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REVIEW ARTICLE

Review of clinical studies and recommendation for a therapeutic flow chart for diabetic macular edema

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Abstract

Diabetic macular edema (DME), characterized by exudative fluid accumulation in the macula, is the most common form of sight-threatening retinopathy in patients with diabetes. The management of DME has changed considerably in recent years, especially following the development of intravitreal anti-vascular endothelial growth factor therapy which has emerged as a first-line therapy for center-involved DME. Laser treatment, intravitreal steroid therapy, and vitrectomy are also important treatment options for DME. We believe that it is important to choose the most appropriate treatment option for DME based on the clinical evidences, in addition to the careful consideration of individual patients' general or ocular condition, DME characteristics, patients' motivation, and compliance to the treatment in real-world clinical practice. In this review, we have summarized important clinical evidences for the main treatments for DME, presented an expert review for these evidences, and proposed a recommended therapeutic flow chart for DME. We hope that our review of the clinical evidences and the recommended therapeutic flow chart for DME will contribute to better treatment outcome for DME.

Keywords Review · Clinical evidence · Therapeutic flow chart · Diabetic macular edema

Introduction

Diabetic macular edema (DME), characterized by exudative fluid accumulation in the macula, is the most common form of sight-threatening retinopathy in patients with diabetes. DME is estimated to affect one in 15 patients with diabetes resulting in more than 20 million cases worldwide [1]. The pathogenesis of DME is multifactorial and complex, in which the hyperglycemic state caused by diabetes induces multiple pathologic abnormalities, such as angiogenic, inflammatory, hypoxic, and hemodynamic processes that lead to the breakdown of the blood-retinal barrier and leakage of the intraretinal fluid.

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Key messages

- Diabetic macular edema (DME) is the most common form of sight-threatening retinopathy in patients with diabetes.
- It is important to choose the most appropriate treatment option for DME based on the clinical evidences, in addition to the careful consideration of individual patients' general or ocular condition, DME characteristics, patients' motivation, and compliance to the treatment in real-world clinical practice.
- In this review, we have proposed a recommended therapeutic flow chart for DME, after summarizing important clinical evidences for the main treatments for DME, and presenting an expert review for these evidences.

These pathologic abnormalities ultimately lead to sight-threatening conditions of macular edema and proliferative, neovascular retinopathy [2].

The management of DME has changed significantly in recent years, especially with the emergence of intravitreal anti-vascular endothelial growth factor (VEGF) therapy that has emerged as a first-line therapy for center-involved DME [3]. Before the emergence of anti-VEGF therapy, the predominant goal of treatment was visual acuity stabilization. With the approval of anti-VEGF agents for the treatment of visual impairment caused by DME, the primary goal of therapy has now become the improvement or restoration of visual acuity, with the stabilization of vision and prevention of further vision loss as the key secondary goals [4]. However, anti-VEGF therapy has some limitations for routine use in real-world clinical practice, such as the multiple visits required for injections, the accompanying economic and time burden, and risks of the potential systemic side effects [3, 5].

Laser treatment for DME remains to be an important adjunctive therapy in real-world practice [6]. Several studies have reported the clinical usefulness of combining laser and anti-VEGF therapies. In addition, with the development of new laser technologies, such as subthreshold micropulse laser and Navilas® navigated laser (OD-OS GmbH, Germany), laser photocoagulation has again become a topic of interest [7, 8]. Inhibiting the inflammatory processes by the intravitreal application of steroids is an important pharmacotherapy for DME, as is VEGF inhibition caused by the intravitreal injection of an anti-VEGF agent [9]. Early vitrectomy may reduce treatment burden for patients with diabetes, prevent vision loss, and provide the long-term stabilization of retinopathy in patients with diabetes [10].

The main clinical treatments for DME in Japan are intravitreal anti-VEGF therapy, laser treatment, intravitreal steroid therapy, and vitrectomy. We believe that it is important to choose the most appropriate treatment option for DME based on the clinical evidences, careful consideration of the individual patients' general or ocular condition, DME characteristics, the patients' motivation, and compliance to the treatment in real-world clinical practice. In this review, the authors have summarized the important clinical evidences for the main treatments of DME, presented an expert review of these evidences, and have proposed a recommended therapeutic flow chart for DME. At the Retina Deep Dive, a conference held by Bayer Yakuhin, Ltd. in 2018, the authors firstly discussed about the proposal of a therapeutic flow chart for DME. The authors continued the discussion and review of clinical evidences after the conference, and have developed the proposal of this therapeutic flow chart. Bayer Yakuhin, Ltd. has not been involved in the preparation process of this proposal, and the authors have prepared this proposal neutrally based on the clinical evidences.

Anti-VEGF therapy

Focal/grid laser had been the only evidence-based treatment for DME since the 1980s [11]. Since 2010, several large trials have demonstrated that the intravitreal injection of an anti-VEGF agent yielded greater improvements in visual acuity than laser photocoagulation in patients with DME. Anti-VEGF therapy has been used increasingly for the treatment of DME in clinical practice [12, 13], and has now replaced laser photocoagulation as the standard of care for this disease. Two anti-VEGF agents, ranibizumab and aflibercept, have been approved for DME in Japan. In this section, we have summarized and reviewed the clinical evidences for these two anti-VEGF therapies, and have discussed recent updates in these evidences.

Ranibizumab

Ranibizumab is a humanized, recombinant antibody fragment of a monoclonal antibody active against all VEGF-A isoforms.

Protocol I from the DRCR.net was the first definitive phase 3 study to address the efficacy and safety of an intravitreal ranibizumab for the treatment of DME in a total of 854 study eyes of 691 participants. This study compared four treatments for DME: ranibizumab given pro re nata (PRN) with prompt laser, ranibizumab with deferred (≥ 24 weeks) laser given only for persistent DME, intraocular triamcinolone with prompt laser, and sham injections with prompt laser. Vision improved by an average of 9 letters in the ranibizumab with laser groups compared with only 3 letters in the sham injection with laser group at the 1-year primary endpoint. This study clearly showed that intravitreal ranibizumab was highly effective for the treatment of DME. The safety evaluation of ranibizumab concluded that the incidence of endophthalmitis should be considered, although ranibizumab therapy was rarely associated with endophthalmitis in this study [14]. The subsequent follow-up of the ranibizumab groups in Protocol I demonstrated sustained vision gains obtained in the first year to 5 years with little additional treatment after 3 years [15].

The RESTORE phase 3 study conducted in Europe randomized 345 subjects into 3 different groups: ranibizumab (given PRN) only, ranibizumab plus laser, and laser only. In the 1-year analysis, visual acuity improved by 6.1 letters in the ranibizumab-only group, by 5.9 letters in the ranibizumab plus laser group, and by 0.8 letters in the laser-only group. There was a statistically significant difference between both ranibizumab groups and the laser-only group, but not between the ranibizumab groups. The mean number of injections was 7.0 in the ranibizumab-only group and 6.8 in the ranibizumab plus laser group. No safety issues were observed in this study (Fig. 1) [16]. The RESTORE extension study followed up 240 patients who completed the RESTORE study and demonstrated that ranibizumab was effective for the improvement and maintenance of visual acuity outcomes with a progressively declining number of injections over 3 years of the PRN regimen. Ranibizumab was generally well tolerated, with no new safety concerns over the 3-year period [17]. The REVEAL study was a randomized controlled study with a design similar to that of the RESTORE study, and was conducted in an Asian population (including Japanese patients). The visual acuity improved by 5.9 letters in the ranibizumab-only group, by 5.7 letters in the ranibizumab plus laser group, and 1.4 letters in the laser-only group. No new ocular or non-ocular safety findings were observed and treatment was well tolerated over 1 year (Fig. 1) [18]. These 2 randomized controlled studies, RESTORE and REVEAL, have demonstrated that the general results for anti-VEGF therapy are applicable across various racial and ethnic groups.

Two methodologically identical phase 3 studies of ranibizumab (monthly injection), RISE, and RIDE (parallel, multicenter, double-masked, sham injection-controlled, randomized studies) were conducted in the USA and South America. RISE enrolled 377 patients with DME, and RIDE enrolled 382 patients. The main outcome measure was improvement of 15 letters or more at 2 years, and the achievement rate was 18.1%, 44.8%, and 39.2% in RISE and 12.3%, 33.6%, and 45.7% in RIDE for patients in the sham injection, 0.3-mg ranibizumab, and 0.5-mg ranibizumab groups, respectively. Similarly to other ranibizumab trials, safety findings were acceptable [19]. The main outcome measure was also evaluated at 3 years, and visual acuity gains achieved at 2 years were sustained throughout the third year [20].

The RETAIN study was a 2-year single-masked study to demonstrate non-inferiority of ranibizumab treat-and-extend (TAE) with and without laser to ranibizumab PRN for visual acuity in patients with DME. Patients with DME were randomized 1:1:1 to ranibizumab TAE with laser (n = 121), ranibizumab TAE (n = 128), and ranibizumab PRN (n = 123) groups. The TAE regimens were non-inferior to PRN based on mean average visual acuity change at 1 year (+ 6.1 and + 6.2 letters in the ranibizumab TAE and PRN groups, respectively). At 2 years, the mean average visual acuity

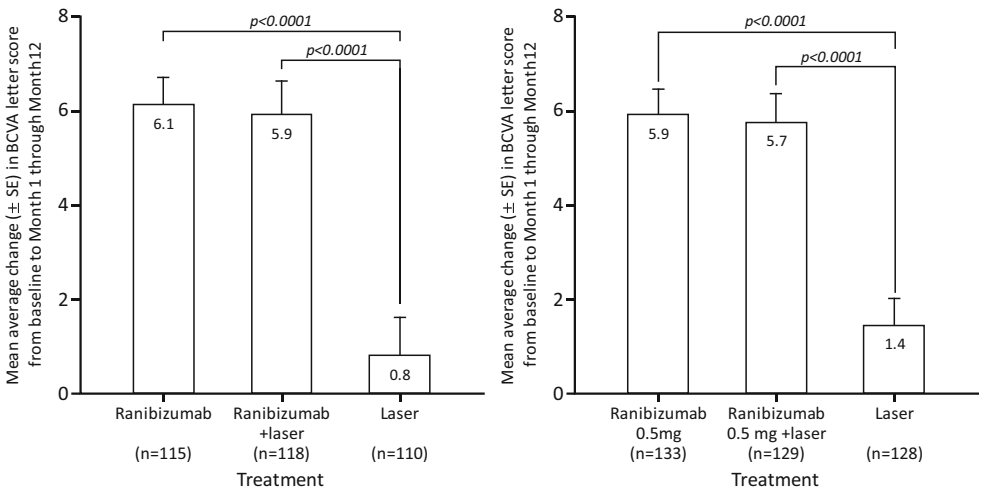

Fig. 1 Visual acuity improvement in the RESTORE (left) [16] and REVEAL (right) [18] study of ranibizumab. The figure is reprinted with the permission from the publisher of original article

change was similar in both the groups (+ 6.5 and + 8.1 letters, respectively). The mean number of injections was 12.8 in the TAE group and 10.7 in the PRN group. The TAE regimens led to a 46% reduction in the number of clinic visits. The RETAIN study suggested that TAE was a feasible treatment option for patients with DME, with the potential to reduce treatment burden (although slightly more injections were required compared with PRN, likely because of the specifics of the TAE regimen applied in this study) [21].

Aflibercept

Aflibercept is a recombinant fusion protein comprising the key VEGF-binding domains of human VEGF receptors 1 and 2 fused to the constant region of human immunoglobulin G1. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and placental growth factor with higher affinity than naturally occurring VEGF receptors.

Two randomized controlled phase 3 studies of aflibercept, VISTA-DME, and VIVID-DME were conducted to investigate the efficacy and safety of repeated doses of intravitreal aflibercept in patients with DME. The VISTA study conducted in the USA enrolled 461 patients with DME, and the VIVID study conducted in Europe, Japan, and Australia enrolled 404 patients with DME. These patients were randomized into 3 groups: the monthly aflibercept group, the bimonthly aflibercept (after 5 initial monthly doses) group, and the laser group. The primary endpoint was the mean change in visual acuity after 1 year. The patients were scheduled for continued treatment for 3 years. After the first year, the primary results showed the superiority of the aflibercept treatments over the laser treatment. The mean change in visual acuity in the VISTA study was + 12.5 and + 10.7 versus + 0.2 letters for the monthly and bimonthly aflibercept groups versus laser group, respectively. The VIVID study showed a similar mean change in visual acuity of + 10.5 and + 10.7 versus + 1.2 letters, respectively. The overall incidences of ocular and non-ocular adverse events and serious adverse events, including the Anti-Platelet Trialists' Collaboration-defined arterial thromboembolic events and vascular deaths, were similar across treatment groups [22]. In both the VISTA and VIVID studies, the 1-year visual superiority of aflibercept treatment over laser treatment was sustained throughout the second and third years, with similar efficacy in the monthly and bimonthly aflibercept groups. Over 3 years, the safety results in these studies were consistent with known safety profile of aflibercept [23, 24].

The recent Protocol V from the DRCR Retina Network, a randomized clinical study conducted at 91 US and Canadian sites, enrolled 702 patients with DME and a visual acuity of 20/25 or better. This study randomized patients to initial management with intravitreal aflibercept, or laser versus observation without treatment. In the laser and observation groups, patients were treated with aflibercept if vision worsened during subsequent follow-up. The primary outcome was at least a 5-letter visual acuity decrease from baseline to 2 years, and the percentage achievement of this primary outcome was 16% (33/205), 17% (36/212), and 19% (39/208) in the aflibercept, laser, and observation groups, respectively. After 1 and 2 years, the mean visual acuity was 20/20 in each group (Fig. 2) [25]. Vascular events, as defined by the Antiplatelet Trialists' Collaboration occurred in 15 (7%), 13 (5%), and 8 (3%) patients, respectively. It was concluded that in eyes with DME and good visual acuity, there was no significant difference in vision loss at 2 years whether the eyes were initially managed with aflibercept or with laser or observation and were then managed with aflibercept if visual acuity worsened. Thus, observation without treatment, unless visual acuity worsens, may be a reasonable strategy for DME [25].

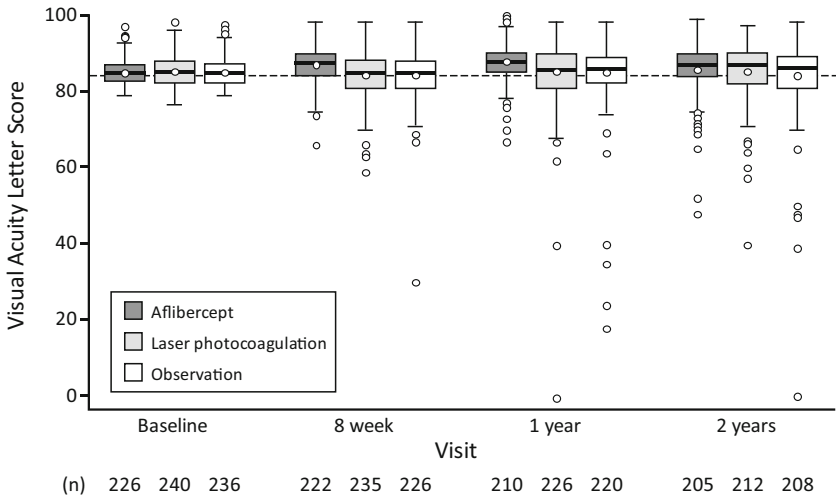

Fig. 2 Visual acuity improvement in the DRCR.net Protocol V to compare aflibercept, laser and observation groups in DME patients with good visual acuity [25]. The figure is reprinted with the permission from the publisher of original article

Ranibizumab versus aflibercept

The DRCR.net Protocol T was a prospective, randomized, comparative effectiveness study that compared 3 anti-VEGFs, ranibizumab, aflibercept, and bevacizumab (which are not approved in Japan for the indication of DME) for the treatment of DME. In this study, given the possibility that one medication is more effective in eyes with worse vision, which is possibly associated with higher VEGF levels and more active retinopathy, a pre-specified analysis was planned to compare results from two major subgroups. No difference in the efficacy of the 3 anti-VEGF therapies in eyes with a visual acuity of 20/40 or better was found after 1 or 2 years of follow-up. However, in eyes with a visual acuity of 20/50 or worse, aflibercept was superior to ranibizumab and bevacizumab at 1 year, and at 2 years, aflibercept was no longer superior to ranibizumab but remained superior to bevacizumab (Fig. 3) [26, 27].

Switching from ranibizumab to aflibercept

The body of research investigating different treatment protocols for the management of resistant DME is growing. According to the results of the DRCR.net Protocol T, switching from ranibizumab to aflibercept is suggested to be a promising strategy for the treatment of resistant DME with poor presenting vision. Some retrospective and prospective studies support this hypothesis [28–30]. In one such study, a prospective interventional case series study recruited 42 patients with DME with a suboptimal response to bevacizumab or ranibizumab (at least 3 consecutive monthly injections in the previous 6 months) and demonstrated that three consecutive monthly injections of aflibercept significantly improved visual acuity with a baseline logMAR visual acuity of 0.87 ± 0.23 to 0.46 ± 0.35 at 3 months [30].

Factors associated with outcomes of anti-VEGF therapy for DME

Additional or post hoc analyses of the randomized clinical study of ranibizumab suggested that baseline central subfield thickness and the presence of subretinal fluid at baseline were associated with better vision outcomes after ranibizumab therapy [31, 32]. Alternatively, a post hoc analysis of the randomized clinical study of aflibercept indicated a strong association between baseline Diabetic Retinopathy Severity Scale (DRSS) score and ≥ 2-step DRSS score improvement after 2 years for patients with DME [33]. A retrospective study that reviewed 66 eyes of 61 Japanese patients with DME who received ranibizumab suggested that the hyperreflective foci in foveal cystoid spaces at baseline were predictive of a poorer short-term (3 months) response to ranibizumab [34]. Recently, a retrospective study was conducted to investigate the factors influencing the clinical outcomes in 73 patients (94 eyes) with DME treated with ranibizumab. This study reported that younger age, better baseline visual acuity, and glycemic control were associated with better visual outcomes after treatment [35].

Systemic safety of anti-VEGF therapy in patients with DME

Intravitreal anti-VEGF therapy is commonly used to treat numerous retinal conditions, including DME, and appears safe; however, its systemic safety remains controversial. In a systematic review and meta-analysis reported in 2016, randomized clinical studies were selected that evaluated monthly anti-

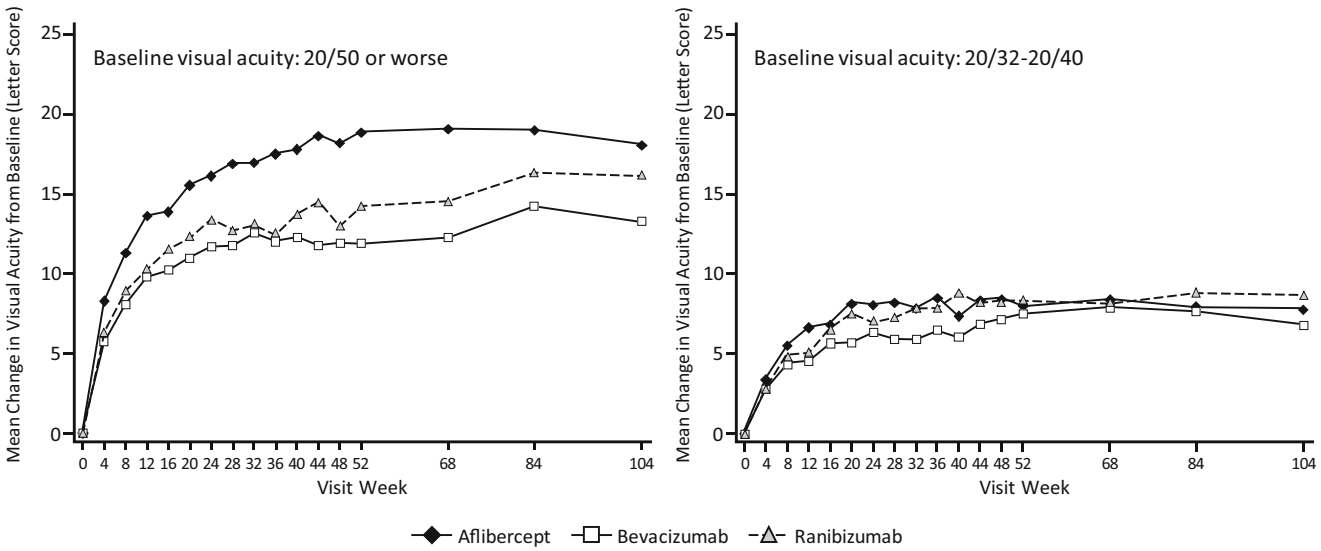

Fig. 3 Visual acuity improvement in the DRCR.net Protocol T to compare the 3 anti-VEGFs, ranibizumab, aflibercept, and bevacizumab [27]. The figure is reprinted with the permission from the publisher of original article

VEGF injections for DME for 2 years and reported the following outcome measures: cerebrovascular accidents, myocardial infarctions, arteriothrombotic events, and mortality. Four studies were selected for the meta-analysis that met the search criteria: 2 trials reporting the use of monthly aflibercept and 2 trials reporting the use of monthly ranibizumab. The four studies enrolled 1328 patients in total. The assessment of the highest-level exposure group (high-risk patients with DME who received monthly treatment for 2 years) revealed a potential increase in the risks of death and cerebrovascular accidents (Table 1) [36]. In addition, a recent Cochrane meta-analysis of anti-VEGF therapies (ranibizumab, aflibercept, bevacizumab, and pegaptanib) for DME analyzed 24 studies with 6007 participants. This report concluded no differences in the overall safety between the anti-VEGF therapies, but it demonstrated that the estimates were imprecise for cardiovascular events and death [37].

Expert review

The efficacy and safety of intravitreal injection of two anti-VEGFs, ranibizumab and aflibercept, for center-involved DME have been proven by many large randomized controlled studies with a high evidence level. Some studies were conducted in non-Japanese populations. However, two randomized controlled studies with similar study design, RESTORE and REVEAL, were conducted in European and Asian population (including Japanese patients) and demonstrated that the general results of anti-VEGF therapy were applicable to various racial and ethnic groups. Consequently, the intravitreal injection of the anti-VEGF agents, ranibizumab or aflibercept, is the current definitive first-line therapy for center-involved DME in the Japanese real-world clinical setting.

There are no definitive criteria for selecting ranibizumab or aflibercept for the treatment of center-involved DME. The results of the DRCR.net Protocol T suggested that aflibercept was superior to ranibizumab for the treatment of DME, and some retrospective and prospective studies have indicated the usefulness of switching from ranibizumab to aflibercept for the treatment of resistant DME associated with poor vision. These hypotheses could be explained by the different molecular structure [38], greater binding affinity [39], and/or the longer intravitreal bioavailability of aflibercept compared with other anti-VEGFs [40]. Therefore, although there is limited evidence, aflibercept is recommended especially for the treatment of severe or resistant DME.

Findings from the randomized clinical studies of anti-VEGF therapies mentioned above strongly support the use of anti-VEGF therapies for the management of center-involved DME with vision impairment. However, in the post hoc, exploratory analysis of Protocol I from the DRCR.net, less than half of the eyes treated for DME with anti-VEGF therapy, had persistent DME at 6 months after the initiation of treatment. Among these, 40% then had chronic persistent DME throughout 3 years [41]. A similar prevalence of chronic persistent DME through 2 years was also reported from the post-hoc analysis of Protocol T from the DRCR.net [42]. The identification of risk factors that can predict treatment success or failure will help investigators in making informed decisions as to which patients should be treated with each therapy. As introduced above, there are many reports suggesting the predictive factors associated with the outcomes of anti-VEGF therapy for DME. Additionally, two studies (one that was conducted in Japan) demonstrated that an early

Table 1 Systemic adverse effects of prolonged (2-years) monthly anti-VEGF therapy for DME [36]

Summary of the main findings[a]	Anticipated absolute risk per 1000 study population, OR (95% CI)[b]		Relative effect (95% CI)	Number of participants/ RCTs	Quality of evidence[c]	Overall heterogeneity, I^2
Outcome	Sham/laser treatment	Anti-VEGF injection				
All-cause mortality	13	38 (1–75)	2.98 (1.44–6.14)	1078/4	Moderate	0%
Cerebrovascular accident	13	30 (14–64)	2.33 (1.04–5.22)	1078/4	Moderate	0%
Vascular-related death	11	28 (12–62)	2.51 (1.08–5.82)	1078/4	Moderate	0%
Arteriothrombotic event	47	72 (44–113)	1.58 (0.95–2.62)	1078/4	Moderate	0%
Myocardial infarction	32	35 (18–66)	1.11 (0.57–2.16)	1078/4	Moderate	0%

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OR odds ratio, *RCTs* randomized clinical trials, *VEGF* vascular endothelial growth factor

[a] Monthly anti-VEGF injections (intensive treatment) for 2 years were compared with sham and/or laser treatment in patients with diabetic macular edema in ophthalmology clinics. For overall heterogeneity, $I^2 = 0\%$

[b] The risk (95% CI) in the intervention group is based on the assumed risk in the comparison group and the relative effect (95% CI) of the intervention

[c] Indicates GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group grade of evidence (range, high to very low quality). Moderate indicates that the true effect is likely to be close to the estimate of the effect but with a possible substantial difference. Owing to the low number of events, the optimal information size criterion was not met

response to anti-VEGF therapy (change in visual acuity from baseline to month 3) may predict the visual outcome after 1 year in DME patients treated with anti-VEGF therapy (Fig. 4) [43, 44].

In a recent retrospective study of 21 eyes in DME patients who received anti-VEGF injections, Mori et al. reported that the number of microaneurysms detected by indocyanine green angiography may be useful predictors of DME recurrence [45].

Serious ocular adverse events of intravitreal anti-VEGF injections occur at a low frequency and include endophthalmitis, uveitis, and retinal detachment; likewise, the risk of occurrence does not appear to be greater in patients with center-involved DME than in patients with AMD. The serious systemic adverse events of intravitreal anti-VEGF injections include death, myocardial infarction, and stroke. A systematic review and meta-analysis of four randomized clinical studies with 1328 patients indicated that high-risk patients with DME who received 2 years of monthly treatment may have an increased risk of death and potential cerebrovascular accidents. The risks of occurrence of these systemic adverse events appeared to be slightly higher in patients with center-involved DME than in patients with AMD. Moreover, a recent Cochrane meta-analysis of anti-VEGF therapies failed to identify issues regarding the systemic events related to intravitreal anti-VEGF injection. The risks of occurrence of serious ocular and systemic adverse events after anti-VEGF therapy are different for each patient with center-involved DME; therefore, physicians should use anti-VEGF for center-involved DME after careful consideration of the risks of these adverse events. The recent Protocol V from the DRCR Retina Network addressed the best therapeutic strategy for eyes with center-involved DME and good vision (20/25 or better). After 2 years, the visual outcomes were similar in all three groups. Given the costs and potential adverse events associated with the intravitreal injections of anti-VEGF, observation is suggested to be a reasonable initial strategy for treatment-naïve eyes with good vision, despite the presence of center-involved DME, as long as the eyes are followed closely and treated with anti-VEGF therapy if vision worsens.

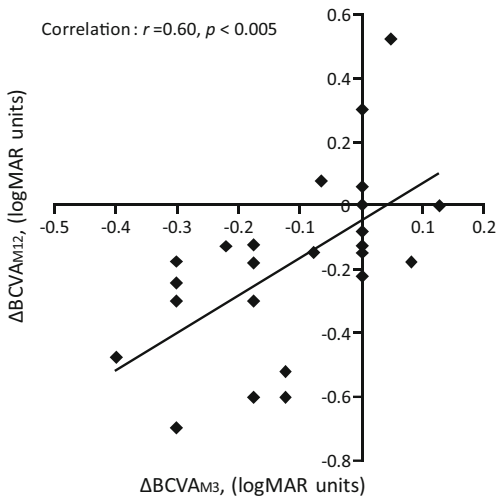

Fig. 4 Correlation between early response to anti-VEGF therapy (change in visual acuity from baseline to month 3) and visual outcome at year 1 in Japanese DME patients treated with anti-VEGF [44]. BCVA, best-corrected visual acuity; $\Delta BCVA_{M3}$, logMAR BCVA change from baseline to month 3; $\Delta BCVA_{M12}$, logMAR BCVA change from baseline to month 12; logMAR, logarithm of the minimum angle of resolution. The figure is reprinted with the permission from the publisher of original article

Laser photocoagulation therapy

Focal/grid laser photocoagulation was the standard of care for the treatment of DME from 1985 to 2010 [11]. As intravitreal anti-VEGF injection has replaced laser photocoagulation as the standard of care for DME, laser photocoagulation therapy remains an important treatment option for DME because this therapy is cheaper and often requires significantly fewer patient visits. Moreover, it does not have the potential for systemic cardiovascular side effects, such as stroke, along with local risks, such as endophthalmitis, cataracts, and retinal tear or detachment [8].

Recently, some studies have suggested the clinical usefulness of laser and anti-VEGF therapy combination; following the development of new laser technologies such as the subthreshold micropulse laser and the Navilas navigated laser, laser photocoagulation is once again becoming an attractive therapeutic option. In this section, we have especially summarized the latest developments in laser photocoagulation therapy for DME.

Laser and anti-VEGF therapy combination

In a 5-year follow-up of the Protocol I from the DRCR.net, visual benefit and the number of ranibizumab injections were compared between ranibizumab administered PRN with prompt versus deferred (for ≥ 24 weeks) focal/grid laser treatment for DME. The mean change in visual acuity letter score from baseline to the 5-year visit tended to be superior in the ranibizumab with deferred laser group than in the ranibizumab with prompt laser group, with + 9.8 letters versus + 7.2 letters, respectively ($p = 0.09$). The significant difference in favor of the deferred laser group versus the prompt laser group was observed after 5 years among the subgroup of eyes with worse visual acuity at baseline (approximate Snellen equivalent less than 20/50) ($p < 0.001$). The median number of injections was 17 versus 13 in the deferred and prompt laser groups, respectively [15].

A retrospective study compared a group of 19 eyes with DME treated with ranibizumab injections plus subthreshold micropulse laser versus a matched control group of 19 eyes with DME treated with ranibizumab injections without the laser. At 12 months, the subthreshold micropulse laser with

ranibizumab was a safe and effective treatment for DME, and achieved comparable improvement in visual acuity, along with a significant reduction in the burden of ranibizumab injections compared with the control group (1.7 ± 2.3 versus 5.6 ± 2.1) [46]. Recently, precise focal laser photocoagulation using Navilas combined with ranibizumab therapy (PRN) was shown to have promising efficacy while reducing the burden of the ranibizumab injections in a 1-year prospective study (Table 2) [47]. In addition, a retrospective study also determined the long-term visual gains and injection requirements in the 3-year follow-up period. The combination of Navilas navigated laser and ranibizumab achieved the best corrected visual acuity gains equivalent to ranibizumab monotherapy at year 1, and the results were maintained through to year 3. The required injections were 2.0 times fewer in year 1 and a further 1.3 times fewer in years 2 and 3, in the combination group compared with the monotherapy group [48].

A multicenter prospective randomized clinical study, the TREX-DME study, was conducted to compare monthly dosing versus a TAE algorithm using ranibizumab with and without Navilas navigated laser photocoagulation for DME. In total, 150 eyes from 116 patients were randomized in this study, and the TAE dosing of ranibizumab with and without Navilas significantly decreased the number of injections given and provided similar visual and anatomic outcomes compared with monthly dosing. The addition of Navilas to this dosing algorithm did not significantly improve outcomes at 1 and 2 years [49, 50]. More recently, Inagaki et al. reported that the combination of intravitreal anti-VEGF and minimally invasive laser therapy, including Navilas navigated laser photocoagulation improves the visual acuity, alleviates DME, and may decrease the required number of anti-VEGF injections in a retrospective 1-year study [51].

Table 2 Study results of precise focal laser photocoagulation using Navilas combined with ranibizumab therapy in a 1-year prospective study [47]

	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	$p = 0.255$
Number of injections after loading phase (3 × ranibizumab)			
Mean ± SD	0.9 ± 1.2	3.9 ± 2.3	$p \leq 0.001$
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	$p \leq 0.001$
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	$p \leq 0.001$
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	

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A 6-month randomized controlled study was conducted in Japan to investigate whether targeted retinal photocoagulation (TRP) for nonperfused areas (NPAs) could have a preventive effect on the recurrence of DME after the intravitreal injection of bevacizumab (not approved in Japan for the indication of DME) in 52 patients with DME. Combination therapy with TRP and bevacizumab for NPAs was more effective for the maintenance of reduced central retinal thickness after grid/focal photocoagulation for patients with DME [52]. Further, in a 3-year randomized controlled study, DAVE to evaluate the effect of TRP on visual and anatomic outcomes and treatment burden in 40 eyes with DME, it was shown that there was no evidence that combination therapy of ranibizumab and TRP improved visual outcomes or reduced treatment burden compared with ranibizumab alone treatment [53].

Navigated laser treatment

The Navilas laser system, developed recently for the navigated laser treatment, is a computer-based system combined with a wide-angle imaging camera that has become of current interest. The Navilas has eye-tracking laser delivery system that achieves greater accuracy than conventional focal laser therapy for DME [54, 55]. For safety and patient comfort, the main theoretical advantages lie in retinal navigation, and the device offers retinal navigation owing to computerized image and target assistance systems, resulting in high precision and reproducibility, theoretically of < 60–110 μm. Another difference to slit lamp-based laser devices is the touch screen monitor used for imaging, planning, and treating fundus changes. This allows the retina surgeon to plan laser spots on the screen and then apply automated patterns and single spots, as appropriate [56].

In 2013, Neubauer et al. reported the comparison of clinical outcomes and retreatment rates when using the Navilas navigated macular laser compared with conventional macular laser for the treatment of DME. The best corrected visual acuity after 3 months was significantly superior in the Navilas group (n = 46) than in the conventional laser group (n = 28), with fewer retreatments in the Navilas group than in the conventional laser group within the first 8 months (18% versus 31%, respectively) [57]. A retrospective cohort series of 7 patients with DME indicated that focal Navilas was safe and effective for the treatment of DME with improvements in visual acuity and macular edema on optical coherence tomography over 12 months [58]. In 2018, Kato et al. reported that focal photocoagulation using Navilas was effective for the treatment of 25 eyes with refractory DME with improvement in macular edema on optical coherence tomography (OCT) over 6 months. The Navilas navigated laser photocoagulation was delivered to the microaneurysms using indocyanine green angiography (ICGA) in 21 of 25 eyes, fluorescein angiography (FA) guided in 3 eyes, and OCT angiography guided in 1 eye. Navilas was beneficial for navigated laser photocoagulation based on three modalities of ICGA, FA, and OCT angiography [59]. More recently, Nozaki et al. prospectively evaluated the efficacy of ICGA-guided navigated focal laser photocoagulation using Navilas for 8 eyes with DME. After 6 months, ICGA-guided Navilas had significantly reduced the central retinal thickness, the primary endpoint (Fig. 5), and the macular volume, with a significant improvement in the best corrected visual acuity. They also reported that 5 out of the 8 eyes (63%) underwent additional ICGA-guided Navilas focal laser photocoagulation owing to remnants of microaneurysms that had been confirmed by ICGA at 3 months, and there was no observed recurrence of edema after the photocoagulation during the 6-month follow-up [60].

Subthreshold micropulse laser therapy

Conventional laser photocoagulation therapy has a risk of retinal pigment epithelium atrophy, which may potentially induce central scotoma or scar enlargement. However, recently developed subthreshold micropulse laser therapy has fewer

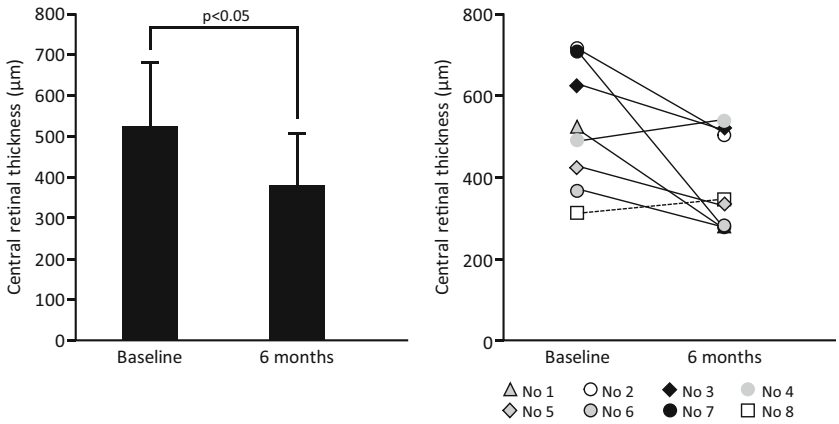

Fig. 5 Change in central retinal thickness after the treatment with ICGA-guided Navilas focal laser photocoagulation in 8 eyes with DME [60]. The figure is reprinted with the permission from the publisher of original article

such side effects as it delivers laser energy below the threshold required for permanent tissue destruction. Laser parameters, such as wavelength, power, spot size, and pulse duration, can be altered to decrease the amount of thermal energy delivered to reduce permanent tissue damage [61]. A schematic explanation of the difference between the mode of action of conventional and subthreshold micropulse laser is presented in Fig. 6 [62].

Subthreshold micropulse laser for the treatment of DME has been investigated in some small clinical studies, including randomized controlled studies [63]. It is reported that patients with DME can attain equal, or even better, visual acuity, as well as better preservation of electrophysiologic function after micropulse laser treatment compared with conventional laser therapy [64, 65]. Subthreshold micropulse laser was demonstrated to be effective for the treatment of DME without causing any adverse treatment effects or complications [66, 67]. A prospective case study of 220 patients with DME demonstrated that subthreshold micropulse laser was an effective minimal intensity therapy that offered the clear advantage of minimizing or avoiding laser-induced visible retinal burn/scarring while reducing the foveal thickness in the management of DME [68]. In 2018, Vujosevic et al. reported prospective assessment results for the changes in OCT angiography in 35 eyes with DME treated with subthreshold micropulse laser over a period of 6-month period. Subthreshold micropulse laser led to a reduction in the foveal avascular zone area at the level of the deep capillary plexus, and a reduced number of microaneurysms and area of cysts in both superficial capillary plexus and deep capillary plexus [69]. A recent prospective study was conducted on 10 patients with DME treated with a subthreshold micropulse laser to evaluate changes in the individual retinal layers and to correlate with functional changes. The increase in best corrected visual acuity was significantly and inversely correlated to central retinal thickness, and inner and outer nuclear layer thickness [70].

Panretinal photocoagulation for proliferative diabetic retinopathy associated with DME

The severity of diabetic retinopathy associated with DME is an important factor in deciding a therapeutic strategy. In 1981, the Diabetic Retinopathy Study Research Group reported that panretinal photocoagulation (PRP) for proliferative diabetic retinopathy (PDR) reduced the risk of severe vision loss by 50% or more and that it definitively proved the benefit of PRP for the treatment of PDR [71]. In Japan, the subcommittee of the Japanese Society of Ophthalmic Diabetology conducted a multicenter randomized clinical study of selective PRP for nonperfusion areas in 69 patients with pre-PDR. The incidence of PDR was significantly lower in the PRP treated group than in the non-PRP treated group, and the PRP was shown to be effective for the prevention of PDR development [72].

Intraocular levels of pro-angiogenic factors, particularly VEGF, were reported to be elevated in patients with active PDR, and VEGF plays a major part in the mediation of active intraocular neovascularization of PDR [73]. Recently, some randomized controlled studies have investigated the efficacy of intravitreal anti-VEGF injection in the patients with PDR compared with the efficacy of PRP. The DRCR.net Protocol S showed that ranibizumab therapy was non-inferior to PRP therapy in terms of visual acuity after 2 and 5 years (Fig. 7) [74, 75]. The extent of visual field loss was lower in the ranibizumab group than in the PRP group, but continuing visual field loss was seen in both groups for up to 5 years [75].

A multicenter, single-blinded randomized controlled study (CLARITY) recruited 232 patients with PDR, and confirmed the non-inferiority of aflibercept compared with PRP. The

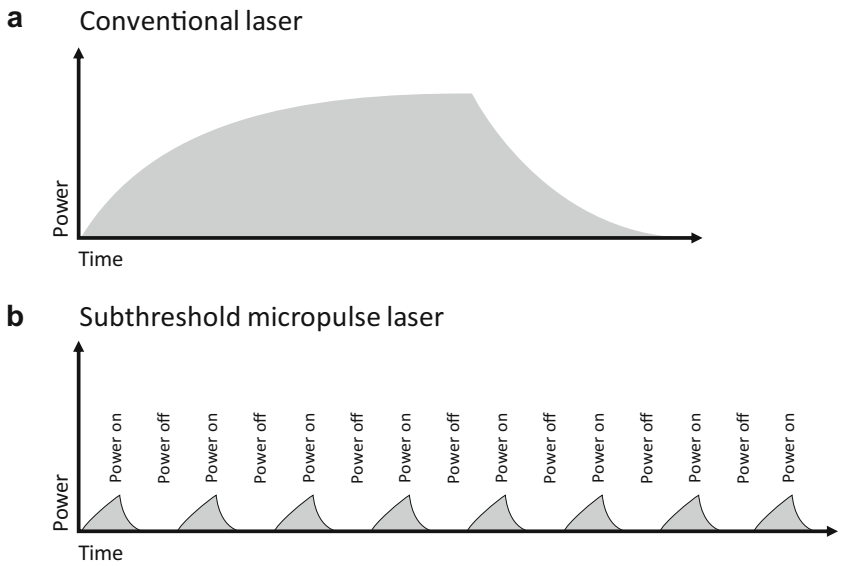

Fig. 6 Schematic explanation of the difference between the mode of action of conventional and subthreshold micropulse laser [62]. The figure is reprinted with the permission from the publisher of original article

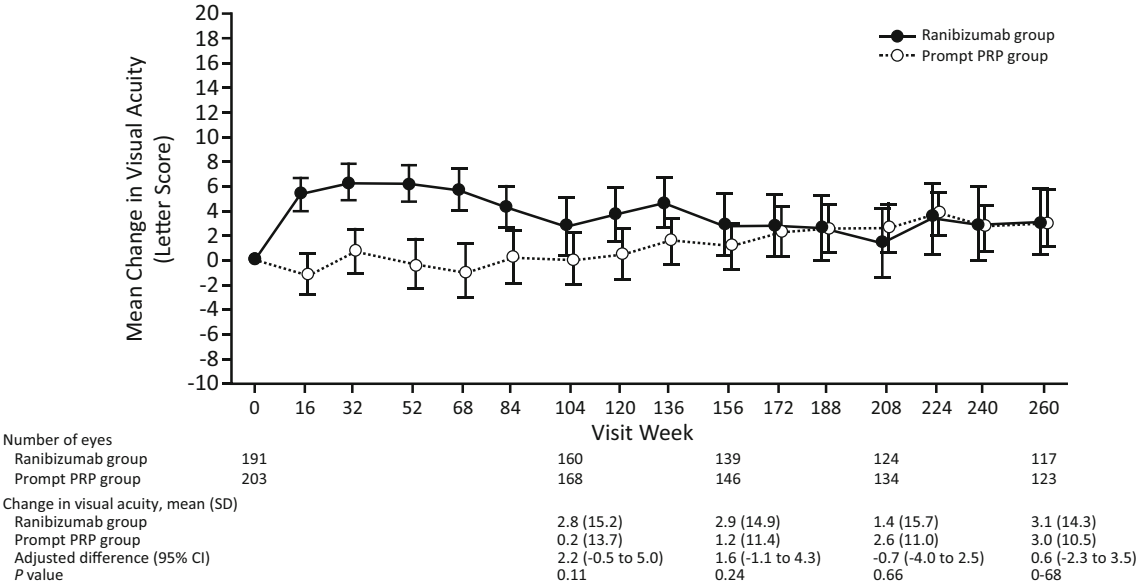

Fig. 7 Mean change in visual acuity from baseline up to 5 years in the DRCR.net Protocol S [75]. The figure is reprinted with the permission from the publisher of original article

primary outcome was defined as a change in best-corrected visual acuity at 1 year. Aflibercept was non-inferior and superior to PRP (mean best corrected visual acuity difference 3.9 letters), with no safety concerns [76]. The PROTEUS study, a prospective randomized multicenter open-label phase 2/3 study, compared the efficacy of ranibizumab plus PRP versus PRP alone in regressing the neovascularization area in patients with high-risk PDR over a 1-year period. After 1 year, 92.7% of patients in the ranibizumab plus PRP group presented a significant total reduction of neovascularization versus 70.5% of patients in the PRP alone group, and the mean best corrected visual acuity was 75.2 letters versus 69.2 letters, which was not significantly different. This study demonstrated that the treatment of ranibizumab plus PRP was more effective than PRP alone for neovascularization regression in patients with high-risk PDR over 1 year (Table 3) [77].

As mentioned above, some randomized controlled studies recently demonstrated that intravitreal anti-VEGF injection provided comparable or potentially even superior outcomes to PRP in patients with PDR. However, both therapies required close follow-up to reassess response to therapy, disease progression, and the need for additional treatment to optimize outcomes; therefore, loss to follow-up (LTFU) may contribute to vision loss in patients with active PDR. Obeid et al. determined and compared the rates of LTFU in 1718 patients with PDR receiving anti-VEGF or PRP over approximately 4 years and reported that a large proportion of patients with PDR were LTFU after receiving both therapies [78]. The authors also compared anatomic and functional outcomes in 76 eyes of 59 patients with PDR that were LTFU for more than 6 months after treatment with either anti-VEGF injection or PRP. Eyes with PDR that received only intravitreal anti-VEGF demonstrated worse anatomic and functional outcomes following LTFU compared with eyes that received PRP (Fig. 8) [79].

Expert review

For the laser and anti-VEGF therapy combination, a 5-year follow-up of the Protocol I from the DRCR.net suggested that ranibizumab with deferred (for ≥ 24 weeks) focal/grid laser

Table 3 Number of patients with reduction of neovascularization total at 1 year in the PROTEUS study [77]

	RBZ + PRP group	PRP monotherapy group	*p* Value*
NVT reduction, frequency (%)	38 (92.7)	31 (70.5)	*0.009*
NVD reduction, frequency (%)	14 (93.3)	11 (68.8)	0.083
NVE reduction, frequency (%)	32 (91.4)	28 (73.7)	*0.048*

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NVD neovascularization on the disc, *NVE* neovascularization elsewhere, *NVT* neovascularization total, *PRP* panretinal photocoagulation, *RBZ* ranibizumab

The italicized values indicate a statistically significant difference between RBZ + PRP and PRP groups

*Chi-square test

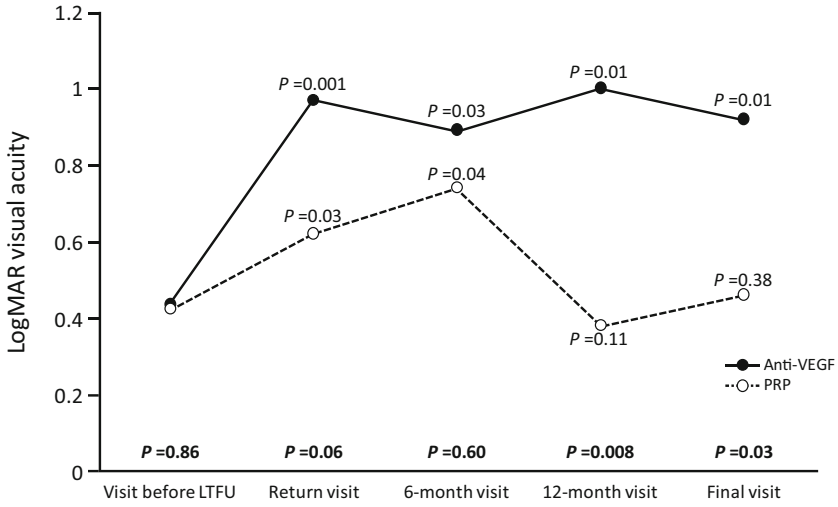

Fig. 8 Change in visual acuity after being LTFU in eyes with PDR receiving either intravitreal anti–VEGF or PRP [79]. LTFU, lost to follow-up. *p* values on the line graphs represent statistical comparisons with the visit before being LTFU. *p* values above the designated visits represent statistical comparisons between the treatment arms at the given time points. The figure is reprinted with the permission from the publisher of original article

treatment for DME was superior to ranibizumab with prompt focal/grid laser treatment, especially among the subgroup of eyes with worse visual acuity at baseline (approximate Snellen equivalent less than 20/50) [15]. There was no other evidence to support this finding; however, this finding was considered as a high-quality evidence, and we therefore can refer this finding when selecting the combination treatment strategy in real-world clinical practice.

Hirano et al. reported that eyes with perifoveal leaking microaneurysms required a larger number of anti-VEGF injections, even when combined with focal/grid laser treatment, owing to the fact that the focal/grid laser can only be applied to the outside of the fovea [80]. The utilization of a precise focal laser with Navilas is useful for the treatment of perifoveal microaneurysms, and this hypothesis is supported by the evidence that the additional ICGA-guided Navilas focal laser photocoagulation for the remnants of microaneurysms was effective for preventing the recurrence of edema after photocoagulation [60].

It has been reported that the efficacy of subthreshold micropulse laser for the treatment of DME was influenced by pretreatment central foveal thickness (CFT) [81]. This report suggested that subthreshold micropulse laser treatment was less effective in DME patients with a baseline CFT of > 400 μm. Therefore, we recommend the therapeutic option of subthreshold micropulse laser and anti-VEGF therapy combination in DME patients with a baseline CFT of > 400 μm in clinical practice.

Some recent randomized controlled studies have demonstrated that intravitreal anti-VEGF injection provides comparable or even potentially superior outcomes to PRP in patients with PDR. However, as Obeid et al. reported [78, 79], given the potential sequelae of being LTFU, the choice of treatment for PDR must be considered carefully.

With the development of these new technologies, laser photocoagulation therapy has become more efficient and effective with less pain and fewer adverse events. We believe that the further accumulation of evidence for utilizing these new technologies may contribute to continuing innovations in laser technology. Additionally, the progress in understanding laser-tissue interactions make us believe that laser therapy will continue to play a critical role in the treatment of retinal disease for many years to come.

Steroid therapy

The use of the intravitreal injection of triamcinolone acetonide for the treatment of DME was first reported in 2001 [82]. This therapy was effective for the treatment of DME, but the complications of intravitreal triamcinolone therapy included secondary ocular hypertension in approximately 40% of the injected eyes, cataracts, and postoperative infectious or non-infectious endophthalmitis. After the introduction of anti-VEGF therapy into clinical practice for DME, intravitreal triamcinolone has lost its prime position as the drug most often injected intravitreally [83]. However, owing to its widespread biological effects as a steroid, the relatively large therapeutic window, and cost-effectiveness, triamcinolone therapy has remained essential for clinical use in patients with DME [83]. In this section, we have summarized the evidences for the steroid therapy, with a particular focus on the evidences important for the real-world management of DME.

Intravitreal steroid therapy for pseudophakic eyes with DME

A subgroup analysis of Protocol I from the DRCR.net demonstrated that by limiting the analysis to 273 eyes that were pseudophakic at baseline, the pseudophakic eyes at baseline in the triamcinolone with prompt laser group, visual acuity results appeared comparable with those of the pseudophakic eyes in the ranibizumab with prompt laser groups, and

superior to that of the pseudophakic eyes in the sham with prompt laser group after 2 years (Fig. 9) [14].

Steroid and anti-VEGF therapy combination

The Cochrane database of systematic review published in 2018 reported that the combination of intravitreal anti-VEGF plus intravitreal steroid did not appear to offer additional visual benefits compared with monotherapy for DME; at present, the evidence for this is of low certainty. There was an increased rate of cataract development and increased intraocular pressure in eyes treated with anti-VEGF plus steroid versus anti-VEGF alone (Fig. 10) [84].

Some studies have demonstrated that subtenon injection of triamcinolone is effective for the reduction DME [85–87]. Shimura et al. treated 124 eyes with DME with subtenon injection of triamcinolone, and investigated the influence of triamcinolone reflux after the injection on the regression of DME and postoperative intraocular pressure. They demonstrated that triamcinolone reflux after subtenon injection was a risk factor not only for the insufficient reduction of edema but also for the postoperative intraocular pressure elevation in eyes with DME [87]. In 2016, Shimura et al. also reported that the adjunctive subtenon injection of triamcinolone to intravitreal anti-VEGF injection for the treatment of DME not only improved the morphological and functional regression but also reduced the frequency of intravitreal anti-VEGF therapy (Fig. 11) [88].

Expert review

Serial injections of anti-VEGF therapy are the first-line therapy for DME, and the intravitreal injection of triamcinolone has a secondary role in particular cases. We believe that DME patients with pseudophakic eyes may be treated with intravitreal injections of triamcinolone because as described above, a subgroup analysis of Protocol I from the DRCR.net suggested that intravitreal injection of triamcinolone may have similar effects for improving visual acuity compared with anti-VEGF in pseudophakic eyes with DME. There is no obvious evidence for supporting the usefulness of intravitreal triamcinolone and anti-VEGF combination therapy for DME. Some evidences support the usefulness of subtenon injection of triamcinolone for DME, as described above. In addition, a prospective study was conducted to evaluate the efficacy of subtenon injection of triamcinolone against PRP-induced macular thickening and visual disturbance in 20 eyes of patients with severe diabetic retinopathy and good vision. As a pretreatment for PRP, a single subtenon injection of triamcinolone had beneficial effects for the prevention of PRP-induced foveal thickening and visual dysfunction in patients with severe diabetic retinopathy and good vision (Fig. 12) [89]. Subtenon injection of triamcinolone may also be useful for the prevention of PRP-induced macular thickening and visual disturbance in PDR associated with DME.

Recently, Protocol U from the DRCR.net enrolling patients with persistent DME demonstrated that the addition of an intravitreal dexamethasone sustained release device (Ozurdex®) to a regimen of intravitreal ranibizumab injection did not improve visual acuity outcomes after 6 months, although macular thinning was greater than that with intravitreal ranibizumab injection alone [90]. Although this was a phase 2 study with a relatively small number of patients, it was decided that additional therapeutic studies on this topic were not indicated because of the difficulty in recruitment, and because of the continued improvement of many eyes after 6 months of treatment with anti-VEGF therapy alone [91]. In Japan, Ozurdex is not approved, but a preservative-free formulation

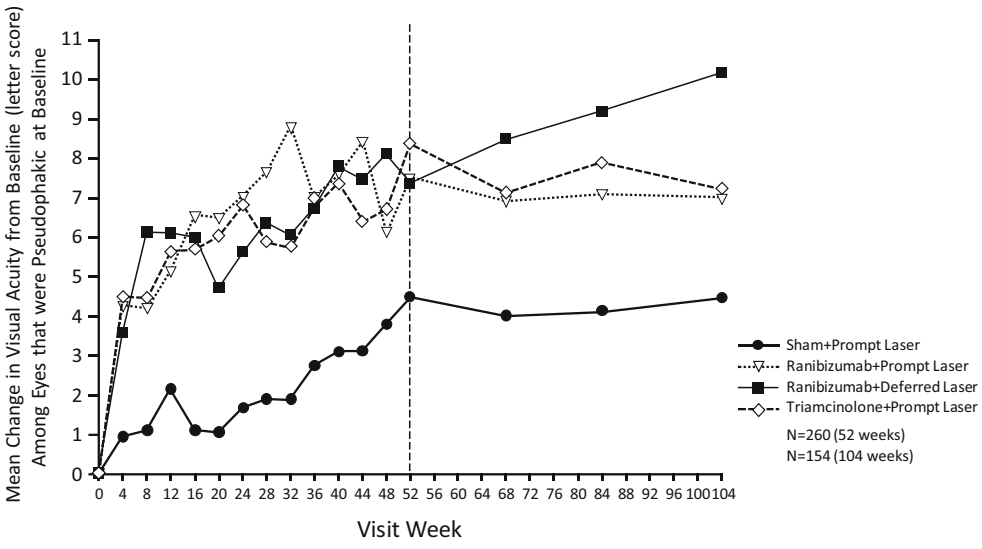

Fig. 9 Mean change in visual acuity at follow-up visits among eyes that were pseudophakic at baseline in the Protocol I from the DRCR.net [14]. The figure is reprinted with the permission from the publisher of original article

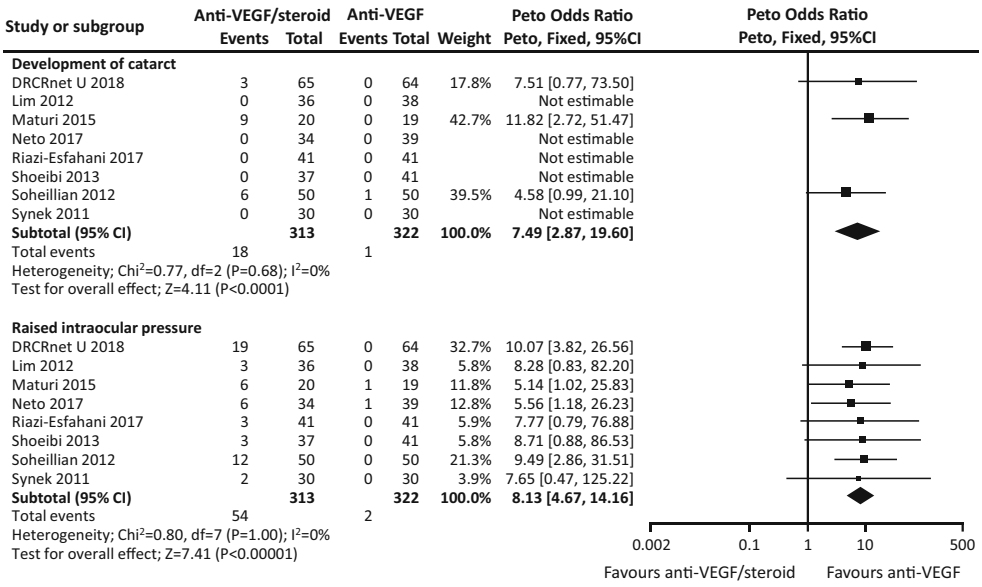

Fig. 10 Forest plot of comparison for the adverse events: intravitreal anti-VEGF plus intravitreal steroid versus intravitreal anti-VEGF alone for the treatment of DME in a Cochrane database of systematic review [84]. The figure is reprinted with the permission from the publisher of original article

of triamcinolone acetonide (MaQaid® 40 mg/vial; Wakamoto Pharmaceutical, Tokyo, Japan) has been approved for intravitreal and subtenon injections.

Pars plana vitrectomy

Pars plana vitrectomy for DME was first reported by Lewis et al. in 1992, and they reported that vitrectomy was effective in 10 eyes with DME and traction associated with a thickened and taut premacular posterior hyaloid [92]. Tachi et al. first showed that vitrectomy with posterior vitreous detachment was effective in eyes with diffuse DME without posterior vitreous detachment [93]. Although the precise mechanism by which vitrectomy exerts the efficacy remains to be unclear, many reports indicate that vitrectomy was effective for the improvement of macular edema and visual acuity in patients with DME [94–101]. In 2010, a prospective observational study performed by the DRCR.net was reported, and vitrectomy for DME was evaluated in 87 DME eyes with at least moderate vision loss and vitreomacular traction. At 6 months, visual acuity improved by ≥ 10 letters in 38% of the DME patients and deteriorated by ≥ 10 letters in 22% of the DME patients (Fig. 13). Median OCT central subfield thickness significantly decreased by 160 μm from baseline, with 43% of patients having central subfield thickness of < 250 μm and 68% of patients having at least a 50% reduction in thickening. Eyes with greater central subfield thickness at baseline had a significantly greater reduction in thickness after vitrectomy for DME (Fig. 14). Postoperative complications through 6 months included vitreous hemorrhage (5 eyes), elevated intraocular pressure requiring treatment (7 eyes), retinal detachment (3 eyes), and endophthalmitis (1 eye). Similar results were also observed at 1 year [102].

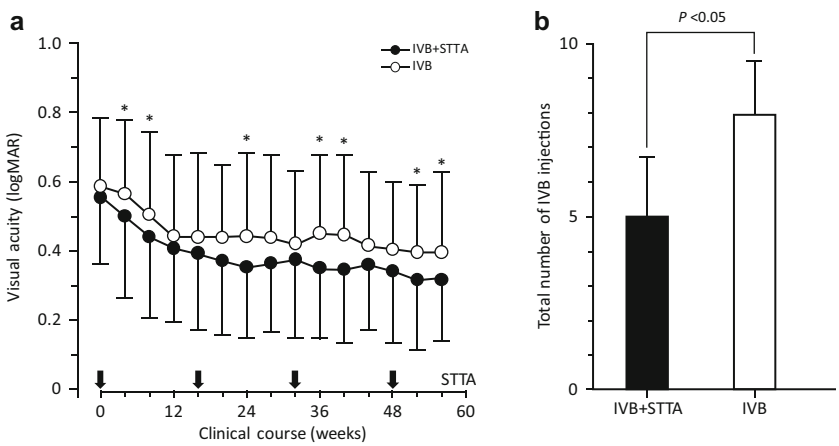

Fig. 11 Visual acuity and frequency of intravitreal anti-VEGF treatments after adjunctive subtenon injection of triamcinolone to intravitreal anti-VEGF versus intravitreal anti-VEGF alone for the treatment of DME [88]. IVB, intravitreal bevacizumab; STTA, subtenon injection of triamcinolone. *Statistically significant difference between two treatment groups at each time point. The figure is reprinted with the permission from the publisher of original article

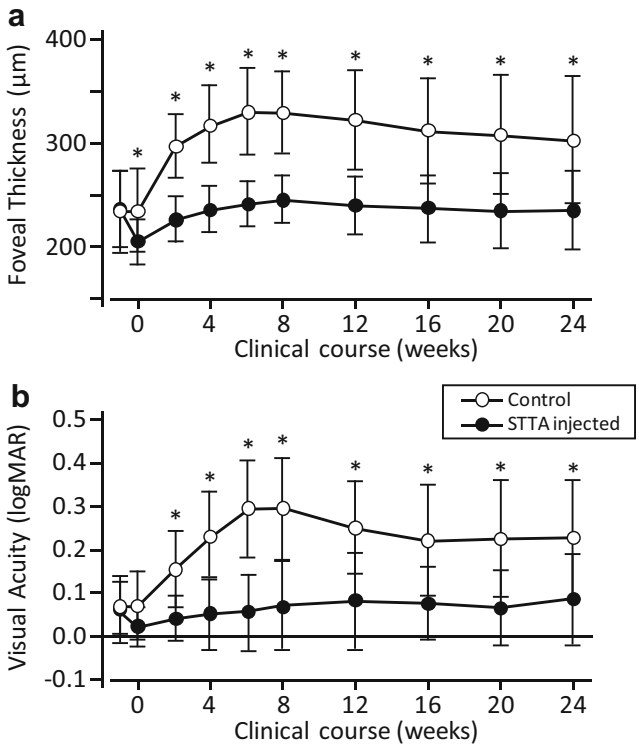

Fig. 12 Efficacy of subtenon injection of triamcinolone against panretinal photocoagulation-induced macular thickening and visual disturbance in eyes with severe diabetic retinopathy and good vision [89]. STTA, subtenon injection of triamcinolone. *Statistically significant difference between the STTA injected and control eyes at each time point. The figure is reprinted with the permission from the publisher of original article

A systematic review and meta-analysis from 11 randomized controlled studies concluded that there was little evidence to support vitrectomy as an intervention for DME in the absence of the epiretinal membrane or vitreomacular traction. Although vitrectomy appeared to be superior to laser in its effects on retinal structure at 6 months, no such benefit was proved at 12 months. There was no evidence to suggest the superiority of vitrectomy over laser in terms of functional outcomes (Fig. 15) [103].

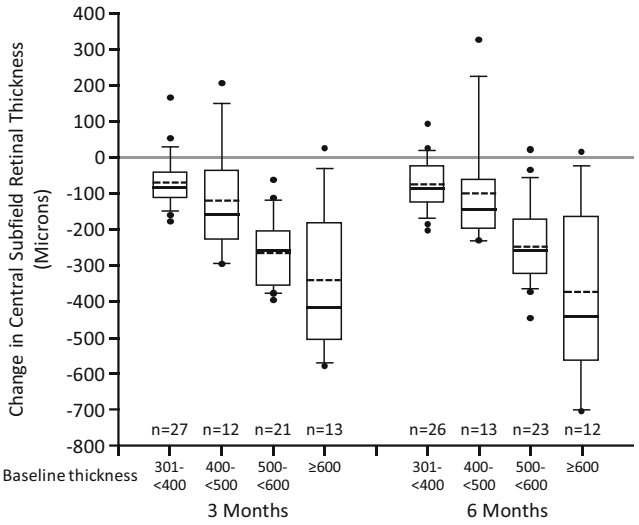

Fig. 14 Distribution of change in optical coherence tomography central subfield thickness in categories according to baseline thickness in the DRCR.net study [102]. The figure is reprinted with the permission from the publisher of original article

The European Vitreo-Retinal Society (EVRS) conducted the EVRS Macular Edema Study, a non-randomized multicenter study in which a total of 86 retina specialists from 29 countries provided information on 2603 patients with macular edema including 870 patients with DME, with a follow-up of at least 6 months. In this study, the efficacy of different therapies for DME was compared. Treatment with vitrectomy and internal limiting membrane peeling alone resulted in better visual improvement than with other therapies, including intravitreal triamcinolone monotherapy, treatment with threshold or subthreshold grid laser, and intravitreal anti-VEGF monotherapy (Fig. 16) [104].

Expert review

As described above, many studies have indicated that pars plana vitrectomy is effective for the treatment of DME.

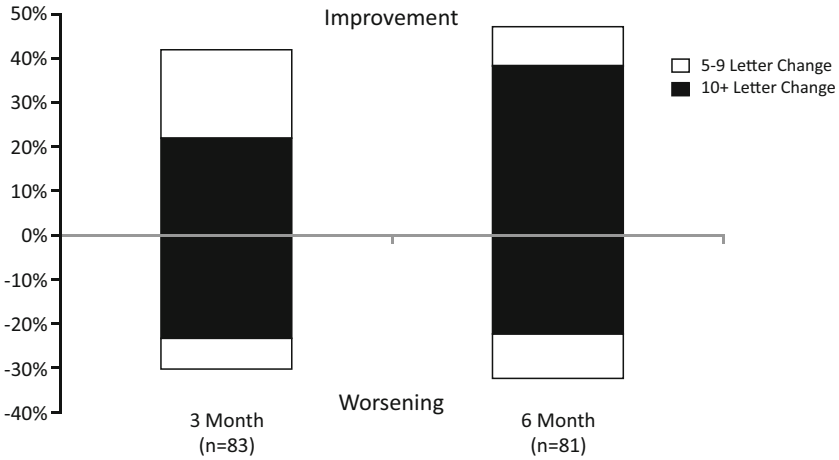

Fig. 13 Distribution of change in visual acuity from baseline in the DRCR.net study [102]. The figure is reprinted with the permission from the publisher of original article

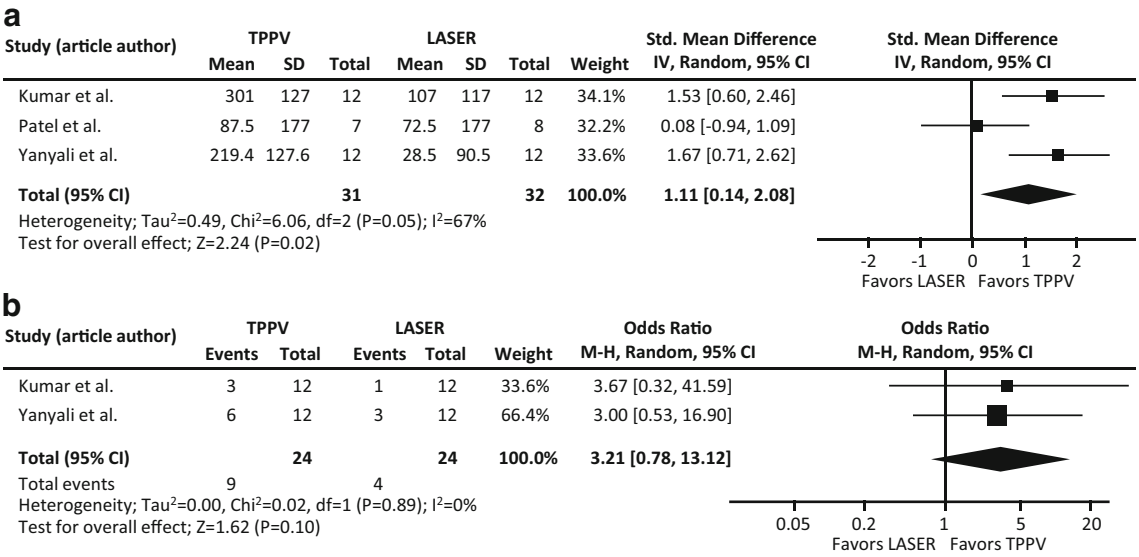

Fig. 15 A systematic review and meta-analysis for the effects of vitrectomy versus laser therapy on structural (**a**) and functional (**b**) outcomes at 6 months [103]. **a** Trans pars plana vitrectomy (TPPV) versus laser. Structural (reduction in foveal thickness) outcomes at 6 months (positive values better). **b** TPPV versus laser. Functional (likelihood of achieving ≥ 2 lines improvement in acuity) outcomes at 6 months. The figure is reprinted with the permission from the publisher of original article

However, serial injections of anti-VEGF therapy are the first-line therapy for DME at present, and the target patients of vitrectomy are limited to patients with DME that have vitreomacular traction and/or epiretinal membrane detected by OCT in current practice in Japan [105]. The efficacy and safety of vitrectomy for the treatment of DME with vitreomacular traction were reported in a prospective observational study performed by the DRCR.net described above [102]. Thirty-four eyes with resistant DME treated with vitrectomy were investigated for the predictors of visual improvement using spectral-domain OCT in a retrospective manner. This study indicated that the evaluation of epiretinal membrane preoperatively predicted the vision improvement more accurately than the photoreceptor inner segment/outer segment junction and central macular thickness in eyes with DME treated with vitrectomy [106]. These two studies support the use of vitrectomy for the treatment of DME especially with a vitreomacular traction and/or epiretinal membrane.

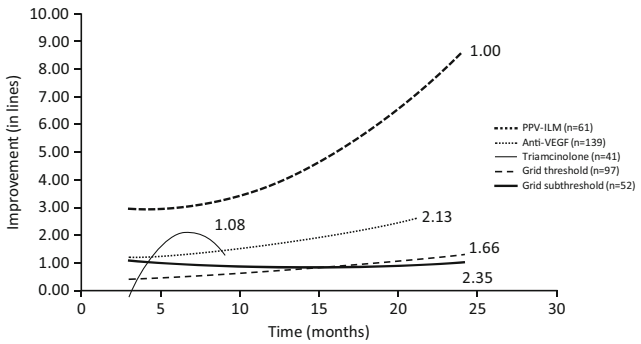

Fig. 16 Change in visual acuity (in lines) after different monotherapies for DME in the EVRS Macular Edema Study [104]. The figure is reprinted with the permission from the publisher of original article

Preoperative factors on the foveal thickness following vitrectomy for DME were investigated, and the decrease in foveal thickness was reported to be related to the preoperative glycemic control [95]. Yamada et al. also reported that improvement for the best corrected visual acuity and central subfield macular thickness after the vitrectomy was significantly associated with postoperative glycemic control and that glycemic control was important for ocular outcomes after vitrectomy for DME [107]. We think that vitrectomy may be a suitable treatment option for DME patients who did not respond to anti-VEGF therapy or had multiple relapses after the anti-VEGF therapy with sufficient glycemic control. A subanalysis of Protocol I from the DRCR.net demonstrated that a larger visual acuity treatment benefit of anti-VEGF therapy for DME was associated with younger age, less severe diabetic retinopathy, and the absence of surface wrinkling retinopathy [31]. Therefore, vitrectomy may also be a treatment option for DME patients with older age, more severe diabetic retinopathy, and the presence of surface wrinkling retinopathy. Anti-VEGF therapy can also be a treatment option, even for vitrectomized DME eyes, because the difference in the effectiveness of anti-VEGF therapy between DME eyes with and without previous vitrectomy was reported to be not significant in the prospective study [108]. This is also supported from an exploratory post hoc assessment of 3-year data from eyes with and without vitrectomy before randomization in a DRCR.net trial [109].

In a multicenter, prospective, controlled clinical trial, the benefits and potential complications of the use of triamcinolone

acetonide (TA) in vitrectomy were evaluated in 774 patients from 8 Japanese hospitals: 391 patients underwent TA-assisted vitrectomy and 383 control patients underwent conventional vitrectomy. The incidence of both retinal breaks and intraoperative retinal detachment was significantly lower in TA-assisted vitrectomy than in conventional vitrectomy, and there were no serious adverse events related to the intraoperative use of TA [110]. This evidence suggested the benefits of using TA in vitrectomy, although more careful control of intraocular pressure is required than for conventional vitrectomy.

A standard protocol for pars plana vitrectomy has not been established. In a prospective observational study performed by the DRCR.net described above, general guidelines for pars plana vitrectomy included (1) three pars plana sclerotomies, (2) the removal of the vitreous gel with peeling of the posterior hyaloid, if attached, and removal of the peripheral vitreous leaving only a small residual vitreous skirt, (3) engagement and peeling of epiretinal membranes judged visually significant, and (4) examination of the peripheral retina at the close of the procedure and treatment of peripheral breaks with laser or cryotherapy [102]. These general guidelines may provide a reference for performing vitrectomy in clinical practice.

Recommendation for a therapeutic flow chart for DME

In this chapter, we have proposed the recommended therapeutic flow chart for DME (Fig. 17), after consideration of the recent clinical evidences reviewed in Chapters I to IV.

Intravitreal injection of anti-VEGF agents, ranibizumab or aflibercept, should generally be the first-line therapy for center-involved DME (see Expert review of Chapter I). For the selection of ranibizumab or aflibercept, there are currently no definitive criteria. With the presence of perifoveal leaking microaneurysms related to macular edema, focal laser photocoagulation is recommended as an additional therapeutic option to anti-VEGF therapy (see Expert review of Chapter II). Furthermore, depending on the patient's condition of DME, such as the existence of PDR and vitreomacular traction/epiretinal membrane, and non-center-involved DME, additional and/or alternative treatments for anti-VEGF therapy should be considered, with the aim of effective disease control and function improvement (see Expert review of Chapters II to IV).

PDR, as well as DME, is a vision-threatening diabetic retinopathy. For patients with both PDR and DME, simultaneous interventions for these two disease conditions are needed to prevent vision loss. Instead of conventional PRP monotherapy, the combination of pharmacotherapy and PRP has become the predominant therapy for PDR along with the advent of anti-VEGF agents or steroids (see Expert review of Chapter II). The DRCR.net Protocol S showed that anti-VEGF therapy was non-inferior to PRP therapy in terms of the improvement of visual acuity and the prevention of PDR-related complications (see 4th section of Chapter II). However, poor prognosis has also been reported in some dropout cases. Based on these evidences, anti-VEGF therapy combined with PRP at the appropriate timing for achieving vision improvement and for lowering the risk of serious complications accompanying PDR was a rational therapeutic approach for DME patients with PDR. Moreover, the benefits of anti-VEGF therapy combined with PRP for patients with high-risk PDR have been addressed by the PROTEUS study. With regard to the combination of the subtenon injection of triamcinolone and PRP treatment, this is less evidence for its long-term effectiveness. In our clinical experience, PRP

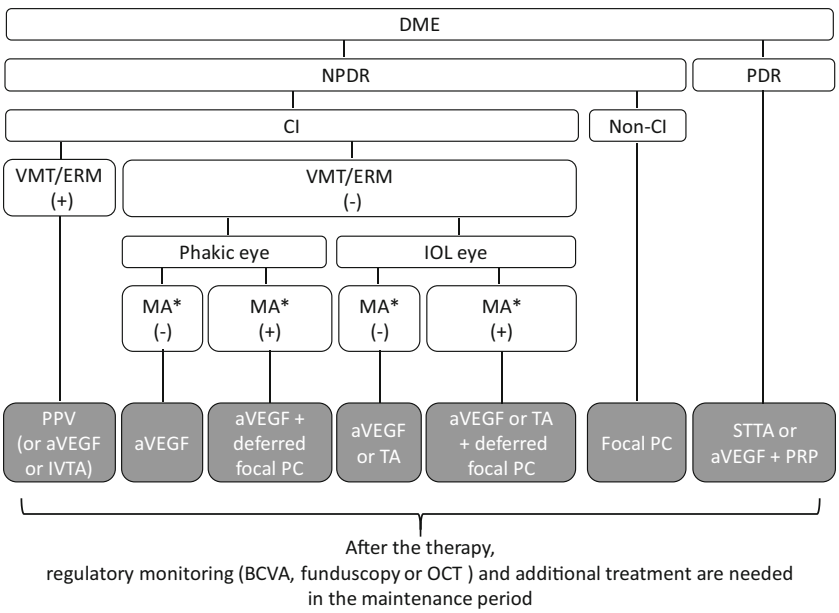

Fig. 17 Recommended therapeutic flow chart for DME. *Microaneurysm related to macular edema. NPDR, non PDR; CI, center-involved DME; Non-CI, non-center-involved DME; VMT, vitreomacular traction; EPM, epiretinal membrane; IOL, intraocular lens. The figure is reprinted with the permission from the publisher of original article

monotherapy often induces severe inflammation, and therefore, the subtenon injection of triamcinolone is believed to be useful for the suppression of PRP-induced inflammation (see Expert review of Chapter III). Further prospective studies to investigate the long-term efficacy of subtenon injection of triamcinolone and PRP treatment are expected in the future.

Non-center-involved DME without PDR should be treated by photocoagulation, as clinically significant macular edema. Among non-center-involved DME, photocoagulation is reported to be highly effective in patients with circinate retinopathy from the finding that the circinate complex was eliminated in 23 of the 24 treated eyes (96%) [111]. For the presence of perifoveal leaking microaneurysms related to macular edema, focal laser photocoagulation is recommended. The utilization of a precise focal laser with Navilas is expected to be useful for the treatment of perifoveal microaneurysms; however, more prospective studies are necessary to verify the efficacy of this new therapy (see Expert review of Chapter II).

For cases of diffuse macular edema without obvious microaneurysms related to macular edema, conventional grid laser photocoagulation treatment has been employed. However, the laser photocoagulation of the retinal pigment epithelium has a risk of the possible development of atrophic creep during a long course of therapy. New technologies, including subthreshold and micropulse laser therapy, is expected to be useful for the treatment of diffuse macular edema without obvious microaneurysms, although further assessments are needed to confirm their potential efficacy and safety (see 3rd section of Chapter II).

Vitrectomy is recommended for the treatment of DME especially with vitreomacular traction and/or epiretinal membrane, and it is the only way to treat complicated vitreoretinal disorders (see Expert review of Chapter IV). The DRCR.net Protocol D confirmed the beneficial result of the vitrectomy with epiretinal membrane peeling for visual improvement. In a subgroup analysis of the DRCR.net Protocol I, no statistically significant differences have been observed between the vitrectomized eyes and the non-vitrectomized eyes with regard to vision improvement and the decreased number of injections related to anti-VEGF therapy. Therefore, it is reasonable to perform vitrectomy before anti-VEGF treatment for patients with vitreomacular abnormalities. Postoperative treatment with anti-VEGF or triamcinolone should also be considered when DME persists after vitrectomy.

Anti-VEGF therapy is the first-line treatment for general DME without PDR. When obvious microaneurysms related to macular edema are present, deferred focal laser photocoagulation should be added to anti-VEGF therapy; the anti-VEGF therapy can first be used to gain an overall improvement, and then additional focal laser photocoagulation can be used to improve persistently leaking microaneurysms. Two evidences support this therapy procedure. One is that the occlusion of microaneurysms or the suppression of microaneurysms leakage in response to anti-VEGF therapy has often been observed. The other is the long-term outcome of deferred focal laser photocoagulation superior to that of prompt focal laser photocoagulation in the DRCR.net Protocol I (see Expert review of Chapter II). Further studies are expected to help develop a useful method for the identification of the microaneurysms related to macular edema and optimize the timing of the addition of focal laser photocoagulation.

For DME patients with pseudophakic eyes, triamcinolone could be considered as an alternative treatment of anti-VEGF agents, of which the socioeconomic burden is great. According to the post hoc analysis of the DRCR.net Protocol I, there was no statistically significant difference in the effect on improving visual acuity between the intravitreal injections of triamcinolone and the anti-VEGF agent combined with laser photocoagulation in pseudophakic eyes with DME. The socioeconomic burden is low in triamcinolone treatment; however, close attention should be paid to the occurrence of adverse events, such as glaucoma and ocular hypertension. Although remarkable progress has taken in microincision glaucoma surgery (MIGS), appropriate informed consent is of great significance (see Expert review of Chapter III). The identification of the prognostic factors for pharmacotherapy is expected to optimize the selection of an appropriate pharmacotherapy for individual patients with DME.

Conclusions

It is our strong desire that the treatment outcome of DME in real-world clinical practice is further improved by the selection and performance of the most appropriate therapies for individual patients with DME based on high-quality and most recent clinical evidences. We believe that our review of clinical evidence and the recommended therapeutic flow chart for DME will help for achieving better treatment outcomes for DME.

Compliance with ethical standards

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