Opthalmology

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Critical review

Management of retinal diseases

N Kumar*

Abstract

Introduction

Many recent researches have contributed immensely in the management of retinal diseases. In this critical review, we discuss the management of retinal diseases.

Conclusion

Currently, age-related macular degeneration is managed primarily by anti-vascular growth factor agents. Newer reports on combination therapy may help in managing this visually debilitating condition in a better way. There are many new reports regarding the use of aflibercept and Ozurdex® (Allergan Inc., Irvine, California, USA) in the management of diabetic macular oedema and macular oedema associated with retinal vein occlusions. In the light of recent reports, retinopathy of prematurity may be often managed with bevacizumab. Introduction of ocriplasmin and Argus-II Retinal Prosthesis System (Second Sight Medical Products, Inc., Sylmar, California, USA) may offer ophthalmologists newer ways to treat some important vitreoretinal conditions.

Introduction

Retinal diseases constitute a significant part of the visually disabling ocular disease spectrum. Recently, there have been many exciting developments in the understanding, diagnosis and management of retinal diseases. It is important to critically review important ones to adopt them into our clinical practice. In this critical review, we shall discuss conditions like age-related macular degeneration (AMD), diabetic retinopathy (DR), retinal vein occlusion (RVO), vitreomacular traction syndrome and retinopathy of prematurity (ROP), in addition to vitreoretinal surgery.

Discussion

Age-related macular degeneration

AMD is the leading cause of visual loss, in the western world, in adults over 65 years of age. Choroidal neovascular membrane (CNVM; Figure 1) caused due to AMD, has been treated in the past with laser photo coagulation[1] and photodynamic therapy[2].

A macular photocoagulation study group reported benefits of photocoagulation in the management of classical CNVM with well defined boundaries[1]. Patients with extrafoveal CNVM lost six lines or more in 48% of treated eyes as compared with 64% of untreated eyes, at five years. In cases of juxtafoveal CNVM, the loss was 49% in treated eyes and 68% in untreated eyes at three years. This landmark study, for the first time, showed that some stabilisation of visual acuity could be achieved in selected types of CNVM. However, this form of therapy had many drawbacks like the fact that the selected patients constituted only a minority of AMD cases. Additionally, patients did not have visual improvements. Scar formation and recurrences were common.

Treatment of subfoveal CNVM with laser photocoagulation left permanent scars and visual loss.

Photodynamic therapy (PDT) was introduced to overcome limitations of laser photocoagulation in the treatment of CNVM[2]. PDT comprises of a two-step procedure. The first step is to inject a photosensitising drug verteporfin (Visudyne, QLT Inc., Vancouver, British Columbia, Canada), intravenously. The second step is the activation of verteporfin with light from a non-thermal diode laser to treat CNVM. The TAP study[2] showed that PDT-treated eyes had

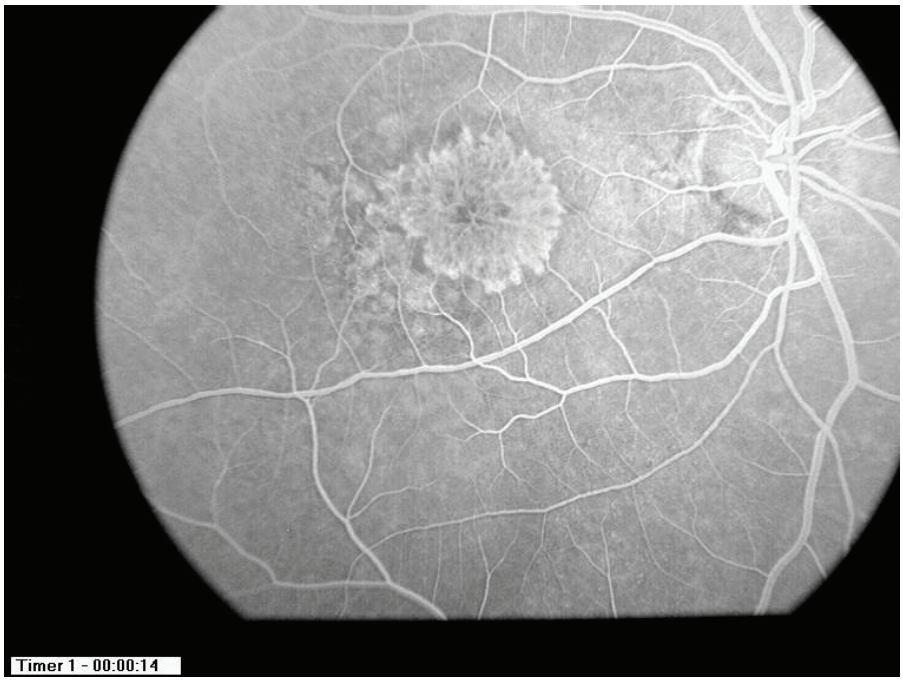

Figure 1: Fluorescein angiogram showing CNVM.

* Corresponding author
Email: nkumareyemd@gmail.com

Al Bahar Eye Center, Ibn Sina Hospital, Shuwaikh, Kuwait

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Critical review

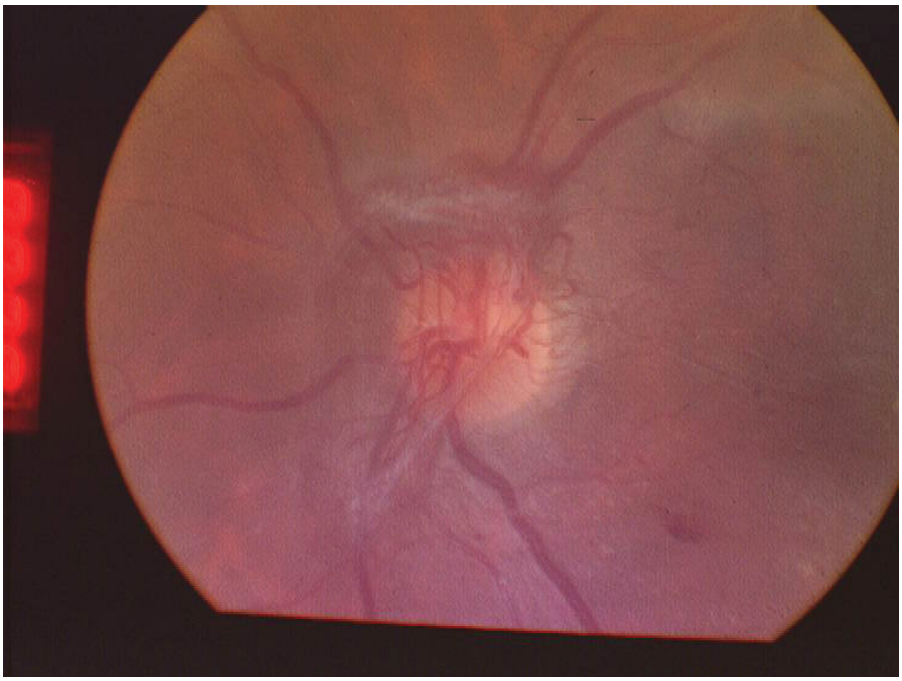

Figure 2: Colour fundus photograph showing PDR (neovascularisation of the optic disc).

better visual outcome than placebo-treated eyes. It was seen that 61% verteporfin-treated eyes compared with 46% placebo-treated ones, lost fewer than 15 letters of visual acuity from baseline at the end of one-year follow up. Common complications of PDT therapy include severe visual loss, infusion site extravasation, back pain and photosensitivity reaction. Closure of blood vessels in CNVM lesions is seen initially following PDT treatment, but unfortunately, most of them start leaking again after a few weeks. Therefore, retreatments (TAP study[2]: 3,4 during first year) and regular follow up are necessary.

Introduction of anti vascular endothelial growth factor (VEGF) agents has revolutionised the management of AMD[3-6]. The MARINA study group evaluated ranibizumab, a recombinant, humanised, monoclonal antibody that neutralises all active forms of VGEF for the treatment of neovascular AMD[3]. They showed that 94.5% of the group given 0.3 mg of ranibizumab and 94.6% given 0.5 mg, lost fewer than 15 letters, as compared with 62.2% of patients receiving placebo injections at 12 months. Visual acuity improved by 15 or more letters in 24.8% of the 0.3-mg group and 33.8% of the 0.5-mg group, as compared with 5.0% of the placebo-injection group. The ANCHOR study group compared the effectiveness of ranibizumab with verteporfin (PDT)[4]. They showed that 94.3% of those given 0.3 mg of ranibizumab and 96.4% of those given 0.5 mg, lost fewer than 15 letters, as compared with 64.3% of those in the verteporfin group. Visual acuity improved by 15 letters or more in 35.7% of the 0.3-mg group and 40.3% of the 0.5-mg group, as compared with 5.6% of the verteporfin group. These studies demonstrated that monthly intravitreal injections of ranibizumab not only stabilised visual acuity but also improved it in a significant number of patients. However, ranibizumab is an expensive drug. Bevacizumab, an off-label, anti-VEGF drug, was investigated as a cheaper alternative to ranibizumab[5]. Spaide et al.[5] reported mean visual acuity improvement from 20/184 to 20/109 ($p < 0.001$); 38.3% of patients had visual acuity improvement after intravitreal injection of bevacizumab. The mean central macular thickness improved from 340 micron to 213 micron in the third month ($p < 0.001$). Later, the CATT and IVAN trials demonstrated similar efficacies of ranibizumab and bevacizumab in the management of neovascular AMD[6,7]. Bevacizumab was associated with higher cardiovascular complications in these trials although these results were not statistically significant.

Another anti-VEGF drug, aflibercept, has recently been studied[8]. Patients were randomised to intravitreal aflibercept of 0.5 mg monthly, 2 mg monthly, 2 mg every two months after three initial monthly doses or ranibizumab 0.5 mg monthly. They concluded that intravitreal aflibercept dosed monthly or every two months after three initial monthly doses, produced similar efficacy and safety outcomes as monthly ranibizumab. Less frequent dosing of aflibercept is generating lots of interest.

Now ranibizumab is being combined with other agents to further enhance its potency. The MONET clinical study group reported that the combination of siRNA PF-04523655 with ranibizumab led to an average gain in best-corrected visual acuity that was more than with ranibizumab monotherapy[9]. In a prospective, randomised, controlled, phase 2b trial, the combination of anti-platelet derived growth factor Fovista (Ophthotech, Princeton, New Jersey, USA) and ranibizumab, was shown to have superior efficacy as compared with ranibizumab monotherapy[10]. Patients who received the combination gained a mean of 10.6 letters of vision on the early treatment diabetic retinopathy study (ETDRS) standardised chart, whereas those who received ranibizumab monotherapy gained a mean of 6.5 letters of vision.

Diabetic retinopathy

DR is the leading cause of blindness in the adult population (20–64 years) in the USA. The DR study was

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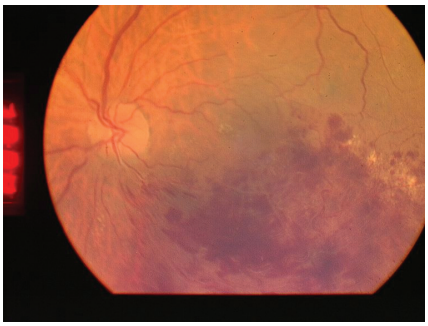

Figure 3: Colour fundus photograph showing BRVO.

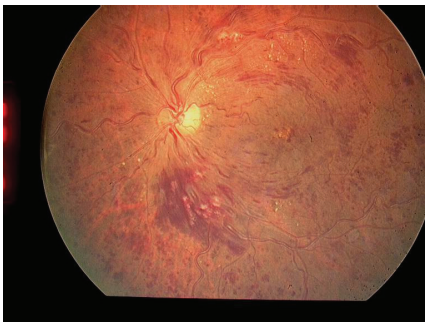

Figure 4: Colour fundus photograph showing CRVO.

a randomised, controlled clinical trial involving more than 1700 patients enrolled at 15 medical centres. This pioneering study demonstrated that both argon and xenon photocoagulation reduced the risk of severe visual loss by more than 50% in eyes with proliferative DR (Figure 2) with high risk characteristics[11]. The ETDRS was a randomised clinical trial supported by the National Eye Institute. In this study, 754 eyes that had macular oedema and mild to moderate DR were randomly assigned to focal argon laser photocoagulation, while 1490 such eyes were randomly assigned to a deferral of photocoagulation. The study demonstrated that laser photocoagulation of 'clinically significant' diabetic macular oedema (CSME) substantially reduces the risk of moderate visual loss (24% in treated eyes vs. 12% in untreated eyes)[12]. This left many patients with diabetic macular oedema (DME) who did not respond to laser photocoagulation. Anti-VEGF agents have helped some of these patients[13-15]. In a prospective, randomised, interventional, multicentre, clinical trial, the READ-2 study group investigators compared ranibizumab with focal/grid laser or a combination of both in DME. They concluded that ranibizumab injections had a significantly better visual outcome than focal/grid laser treatment in patients with DME[13]. Another anti-VEGF agent, bevacizumab, has also been extensively studied in the management of DME. The BOLT study group investigators, in a prospective, randomised, masked, single-centre, 2-year, 2-arm, clinical trial, compared repeated intravitreal bevacizumab and macular laser therapy in patients with persistent CSME[14]. The study concluded that there is an evidence to support the use of bevacizumab in patients with centre-involving CSME without advanced macular ischemia. Recently, a new anti-VEGF agent, aflibercept, has been investigated in the management of DME[15]. The DA VINCI study group authors compared aflibercept with laser photocoagulation in eyes with DME. They reported significant gains in visual acuity in eyes treated with aflibercept. Intravitreal injection of corticosteroids has also been used in the management of DME. Now a dexamethasone intravitreal implant (Ozurdex®; Allergan Inc., Irvine, California, USA) has been studied in the management of DME[16]. Study investigators in a prospective, multicentre, open-label study, reported that treatment with dexamethasone intravitreal implant led to statistically and clinically significant improvements in both vision and vascular leakage from DME with an acceptable safety profile.

Retinal vein occlusions

RVOs (branch and central) are important retinal conditions with significant ocular morbidity. The branch RVO study was a prospective, randomised, controlled, multicentre study[17,18]. It recommended laser photocoagulation for macular oedema due to branch retinal vein occlusion (BRVO; Figure 3) in selected patients. In this study, 63% of laser-treated eyes improved two or more lines of vision compared to 36% of control eyes after three years of follow-up care. It also recommended peripheral scatter laser photocoagulation for patients with branch vein occlusion who had developed neovascularisation. The development of vitreous haemorrhage was significantly less in laser-treated eyes (30% in laser-treated eyes vs. 60% in control eyes). Recently, anti-VEGF agents have been studied in the management of BRVO. The BRAVO study investigators reported that intravitreal injections of ranibizumab provided rapid and effective treatment for macular oedema following BRVO[19]. The percentage of patients who gained > or = 15 letters of vision at six months was 55.2% (0.3 mg) and 61.1% (0.5 mg) in the ranibizumab groups and 28.8% in the placebo group. The management of central retinal vein occlusion (CRVO; Figure 4) was studied by a National Eye Institute sponsored multicentre, central vein occlusion study group[20,21]. CRVO-associated macular oedema was treated by macular grid laser photocoagulation[20]. They found no difference between treated and untreated eyes in visual acuity. So treatment of macular oedema by macular grid photocoagulation in CRVO was not recommended. However, they recommended panretinal laser photocoagulation (PRP) of eyes, which developed two clock hours of iris neovascularisation or any angle neovascularisation following CRVO[21]. They also concluded that prophylactic PRP did not prevent the development of iris neovascularisation and recommended to wait for the development of early iris neovascularisation and then do PRP. The CRUISE investigators studied ranibizumab for macular oedema following CRVO[22]. Ranibizumab-treated patients (0.3 mg = 43.9%; 0.5 mg = 46.9%) had

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significantly better visual acuity of > or = 20/40 compared with placebo patients (20.8%). Recently, Brown et al. (COPERNICUS study)[23] reported favourable outcomes in the treatment of macular oedema following CRVO by aflibercept. At week 24, 56.1% of aflibercept-treated patients gained ≥ 15 letters from baseline compared with 12.3% of placebo patients[23]. This trend continued later at one year follow up. Dexamethasone intravitreal implant also has been studied in patients with macular oedema due to RVO. The OZURDEX GENEVA study group reported that the dexamethasone intravitreal implant can both reduce the risk of vision loss and improve the speed and incidence of visual improvement in eyes with macular oedema secondary to BRVO or CRVO[24].

Retinopathy of prematurity

ROP is a vasoproliferative disorder of the eye affecting premature infants. It may result in profound visual impairment or blindness in its severe forms. Cryotherapy for Retinopathy of Prematurity Cooperative Group, in a landmark study, reported a beneficial role of cryotherapy in the management of ROP[25]. They demonstrated that unfavourable outcome was significantly less frequent in the eyes undergoing cryotherapy (21.8%) as compared with the untreated eyes (43%). Later, indirect laser photocoagulation of the avascular retina was shown to be equally effective with lesser morbidity in the management of ROP[26]. Recently, intravitreal injection of bevacizumab has shown promise in the management of posterior Zone-I ROP. The BEAT-ROP Cooperative Group reported that ROP recurred in 4% infants in the bevacizumab group and 22% infants in the laser-therapy group[27]. However, there are many issues with this form of therapy like ocular complications, systemic safety, organogenesis and off-label use of the drug.

Vitreoretinal surgery

Recently, many innovations have been introduced in the field of vitreoretinal surgery. The MIVI-TRUST study group reported enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes[28]. In this study, vitreomacular adhesion resolved in 26.5% of ocriplasmin-injected eyes and in 10.1% of placebo-injected eyes. Nonsurgical closure of macular holes was achieved in 40.6% of ocriplasmin-injected eyes, as compared with 10.6% of placebo-injected eyes. The Diabetic Retinopathy Clinical Research Network tried to answer whether intravitreal ranibizumab could reduce vitrectomy rates as compared with saline for vitreous haemorrhage from proliferative diabetic retinopathy (PDR)[29]. They concluded that there was little likelihood of a clinically important difference between ranibizumab and saline on the rate of vitrectomy in eyes with vitreous haemorrhage from PDR. However, there was visual acuity improvement, increased panretinal photocoagulation completion rates and reduced recurrent vitreous haemorrhage rates, in the ranibizumab group. Research is ongoing to restore vision in eyes with diseases like retinitis pigmentosa. Humayun et al. have evaluated the Argus II Retinal Prosthesis System (Second Sight Medical Products, Inc., Sylmar, California, USA) in blind subjects[30]. The electronic stimulator and antenna of the implant were sutured onto the sclera. The microelectrode array was tacked to the epiretinal surface after performing pars plana vitrectomy. Patients performed better in object localisation, motion discrimination and discrimination of oriented gratings.

Conclusion

Newer studies about aflibercept, combination therapy of ranibizumab, Ozurdex® (Allergan Inc., Irvine, California, USA), ocriplasmin and Argus-II Retinal Prosthesis System (Second Sight Medical Products, Inc., Sylmar, California, USA), hold promise for better management of vitreoretinal disorders.

Abbreviations list

AMD, age-related macular degeneration; BRVO, branch retinal vein occlusion; CNVM, choroidal neovascular membrane; CRVO, central retinal vein occlusion; CSME, clinically significant diabetic macular oedema; DME, diabetic macular oedema; DR, diabetic retinopathy; ETDRS, early treatment diabetic retinopathy study; PDR, proliferative diabetic retinopathy; PDT, photodynamic therapy; PRP, panretinal laser photocoagulation; ROP, retinopathy of prematurity; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor

References

1. Argon laser photocoagulation for neovascular maculopathy. Five-year results from randomized clinical trials. Macular Photocoagulation Study Group. Arch Ophthalmol. 1991 Aug;109(8):1109–14.
2. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials–TAP report. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. Arch Ophthalmol. 1999 Oct;117(10):1329–45.
3. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006 Oct;355(14):1419–31.
4. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006 Oct;355(14):1432–44.
5. Spaide RF, Laud K, Fine HF, Klancnik JM Jr, Meyerle CB, Yannuzzi LA, et al. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina. 2006 Apr; 26(4):383–90.

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6. CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011 May;364(20):1897–908.
7. IVAN Study Investigators, Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology. 2012 Jul;119(7):1399–411.
8. Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, et al; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age related macular degeneration. Ophthalmology. 2012 Dec;119(12):2537–48.
9. Nguyen QD, Schachar RA, Nduaka CI, Sperling M, Klamerus KJ, Chi-Burris K, et al; MONET Clinical Study Group. Evaluation of the siRNA PF-04523655 versus ranibizumab for the treatment of neovascular age-related macular degeneration (MONET Study). Ophthalmology. 2012 Sep;119(9):1867–73.
10. http://www.ophthotech.com/ophthotechs-anti-pdgf-fovista-superior-efficacy-phase2b/ (Accessed on 16 February 2013).
11. Photocoagulation treatment of proliferative diabetic retinopathy: Clinical application of Diabetic Retinopathy Study (DRS) findings. Diabetic Retinopathy Study (DRS) Report Number 8. The Diabetic Retinopathy Study Research Group. Ophthalmology. 1981 Jul;88(7):583–600.
12. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991 May;98(5 Suppl):766–85.
13. Nguyen QD, Shah SM, Heier JS, Do DV, Lim J, Boyer D, et al; READ-2 Study Group. Primary end point (six months) results of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. Ophthalmology. 2009 Nov;116(11):2175–81.
14. Michaelides M, Kaines A, Hamilton RD, Fraser-Bell S, Rajendram R, Quhill F, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. Ophthalmology. 2010 Jun;117(6):1078–86.
15. Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, et al; DA VINCI Study Group. One-year outcomes of the DA VINCI Study of VEGF Trap-Eye in eyes with diabetic macular edema. Ophthalmology. 2012 Aug;119(8):1658–65.
16. Boyer DS, Faber D, Gupta S, Patel SS, Tabandeh H, Li XY, et al; Ozurdex CHAMPLAIN Study Group. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. Retina. 2011 May;31(5):915–23.
17. Argon laser photocoagulation for macular edema in branch vein occlusion. The Branch Vein Occlusion Study Group. Am J Ophthalmol. 1984 Sep;98(3):271–82.
18. Argon laser scatter photocoagulation for prevention of neovascularization and vitreous hemorrhage in branch vein occlusion. A randomized clinical trial. Branch Vein Occlusion Study Group. Arch Ophthalmol. 1986 Jan;104(1):34–41.
19. Campochiaro PA, Heier JS, Feiner L, Gray S, Saroj N, Rundle AC, et al; BRAVO Investigators. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010 Jun;117(6):1102–12.
20. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The Central Vein Occlusion Study Group M report. Ophthalmology. 1995 Oct;102(10):1425–33.
21. A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. The Central Vein Occlusion Study Group N report. Ophthalmology. 1995 Oct;102(10):1434–44.
22. Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, Saroj N, et al; CRUISE Investigators. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010 Jun;117(6):1124–33.
23. Brown DM, Heier JS, Clark WL, Boyer DS, Vitti R, Berliner AJ, et al. Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study. Am J Ophthalmol. 2013 Mar;155(3):429–37.
24. Haller JA, Bandello F, Belfort R Jr, Blumenkranz MS, Gillies M, Heier J, et al; OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology. 2010 Jun;117(6):1134–46.
25. Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Arch Ophthalmol. 1988 Apr;106(4):471–9.
26. McNamara JA, Tasman W, Brown GC, Federman JL. Laser photocoagulation for stage 3+ retinopathy of prematurity. Ophthalmology. 1991 May;98(5):576–80.
27. Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011 Feb;364(7):603–15.
28. Stalmans P, Benz MS, Gandorfer A, Kampik A, Girach A, Pakola S, et al; MIVI-TRUST Study Group. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes. N Engl J Med. 2012 Aug;367(7):606–15.
29. Diabetic Retinopathy Clinical Research Network. Randomized clinical trial evaluating intravitreal ranibizumab or saline for vitreous hemorrhage from proliferative diabetic retinopathy. JAMA Ophthalmol. 2013 Mar;131(3):283–93.
30. Humayun MS, Dorn JD, da Cruz L, Dagnelie G, Sahel JA, Stanga PE, et al; Argus II Study Group. Interim results from the international trial of Second Sight's visual prosthesis. Ophthalmology. 2012 Apr;119(4):779–88.

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