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ORIGINAL RESEARCH

The Cost-Effectiveness of Ranibizumab Treat and Extend Regimen Versus Aflibercept in the UK

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ABSTRACT

Introduction: Wet age-related macular degeneration (AMD) is a chronic eye condition that causes severe deterioration of vision and even blindness. Current wet AMD treatment in the UK involves the vascular endothelial growth factor inhibitors ranibizumab and aflibercept. Patients with wet AMD require frequent and long-term monitoring for treatment to be effective, contributing to a substantial resource burden at wet AMD centers. The European license for ranibizumab was recently updated with an individualized 'treat and extend' (T&E) regimen, comprising a structured monitoring and treatment protocol. This study evaluated the cost-effectiveness of ranibizumab T&E versus aflibercept within a UK setting.

Methods: An individual patient-level simulation model was developed utilizing treatment effects from a network meta-analysis of randomized controlled trials. The model was conducted from a UK National Health Service (NHS) perspective over a lifetime horizon and the base case utilized probabilistic sensitivity analysis to assess uncertainty in the model. Additional scenario analyses were conducted to assess the impact of changes to the model inputs.

Results: Ranibizumab T&E was found to be more effective and less costly than aflibercept, providing, on average, an additional 1.058 quality-adjusted life years (QALYs) and a cost-saving of £19,604 over a lifetime horizon. At list price, ranibizumab T&E was found to be cost-effective versus aflibercept in 100% of simulations at a willingness-to-pay threshold of £20,000 per QALY. The robustness of the results was tested in several scenario analyses;

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ranibizumab T&E was found to be more effective, and less costly, than aflibercept in the vast majority of cases.

Conclusion: This evaluation suggests that treating patients with ranibizumab according to the T&E regimen could be a better use of NHS resources than aflibercept, and could, therefore, be considered as a first-line regimen for patients with wet AMD in the UK.

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Keywords: Age-related macular degeneration; Aflibercept; Cost-effectiveness; Ophthalmology; Ranibizumab; Treat and extend

INTRODUCTION

Wet age-related macular degeneration (AMD) is a chronic eye condition in which damage to the macula, the central region of the retina specialized for visual acuity (VA), results in progressive deterioration of vision [1]. In the UK, wet AMD accounts for more than half of all cases of severe sight impairment. In 2013, over 338,000 individuals in the UK were affected by wet AMD, with 50,000 cases resulting in blindness [2–4].

Current treatment for wet AMD in the UK relies upon the use of pharmacological agents that specifically target and inhibit vascular endothelial growth factor (VEGF), preventing the formation of abnormal blood vessels implicated in the progression of the disease. Two intravitreal VEGF inhibitors are currently licensed in Europe and approved by the National Institute for Health and Care Excellence (NICE) for the treatment of wet AMD in the UK: ranibizumab (Lucentis®, Genentech Inc./Novartis) and aflibercept (Eylea®, Bayer plc) [5, 6].

Until recently, the licensed dosing regimen for ranibizumab in Europe involved fixed monthly dosing until maximum VA is achieved, followed by monitoring and treatment intervals determined by the physician and based on disease activity (ranibizumab pro-re-nata [PRN; as required]) [5]. The clinical workload associated with the frequent follow-up required with this regimen is substantial and, furthermore, the demand in ophthalmology is increasing with the ageing population [7, 8]. Real-world studies have revealed that ongoing capacity issues at some wet AMD clinics have prevented the maintenance of regular monitoring visits, ultimately leading to delays in follow-up and patients receiving fewer injections than required, which may cause unnecessary permanent vision loss [9, 10]. Moreover, key trials for ranibizumab PRN have demonstrated a wide variability in the number of injections required by patients over time, suggesting heterogeneity in disease reactivation intervals between patients and supporting the need for alternative, individualized treatment regimens [11–13].

In September 2014, the European license for ranibizumab was updated to include a new 'treat and extend' (T&E) regimen, in which patients are treated monthly until maximum VA is achieved and/or there are no signs of disease activity, then treatment intervals are extended in a stepwise manner of no more than two weeks at a time until signs of disease activity or visual impairment recur (see Fig. 1) [5]. This offers patients a truly flexible, yet structured, dosing regimen. The effectiveness of treating wet AMD patients with ranibizumab according to the T&E regimen has been demonstrated in two pivotal randomized controlled trials (RCTs) [14–16]. With T&E, the number of clinic visits required is expected to reduce in the long-term compared with current regimens that treat patients as necessary. Monitoring visits are not required between injection visits, hence a T&E regimen

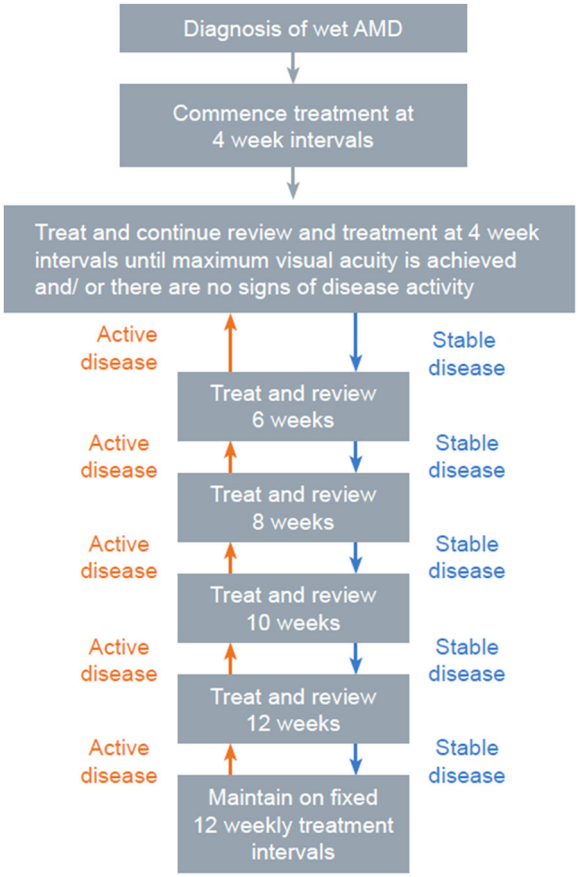

Fig. 1 Ranibizumab treat and extend protocol [5, 15, 16]. †The LUCAS and TREX trials used a maximum treatment interval of 12 weeks. The European license for ranibizumab does not state a maximum treatment interval. *AMD* age-related macular degeneration

may help to reduce the capacity issues at wet AMD centers across the UK.

In clinical practice in the UK, both ranibizumab and aflibercept are recommended as first-line agents for the treatment of wet AMD and the decision to use either agent is left to the treating physician. The aim of this study was to evaluate the cost-effectiveness of ranibizumab when administered according to the recently approved T&E regimen versus aflibercept for the treatment of wet AMD in the UK National Health Service (NHS). The dosing regimen evaluated for aflibercept was that stated in the European license: patients are given one injection per month for three consecutive doses, followed by one injection every two months; after the first 12 months, the treatment interval may be extended based on visual and/or anatomic outcomes [6, 17].

METHODS

An individual patient-level simulation (PLS) was run in Microsoft Excel 2010® (Microsoft Corporation). The evaluation was conducted from a UK NHS and personal social services perspective over a lifetime horizon with a discount rate of 3.5% applied to both costs and health benefits, consistent with the NICE Methods Guide [18].

Model Structure

Patients were modeled on an individual basis, moving through the model one at a time. The two treatment arms were ranibizumab T&E and aflibercept, and the effectiveness of each therapy was measured according to monthly best-corrected VA (BCVA) change, in Early Treatment Diabetic Retinopathy Study (ETDRS) letters.

A total of 1000 first-order iterations of individual patients were run to inform 1000 second-order iterations, where input values were drawn randomly from assigned probability distributions. The distributions used to inform each of the parameters for the second-order iterations can be found in the supplementary appendices. A number of scenario analyses were performed using 1000 first-order iterations to test the assumptions used in the base case analysis.

Patient Population

Baseline characteristics of the patient population were taken from the EXCITE phase

III study (ClinicalTrials.gov identifier: NCT00275821), the most recent study conducted in VEGF inhibitor-naïve wet AMD patients with individual patient-level data available [13]. Compared to subjects from recent UK-based clinical studies such as the IVAN trial (ISRCTN.com identifier: ISRCTN92166560) and 'The Neovascular Age-Related Macular Degeneration Database', the population used in the model was of a similar age (see Table 1). Only patients with a baseline VA <73 ETDRS letters were included in the evaluation in alignment with NICE guidance for the use of ranibizumab and aflibercept [19, 20]. Patients with a baseline VA >73 ETDRS letters were evaluated in a scenario analysis.

Clinical Effectiveness

The relative effectiveness of ranibizumab T&E versus aflibercept was derived from a network meta-analysis (NMA) of RCTs, populated from a previously performed systematic literature review (SLR) and updated with data for ranibizumab T&E from the LUCAS (ClinicalTrials.gov identifier: NCT01127360) and TREX trials (ClinicalTrials.gov identifier: NCT01748292) [14–16]. Further details of the SLR methodology can be found in the supplementary material. The equivalence of the ranibizumab dosing regimens used in the trials informing the NMA required three separate networks to be developed, one for months 1–3, one for months 1–12 (which informs months 4–12 in the model) and one for months 1–24 (which informs months 13–24 in the model). The only trial connecting the ranibizumab T&E dosing regimen to the NMA was the TREX trial, which only reported mean BCVA change in the intention-to-treat population at 12 months. Results were estimated from baseline to month 24 using the method by Ding and Fu [21].

Mean monthly BCVA change for ranibizumab T&E was modeled stochastically using the mean relative effectiveness of ranibizumab T&E with respect to ranibizumab PRN from the NMA (presented in Table 2), and the mean monthly BCVA for ranibizumab PRN was estimated stochastically using data from the IVAN trial, an independent UK-based RCT that evaluated the effectiveness of ranibizumab according to the PRN regimen [22]. Mean monthly BCVA change for aflibercept was then estimated stochastically using the relative effectiveness of ranibizumab T&E versus aflibercept, with the distribution derived from the NMA (the median relative effectiveness data are presented in Fig. 2, and

Table 1 Comparison of present model population characteristics and other UK wet AMD studies

Characteristics	Present model[a]	IVAN trial[b]	The neovascular age-related macular degeneration database[c]
Starting age (years)	75.5	77.7	78.9
Study eye BCVA (ETDRS letters)	55.6	61.4	52.0
Fellow eye BCVA (ETDRS letters)	55.4	62.9	64.5

AMD age-related macular degeneration, *BCVA* best-corrected visual acuity, *ETDRS* Early Treatment Diabetic Retinopathy Study, *IVAN* alternative treatments to inhibit VEGF in age-related choroidal neovascularization

[a] Schmidt-Erfurth et al. [13]

[b] Chakravarthy et al. [22]

[c] Tufail et al. [9]

Table 2 Clinical efficacy data inputs from the network meta-analysis and other model inputs used for the base case analysis

Month	Relative effectiveness of ranibizumab T&E versus ranibizumab PRN		Relative effectiveness of ranibizumab T&E versus aflibercept	
	Mean	SD	Mean	SD
1	0.000[a]	0.000	0.000[a]	0.000
2	0.000[a]	0.000	0.000[a]	0.000
3	0.000[a]	0.000	0.000[a]	0.000
4	1.995	3.308	1.950	3.319
5	1.790	3.131	1.821	3.146
6	1.733	3.013	1.803	3.030
7	1.733	2.932	1.823	2.950
8	1.755	2.876	1.855	2.895
9	1.783	2.839	1.887	2.859
10	1.811	2.817	1.918	2.838
11	1.837	2.807	1.946	2.828
12	1.861	2.806	1.970	2.827
13	2.306	2.831	3.317	3.121
14	2.312	2.830	3.323	3.119
15	2.317	2.829	3.328	3.118
16	2.321	2.829	3.332	3.118
17	2.325	2.829	3.336	3.118
18	2.328	2.829	3.339	3.119
19	2.330	2.830	3.341	3.119
20	2.332	2.831	3.343	3.120
21	2.334	2.831	3.345	3.120
22	2.336	2.832	3.347	3.121
23	2.337	2.833	3.348	3.122
24	2.338	2.834	3.349	3.123

Variable	Value	Source
Drug costs		
Ranibizumab	£551.00 per dose	MIMS 2016 [39]
Aflibercept	£816.00 per dose	MIMS 2016 [39]

Table 2 continued

	Ranibizumab T&E	Aflibercept	
Number of treatment visits			
Year 1	8	8	Berg et al. [14]; Aflibercept NICE [TA294] costing template [27]
Year 2	8	4	Berg et al. [14]; Aflibercept NICE [TA294] costing template [27]
Number of monitoring visits[b]			
Year 1	8[b]	8[b]	Berg et al. [14]; Aflibercept NICE [TA294] costing template [27]
Year 2	8[b]	7[b]	Berg et al. [14]; Aflibercept NICE [TA294] costing template [27]
Resource use costs			
Treatment procedure		£111.00	Outpatient procedures, minor vitreous retinal procedures, 19 years and over, ophthalmology (HRG code BZ87A), NHS reference costs 2014–2015 [40]
OCT scan		£77.00	Outpatient procedures, retinal tomography, 19 years and over, medical ophthalmology (HRG code BZ88A), NHS reference costs 2014–2015 [40]
Outpatient ophthalmology consultant follow-up		£89.00	Outpatient face-to-face consultant follow-up, ophthalmology (HRG code WF10A), NHS reference costs 2014–2015 [40]

HRG Healthcare Resource Group, *MIMS* Monthly Index of Medical Specialities, *NHS* National Health Service, *NICE* National Institute for Health and Care Excellence, *OCT* optical coherence tomography, *PRN* pro-re-nata, *SD* standard deviation, *T&E* treat and extend

[a] Due to the uncertainty of the data for ranibizumab T&E in the month 1–3 network, it was assumed in the base case analysis that for months 1–3, that the efficacy of ranibizumab T&E versus ranibizumab PRN and versus aflibercept was the same (relative effectiveness equals zero)

[b] In the base case, a one-stop service model was assumed so the monitoring visit cost was only applied to the number of monitoring visits over and above the number of treatment visits

the mean relative effectiveness data used in the model are presented in Table 2). For each patient, values were drawn at random from normal distributions derived from the means and standard deviations. Due to the uncertainty of the data for ranibizumab T&E in the month 1–3 network, ranibizumab T&E was not included. It was therefore assumed in the base case analysis that for months 1–3, the efficacy of ranibizumab T&E versus ranibizumab PRN was the same, and as a conservative estimate, the efficacy of ranibizumab T&E versus aflibercept in months 1–3 was also assumed to be the same.

In the base case analysis, patients were assumed to receive either ranibizumab T&E or aflibercept over a maximum of 24 months. Beyond 24 months, BCVA was modeled using natural history data from a meta-analysis by Wong et al., and after treatment discontinuation, BCVA was modeled from Frisen and Frisen and Elliot et al. [23–25]. Adverse event rates were not included in the model, since the VIEW trials (ClinicalTrials.gov identifers: NCT00509795 and NCT00637377) found there to be no clinically meaningful differences in adverse event rates between ranibizumab and aflibercept [26].

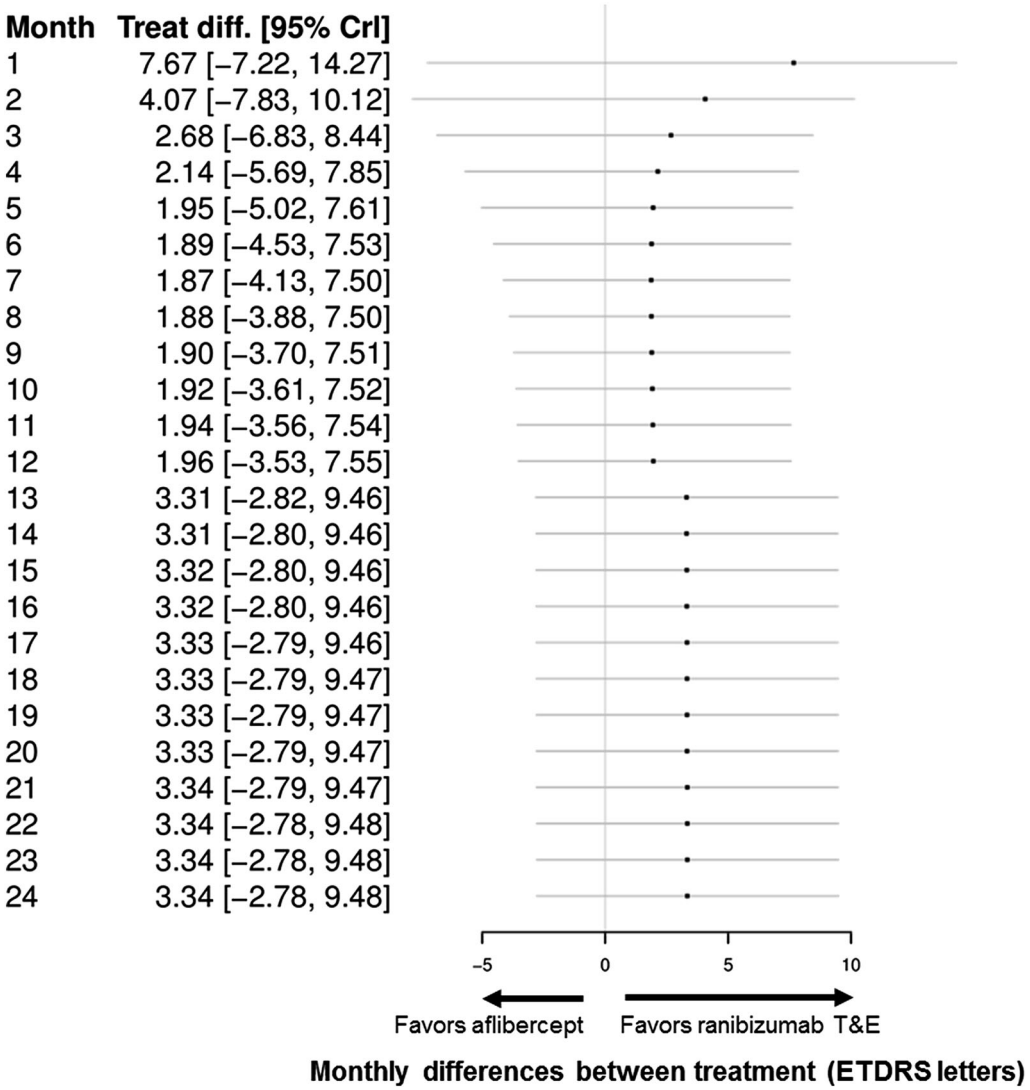

Fig. 2 Relative efficacy of ranibizumab T&E versus aflibercept. Forest plot presents the median treatment differences and 95% CrIs. Due to the uncertainty of the data for ranibizumab T&E in the month 1–3 network, it was assumed in the base case analysis that for months 1–3, the efficacy of ranibizumab T&E versus aflibercept was the same (relative effectiveness equals zero). *CrI* credible interval, *ETDRS* Early Treatment Diabetic Retinopathy Study, *T&E* treat and extend, *treat diff.* treatment differences

Costs and Resource Use

The key costs incorporated in the model were drug acquisition costs, treatment visit costs, monitoring visit costs, and the cost of blindness. For this model, the number of treatment and monitoring visits for the first 24 months of treatment were taken from the LUCAS RCT for ranibizumab T&E, and from the aflibercept NICE single technology appraisal (STA) costing template for aflibercept [14, 15, 27]. In the base case analysis, it was assumed that all patients were treated according to a 'one-stop service model', in which patients are monitored and treated (if needed) within the same appointment. The cost of a monitoring visit was, therefore, only applied to the number of monitoring visits

Table 3 Utility regression analysis inputs

Utility regression model	VA BSE		VA WSE		Both eyes		Blindness		Constant	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Two-eye model (no interaction)	−0.18	0.09	−0.15	0.10	0.00	0.00	0.00	0.00	0.85	0.04
Two-eye model (interaction)	−0.04	0.15	−0.08	0.11	−0.11	0.09	0.00	0.00	0.77	0.07
Two-eye model (blindness threshold)	−0.04	0.16	−0.08	0.11	−0.11	0.12	−0.01	0.08	0.77	0.07

BSE better seeing eye, *SE* standard error, *VA* visual acuity, *WSE* worse seeing eye

over and above the number of treatment visits. The costs of treatment and monitoring visits can be found in Table 2. If the BCVA in either the study eye or the fellow eye fell below 35 letters, treatment was terminated in that eye; if both eyes reached a BCVA of <35 letters, the cost of blindness was applied. Details of the resource utilization for the cost of blindness can be found in the supplementary appendices.

Health-Related Quality of Life and Mortality

Health outcomes were measured in quality-adjusted life years (QALYs), with mean utilities estimated for both the study eye and fellow eye each month using a regression analysis of a real-world data set obtained from Czoski-Murray et al. [28]. In the base case analysis, health-related quality of life (HRQoL) was modeled as a function of BCVA in both the study and fellow eye, and assumed a correlation between the two eyes. Age-specific all-cause mortality for the general population was estimated from UK life tables, with different relative risks applied to individuals with some and severe visual impairment, to reflect the increased mortality risk associated with vision loss (see Table 3) [29, 30].

A summary of the unit costs and resource use estimates used in the base case analysis is provided in Table 2. Further details of the other model inputs can be found in the supplementary material.

Scenario Analyses

A number of scenario analyses were performed to explore any uncertainty in the assumptions used within the model. Details of any model inputs that were adjusted for the scenario analyses can be found in the supplementary appendices. One-way sensitivity analyses were also performed on the principal model parameters and the tornado plot can be found in the supplementary appendices.

Proportion of Patients Treated According to the One-Stop Service Model

The base case analysis assumed all patients were treated according to the one-stop service model. The extent to which this assumption affects the cost-effectiveness of the ranibizumab T&E regimen was tested in two scenario analyses, where the proportion of patients treated according to the one-stop service model was reduced to 50% for ranibizumab T&E and aflibercept, separately. The other 50% of patients were assumed to be treated according to the two-stop service model, in which patients are reviewed at one appointment (monitoring visit) and return for a second appointment to receive treatment (treatment visit).

Alternative Sources for Treatment and Monitoring Visits

A number of real-world evidence studies have reported the yearly monitoring and treatment visits required when patients are treated with ranibizumab according to the T&E regimen. As a scenario analysis, the number of treatment and monitoring visits for ranibizumab T&E in years 1 and 2 were taken from the real-world evidence study by Arnold et al. [31] (7.5 and 5.5 treatment visits in years 1 and 2, respectively; 7.9 and 6.7 monitoring visits in years 1 and 2, respectively). An additional analysis was performed taking the year 1 treatment visits for ranibizumab T&E from the TREX study (10.1 visits), assuming the number of monitoring visits was the same, and assuming they were maintained in year 2 [16].

Patient Access Scheme

Scenario analyses were performed to investigate the utilization of a Patient Access Scheme (PAS) price for both ranibizumab and aflibercept. In the absence of knowing the confidential PAS discount for either drug, four scenario analyses were performed, applying a 25% and 50% discount to each drug separately, and to both therapies at the same time.

Quality of Life Estimates

Two scenario analyses were performed to explore the use of different regression models to estimate the HRQoL of patients throughout the model. The first scenario considered HRQoL as a function of VA in both the study eye and the fellow eye assuming no correlation (compared with the base case, in which both eyes were modeled assuming a correlation), and the second scenario included an interaction term for blindness, with a blindness threshold implemented for patients with a BCVA of <35 letters in both eyes. Details of the alternative regression analysis models for estimating HRQoL can be found in Table 3.

Extended Treatment Period

A scenario analysis was performed to evaluate the cost-effectiveness of the two treatments over a treatment period of 5 years. Patients could be treated with ranibizumab T&E or aflibercept for a maximum of 5 years. Mean monthly BCVA change was modeled up to 24 months as in the base case analysis then remained constant beyond this point up to a maximum of 5 years, after which BCVA was modeled according to natural history data. The number of treatment and monitoring visits in years 3–5 for ranibizumab T&E and aflibercept were assumed to be the same. Treatment visits were 3.7 per year, based on the real-world study by Tufail et al. [9] and monitoring visits were 4 per year, based upon the assumption of a maximum treatment interval of 12 weeks as used in the LUCAS trial [14].

Cost of Blindness

A scenario analysis removing the cost of blindness was performed to investigate the effect of this parameter on the cost-effectiveness of the two treatments.

Baseline Visual Acuity

NICE guidance for the use of ranibizumab and aflibercept states only patients with a VA <73 letters are eligible for treatment [19, 20]. As such, only patients satisfying this criterion were included in the base case analysis. A scenario analysis was performed to investigate the cost-effectiveness of the two treatments in patients with baseline VA >73 letters.

Clinical Effectiveness

Scenario analyses were performed to evaluate the cost-effectiveness of ranibizumab T&E with changes to the clinical effectiveness. The first assumed the relative effectiveness of ranibizumab T&E to be 50% less versus aflibercept, and the second assumed both drugs to have the same effectiveness. In addition, once the effectiveness of both drugs was set to the same, two scenarios were run to evaluate the effect of reducing the drug acquisition costs of both treatments by 50%. A further analysis was performed adjusting the relative effectiveness of ranibizumab T&E versus aflibercept in months 1–3 to that reported in the month 1–12 model of the NMA.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Base Case Results

Results from the base case analysis are shown in Table 4. After running 1000 second-order iterations of 1000 first-order iterations, ranibizumab T&E was found to be dominant over aflibercept, and was associated with a mean incremental benefit of 1.058 QALYs and a cost-saving of £19,604 over a lifetime horizon. The probabilistic second-order iterations are presented graphically in Fig. 3 where it can be seen that ranibizumab T&E was cost-effective in 100% of simulations at a willingness-to-pay threshold of £20,000 per QALY.

Scenario Analyses Results

The results of the scenario analyses that were employed to explore some of the key assumptions in the model are presented in Table 5. These demonstrate that the base case results are robust to changes in the model inputs and assumptions. Even with a 50% discount on the list price of aflibercept, ranibizumab T&E was still found to be dominant. It was found that the cost of blindness and the clinical efficacy derived from the NMA were the parameters driving the model to the greatest extent.

DISCUSSION

To the knowledge of the authors at the time of publication, this is the first economic evaluation to investigate the cost-effectiveness of the recently approved ranibizumab T&E regimen versus aflibercept. The base case analysis found that ranibizumab T&E was likely to be both a more effective and less costly option (at list price) than aflibercept for patients with wet AMD within a UK setting. This cost difference was almost entirely due to the cost of blindness being much lower for ranibizumab T&E versus aflibercept.

A number of additional scenario analyses were performed to assess the impact of changes in the various model inputs and ranibizumab T&E was found to dominate aflibercept in the vast majority of scenarios, demonstrating the robustness of the results. In the absence of knowing the confidential PAS discounts for both treatments, a set of scenario analyses were run to test hypothetical discounts. Even when a 50% discount is applied to the list price of aflibercept, ranibizumab T&E was still found to be dominant, providing an extra 1.055

Table 4 Base case second-order probabilistic analysis

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
Ranibizumab T&E	£29,282	4.69	−£19,604	1.058	Dominant
Aflibercept	£48,887	3.63	–	–	–

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life year, *T&E* treat and extend

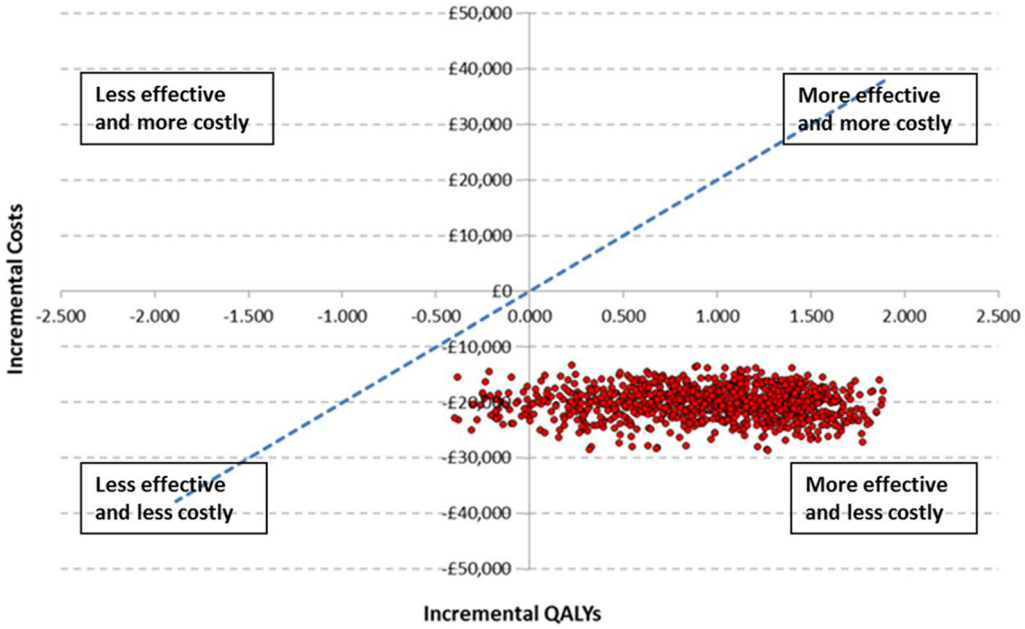

Fig. 3 Second-order probabilistic results for ranibizumab T&E versus aflibercept. ICER threshold at a willingness-to-pay of £20,000 per QALY represented by *blue dashed line*. First-order iterations not shown; each second-order iteration is an average of 1000 first-order iterations. *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life year, *T&E* treat and extend

QALYs and a cost-saving of £15,406 over a lifetime horizon. Moreover, another scenario analysis found that even after removing the cost of blindness from both treatment arms, ranibizumab T&E was still the more cost-effective treatment option, providing an incremental cost-effectiveness ratio (ICER) of £1417 per QALY gained, much lower than the commonly accepted £20,000 willingness-to-pay threshold. Overall, the scenario analyses demonstrate that even in extreme scenarios, ranibizumab T&E still provides value for money to the NHS.

Prior studies have suggested that the T&E regimen would provide socioeconomic benefits and this economic evaluation supports these suggestions [32, 33]. As the population continues to age and more patients are diagnosed with wet AMD, it is vital that clinical services continue to adapt to cope with the increased demand being seen in ophthalmology, and the introduction of the T&E regimen across the NHS could help alleviate this [7, 8]. In the USA, the T&E regimen is currently the most commonly employed treatment approach for wet AMD,

Table 5 Results of scenario analyses for ranibizumab T&E versus aflibercept

Scenario		Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
Scenarios: Adjusting the proportion of patients treated according to the one-stop service model				
1	Ranibizumab: 100% one-stop Aflibercept: 50% one-stop, 50% two-stop	−£19,836	1.036	Dominant
2	Ranibizumab: 50% one-stop, 50% two-stop Aflibercept: 100% one-stop	−£18,500	1.031	Dominant
3	Ranibizumab: 50% one-stop, 50% two-stop Aflibercept: 50% one-stop, 50% two-stop	−£19,758	1.080	Dominant
Scenarios: Alternative source for number of injection and monitoring visits				
4	Injection and monitoring visits in years 1 and 2 taken from Arnold et al. [33]	−£22,211	1.083	Dominant
5	Injection and monitoring visits for ranibizumab T&E taken from the TREX trial [16]	−£15,601	1.032	Dominant
Scenarios: Incorporation of possible Patient Access Scheme discounts				
6	25% discount on the list price of both ranibizumab and aflibercept	−£19,973	1.011	Dominant
7	50% discount on the list price of both ranibizumab and aflibercept	−£20,309	1.057	Dominant
8	50% discount on the list price of just ranibizumab	−£25,683	1.056	Dominant
9	50% discount on the list price of just aflibercept	−£15,406	1.055	Dominant
Scenarios: Adjustment of quality of life estimates				
10	Two-eye model (no interaction)	−£20,828	1.070	Dominant
11	Two-eye model (blindness threshold)	−£19,340	1.067	Dominant
Scenario: Adjusting patient baseline VA				
12	Patient baseline VA > 73 ETDRS letters	−£20,783	1.075	Dominant
Scenario: Adjusting the treatment period				
13	Patients could be treated for up to 5 years	−£14,586	1.208	Dominant
Scenario: Removing the cost of blindness				
14	Removing the cost of blindness	£1566	1.105	£1417
Scenarios: Adjusting the efficacy of both treatments				
15	Reducing the relative efficacy of ranibizumab T&E vs. aflibercept by 50%	−£6471	0.320	Dominant
16	Setting the efficacy of both drugs to be the same (by setting the relative effectiveness to zero)	£1168	0.000	Equal efficacy

Table 5 continued

Scenario		Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
17	Setting the relative efficacy of ranibizumab T&E versus aflibercept in months 1–3 to that reported in the month 1–12 network of the network meta-analysis	−£19,226	1.265	Dominant
Scenarios: adjusting the efficacy and the list price simultaneously				
18	Setting the efficacy of both drugs to be the same, and reducing the list price of ranibizumab by 50%	−£6487	0.000	Equal efficacy
19	Setting the efficacy of both drugs to be the same, and reducing the list price of aflibercept by 50%	£4911	0.000	Equal efficacy

ETDRS Early Treatment Diabetic Retinopathy Study, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life year, *T&E* treat and extend, *VA* visual acuity

with approximately 78% of retina specialists favoring this style of treatment [34]. Furthermore, the long-term benefits of ranibizumab T&E on visual outcomes have been demonstrated in a number of real-world observational studies [35, 36]. In the largest series of long-term outcomes in wet AMD to date, treatment with ranibizumab T&E was associated with more treatments and fewer visits than ranibizumab PRN, and visual outcomes were found to be superior for ranibizumab T&E [36]. Moreover, treatment with ranibizumab according to the T&E regimen provides additional benefits to wet AMD patients themselves. Patients are provided with a truly individualized treatment regimen and the ability to have both monitoring and treatment at the same appointment. This necessitates fewer hospital visits and less travelling for patients, many of whom may have sight and mobility challenges [33]. The flexible, yet structured, T&E regimen also provides certainty for patients that their disease will be adequately and continually monitored and treated.

The principal strength of this study was in the use of an individual PLS model, which was able to model both eyes independently, allowing incorporation of BCVA in the fellow eye, which contributes to patients' overall HRQoL. In addition, BCVA was estimated directly as a continuous variable, rather than artificially dividing it into a number of mutually exclusive health states with an assumed HRQoL (as would be the case with a Markov model which has been used in previous ophthalmology economic evaluations) [19, 37]. The clinical effectiveness data for ranibizumab T&E was taken from an NMA with robust methodology, providing accurate estimates of the effects of ranibizumab T&E in the absence of head-to-head RCT data. However, it should be noted that only two RCTs provide data on the efficacy of the ranibizumab T&E regimen (more details can be found in the supplementary material).

On the other hand, the use of the NMA meant that in the model both ranibizumab T&E and aflibercept had to be compared with ranibizumab PRN, and that the base monthly BCVA change for ranibizumab PRN had to be taken from another data source, the IVAN trial. In addition, different sources had to be used to derive the number of injection and monitoring

visits for each treatment arm and the patient baseline characteristics that informed the model. Although it is recognized that a wide variety of sources were used for data inputs to the model, no major differences in baseline characteristics were identified across all of the clinical studies that informed the model inputs, which supports the synthesis of their results. A key driver of the costs in the model was the cost of blindness. A number of economic evaluations report various estimates for the cost of blindness in the UK. Therefore, a conservative approach was taken based on that used previously by NICE, and the most up-to-date sources were used where possible [19, 20, 37]. A further limitation of this analysis is the confidential nature of the PAS discounts provided to the NHS for both ranibizumab and aflibercept. Despite this, scenario analyses demonstrated the dominance of ranibizumab T&E even if a 50% discount is applied to the list price of aflibercept.

In addition, the NMA used a random effects model, adapted from Ding and Fu [21]. For each treatment within each study, the longitudinal NMA model was based on estimates of the change from baseline in BCVA and their variance. However, the variances were not available for more than 50% of the time points; for ranibizumab T&E, the TREX trial was the only trial that connected the regimen to the network, and only reported mean BCVA change at month 12. The missing variances were, therefore, imputed following the approach of Dakin et al. [38]. Although this approach is justified, the lack of data contributes to uncertainty in the NMA results.

As ranibizumab T&E is increasingly implemented in clinical practice, further studies are needed to collect real-world data comparing the resource use associated with this new regimen with the existing licensed aflibercept regimen. In addition, the cost-effectiveness of patients switching between VEGF inhibitor therapies following treatment failure has not been fully investigated. A number of studies have evaluated the clinical effectiveness of switching between VEGF inhibitors following treatment failure but the majority of these have been small, retrospective studies. Larger, phase IV prospective studies are needed to investigate the effectiveness of switching between VEGF inhibitors further, and the Safety and Efficacy of Switching From Aflibercept to Ranibizumab in Patients With nAMD trial (SAFARI; ClinicalTrials.gov identifier: NCT02161575) is one such trial on the horizon. Allowing patients to switch between different VEGF inhibitors following treatment failure may provide the ability to maintain VA longer term, however, further economic analyses will need to be performed to establish whether switching between treatments is cost-effective for the NHS.

CONCLUSIONS

Ranibizumab T&E allows a flexible, yet structured, monitoring and treatment regimen for patients with wet AMD from the start of treatment, an element that the European license for aflibercept does not currently allow in the first year of treatment. This study has shown that ranibizumab T&E is likely to be a more effective and less costly treatment option compared with the currently licensed regimen of aflibercept within the UK setting.

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