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Navigierte Laserkoagulation und intravitreale Ranibizumab Injektion im Vergleich zur alleinigen Ranibizumab Therapie bei der Behandlung des diabetischen Makulaödems – Erarbeitung eines Therapieschemas

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Inhaltsverzeichnis

EIDESSTATTLICHE VERSICHERUNG

Hiermit erkläre ich, die hier vorliegenden Veröffentlichungen im Rahmen einer kumulativen Dissertation mit dem Thema

Navigierte Laserkoagulation und intravitreale Ranibizumab Injektion im Vergleich zur alleinigen Ranibizumab Therapie bei der Behandlung des diabetischen Makulaödems – Erarbeitung eines Therapieschemas

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Abkürzungsverzeichnis

AGE	Advanced Glycation Endproduct
BVZ	Bevacizumab
BCVA	Best corrected visual acuity
CRT	Central retinal thickness
CSME	Clinical significant macular edema
DMÖ	Diabetisches Makulaödem
DOG	Deutsche ophthalmologische Gesellschaft
DR	Diabetische Retinopathie
FLA	Fluoreszenzangiographie
fLK	Fokale Laserkoagulation
IGF	Insulin-like growth factor
IRMA	Intraretinal microvascular abnormalities
IVOM	Intravitreale operative Medikamenteneingabe
IVT	Intravitreale Injektionen
MLT	Makula Lasertherapie
NMLT	Navigierte Makula Lasertherapie
NPDR	Nicht-proliferative diabetische RP
OCT / SD-OCT	Optical Coherence Tomography
PDGF	Platelet-derived Growth Factor
PDR	Proliferative diabetische Retinopathie
PIGF	Placental Growth Factor
PRN	Pro re nata
Rbz	Ranibizumab
ROS	Reactive Oxygen Species
VEGF	Vascular Endothelial Growth Factor
nm	Nanometer
µm	Mikrometer
mm	Millimeter

1. Einleitung

Die Häufigkeit des Diabetes mellitus ist in den letzten Jahrzehnten weltweit stark angestiegen. Bis zum Jahre 2045 wird mit bis zu 625 Millionen Erkrankten gerechnet. Dies entspricht einer deutlichen Zunahme der derzeit etwa 422 Millionen bekannten Fälle. (1) Es ist daher mit einer erhöhten Inzidenz diabetischer Folgeerkrankungen wie der diabetischen Retinopathie (DR) und den daraus resultierenden sozioökonomischen Folgen zu rechen. (2, 3)

Die diabetische Retinopathie (DR) ist eine häufige Komplikation des Diabetes mellitus und ist in den westlichen Industrienationen die häufigste Ursache schwerer Visusminderung und Erblindung im erwerbstätigen Alter. (4-7)
Die Pathogenese der DR ist ein komplexes Zusammenspiel vieler Faktoren das bis heute noch nicht vollständig aufgeklärt ist. (8, 9) Ausgangspunkt ist dabei die durch eine Dysfunktion des Glukosestoffwechsels hervorgerufene Hyperglykämie. Diese entsteht entweder durch eine Zerstörung exokriner Pankreaszellen mit der Folge einer fehlenden Insulinproduktion (Typ I Diabetes) oder durch eine verminderte Wirkung von Insulin an den Zielzellen des menschlichen Organismus (Typ II Diabetes). (10)
Bedingt durch die Hyperglykämie führen neuronale Dysfunktionen, oxidativer Stress und die Akkumulation von Advanced Glycation Endproduct (AGE) zur Ausbildung einer Mikroangiopathie. Gekennzeichnet ist diese Mikroangiopathie durch einen Verlust von Perizyten an der Basalmembran und eine durch AGE induzierte Basalmembranverdickung. Des weiteren wird durch eine verminderte Proliferation der Endothelzellen eine Endothelzellschädigung bedingt welche im weiteren Verlauf zu einer erhöhten Gefässpermeabilität und Mikroinfarkten führt. (11)
Veränderte Sauerstofftransporteigenschaften der Erythrozyten, Mikroangiopathie und erhöhte Thrombozytenaggregation, bedingt durch den erhöhten Blutzucker, führen zudem zu einer Hypoxie in den retinalen Gefäßen. Als Folge dieser morphologischen und biochemischen Veränderungen werden vermehrt proinflammatorische Faktoren wie z.B. Vascular Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF), Zytokine und Reactive Oxygen Species (ROS) freigesetzt. (12, 13)

VEGF wird vor allem in den Monozyten, Perizyten und Endothelzellen gebildet und wird in fünf Subtypen unterteilt, wobei VEGF-A für die pathologischen Veränderungen der Netzhaut ursächlich ist. Als vasoaktiver Faktor führt VEGF durch Phosphorilisation an den Tight-junctions der Endothelzellen der Retina, und über eine rezeptorvermittelte Leukostase zu einem Zusammenbruch der Blut-Retinaschranke und somit zu einer Leckage von u.a. Proteinen und Serumbestandteilen in den subretinalen Raum. (14-18) Weiterhin fördert ein erhöhter VEGF-Spiegel über eine Signalkaskade die Ausbildung von Neovaskularisationen, deren fragiler Gefäßwandaufbau unter anderem zu Glaskörperblutungen und Exsudationen führen kann.(19, 20)

1.1. Diabetische Retinopathie

Als diabetische Retinopathie (DR) werden die durch die Hyperglykämie bedingten biochemischen und morphologischen Prozesse bezeichnet, die zu einer Veränderung der Netzhaut führen. Je nach Progression der Veränderungen wird zwischen einer oft unbemerkten einfachen DR, einer nicht-proliferativen DR (NPDR) und einer proliferativen DR (PDR) unterschieden.

1.1.1. Nicht-proliferative diabetische Retinopathie

Bei der NPDR kommt es in Folge des erhöhten Blutzuckers zu Zellveränderungen und Zellschäden mit mikroangiopathischen Veränderungen der Netzhaut. Es bilden sich sowohl Mikroaneurysmen und intraretinale Blutungen als auch Lipidablagerungen und intraretinale mikrovaskuläre Anomalien (IRMA) aus. (6, 21-24)

1.1.2. Proliferative diabetische Retinopathie

Als Folge des Zelluntergangs und der zunehmenden Gewebshypoxie führt eine gesteigerte Ausschüttung von Wachstumsfaktoren wie VEGF, PDGF, IGF und PIGF zu einer von der Papille oder der Netzhautoberfläche ausgehenden Gefäßneubildung. (25-29)

1.1.3. Diabetisches Makulaödem

Ein diabetisches Makulaödem kann sich in jedem Stadium der DR ausbilden. Es ist bedingt durch den Zusammenbruch der Blut-Retinaschranke und folglich bedingtem Austritt von Proteinen in den subretinalen Raum. Als Folge wird der osmotische Gradient für den Flüssigkeitsabtransport vermindert, und somit der Rücktransport des durch die erhöhte Gefäßpermeabilität bedingten Austritts von Serum durch die Pumpen des retinalen Pigmentepithels erschwert. (17, 23)

1.2. Therapie der diabetischen Retinopathie

1.2.1. Reduzierung begünstigender Risikofaktoren

Ein entscheidender prognostischer Faktor ist die konsequente Einstellung des Blutzuckers und des Blutdrucks. Nikotinkarenz, Gewichtsreduktion und die Normalisierung der Blutfette können das Risiko der Entstehung und der Progression der pathologischen Netzhautveränderungen vermindern.

1.2.2. Lasertherapie

Eine erfolgreiche retinale Laserphotokoagulation wurde erstmals von Campbell et al. 1964 beschrieben. (30, 31) Mit den Ergebnissen der ETDRS-Studie konnte erstmals eine langfristig signifikante Risikoreduktion für den Verlust der zentralen Sehschärfe bei rechtzeitig erfolgter fokaler Laserphotokoagulation (fLK) gezeigt und somit die Wirksamkeit der Laserphotokoagulation bestätigt werden. (32-34)
Seither wurde die Laserphotokoagulation durch die Einführung zahlreicher technischer Veränderungen zu einer schmerzloseren und präziseren Behandlungsform für retinale Erkrankungen weiterentwickelt. (35, 36)
Der Wirkmechanismus dieser Behandlungsform ist bis zum heutigen Stand letztlich nicht vollständig geklärt. Es wird jedoch davon ausgegangen, dass durch die Photokoagulation

stark sauerstoffverbrauchenden Photorezeptoren in der Peripherie zerstört und somit die Sauerstoffversorgung der zentralen Photorezeptoren verbessert wird. (37)
Die Indikation zu einer Lasertherapie besteht bei einem Vorliegen eines klinisch signifikanten Makulaödems (CSME). Dies wird als eine Zunahme der zentralen Netzhautdicke oder Lipidablagerungen in der Netzhaut innerhalb eines Radius von 500µm um die Fovea oder einer Verdickung der Netzhaut von mindestens der Größe einer Papillenfläche in einem Radius des Papillendurchmesser um die Fovea definiert. (23) Vor Einführung der VEGF-Inhibitoren galt die fokale Laserkoagulation der Netzhaut als therapeutischer Goldstandart eines CSME ohne foveale Beteiligung. Hierdurch konnte das Risiko einer Verschlechterung der Sehschärfe verringert werden. Eine Verbesserung der Sehschärfe wurde aufgrund der häufig mitbetroffenen Fovea jedoch nicht erzielt. (33, 34)

1.2.3. Intravitreale Therapieoptionen

Intravitreale Injektionen sind in den letzten Jahren durch die Erfolge der pharmakologischen Behandlung mit Kortikosteroide und VEGF-Inhibitoren zu einer wirksamen Behandlungsform und somit zu einer weiteren Therapieoption bei diabetischen Makulaödem (DME) und der profilerativen diabetischen Retinopathie (PDR) geworden. (38)
Die intravitreale Eingabe des Medikamentes mittels einer dünnen Kanüle erfolgt in 3,5 - 4mm Abstand zum Limbus durch die Sklera in den Glaskörperraum. Das Medikament gelangt so in maximaler Konzentration direkt an die Stelle hoher VEGF-Spiegel und proinflammatorischer Mediatoren. (23)

1.2.3.1. Intravitreale Kortikosteroidtherapie

Auf Grund ihrer anti-inflammatorischen Wirkung sind Kortikosteroide eine Therapieoption bei einer Vielzahl von Erkrankungen des hinteren Augenabschnittes. Dort führen sie zu einer verringerten Gefäßpermeabilität und verminderten Einwanderung von Entzündungszellen. (39-42)

Die Kortikosteroidtherapie erreicht gute Ergebnisse in Bezug auf die Visusentwicklung und die Makulaödemrückbildung bei der DR. Gleichzeitig erhöht sich jedoch das Risiko eines intraokularen Druckanstieges und einer Kataraktentstehung. (43, 44)

1.2.3.2. Intravitreale Therapie mit VEGF-Inhibitoren

Durch die Entwicklung intravitreal applizierbarer VEGF-Inhibitoren wie Bevacizumab (Avastin®, Genentech Inc., South San Francisco, CA, USA), Pegaptanib (Macugen®, Eyetech, NY, USA) und Ranibizumab (Lucentis®, Genentech, CA, USA) wurde die Behandlung vaskulärer Netzhauterkrankungen um eine zusätzliche Option erweitert.

Ranibizumab

Ranibizumab ist ein VEGF-Antiköperfragment welches an alle Isoformen des VEGF-A und deren Untereinheiten bindet und somit ihre biologische Aktivität aufhebt. (45)
In Studien konnte gezeigt werden, dass bei einem DMÖ unter regelmäßiger Ranibizumabtherapie eine langfristige Stabilisierung und Verbesserung des bestkorrigierten Visus als auch eine Abnahme der zentralen Netzhautdicke erreicht werden kann. (46-48)
Diese Ergebnisse konnten auch über einen längeren Zeitraum von 24 bis 36 Monaten bestätigt werden und zeigten weiterhin im Vergleich zur alleinigen Lasertherapie bei foveal mitbetroffener DMÖ einen verbesserten bestkorrigierten Visus und Reduktion der Netzhautdicke. (49-51) Die Deutsche Ophthalmologische Gesellschaft (DOG) und der Berufsverband der Augenärzte Deutschands (BVA) empfehlen daher die Therapie mit VEGF-Inhibitoren bei DMÖ als Primärtherapie.

2. Zielsetzung

Das Ziel der vorgestellten Studien war es die Kombination einer IVOM Therapie mit navigierter Makulalasertherapie zu prüfen und ein Behandlungsschema für die Kombinationstherapie zu erarbeiten.
Regelmäßige intravitreale Injektionen mit VEGF-Inhibitoren haben in Studien ihre Wirksamkeit in Bezug auf den bestkorrigierten Visus und die Reduktion der zentralen Netzhautdicke bei Patienten mit DMÖ gezeigt. (49, 52-55) Auf Grund dieser Ergebnisse empfehlen die Fachgesellschaften DOG und BVA zur Therapie des Fovea involvierenden DMÖ drei intravitreale Injektionen im monatlichen Abstand. Nach der Initialsphase sind die Befunde zu reevaluieren und es ist über die Weiterführung der Therapie zu entscheiden. In diesen Studien zeigte sich weiterhin, dass zur Aufrechterhaltung des Therapieerfolges im ersten Jahr weitere 7-12 Injektionen in regelmäßigen Abständen notwendig sind. Im zweiten Jahr waren laut diesen Studien weniger Injektionen zur Aufrechterhaltung des Therapieerfolges notwendig. (54, 56) Als Monotherapie konnte die konventionelle Makulalasertherapie in der ETDRS-Studie und ähnlichen Studien eine Stabilisierung der Sehschärfe bei einer geringen Behandlungshäufigkeit zeigen. Bisher konnte jedoch noch kein klarer Vorteil in Bezug auf die Entwicklung der Sehschärfe und die Verringerung der Behandlungsbelastungen bei der Kombination einer IVOM-Therapie mit einer konventionellen Makulalasertherapie gezeigt werden. (51, 54, 56, 57).

3. Material und Methoden

3.1. Material und Methoden der ersten Publikation

In der Studie „Comparative Evaluation of Combined Navigated Laser Photocoagulation and Intravitreal Ranibizumab in the Treatment of Diabetic Macular Edema“ wurden 66 Patienten mit Fovea involvierendem DMÖ eingeschlossen und in zwei Kohorten aufgeteilt. Kohorte 1 mit 34 Patienten erhielt eine Ranibizumab Monotherapie mit initial drei anti-VEGF Injektionen in monatlichen Abstand und nachfolgend im pro re nata Schema (PRN). Kohorte 2 mit 34 Patienten erhielt zusätzlich nach der dritten anti-VEGF Injektion und einem CRT von weniger als 445nm eine mit der Navilas Lasereinheit durchgeführte navigierte fokale Lasertherapie. Bei einem CRT über 445nm wurde eine weitere anti-VEGF Injektion durchgeführt und die fokale Lasertherapie 4 Wochen danach appliziert. Der Beobachtungszeitraum dieser prospektiv vergleichenden Studie belief sich auf 12 Monate. Alle Patienten erhielten vor Therapiebeginn eine Basisuntersuchung bestehend aus best-korrigierter Sehschärfe mithilfe des ETDRS-Charts, einer Spaltlampenuntersuchung mit Funduskopie, eine Spectral-Domain-optische Koherenztomographie (SD-OCT) sowie einer Fluoreszenzangiographie (FLA).
In Bezug auf das PRN Schema wurden die anti-VEGF Injektionen nach der dritten Injektion bei Patienten mit in zwei aufeinander folgenden Kontrollterminen stabilem BCVA und CRT unterbrochen. Weiterhin wurde bei Erreichen eines BCVA von 85 EDTRS Buchstaben oder einer vollständigen Rückbildung des DMÖ (CRT < 300nm) die Injektionstherapie ebenfalls unterbrochen.
Monatlich erfolgte eine Kontrolle des BCVA und CRT. Im Falle einer Reduktion des BCVA um 5 EDTRS Buchstaben oder einem Anstieg des CRT um mehr als 20% im Vergleich zur Basisuntersuchung wurde die anti-VEGF Therapie bis zur Stabilisierung des BCVA und CRT in zwei aufeinander folgenden Kontrollterminen fortgeführt.

3.2. Material und Methoden der zweiten Publikation

In der prospektiven Studie „ Navigated macular laser decreases retreatment rate for diabetic macular edema: a comparison with conventional macular laser“ wurden 46 Augen von 46 Patienten mit DMÖ unter navigierter fokaler Lasertherapie mit der Navilas Lasereinheit mit 119 Patienten unter konventioneller fokaler Lasertherapie in Hinsicht auf das klinische Ergebnis und die Wiederbehandlungsrate verglichen. Nach der Propensity-Score-Analyse, der für Alter, Geschlecht, Ausgangsvisus und Anzahl der Laserspots ermittelt wurde, ergab 28 übereinstimmende Patienten für die Kontrollgruppe. Alle Patienten erhielten vor Therapiebeginn eine OCT Bildgebung und eine FLA. Die Patienten unter navigierter Lasertherapie erhielten zur Planung an der Navilas Lasereinheit zusätzliche Fundusfarbaufnahme. Eine Follow-Up Untersuchung wurde mindestens alle 3 Monate über einen Zeitraum von 12 Monaten durchgeführt. Eine erneute Behandlung wurde bei ausbleibender Reduktion der retinalen Netzhautdicken von ≥ 100nm oder eines gesunkenen BCVA von 5 ETDRS Buchstaben oder mehr an derselben Lasereinheit wie zuvor durchgeführt.

4. Diskussion / Zusammenfassung

4.1. Diskussion / Zusammenfassung der ersten Publikation

Die Studie „Comparative Evaluation of Combined Navigated Laser Photocoagulation and Intravitreal Ranibizumab in the Treatment of Diabetic Macular Edema“ untersuchte die Wirksamkeit eines standardisierten Kombinationstherapieschemas (Rbz + NMLT) im Vergleich zu einer Rbz Monotherapie. Wir konnten darlegen, dass eine Kombination aus Rbz und NMLT in der Lage ist die Wiederbehandlungsrate zu senken und dadurch die Belastungen für den Patienten durch die Injektionen zu reduzieren. Bereits nach der Initialphase (3x Rbz) erlangten Patienten beider Kohorten einen mit der Zulassungsstudie für Rbz vergleichbaren und signifikanten Anstieg des BCVA und zugleich eine Abnahme des CRT (50, 54).

Die Wiederbehandlungsrate in der Kombinationstherapiekohorte zeigte sich wesentlich geringer im Vergleich zu Patienten in der Monotherapiekohorte.

Im Durchschnitt benötigten Patienten nach NMLT weniger als eine weitere Rbz Injektion. Unter Rbz-Monotherapie waren dagegen im Schnitt weitere 3 Injektionen notwendig.
Die Kombination aus einer Rbz Initialphase und anschließender NMLT kann somit die Anzahl der notwendigen Injektionen und somit die daraus resultierenden Belastungen verringern, ohne dabei den durch die Anti-VEGF-Therapie gewonnenen Anstieg der zentralen Sehschärfe zu beeinflussen.
Vergleichbare Studien wie die RESTORE Studie kamen bei ähnlichem Studiendesign jedoch unter Verwendung eines konventionellen Spaltlampenlasers dagegen zu keinem signifikanten Unterschied in Bezug auf BCVA und CRT gegenüber der Rbz Monotherapie (RESTORE). Die DRCR.net Studie zeigte bei unterschiedlichem Studiendesign in Bezug auf das Behandlungsvorgehen und die Wiederbehandlungsrate keinen Unterschied zwischen sofortiger oder verzögerter MLT (DRCR.net). Im Gegensatz hierzu ergaben die Beobachtungen der READ-2 Studie eine Verringerung der notwenigen Injektionen unter der Kombination von Anti-VEGF Injektionen und konventioneller Lasertherapie (50). Insgesamt konnte kein reproduzierbarer Vorteil durch die Kombination aus konventioneller Lasertherapie und Ranibizumab ermittelt werden. Ursächlich hierfür könnte neben dem unterschiedlichen Studiendesign, die Einschränkungen der Spaltlampen basierten Lasers in Bezug auf die Standardisierung der Laseranwendung im klinischen Alltag sein. Auch die im Vergleich zum Navilas System geringere Präzision der Laserspotapplikation könnte eine Begründung hierfür liefern. Eine vergleichbare Studie der University of California in San Diego zeigte bei ähnlichem Studiendesign unter der Kombination von Bevacizumab und einer navigierter MLT fast identische Ergebnisse über 12 Monate (58)
Trotz unserer guten Ergebnisse sollte große multizentrisch, randomisierte Studien abgewartet werden um diesen möglicherweise großen Vorteil der Kombinationstherapie zu bestätigen.

4.2. Discussion / summary of the first publication

The study "Comparative Evaluation of Combined Navigated Laser Photocoagulation and Intravitreal Ranibizumab in the Treatment of Diabetic Macular Edema" examined the efficacy of a standardised combination therapy regimen (Rbz + NMLT) compared to Rbz monotherapy. We were able to demonstrate that a combination of Rbz and NMLT is able to lower the re-treatment rate and thus reduce the burden of injections. After the loading phase (3x Rbz), patients of both cohorts achieved a significant increase in BCVA and a decrease in CRT, comparable to the pivotal study for Rbz (49, 53). The re-treatment rate in the combination therapy cohort was significantly lower (35%) compared to patients in the monotherapy cohort (84%).

On average, patients after NMLT needed less than one additional Rbz injection. In contrast, Rbz monotherapy required an average of 3 more injections.

The combination of a Rbz Loading Phase and subsequent NMLT can therefore reduce the number of injections required and thus the resulting strain without affecting the increase in central visual acuity gained through anti-VEGF therapy.

Comparable studies like the RESTORE study, however, did not show a significant difference in BCVA and CRT compared to Rbz monotherapy (RESTORE) when using a conventional slit-lamp laser with a similar study design. The DRCR.net study showed no difference between immediate or delayed MLT (DRCR.net) with different study designs in terms of treatment procedure and recovery rate. In contrast, the observations of the READ-2 study showed a reduction in the need for injections when anti-VEGF injections were combined with conventional laser therapy (49). Overall, no constant benefit could be found from the combination of conventional laser therapy and ranibizumab. The reason for this could be, apart from the different study design, the limitations of the slit-lamp-based laser in terms of standardisation of laser application in everyday clinical practice. The low precision of the laser spot application compared to the Navilas system could also be a reason for this. A comparable study at the University of California in San Diego showed almost identical results over 12 months with a similar study design using a combination of bevacizumab and a navigated MLT (57)

Despite our good results, we should wait for large multicentre, randomised trials to confirm this potentially big advantage of combination therapy.

PLOS ONE

RESEARCH ARTICLE

Comparative Evaluation of Combined Navigated Laser Photocoagulation and Intravitreal Ranibizumab in the Treatment of Diabetic Macular Edema

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Data Availability: The authors confirm that, for approved reasons, some access restrictions apply to the data underlying the findings. According to the data protection guidelines data cannot be easily stored in a public depository. However, the authors can confirm that all data underlying the findings that are necessary for our conclusion are within the manuscript. As this study involved human participants, data for these cannot be made completely public without restrictions. For more details on the data any reader may feel free to contact the corresponding author: Marcus Kernt, MD, Department of Ophthalmology, Ludwig-Maximilians-University, Munich Mathildenstrasse, 880336 Munich, Germany.

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Abstract

Objective: To evaluate if a standardized combination therapy regimen, utilizing 3 monthly ranibizumab injections followed by navigated laser photocoagulation, reduces the number of total ranibizumab injections required for treatment of diabetic macular edema (DME).

Research Design and Methods: A 12-month, prospective comparison of 66 patients with center-involving DME: 34 patients with combination therapy were compared to 32 patients treated with ranibizumab monotherapy. All patients initially received 3 monthly ranibizumab injections (loading phase) and additional injections pro re nata (PRN). Combination therapy patients additionally received navigated laser photocoagulation after the loading phase. Main outcome measures were mean number of injections after the loading phase and change in BCVA from baseline to month 12.

Results: Navigated laser combination therapy and ranibizumab monotherapy similarly improved mean BCVA letter score (+8.41 vs. +6.31 letters, $p=0.258$). In the combination group significantly less injections were required after the 3 injection loading phase (0.88 ± 1.23 vs. 3.88 ± 2.32, $p<=0.001$). By month 12, 84% of patients in the monotherapy group had required additional ranibizumab injections as compared to 35% in the combination group ($p<=0.001$).

Conclusions: Navigated laser combination therapy demonstrated significant visual gains in most patients. Retreatment rate and number of injections were significantly lower compared to ranibizumab monotherapy and compared to the results of

conventional laser combination therapy previously reported in pivotal anti-VEGF studies.

Introduction

The development of antibody-derived inhibitors of vascular endothelial growth factor (VEGF), such as ranibizumab (Rbz), have dramatically changed the management of DME and progressively replaced Macular Laser Therapy (MLT) as a first-line treatment option.

Major randomized controlled trials have demonstrated that intravitreal anti-VEGF injections not only help to maintain visual acuity in patients suffering from fovea-involving DME, but can also improve vision significantly (by an average of at least six letters in the first year) [1–5].

The same trials have also documented that frequent intravitreal injections, on the order of seven to twelve in the first year and slightly fewer in subsequent years, were needed to accomplish and maintain these results [4, 6].

The significant treatment burden placed on patients, doctors, healthcare providers and payers, as well as, reports of inferior results with inadvertent under-treatment in everyday clinical settings, highlight the need for a treatment paradigm providing optimal visual outcomes with fewer injections [7, 8].

While conventional MLT, applied as monotherapy, demonstrated a stabilizing effect on vision at a low treatment frequency in the ETDRS and subsequent studies, so far no clear benefit has been demonstrated when added to Anti-VEGF, either with respect to enhanced visual acuity gains or reduced injection burden [4, 6, 9, 10].

A new computer-guided technology for navigated MLT, developed to overcome some of the limitations of manual, slit-lamp based laser application, has recently become available (Navilas Laser System, OD-OS GmbH, Teltow, Germany) [11–15].

Using digital planning and image-guidance, navigated laser therapy has demonstrated a significantly higher accuracy in laser spot application, with the potential to reduce the retreatment rate compared to conventional laser monotherapy [11–15].

We hypothesized, that the potential for earlier disease stabilization with navigated MLT could also translate into earlier stabilization of Anti-VEGF visual gains and therefore reduced Anti-VEGF retreatment rate and overall injection burden.

To evaluate this hypothesis, we developed a standardized treatment regimen based on the *pro re nata* (PRN) scheme of the European approval for ranibizumab and a navigated MLT application after the first three monthly injections.

Study Population and Methods

Study Design

This was a 12-month, prospective comparison of 66 patients with center-involving DME conducted at the Department of Ophthalmology, Ludwig-Maximilians-University, Munich, Germany. Patients either received a combination treatment consisting of ranibizumab injections plus navigated MLT or ranibizumab monotherapy as two co-existing standard treatments. Physicians that had not undergone training with navigated MLT performed Rbz monotherapy, while trained physicians performed combination therapy, leading to a quasi-random assignment of patients to their respective cohort.

The study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the institutional review board and written informed consent provided by each patient.

Participants

Consecutive patients were enrolled in 2011 and 2012 from the outpatient clinic of the Department of Ophthalmology, Ludwig-Maximilians-University, Munich. Key eligibility criteria for all participants were: female or male with a minimum age of 18 years and a diagnosed diabetes mellitus Type I or II with clinically significant DME according to the criteria of the ETDRS [16]. Further criteria included (1) best-corrected visual acuity (BCVA) of at least 10 letters on the ETDRS chart, (2) central retinal thickening (CRT) of at least 400 µm (with foveal involvement); measured by spectral domain OCT [(SD-OCT) Spectralis OCT, Heidelberg Engineering GmbH, Heidelberg, Germany] and, based on clinical examination made by two experienced retina specialists, (3) no ischemic maculopathy seen in fluorescein angiography, (4) no severe proliferative diabetic retinopathy (PDR) or macular edema due to other underlying retinal vascular disease, vitreomacular traction or epiretinal membranes, (5) no previous anti-VEGF, MLT or other major ocular surgeries within the last 4 months, (6) no pre-existing ocular conditions that would preclude improvement in visual acuity despite reduction of the edema, (7) no pregnant or lactating subjects and (8) no subjects currently enrolled in other clinical trials.

Standardized Treatment Regimen

All patients underwent a baseline examination including best-corrected visual acuity, slit-lamp examination, dilated fundoscopy, OCT-imaging and measurement and fluorescein angiography. We assessed BCVA at every study visit using ETDRS charts at a starting distance of 4 meters. OCT imaging was performed on spectral domain OCT with eye-tracking and rescan support in follow-up measurements (Spectralis OCT, Heidelberg Engineering GmbH, Heidelberg, Germany).

After eligibility was confirmed, all participants then received intravitreal injection therapy (IVT) with 0.5 mg ranibizumab (Rbz) closely following the

European label, which details a *pro re nata* (PRN) protocol based on the RESTORE study with or without adjunct MLT. It must be noted, that this treatment paradigm differs in this regard from the U.S. label for 0.3 mg ranibizumab in DME.

As outlined above, navigated MLT was applied only to cohort 2, while cohort 1 received Rbz monotherapy:

- Cohort 1 – Ranibizumab Monotherapy: Patients were initially treated with three anti-VEGF injections in one-month intervals. After the "loading phase" injections were delivered *pro re nata* (PRN).
- Cohort 2 – Navigated Laser Combination Therapy: Three initial anti-VEGF injections were given in one-month intervals with a Navilas navigated MLT delivered one month after the third injection if CRT had decreased to 445 µm or below. Otherwise one more injection was given and navigated MLT applied four weeks after. Further anti-VEGF injections were delivered *pro re nata* (PRN) as described below.

According to the PRN scheme, injection therapy was paused after the loading phase in patients who demonstrated stable BCVA and CRT on two consecutive examinations, or if the BCVA reached 85 ETDRS letters or the DME was completely resolved (CRT$<$300 µm). Patients were followed monthly with BCVA and CRT obtained at each visit and intravitreal injections were resumed if a reduction in BCVA of more than 5 letters compared to baseline BCVA or an increase of CRT of at least 20% was observed. Retreatment was continued until BCVA and CRT were again stable for at least two consecutive visits.

Intravitreal injections

Patients received intravitreal injections of ranibizumab as delineated above. Injections were performed according to a standard procedure: topical antibiotics were used both pre and post injection under aseptic operating theatre conditions. After draping a 30-gauge needle was inserted into the vitreous cavity through pars plana and 0.5 mg/mL RBZ were injected. The cannula was then withdrawn and a sterile cotton tip was placed on the injection site.

Navigated MLT

Navigated MLT procedures were performed with the scanning slit laser photocoagulator, Navilas Laser System (OD-OS GmbH, Teltow, Germany), which was CE-marked and approved by the US Food and Drug Administration in 2009. Its principal operation has been described elsewhere [13]. In brief, it combines imaging, laser application planning, and treatment in a computer-based device. It fundamentally differs from other laser devices by using a scanning slit-based principle to acquire and display high-resolution images on a touch screen monitor.

Navigated MLT procedures in this study were digitally planned on Color and FA images acquired by the instrument and/or imported OCT thickness maps by placing single spots and grid patterns according to ETDRS guidelines. The spot size was typically set to 100 µm and applied with a pulse duration of 100 ms. Based on color snap images taken during treatment, laser power was individually adjusted to values around 100 mW to achieve a pale grayish, barely visible laser burn. The treatment was administered using the plan overlay and laser-beam prepositioning features of the device.

In cases were navigated MLT and anti-VEGF injections were given on the same day, we always delivered navigated MLT first and anti-VEGF injections at minimum two hours afterwards.

Statistical Methods

All data were collected in a MS-Excel 2010 spreadsheet (Microsoft Corporation, Redmond, WA) and analyzed using the Statistical Package for Social Sciences version 21.0 for Windows (IBM, New York, USA).

Results

A total of 66 patients were included into this prospective comparison: 34 patients received ranibizumab/navigated laser combination therapy and 32 patients received ranibizumab monotherapy. A total of 99 patients were initially screened for this study of which 33 dropped out as they either did not meet all the inclusion criteria or refused to take part in this study. From the 66 patients that were included, none dropped out at a later stage over the study period or completely missed a follow-up. All data gathered at follow-ups were within a ten day time frame of the protocol requirements and therefore included in our study results. (Fig. 1)

Baseline characteristics, which are similar in both cohorts, are summarized in Table 1. Mean baseline BCVA was 30.8±12.6 and 24.6±14.4 letters for combination and monotherapy cohorts, respectively ($p=0.065$). Mean baseline CRT values were 441±162 and 444±117, respectively ($p=0.928$).

Visual Acuity and CRT development

Immediately following the baseline exam, treatment was initiated with three ranibizumab intravitreal injections spaced approximately one month apart. By one month after this loading phase, both cohorts had reached equivalent and significant BCVA gains (Fig. 2, 3 months time point). Combination therapy eyes had improved by 7.9±7.6 letters and monotherapy eyes had improved by 5.5±5.8 letters ($p=0.150$).

Navigated MLT was applied to combination therapy eyes 115±113 days mean after starting the ranibizumab intravitreal loading phase injections.

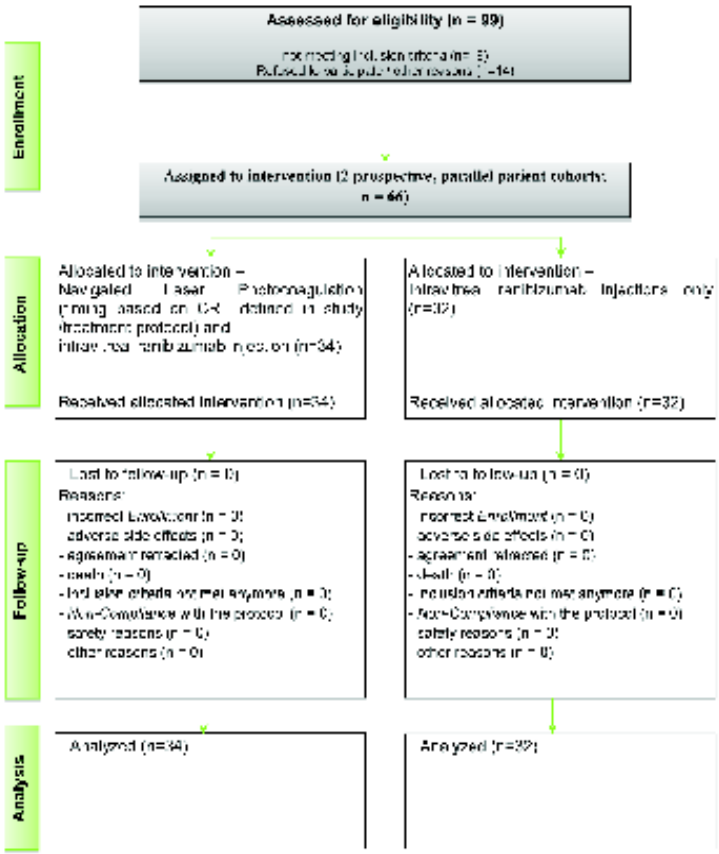

Fig. 1. Flow chart of the study. Enrollment, Assignment and Follow-up of the patients that were included in this prospective comparison of combined navigated macula laser therapy and mono anti-VEGF therapy.

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Table 1. Baseline Characteristics of the Sample.

	Navilas + Ranibizumab n = 34	Ranibizumab Monotherapy n = 32	Test for difference (P-Value)
Mean age ± SD, years	64.9 ± 11.6	68.2 ± 11.3	p = 0.255
Gender (% (n) female)	47% (16)	40% (13)	p = 0.605
Mean BCVA ± SD, ETDRS letter score	30.8 ± 12.6	24.6 ± 14.4	p = 0.065
Mean CRT ± SD, µm	441 ± 162	444 ± 117	p = 0.928

SD, standard deviation; CRT, central retinal thickness; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

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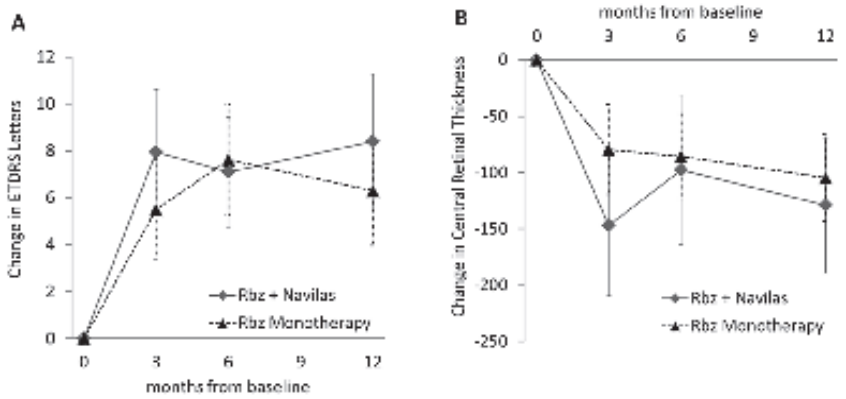

Fig. 2. Course of best-corrected visual acuity (BCVA) and central retinal thickness (CRT). (A) Change in best-corrected visual acuity (BCVA) and (B) change in central retinal thickness (CRT) during 12 months follow-up (Error bars: 95% CI). Eyes received three Rbz loading injections and combination therapy eyes additionally received Navigated MLT 115±113 days mean from baseline. Thereafter, all eyes received PRN injections. Three months from baseline, combination therapy eyes had improved by a mean 7.9±7.6 letters and monotherapy eyes had improved by 5.5±5.8 letters (difference p=0.150) and remained stable through the PRN phase. Twelve-month values were 8.4 ±8.3 letters and 6.3 ±6.5 letters, respectively (difference p=0.258). Similarly, during 12 months CRT in the combination therapy cohort had improved by a mean -129 ±170 µm and in the monotherapy cohort from by a mean −105 ±107 µm (difference p=0.487).

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Initial BCVA gains remained stable in the PRN phase through months 6 and 12, with 6 month values of +7.1 ±6.2 letters and +7.6 ±6.5 letters in combination therapy and monotherapy eyes, respectively (p=0.750).

By month 12 combination therapy eyes had improved 8.4±8.3 letters and monotherapy eyes had improved 6.3 ±6.5 letters. While there is a trend towards a better mean BCVA outcome for the combination therapy cohort, this difference did not reach statistical significance (p=0.258).

Categorized BCVA outcomes are detailed in Table 2. By month 12, 47% of combination therapy eyes vs. 31% of monotherapy eyes had gained 10 letters or more and 21% vs. 9% had gained 15 letters or more. One patient in the combination therapy cohort had lost more than 15 letters and one patient in the monotherapy arm had lost more than 10 letters (3% of patients each).

Improvements in visual acuity were reflected by significant anatomic improvement from baseline: in the combination therapy arm central retinal thickness improved from 441 ±162 to 313± 98 (mean improvement of −129 ±170 um) and in the monotherapy cohort from 444 ±117 to 339± 82 (mean improvement of −105 ±107 um (Fig. 2); group difference p=0.487).

Retreatment rates and number of injections

Injection retreatment data in both cohorts was subjected to Kaplan-Meier analysis, which shows an early separation of the two curves (Fig. 3). The median time to retreatment calculated over all monotherapy eyes was 63 days, while at the

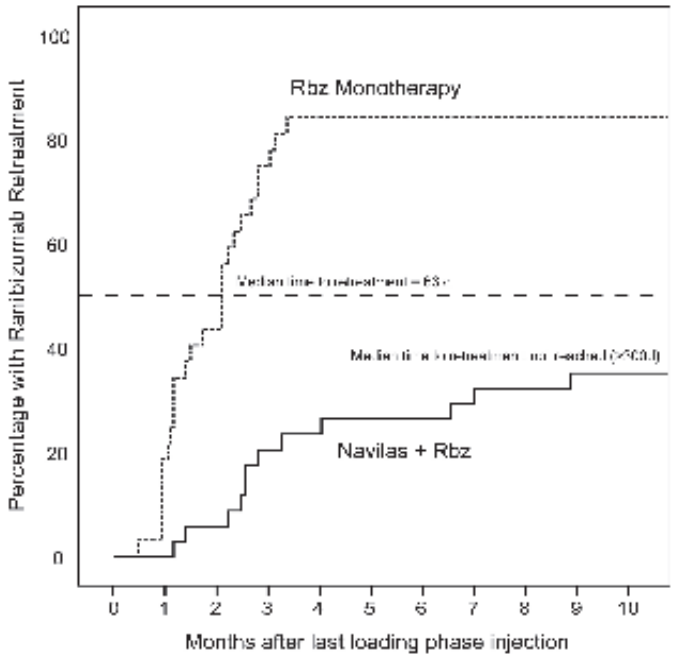

Fig. 3. Kaplan-Meier analysis of injection retreatment after the last loading phase injection. A significantly higher proportion of Rbz monotherapy patients (84%) required injection retreatment compared to the navigated laser combination therapy cohort (35%, difference p≤0.001). Median time to retreatment was 63 and>300 days (median not reached during follow-up), respectively.

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end of the study at 10 months after the third injection (12 months of total follow-up) the median had not been reached in the combination therapy cohort. At the end of the study the combination therapy cohort had a significantly higher proportion of patients that required no further injections after the anti-VEGF loading phase than the monotherapy cohort: 65% vs. 16% (p≤0.001). The reduced retreatment rate in the combination therapy cohort corresponds to a significantly lower requirement for injections as compared to monotherapy: 0.9±1.2 vs. 3.9±2.3 after the loading phase, 3.9±1.3 vs. 6.9±2.3 total during 12 months follow-up, p≤0.001 for both comparisons. (Table 3)

At 12 months from baseline, combination therapy eyes received a mean of 1.24±0.43 navigated laser treatments. Twenty-six eyes received the minimum of one navigated laser treatment and eight eyes received two treatments.

No adverse effects of intravitreal injections or navigated laser were observed during the study.

Table 2. Best-Corrected Visual Acuity (BCVA) and Central Retinal Thickness (CRT) changes at month 12.

	Navilas + Ranibizumab n=34	Ranibizumab Monotherapy n=32	Test for difference (P-Value)
BCVA change			
– Mean ± SD	8.4±8.3	6.3±6.5	p=0.258
– Median (range)	9 (−21 to +25)	6.5 (−12 to +17)	
–95% CI for mean	5.51, 11.31	3.99, 8.64	
Categorized BCVA outcome (ETDRS letter score)			
– Gain: 15 letters or more	21% (7)	9% (3)	p=0.210
– Gain: 10 letters or more	47% (16)	31% (10)	p=0.195
– Loss: 10 letters or more	3% (1)	3% (1)	p=0.336
– Loss: 15 letters or more	3% (1)	0% (0)	p=0.966
Mean CRT ± SD (µm)			
– Baseline	441±162	444±117	p=0.928
–12 months	313±98	339±82	p=0.255

SD, standard deviation; CI, confidence interval; CRT, central retinal thickness; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

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Table 3. Analysis of required treatments.

	Navilas + Ranibizumab n=34	Ranibizumab Monotherapy n=32	Test for difference - P-Value
Number of injections after loading phase (3x ranibizumab)			
– Mean ± SD	0.9±1.2	3.9±2.3	p≤0.001
– Median (range)	0 (0 to 4)	4 (0 to 8)	
–95% CI for mean	0.45, 1.31	3.04, 4.71	
– Difference in mean number of injections vs. Ranibizumab Monotherapy (n, %)	−3.0, −77%		
Total number of injections at 12 month including loading phase			
– Mean ± SD	3.9±1.3	6.9±2.3	p≤0.001
– Median (range)	3 (3 to 7)	7 (3 to 11)	
–95% CI for mean	3.47; 4;35	6.04; 7.71	
– Difference in mean number of injections vs. Ranibizumab Monotherapy (n, %)	−3.0, −43%		
Proportion of eyes with no need for injections after loading phase (%, n)	65%, 22	16%, 5	p≤0.001
Median time to retreatment (months)	>10 (not reached during follow-up)	2.1	
Number of navigated laser treatments Mean, Median (range)	1.24, 1 (1–2)		
Proportion of eyes with more than one navigated laser treatment	24% (8)	N/A	

SD, standard deviation.

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Discussion

Diabetic macular edema is one of the most common reasons for significant visual impairment in the western world. It may affect people from all age groups and strongly affects patient's quality of life [9, 17].

The development of anti-VEGF therapeutics placed an important treatment option into the hands of the retinal physician to rapidly stabilize or even restore vision in DME. However, it is now apparent that chronic intravitreal injection therapy is needed to preserve or slightly extend these visual gains [4, 6].

This 12-month, prospective comparison on the efficacy of a standardized combination therapy regimen (three ranibizumab injections followed by navigated MLT) compared to anti-VEGF monotherapy, demonstrated that the combination of Rbz and navigated MLT may be superior in terms of retreatment rate and overall injection burden.

Both cohorts achieved significant and comparable visual gains attributable to the Rbz loading phase. Combination therapy gains were in trend higher (8.6 ETDRS letters) and non-inferior to Rbz monotherapy gains (6.3 letters, difference n.s.). Combination therapy patients had a significantly lower retreatment rate with 65% (vs. 16%) of patients not receiving further Rbz after loading/navigated MLT. On average, less than one injection was required after Rbz loading, corresponding to a reduction of 3 injections vs. Rbz monotherapy.(Table 3) Therefore, the application of navigated MLT after Rbz loading appears to reduce the injection burden considerably without compromising anti-VEGF visual gains.

With regard to similar combination therapies using conventional laser instead of navigated MLT, evidence from pivotal trials is inconclusive. In the RESTORE study, patients received a minimum of 3 initial injections until BCVA was stable at two consecutive visits and in one arm of this study patients received conventional laser photocoagulation at baseline and as needed at 3 month intervals [9]. As in this study, follow-up was 12 months from baseline, conventional laser combination therapy and Rbz monotherapy reached average BCVA gains of 6.1 and 5.9 ETDRS letters, requiring a mean of 7.0 and 6.8 injections, respectively. These insignificant differences between study arms indicate no benefit from adding conventional laser. Similarly, the DRCR.net trial using a different treatment and retreatment algorithm, did not demonstrate significant differences between a prompt laser arm and a deferred laser arm (no laser in 70% of patients during year one) [10]. Median visual gains were 9 letters each achieved with 8 and 9 injections median, respectively. In contrast, the smaller READ-2 study did show a reduced number of 4.9 vs. 9.3 injections in a 24-month period, when adding a mean number of 2.7 conventional laser treatments to anti-VEGF therapy. However, visual gains were slightly, but not significantly lower in the combination arm (6.8 vs. 7.7 letters gain) [18].

In summary, no consistent benefit from added conventional laser can be inferred. Reasons, besides a different study objective, may include the lack of standardization and accuracy of slit-lamp based laser application in the clinical setting.

Navigated MLT was developed to overcome these limitations with multimodal planning and treatment functions ("eye tracking"), e.g. accurately pinpointing microaneurysms on fluorescein angiography images and outlining edematous areas on OCT thickness maps for subsequent grid laser treatment. During treatment each spot is prepositioned and tracked with the physician remaining in control. We observed a significantly lower retreatment rate of navigated MLT monotherapy compared to conventional laser in a previous study, suggesting stabilization may be reached earlier after navigated therapy (i.e. frequently after the first treatment).

In contrast, most Rbz monotherapy patients in this study required retreatment within the first 3 months after Rbz loading (Median: 63 days). This may highlight the importance of using a standardized, fast-acting MLT that achieves most of its effects with the first treatment in order to reduce the requirements for additional injections.

Our study supports the results of a similar study conducted by the University of California in San Diego that included patients that had been treated with a similar standardized combination therapy regimen utilizing navigated MLT and bevacizumab. In these patients, an average of 4 injections were necessary during 12 months follow up period [19].

Generally, while these results suggest a compelling benefit of adding navigated MLT to anti-VEGF therapy, they await confirmation by larger multicentric, randomized controlled trials.

Considering the developments on drug based therapies together with the promising results of the presented study, we believe that the combination of two well-studied treatment modalities, intravitreal Rbz as well as navigated MLT offers the potential to improve DME management even further.

Acknowledgments

Preliminary data and parts from this study were presented in abstract form at the ARVO Annual Meeting, May 5–9, 2013, Seattle, WA., at the 13 EURETINA congress, September 26–29, 2013, Hamburg, Germany and at the AAO Annual Meeting, November 16–19, 2013, New Orleans, MS.

Author Contributions

Conceived and designed the experiments: AK MK ASN CH MWU. Performed the experiments: RL JL FS LR. Analyzed the data: ASN MK. Wrote the paper: RL MK ASN. Patient Recruitment: MK RL.

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4.3. Diskussion / Zusammenfassung der zweiten Publikation

Unsere Studie „Navigated macular laser decreases treatment rate for diabetic macular edema: a comparison with conventional macular laser“ untersuchte die Wirkung einer navigierten Makula-Laserbehandlung im Vergleich zu einer konventionellen Makula-Laserbehandlung. Mit dieser Studie konnten wir zeigen, dass die navigierte Makula-Lasertherapie durch eine höhere Präzision der Laserspotapplikation die Wiederbehandlungsrate in dem von uns beobachteten Zeitraum, im Vergleich zum konventionellen Spaltlampen basierten Lasersystem, senken kann. Gleichzeitig zeigte sich auch ein schnellerer Eintritt bzw. Besserung des BCVA unter navigierter Macula-Lasertherapie. Gründe hierfür können die schon oben erwähnte höhere Präzision der Laserspotapplikation sein, die es dem behandelnden Arzt unter anderem ermöglicht mit höherer Genauigkeit die an die Fovea angrenzenden Mikroaneurysmen zu therapieren. Durch die digitale Planung und Durchführung ergibt sich weiterhin die Möglichkeit einer Standardisierung der Lasertherapie. Der behandelnde Arzt kann direkt den Status seiner Lasersitzung beobachten, und anhand des vorher digital erstellten Behandlungsplans die Anzahl der schon durchgeführten und noch durchzuführenden Laserspots erkennen. Nachteil dieser Studie war das kleine Patientenkollektiv, und die nicht randomisierte Zuteilung der Patienten zu einer Therapie. Durch die Anwendung des Propensity Score Matching konnte eine mögliche Verzerrung jedoch minimiert werden. Die navigierte Macula-Lasertherapie bietet eine höhere Effektivität im Vergleich zur konventionellen Lasertherapie. Sie könnte somit als Teil einer Kombinationstherapie mit Anti-VEGF, aber auch als Monotherapie bei Nonrespondern zu einem besseren Therapieerfolg beitragen.

4.4. Discussion / Summary of the second publication

Our study "Navigated macular laser decreases treatment rate for diabetic macular edema: a comparison with conventional macular laser" examined the effect of navigated macular laser treatment in comparison to conventional macular laser treatment. With this study we could show that navigated macular laser therapy can reduce the treatment rate in the time period we observed compared to conventional slit-lamp based laser systems by a higher precision of the laser spot application. At the same time, a faster entry or improvement of BCVA under navigated macular laser therapy was observed. Reasons for this may be the already mentioned higher precision of the laser spot application, which enables the treating physician to treat the microaneurysms adjacent to the fovea with higher accuracy. Furthermore, the digital planning and execution allows for a standardization of the laser therapy. The attending physician can directly observe the status of his laser session and, based on the previously digitally created treatment plan, can identify the number of laser spots already performed and those still to be performed. The disadvantage of this study was the small patient collective and the non-randomized allocation of patients to a therapy. However, by applying Propensity Score Matching, a possible bias could be minimized. The navigated macular laser therapy offers a higher effectiveness compared to conventional laser therapy. It could therefore contribute to a better therapy success as part of a combination therapy with anti-VEGF, but also as monotherapy for non-responders.

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ORIGINAL RESEARCH

Navigated macular laser decreases retreatment rate for diabetic macular edema: a comparison with conventional macular laser

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Background: The purpose of this study was to evaluate and compare clinical outcomes and retreatment rates using navigated macular laser versus conventional laser for the treatment of diabetic macular edema (DME).

Methods: In this prospective, interventional pilot study, 46 eyes from 46 consecutive patients with DME were allocated to receive macular laser photocoagulation using navigated laser. Best corrected visual acuity and retreatment rate were evaluated for up to 12 months after treatment. The control group was drawn based on chart review of 119 patients treated by conventional laser at the same institutions during the same time period. Propensity score matching was performed with Stata, based on the nearest-neighbor method.

Results: Propensity score matching for age, gender, baseline visual acuity, and number of laser spots yielded 28 matched patients for the control group. Visual acuity after navigated macular laser improved from a mean 0.48 ± 0.37 logMAR by a mean +2.9 letters after 3 months, while the control group showed a mean −4.0 letters ($P = 0.03$). After 6 months, navigated laser maintained a mean visual gain of +3.3 letters, and the conventional laser group showed a slower mean increase to +1.9 letters versus baseline. Using Kaplan-Meier analysis, the laser retreatment rate showed separation of the survival curves after 2 months, with fewer retreatments in the navigated group than in the conventional laser group during the first 8 months (18% versus 31%, respectively, $P = 0.02$).

Conclusion: The short-term results of this pilot study suggest that navigated macular photocoagulation is an effective technique and could be considered as a valid alternative to conventional slit-lamp laser for DME when focal laser photocoagulation is indicated. The observed lower retreatment rates with navigated retinal laser therapy in the first 8 months suggest a more durable treatment effect.

Keywords: navigated focal laser, macular laser, Navilas®, diabetic macular edema, diabetes mellitus, diabetic retinopathy

Introduction

Diabetic macular edema (DME) is the leading cause of vision impairment in patients with diabetes mellitus.[1–5] It is estimated that 29% of diabetic patients with more than 20 years of diagnosed diabetes mellitus will develop DME.[2,6] It mostly affects the working age population, imposing a significant burden both on society and on individual patients, a burden that is expected to increase with the rising prevalence of diabetes.[6,7]

With the introduction of various pharmacological therapies, such as steroids and antiangiogenic agents, the treatment of DME has been expanded, and is not limited to standard laser photocoagulation anymore. However, although improvements

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in best-corrected visual acuity have been observed with steroids and anti-vascular endothelial growth factor (VEGF) agents, robust long-term clinical trial evidence is currently limited.[8–11] Recently, the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol was demonstrated to be better at stabilizing vision and had a longer sustained benefit than intravitreal triamcinolone,[12] and while anti-VEGF therapy has been proven to be an effective therapy to restore vision at 3 years, studies to date support a continued role for laser photocoagulation in primary and salvage scenarios.[13] Most recently, ranibizumab, an anti-VEGF agent, received approval from the US Food and Drug Administration for DME. Currently, treatment recommendations for DME are based on involvement of the center of the macula. Laser photocoagulation remains the standard of care for DME without center involvement or for DME with center involvement without vision loss, and current ETDRS guidelines remain appropriate for this subpopulation of DME.[14] It also remains a good treatment option given that it is the most cost-effective long-term treatment for DME.[15,16]

Furthermore, the original ETDRS protocol using argon laser photocoagulation with a visible end point has been modified over the years as new technology has evolved.[17–20] Technical advances, including subthreshold techniques,[21] and pattern laser generation[22] have transformed laser photocoagulation into a less painful and more efficient mode in the treatment of retinal diseases. More recently, the development of navigated laser photocoagulation that combines fluorescein angiography with image stabilization and tracking has facilitated more efficient, accurate, and precise focal photocoagulation, allowing delineation of the spots/areas most appropriate for treatment.[23–25] The ability to preplan and deliver the planned spots in an automatic mode is an additional advantage over conventional slit-lamp manual lasers. It makes necessary the completion of the planned spots led by the system and not by the memory of the surgeon. This translates finally into a more standardized and complete laser treatment. In addition to documentation, safety, and patient comfort, the main theoretical advantage lies in retinal navigation, which may help to improve clinical outcomes with laser application.

However, to date, there are limited data regarding the clinical efficacy and benefits of using navigated retinal laser therapy over traditional slit-lamp laser. Randomized controlled trial data comparing navigated laser therapy versus conventional slit-lamp microscope-based laser treatment, are lacking. We performed a propensity score matched-pairs study based on prospective patient data from two specialist centers using navigated retinal therapy. The aim was to investigate the necessity of retreatment and visual acuity outcome of navigated retinal laser therapy for DME.

Materials and methods

Navigated laser therapy

The scanning slit laser photocoagulator, Navilas® (OD-OS GmbH, Teltow, Germany) was CE-marked and approved by the US Food and Drug Administration in 2009, and its principal operation has been described elsewhere.[23] In brief, the Navilas combines imaging, laser application planning, and treatment in one computer-based device. It fundamentally differs from most other laser devices by not being added to a slit-lamp, but being a scanning slit-based instrument, capturing approximately 25 images per second in imaging or treatment mode. For focal laser treatment, the field of view is 50 degrees, which is displayed on a monitor. Optical resolution with the instrument used in this study was 1280 × 1024 pixels for that angle, resulting in approximately 20–26 pixels per degree. Because of the slit imaging principle, color images of high contrast and sharpness are obtained.[23] Another difference from the slit-lamp-based laser devices is the touch screen monitor used for imaging, planning, and treating fundus changes. This allows the retina specialist to plan laser spots on the screen for focal treatments, and then apply either semiautomated patterns or single spots. A prepositioning mode may be used to advance the targeted aiming beam from the target position automatically to the next position, and the preplanned target can be stabilized on the fundus. For treatment, the surgeon performs the laser treatment manually after verifying the target lock.

Patients treated with laser photocoagulation

Consecutive patients were recruited in 2009 and 2010 from the outpatient clinic of the Department of Ophthalmology, Ludwig-Maximilians-University, Munich, and from Jacobs Retina Center, University of California, San Diego. Patients with diabetes mellitus (based on World Health Organization criteria) who were eligible for focal laser treatment as defined by ETDRS criteria were included in this study. Written informed consent was obtained from all patients. The study conformed to the principles expressed in the Declaration of Helsinki, and institutional review board approval was obtained at each participating center. Eyes were excluded if there were pre-existing retinal conditions that preclude visual improvement despite resolution of macular edema, such as age-related macular degeneration. All patients had follow-up

at least every 3 months. Retreatment was performed with the same device if retinal thickening did not improve (≥100 µm on optical coherence tomography [OCT]) or visual acuity did not improve by at least five letters.

Imaging

Navilas imaging was performed with a fully dilated pupil after clinical examination and before laser therapy, and consisted of several color images. Fluorescein angiography was performed as needed for treatment planning, ie, before treatment and during follow-up either on the navigated laser device or on a separate imaging system (HRA, Heidelberg Engineering, Heidelberg, Germany). Spectral-domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) was performed as needed for individual patient management.

Laser planning and treatment

Laser planning and treatment was performed adhering to ETDRS principles. Microaneurysms were targeted if identified as source of leakage on fluorescein angiography. With the Navilas, the obtained color image was used for planning laser spots. The retina specialist manually planned laser spots by applying automated patterns and single spots as appropriate on the color image, thus generating a detailed treatment plan. For navigated laser application, semiautomatic pattern laser application was conducted based on the treatment plan. A spot size of 100 µm was always selected, with a time per spot of 100 msec. Power settings of the green (532 nm) frequency doubled Nd:YAG laser were adjusted manually from a standard 100 mW such that spots showed a moderate whitening. The prepositioning mode was used to advance the targeting aiming beam automatically from each targeted retinal position to the next position after the aiming beam and preplanned target were stabilized on the living fundus. The retina surgeon actuated the laser manually after verifying the target lock. An alternating infrared to color video fundus visualization mode was applied to allow post treatment observation of the retinal burn for 2–3 seconds after each application without patient discomfort.

Conventional laser therapy

Conventional laser therapy was performed during the same time period. Planning was performed on paper, adhering to the same principles (modified ETDRS scheme, targeting microaneurysms only in case of leakage). All treatment plans were performed by an experienced attending physician at the respective institution. Laser therapy was performed using a slit-lamp-based green laser (532 nm wavelength, Visulas 532s, Carl Zeiss Meditec AG, Jena, Germany; laser settings: 100 mW power, 100 msec pulse duration, 100 µm spot size). A suitable contact glass, either Volk Area Centralis® or Mainster®, was used. Documentation was performed by paper drawing and recording laser parameters. Figure 1 shows a sample of planning and post treatment images for conventional and Navilas laser treatment.

Propensity score matching and data analysis

All data were collected in a MS-Excel 2000 spreadsheet (Microsoft Corporation, Redmond, WA) and analyzed using the Statistical Package for Social Sciences version 19.0 for Windows® (SPSS Inc, Chicago, IL). Patients were either treated with navigated retinal laser (Navilas) or conventional, slit-lamp-based laser during the same time period. To minimize bias when comparing the two groups, we matched the patient group treated with Navilas with the patient group receiving conventional laser treatment for DME. Propensity score matching was applied for this. Propensity score matching is a method of balancing observed characteristics that reduces selection bias and strengthens causal inferences in observational studies,[26,27] and is a method of multivariate matching that also

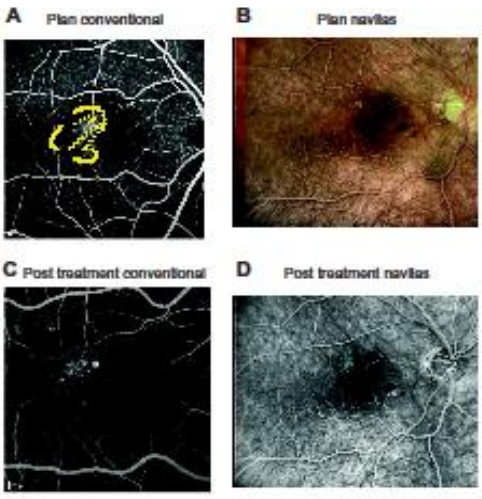

Figure 1 Examples before and after laser. Two sample patients conventionally treated (patient A) or treated by Navilas® (patient B). (A) Fluorescein angiography with treatment area marked. (B) Navilas fundus photography with fluorescein angiography overlay and preplanned laser spots. (C) Three-month follow-up on fluorescein angiography. (D) Fluorescein angiogram with executed laser treatment spots marked by Navilas.

allows for close but not exact matches.[28] This allows for simultaneous matching with respect to a large number of covariates in relatively small data sets, unlike exact matching, for which the minimal sample size required increases exponentially with each additional covariate matched. Propensity scores were estimated from a logistic regression model that included all control variables. In this case, the propensity score was the predicted probability, on the basis of observed variables, of a given patient being treated with navigated retinal laser for DME. The resulting propensity scores were then entered into the Stata PSMATCH2 command for 3:1 matching. Matching was limited to the area of common support of the propensity score, ie, the area in which the distribution of propensity scores for patient being treated with navigated retinal laser for DME overlaps with the distribution of propensity scores for patient having had conventional laser for DME.

This excluded patients in the conventional laser group who, on the basis of observed characteristics, were the least like those in the opposing group and thus were least likely to produce a close match. Matches were made within a defined distance of 0.1 standard deviation of the propensity score. The resulting matched sample was used for analysis of all outcomes. Because small differences between groups remain after propensity score matching, the estimated propensity scores and all covariates were included in all analyses of the matched samples.[29] All analyses were conducted with Stata MP 11.0 (Stata, College Station, TX).

Results

Baseline data for unmatched and matched groups

A total of 46 eyes were treated by navigated laser therapy and 119 by conventional laser. Before matching, the number of laser spots performed per patient with navigated therapy was 105 ± 94, which was significantly higher than with conventional laser (43 ± 36; $P < 0.001$). Follow-up time was significantly shorter for Navilas patients than for conventional patients (median 6.8 versus 13.5 months, $P < 0.001$). Propensity score matching for age, gender, baseline visual acuity, number of laser spots, and follow-up time yielded 28 matched patients for the control group. Visual acuity at baseline was 0.48 ± 0.37 logMAR for Navilas and 0.43 ± 0.36 logMAR (not statistically significant) for conventional laser before matching. Table 1 lists the baseline characteristics for the matched patient groups, which were very similar between the two groups.

Clinical outcomes

Change in BCVA

BCVA remained stable (no loss > 3 lines/15 letters) in all patients included in the matched comparison after 3 and 6 months. Mean increase from baseline 0.48 ± 0.37 logMAR was 3.3 letters for the navigated laser therapy group after 6 months, while the conventional laser group increased from baseline 0.49 ± 0.40 logMar by mean 1.9 letters. Visual outcomes at the 3-month time point were better for the Navilas group (mean increase 2.9 letters) versus conventional laser group, which lost a mean –4.0 letters ($P = 0.03$). However, the difference did not reach statistical significance after matching data for age, gender, baseline visual acuity, and number of laser spots after 6 months ($P = 0.08$). Figure 2 shows the course of visual acuity, illustrating the significantly faster gain in visual acuity in the Navilas group. In addition, after matching for age, gender, baseline visual acuity but unmatched for the number of laser spots, the difference between groups increased numerically. At the 3-month time point, visual acuity was significantly better for the Navilas group ($P = 0.03$) than for the conventional laser group (mean increase 2.9 letters [Navilas] versus mean decrease –6.3 letters [conventional laser], see Figure 3).

Retreatment rate

The laser retreatment rate using Kaplan-Meier analysis showed separation of the survival curves after 2 months, with fewer retreatments in the navigated group during the first 8 months ($P = 0.02$). Figure 4 shows the retreatments over time. The cumulative retreatment rate in the eyes that received navigated laser was 18% and 31% in the eyes

Table 1 Baseline patient characteristics

Variable	Navilas group (n = 46)	Conventional laser control group (after matching), n = 28	Statistical significance
Age (years)	61 ± 11.02	61 ± 11.7	$P = 0.94$
Gender (% female)	24%	18%	$P = 0.48$
Baseline visual acuity	0.48 ± 0.37	0.49 ± 0.40	$P = 0.90$
Laser spots planned (n)	105 ± 94	74 ± 48	$P = 0.20$

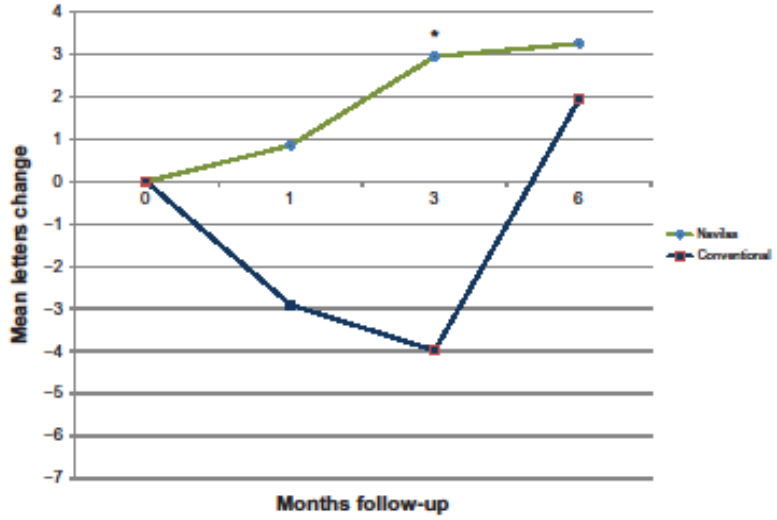

Figure 2 Visual acuity change over time (mean letters gained).
Note: *Indicates statistical significance.

that received conventional slit lamp laser at 8 months after treatment.

Discussion

Over the past three decades, the standard treatment for DME has been macular laser photocoagulation. In the ETDRS, laser therapy reduced the relative risk of losing 15 letters of visual acuity by 50% compared with untreated eyes.[30,31] Visual improvement ranging from 0.9 letters[9] to three letters[32] for patients receiving macular laser has been reported recently according to ETDRS guidelines. At 2 years, 21% eyes exhibited more than three lines of improvement, suggesting a delayed effect.[8]

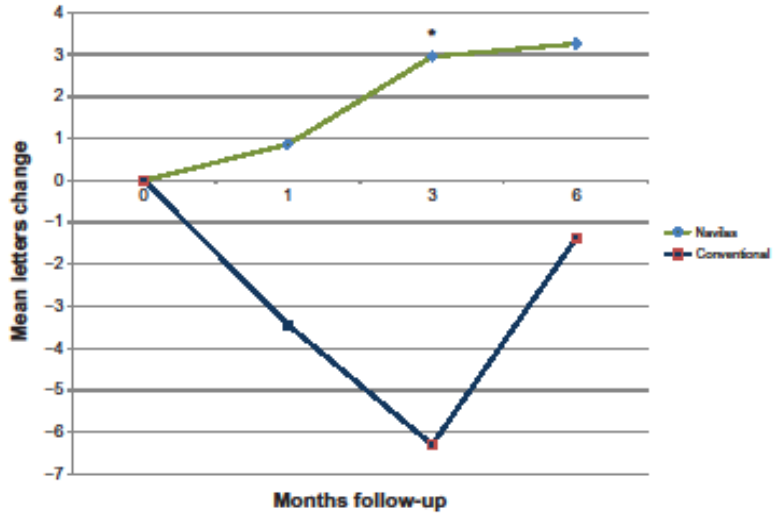

Figure 3 Visual acuity change over time (letters gained) matched for age, gender, and baseline visual acuity but unmatched for the number of laser spots.
Note: *Indicates significant difference.

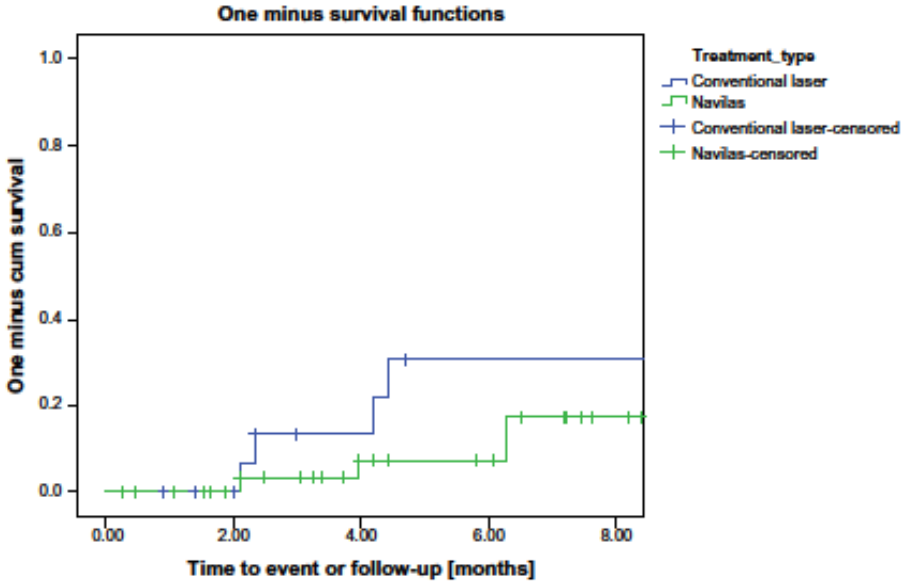

Figure 4 Kaplan-Meier analysis of retreatment rate.
Notes: After approximately 2 months, the survival curves separate, indicating more retreatments for the conventional laser group ($P = 0.02$). The 3-month period after first laser treatment, in which usually no retreatment is performed, is marked green.

Slit-lamp manual laser photocoagulation has been the conventional way of delivering focal/grid treatment for DME. With the introduction of navigated laser photocoagulation, this traditional concept has changed to a computer-based treatment with an eye-tracking system. This method of laser delivery has been shown to have several advantages over standard manual laser. First, it is more accurate compared with manual laser,[25] and accuracy becomes crucial when treating close to the fovea and targeting individual microaneurysms. Reports by the Diabetic Retinopathy Clinical Research (DRCR) network have demonstrated that focal microaneurysm treatment with light grid was superior to modified grid therapy alone in DME as judged by vision improvement and retinal thickness reduction.[33] Second, it allows standardization of macular laser treatments. The present study reports for the first time that higher accuracy resulted in less retreatment over the first 6–8 months when compared with slit-lamp laser treatments. Visual acuity improved consistently, indicating effective laser treatment. Even if the beneficial effect of laser is slow and delayed per se, we believe that 6–8-month follow-up was enough to assess the differential clinical effect of navigated laser treatment versus conventional laser application in this pilot study. The course of visual acuity confirms that the differences between the two methods were largest after 1–3 months, showing a statistically significant difference 3 months after laser treatment.

Interestingly, we observed that before statistically matching the study groups, the total number of laser spots was significantly higher when using navigated laser than conventional laser. While this effect was mostly eliminated after propensity score matching (differences not statistically significant) our explanation is that, in the navigated group, the physician can directly observe execution of the treatment plan that is projected real-time and can see how many laser spots remain to be applied. That is why (s)he is obliged to complete the treatment.

Recently, the therapeutic options for center-involved DME have been shifted to intravitreal anti-VEGF therapy. Initial anti-VEGF monotherapy is widely accepted and although the role of adjunctive laser is unclear, the 2-year outcomes from the READ-2[10] and DRCR.net studies[8] provide the first evidence for a reduction in the number of ranibizumab injections when combined with laser. However, anti-VEGF therapy still leaves an unmet clinical need and unanswered questions that include how to improve vision in patients who do not respond to anti-VEGF and ways towards reducing the

treatment burden in patients with DME. Our current report aimed to confirm that a more accurate laser treatment resulted in a more effective treatment measured by the number of retreatments. The second step will be to standardize this method of performing macular laser therapy and use it as part of combination therapies. Ultimately, this will likely reduce the number of intravitreal injections and reduce the patient burden.

The limitations of our current study include the relatively small patient series and the fact that patients were not randomized to treatment. However, by propensity score matching, we could minimize any potential bias. This method is becoming increasingly popular for analysis of nonrandomized data and to obtain best possible evidence.

Taken together, we have demonstrated that navigated laser therapy enables a reduced retreatment rate and faster visual acuity gain compared with conventional laser during the first 6–8 months after treatment. These data suggest a more durable treatment effect that can potentially maintain visual outcomes improved by anti-VEGF for patients with DME. It would also offer a more effective laser treatment for eyes in which laser is still the primary indication or rescue treatment for nonresponders to anti-VEGF.

Disclosure

The authors report no conflicts of interest in this work.

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Eigenanteil

Die im Rahmen meiner Promotion hier vorgestellten Veröffentlichungen habe ich in enger Zusammenarbeit mit Prof. Dr. Kernt, Prof. Dr. Neubauer und Dr. Liegl durchgeführt. Ich habe in beiden Arbeiten die Ausarbeitung des Therapieschemas sowie die Festlegung bestimmter Analysekriterien erhoben. Sowohl die Datenerhebung und Auswertung als auch die Betreuung der Patienten und Koordination der Studie führte ich eigenständig durch.
Die vorgestellten Manuskripte habe ich mit den jeweilig geteilten Miterstautoren in enger Rücksprache und Betreuung erstellt.

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