

Navigated laser in diabetic macular edema: the impact of reduced injection burden on patients and physicians—who wins and who loses?

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Abstract

• We inquired the impact of reduced therapy discontinuation in diabetic macular edema (DME) on physician's revenue considering anti-vascular endothelial growth factor (VEGF) monotherapy and its combination with Navilas treatment. Data were collected on injection frequency, treatment discontinuation and reimbursement fees for DME treatment with anti-VEGF compared to anti-VEGF in combination with navigated laser. Based on these data an economic model was built to compare physicians revenue over a 5y period using either therapy for 4 European countries and the USA. Due to patients' higher therapy adherence, physicians using navigated laser therapy with anti-VEGF generate similar or higher revenues compared to VEGF monotherapy in all analyzed countries. The use of Navilas decreases the patient's injection burden at the same clinical outcome, while the physician's revenue remained stable or increased. Therewith, therapy discontinuation in DME can be reduced using the combination therapy with Navilas.

• **KEYWORDS:** diabetic macular edema; laser therapy; Navilas; cost-effectiveness; injection burden; adherence

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INTRODUCTION

Anti-vascular endothelial growth factor (VEGF) treatment of diabetic macular edema (DME) has significantly improved visual outcomes compared to previous laser photocoagulation therapy. Although intravitreal injections have become routine, their number and frequency put a significant burden on patients raising compliance issues in addition to manage their systemic diabetes and other complications and risks. A relevant decrease in the number of injections has only been shown in studies, withholding anti-VEGF drugs in the case of persistent fluid and frequent application of focal laser treatment^[1]. Continued adherence to chronic intravitreal injections over several years is required to maintain the initial vision gain for a successful treatment. For many patients, the efforts and time consumption of injection visits limits their adherence to an insufficient level in real-life^[2]. This has resulted in ongoing development of drugs with extended durability or long term drug delivery systems. An alternative to anti-VEGF monotherapy is the combination with other second-line treatments such as navigated laser therapy (Navilas[®]) to reduce injection burden for improved long term adherence while securing better outcomes.

SUBJECTS AND METHODS

Ethical Approval All studies cited in this paper were conducted in accordance with the Declaration of Helsinki.

Anti-VEGF monotherapy in DME requires a strict regime of intravitreal injections. We collected estimates on drop-out rates from anti-VEGF therapy from clinical research and real world data. From clinical data we estimated the impact of Navilas use on visual acuity when combined with anti-VEGF therapy and the resulting decrease in intravitreal injections (Table 1)^[3-5].

Revenues for physicians in Germany, France, Switzerland, Holland and the USA were calculated from public reimbursement fees for the relevant DME treatment services as published by national authorities (Table 2). These data were used to build an MS-Excel model comparing the revenues earned by physicians using either therapy over a 5y period.

RESULTS

Injection Burden and Adherence Injection frequency and patient adherence are inversely related^[6] and this plays

Table 1 Effect of navigated laser therapy on injection number, visual acuity and retinal swelling

| Study | Patients | | Injection number | | BCVA score at 12mo | | CRT baseline (μm) | | Mean CRT at 12mo (μm) | |
|--|----------|----|------------------|---------|--------------------|---------|-------------------|---------|-----------------------|---------|
| | L+A | A | L+A | A | L+A | A | L+A | A | L+A | A |
| Liegl <i>et al</i> ^[3] | 34 | 32 | 3.9±1.3 | 6.9±2.3 | 8.4±8.3 | 6.3±6.5 | 441±162 | 444±117 | -129±170 | 105±107 |
| Barteselli <i>et al</i> ^[4] | 20 | | 4.0±1.2 | | 10.6±18 | | 484±117 | | -137±126 | |
| Payne <i>et al</i> ^[5] | 60 | 60 | 10.1 | 10.6 | +9.4 | +9.5 | 475 | 480 | -166 | -146 |

BCVA: Best-corrected visual acuity; CRT: Central retinal thickness; L+A: Laser+anti-vascular endothelial growth factor; A: Anti-vascular endothelial growth factor.

Table 2 Treatment remunerations in the USA and four European countries (cost may vary from region to region or within certain frameworks)

| Treatments | Germany (EUR) | Swiss (CHF) | Netherlands (EUR) | France (EUR) | USA (USD) |
|------------------------------|---------------|-------------|-------------------|--------------|-----------|
| Intravitreal injection | 170 | 120 | 460 | 84 | 132 |
| Optical coherence tomography | 70 | 141 | - | 72 | 43 |
| Follow-up | 30 | - | 93 | 28 | 52 |
| Angiography | 65 | 118 | - | 64 | 115 |
| Fundus photography | 20 | 94 | 39 | 19 | 64 |
| Navilas treatment | 125 | 140 | 339 | 146 | 526 |

a significant role in the therapy of DME. In randomized controlled trials (RCTs) for DME the average drop-out rate in the first year is about 18%, consistent with age-related macular degeneration (AMD) studies^[7-9]. In real-world clinical practice, however, a significant percentage of patients tend to be less motivated due to anxiety, comorbidities, age or socioeconomic reasons^[10]. In a recent survey, DME patients complained about injection stress and time-consuming organization of the multiple injection sessions. Consequently, they desired a reduction in the number of injections^[2]. Therefore, discontinuation rates in real world are much higher than in RCTs: in a French real world study it was estimated that less than 50% of AMD patients receive the regular number of injections in the prescribed intervals^[11-12]. DME patients in the USA also attend less injection procedures than prescribed, accepting a less effective treatment to save time and minimize injection induced stress^[12]. Consistently, in Europe, Wecker *et al*^[13] reported a 40% loss of patients within the first year. Based on these data we would conservatively estimate that about 30% of patients will drop-out from the treatment within one year.

If the number of injections can be reduced patients should be more likely to adhere to the scheduled scheme. A frequency-adherence relationship is well known from oral medication across many therapeutic areas^[10]. When patients drop out from regular therapy to reduce their individual injection burden, this endangers not only vision but also puts physicians and pharmaceutical companies under pressure to provide alternatives. Consequently, the need for less frequent injection schemes is driving research for future therapies developed by the pharmaceutical industry such as long-lasting anti-VEGF therapies^[14]. Brown *et al*^[15] reported that conventional laser treatment directed to non-perfused areas only based on

ultrawide-field imaging was not able to reduce significantly the burden of treatment. In contrast, navigated laser therapy (Navilas[®]) in the macular region, which has been introduced as a relevant step to reduce invasive eye treatment, is available and in use today.

Navilas[®] provides automated high precision retinal laser interventions, reducing the number of necessary injections and improving adherence and long term outcome. The navigated laser optimizes the effect of intravitreal injections by directly decreasing retinal leakage and swelling. As a consequence, the injection burden decreases significantly without compromising therapeutic success.

Navilas is a device (ODOS GmbH, Teltow, Germany) that combines imaging (infrared, colour or fluorescein angiography) and integrated laser treatment of the retina, including pattern laser generation. The device offers as main characteristic a fast retina tracking by computerized image and target assistance systems, resulting in high precision and reproducibility of theoretically less than 60-110 μm. It fundamentally differs from other laser devices by applying not a slitlamp, but a scanning slit-based instrument. The instrument takes about 25 images per seconds in imaging or treatment mode. For focal laser treatment, the field of view is 50°, and the optical resolution is 1280×1024 pixels, for that angle, resulting in approximately 20-26 pixels per degree. For panretinal laser treatment, a specific widefield lens, resulting in 85° field of view, is used. Because of the slit imaging principle, images of high contrast and sharpness can be obtained. The laser treatment plan is made by physicians on a static image from the fluorescein angiogram and then registered and overlaid onto the live retinal image in real time. Navilas Laser system automatically prepositions the laser beam to the planned

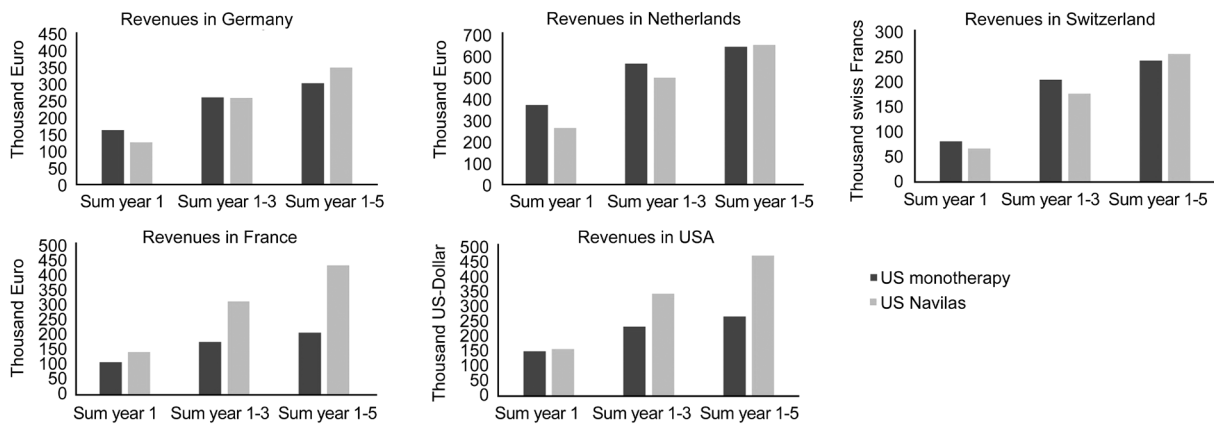


Figure 1 Revenues for anti-VEGF monotherapy (dark grey) and combination-therapy with Navilas® (green) were cumulated over a one, three and five-year time-horizon Revenues for anti-VEGF monotherapy in Germany, Netherlands, Switzerland, France and USA indicated in grey. Adjacent green bars indicate revenues for Navilas®-anti-VEGF combination therapy in the respective country. All numbers denominate country specific currencies.

treatment locations using eye-tracking feature, allowing the surgeon to complete the treatment plan with great accuracy. A post-treatment report by the device documents the location and parameters for each laser spot. The clinical efficacy of Navilas® treatment was demonstrated in three clinical studies, whose clinical results are summarized in Table 1.

In all studies, Navilas®, in addition to anti-VEGF injections, reduces retinal thickness as a proxy for retinal pathology and improves visual acuity^[3-5]. Moreover, the number of anti-VEGF injections is significantly reduced without affecting the physiologic and functional outcome^[3]. The reduced injection burden at comparable improved visual performance is expected to have a positive impact on patients' adherence. Low-responders to anti-VEGF therapy are expected to benefit from Navilas® as a second-line therapy option. We estimate that from an assumed 30% drop-out rate in a real-world setting, Navilas® treatment will reduce the rate to 15%. This value is equivalent to the drop-out rates in highly motivated study populations as observed in anti-VEGF clinical trials for DME^[7,9].

From an ophthalmologist's perspective besides patient outcomes the adoption of Navilas® therapy has several aspects, such as the impact on time and clinic resources, but also on overall revenues for the practice or clinic. Worldwide, intravitreal injections and navigated laser therapy are reimbursed by public and private insurances. The overall revenues per patient receiving intravitreal injections depend on patient adherence. In detail, the question arises, if and how much the revenues differ for patients managed with a combination therapy of Navilas® and anti-VEGF vs anti-VEGF monotherapy. Besides the number of injections and the laser fees also discontinuation of the injection scheme needs to be considered.

Cumulated Revenues by Country We therefore built a short-term cost model with a 5-year time horizon using MS-Excel.

The injection scheme for anti-VEGF was based on recent guideline recommendations and the reduction of intravitreal injections with Navilas was derived from the respective clinical trials^[3,13]. We assumed three main cost components: reimbursement for intravitreal injections, Navilas treatment and follow-up consultations including optical coherence tomography/angiography and funduscopy. Sources were the respective national insurance reimbursement schemes like (e.g. EBM in Germany or NZA Zorglijste in the Netherlands). As we aim to investigate revenues of ophthalmologists, pharmaceutical costs were excluded. Only services reimbursed by public health insurances were included, self-payments and special insurance plans were not considered. The costs/reimbursements included are listed in Table 2.

The simulation model of total revenues included 100 hypothetical patients over a 5-year time period, assuming that Navilas® reduces drop-out rates from 30% to 15% over one year. In the model it was assumed, that all patients started therapy with anti-VEGF and therefore received 3 initial loading phase injections.

Cumulated revenues for Navilas® therapy combined with reduced anti-VEGF injections and increased adherence reaches or exceeds the monotherapy revenues over a 5y time-period in most countries.

Figure 1 displays the revenues for the respective countries for anti-VEGF monotherapy (grey columns) and the combination therapy with Navilas® (green columns) over a time period of 1, 3 and 5y. For injections only, the first year creates most revenues, while for the Navilas®-anti-VEGF combination the higher patient adherence results in increased revenues over the subsequent years. Therefore, the combination therapy with Navilas® results in higher total physician revenues in most countries. This means for the patients, that visual acuity results were achieved with less burden by received injections.

For all stakeholders, physicians, patients and society, less treatment discontinuations translate into a more efficient use of resources: fewer injections are “wasted” without a contribution to maintaining visual acuity results. A higher amount of free treatment capacity can help to avoid bottlenecks for those with the need of earlier injections. The total number of injections per patient and for all patients remains rather relatively stable. Thus, even for the pharmaceutical manufacturers of anti-VEGF a positive effect by better clinical outcomes without relevant reductions in numbers exists.

DISCUSSION

For patients with DME, the current data shows that the combination of Navilas[®] with intravitreal anti-VEGF provides equal clinical outcomes with a reduced injection burden. This reduces the stress level that frequent injections put on patients and saves their time. The combination of injections with early addition of Navilas[®] provides additional assurance, that the initial therapeutic effect is preserved in the mid- and long-term. For physicians, Navilas[®] is a good option to reduce their patients’ injection burden. The effect of adding Navilas[®] to anti-VEGF therapy in DME on the total revenues per patient were investigated in a short-term economic model and were found to remain stable or increased based on the individual countries reimbursement scheme. In summary, patients, physicians, and society would benefit from this increased efficiency.

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