COST EFFECTIVENESS ANALYSIS OF RANIBIZUMAB COMPARED TO AFLIBERCEPT AND LASER INTERVENTION IN TREATMENT OF DIABETIC MACULAR EDEMA (DME) IN THE CZECH REPUBLIC

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BACKGROUND

Diabetic retinopathy/ diabetic macular edema (DME) are substantial complications of diabetes leading to blindness [1]. Ranibizumab (RBZ) and aflibercept (ABC), antibodies to vascular endothelial growth factor (anti-VEGF) change the DME-treatment paradigm. RBZ in DME is reimbursed in the Czech Republic since 2012 and ABC will be reimbursed by the end of this year. However, these therapies are restricted for DME patients with HbA1c level below 7.0. Hence, for patients with H1bA1c level above 7.0, there is the only reimbursed therapy laser intervention, which was also standard of care before year 2012 (RBZ launch in DME in the Czech Republic).

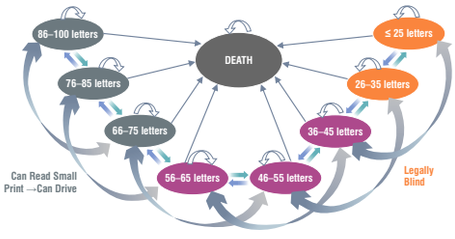
OBJECTIVES

We estimated the cost-effectiveness of RBZ vs. ABC and also vs. laser intervention in DME patients. Our aim was to investigate, what is the impact (health gain and expenses/ savings) by using RBZ 0.5 mg PRN (*pro re nata*) instead of ABC 2×2m (2 mg administered bi-monthly after 5 initial monthly doses) in DME patients from the Czech health care system perspective. Moreover, we investigate, if less restrictive RBZ indication for DME patients (i.e. extension for patients with HbA1c level between 7.0 – 8.0), is cost-effective from the Czech health care system perspective.

METHODS

We used a Markov cohort model with 8 health states (based on visual acuity; VA) + dead in life-time horizon (3% discount rate), the cycle length was 3 months, half-cycle correction was applied to each cycle. This structure of the model was used in NICE and also in Czech previous submission for RBZ in DME, the model was also published in previous analysis from the UK health care perspective elsewhere [2], see ***Figure 1***. Base-line patient characteristics (mean age of cohort 63 years) came from the RESTORE study [3] (***Table 1***); 60% of patients were treated for their worse seeing-eye (assumption came from RESTORE). Patients who were treated in both eyes were not included in the analysis, this restriction (for 1 treated eye) comes from the Czech indication criteria for anti-VEGF in DME.

Figure 1 • Structure of the health-economic Markov cohort model



EDTRS letters	approximate Schnellen equivalents
86 – 100	20/20 – 20/10
76 – 85	20/32 – 20/20
66 – 75	20/50 – 20/32
56 – 65	20/80 – 20/50
46 – 55	20/125 – 20/80
36 – 45	20/200 – 20/125
26 – 35	20/320 – 20/200
< 25	< 20/320

Table 1 • Baseline ocular patient characteristics entering the model: Treatment eye

Health state (EDTRS)	86 – 100 letters	76 – 85 letters	66 – 75 letters	56 – 65 letters	46 – 55 letters	36 – 45 letters	26 – 35 letters	<25 letters	
Distribution of patients – RESTORE study	0.0 %	11.1 %	39.1 %	27.1 %	14.9 %	7.9 %	0.0 %	0.0 %	100 %

Efficacy (Transition probabilities; TP) for the first 3 years of treatment for RBZ 0.5mg were derived from RESTORE study [4]. TPs for laser intervention were derived from RESTORE for the 1st year and from DRCR.net [5] for subsequent 2 years. TPs for ABC for the 1st year were derived from a published network meta-analysis (NMA) [6], that utilize 1 year data from 8 clinical studies, for ABC namely data from VIVID, VISTA clinical program [7]. In this NMA, there was calculated gain in at least 10 letters for RBZ vs. ABC: odds ratio; OR = 1.59; 95%CrI 0.61 – 5.37 [6]. The re-calculation of transition probabilities for ABC by using this OR is mentioned in the supplementary materials Régnier et al, 2015 [2]. For ABC the TPs for subsequent 2 years were assumed to be equal like in RBZ arm. Natural progression of disease, applied from the beginning of the 4th year, came from Wisconsin Epidemiologic Study (WESDR) [8].

For RBZ 0.5 PRN and ABC 2×2m, the dosing schemes came from RESTORE study (RBZ 0.5 PRN) [4] and from VIVID-DME, VISTA-DME study (bi-monthly after 5 initial monthly doses) [7,9], respectively. For the 3rd year of ABC 2x2m dosing scheme, we assumed same decrease like for RBZ between year 2&3, i.e 3.8 doses of ABC. The numbers of laser photocoagulations administered were derived from RESTORE and DRCR.net [3,5]. For the summary of the efficacy data inputs and for resource used, see ***Table 2***.

Table 2 • Summary of the data inputs for TPs (efficacy) and number of anti-VEGF administration and other resources used

	Model inputs	Ranibizumab 0.5 PRN	Aflibercept 2×2m	Laser photocoagulation
Year 1	BCVA data source for TP # administrations antiVEGF/ laser # monitoring visits	RESTORE [3] 7.0 (RESTORE) [3] 5.0 (12.0 – 7.0), assumption	NMA [6] 8.5 (VIVID, VISTA DME) [7] 3.5 (12.0 – 8.5) assumption	RESTORE [3] 2.0 laser application (RESTORE) [3] 4.0, assumption
Year 2	BCVA data source for TP # administrations antiVEGF/ laser # monitoring visits	RESTORE extension (data 12 – 24 months) [4] 3.9 (RESTORE) [4] 8.1 (12.0 – 3.9), assumption	Assumption same TPs as RBZ PRN 5.1 (13.6 – 8.5) (VIVID, VISTA DME extension) [9] 6.9 (12.0 – 5.1), assumption	DRDCR.net study [5] 3% probability of worse, 3% improve 0.55 lase application, DRDCR.net [5] 4.0, assumption
Year 3	BCVA data source for TP # administrations antiVEGF/ laser # monitoring visits	RESTORE extension (data 25 – 36 months) [4] 2.9 (RESTORE) [4] 4.0 assumption	Assumption same TPs as RBZ PRN 3.8 (5.1*2.9)/3.9, assumption; same decrease like for RBZ between year 2&3 4.0 assumption	DRDCR.net study [5] 3% probability of worse, 3% improve 0.55 lase application, DRDCR.net [5] 4.0 assumption
Year 4+	BCVA data source for TP # administrations antiVEGF/ laser # monitoring visits	Natural BCVA progression, WESDR [8]; 4.5% probability of worse, 3.5% improve, 92% stable 0.0; laser photocoagulation PRN 4.0 assumption		

TP; Transition probabilities | PRN; *pro re nata* | NMA; network meta-analysis | BCVA; Best-corrected visual acuity

In the Czech Republic, there is cost/ reimbursed price parity per dose of anti-VEGF (€855), for the other cost input (anti-VEGF administration, monitoring, laser and cost for patients with BCVA impairment), see ***Table 3***. These cost inputs were used in the previous submission within Czech HTA procedure. All cost were calculated in Czech crowns (CZK) and converted to EUR (exchange rate €1 = 27.4 CZK).

Utility/ QoL weights for better seeing eye (BSE) were derived from regression analysis by Czoski-Murray [10], for worse seeing-eye (WSE), it was assumed the difference between the best and worse VA health state 0.3, which was accepted in previous Czech HTA procedures with RBZ. For particular utility inputs, see ***Figure 2***.

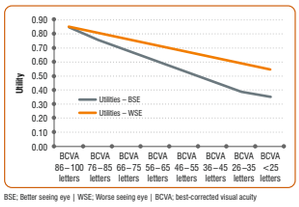
The general background mortality from the Czech statistical office (data for inhabitant 63 – 95 years, as of year 2013) was used by multiplying with RR = 2.45 [11,12], to get the mortality of DME patients.

We did not model adverse events either from the perspective of cost nor utility. We assumed the same rate of adverse events for all interventions.

Table 3 • Unit costs (reimbursed prices)

Unit	Cost/ reimb.price
Ranibizumab 0.5 mg (RBZ)/ vial Aflibercept 2 mg (ABC)/ vial	€ 854.9
Visit with injection (RBZ, ABC)	€ 51.7
Laser photocoagulation	€ 30.2
Control visit	€ 25.0
1 year cost for patients with BCVA impairment	
BCVA ≥ 56	€ 64.7
BCVA 36 – 55	€ 44.0
BCVA ≤ 35	€ 41.7

Figure 2 • Utility for BSE; Better seeing eye and WSE; Worse seeing eye



	Utility WSE	Utility BSE
BCVA 86 – 100 letters	0.8500	0.8500
BCVA 76 – 85 letters	0.8071	0.7580
BCVA 66 – 75 letters	0.7643	0.6850
BCVA 56 – 65 letters	0.7214	0.6110
BCVA 46 – 55 letters	0.6786	0.5370
BCVA 36 – 45 letters	0.6357	0.4640
BCVA 26 – 35 letters	0.5929	0.3900
BCVA <25 letters	0.5500	0.3530

BSE; Better seeing eye | WSE; Worse seeing eye | BCVA; best-corrected visual acuity

We performed probabilistic sensitivity analysis (PSA), in life time horizon with 3% discount rate, with 1000 iterations using key variable inputs, see ***Table 4***.

RESULTS

In the analysis comparing RBZ 0.5 PRN vs. ABC 2×2 m in a life-time horizon total (discounted) costs and QALYs for RBZ, ABC were: € 7,010, € 9,345; and 7.589, 7.502 QALYs, respectively. The incremental QALYs and costs for RBZ vs. ABC were 0.087 QALY gain with € 2,335 savings, reflecting dominance of RBZ over ABC. The net monetary benefit (NMB) was € 6,150 (***Table 5***). According to PSA, there is 64% probability that RBZ's ICER is below WTP threshold (€ 43,800) compared to ABC. There is 56% probability that RBZ compared to ABC brings more QALY with lower costs (quadrant IV), and there is 94% probability that RBZ is less costly compared to ABC (quadrant III, IV), see ***Figure 3***.

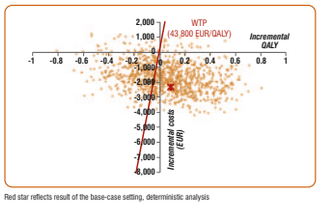
In the analysis of sub-group DME patients with HbA1c level between 7.0 – 8.0 comparing RBZ 0.5 PRN vs. laser intervention in a life-time horizon total (discounted) costs and QALYs for RBZ and laser were: € 6927, € 1,458; and 7.503, 6.954 QALYs, respectively. The incremental QALYs and costs for RBZ vs. laser were 0.549 QALY and € 5,468, resulting in ICER of RBZ over laser € 9,963/ QALY. The net monetary benefit (NMB) was € 18,573 (***Table 5***). According to PSA, there is 89% probability that RBZ's ICER is below WTP threshold (€ 43,800) compared to laser for patients with HbA1c 7.0 – 8.0, see ***Figure 4***.

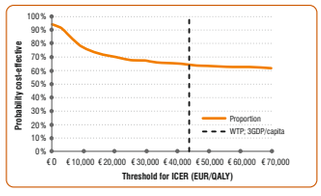
Table 5 • Base-case results in life time horizon

	All RESTORE patients			Patients with HbA1c level 7.0 – 8.0		
	RBZ 0,5 PRN	ABC 2×2 m	Increment	RBZ 0,5 PRN	Laser	Increment
Total Costs	€ 7,010	€ 9,345	€ - 2,335	€ 6 927	€ 1 458	€ 5,468
Total QALYs	7.589	7.502	0.087	7.503	6.954	0.549
ICUR (CZK/ QALY)			€ - 26,797			€ 9,963
Net monetary benefit; NMB			€ 6,150			€ 18,573

WTP; willingness to pay threshold = approx. 43 800 €

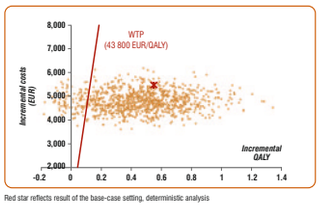
Figure 3 • Results of the PSA: RBZ 0.5 PRN vs. ABC 2x2m; Cost-effectiveness scatter plot and Cost-effectiveness acceptability curve; WTP = € 43 800/ QALY

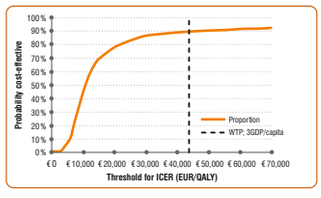




Red star reflects result of the base-case setting, deterministic analysis

Figure 4 • Results of the PSA: RBZ 0.5 PRN vs. Laser in patients with HbA1c between 7.0 – 8.0; Cost-effectiveness scatter plot and Cost-effectiveness acceptability curve; WTP = € 43 800/ QALY





Red star reflects result of the base-case setting, deterministic analysis

DISCUSSIONS

For Czech Republic, this is the first health-economic analysis comparing active (anti-VEGF) DME treatment in EU approved dosing schemes. Moreover, such sub-group patient analysis (patients with HbA1c level 7.0 – 8.0), has not to our knowledge been presented anywhere before.

The limitations of this analysis could be the great variability that occurs in the comparative efficacy of RBZ 0.5 PRN vs. ABC 2×2m that is derived from the indirect comparison. However, in the absence of relevant (from the perspective of EU approved dosing schemes) head-to-head trial, there were no other possibility how to address relative efficacy. The limitations of the indirect comparison could be also the absence of 2 or 3 years data for NMA. However, most of the studies included in the NMA loop lack the long-term (2 or 3 years) data. On the other hand, the assumption of using the same TP for ABC in year 2 and 3 like in RBZ arm seems to be very reasonable, since the percentage of patients who gain ≥ 15 letters were for RBZ similar in year 2 and year 1 [4], this (same percentage in this outcome) was also observed for ABC studies in year 2 and year 1 [9].

Further limitation of this comparative health economic analysis (RBZ vs. ABC) from the Czech heath care system perspective, could be the absence of particular patient data for reimbursement of antiVEGF (i.e. HbA1c up to 7.0). However, the comparative efficacy that comes from NMA addresses just the whole patient population described in the RESTORE study. We assumed that relative efficacy in subpopulation of patients with HbA1c up to 7.0 for RBZ vs. ABC will be same like in all RESTORE patients

The general limitation (and underestimation) of the results for more efficacy intervention is the absence of broader perspective for the health economic analysis. Since, there are some other expenses for patients with impaired vision. However, this cost are not covered by health insurance, hence are not relevant from the Czech heath care system perspective.

Moreover, once, there will be data from real life clinical practice (effectiveness under real life anti-VEGF dosing), it would be great to do such up-date of this analysis.

CONCLUSIONS

RBZ 0.5 PRN is dominant intervention (brings more QALY gain simultaneously with cost savings) compared to ABC 2×2m in DME patients from the Czech health care system perspective, the saving attributed to RBZ 0.5 PRN use came mainly from the lower number of administrations needed compared to ABC. Hence RBZ should be the preferred anti-VEGF in DME therapy from the perspective of Czech health care system.

In the DME patients population with HbA1c level between 7.0 – 8.0, RBZ 0.5 PRN is highly cost-effective compared laser intervention approach (currently the only reimbursed health care in this patients sub-population) from the Czech health care system perspective. Hence, RBZ provides great value for money and should be also reimbursed in this DME patient sub-population in the Czech health care system.

Table 4 • Inputs into Probabilistic sensitivity analysis

Parameter	Mean (SE)	Distribution	Source of uncertainty parameters
OR of gain ≥ 10 letters (RBZ PRN vs. ABC 2×2m)	1.59 (1.21)	Log normal	NMA
RBZ injections year 1	7.0 (0.2630)	Normal	RESTORE
ABC injections year 1	8.54 (0.11)	Normal	VIVID, VISTA
Laser treatments year 1	2 (0.0992)	Normal	RESTORE
RBZ injections year 2	3.9 (0.3800)	Normal	RESTORE
ABC injections year 2	5.1 (0.38)	Normal	VIVID, VISTA
Laser treatments year 2	0.55 (0.1000)	Normal	DRCR and assumption
RBZ injections year 3	2.9 (0.32)	Normal	RESTORE
ABC injections year 3	3.8 (0.32)	Normal	assume same decrease as for RBZ
Laser treatments year 3, mono	0.55 (0.1000)	Normal	DRCR and assumption
Regression model for BSE utility Constant LogMAR coefficient Age coefficient	 0.86 (0.068) -0.386 (0.046) -0.001 (0.002)	 Normal Normal Normal	 Czoski-Murray
Cost of visual impairment (annuall)	€ 64.7 (25%) € 44.0 (25%) € 41.7 (25%)	Gamma	Literature and assumption
TP of change of VA years 1 – 3 (by treatment arms, health state and cycle)	Matrix of counts	Dirichlet	RESTORE (counts by treatment arms, health state and cycles)
TP of withdrawal years 1 – 3 (by treatment arms)	Matrix of counts	Beta	RESTORE (counts cycles)
Long term TP of change in VA, adjusted WESDR	0.045 worsening, 0.035 improving	Dirichlet	Literature and assumption
Proportion treated in WSE	0.596	Beta	RESTORE
RR mortality in DME	2.45 (0.15)	Normal	Literature, reported RR and SE (or 95% conf. intervals)

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