis Activity Score for WG (BVAS/WG) [46] of 0. Secondary endpoints included the rates of disease flares, a BVAS/WG of 0 with less than 10 mg per day of prednisone use, the cumulative glucocorticoid dose, rates of AEs, and HRQoL measured using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) [47]. A disease flare was defined as an increase in the BVAS/WG of ≥ 1 point.

The manufacturer reported the results of the RAVE trial, which are published elsewhere [35]. The trial demonstrated noninferiority of RTX compared with CYC because the lower bound of the 95 % confidence interval for the primary endpoint was higher than the pre-determined noninferiority margin of -20% ($p < 0.001$). Sixty-three patients (63.6 %) in the RTX group achieved complete remission, compared with 52 patients (53.1 %) in the CYC group, an absolute difference of 10.6 % (95 % confidence interval [CI] -3.2 to 24.3 %, $p = 0.132$), hence a statistically significant advantage associated with RTX was not observed. Statistically significant changes in the secondary efficacy endpoints measured in RAVE were not observed, other than in exploratory subgroup analyses [35]. Exploratory subgroup analysis of complete remission in newly diagnosed patients gave an absolute difference of -4.2% (95 % CI -23.6 to 15.3 %, $p = 0.673$) in favour of CYC (60.4 % in the RTX group compared with 64.6% in the CYC group). A similar analysis in patients with recurrent disease gave a statistically significant absolute difference of 24.7 % (95 % CI 5.8 to 43.6 %, $p = 0.013$) in favour of RTX (66.7 % in the RTX group compared with 42.0 % in the CYC group).

In RITUXVAS, the primary endpoints were sustained remission (defined as an absence of disease activity

[BVAS = 0] for at least 6 months) and the rates of severe AEs at 12 months. Sustained remission occurred in 25 of 33 patients in the RTX group (76 %) and in 9 of 11 patients in the control group (82 %). The absolute difference in sustained remission with RTX as compared with CYC was -6 percentage points (95 % CI -33 to 21, $p = 0.68$). Among the patients who remained alive at 12 months, 93 % of the patients in the RTX group and 90 % of those in the control group had sustained remission ($p = 0.80$). There were no significant differences between the treatment arms for any of the secondary efficacy outcomes, such as the median time to remission, the median BVAS and the prednisone doses.

The manufacturer submitted evidence on the safety of RTX, focussed on 18 months of data collected in RAVE. There were no reported significant differences between the treatment groups in almost all AE outcomes, but there were some notable disparities regarding leucopenia and malignancies. More patients in the CYC group than in the RTX group (32 [33 %] versus 22 [22 %], $p = 0.01$) had one or more of the predefined selected AEs (including death, malignant conditions, grade 2 or higher leucopenia or thrombocytopenia, grade 3 or higher infections, drug-induced cystitis, venous thromboembolic events, stroke, hospitalizations and infusion reactions that contraindicated further infusions), but more episodes of grade 2 or higher leucopenia in the control group (10 versus 3) accounted for most of this difference. Malignant conditions developed in 7 patients after 6 months: 6 of 124 patients (5 %) who were exposed to RTX at any point during the trial (including after 6 months), as compared with 1 of 73 patients (1 %) without exposure to RTX ($p = 0.26$).

The manufacturer presented limited safety results from the RITUXVAS trial, but the ERG noted that a total of 31 severe AEs had occurred in 14 of the 33 patients in the RTX group (42 %), and 12 severe AEs had occurred in 4 of the 11 patients in the control group (36 %). The incidence rates of severe AEs did not differ significantly between the groups ($p = 0.77$). Six of the 33 patients in the RTX group (18 %) and 2 of the 11 patients in the control group (18 %) died ($p = 1.00$). The causes of death were infections (in 3 patients in the RTX group and in 1 patient in the control group), cardiovascular disease (in 1 patient in the RTX group and in 1 patient in the control group), and complications of end-stage renal failure (in 2 patients in the RTX group).

3.1.1 Critique of Clinical Evidence and Interpretation

The ERG noted that the manufacturer identified the two randomized, controlled trials comparing RTX with CYC as induction therapy for adults with what can be described as generalized, severe AAV. The manufacturer did not conduct a meta-analysis or synthesis, and thus the results were

reported as they were in the relevant published studies. The ERG considered that evidence from RAVE suggests that RTX given at a dose of $4 \times 375 \text{ mg/m}^2$ is noninferior to oral CYC in terms of induction of remission in adults with AAV and de novo disease, and is superior to oral CYC in terms of remission in adults with generalized, severe AAV who have relapsed one time on CYC, on the basis of the exploratory subgroup analysis. Evidence from RITUXVAS suggests that RTX given at a dose of $4 \times 375 \text{ mg/m}^2$ plus 2–3 intravenous pulses of CYC is noninferior to intravenous pulse CYC in terms of remission in adults with generalized, severe AAV and de novo disease. The ERG stated that the evidence relates only to induction of remission with these specific regimens in adult populations with generalized, severe AAV, and only evidence on the $4 \times 375 \text{ mg/m}^2$ RTX dose was submitted by the manufacturer, rather than the $2 \times 1 \text{ mg}$ dose, which the manufacturer recognized as the most widely used off-label dose in the UK for AAV, and which represents a smaller overall dose. No evidence was presented on the efficacy or safety of RTX in adults intolerant of CYC, with contraindications against CYC or with mild AAV; in children; or for use of this regimen as maintenance therapy or for relapse after RTX.

The ERG applied the Cochrane risk-of-bias tool to appraise the RAVE and RITUXVAS trials [48], as well as the noninferiority trial extension of the CONSORT statement for the RAVE trial [49]. In general, both trials were considered to be at low risk of bias, although there was a high risk of performance and detection bias in the RITUXVAS trial because of its open-label nature. In addition, the ERG had concerns over the populations, interventions, comparators and outcomes included in the studies, with regard to their usefulness for informing UK recommendations. The RAVE trial considered relatively young adults only (the mean ages were 54 and 51 years in the RTX and CYC treatment arms, respectively) with moderately severe AAV and either de novo disease or following relapse after CYC. The trial did not include adults with severe renal impairment or life-threatening pulmonary haemorrhage, those who had contraindications against CYC or those who were CYC refractory. It is uncertain if RTX alone will demonstrate equal efficacy and safety in other adult populations or children. The RITUXVAS trial considered a much older population (with median ages of 68 and 67 years in the RTX and control treatment arms, respectively) with severe renal impairment, but both arms of the trial included CYC treatment. In the absence of a head-to-head trial, it is uncertain whether RTX combined with CYC is inferior, equivalent or superior to RTX alone.

The ERG noted that the manufacturer's submission focused upon oral CYC as a comparator. It is uncertain whether RTX without CYC would demonstrate equal efficacy and safety if it were compared with intravenous

CYC. The ERG received clinical expert advice that intravenous CYC is used more often in expert clinical practice, and this might have a better safety profile [50, 51]. In addition, the ERG noted that no evidence was submitted on the comparability of RTX with other potentially relevant comparators specified in the NICE scope, such as mycophenolate mofetil and methotrexate. The ERG noted that some evidence on these interventions—such as the NORAM trial [36, 52] and the MYCYC trial [37]—is available, which could have informed an indirect comparison; however, the manufacturer's submission did not contain such an analysis.

The ERG considered the lack of longer-term data on efficacy and safety to be a significant concern. RAVE and RITUXVAS did not monitor outcomes beyond 18 months, and primary endpoints were measured at 6 and 12 months, respectively. The duration of remission was not reported as an outcome in either trial, yet it has important implications from both a clinical perspective and an economic perspective. Regarding safety, RAVE provided evidence that RTX with concurrent glucocorticoid therapy has a safety profile similar to that of oral CYC with concurrent glucocorticoid therapy, and the RITUXVAS trial suggested that RTX plus intravenous pulse CYC with concurrent glucocorticoid therapy has a safety profile similar to that of intravenous pulse CYC with concurrent glucocorticoid therapy. However, the safety data were collected over relatively short time periods (maximum 18 months), and much of the observed toxicity was related to steroids rather than to RTX or CYC. Thus it is not possible to draw conclusions specifically comparing the safety of RTX and CYC. In addition, part of the hypothesis for the RITUXVAS trial was the potential for improved safety through treatment with RTX rather than CYC. This was not demonstrated in RAVE or RITUXVAS. One reason suggested for the comparable rather than superior safety profile of RTX in the RITUXVAS and RAVE trials relates to the short durations of these trials [35]. A further reason might be that the high cumulative dose of RTX in both trials [53–55] caused AEs. The ERG concluded that longer-duration trials with more comparable groups are needed—particularly to assess malignancies and fertility outcomes—and patients who have previously received CYC need to be included in such trials.

3.2 Cost-Effectiveness Evidence

The manufacturer conducted a systematic review on the cost effectiveness of one or more interventions for patients with AAV. No suitable studies were found, and the manufacturer therefore submitted a de novo model-based economic evaluation, which assessed the cost effectiveness of different treatment strategies for patients with AAV.

Separate analyses were undertaken for patients with newly diagnosed AAV, people with recurrent AAV, all patients (including both newly diagnosed and relapsed patients) and patients intolerant of CYC. The model was constructed using a cohort Markov approach with a 6-month cycle length. Patients entered the model at an age of 52.8 years, based upon the mean age at baseline in the RAVE trial. A lifetime time horizon was modelled. Health states were included for remission, non-remission, uncontrolled disease and death (Fig. 1). The structure of the model is outlined in the ERG report [2].

Model parameter values for response rates were primarily taken from the RAVE trial. However, the model incorporated various treatment sequences, including two courses of CYC and RTX for selected patients, and for some sequences, data were not available from RAVE, and so assumptions were made. For each subgroup that was modelled, the relevant response rate was taken from RAVE where possible—RAVE provided data on response rates for CYC and RTX in the treatment-naïve subgroup, the recurrent-disease subgroup and all patients. For the recurrent-disease subgroup, no data on remission rates associated with a second course of CYC could be derived from the RAVE trial, and no data were available on the remission rates associated with a second course of RTX. The manufacturer assumed reduced response rates for these parameters.

The relapse rates used in the manufacturer's model were derived from the RAVE trial. Exponential models were fitted to flare data from patients who had experienced remission at 6 months, in order to estimate the time-to-event for relapse. The same relapse rate was applied after different courses of treatment within each subgroup analysis, but different relapse rates were used in each subgroup.

Age- and sex-specific mortality risks were based upon UK life tables [56], adjusted according to the age and gender distributions in the RAVE trial and a published standardized mortality ratio (SMR) comparing a general population with an AAV population [57]. The AAV SMR was applied directly to the non-remission health state, and the SMR was arbitrarily altered by $\pm 10\%$ to reflect mortality in the remission and uncontrolled-disease states.

Utility scores were based upon UK evidence for the general population [58], adjusted according to the RAVE trial demographics and weighted for remission (weight = 0.98) and non-remission (weight = 0.88) health states, according to SF-36 data (subsequently transformed into EQ-5D utility scores) collected from the RAVE trial. An additional utility decrement was applied to patients in the uncontrolled-disease health state (weight = 0.79), assuming that the difference between the non-remission and uncontrolled-disease health states is the same as the difference between the remission and non-remission health states. Further decrements were made according to the

probability of experiencing AEs in each health state. The AE rates were based upon data from RAVE and included anaemia, leucopenia, deep vein thrombosis, dyspnoea, diarrhoea and pneumonia. The costs of managing these AEs were based upon relevant costs taken from the NHS Trusts reference costs schedules for 2009–2010 [59].

Drug acquisition costs were taken from British National Formulary No. 64 [60] and were based upon licensed doses, apart from glucocorticoid costs, which were based upon the average dose used in the RAVE trial. Administration costs for RTX and intravenous CYC were assumed to be equal and were based upon a previous economic evaluation of infliximab [61]. Monitoring costs were included for oral CYC and for patients receiving azathioprine maintenance therapy. Regular outpatient appointments with relevant consultant specialists were also assumed, the frequency of which differed across health states—notably, once patients were in the uncontrolled-disease health state, it was assumed that they attended one specialist palliative care outpatient appointment every 1.5 weeks for all remaining years of life. The costs of these appointments were valued using NHS reference costs.

The results from the manufacturer's base-case analysis are shown in Table 1. These results represent those provided by the manufacturer after it responded to clarifications requested by the ERG, as some amendments were made to the economic model. They indicate that the RTX treatment strategy results in an incremental cost-effectiveness ratio (ICER) of £8,544 per QALY gained for all patients, but in the treatment-naïve and recurrent-disease subgroups, the ICERs were £55,175 per QALY gained and £43,003 per QALY gained, respectively. In the CYC-intolerant subgroup analysis, RTX dominated the comparator, which was deemed to represent best supportive care. The manufacturer undertook probabilistic sensitivity analysis but did not report the probabilistic ICERs. For the all-patients analysis, the manufacturer reported that the probabilities of the RTX treatment sequence being cost effective, compared with the CYC treatment sequence, were 61.7% and 64.6% for cost-effectiveness thresholds of £20,000 and £30,000 per QALY gained, respectively. The manufacturer presented several deterministic sensitivity analyses and found that the results of the all-patients analysis were relatively insensitive to variations in the tested model input parameters, with the exception of (i) the CYC remission rate; (ii) the uncontrolled-disease utility; (iii) the frequency of consultant visits in each health state; and (iv) the reference cost applied to the consultant appointments in the uncontrolled-disease health state. In addition, several structural sensitivity analyses were presented, testing different numbers of CYC and RTX courses for different patient groups. As would be expected, the results were highly sensitive to these structural assumptions.

Table 1 Headline cost-effectiveness results presented by the manufacturer

Option	QALYs	Cost	Incremental QALYs	Incremental cost	Incremental cost per QALY gained
<i>All patients</i>					
CYC	8.03	£95,819	–	–	–
RTX	8.19	£97,210	0.1628	£1,391	£8,543.69
<i>Treatment-naïve subgroup</i>					
CYC	8.45	£81,327	–	–	–
RTX	8.53	£86,021	0.0851	£4,694	£55,174.92
<i>Recurrent-disease subgroup</i>					
CYC	7.89	£100,699	–	–	–
RTX	7.98	£104,550	0.0896	£3,851	£43,003.05
<i>CYC-intolerant subgroup</i>					
BSC	7.49	£102,721	–	–	–
RTX	8.02	£97,836	0.5386	–£4,885	RTX dominates

BSC best supportive care, CYC cyclophosphamide, QALY quality-adjusted life-year, RTX rituximab

3.2.1 Critique of the Cost-Effectiveness Evidence and Interpretation

The ERG had serious concerns with the manufacturer's economic model. These included technical errors, such as minor mistakes in the estimation of mortality rates, some inaccuracies in the estimation of standard errors for relapse rates and cost parameters, and a failure to characterize uncertainty around all uncertain parameters. In addition, some parameter value estimates were inappropriate, and some structural assumptions were implausible [2]. The ERG took the view that the manufacturer's economic model could not be considered reliable or robust.

The most important issues highlighted by the ERG surrounded the treatment sequences modelled by the manufacturer, and the definition of the uncontrolled-disease health state. Clinical advice received by the ERG suggested that a lifetime cumulative dose of 20–30 g of CYC should not be exceeded. Typically, this represents 1–2 courses of oral CYC or 2–3 courses of intravenous CYC. Hence, the treatment sequence that was modelled should reflect the treatment history of the patient, and thus it should differ for the different subgroups that were modelled. For treatment-naïve patients, the ERG suggested that two courses of CYC were plausible, whereas for patients with recurrent disease, only one course of CYC was likely to be plausible. In addition, the manufacturer considered treatment sequences only in which RTX was given first-line; the ERG stated that there was no reason to assume that this should be the case—it was relevant to consider its cost effectiveness when it was given both before and after CYC. Finally, the ERG disagreed with the manufacturer's assumption that patients who did not respond to an initial course of RTX would immediately receive a second course of RTX—the ERG believed it was

more appropriate to include only one course of RTX within the modelled treatment sequences.

The ERG's clinical advisors suggested that the uncontrolled-disease health state modelled by the manufacturer was unrealistic, and that a more common health state is one in which the most effective induction treatments have been used but some other treatment or combination of treatments is utilized in order to afford patients a reasonable level of disease control. This may be described as low-grade 'grumbling' disease [62]. The ERG noted that the level of HRQoL associated with such a health state was unlikely to be substantially worse than that experienced in the non-remission health state. Also, although treatment would be received in this state, the manufacturer's assumption that specialist palliative care is received at hospital outpatient appointments once every 1.5 weeks for all remaining years of life appeared to be a substantial overestimate. The ERG's clinical advisors suggested it would be more appropriate to assume that patients in this health state would continue to receive maintenance treatment, and that outpatient appointments would occur each month initially, followed by less frequent visits over time. In the base-case version of the manufacturer's model, patients in the CYC group spent 70.7 % of their mean life expectancy in the uncontrolled-disease health state, compared with 63.2 % in the RTX group. The cost savings and utility benefits associated with RTX due to this were likely to be substantially overestimated.

3.3 Additional Work Undertaken By the Evidence Review Group

The ERG amended the identified technical errors in the manufacturer's model, amended several parameter value estimates to better reflect reality (particularly for the

Table 2 Cost-effectiveness results of the Evidence Review Group's preferred analyses

Strategy	Total cost	Total QALYs	Incremental QALYs	Incremental cost	ICER
<i>All patients</i>					
CYC → CYC → BSC	£18,926.57	8.5810	–	–	–
CYC → CYC → RTX → BSC	£22,820.93	8.9035	0.32	£3,894.36	£12,075.42
CYC → RTX → CYC → BSC	£23,176.00	8.9086	0.0051	£355.07	£69,709.63
RTX → CYC → CYC → BSC	£23,755.25	8.9131	0.0045	£579.25	£127,456.12
<i>Treatment-naïve subgroup</i>					
CYC → CYC → BSC	£18,645.81	8.6491	–	–	–
CYC → CYC → RTX → BSC	£22,429.08	8.9435	0.29	£3,783.27	£12,850.76
CYC → RTX → CYC → BSC	£22,793.54	8.9480	0.0045	£364.46	£81,603.50
RTX → CYC → CYC → BSC	£23,636.83	8.9507	0.0027	£843.29	£317,037.96
<i>Recurrent-disease subgroup (eligible for additional CYC treatment)</i>					
CYC → BSC	£17,593.48	8.2548	–	–	–
CYC → RTX → BSC	£22,295.52	8.6773	0.4225	£4,702.04	£11,129.22
RTX → CYC → BSC	£22,620.65	8.6836	0.0063	£325.14	£51,841.87
<i>Recurrent-disease subgroup (ineligible for additional CYC treatment)</i>					
BSC	£15,747.48	7.9379	–	–	–
RTX → BSC	£21,132.39	8.4412	0.5033	£5,384.90	£10,699.45
<i>CYC-intolerant subgroup</i>					
BSC	£15,747.48	7.9379	–	–	–
RTX → BSC	£21,184.13	8.4200	0.48	£5,436.64	£11,277.29

BSC best supportive care, CYC cyclophosphamide, ICER incremental cost-effectiveness ratio, QALY quality-adjusted life-year, RTX rituximab

uncontrolled-disease health state) and amended the modelled treatment sequences to allow for fully incremental analyses of introducing RTX into the treatment sequence either before or after CYC. The cost-effectiveness results for all patients and for the treatment-naïve, recurrent-disease and CYC-intolerant subgroups are shown in Table 2.

The additional work undertaken by the ERG indicated that including RTX in the treatment sequence increases health benefits, compared with the current standard treatment sequence (that is, a treatment sequence that does not include RTX). In the analyses for all patients, the treatment-naïve subgroup and the recurrent-disease subgroup (for patients who are eligible for further CYC treatment), the ICER associated with adding RTX after CYC treatment had been exhausted was in the range of £11,129 to £12,851 per QALY gained. However, in each of these analyses, the ICERs associated with administering RTX earlier in the treatment sequence were greater than £50,000 per QALY gained—sometimes substantially so. It is particularly important to note the substantial reductions in total lifetime costs resulting from the ERG's amended model, compared with the manufacturer's original model (the manufacturer estimated lifetime costs in the region of £100,000 per patient, compared with the ERG's estimates of around £20,000). This is almost entirely due to the apparent substantial overestimation of costs associated with the

uncontrolled-disease health state in the manufacturer's original model.

In the recurrent-disease subgroup (for patients who are ineligible for further CYC treatment) and in the CYC-intolerant subgroup, the ICER associated with treating patients with RTX rather than best supportive care was in the range of £10,699 to £11,277 per QALY gained. In these scenarios (and in all other scenarios), best supportive care represents continued treatment to maintain patients in a state of low-grade 'grumbling' disease. The ERG noted that while these analyses were useful, they were limited and may represent underestimates of the true ICER because relevant comparators such as mycophenolate mofetil were not included in the model.

3.4 Conclusions of the Evidence Review Group Report

On the basis of the clinical evidence provided in the manufacturer's submission, RTX given at a dose of $4 \times 375 \text{ mg/m}^2$ has an effectiveness and safety profile similar to that of oral CYC in terms of induction of remission in adults with AAV and de novo disease. For patients who have relapsed once on CYC, RTX appears to be more effective than oral CYC in terms of inducing remission in adults with generalized, severe AAV. However, the submitted evidence was limited because it

included only one trial that incorporated the licensed regimen, and it did not include evidence on long-term safety and effectiveness.

The ERG could not offer robust estimates of the likely cost effectiveness of RTX based upon the original version of the manufacturer's economic model. Several amendments had to be made. On the basis of the ERG's amended version of the manufacturer's economic model, RTX appeared to represent a cost-effective addition to the treatment sequence at a cost-effectiveness threshold of £20,000 per QALY gained, provided it was received only by patients who had exhausted their use of CYC.

4 Key Methodological Issues

Several important methodological issues were highlighted during the appraisal. The manufacturer made implausible assumptions regarding the resource use associated with different health states included in the model, and did not model all relevant treatment sequences. In addition, the ERG questioned the methodological approach taken by the manufacturer to estimate relapse rates: the manufacturer used summary data from the RAVE trial to fit an exponential model to represent the time to relapse in the RTX and CYC groups, implying an assumption that the relapse rate was constant over time. Proportional hazards were assumed even though Kaplan–Meier curves for the two treatment groups crossed, alternative parametric models (such as Weibull, Gompertz, log-normal, log-logistic, generalized gamma) were not considered, and the use of summary data rather than patient-level data precluded the use of model fit statistics such as Akaike's information criterion and the Bayesian information criterion. Also, the ERG suggested that the economic model could have been made more appropriate through inclusion of an additional health state for patients who experience a partial response to treatment.

The methodological issues that had the largest impacts on the results and interpretation of the economic evaluation concerned the modelling of the disease and treatment pathway for patients with AAV. The manufacturer did not consider scenarios in which RTX could be given after CYC in the treatment pathway; this substantially affected the cost-effectiveness results. This reflects the importance of incorporating all relevant treatment sequences in economic evaluations where multiple lines of treatment are possible. In addition, the manufacturer modelled a disease pathway in which patients transited into an uncontrolled-disease health state once they had exhausted RTX or CYC treatment; this health state was characterized by low HRQoL and very high costs. Clinical advice received by the ERG suggested that modern treatment practices mean that in

reality, patients rarely enter such a health state—instead, a myriad of alternative therapies can be used to maintain higher HRQoL, at lower cost. Re-defining the uncontrolled-disease health state to reflect this reduced the total costs estimated by the economic model by approximately 80 % and substantially altered the cost-effectiveness results. This reflects the importance of ensuring that modelled health states adequately represent the burden of disease experienced by patients.

5 National Institute for Health and Care Excellence Guidance

In July 2013, on the basis of the evidence available (including verbal testimony from invited clinical experts and patient representatives), the Appraisal Committee recommended that NICE request further clarification from the manufacturer, which should be made available for a second Appraisal Committee meeting. In the meantime, the Appraisal Committee was of a mind not to recommend RTX for inducing remission in adults with AAV. The requested information concerned the definition of severe disease, longer-term effectiveness and safety data, and information about UK clinical practice relating to the maximum lifetime cumulative CYC dose. The Appraisal Committee also requested that the manufacturer make several amendments to the economic model in line with those suggested by the ERG.

In response to this, the manufacturer provided some additional information: no further data beyond 18 months were available from the RAVE trial, but the manufacturer provided information on the long-term safety of RTX when used as a treatment for rheumatoid arthritis. The manufacturer clarified its definition of severe disease and—in line with draft guidelines from the British Society of Rheumatology—stated that the maximum lifetime cumulative dose of CYC was 25 g. An updated economic model was submitted by the manufacturer and subsequently reviewed by the ERG.

In September 2013, the Appraisal Committee produced preliminary advice that RTX, in combination with glucocorticoids, was recommended as an option for inducing remission in adults with AAV only if further CYC treatment would exceed the maximum cumulative CYC dose. A recommendation was not made for patients intolerant of CYC. Following further consultation, in January 2014, NICE issued its final guidance on the use of RTX for AAV. RTX, in combination with glucocorticoids, was recommended as an option for inducing remission in adults with AAV only if further CYC treatment would exceed the maximum lifetime cumulative CYC dose; CYC is contraindicated or not tolerated; the person has not completed

their family and treatment with CYC may materially affect their fertility; the disease has remained active or has progressed despite a course of CYC lasting 3–6 months; or the person has had uroepithelial malignancy [63].

5.1 Consideration of Clinical And Cost-Effectiveness Issues

This section discusses the key issues considered by the Appraisal Committee. The full list can be found in the Appraisal Committee's FAD [63].

5.1.1 Treatment Sequences

The Appraisal Committee considered the treatment sequences included in the manufacturer's original economic analysis to be incomplete and unsuitable because they did not enable fully incremental analyses for all populations of interest. The Appraisal Committee agreed that the treatment sequences used by the ERG in its exploratory analysis were more comprehensive and more appropriate. It was noted that the manufacturer's updated economic analysis again did not consider all relevant treatment sequences.

The Appraisal Committee concluded that there was uncertainty about the appropriate comparator for people who cannot have CYC. In the original analyses undertaken by the manufacturer and the ERG, best supportive care was incorporated as the comparator. In response to consultation, the manufacturer provided an updated economic analysis, which incorporated mycophenolate mofetil and methotrexate as comparators. Clinical specialists advised the Appraisal Committee that neither of these drugs represents a treatment of choice for people with severe disease, while the manufacturer stated that clinical specialists whom it consulted advised that these would be used in people who cannot have CYC. The Appraisal Committee noted that there was substantial uncertainty around the economic analysis presented for this subgroup of patients, and that a comparison with mycophenolate mofetil or methotrexate yielded an ICER of £60,600 per QALY gained (although this fell to £26,400 per QALY gained in the analyses provided by the ERG), whereas a comparison with best supportive care resulted in an ICER of £11,300 per QALY gained. The Appraisal Committee concluded that, on balance, the ICER was likely to be lower than £30,000 per QALY gained.

5.1.2 Safety

The Appraisal Committee recognized that the risk of long-term toxicity increases with the cumulative dose of CYC and that this should not exceed 25 g. However, the

Appraisal Committee concluded that the safety profiles of CYC and RTX were similar in the short term, and that there was uncertainty about any long-term safety benefits associated with RTX because of a lack of data from patients with AAV.

5.1.3 The Uncontrolled-Disease Health State

The Appraisal Committee agreed that the utility value had been underestimated and the costs had been overestimated for the uncontrolled-disease health state in the manufacturer's economic model. It was concluded that the revised utility value applied to the uncontrolled-disease health state was more plausible than the value in the original model but remained a source of uncertainty.

6 Conclusion

On the basis of the evidence submitted by the manufacturer, the ERG concluded that RTX given at a dose of $4 \times 375 \text{ mg/m}^2$ has an effectiveness profile similar to that of oral CYC in terms of induction of remission in adults with AAV and de novo disease, and it appears to be more effective than oral CYC in terms of inducing remission in adults who have relapsed once on CYC. However, the evidence was restricted to adults with generalized, severe AAV, and longer-term data on safety are required. The ERG believed that robust estimates of the likely cost effectiveness of RTX could not be made on the basis of the original version of the manufacturer's economic model. However, on the basis of the ERG's amended version of the manufacturer's economic model, RTX appeared to represent a cost-effective addition to the treatment sequence at a cost-effectiveness threshold of £20,000 per QALY gained, provided it was received only by patients who had exhausted their use of CYC. The NICE Appraisal Committee recommended RTX within its licensed indication. However, the recommendation was not as first-line treatment, except in patients who could not have CYC.

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N.L. drafted the final version of the manuscript and takes responsibility as the overall guarantor of the content. C.C., P.T., R.W., R.L. and M.V. revised the manuscript for important intellectual content. All authors have given their approval for the final version to be published.

The views and opinions expressed herein are those of the authors and do not necessarily reflect those of NICE or the Department of Health.

Conflicts of Interest N.L. undertook 1 day of consultancy for Pfizer in 2012, providing advice on the analysis of an unrelated drug in an unrelated disease area. Pfizer manufactures cyclophosphamide and methotrexate (both of which are available on a nonproprietary basis). R.L. declares that the University of Oxford received an honorarium from Roche Oy for an academic presentation given by R.L. in 2012. M.V. received a 1-year competitive research grant (to co-fund an NIHR Collaborations for Leadership in Applied Health Research and Care [CLAHRC] grant) from Roche in October 2010 and undertook 1 day of consultancy for Chemocentryx in January 2014 after this appraisal was undertaken.

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