Eye (2020) 34:609–610
https://doi.org/10.1038/s41433-019-0652-3

The ROYAL COLLEGE of OPHTHALMOLOGISTS

EDITORIAL

Anti-VEGF therapy is not a magic bullet for diabetic retinopathy

Mingwei Zhao[1,2,3] · Yaoyao Sun[1,2,3] · Yuzhen Jiang[4,5]

Received: 13 October 2019 / Accepted: 17 October 2019 / Published online: 28 October 2019

With the emergence of significant number of recent clinical trials on different indications of anti-vascular endothelial growth factor (anti-VEGF) in diabetic eye disease, it is time to re-think whether anti-VEGF therapy is the be all and end all treatment for complications of diabetic retinopathy (DR) [1–5]. Initial studies of anti-VEGF therapy for visual impairment due to diabetic macular oedema (DMO) highlighted the importance of aggressive therapy or treat to stability [5]. In addition, anti-VEGF therapy also resulted in two-step improvement in severity of DR in about 35% of patients [6]. Given these very encouraging results, in China, the Chinese clinical guidelines state that anti-VEGF therapy should be chosen as the first-line treatment when DMO involves the macular centre [7]. However, with the popularity of anti-VEGF therapy in China, this therapy tends to be used far more commonly than this indication for DMO. For example, it is used in DMO threatening the fovea and also for DMO with no visual impairment.

Recent data from Protocol V indicates that anti-VEGF do not need to be initiated aggressively in eyes with DMO with minimal visual impairment and that we could patiently wait until the patient experiences a loss of at least five ETDRS letters before initiating anti-VEGF therapy [1]. This requires a change in culture and behaviour of the retinal specialists in China as anti-VEGF is now considered a magic bullet for any macular oedema.

Secondly, as visual field loss is a concern in eyes with proliferative DR (PDR) treated with panretinal photocoagulation (PRP), the short terms results from Protocol S and the CLARITY studies were also very encouraging and resulted in widespread use of anti-VEGF for PDR [2, 3]. However, the 5-year results of Protocol S question the long-term benefit of anti-VEGF in PDR as the dramatic visual field loss after 2 years of follow-up indicate that anti-VEGF is actually not a magic bullet and that we require further studies to understand the deterioration of visual field after 2 years [4]. The research question that needs to be asked is why does visual field loss occur quite abruptly after 2 years and does this worsening correlate with increasing area of non-perfusion as the natural history of the disease progresses over time? Moreover, there is now sufficient evidence that anti-VEGF treatment itself does not reverse the pathological process of non-perfusion in DR [8].

Considering the new evidence on anti-VEGF in DMO and PDR, the rising prevalence of DMO and PDR with the diabetes epidemic and the fact that many people in China cannot afford anti-VEGF treatment, we recently published an editorial in the *Chinese Journal of Ophthalmology*, putting forward the strategies of anti-VEGF therapy in DR, emphasizing that anti-VEGF therapies cannot replace PRP and one should not exaggerate its clinical indication [9]. Specific treatment strategies include: (1) for visual impairment due to centre-involving DMO in eyes with non-PDR (NPDR), anti-VEGF therapy is the first choice of treatment. When DR progresses to severe NPDR and PDR, PRP is the standard of care and anti-VEGF therapy should be used as an adjuvant or to prevent the aggravation of DMO after PRP; (2) for high-risk PDR, anti-VEGF therapy may be used to inhibit neovascularization prior to completion of PRP within the effective period of drug action, so as to avoid the disease progression caused by the slow uptake of PRP; (3) for patients in whom PRP is indicated but cannot complete PRP immediately, anti-VEGF therapy may be used or even repeated as a temporary measure. Anti-VEGF

✉ Mingwei Zhao
dr_zhaomingwei@163.com

1 Department of Ophthalmology, People's Hospital, Peking University, 11 South Avenue Xi Zhi Men, 100044 Beijing, China

2 Eye Diseases and Optometry Institute, Beijing Key Laboratory of Diagnosis and Therapy of Retinal and Choroid Diseases, 11 South Avenue Xi Zhi Men, 100044 Beijing, China

3 College of Optometry, Peking University Health Science Center, Peking University, 11 South Avenue Xi Zhi Men, 100044 Beijing, China

4 Moorfields Eye Hospital, 162 City Rd, London EC1V 2PD, UK

5 UCL Institute of Ophthalmology, 43 Bath Street, London EC1V 9EL, UK

therapy can be terminated after completion of PRP; (4) for patients with advanced PDR, anti-VEGF therapy is recommended before vitrectomy to reduce the probability of intraoperative and postoperative haemorrhage, to create a bloodless field for the operation and to avoid postoperative complications. However, it is necessary to strictly adhere to the timing of anti-VEGF injection; (5) for neovascular glaucoma secondary to DR, a comprehensive treatment strategy of anti-VEGF treatment, completion of PRP and anti-glaucoma surgery has to be adopted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Baker CW, Glassman AR, Beaulieu WT, Antoszyk AN, Browning DJ, Chalam KV, et al. DRCR retina network. Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. JAMA. 2019;231:1880–94.
2. Writing Committee for the Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy:a randomized clinical trial. JAMA. 2015;314:2137–46.
3. Sivaprasad S, Prevost AT, Vasconcelos JC, Riddell A, Murphy C, Kelly J, et al. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. Lancet. 2017; 389:2193–203.
4. Gross JG, Glassman AR, Liu D, Sun JK, Antoszyk AN, Baker CW, et al. Diabetic retinopathy clinical research network. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA Opthalmol. 2018;136:1138–48.
5. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology. 2016;123:1351–9.
6. Wykoff CC, Eichenbaum DA, Roth DB, Hill L, Fung AE, Haskova Z. Ranibizumab induces regression of diabetic retinopathy in most patients at high risk of progression to proliferative diabetic retinopathy. Ophthalmol Retin. 2018;2:997–1009.
7. Guidelines for clinical diagnosis and treatment of diabetic retinopathy. Fundus workshop of Chinese Ophthalmological Society. Chin J Ophthalmol. 2014;50:851–65.
8. Nicholson L, Crosby-Nwaobi R, Vasconcelos JC, Prevost AT, Ramu J, Riddell A, et al. Mechanistic evaluation of panretinal photocoagulation versus aflibercept in proliferative diabetic retinopathy: CLARITY substudy. Investig Ophthalmol Vis Sci. 2018;59:4277–84.
9. Zhao M, Sun Y, Xu X. The rational use of anti-vegf drugs to assist the treatment of diabetic retinopathy. Chin J Ophthalmol. 2019;55:565–8.