Review Article

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Evaluation of Anti-VEGF and Pan-Retinal Photocoagulation Laser Therapies in Proliferative Diabetic Retinopathy Patients: A Systematic Review

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ABSTRACT

Diabetic retinopathy is a complication of diabetes that is one of the top five causes of blindness in those over 50. The standard treatment is pan-retinal photocoagulation, which is effective but has established side effects. Anti-vascular endothelial growth factor (anti-VEGF) therapy becomes an alternative to avoid the side effects caused by laser therapy. This systematic review aims to know the effectiveness of anti-VEGF therapy compared to the pan-retinal photocoagulation laser therapy in patients with proliferative diabetic retinopathy. This review was carried out using a systematic review checklist on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The articles reviewed were randomized controlled trial articles that met the inclusion and exclusion criteria. Based on inclusion and exclusion criteria, six articles were selected from a total of 215. Patients who received anti-VEGF medication had better visual acuity (positive values), whereas patients who received laser therapy had poorer visual acuity (negative values). Those results are because the laser directs light towards the retina, damaging photoreceptors and retinal cells as well as reducing visual acuity. On the contrary, anti-VEGF prevents damage to retinal endothelial cells and blood leaks in the vitreous by decreasing VEGF expression and thus resulting in improved visual acuity. Anti-VEGF proved to be a more practical alternative therapy in improving visual acuity than pan-retinal photocoagulation for patients with proliferative diabetic retinopathy.

Keywords: *anti- VEGF; laser therapy; proliferative diabetic retinopathy*

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INTRODUCTION

Impaired vision and degenerative eye disorders can influence economic issues, education, quality of life, and even mortality (Bourne et al., 2017). According to global estimates from 2020, 43.3 million individuals are blind, 295 million have moderate to severe vision impairment, and 258 million have mild visual impairment. Between 1990 and 2020, the prevalence of blindness grew by 50.6%, while visual impairment increased by 91.7% (Bourne et al., 2021). The prevalence also rises with the rising population and age (Flaxman et al., 2017).

According to the International Diabetes Federation (IDF), the prevalence of diabetes mellitus (DM) was 463 million in 2019 and is predicted to rise to 700 million by 2045 (Teo et al., 2021). Diabetic retinopathy (DR) is a widespread consequence of diabetes. According to the Global Burden of Disease Study (GBD) for 2020, DR is one of the top five causes of blindness in persons aged 50 and over (Bourne et al., 2021). High amounts of sugar in the blood can induce DR by obstructing the process of blood distribution and nutrient distribution in the retina's tiny blood capillaries. This disease eventually causes the eye to produce new blood vessels. However, because these new blood arteries do not function effectively, they are prone to leaking (Wang & Lo, 2018).

There are no symptoms in the early stages of DR, also known as non-proliferative diabetic retinopathy (NPDR). However, increases in vascular permeability and damage to the retinal pigment epithelium can be observed (Duh et al., 2017; Wang & Lo, 2018). Neovascularization, or the development of new aberrant blood vessels in the retina, happens in a more advanced stage, known as proliferative diabetic retinopathy (PDR) (Martinez-zapata et al., 2014; Wang & Lo, 2018). These new blood vessels can leak and cause fibrosis and retinal detachment (Martinez-zapata et al., 2014). Neovascularization will also increase osmotic pressure in the eye, leading to problems including glaucoma and cataracts (Duh et al., 2017; Kiziltoprak et al., 2019; Wang & Lo, 2018). These mechanisms are inextricably linked to the aging or degeneration factor (Grossniklaus et al., 2012).

The anatomy of the eye changes with age in humans. These alterations are accompanied by additional health variables that contribute to the development of certain degenerative illnesses. Those facts will reduce bodily function and may result in the loss of vision (Grossniklaus et al., 2012). Vascular Endothelial Growth Factor (VEGF), in addition to degenerative factors, plays an essential role in the etiology and progression of PDR (Behl & Kotwani, 2015; Gupta et al., 2013). VEGF will selectively bind to the receptor tyrosine kinase on vascular endothelial cells under normal circumstances. Furthermore, VEGF also functions in angiogenesis and can enhance vascular permeability (Behl & Kotwani, 2015; Gupta et al., 2013; Yuan et al., 2014). VEGF, on the other hand, becomes pathogenic in patients with hyperglycemia (Yuan et al., 2014). Hyperglycemia induces oxidative stress in ischemia and tissue hypoxia, which causes VEGF production to rise (Behl & Kotwani, 2015). Excess VEGF expression causes the production of inflammatory mediators in retinal endothelial cells, which destroys these endothelial cells and causes retinal damage, vitreous blood leakage, and reduced vision in PDR patients (Yuan et al., 2014; Zong et al., 2011).

Laser photocoagulation has remained the gold standard treatment for PDR until recently (Giuliari, 2012; Osaadon et al., 2014; Platt & Bakri, 1949). This therapy helps avoid additional damage by assisting in ocular oxygen and nutrition delivery, waste elimination, and decreasing metabolic signals and absorption of pro-angiogenic or permeability cytokines that concentrate in photoreceptors under hypoxic circumstances, therefore lowering VEGF burden (Giuliari, 2012; Platt & Bakri, 1949). However, due to its physically destructive nature, laser photocoagulation produces side effects that severely impair some individuals' visual function and quality of life. Pain, loss of peripheral vision, and reduced night vision are some possible adverse effects. A laser beam striking the fovea by accident might result in loss of central vision (Platt & Bakri, 1949).

Anti-VEGF treatment is another option in the care of PDR that is gaining traction in the community to prevent the adverse effects of laser therapy, particularly in patients with vitreous hemorrhage (Behl & Kotwani, 2015; Salam et al., 2011). Anti-VEGF allows neovascularization secondary to PDR to regress, reducing macular thickness owing to edema and increasing visual field (Salam et al., 2011; Zong et al., 2011). Anti-VEGF therapy is thought to be less dangerous than laser photocoagulation therapy (Giuliari, 2012). As a result, this systematic review aimed to evaluate the efficacy of anti-VEGF therapy to laser photocoagulation therapy in patients with PDR.

METHODS

The review was conducted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) approach using a systematic review checklist. The journals were found using the search terms proliferative diabetic retinopathy, laser treatment, and anti-VEGF in scientific databases such as Google Scholar, Pubmed, ScienceDirect, Cochrane, and Researchgate. The three keywords are combined with Boolean operations and Medical Subject Headings to search (MeSH).

The article inclusion criteria used are:

1. Published in English from January 2016 to June 2020 (last five years)
2. Randomized Controlled Trial (RCT) study design
3. Based on the specified PICO (patient, intervention, comparison, and outcome)
    - Patient: Patients over 45 years old with proliferative diabetic retinopathy
    - Intervention: Anti-VEGF therapy
    - Comparison: Laser therapy
    - Outcome: Changes in visual acuity

The following criteria were used to exclude articles:

1. Published in a language other than English
2. Studies conducted on experimental animals

After completing the literature search, an abstract evaluation of the articles was performed to assess the journal's relevancy and compatibility with the inclusion and exclusion criteria. After an independent assessment, the findings were examined, and the results were summarized. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was applied to evaluate the quality of included studies. The RoB 2 contains five domains, which are (1) randomization bias; (2) intervention bias; (3) missing outcome bias; (4) outcome measurement bias; and (5) reporting bias. Two authors carried out the quality assessment, and a consensus resolved any disagreements. The risk of bias was interpreted as 'low risk', 'high risk', or 'some concerns'. Furthermore, each study data extraction related to the research objectives, research design, setting, subject information, kind of therapy, data collection methods, statistics, and outcomes is tabular.

RESULTS AND DISCUSSION

A comprehensive literature search was performed with a total of 215 articles were selected from search databases, but only 22 articles were screened and assessed based on the title and abstract's relevance to the issue.

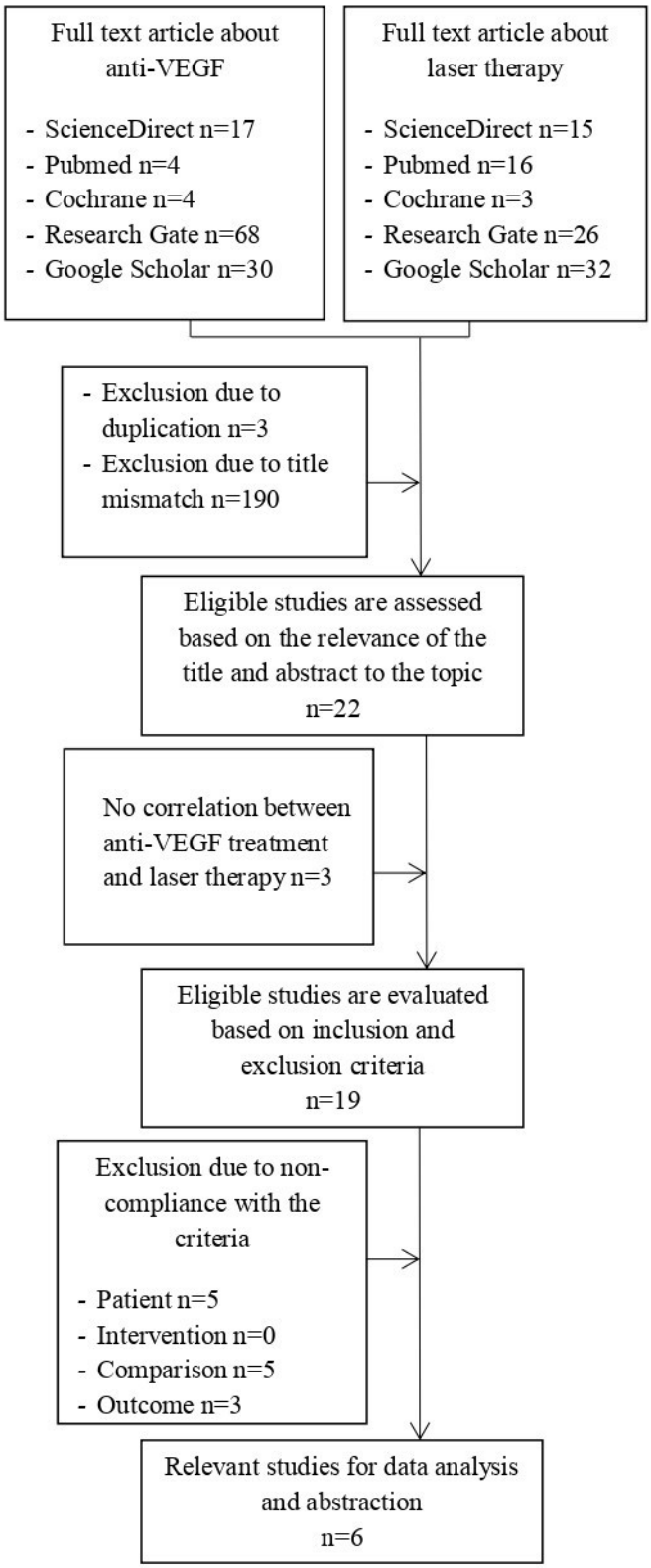

Figure 1. Flowchart of PRISMA diagram

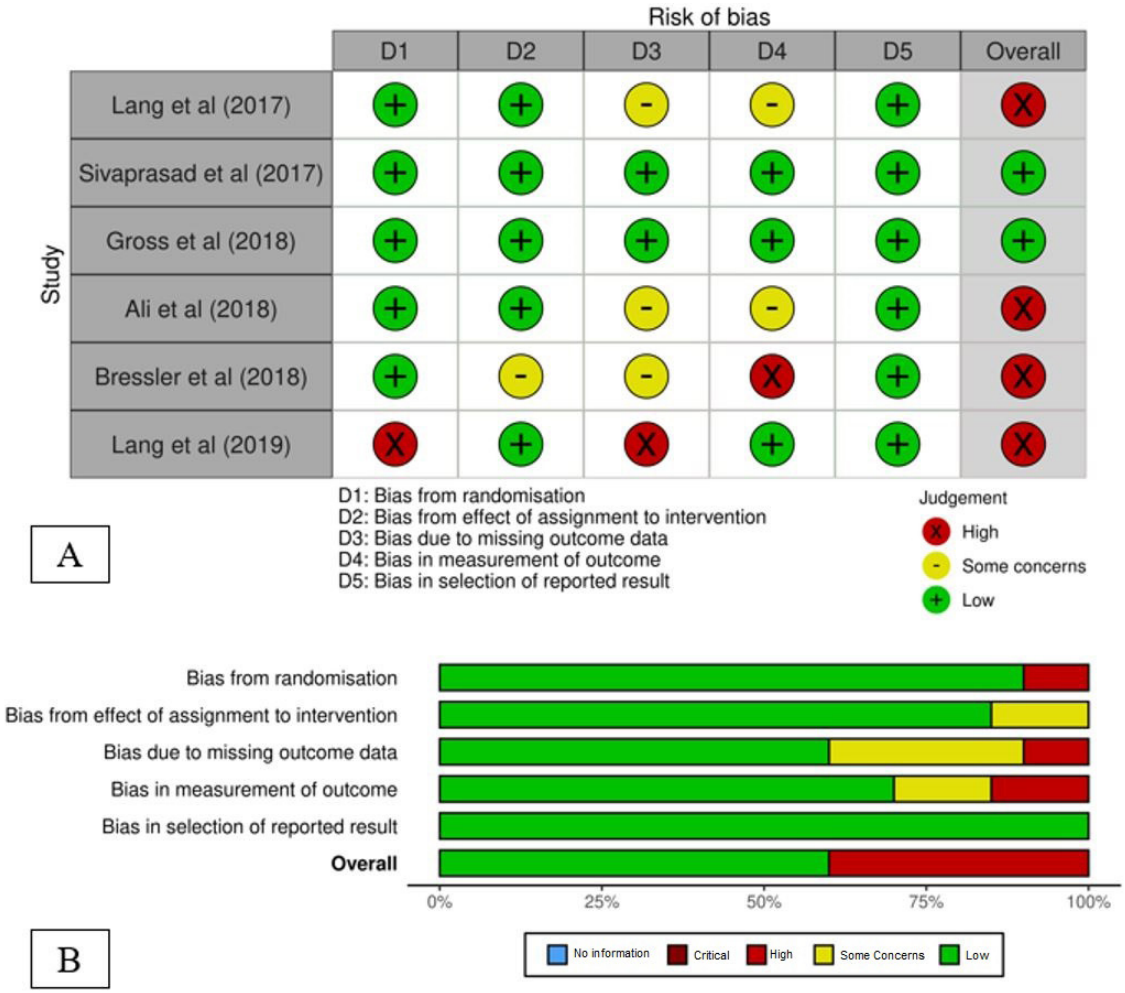

Figure 2. Risk of bias analysis. A, traffic light plot; B, summary plot

19 articles were chosen from the 22 that met the inclusion and exclusion criteria. 16 articles were chosen based on the PICO criteria to be suitable for data analysis and abstraction (Figure 1). Based on the quality assessment, two studies had low risk of bias and the others had high risk of bias (Figure 2).

The characteristics of selected eligible articles based on inclusion and exclusion criteria are presented in Table 1. The anatomy of the eye changes with age in humans. These alterations are accompanied by additional health variables that contribute to the development of certain degenerative illnesses, resulting in a reduction in bodily function and vision loss (Grossniklaus et al., 2012). A study showed that PDR as a complication of type 1 and type 2 diabetes had a prevalence of 56.0% and 30.3%, respectively, where the average age of patients with type 1 diabetes was below 40 years and type 2 diabetes mellitus was above 60 years (Thomas et al., 2015). Another study found that type 2 diabetes affects 25% of older adults (>/= 60-65 years), whereas 50% had prediabetes (Bigelow & Freeland, 2017). According to Table 1, the average age of patients is over 50 years, indicating that old age influences PDR cases. There were two trials with intervention utilizing combination treatment (CT) (Ali et al., 2018; Lang et al., 2018), one of which was a combination of pan-retinal photocoagulation (PRP) and intravitreal ranibizumab IVR (IVR) (Lang et al., 2018), and one research combined PRP with intravitreal bevacizumab (IVB) (Ali et al., 2018). Two articles solely utilized IVR as an intervention (Bressler et al., 2018; Gross et al., 2018), and one publication only used intravitreal Aflibercept (IVA) (Sivaprasad et al., 2017).

Furthermore, information on outcomes and additional outcomes comparison was seen in Table 2. Although we found two studies showing that PRP laser therapy improves visual acuity, we reviewed more studies that showed anti-VEGF therapy significantly increased visual acuity. For instance, studies conducted by Sivaprasad et al. (2017), Lang et al. (2018), Ali et al. (2018), and Lang et al. (2019) discovered a significant difference in visual

acuity improvement between anti-VEGF treatment and the PRP laser ($p<0.05$). Meanwhile, Gross et al. (2018) found no significant findings ($p>0.05$), whereas Bressler et al. (2018) did not contain a p-value. In contrast, four studies by Sivaprasad et al. (2017), Lang et al. (2018), Bressler et al. (2018), and Lang et al. (2019) found a negative value for mean visual acuity in PRP laser therapy, indicating a decrease in the number of letters that can be read after therapy.

Nevertheless, additional outcomes examined by each study are different. For instance, Lang et al. (2018) examined central subfield thickness (CST) alterations at months 4 and 12 to baseline. Both the PRP laser therapy and anti-VEGF treatment groups had a reduction in CST at month 4, with a significant difference ($p=0.007$). At month 12, both groups had decreased CST, although there was no significant difference ($p=0.062$). On the other hand, Lang et al. (2019), which also compared CST at month 12, observed CST decreased only in the anti-VEGF therapy group but not in the PRP laser therapy group, with a significant difference ($p=0.0003$). Lang et al. (2019) also compared neovascularization (NV) areas and found that both groups decreased in the NV area. However, only the anti-VEGF group saw a dramatic decline, with a significant difference in the mean NV area ($p=0.0344$).

Additional outcomes, including retinal detachment, vitreous hemorrhage, and vitrectomy that were evaluated by Gross et al. (2018) revealed anti-VEGF group suffered less of these three components than the PRP laser group, with only significant differences in retinal detachment ($p=0.004$) and vitrectomy ($p=0.008$). Likewise, a study by Sivaprasad et al. (2017) also evaluated various factors, including treatment satisfaction, CST change, macular volume, macular edema, retinal NV regression, and vitreous hemorrhage. As a result, patient satisfaction was significantly greater in the anti-VEGF group than in the PRP group ($p=0.022$). Macular thickness and volume were also significantly higher in the PRP group compared to the anti-VEGF group ($p<0.0001$). Furthermore, the proportion of patients with no macular edema was considerably more remarkable in the anti-VEGF group ($p<0.0001$). The study also found that the incidence of vitreous hemorrhage was higher in the PRP group ($p=0034$). Furthermore, Bressler et al. (2018) contrasted the development of vision-impairing (20/32 or worse) central-involved diabetic macular edema (DME) with a higher percentage of occurrences in the PRP laser group. Meanwhile, Ali et al. (2018) examined neo vessels elsewhere (NVE) and new vessels on disc (NVD), finding that the anti-VEGF group showed much fewer outcomes than the PRP laser group ($p<0.001$).

Pan-retinal Photocoagulation in PDR

PRP is the gold standard therapy for PDR, reducing the risk of vision loss by 50–60% (Çeliker et al., 2017; Palanker & Blumenkranz, 2012; Salam et al., 2011; Zhao & Singh, 2018). Laser beams of 1200-1600 nm are focused on the peripheral retina to delay the development of new blood vessels. The laser light is absorbed by the pigmented cells of the retinal epithelium, and the heat created destroys the outer retinal cells, photoreceptors, and pigmented epithelial cells. The oxygen supply to the inner retina increases because the choriocapillaris is closer to the inner retina, and the photoreceptors that previously absorbed oxygen from the choriocapillaris are no longer present in the laser-exposed region (Palanker & Blumenkranz, 2012). As a result, the number of hypoxic cells that produce VEGF and other growth factors decreases, lowering the stimulus for neovascularization (Evans et al., 2014; Palanker & Blumenkranz, 2012).

Nevertheless, PRP has limitations that it requires cooperative patients because this method is painful for some patients, and most do not want to continue their therapy. Because of the loss of retinal cells and peripheral photoreceptors, peripheral vision will be permanently lost, leading to visual acuity falls (Çeliker et al., 2017; Zhao & Singh, 2018). A study suggested that PRP can disrupt Bruch's membrane and cause mydriasis by damaging the posterior ciliary nerve and causing choroidal neovascularization (Zhao & Singh, 2018). Angle-closure glaucoma, visual field constriction, vitreous hemorrhage, and macular edema are other adverse effects (Ali et al., 2018; Zhao & Singh, 2018). Macular edema may occur or worsen following PRP treatment, impairing vision (Zhao & Singh, 2018). This explains why the outcome of laser therapy in visual acuity has a negative value or has worsened.

VEGF Drives PDR

PDR is a microvascular illness that creates a pro-angiogenic environment in the retina, with VEGF mediating the majority of angiogenesis (Osaadon et al., 2014; Zhao & Singh, 2018). VEGF promotes retinal neovascularization (Palanker & Blumenkranz, 2012). In reaction to ischemia or hypoxia, glial cells, endothelial cells, and retinal epithelial cells generate VEGF, which includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PGF) (Gupta et al., 2013; Hua et al., 2013). According to molecular research, VEGF-A enhances vascular permeability and angiogenesis via its interaction with VEGF 2 receptors (VEGFR-2), particularly VEGF-A165, which is the cause of pathological revascularization in the retina (Zhao & Singh, 2018).

Table 1. Characteristics of eligible studies

Author, year	Study design	Age (Mean (SD) years)	Number of patients (n)	Intervention	Comparison	Outcome	Additional outcome
Lang et al., 2018	RCT	CT= 63.5 (9.3) PRP= 63.5 (10.5)	26 CT= 19 PRP= 7	CT (IVR 0.5 mg + PRP)	PRP	BCVA change	CST change
Lang et al., 2019	RCT	53.5 (12.1)	70 IVR= 35 PRP= 35	IVR 0.5 mg	PRP	BCVA change	- CST change - Area of NV
Gross et al., 2020	RCT	52 (12)	240 IVR= 117 PRP= 123	IVR 0.5 mg	PRP	VA change	- Retinal detachment - Vitreous hemorrhage - Vitrectomy
Bressler et al., 2018	RCT	50 (9.6)	328 IVR=160 PRP=168	IVR 0.5 mg/0.05 ml	PRP	VA change	Development of vision-impairing (20/32 or worse) central-involved DME
Sivaprasad et al., 2017	RCT	IVA=51.5 (14.6) PRP=50.8 (13.2)	232 IVA=116 PRP=116	IVA 2 mg/0·05 mL	PRP	BCVA change	- Treatment satisfaction - CST change - Macular volume - Macular oedema - Total regression of retinal NV - Vitreous hemorrhage
Ali et al., 2018	RCT	52.5 (22.7)	60, CT=30, PRP=30	CT (IVB + PRP)	PRP	BCVA change	Mean NVE and NVD

BCVA=Best Correction Visual Acuity, CST=Central Subfield Thickness, CT=Combination Therapy, IVA=Intravitreal Aflibercept, IVB=Intravitreal Bevacizumab, IVR=Intravitreal Ranibizumab, NV=Neovascularization, NVD=New Vessels on Disc, NVE=Neovessels Elsewhere, PRP=Panretinal Photocoagulation, VA=Visual Acuity.

Table 2. Data abstraction of anti-VEGF and laser therapy outcome comparison

Author, year	Outcome (visual acuity changes) Mean (SD) or Mean (95% CI)			Additional outcome		
	anti-VEGF (letters)	**Laser Therapy (letters)**	***p*-value**	**anti-VEGF**	**Laser Therapy**	***p*-value**
Lang et al., 2018	CT=7.35 (6.81; 21.52)	-7.35 (-33.71; 19.01)	0.01	Month 4=-118.7(130.9) µm Month 12=-96.7 (120.9) µm	Month 4=-41.5(86.1) µm Month 12=-54.0 (89.9) µm	Month 4=0.007 Month 12=0.062
Lang et al., 2019	IVR=1.6 (-2.3; 5.5)	-3.9 (-7.8; 0.1)	0.0495	CST change=-6.0 (15.1) µm Area of NV=9.39 (15.41) to 2.70 (4.11) mm^2	CST change=36.2 (55.9) µm Area of NV=5.40 (9.68) to 4.58 (11.39) mm^2	CST change=0.0003 Area of NV=0.0344
Gross et al., 2018	IVR=3.1 (14.3)	3.0 (10.5)	0.68	Retinal detachment=12 eyes Vitreous hemorrhage=91 eyes Vitrectomy=21 eyes	Retinal detachment=30 eyes Vitreous hemorrhage=93 eyes Vitrectomy=39 eyes	Retinal detachment=0.004 Vitreous hemorrhage=0.47 Vitrectomy=0.008
Bressler et al., 2018	IVR=4.7 (3.8; 5.6)	-0.3 (-1.5; 1.0)	-	15 of 147 eyes (10%)	42 of 155 eyes (27%)	-
Sivaprasad et al., 2017	IVA=1.1 (0.6)	–3.0 (0.7)	<0.0001	Treatment satisfaction=5.5 (1.3) CST change=-14.0 (1.8) Macular volume=-0.53 (0.04) No macular oedema=93 (89%) Total regression of retinal NV=81 (74%) Vitreous hemorrhage=10 (9%)	Treatment satisfaction=-1.8 (1.0) CST change=15.0 (2.9) Macular volume=0.18 (0.04) No macular oedema=(74 (71%) Total regression of retinal NV=25 (24%) Vitreous hemorrhage= 21 (18%)	Treatment satisfaction=0.022 CST change<0.0001 Macular volume<0.0001 No macular oedema=0.007 Total regression of retinal NV<0.0001 Vitreous hemorrhage=0.034
Ali et al., 2018	CT=0.64 to 0.49 (0.17; 0.21)	0.6 to 0.6 (0.16; 0.18)	<0.001	NVE=1.5 (1.06), NVD=11.4 (±5.5)	NVE=3.17 (±0.7), NVD=29.53 (±11.04)	NVE<0.001, NVD<0.001

CST=Central Subfield Thickness, NV=Neovascularization, NVD=New Vessels on Disc, NVE=Neovessels Elsewhere.

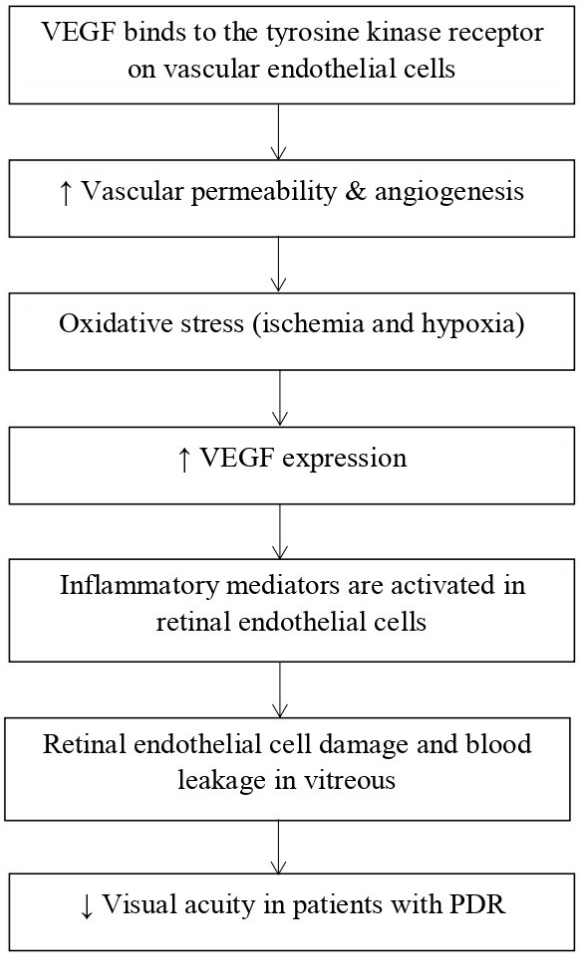

Figure 3. Effect of VEGF on VA (Gupta et al., 2013; Pratheeshkumar et al., 2012; Simo et al., 2014)

Once VEGF is generated by ischemic retinal cells, it diffuses to retinal vascular endothelial cells. The retinal endothelial cells have numerous VEGF tyrosine kinase receptors on their surface. The VEGFR-2 is the main mediator of VEGF's angiogenic and vascular permeabilizing actions. The binding of VEGF to VEGFR-2 causes dimerization and autophosphorylation of intracellular tyrosine residues, which begins signal transduction leading to endothelial proliferation, endothelial survival, transcriptional activation, endothelial migration, and vascular leakage (Koch & Claesson-Welsh, 2012).

Current Therapies Targeting VEGF

Anti-VEGF therapy, which inhibits VEGF and prevents iris neovascularization, is one approach to slow the course of PDR, particularly in increasing visual acuity (Adrian, 2017; Zhao & Singh, 2018). Anti-VEGF binds to VEGF and inhibits its binding to the tyrosine kinase reseptor. It will prevent oxidative stress by inhibiting abnormal angiogenesis. Reduced VEGF expression prevents damage to retinal endothelial cells and blood leaks in the vitreous, resulting in improved visual acuity (Gupta et al., 2013; Pratheeshkumar et al., 2012; Simo et al., 2014) (Figure 3).

Bevacizumab, ranibizumab, pegaptanib, and aflibercept are anti-VEGF drugs authorized by the US Food and Drug Administration (USFDA) (Adrian, 2017). Ranibizumab is a monoclonal antibody fragment that inhibits VEGF-A. Ranibizumab's mechanism of action is to suppress VEGF by attaching to the VEGF receptor-binding site. Endothelial cell proliferation, blood vessel leakage, and the creation of new blood vessels will be reduced due to this suppression (Adrian, 2017; Gupta et al., 2013; Lang et al., 2018).

Bevacizumab, like ranibizumab, is an antibody that binds to the double-sided VEGF-A binding site (Adrian, 2017). Bevacizumab has the exact mechanism of action as ranibizumab (Gupta et al., 2013). Moreover, research done by Nepomuceno (2013) shown that ranibizumab improved VA more than bevacizumab (Nepomuceno et al., 2013). Bevacizumab has significant adverse effects since it might hasten the blockage of new blood vessels and replace them with fibrous tissue, resulting in tractional retinal detachment (TRD) and vitreous hemorrhage (Salam et al., 2011). Meanwhile, aflibercept is a recombinant human fusion protein that functions as a decoy receptor, binding to VEGF-A and PGF but not the tyrosine kinase receptor (Gupta et al., 2013). Aflibercept binds to VEGF more effectively than bevacizumab or ranibizumab, allowing it to function for a more extended period in the eye (Adrian, 2017). Pegaptanib sodium, an RNA aptamer that binds to the 165 VEGF isoform, is the most recent anti-VEGF authorized by the USFDA (Gupta et al., 2013). However, no papers containing this sort of anti-VEGF intervention were discovered.

Systemic hypertension was the most prevalent adverse effect of anti-VEGF medicines (5.6%), followed by other cardiovascular problems (Gupta et al., 2013). Endothelial dysfunction and increased synthesis of endogenous soluble fms like tyrosine kinase-1 (sFlt-1), endothelin-1 (ET1), and other vasoactive chemicals that contribute to hypertension are caused by VEGF inhibition (Brinda et al., 2016). According to the Diabetic Retinopathy Clinical Research Network, ranibizumab is safer than aflibercept and bevacizumab due to its low systemic adverse effects (Wells et al., 2015).

Anti-VEGF Compared with PRP for PDR

As previously stated, functional anti-VEGF can be utilized as an adjuvant to PRP (Ali et al., 2018). Several anti-VEGFs have been proven, including ranibizumab, which has a lower outcome in the development of DME that interferes with vision and provides better VA (Lang et al., 2018, 2019), bevacizumab, which can reduce deterioration in VA and regression of new vessels

in the retina (Ali et al., 2018), and aflibercept, which significantly shows NV regression (Lang et al., 2019).

Overall, anti-VEGF therapy was effective in reversing neovascularization. Some studies showed that anti-VEGF has superior short-term anatomical effects in combination with PRP for high-risk patients (Mirshahi et al., 2008; Simunovic & Maberley, 2015; Yang et al., 2013; Zhou et al., 2016). The disadvantage is that it is only for a limited period, ranging from 2 weeks to 3 months, so it cannot match the exceptional durability of PRP and does not qualify as the gold-standard therapy for PDR (Gupta et al., 2013). Anti-VEGF therapy, which affects the absence of vessels reperfusion or capillary network, also could lead to worsened PDR in case of treatment discontinuation; thus, the therapy must be followed up closely (Bonnin et al., 2019). Another study also showed that intravitreal anti-VEGF could worsen anatomical and functional outcomes in lost-to-follow-up (LTFU) PDR patients compared to PRP treatment (Obeid et al., 2019).

Besides, the recent gold standard treatment for PDR is still PRP, as a long-term treatment beneficial to chronic diseases like diabetic retinopathy (Flaxel et al., 2020; Ghanchi, 2013; Nikkhah et al., 2018). It has some challenges due to its potential complications. PRP has been linked to decreased peripheral and night vision, worsened DME, and decreased contrast sensitivity (Brucker et al., 2009; Preti et al., 2013).

In terms of cost-effectiveness, a previous study showed Anti-VEGF, ranibizumab, 0.5 mg, has been considered better cost-effectiveness compared to PRP during 5 to 10 years of treatment for eyes presenting with PDR and vision-impairing center-involved DME in the United States (Hutton et al., 2019). Most patients also preferred anti-VEGF over PRP in clinical trial conditions. The reduced frequency of macular edema and vitreous hemorrhage in the anti-VEGF group may have contributed to the mean best correction visual acuity (BCVA) improvement. While the incidence of vitreous hemorrhage was twice as high in the PRP group, it enhanced patients' preferences for anti-VEGF (Sivaprasad et al., 2017). Other studies also revealed that the cumulative incidence of vitrectomy was higher in the PRP group compared to the monotherapy anti-VEGF group (Ernst et al., 2012; Figueira et al., 2018; Gross et al., 2015).

There are restrictions in accessing the scientific database used in this systematic review reference. Also, some articles do not compare lasers to pure anti-VEGF but rather a combination of laser therapy and anti-VEGF. It causes a slight bias that makes the authors unable to compare the effectiveness of pure anti-VEGF with laser therapy.

CONCLUSION

Anti-VEGF therapy (ranibizumab, bevacizumab, and aflibercept) may be a more practical alternative than pan-retinal photocoagulation for individuals with proliferative diabetic retinopathy. This systematic review revealed that Anti-VEGF therapy led to better visual acuity outcomes, lower vitreous hemorrhage, and better cost-effectiveness, and is preferred by most patients. Nevertheless, this treatment should be followed up closely in order to prevent a worsening of PDR. More studies on the long-term anti-VEGF impact compared to PRP and large sample size are needed to receive more comprehensive evidence.

CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

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