Cost–effectiveness of autologous retinal pigment epithelium and choroid translocation in neovascular AMD

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Abstract

- AIM: To assess the cost–effectiveness of autologous retinal pigment epithelium and choroid translocation (PATCH) in neovascular age-related macular degeneration (AMD).
- METHODS: Visual acuity and complication rates of published patient series were used to determine the incremental utility of treatment for the patient. The utility data applied assumed that the better eye was affected. Comparator was a meta-analysis of recent control groups, in which patients received best supportive care. To assess cost-effectiveness, costs per quality adjusted life years (QALYs) and costs of avoiding low vision (“legal blindness”, i.e. ≤20/200) were calculated. Costs were based on a German sick fund perspective and in a scenario on US costs. Robustness of the model was investigated by univariate and probabilistic multivariate sensitivity analysis (PSA).
- RESULTS: Cost-utility analysis showed surgery to be the dominant (“cost-saving”) strategy for Germany and for the US in both, cost-effectiveness and cost-utility analysis (costs per QALY). In the sensitivity analysis the intervention remained dominant or cost-effective in all scenarios investigated. Clinical outcomes and duration of modeling were the most influential factors in the sensitivity analyses.
- CONCLUSION: Therapy of neovascular AMD by PATCH is a cost-effective treatment option for selected patients, who are not well suitable for other current treatment options.

KEYWORDS: age-related macular degeneration; choroidal neovascularization; cost-utility analysis; macular surgery; QALY

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INTRODUCTION

During the last years health care expenditures in the major western countries have reached a high level. As a reaction often cost-containment measures were implemented. Furthermore the proportion of elderly people in these countries will keep on growing during the next decade. This development places a heavy burden on the healthcare system (1,2). As a consequence it will become increasingly important for new technologies to show that they are cost-efficient. Increasing expenditures because of the ageing society are expected also in ophthalmic care, where many diseases are related to age and require life-long treatment. This applies especially for age-related macular degeneration (AMD): a major reason of severe visual impairment and blindness in the Western world (3,4), which is associated with a significant reduction in the patient's quality of life (5). With estimated 50 000 newly diagnosed patients with AMD per year for Germany today the treatment costs are estimated between 300 000 and >1 billion € per year (6). Projections for Germany assume that due to the aging society expenditures in 2050 could be more than 4 times higher than the expenditures today (6). A variety of surgical and medical treatment options have recently become available, therefore each treatment option has to show that costs in relation to their benefit are in an acceptable range for the society.

A current surgical procedure, autologous retinal pigment epithelium (RPE) and choroid translocation (PATCH) allows stabilization of visual acuity in a high percentage of patients with neovascular AMD in selected cases which are not well suitable for other treatment options (7,8). In addition, long-term
results up to 4 years are available showing a good long-term stabilization [7]. On the other hand this surgical procedure is associated with surgery and has potential complications, especially during the first year [8]. Still this procedure warrants further investigation, as it allows an active treatment option with good long-term stabilization in patients not well suitable for other treatments, including anti-VEGF (vascular endothelial growth factor) treatments such as with ranibizumab [9,10]. The current study therefore investigates the cost-effectiveness of autologous translocation of the choroid and RPE in patients with neovascular AMD. This includes modeling disease and costs, which allows weighting long-term stabilization versus short-term complications. Thus the overall benefit from the treatment is derived, informing on value for money, or - in the terms of a health economist - cost-effectiveness.

**MATERIALS AND METHODS**

**Methods** Cost-utility analysis (CUA) is a widely accepted international standard in health economics to evaluate the acceptability of a new health care technology or new pharmaceutical products. Briefly, all relevant costs associated with the treatment are compared to its clinical effectiveness. To provide an adequate measure for clinical effectiveness, both the change in the quality of life and duration of the benefit by the intervention (in years) has to be considered. Furthermore, to allow comparison of different new technologies and disease areas, a common measure is advantageous for decision making. Therefore in health economics the clinical effectiveness is frequently transferred into "utilities". An utility of "1" means perfect health while "0" describes death. The incremental utility provided by a new technology integrated over the duration of the benefit provides one single measure for both, quality of life and the duration of treatment effect. Thus of the denominator QALY (quality-adjusted life year) is obtained, describing one theoretically gained life year in perfect health, to which the costs of the necessary technology are compared. Transferred to the case of AMD, the outcome of treatment is usually stabilized or improved visual acuity as compared to the spontaneous course translating into a gain of utility and QALYs for the patient.

Despite this being a widely accepted international standard for evaluations [11] there is a long-standing scientific debate on the appropriateness of the QALY-concept. One other possibility of assessing interventions is to investigate disease-specific cost-effectiveness, such as in "costs per line of vision" [12], "gain ≥ 15 letters" [9,10] or prevented blindness. Prevented "legal blindness" would be a suitable concept for the low-vision AMD patients investigated here, which is at the same time well compatible with the Markov modeling approach taken in the CUA. Therefore in addition to cost-utility analysis the cost-effectiveness is calculated per patient in whom a visual acuity ≤ 0.2 (20/200) is prevented.

**Clinical efficacy and modeling** The model for the cost-utility and cost-effectiveness analysis of choroid and RPE translocation surgery versus supportive care was built in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). The 1 year clinical efficacy data were derived from a published case-series from the Cologne university eye hospital [8]. Early complications were also taken from that publication. Long-term follow-up data were obtained from a relatively large 84 eye cohort study [7]. Table 1 summarizes the main outcomes and complications. For the comparator supportive care was chosen, as the majority of patients were not eligible for other therapies such as intravitreal anti-VEGF. The clinical data from a recent meta-analysis were applied [13], which combines the control-groups of several comparable large randomized AMD trials such as e.g. from MARINA.

As the majority of cost-differences between treatment options occur in the first year - while recurrence and deterioration is more long-term - a two-stage model was built: a relatively detailed decision tree for year one and a Markov model for the longer time horizon (Figure 1). A time horizon of life time was chosen, mean patient age entering the model was assumed to be 74 years based on Heussen et al. [14]. Due to the high patient age death of any cause needs to be considered, which is integrated in the model applying the recent gender-specific German survival tables 2004/2005 of the Federal Office for Statistics, Wiesbaden (http://www.}

### Table 1 Summary of most relevant clinical outcomes

<table>
<thead>
<tr>
<th>Visual Acuity</th>
<th>Peripheral Autologous Translocation of Retinal Pigment Epithelium and Choroid (PATCH)</th>
<th>Supportive Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 months</td>
</tr>
<tr>
<td>Percent of patients with visual acuity &gt; 20/40</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Percent of patients with visual acuity ≥ 20/200</td>
<td>61%</td>
<td>53%</td>
</tr>
<tr>
<td>Percent of patients with ≥ 6 lines decrease</td>
<td>NA</td>
<td>13%</td>
</tr>
<tr>
<td>Percent of patients with &lt; 3 lines decrease</td>
<td>NA</td>
<td>76%</td>
</tr>
<tr>
<td>Mean logMAR deterioration compared to baseline</td>
<td>NA</td>
<td>0.06</td>
</tr>
</tbody>
</table>

1 Combined data from [13] and [17].
2 Metaanalysis data from Wong et al [13]; an asterix "*" indicates significant heterogeneity in the metaanalysis.

NA: does not apply.

NA: does not apply.
It was further assumed that the treatment period (surgical procedures) was one year, and that all surgical patients received at least 2 pars plana vitrectomy (ppV) surgeries (for primary surgery and for silicone oil removal). For the utilities it was assumed, that only the better-seeing eye was treated, which usually is the case [8]. A discount rate of 5% was applied for both costs and QALYs in the baseline scenario, as most commonly recommended for Germany (www.ispor.org).

### Conversion of visual acuity into utilities

In the absence of adequate primary data regarding the benefit for the patients by the treatment, the visual acuity values from the studies were converted into utilities. Therefore data of Bansback [14, 15] were used for the baseline scenario. Those utilities had been obtained by time trade off analysis and are summarized in Neubauer et al [16]. This means that all data-and hence the model-applies to the eye with better visual acuity.

### Costs

An important step of the cost-effectiveness/utility analysis is to determine the costs for the different treatment options. Table 2 gives an overview of all relevant costs used, including those for adverse events. Perspective was limited to direct costs relevant for the German statutory sick funds. Surgery costs were taken from the DRG system 2008 applying weights and assuming an average base rate for Germany of 2800 €. Costs for the different Markov states included in-patient and out-patient costs, and other medical costs such as fall-related fractures. Those costs were derived from detailed research performed in various countries [17-19] and had been calculated and validated by a survey of German experts for the groups of visual acuity in AMD, especially the low vision groups [16]. Results were validated against available published literature [20].

For example, costs of 1245 € per quarter and patient for the total group of patients with visual acuity <0.1. Results were validated against available published literature [20]. For the US scenario costs were taken from recent US cost-utility publications adding the CPT code 67043 for performing vitrectomy [17, 18, 21, 22]. Further details are given in Table 2.

### Sensitivity Analysis

The starting point for the sensitivity analysis was the baseline scenario. All relevant parameters were changed in the univariate sensitivity analysis with baselines:

- Utility values from Bansback et al [14, 15]

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**Table 2  Summary of the most relevant costs used in the model**

<table>
<thead>
<tr>
<th>Costs Germany in €</th>
<th>Source Germany</th>
<th>Costs US in US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitreoretinal surgery (initial and at silicone oil removal, for complications such as retinal detachment and reinserion of the graft)</td>
<td>DRG[1] C15Z</td>
<td>$ 2,530.81 (from CPT code 67043 in year 2008)</td>
</tr>
<tr>
<td>Recurrence of choroidal neovascularization</td>
<td>Laser treatment based on German outpatient tariff (EBM 2008); laser treatment chosen as most relevant therapy option based on[9]</td>
<td>$ 1,374 from Brown et al[21]</td>
</tr>
<tr>
<td>Ophthalmic follow-up and examinations in year 1</td>
<td>Pauleikoff et al. 2008 (in press); considering only medical examination costs per year (physician fees and ophthalmic diagnostics)</td>
<td>$ 1,226 (Calculated based on Brown et al. [17] as: $173 + 6 x $65 + 6 x $44 for OCT+ 3 x $133 FA) Based on Earnshaw et al. [21] and Javitt et al.[19]</td>
</tr>
<tr>
<td>Annual vision-related health care costs</td>
<td>Costs were derived from detailed research performed in various countries [17-19] and had been calculated and validated by a survey of German experts for the groups of visual acuity in AMD, especially the low vision groups [16]. Results were validated against available published literature [20]. Based on Earnshaw et al. [21] and Javitt et al. [19]</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1  Model structure** A combined decision tree (for year 1) and Markov model (for year 2-n) was applied to model cost-effectiveness. Detailed clinical data and costing sources are described in the methods section. The (M) marks those nodes in the decision tree, where the Markov long-term model part starts. Patients may transition to death from any Markov state. The two Markov states [0.05-0.1] and <0.05 together represent "legal blindness" as used in cost-effectiveness modeling.
Intervention remained cost-effective in all sensitivity cost-effectiveness and cost-utility analyses (costs per QALY). A cost-saving (“dominant”) strategy in most cases in both, Germany and the US. Main results and the sensitivity analysis are shown in detail in Table 3. Briefly, surgery was a cost-saving (“dominant”) strategy in most cases in both, cost-effectiveness and cost-utility analysis (costs per QALY). Intervention remained cost-effective in all sensitivity scenarios investigated with clinical outcomes and duration of modeling being the most influential factors. Figure 2 shows the multivariate probabilistic sensitivity analysis, which confirms the intervention being cost-effective for most usually discussed thresholds (e.g. 50 000 USD/QALY).

**DISCUSSION**

Treatment of AMD is an example of increasing health care expenditures as a consequence of an aging society. Cost-utility analysis is a well accepted method to support informed decision making under budgetary constraints. Based on the clinical efficacy of RPE and autologous choroid transplantation surgery [8] this study shows that this regimen also is a cost-effective treatment for certain patients with AMD in Germany and the US. The intervention was dominant in most of the scenarios investigated and cost-effective in all.

### Table 3 Results and univariate sensitivity analysis

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Summary Result</th>
<th>Year 1</th>
<th>Year 2-n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost [€ per QALY]</td>
<td>Incremental costs</td>
<td>Incremental gain in QALYs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.42</td>
<td>3’026</td>
</tr>
<tr>
<td>Altered utility conversion of visual acuity</td>
<td>dominant (-616)</td>
<td>-257 €</td>
<td>3’026</td>
</tr>
<tr>
<td>All costs in year one</td>
<td>-20%</td>
<td>dominant (-1’035)</td>
<td>-257 €</td>
</tr>
<tr>
<td></td>
<td>+20%</td>
<td>dominant (-2’572)</td>
<td>-1’074 €</td>
</tr>
<tr>
<td>Altered discount rate</td>
<td>3%</td>
<td>dominant (-1’187)</td>
<td>-900 €</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>dominant (-1’353)</td>
<td>-370 €</td>
</tr>
<tr>
<td>Patient age</td>
<td>60 years</td>
<td>dominant (-1’740)</td>
<td>-1’195 €</td>
</tr>
<tr>
<td></td>
<td>80 years</td>
<td>dominant (-1’535)</td>
<td>-399 €</td>
</tr>
<tr>
<td></td>
<td>5 years</td>
<td>dominant (-1’211)</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>10 years</td>
<td>dominant (1’466)</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>20 years</td>
<td>0.41</td>
<td>3’026</td>
</tr>
<tr>
<td>Percent of patients with visual acuity of 20/125-20/160 for after year one **</td>
<td>-20%</td>
<td>0.63</td>
<td>3’026</td>
</tr>
<tr>
<td>US base case scenario</td>
<td>0.42</td>
<td>3’026</td>
<td>-0.21</td>
</tr>
</tbody>
</table>

- Discount rate: 5% per year for both, costs and utilities
- Patient age: 74 years
- Model duration: lifetime

In order to investigate the robustness of the model in terms of these assumptions, the above mentioned assumptions were varied within plausible ranges in the context of the univariate sensitivity analysis (Table 3). In addition, a multivariate probabilistic sensitivity analysis (PSA) was performed using Palisade @Risk software (version 4.5, Palisade Corporation, Ithaca, NY, USA) based on the input ranges given in Table 3. The PSA considers all known uncertainties of model inputs and yields the overall probability of being below a certain cost-effectiveness threshold.

**RESULTS**

In the baseline scenario autologous RPE and choroid translocation was found to be the dominant strategy for both Germany and the US. Main results and the sensitivity analysis are shown in detail in Table 3. Briefly, surgery was a cost-saving (“dominant”) strategy in most cases in both, cost-effectiveness and cost-utility analysis (costs per QALY). Intervention remained cost-effective in all sensitivity scenarios investigated with clinical outcomes and duration of modeling being the most influential factors. Figure 2 shows the multivariate probabilistic sensitivity analysis, which confirms the intervention being cost-effective for most usually discussed thresholds (e.g. 50 000 USD/QALY).

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Treatment of AMD is an example of increasing health care expenditures as a consequence of an aging society. Cost-utility analysis is a well accepted method to support informed decision making under budgetary constraints. Based on the clinical efficacy of RPE and autologous choroid transplantation surgery [8] this study shows that this regimen also is a cost-effective treatment for certain patients with AMD in Germany and the US. The intervention was dominant in most of the scenarios investigated and cost-effective in all.

Negative costs per QALY were calculated in the base case, which means cost-savings. For interventions to be cost-effective often thresholds of e.g. 50 000 US$ (36 000 €) are discussed, but any threshold is ultimately arbitrary and disputed (www.smdm.org) [23]. The more relevant question scenarios investigated with clinical outcomes and duration of modeling being the most influential factors. Figure 2 shows the multivariate probabilistic sensitivity analysis, which confirms the intervention being cost-effective for most usually discussed thresholds (e.g. 50 000 USD/QALY).
The graph gives the likelihood of the surgical intervention to be below a given threshold for cost-effectiveness. It can be seen, that therapy is cost-effective even for low thresholds, e.g. >90% probability for 6'874 € /QALY to be asked is how much a society is willing to pay for an improvement by a specific technology or specific medical outcome such as avoiding legal blindness. This can secondarily be translated into Euros per quality-adjusted life year (QALY). Any threshold varies between countries due to different national preferences, perceptions and cultural differences. There are also varying performances of the healthcare systems to be considered. The sensitivity analysis (Table 3) demonstrated that the model is very robust against variations of the input variables. However, due to the overall better long-term prognosis modeling hints that younger patient age appears to be beneficial. In addition, visual acuity >0.1 appears to be advantageous - although it should be kept in mind that the surgical intervention investigated is indicated only if other treatment options are not feasible, including anti-VEGF therapy[6]. This limits its application to selected patients.

In summary, autologous RPE and choroid translocation has extended the treatment options for exudative AMD by providing a technique for patients not eligible for other therapies such as anti-VEGF, which also is cost-neutral or even cost-saving. It certainly meets the criteria of cost-effectiveness.

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Costs and QALYs yielded in summary and in the different model parts (Figure 1). The Costs per QALY and costs per avoiding on patient with "legal blindness" are given. "Dominant" means that the intervention is cost-saving. The base case scenario assumes the better seeing eye to be affected using utility values from Bansback [14,15], a lifetime model duration with a mean patient age at surgery of 74 years. Both, future costs and utilities are discounted at 5% to adapt them to todays costs and patient benefits. * Other lower VA categories equally increased / decreased to match new proportions (baseline case is: 44%).

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