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How do we evaluate the role of focal/grid photocoagulation in the treatment of diabetic macular edema?

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Focal/grid photocoagulation in DME-treatment?

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ABSTRACT

Vascular endothelial growth factor inhibitors (anti-VEGF) have consistently demonstrated efficacy and safety and changed both the aim and perspectives of diabetic macular edema (DME) treatment. Hence, the present and future role of focal/grid laser photocoagulation in DME-treatment has been subjected to some debate. However, extensive insight into technical advances in novel laser systems, treatment protocols of anti-VEGF trials and the functional impact of modern focal/grid photocoagulation is needed to evaluate the present and future role of photocoagulation in DME-treatment.

Across a wide range of clinical trials laser therapy was required as adjunctive/rescue treatment in approximately 20-50% of patients receiving anti-VEGF monotherapy for center involving DME. Further, a lower retreatment rate and a more stable reduction of retinal thickness have been demonstrated in more studies. However, lacking information on the laser systems used, their technical specifications and protocols of application often complicates direct comparison of results in anti-VEGF trials. Hence, this paper aimed to provide an overview of the current available data relevant to the potential role of focal/grid laser photocoagulation in DME-treatment including a thorough overview of the current most commonly used laser systems.

Results with subthreshold diode micropulse laser photocoagulation are intriguing and may offer a valuable option as adjunctive therapy to anti-VEGF treatment. However, more well designed studies on combination therapy are warranted to determine the full potential of modern retinal photocoagulation systems.

In conclusion, current data suggest that focal/grid laser therapy should still be an option for consideration as adjunctive therapy in many patients.

INTRODUCTION

For more than three decades retinal focal/grid laser photocoagulation was considered standard of care for diabetic macular edema (DME). While focal/grid laser photocoagulation reduces the risk of moderate visual loss and blindness, the likelihood of visual improvement is little (Early Treatment Diabetic Retinopathy Study Research Group 1985). In recent years vascular endothelial growth factor (VEGF) inhibitors have consistently demonstrated efficacy and in most patients, visual improvement in DME-treatment (Massin et al. 2010; Do et al. 2012; Nguyen et al. 2012; Brown et al. 2015; Wells et al. 2016). Hence, anti-VEGF agents have not only largely replaced focal/grid photocoagulation as the treatment of choice in DME but also changed the aim and perspectives of treatment.

The present and future role of focal/grid laser photocoagulation in DME-treatment has consequently been subjected to some debate. Especially the destructive nature of retinal photocoagulation and the fear of creeping of laser scars are subjects of concern (Schatz et al. 1991). On the other hand, anti-VEGF treatment is less than perfect especially due to the substantial burden of repetitive intravitreal injections as well as the challenge of compliance. However inconsistent, reports of additive effect of focal/grid laser photocoagulation in regards of a lower treatment burden pose a potential valuable remedy to the challenges of anti-VEGF treatment (Nguyen et al. 2010; Liegl et al. 2014).

Numerous factors have to be taken into account to provide solid arguments for the use of focal/grid laser photocoagulation in DME-treatment and the complexity of data is deterrent. What kind of laser system should be used? How do we evaluate the functional impact of photocoagulation, and how does this correspond to theoretical considerations of its effect? Further, how was photocoagulation applied in studies addressing the efficacy and safety of anti-VEGF in DME-treatment, and how do the settings of clinical trials correspond to clinical practice?

We used PubMed to retrieve full text of the studies that have formed the basis of clinical recommendations for modern DME treatment. Specific information was retrieved from clinicaltrials.gov in cases where criteria of inclusion, protocols for treatment, retreatment and/or rescue treatment could not be identified via the printed full text or online supplementary material.

This paper aims to provide an overview of the current available data relevant to the potential role of focal/grid laser photocoagulation in DME-treatment.

LASER SYSTEMS

Historically, numerous laser systems of various wavelengths have been used for retinal photocoagulation. In general, the wavelength is determinative for the primary site of absorption of laser light in the retinal pigment epithelium (melanin, 400-1000 nm), the neurosensory retina (xantophylls, 420-500 nm) and choroidal melanocytes and hemoglobin (450-550 nm) (Franz Fankhauser 2003). Current available laser systems predominantly use green, yellow or red light as the absorption by macular xanthophyll is low and, hence, they theoretically reduce the risk of iatrogenic damage to the inner retinal layers.

Based on results of predominantly argon green laser (514 nm) photocoagulation, clinical recommendations for focal/grid laser photocoagulation were originally described in the Early Treatment Diabetic Retinopathy Study (ETDRS) (Early Treatment Diabetic Retinopathy Study Research Group 1985; Early Treatment Diabetic Retinopathy Study Research Group 1987). Laser settings used in these report were a spot size of 50-100 microns, pulse duration of 100 ms or less and adequate power to obtain definite whitening. A modified protocol has since been introduced (mETDRS) in which less power and smaller burns are applied to reduce the risk of adverse effects (Roider 1999).

This section discusses the efficacy in terms of visual acuity (VA) and changes in retinal thickness, and the protocols of application of the newest and most commonly used modern laser systems as compared to the results of 'conventional laser' in the first ETDRS report (Early Treatment Diabetic Retinopathy Study Research Group 1985).

Multispot laser systems: There are several multisport laser systems available for clinical use. One of the most widely used multisport lasers is the pattern scanning laser (PASCAL® Laser, Optimedica Corp., Santa Clara, CA, USA) which uses a 532 nm frequency-doubled neodymium-doped yttrium aluminum garnet (Nd:YAG) solid state laser. Besides the slight difference in wavelength, this system is distinguished from the classic argon green laser as described in the ETDRS by two main features. First, the pattern scan system makes it possible to deliver multiple burns in a rapid predetermined sequence, and second, the pulse duration is reduced to 10-30 ms. Whereas the first feature primarily serves to reduce treatment time and in particular patient discomfort during panretinal photocoagulation, the reduced pulse duration also reduces the total laser energy per burn to minimize damage to retinal tissue. The majority of studies that evaluate the safety and efficacy of multisport laser focal/grid laser photocoagulation primarily follow mETDRS treatment protocols.

In brief, short pulse focal/grid laser photocoagulation in DME has demonstrated comparable clinical efficacy to those presented in the first ETDRS report (Sanghvi et al. 2008; Modi et al. 2009; Muqit et al. 2012). Some concern has been raised about the time to completion of some predetermined patterns for grid pho-

tocoagulation in regards to the risk of eye movement (Modi et al. 2009). However, no reports of related complications could be identified from literature review.

All studies agree that significantly more power is needed as pulse duration is decreased. Furthermore, more laser effects are often needed as the dissipation of heat is reduced with shorter pulse duration resulting in smaller burns. As fluence equals $(power * time)/area$, some of the benefit of reduced energy per laser burn is hence diminished. However, animal studies have shown that for a similar spot size, as pulse duration decreases, the power required to produce ophthalmoscopically visible spots does increase but in a much lesser proportion (Blumenkranz et al. 2006). Furthermore, spot duration has been shown to influence the cumulative energy applied to a much greater extent than spot size as an exponential relationship between cumulative energy and duration exists as against a linear relationship to spot size (Jain et al. 2008).

The magnification of most contact lenses for focal/grid photocoagulation equals approximately one and does thereby not affect fluence and will not be further discussed in this review.

Subthreshold diode micropulse laser photocoagulation: True subthreshold describes laser photocoagulation without tissue damage discernable by any known means as biomicroscopy, fundus autoflourescence (FA), optical coherence tomography (OCT) or fundus fluorescein angiography (FFA) (Luttrull & Dorin 2012). Theoretically, all laser systems can be used for subthreshold treatment. However, micropulsed diode laser offers some advantages to other laser systems in subthreshold treatment.

The micropulsed laser delivers laser energy in short pulses as compared to a continuous wave. The laser 'off-time' between consecutive pulses during a duty cycle prevents heat build-up. Hence, with lower duty cycle and longer 'off-time' the less thermal diffusion and damage to the neurosensory retina (Pankratov 1990; Dorin 2003).

The 810 nm near-infrared diode laser is exclusively absorbed by the retinal pigment epithelium (RPE). As no energy is absorbed by hemoglobin, focal treatment of leaking microaneurysms is not an endpoint in treatment protocols for diode laser photocoagulation. Instead, as no structural tissue damage is registered, treatment protocols follow a 'low-intensity/high density' paradigm (Luttrull et al. 2005; Lavinsky et al. 2011).

Only few high-quality studies have compared subthreshold diode micropulse laser photocoagulation to conventional ETDRS/mETDRS focal/grid treatment and found comparable results (Figueira et al. 2009; Vujosevic et al. 2010). In contrast, a randomized clinical trial compared subthreshold diode micropulse photocoagulation to mETDRS focal/grid photocoagulation delivered with a 532 nm Nd:YAG laser system in 123 patients with previously untreated DME. Subthreshold diode micropulse photocoagulation was found superior in terms of mean change in VA while no difference was observed in regards of retinal thickness

(Lavinsky et al. 2011). Additionally, a recent study retrospectively included 38 eyes with DME to either sub-threshold diode micropulse photocoagulation or 3 loading doses of intravitreal injections with ranibizumab. Comparable results in regards of visual acuity were found in both groups but with a significantly lower need for intravitreal ranibizumab in the laser group during 12 months follow-up (Moisseiev et al. 2017).

Navigated laser (Navilas® Laser System, OD-OS GmbH, Teltow, Germany)**:** This laser system is currently the newest development within retinal photocoagulation. In principle the Navilas laser system is also a multi-sport laser. However, the most eminent difference from other devices is the use of a slit-based instrument that captures 25 images per second that are live-displayed on a monitor and hence the absence of a slit lamp. For focal/grid laser photocoagulation the field of view is 50 degrees and planning and treatment is controlled from the monitor and can be performed without the use of a contact lens. The computer-based device offers the advantages of integrated software which allows for capture or import and overlay of e.g. FFA-images and OCT thickness maps to optimize focal treatment of leaking microaneurysms or grid treatment in areas of diffuse edema. Treatment with navigated laser is otherwise performed adhering to the mETDRS principles.

The Navilas® uses a 532 nm (green light) diode-pumped solid state frequency-doubled (Nd:YVO; Class IV) laser but has recently been launched in a new 577 nm (yellow light) version as well. Given that the theoretical and documented clinical advantages of yellow light over green light are sparse, this paper only addresses results obtained with the 532 nm laser (Sramek et al. 2012; Bressler et al. 2013).

Only few studies have addressed the direct clinical comparison of navigated laser and 'conventional' slit-lamp based laser as intravitreal anti-VEGF agents had been introduced as treatment of choice in center involving DME by the time of its approval. As a consequence, most studies examine the clinical benefits of navigated laser as an adjunctive to intravitreal anti-VEGF.

We could not identify comparable studies between navigated laser and argon green laser as described in the ETDRS report number one. One study reported a comparable outcome in regards of VA with a lower retreatment rate after navigated focal/grid laser photocoagulation as compared to slit-lamp based laser treatment performed with a similar wavelength of 532 nm (Neubauer et al. 2013). Another study documented a significantly increased hit-rate in focal treatment of leaking microaneurisms and reduced patient discomfort using navigated laser but did not report any results in regards of VA or central retinal thickness (Kernt et al. 2012).

FUNCTIONAL IMPACT OF FOCAL/GRID LASER PHOTOCOAGULATION

When discussing the potential beneficial effects of focal/grid laser photocoagulation as adjunctive therapy to intravitreal anti-VEGF the risk of adverse events must be taken into account. Even though the incidence has decreased with modified ETDRS protocols and modern laser systems, progressive enlargement of laser scars, subretinal fibrosis and choroidal neovascularization remains among the severe adverse events to focal/grid laser photocoagulation (Lewis et al. 1990; Schatz et al. 1991; Guyer et al. 1992). Further, concern has been raised about the impact on macular function even after successful treatment with no apparent adverse events due to the destructive nature of retinal photocoagulation as compared to intravitreal anti-VEGF treatment.

While OCT provides only a structural measure of retinal morphology a computer perimetric evaluation of the central visual field provides a functional measure of almost the entire macular area presented as retinal sensitivity and may better reflect the subjective experience of visual function than VA measured under standardized conditions.

Conflicting results on changes in retinal sensitivity after focal/grid laser photocoagulation have been presented in recent years. In one study 29 patients with clinically significant diabetic macular edema (CSME) were treated with conventional focal/grid laser photocoagulation as described by the ETDRS. Changes in visual field from baseline to moth 24 were examined with the 10-2 SITA standard algorithm of the Humphrey Field Analyzer. The investigators found no change in retinal sensitivity from baseline to follow-up and no correlation between visual field changes and the number of laser effects or the number of laser sessions (Tababat-Khani et al. 2016).

In contrast, a randomized clinical trial on 62 eyes of 50 patients with CSME found reduced retinal sensitivity by microperimetry at 12-months follow-up after mETDRS green laser focal/grid photocoagulation (Vujosevic et al. 2010). However, increased retinal sensitivity was demonstrated in the second treatment arm in which patients received subthreshold micropulse diode laser with no difference in VA or central retinal thickness between the groups.

In a substudy of the DA VINCI trial pooled data on retinal sensitivity by microperimetry from patients treated with intravitreal aflibecept injections (IAI) were compared to patients treated with mETDRS green laser focal/grid photocoagulation (Gonzalez et al. 2015). In the pooled IAI group retinal sensitivity increased at week 52 whereas retinal sensitivity decreased in the laser group. However, the substudy only included 11 patients in the laser arm and in addition the results were not adjusted for change in retinal thickness which has previously been demonstrated to be significantly associated to retinal sensitivity in patients with CSME (Vujosevic et al. 2006). Additionally, it should be emphasized that even in the IAI groups the mean number of laser sessions were 1.4-1.8.

USE OF FOCAL/GRID PHOTOCOAGULATION IN ANTI-VEGF TRIALS

Whether applied monthly, as pro re nata or as treat and extend the effects of intravitreal anti-VEGF in DME-treatment are compelling and have been abundantly demonstrated (Elman et al. 2010; Massin et al. 2010; Nguyen et al. 2010; Mitchell et al. 2011; Do et al. 2012; Nguyen et al. 2012; Liegl et al. 2014; Berger et al. 2015; Ishibashi et al. 2015; Heier et al. 2016; Prunte et al. 2016; Wells et al. 2016; Payne et al. 2017). Conversely, the potential benefit of focal/grid laser photocoagulation as adjunctive therapy is less consistent and data is much harder to interpret.

Table 1 provides an overview of the design characteristics, results and the use of laser in clinical trials with anti-VEGF for DME. The somewhat heterogeneous methods and outcome measures do not allow for a complete and uniform presentation of data and thus the results will be further discussed in this section. As bevacizumab is not approved for treatment of DME, results with bevacizumab will not be discussed in detail. However, bevacizumab is abundantly used off-license in many health care systems and thus deserves mentioning. In brief, bevacizumab has been demonstrated superior to focal/grid laser photocoagulation in regards of retinal thickness and VA but inferior to both aflibercept and ranibizumab in regards of retinal thickness and aflibercept in regards of VA (Michaelides et al. 2010; Wells et al. 2016).

All studies presented in Table 1 include the use of focal/grid laser photocoagulation as either rescue treatment, in active treatment arms as controls or in combination therapy with anti-VEGF.

With regards of laser as rescue treatment the reported use varies from in approximately 5% to as much as in 50% of patients and reflects the great variety in criteria for rescue laser. The REVEAL study discontinued patients from the ranibizumab monotherapy arm if rescue laser was needed and patients in the VISTA and VIVID trials only met the criteria for rescue laser if DME worsened as defined by a ≥10-letter loss at two consecutive visits or a ≥15-letter loss at one visit from the previous visit. Conversely, patients in the DRCR.net Protocol T met the criteria for focal/grid laser photocoagulation if DME persisted and was not improving at month six (Heier et al. 2016; Wells et al. 2016).

Considering only studies with planned combination therapy with anti-VEGF and focal/grid laser photocoagulation, the READ-2 trial and the study by Liegl et al. demonstrated a decreased need for intravitreal ranibizumab during follow-up in the combination arm as compared with ranibizumab monotherapy with similar outcomes in regards of VA (Nguyen et al. 2010; Liegl et al. 2014). Further, the READ-2 study demonstrated that while foveal thickness increased during follow-up from month six to month 24 with ranibizumab monotherapy, a continuous decrease in foveal thickness was seen with combination therapy. These results were, however, not reproduced by the remaining studies presented in Table 1.

Several differences in trial design in regards of e.g. loading phases, criteria for retreatment and rescue treatment, length of follow-up and outcome measures complicates direct comparison of result. A recurrent issue is inadequate descriptions of the laser systems used and treatment protocols for its application, especially among studies that include focal/grid laser photocoagulation as active treatment arms. Of eighth studies that aimed to evaluate combination therapy with anti-VEGF and focal/grid laser photocoagulation, only two studies presented a description of the applied laser system and treatment protocol thorough enough to allows for accurate replication (Liegl et al. 2014; Payne et al. 2017). The Navilas® laser system was used in both these studies. However, very different protocols for the application of navigated laser treatment were applied which allows for a discussion of the differences in outcome. Whereas the study by Liegl et al. applied focal/grid laser treatment according to the ETDRS guidelines and found a reduced need for ranibizumab in the combination arm as compared to ranibizumab monotherapy, the same number of ranibizumab injections was needed in the T&E groups with and without adjunctive laser therapy in the TREX-DME trial. However, in the TREX-DME trial laser photocoagulation was only applied as angiography guided focal treatment to microaneurysms with continuous leakage after initiated treatment with intravitreal ranibizumab at week four and again every three months. Hence, the results from the TREX-DME trial may reflect insufficient treatment rather than lack of efficacy when compared to results achieved with ETDRS/mETDRS focal/grid laser photocoagulation protocols.

TABLE 1

DISCUSSION

Given the technical advances and differences of application within laser photocoagulation systems, an evaluation of photocoagulation as a general term seems obsolete and future studies ought to describe the methods for application of photocoagulation as thoroughly as it is the case with anti-VEGF protocols. As shown in Table 1, current data on anti-VEGF treatment for DME is still greatly influenced by focal/grid laser photocoagulation. Though data on combination therapy is inconsistent, laser therapy was required as adjunctive/rescue treatment in approximately 20-50% of patients receiving anti-VEGF monotherapy for center involving DME across a wide range of clinical trials. Further, a lower retreatment rate and a more stable reduction of retinal thickness have been demonstrated in more studies. This is not only encouraging in regards of a lower treatment burden for both patients and healthcare systems, but also in regards of the discrepancy between the settings of clinical trials and clinical practice. Patient selection, competing disorders and compliance may negatively influence the beneficial effects of anti-VEGF demonstrated in clinical trials and calls for additional treatment options.

Based on the limited available data, subthreshold diode micropulse laser photocoagulation may be superior to conventional and multispot ETDRS/mETDRS laser photocoagulation and may offer a valuable option as adjunctive therapy to anti-VEGF treatment. Additional to superior outcome in regards of VA, the subthreshold diode micropulse laser photocoagulation system has the theoretical advantage of multiple optional retreatments without compromised retinal function as no thermal damage to retinal tissue is present. It must, however, be emphasized that the impact of photocoagulation on retinal sensitivity is ambiguous and the differences in results may be explained more by differences in methods of measurement than actual functional differences.

The navigated laser system has demonstrated a lower retreatment rate with and without anti-VEGF therapy though data is not consistent. The system benefits from the technical advances in retinal imaging and image processing and is optimal for individually planned laser treatment. The increased accuracy in focal treatment may offer additional effect to anti-VEGF monotherapy in selected patients which, however, needs to be further explored.

The very different approaches to focal/grid laser photocoagulation over various laser systems also suggests different mechanisms of treatment effect. The oxygen theory is one of the most solid theories on the beneficial effect of retinal photocoagulation (Stefansson 2006). It suggests that photocoagulation reduces the metabolic demand and increases the oxygen supply to the remaining tissue through increased oxygen flux from the choroid through laser scars. The theory is substantiated by observational studies in which supplemental oxygen in breathing air reduced DME over three months, presumably due to reduced VEGF expression and decreased hydrostatic pressure through autoregulatory vascular constriction (Gottfredsdottir et al. 1993; Aiello et al. 1994; Bek 1999; Augustin et al. 2001; Nguyen et al. 2004). However, the demonstration of comparable results to conventional ETDRS photocoagulation with subthreshold diode micropulse laser photocoagulation without visible damage to the retinal tissue suggests altered expression of inflammatory mediators including VEGF as the dominant mechanism of effect over increased oxygen tension (Gao & Xing 2009). Whether one theory holds true over the other is uncertain and further, the demonstration of reduced effect of focal/grid photocoagulation without targeted treatment of microaneurysms suggests that various mechanisms are involved (Fong et al. 2007).

In conclusion, current data suggest that focal/grid laser therapy should still be an option for consideration as adjunctive therapy in many patients. More well designed studies on combination therapy are warranted

to determine the full potential of modern retinal photocoagulation systems and whether individual patient characteristics can be used to predict treatment outcome through customized photocoagulation.

Aiello LP, RL Avery, PG Arrigg, BA Keyt, HD Jampel, ST Shah, LR Pasquale, H Thieme, MA Iwamoto, JE Park & et al. (1994): Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. The New England journal of medicine **331**: 1480-1487.

Augustin AJ, A Keller, F Koch, B Jurklies & B Dick (2001): [Effect of retinal coagulation status on oxidative metabolite and VEGF in 208 patients with proliferative diabetic retinopathy]. Klinische Monatsblatter fur Augenheilkunde **218**: 89-94.

Bek T (1999): Diabetic maculopathy caused by disturbances in retinal vasomotion. A new hypothesis. Acta ophthalmologica Scandinavica **77**: 376-380.

Berger A, T Sheidow, AF Cruess, JD Arbour, AS Courseau & F de Takacsy (2015): Efficacy/safety of ranibizumab monotherapy or with laser versus laser monotherapy in DME. Canadian journal of ophthalmology. Journal canadien d'ophtalmologie **50**: 209-216.

Blumenkranz MS, D Yellachich, DE Andersen, MW Wiltberger, D Mordaunt, GR Marcellino & D Palanker (2006): Semiautomated patterned scanning laser for retinal photocoagulation. Retina (Philadelphia, Pa.) **26**: 370-376.

Bressler SB, T Almukhtar, LP Aiello, NM Bressler, FL Ferris, 3rd, AR Glassman & CM Greven (2013): Green or yellow laser treatment for diabetic macular edema: exploratory assessment within the Diabetic Retinopathy Clinical Research Network. Retina (Philadelphia, Pa.) **33**: 2080-2088.

Brown DM, U Schmidt-Erfurth, DV Do, FG Holz, DS Boyer, E Midena, JS Heier, H Terasaki, PK Kaiser, DM Marcus, QD Nguyen, GJ Jaffe, JS Slakter, C Simader, Y Soo, T Schmelter, GD Yancopoulos, N Stahl, R Vitti, AJ Berliner, O Zeitz, C Metzig & JF Korobelnik (2015): Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. Ophthalmology **122**: 2044-2052.

Do DV, QD Nguyen, D Boyer, U Schmidt-Erfurth, DM Brown, R Vitti, AJ Berliner, B Gao, O Zeitz, R Ruckert, T Schmelter, R Sandbrink & JS Heier (2012): One-year outcomes of the da Vinci Study of VEGF Trap-Eye in eyes with diabetic macular edema. Ophthalmology **119**: 1658-1665.

Dorin G (2003): Subthreshold and micropulse diode laser photocoagulation. Seminars in ophthalmology **18**: 147-153.

Early Treatment Diabetic Retinopathy Study Research Group (1985): Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Archives of ophthalmology **103**: 1796-1806.

Early Treatment Diabetic Retinopathy Study Research Group (1987): Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology **94**: 761-774.

Elman MJ, LP Aiello, RW Beck, NM Bressler, SB Bressler, AR Edwards, FL Ferris, 3rd, SM Friedman, AR Glassman, KM Miller, IU Scott, CR Stockdale & JK Sun (2010): Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology **117**: 1064-1077.e1035.

Figueira J, J Khan, S Nunes, S Sivaprasad, A Rosa, JF de Abreu, JG Cunha-Vaz & NV Chong (2009): Prospective randomised controlled trial comparing sub-threshold micropulse diode laser photocoagulation and conventional green laser for clinically significant diabetic macular oedema. The British journal of ophthalmology **93**: 1341-1344.

Fong DS, SF Strauber, LP Aiello, RW Beck, DG Callanan, RP Danis, MD Davis, SS Feman, F Ferris, SM Friedman, CA Garcia, AR Glassman, DP Han, D Le, C Kollman, AK Lauer, FM Recchia & SD Solomon (2007): Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema. Archives of ophthalmology **125**: 469-480.

Franz Fankhauser SK (2003): Lasers in Ophthalmology: Basic, Diagnostic, and Surgical Aspects : a Review. Kugler Publications: p. 175.

Gao X & D Xing (2009): Molecular mechanisms of cell proliferation induced by low power laser irradiation. Journal of biomedical science **16**: 4.

Gonzalez VH, DS Boyer, U Schmidt-Erfurth, JS Heier, C Gordon, MS Benz, DM Marcus, NR Sabates, R Vitti, H Kazmi, AJ Berliner, Y Soo, X Zhu, H Moini, O Zeitz, R Sandbrink & DV Do (2015): Microperimetric assessment of retinal sensitivity in eyes with diabetic macular edema from a phase 2 study of intravitreal aflibercept. Retina (Philadelphia, Pa.) **35**: 687-694.

Gottfredsdottir MS, E Stefansson, F Jonasson & I Gislason (1993): Retinal vasoconstriction after laser treatment for diabetic macular edema. American journal of ophthalmology **115**: 64-67.

Guyer DR, DJ D'Amico & CW Smith (1992): Subretinal fibrosis after laser photocoagulation for diabetic macular edema. American journal of ophthalmology **113**: 652-656.

Heier JS, JF Korobelnik, DM Brown, U Schmidt-Erfurth, DV Do, E Midena, DS Boyer, H Terasaki, PK Kaiser, DM Marcus, QD Nguyen, GJ Jaffe, JS Slakter, C Simader, Y Soo, T Schmelter, R Vitti, AJ Berliner, O Zeitz, C Metzig & FG Holz (2016): Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies. Ophthalmology **123**: 2376-2385.

Ishibashi T, X Li, A Koh, TY Lai, FL Lee, WK Lee, Z Ma, M Ohji, N Tan, SB Cha, J Shamsazar & CL Yau (2015): The REVEAL Study: Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy in Asian Patients with Diabetic Macular Edema. Ophthalmology **122**: 1402-1415.

Jain A, MS Blumenkranz, Y Paulus, MW Wiltberger, DE Andersen, P Huie & D Palanker (2008): Effect of pulse duration on size and character of the lesion in retinal photocoagulation. Archives of ophthalmology **126**: 78-85.

Kernt M, RE Cheuteu, S Cserhati, F Seidensticker, RG Liegl, J Lang, C Haritoglou, A Kampik, MW Ulbig & AS Neubauer (2012): Pain and accuracy of focal laser treatment for diabetic macular edema using a retinal navigated laser (Navilas). Clinical ophthalmology (Auckland, N.Z.) **6**: 289-296.

Lavinsky D, JA Cardillo, LA Melo, Jr., A Dare, ME Farah & R Belfort, Jr. (2011): Randomized clinical trial evaluating mETDRS versus normal or high-density micropulse photocoagulation for diabetic macular edema. Investigative ophthalmology & visual science **52**: 4314-4323.

Lewis H, AP Schachat, MH Haimann, JA Haller, P Quinlan, MA von Fricken, SL Fine & RP Murphy (1990): Choroidal neovascularization after laser photocoagulation for diabetic macular edema. Ophthalmology **97**: 503-510; discussion 510-501.

Liegl R, J Langer, F Seidensticker, L Reznicek, C Haritoglou, MW Ulbig, AS Neubauer, A Kampik & M Kernt (2014): Comparative evaluation of combined navigated laser photocoagulation and intravitreal ranibizumab in the treatment of diabetic macular edema. PloS one **9**: e113981.

Luttrull JK & G Dorin (2012): Subthreshold diode micropulse laser photocoagulation (SDM) as invisible retinal phototherapy for diabetic macular edema: a review. Current diabetes reviews **8**: 274-284.

Luttrull JK, DC Musch & MA Mainster (2005): Subthreshold diode micropulse photocoagulation for the treatment of clinically significant diabetic macular oedema. The British journal of ophthalmology **89**: 74-80.

Massin P, F Bandello, JG Garweg, LL Hansen, SP Harding, M Larsen, P Mitchell, D Sharp, UE Wolf-Schnurrbusch, M Gekkieva, A Weichselberger & S Wolf (2010): Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. Diabetes Care **33**: 2399-2405.

Michaelides M, A Kaines, RD Hamilton, S Fraser-Bell, R Rajendram, F Quhill, CJ Boos, W Xing, C Egan, T Peto, C Bunce, RD Leslie & PG Hykin (2010): A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. Ophthalmology **117**: 1078-1086.e1072.

Mitchell P, F Bandello, U Schmidt-Erfurth, GE Lang, P Massin, RO Schlingemann, F Sutter, C Simader, G Burian, O Gerstner & A Weichselberger (2011): The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology **118**: 615-625.

Modi D, P Chiranand & L Akduman (2009): Efficacy of patterned scan laser in treatment of macular edema and retinal neovascularization. Clinical ophthalmology (Auckland, N.Z.) **3**: 465-470.

Moisseiev E, S Abbassi, S Thinda, J Yoon, G Yiu & LS Morse (2017): Subthreshold micropulse laser reduces anti-VEGF injection burden in patients with diabetic macular edema. European journal of ophthalmology: 0.

Muqit MM, C Sanghvi, R McLauchlan, C Delgado, LB Young, SJ Charles, GR Marcellino & PE Stanga (2012): Study of clinical applications and safety for Pascal(R) laser photocoagulation in retinal vascular disorders. Acta Ophthalmol **90**: 155-161.

Neubauer AS, J Langer, R Liegl, C Haritoglou, A Wolf, I Kozak, F Seidensticker, M Ulbig, WR Freeman, A Kampik & M Kernt (2013): Navigated macular laser decreases retreatment rate for diabetic macular edema: a comparison with conventional macular laser. Clinical ophthalmology (Auckland, N.Z.) **7**: 121-128.

Nguyen QD, DM Brown, DM Marcus, DS Boyer, S Patel, L Feiner, A Gibson, J Sy, AC Rundle, JJ Hopkins, RG Rubio & JS Ehrlich (2012): Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology **119**: 789-801.

Nguyen QD, SM Shah, AA Khwaja, R Channa, E Hatef, DV Do, D Boyer, JS Heier, P Abraham, AB Thach, ES Lit, BS Foster, E Kruger, P Dugel, T Chang, A Das, TA Ciulla, JS Pollack, JI Lim, D Eliott & PA Campochiaro (2010): Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. Ophthalmology **117**: 2146-2151.

Nguyen QD, SM Shah, E Van Anden, JU Sung, S Vitale & PA Campochiaro (2004): Supplemental oxygen improves diabetic macular edema: a pilot study. Investigative ophthalmology & visual science **45**: 617-624.

Pankratov MM (1990): Pulsed delivery of laser energy in experimental thermal retinal photocoagulation: 205-213.

Payne JF, CC Wykoff, WL Clark, BB Bruce, DS Boyer & DM Brown (2017): Randomized Trial of Treat and Extend Ranibizumab with and without Navigated Laser for Diabetic Macular Edema: TREX-DME 1 Year Outcomes. Ophthalmology **124**: 74-81.

Prunte C, F Fajnkuchen, S Mahmood, F Ricci, K Hatz, J Studnicka, V Bezlyak, S Parikh, WJ Stubbings, A Wenzel & J Figueira (2016): Ranibizumab 0.5 mg treat-and-extend regimen for diabetic macular oedema: the RETAIN study. The British journal of ophthalmology **100**: 787-795.

Roider J (1999): Laser treatment of retinal diseases by subthreshold laser effects. Seminars in ophthalmology **14**: 19-26.

Sanghvi C, R McLauchlan, C Delgado, L Young, SJ Charles, G Marcellino & PE Stanga (2008): Initial experience with the Pascal photocoagulator: a pilot study of 75 procedures. The British journal of ophthalmology **92**: 1061-1064.

Schatz H, D Madeira, HR McDonald & RN Johnson (1991): Progressive enlargement of laser scars following grid laser photocoagulation for diffuse diabetic macular edema. Archives of ophthalmology **109**: 1549-1551.

Sramek CK, LS Leung, YM Paulus & DV Palanker (2012): Therapeutic window of retinal photocoagulation with green (532-nm) and yellow (577-nm) lasers. Ophthalmic surgery, lasers & imaging : the official journal of the International Society for Imaging in the Eye **43**: 341-347.

Stefansson E (2006): Ocular oxygenation and the treatment of diabetic retinopathy. Survey of ophthalmology **51**: 364-380.

Tababat-Khani P, B Bengtsson & E Agardh (2016): Effects of focal/grid laser treatment on the central visual field in diabetic macular oedema: a 2-year follow-up study. Acta Ophthalmol.

Vujosevic S, E Bottega, M Casciano, E Pilotto, E Convento & E Midena (2010): Microperimetry and fundus autofluorescence in diabetic macular edema: subthreshold micropulse diode laser versus modified early treatment diabetic retinopathy study laser photocoagulation. Retina (Philadelphia, Pa.) **30**: 908-916.

Vujosevic S, E Midena, E Pilotto, PP Radin, L Chiesa & F Cavarzeran (2006): Diabetic macular edema: correlation between microperimetry and optical coherence tomography findings. Investigative ophthalmology & visual science **47**: 3044-3051.

Wells JA, AR Glassman, AR Ayala, LM Jampol, NM Bressler, SB Bressler, AJ Brucker, FL Ferris, GR Hampton, C Jhaveri, M Melia & RW Beck (2016): Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology.

Table 1: Overview of characteristics, results and the use of laser in clinical trials with anti-VEGF for diabetic macular edema

Clinical Trial (Phase)	Year published	Inclusion criteria		Follow-up, months	Treatment arms	Laser system	Active laser sessions, mean ±SD and/or *%**	Number of active injections during follow-up, mean ±SD or *median (25th, 75th percentile)*	Mean VA gain ±SD	Mean change in CRT ±SD or *% ±SD*
		VA, ETDRS	CRT, µm							
RCTs with focal/grid photocoagulation only as rescue treatment										
RESOLVE (2)	2010	73-39	≥300	12	PRN Ranibizumab (n=102)‡ PRN Sham injection (n=49)	Not specified	*5* *35*	10.2±2.5 -	10.3±9.1 -1.4±14.2	-194.2±135.1 -48.4±153.4
DA VINCI (2)	2012	73-24	≥250	12	Q4 Aflibercept 2.0 mg + sham laser (n=44) PRN Aflibercept 2.0 mg + sham laser (n=45) Q4 Sham injections + laser (n=44)	Not specified	0.5±0.66 0.7±0.77 2.5±0.87	10.8±2.87 7.4±3.19 -	11.0±NA 12.0±NA -1.3±NA	-227.4±NA -187.8±NA -58.4±NA
RIDE (3)	2012	70-35	≥275	24	Q4 Ranibizumab 0.5 mg (n=127) Q4 Sham injection (n=130)	Not specified	0.3±0.7 / *19.7* 1.6±1.6 / *70.0*	21.9±5.8 -	12.0±14.9 2.3±14.2	-270.7±201.6 -125.8±198.3
RISE (3)	2012	70-35	≥275	24	Q4 Ranibizumab 0.5 mg (n=125) Q4 Sham injection (n=127)	Not specified	0.8±1.3 / *35.2* 1.8±1.8 / *74.0*	20.9±6.3 -	11.9±12.1 2.6±13.9	-253.1±183.7 -133.4±209.0
VISTA (3)	2016	73-24	Not specified	34	Q4 Aflibercept 2 mg (n=155) Q8 Aflibercept 2 mg (n=152) Laser (n=154)	Not specified	1.4±0.8 / *4.5* 1.4±1.1 / *10.5* 3.8±2.4	29.6±9.8 18.1±4.8 13.5±3.9	10.4±14.2 10.5±12.7 1.4±14.5	-200.4±NA -190.1±NA -109.8±NA
VIVID (3)	2016	73-24	Not specified	34	Q4 Aflibercept 2 mg (n=136) Q8 Aflibercept 2 mg (n=135) Laser (n=133)	Not specified	2.3±1.5 / *7.4* 1.9±1.0 / *11.9* 2.6±2.0	32.0±9.7 18.1±5.1 13.5±4.3	10.3±12.5 11.7±10.1 1.6±12.7	-215.2±NA -202.8±NA -122.6±NA
Protocol T, DRCR.net	2016	78-24	>250	24	PRN Aflibercept 2.0 mg (n=98) PRN Ranibizumab 0.3 mg (n=94)	Not specified	*46* *52*	*15 (11, 17)* *15 (11, 19)*	18.1±13.8 16.1±12.1	-171±141 -149±141
RCTs with planned combination therapy with anti-VEGF and focal/grid laser photocoagulation										
READ-2ϕ (2)	2010	70-25	≥250	24	PRN Ranibizumab 0.5 mg (n=33) PRN Ranibizumab 0.5 mg + laser (n=34) Laser (n=34)	Not specified	NA NA NA	5.3±NA 2.9±NA 4.4±NA	7.7±NA 6.8±NA 5.1±NA	NA NA NA
Protocol I, DRCR.net	2010	78-24	≥250	12	PRN Ranibizumab 0.5 mg + prompt laser (n=187) PRN Ranibizumab 0.5 mg + deferred laser (n=188) PRN Sham injection + laser (n=293)	Green laser only (2/3), yellow laser only (1/5) or combination.	*16* *8* *26*	*8 (6, 10)* *9 (6, 11)* -	9±11 9±12 3±13	-131±129 -137±136 -102±151
RESTORE (3)	2011	78-39	Not specified	12	PRN Ranibizumab 0.5 mg + sham laser (n=116) PRN Ranibizumab 0.5 mg + laser (n=118) PRN Sham injection + laser (n=111)	Not specified	- 1.7±0.89 2.1±1.04	7.0±2.81 6.8±2.95 0.0	6.1±6.43 6.0±7.92 0.8±8.56	-118.7±115.07 -128±114.34 -61±132.29
Berger et al	2014	78-39	Not specified	12	PRN Ranibizumab 0.5 mg (n=75) PRN Ranibizumab + laser (n=73) Laser (n=72)	Not specified	- 1.6±1.0 2.6±2.1	9.2±2.8 8.8±2.9 -	8.9±NA 8.2±NA 0.3±NA	-143.5±NA -152.2±NA -107.1±NA
REVEAL (3)	2015	78-39	Not specified	12	PRN Ranibizumab 0.5 mg + sham laser (n=133) PRN Ranibizumab 0.5 mg + laser (n=132) PRN Sham injection + laser (n=131)	Not specified	0.0† 1.5±0.85 1.9±1.02	7.8±2.94 7.0±3.07 0.0	5.9±6.02 5.7±7.20 1.4±6.49	-134.6 (-) -171.8 (-) -57.2 (-)
RETAIN (3)	2015	78-39	Not specified	24	T&E Ranibizumab 0.5 mg (n=128) T&E Ranibizumab 0.5 mg + laser (n=121) PRN Ranibizuman 0.5 mg (n=123)	Not specified	- 1.2±0.66 -	12.8±3.7 12.4±3.8 10.7±5.6	6.49±10.85 8.30±8.13 8.06±8.46	*-24.98±26.41* *-32.02±25.63* *-24.97±26.68*
TREX-DME (1/2)	2017	79-24	Not specified	12	Q4 Ranibizumab 0.3 mg (n=30) T&E Ranibizumab 0.3 mg (n=60) T&E Ranibizumab 0.3 mg + laser (60)	Navilas®	- - 2.9±NA	13.1±NA 10.7±NA 10.1±NA	8.6±NA 9.6±NA 9.5±NA	-123±NA -146±NA -166±NA
Non-RCTs with planned combination therapy with anti-VEGF and focal/grid laser photocoagulation										
Liegl et al	2014	≥10	≥400	12	PRN Ranibizumab 0.5 mg (n=32) PRN Ranibizumab 0.5 mg + laser (n=34)	Navilas®	- 1.24±0.43	6.9±2.3 3.9±1.3	6.3±6.5 8.4±8.3	-105±107 -129±170

VA: Visual acuity. *CRT:* Central retinal thickness. *RCT:* Randomized clinical trials. *PRN:* Pro re nata. *Q4/Q8:* Monthly/8 weeks interval. *T&E:* Treat and Extend.

*Active laser sessions incl. rescue laser. (%): The percentage of patients that received laser during study period. ‡Pooled data for Ranibizumab 0.3 mg and 0.5 mg. ϕNumber of active injections during follow-up specified as from month 6 to month 24 after a loading phase of 4, 2 and 0 Ranibizumab injections respectively. †Patients were discontinued from study if active laser was needed.