

Intravitreal triamcinolone acetonide vs bevacizumab for treatment of macular oedema due to central retinal vein occlusion

W-C Wu^{1,2}, K-C Cheng³ and H-J Wu¹

CLINICAL STUDY

Abstract

Purpose To compare the efficacy of intravitreal triamcinolone acetonide vs intravitreal bevacizumab in eyes with macular oedema caused by central retinal vein occlusion (CRVO).

Design Retrospective consecutive case series.

Methods Retrospective review of the medical records of 35 consecutive patients (35 eyes) with macular oedema associated with CRVO. Twenty-two patients were treated with intravitreal injection of 4 mg/0.1 ml triamcinolone acetonide. The other 13 patients accepted intravitreal bevacizumab 1.25 mg in 0.05 ml. Initial visual acuity, intraocular pressure (IOP), and macular thickness were recorded. Final visual acuity, IOP, macular thickness, and adverse events were recorded during the treatment period.

Results The mean follow-up was 282.73 ± 70.62 days in the group administered with triamcinolone acetonide and 253.92 ± 36.10 days in the study group who accepted bevacizumab, respectively. Visual acuity measurements improved significantly and showed significant macular oedema resolution in optical coherence tomography examination in both the two groups. However, the therapeutic effects had no significant difference between these two groups with regard to visual results ($F = 1.723$, $P = 0.240$) and macular thickness decrease ($F = 1.814$, $P = 0.832$). Thirteen eyes developed recurrent macular oedema and received repeat injections of triamcinolone acetonide or bevacizumab.

Conclusion Intravitreal injection of triamcinolone acetonide or bevacizumab can both lead to a significant improvement in visual acuity and a resolution of macular oedema in patients with CRVO. However, the significant effect was not permanent. Besides, the efficacy of intravitreal triamcinolone acetonide showed no significant differences compared with intravitreal bevacizumab but seemed to cause more adverse events than bevacizumab.

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Keywords: central retinal vein occlusion; macular oedema; intravitreal triamcinolone acetonide; intravitreal bevacizumab

Introduction

Central retinal vein occlusion (CRVO) is the second most common retinal vascular disorder in the eye after diabetic retinopathy and can be associated with potentially blinding complications. The ocular findings include intraretinal haemorrhage in all four retinal quadrants, tortuous and dilated retinal veins, different levels of ischaemia,¹ and optic disc swelling in some cases. Some patients may have the possibility to develop the neovascular complications such as rubeosis iridis and neovascular glaucoma. The pathological finding suggests that the site of obstruction is located in the lamina cribrosa.² Macular oedema and neovascularisation are the two major

¹Department of Ophthalmology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

²Faculty of Medicine, Department of Ophthalmology, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

³Department of Ophthalmology, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung, Taiwan

Correspondence: K-C Cheng, Department of Ophthalmology, Kaohsiung Municipal Hsiao-Kang Hospital, No.482, San-ming Road, Hsiaokang District, Kaohsiung 812, Taiwan
Tel: +886 7 8036783 ext. 3243;
Fax: +886 7 8071855.
E-mail: pington@ms1.url.com.tw

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complications responsible for severe visual impairment in CRVO patients. The degree of visual impairment is determined by the level of macular involvement. Usually, the CRVO patients often suffer severe irreversible visual loss, and only 20% of cases have improvement in vision.^{2,3} However, there is no proven effective therapy to treat visual decline associated with CRVO.

The standard of therapy currently remains limited to the management of the neovascular sequelae with panretinal photocoagulation. The Central Vein Occlusion Study showed that the grid pattern photocoagulation definitely reduced macular oedema on fluorescein angiography but failed to show statistically significant visual acuity benefit.⁴ Recent reports have suggested other treatment modalities investigated in case series, including laser-induced chorioretinal venous anastomosis,⁵ intravitreal tissue plasminogen activator,^{6,7} surgical induction of chorioretinal venous anastomosis,⁸ and radial optic neurotomy,⁹ to improve the circulatory status of the retina after CRVO. However, these studies, although encouraging, are still controversial and have not yet been sufficiently supported by larger randomised clinical trials.

Recently, the effect of intravitreal injection of triamcinolone acetonide¹⁰⁻¹⁷ and of anti-VEGF agents, such as bevacizumab¹⁸ and ranibizumab,¹⁹ has been widely discussed. They have been reported to be associated with short-term favourable anatomic and functional improvement in some patients with macular oedema due to CRVO. In the view of these promising preliminary results, we performed a retrospective review of data to compare the morphological and visual acuity outcomes associated with intravitreal injection of triamcinolone acetonide *vs* bevacizumab in the management of macular oedema secondary to CRVO.

Materials and methods

Data collection

We conducted a retrospective review of data of 35 eyes of 35 patients with macular oedema due to CRVO. Medical records were reviewed for all patients with CRVO and macular oedema at the Department of Ophthalmology, Kaohsiung Medical University, Chung-Ho Memorial Hospital between May 2004 and January 2008. Twenty-two eyes accepted 4 mg/0.1 ml intravitreal triamcinolone acetonide and 13 eyes were given off-label 1.25 mg/0.05 ml intravitreal bevacizumab. Patients accepted intravitreal triamcinolone constituted the 'ITA' group and those received intravitreal bevacizumab constituted the 'IBe' group. Informed consent was obtained from all patients.

No cataract surgery was performed either before, in combination with, or after, the intravitreal injection. The

following data were collected: ophthalmic and medical history; duration of symptoms; best-corrected visual acuity (the best-corrected visual acuity was determined from Snellen chart and converted to the logarithm of minimal angle of resolution (LogMAR) equivalents to perform the appropriate statistical manipulation. Counting fingers, and hand movements at 1 m were converted to 1.6 and 1.9, respectively); slit-lamp examination of the anterior segment; intraocular pressure (IOP) measurement (Full auto Tonometer TX-F; Canon, New York, USA); dilated fundus examination with indirect ophthalmoscopy and Goldmann 3-mirror contact lens; and optical coherence tomography (Stratus OCT™ III Model 3000; Zeiss Humphrey, New York, USA). In each patient, the same instrument (optical coherence tomography) was used throughout with 6-mm radial lines employed. Retinal thickness mapping was performed and the 1-mm mean central retinal thickness was recorded.

The patients were initially followed up at the first week post-injection, and twice at two-weekly intervals, then at routine monthly intervals. Repeated injection of ITA or IBe was performed as needed based on the recurrence of macular oedema on optical coherence tomography (OCT) or deterioration in visual acuity. The interval of follow-up examinations was increased to longer periods once the macular oedema resolved or the visual acuity became stable or improved.

Eyes were categorised as nonischaemic CRVO if there was no rubeosis iridis, and capillary nonperfusion on fluorescein angiography less than 10 disc areas. Otherwise, eyes with 10 or more optic disc areas of nonperfusion on fluorescein angiography or rubeosis iridis were classified as ischaemic CRVO.

Main outcome measures were best-corrected visual acuity, macular thickness assessed with OCT, and postoperative complications.

Surgical procedure

All intravitreal injections were performed according to a standard protocol at the Department of Ophthalmology, Kaohsiung Medical University, Chung-Ho Memorial Hospital. The intravitreal injection of triamcinolone acetonide or bevacizumab was performed under sterile conditions in the ophthalmologic operation theatre with an operation microscope. After obtaining informed consent, the affected eye was applied with a drop of proparacaine hydrochloride (0.5%) ophthalmic solution to the ocular surface for local anaesthesia, followed by topical application of 5% Povidone-iodine (Saint-iodine®; Patron, Gangshan, Taiwan) for the lids and conjunctiva before the intravitreal injection. Then, the patient was completely draped. An eyelid speculum was used to stabilise the eyelids. A paracentesis into the

anterior chamber was performed and 0.1 ml of aqueous fluid was aspirated by 26-gauge needle with a 1.0-ml tuberculin syringe to decrease the volume of the eye, thereby avoiding a rise in IOP. The injection of 4 mg (0.1 ml) crystalline triamcinolone acetonide (Kenacort™-A; Bristol-Myers Squibb, Taipei, Taiwan) or 1.25 mg (0.05 ml) bevacizumab (Avastin®, Genentech, San Francisco, USA/Hoffmann La Roche, Basel, Switzerland) into the vitreous cavity was performed through the pars plana 3.5 to 4 mm posterior to the limbus using a sharp 27-gauge needle. The inferior pars plana was preferred to minimise postoperative floaters because the injected triamcinolone acetonide rapidly deposits to dependent areas of the vitreous cavity following treatment. After surgery, an antibiotic eyedrop (Tobramycin-Tobrex®; Alcon, Belgium, China) was applied.

Statistical analysis

The visual acuity was converted to logMAR before analysis. Visual acuity and macular thickness at the baseline and final follow-up visits were summarised using mean ± SD. The change in the visual acuity and macular thickness during follow-up was calculated for each case, and the mean change across all cases was compared between the ITA and IBe groups. Statistical analyses were carried out using commercially available software (SPSS, version 12.0; SPSS Inc., Chicago, IL, USA). For the comparison between ITA and IBe groups (change during follow-up), independent-samples *t*-test was used. To analyse changes before and after treatment in each group (for visual acuity and macular thickness), a paired *t*-test was performed. The level of statistical significance was set at two-tailed *P*-value < 0.05.

Results

Baseline characteristics

A total of 22 cases treated with triamcinolone acetonide between May 2004 and February 2007 and 13 cases

treated with bevacizumab between December 2006 and January 2008 were eligible for analysis. The mean age of the ITA group was 56.45 ± 14.67 years, and the mean age of the IBe group was 61.69 ± 20.30 years. The patients were injected on average 11.77 ± 8.51 days (rang, 4–30 days) after the diagnosis in the ITA group and on average 15.31 ± 8.87 days (rang, 3–30 days) after the diagnosis in the IBe group, respectively. The mean follow-up times were 282.73 ± 70.62 days (ranging from 185 to 423 days) in the ITA group and 253.92 ± 36.10 days (ranging from 220 to 348 days) in the IBe group, respectively. Of the 22 eyes in the ITA group, 19 eyes were assigned as nonischaemic CRVO and 3 eyes (cases 7, 18, 22) were assigned as ischaemic CRVO. Panretinal photocoagulation was performed on these three cases (cases 7, 18, 22) during the follow-up periods to prevent neovascular sequelae. Five of 13 eyes (cases 3, 5, 6, 8, 11) in the IBe group classified as ischaemic CRVO had been treated with panretinal photocoagulation during the follow-up periods as the prophylactic management of the neovascular sequelae. Six patients (cases 10, 17, 18, 19, 20, 21) received one-time reinjection of triamcinolone acetonide between baseline and the follow-up. Six patients (cases 1, 2, 5, 7, 8, 13) received reinjection once and one patient (case 6) received three reinjections of bevacizumab within the follow-up period. There were no significant differences between the two treatment groups with regard to patient age, sex, follow-up period, baseline visual acuity, and retinal thickness. Baseline characteristics by group are summarised in Table 1.

Outcome measures

In the ITA group, visual acuity measurements improved significantly (*P* = 0.007) from 1.00 ± 0.45 LogMAR preoperatively to a final best postoperative visual acuity of 0.69 ± 0.65 LogMAR. Seventeen eyes (77.3%) showed visual acuity improvement, two eyes (9.1%) remained the same, and three eyes (13.6%) became worse during the follow-up period compared with the baseline

Table 1 Baseline clinical characteristics

| | ITA group | IBe group | <i>P</i> -value |
|---|--------------------------------------|-------------------------------------|-----------------|
| Number | 22 patients (22 eyes; 10 right eyes) | 13 patients (13 eyes; 2 right eyes) | |
| Male: Female | 9:13 | 9:4 | 0.105 |
| Mean age (years) | 56.45 ± 14.67 | 61.69 ± 20.30 | 0.383 |
| Mean follow-up time (days) | 282.73 ± 70.62 | 253.92 ± 36.10 | 0.121 |
| Duration of symptom (days) | 11.77 ± 8.51 | 15.31 ± 8.87 | 0.251 |
| Preoperative mean BCVA (LogMAR) | 1.00 ± 0.45 | 1.15 ± 0.59 | 0.400 |
| Preoperative mean central foveal thickness (µm) | 606.32 ± 166.59 | 552.15 ± 140.02 | 0.333 |

P-value calculated using independent-samples *t*-test (age, mean follow-up time, duration of symptom, preoperative mean BCVA, preoperative mean central foveal thickness) and χ^2 test (gender).

BCVA = best-corrected visual acuity; LogMAR = logarithm of minimal angle of resolution; ITA = intravitreal triamcinolone acetonide; IBe = intravitreal bevacizumab.

measurement of the study. Measured in Snellen lines, 12 eyes (54.5%) showed an improvement by at least two Snellen lines or more (Table 2). In the IBe group, visual acuity measurements also improved significantly ($P = 0.035$) from 1.15 ± 0.59 LogMAR preoperatively to a final best postoperative visual acuity of 1.01 ± 0.66 LogMAR. Seven eyes (53.8%) showed visual acuity improvement, four eyes (30.8%) remained the same, and two eyes (15.4%) became worse during the follow-up period compared with the baseline measurement of the study. Measured in Snellen lines, three eyes (23.1%) showed an improvement by at least two Snellen lines or more (Table 3). However, the differences between these two treatment groups with respect to change in visual acuity were not statistically significant ($F = 1.723$, $P = 0.240$) (Figure 1a).

The decline of cotton wool spots, retinal haemorrhage, and macular oedema were noted at all the cases in these two groups during fundus examination after intravitreal injection of triamcinolone acetonide or bevacizumab, and the fluorescein angiography showed vascular leakage decrease postoperatively.

The OCT examination of the ITA group showed clinical improvement in macular oedema ($P < 0.001$)

postoperatively. The preinjection foveal thickness ranged from 345 to 895 μm (mean, $606.32 \pm 166.59 \mu\text{m}$). The final foveal thickness ranged from 169 to 753 μm (mean, $339.36 \pm 192.33 \mu\text{m}$) with an average decrease of 44.11% in foveal thickness (Table 2). In the IBe group, the foveal thickness measured by OCT between baseline and postoperative data also show significant resolution ($P < 0.001$). The preinjection foveal thickness ranged from 332 to 718 μm (mean, $552.15 \pm 140.02 \mu\text{m}$). The final foveal thickness ranged from 117 to 509 μm (mean, $280.23 \pm 119.22 \mu\text{m}$) with an average decrease of 48.01% in foveal thickness (Table 3). However, changes in the foveal thickness did not statistically significantly differ between these two treatment groups ($F = 1.814$, $P = 0.832$) (Figure 1b).

Recurrence of macular oedema and a concomitant decrease in visual acuity occurred in six cases of the ITA group (cases 10, 17, 18, 19, 20, 21) with an average of 226.50 ± 61.50 days (ranging from 133 to 295 days) postoperatively, and in seven cases of the IBe group (cases 1, 2, 5, 6, 7, 8, 13) with an average of 86.78 ± 46.80 days (ranging from 35 to 168 days) postoperatively. Subsequently, all these six patients in the ITA group accepted a second injection of triamcinolone acetonide.

Table 2 Clinical data of the patients before and after intravitreal injection of triamcinolone acetonide

| Case no. | Age | Gender | Type | Preoperative data | | Postoperative data | | | Visual acuity improvement | Visual acuity improvement ≥ 2 Snellen lines | |
|----------|-----|--------|--------------|-------------------|------------------------------------|---------------------|--|-----------------------------|---------------------------|--|------------------|
| | | | | BCVA (LogMAR) | Foveal thickness (μm) | Final BCVA (LogMAR) | Final foveal thickness (μm) | Foveal thickness change (%) | | | Follow-up (days) |
| 1 | 49 | F | Nonischaemia | 1.0 | 590 | 0.7 | 210 | -64.41 | 220 | Yes | No |
| 2 | 70 | F | Nonischaemia | 1.0 | 597 | 0.3 | 203 | -66.00 | 273 | Yes | Yes |
| 3 | 66 | M | Nonischaemia | 1.0 | 663 | 0.4 | 190 | -71.34 | 185 | Yes | Yes |
| 4 | 46 | M | Nonischaemia | 0.5 | 632 | 0.0 | 180 | -71.52 | 251 | Yes | Yes |
| 5 | 77 | M | Nonischaemia | 1.0 | 623 | 1.1 | 603 | -3.21 | 190 | No | No |
| 6 | 53 | F | Nonischaemia | 1.0 | 579 | 0.7 | 221 | -61.83 | 331 | Yes | No |
| 7 | 70 | F | Ischaemia | 1.6 | 889 | 1.6 | 742 | -16.54 | 223 | No | No |
| 8 | 75 | M | Nonischaemia | 1.4 | 775 | 1.1 | 703 | -9.29 | 235 | Yes | No |
| 9 | 75 | F | Nonischaemia | 0.4 | 483 | -0.1 | 188 | -61.08 | 238 | Yes | Yes |
| 10 | 51 | F | Nonischaemia | 1.3 | 848 | 0.5 | 300 | -64.62 | 363 | Yes | Yes |
| 11 | 68 | F | Nonischaemia | 1.3 | 369 | 0.3 | 333 | -9.76 | 217 | Yes | Yes |
| 12 | 45 | F | Nonischaemia | 0.7 | 854 | 0.3 | 280 | -67.21 | 303 | Yes | Yes |
| 13 | 57 | M | Nonischaemia | 1.0 | 587 | 0.2 | 169 | -71.21 | 272 | Yes | Yes |
| 14 | 24 | F | Nonischaemia | 0.5 | 526 | 0.0 | 193 | -63.31 | 274 | Yes | Yes |
| 15 | 24 | F | Nonischaemia | 0.5 | 345 | 0.1 | 219 | -36.52 | 191 | Yes | Yes |
| 16 | 69 | F | Nonischaemia | 1.6 | 613 | 1.3 | 413 | -32.63 | 275 | Yes | No |
| 17 | 55 | M | Nonischaemia | 0.3 | 350 | 0.0 | 221 | -36.86 | 393 | Yes | Yes |
| 18 | 64 | F | Ischaemia | 1.2 | 459 | 1.4 | 352 | -23.31 | 382 | No | No |
| 19 | 51 | M | Nonischaemia | 0.7 | 435 | 0.1 | 194 | -55.40 | 423 | Yes | Yes |
| 20 | 56 | M | Nonischaemia | 1.5 | 649 | 1.3 | 355 | -45.30 | 319 | Yes | No |
| 21 | 49 | F | Nonischaemia | 0.5 | 578 | 1.9 | 444 | -23.18 | 375 | No | No |
| 22 | 48 | M | Ischaemia | 1.9 | 895 | 1.9 | 753 | -15.87 | 287 | No | No |

BCVA = best-corrected visual acuity; F = female; LogMAR = logarithm of minimal angle of resolution; M = male.

Table 3 Clinical data of the patients before and after intravitreal injection of bevacizumab

| Case no. | Age | Gender | Type | Preoperative data | | Postoperative data | | | Visual acuity improvement | Visual acuity improvement ≥ 2 Snellen lines | |
|----------|-----|--------|--------------|-------------------|------------------------------------|---------------------|--|-----------------------------|---------------------------|--|------------------|
| | | | | BCVA (logMAR) | Foveal thickness (μm) | Final BCVA (logMAR) | Final foveal thickness (μm) | Foveal thickness change (%) | | | Follow-up (days) |
| 1 | 37 | M | Nonischaemia | 0.3 | 617 | 0.0 | 330 | -46.52 | 229 | Yes | Yes |
| 2 | 84 | M | Nonischaemia | 1.6 | 591 | 1.6 | 340 | -42.47 | 220 | No | No |
| 3 | 55 | F | Ischaemia | 1.4 | 324 | 1.5 | 175 | -45.99 | 263 | No | No |
| 4 | 79 | F | Nonischaemia | 1.6 | 574 | 1.6 | 117 | -79.62 | 348 | No | No |
| 5 | 42 | M | Ischaemia | 1.0 | 647 | 1.1 | 343 | -46.99 | 281 | No | No |
| 6 | 81 | M | Ischaemia | 1.0 | 442 | 1.0 | 389 | -11.99 | 241 | No | No |
| 7 | 32 | M | Nonischaemia | 1.6 | 718 | 1.0 | 171 | -76.18 | 282 | Yes | No |
| 8 | 86 | M | Ischaemia | 1.9 | 385 | 1.6 | 141 | -63.38 | 248 | Yes | No |
| 9 | 31 | M | Nonischaemia | 0.0 | 332 | -0.2 | 205 | -38.25 | 223 | Yes | Yes |
| 10 | 76 | F | Nonischaemia | 1.6 | 708 | 1.5 | 261 | -63.14 | 251 | Yes | No |
| 11 | 63 | F | Ischaemia | 1.5 | 588 | 1.4 | 509 | -13.44 | 220 | Yes | No |
| 12 | 64 | M | Nonischaemia | 0.4 | 538 | 0.0 | 241 | -55.20 | 225 | Yes | Yes |
| 13 | 72 | M | Nonischaemia | 1.0 | 714 | 1.0 | 421 | -41.04 | 270 | No | No |

BCVA = best-corrected visual acuity; F = female; LogMAR = logarithm of minimal angle of resolution; M = male.

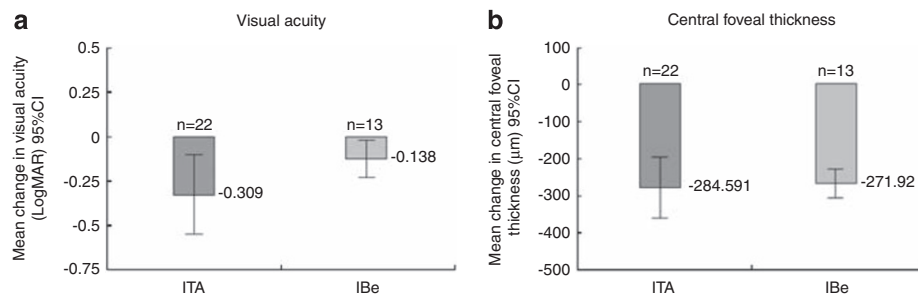


Figure 1 Comparison between the ITA group and the IBe group for changes in mean visual acuity (a) and mean central foveal thickness (b) postoperatively. Negative values represent an increase in visual acuity and a reduction in central foveal thickness. For the ITA group and the IBe group, neither visual acuity improvement nor central foveal thickness reduction shows a significant difference between the two groups. ($P=0.240$ in visual acuity improvement and $P=0.832$ in central foveal thickness reduction).

In the IBe group, six cases received reinjection once and one case (case 6) received reinjection thrice of bevacizumab. After that the macular oedema in all 13 patients subsided and visual acuity improved again in four patients (cases 10, 17, 19, 20) of the ITA group and in three patients (cases 1, 7, 8) of the IBe group, respectively.

Seven patients (31.82%) in the ITA group had ocular hypertension (IOP ≥ 22 mm Hg) postoperatively. Six patients (cases 2, 12, 14, 20, 21, 22) could be controlled to a normal range by topical antiglaucomatous medication. One patient (case 19) required trabeculectomy. No cases of neovascular glaucoma occurred. There was no case with increase in IOP after intravitreal injection in the IBe group.

In the ITA group, 19 cases were assigned as nonischaemic CRVO and three patients (case 7, 18, 22) were assigned as ischaemic CRVO. In the IBe group,

eight cases were classified as nonischaemic CRVO and five patients (cases 3, 5, 6, 8, 11) were classified as ischaemic CRVO. Panretinal photocoagulation was performed on these eight cases with ischaemic CRVO during the follow-up periods to prevent neovascular sequelae. Those who were ischaemic CRVO had no significant improvement in visual acuity ($P=0.058$ in the ITA group; $P=0.14$ in the IBe group) and those who were nonischaemic CRVO had significant visual acuity improvement ($P=0.007$ in the ITA group; $P=0.035$ in the IBe group) at the end of the follow-up.

Adverse events

Excluding elevated IOP, no obvious complication was noted in the ITA group postoperatively, except for one patient (case 21) who developed a mature cataract during

follow-up. No increase in IOP and no cataract progression were observed in the IBe group postoperatively. No serious side effects were observed throughout the study. No systemic or serious drug-related adverse events were observed. Both treatment procedures were well tolerated and no clinical evidence of inflammation, uveitis, postoperative endophthalmitis, retinal detachment, or ocular toxicity occurred.

Discussion

As far as we know, and according to Medline searches, this study is the first retrospective data to compare intravitreal triamcinolone with bevacizumab for management of patients with maculae oedema secondary to CRVO. Best-corrected visual acuity and foveal thickness were used to evaluate disease control. In this study, intravitreal injection of triamcinolone acetonide provided similar therapeutic efficacy in patients with macular oedema due to CRVO compared with intravitreal injection of bevacizumab in the short-term.

These patients of the ITA group experienced a significant increase in visual acuity ($P = 0.007$) from 1.00 ± 0.45 LogMAR preoperatively to a final best postoperative visual acuity of 0.69 ± 0.65 LogMAR, and those in the IBe group also had significant visual acuity improvement ($P = 0.035$) from 1.15 ± 0.59 LogMAR preoperatively to a final best postoperative visual acuity of 1.01 ± 0.66 LogMAR. We observed significant improvement in central foveal thickness after intravitreal injection of intravitreal triamcinolone acetonide (average decrease percentage: 44.11%, $P < 0.001$) or bevacizumab (average decrease percentage: 48.01%, $P < 0.001$). From our results, both intravitreal triamcinolone acetonide and bevacizumab have been shown to decrease vascular leakage and improve the anatomical and functional outcomes in patients with macula oedema associated with CRVO. However, the changes in visual acuity and foveal thickness did not show significant differences between the ITA group and the IBe group ($P = 0.240$ in visual acuity improvement and $P = 0.832$ in foveal thickness decrease). Therefore, the overall results of our study suggest that intravitreal injection of triamcinolone acetonide may have the same beneficial effects on vision and macular remodelling with intravitreal injection of bevacizumab for the short-term management of macula oedema associated with CRVO.

The mechanism of action of corticosteroids for macular oedema in CRVO is still under investigation, but it is postulated that anti-inflammation, vascular endothelial growth factor downregulation, and antipermeability functions of corticosteroid were the major roles for its effect.^{20–22} Park *et al*¹¹ reported that after administration

of 4 mg intravitreal triamcinolone acetonide for macular oedema due to nonischaemic CRVO, all 10 eyes showed biomicroscopic improvement in cystoid macular oedema with visual gain and 6 of 10 eyes had ≥ 2 lines of visual improvement. Williamson and O'Donnell¹⁴ showed the use of intravitreal triamcinolone acetonide for the treatment of macular oedema associated with nonischaemic CRVO. This prospective study showed a significant visual acuity benefit as well as biomicroscopic and volumetric OCT improvement in macular oedema. Those results were similar to the findings in our study.

Intravitreal bevacizumab was first used by Rosenfeld *et al*²³ as a treatment for macular oedema related to CRVO. Consequently, there have been other reports of short-term beneficial effect of intravitreal bevacizumab to treat macular oedema secondary to retinal vascular disease, including branch retinal vein occlusion^{24,25} and diabetic retinopathy.^{26,27} More recently, Ferrara *et al*²⁸ reported a dramatic improvement in the visual acuity and clinical fundus appearance with significant macular thickness reduction after the early intravitreal bevacizumab injections. In our case series, we observed significant improvement in visual acuity and central foveal thickness decrease after injection of 1.25 mg bevacizumab.

Recent clinical and experimental studies have demonstrated that intravitreal triamcinolone acetonide or bevacizumab have been shown to be nontoxic to the retina.^{29–35} The most common side effect reported after intravitreal injection of triamcinolone acetonide is the risk of IOP elevation.^{13,14,17} In this study, seven of 22 CRVO patients without preexisting glaucoma developed steroid-induced elevated IOP after intravitreal triamcinolone acetonide injection and six were controlled with topical antiglaucomatous medication but one needed trabeculectomy. In the IBe group, the IOP was normal even after intravitreal injection. It is important to point out that ITA has a higher risk of short-term elevation of IOP than IBe. Additionally, the incidence of cataract formation may increase with ITA treatments.^{11,13} In our study, one case (case 21) in the ITA group developed mature cataracts and visual acuity deterioration during the follow-up. For these reasons, intravitreal bevacizumab may be an attractive alternative therapeutic option for phakic patients and steroid responders because it provides visual acuity improvement and macular thickness reduction without the side effects of ocular hypertension and cataract progression. Additional injection-related complications reported in other studies, such as conjunctival ulceration,³⁶ retinal detachment,³⁷ infectious, or non-infectious endophthalmitis,^{37–39} were not observed in our study.

The effects of intravitreal triamcinolone acetonide or bevacizumab are not permanent, and the period of the

effect is related to its clearance from the eye. Cekic *et al*¹³ showed that the eyes requiring second injection were performed at an average of 7 months after the first injection, and third injections were at 12 months, thus indicating that the therapeutic effect of triamcinolone acetonide probably persisted 6–7 months with CRVO and hemiretinal vein occlusion. Hsu *et al*⁴⁰ reported that the duration of IBe effect appears to be limited to 2 months for most CRVO patients. These are similar to our findings that average recurrence duration was 226.50 ± 61.50 days in the ITA group and 86.78 ± 46.80 days in the IBe group, respectively. According to the above results, ITA seems to persist longer than IBe, which may allow a more prolonged inhibition of VEGF and reduce the numbers of reinjections. Another merit of triamcinolone acetonide is the relatively low price compared with bevacizumab. In our country, bevacizumab is far more expensive than triamcinolone acetonide.

Ip *et al*¹² showed that both nonischaemic and ischaemic eyes with CRVO had a significant decrease in retinal thickness after administration of intravitreal triamcinolone acetonide. However, only nonischaemic eyes showed statistically significant visual acuity improvement at each time point. Priglinger *et al*⁴¹ reported that the efficacy of intravitreal bevacizumab was similar between non-ischaemic CRVO and ischaemic CRVO. However, ischaemic CRVO was associated with significantly lower visual acuity than nonischaemic CRVO ($P < 0.001$). In our case series, 27 patients were classified as nonischaemic CRVO (19 patients in the ITA group and 8 patients in the IBe group) and eight patients (three patients in the ITA group and five patients in the IBe group) were classified as ischaemic CRVO. Those who were ischaemic CRVO had no improvement in visual acuity ($P = 0.058$ in the ITA group; $P = 0.14$ in the IBe group) and those who were nonischaemic CRVO had visual acuity improvement ($P = 0.007$ in the ITA group; $P = 0.035$ in the IBe group) at the end of the follow-up, favoring improvement for the nonischaemic group. From this study, we observed that patients with nonischaemic CRVO have both good anatomical and visual outcomes to intravitreal triamcinolone acetonide or bevacizumab injection. Patients with ischaemic CRVO also have a favourable anatomical response, but do not appear to respond as well functionally. It does imply that nonischaemic patients may have a better outcome to intravitreal triamcinolone acetonide or bevacizumab. However, these results should be interpreted with caution due to the small sample size of ischaemic eyes compared with nonischaemic eyes.

The major shortcomings of our study are small sample size in both the ITA and the IBe group, the retrospective study design, inadequate follow-up duration, non-standardised guidelines for repeated injection, and

nonrandomised trial. Large prospective, randomised clinical trials are necessary to compare the long-term efficacy and safety of intravitreal triamcinolone acetonide and bevacizumab for patients with macular oedema associated with CRVO.

Conclusion

In conclusion, intravitreal injection of 4 mg triamcinolone acetonide appears to provide the same short-term advantages with 1.25 mg IBe for the management of patients with macula oedema secondary to CRVO. Intraocular steroid or anti-VEGF can cause rapid resolution of oedema and visual acuity improvement but the effects are not permanent. Reinjections may be necessary in some patients. The potential benefits for intravitreal triamcinolone acetonide to manage macular oedema associated with CRVO are the relatively low cost and longer half-life. However, the well-known adverse effects of triamcinolone acetonide must be considered.

References

- 1 Hayreh SS. Classification of central retinal vein occlusion. *Ophthalmology* 1983; **90**(5): 458–474.
- 2 Green WR, Chan CC, Hutchins GM, Terry JM. Central retinal vein occlusion: a prospective histopathologic study of 29 eyes in 28 cases. *Trans Am Ophthalmol Soc* 1981; **79**: 371–422.
- 3 Natural history and clinical management of central retinal vein occlusion. The Central Vein Occlusion Study Group. *Arch Ophthalmol* 1997; **115**(4): 486–491.
- 4 Evaluation of grid pattern photocoagulation for macular oedema in central vein occlusion. The Central Vein Occlusion Study Group M report. *Ophthalmology* 1995; **102**(10): 1425–1433.
- 5 McAllister IL, Douglas JP, Constable IJ, Yu DY. Laser-induced chorioretinal venous anastomosis for nonischemic central retinal vein occlusion: evaluation of the complications and their risk factors. *Am J Ophthalmol* 1998; **126**(2): 219–229.
- 6 Elman MJ, Raden RZ, Carrigan A. Intravitreal injection of tissue plasminogen activator for central retinal vein occlusion. *Trans Am Ophthalmol Soc* 2001; **99**: 219–221; discussion 222–213.
- 7 Weiss JN, Bynoe LA. Injection of tissue plasminogen activator into a branch retinal vein in eyes with central retinal vein occlusion. *Ophthalmology* 2001; **108**(12): 2249–2257.
- 8 Mirshahi A, Roohipoor R, Lashay A, Mohammadi SF, Mansouri MR. Surgical induction of chorioretinal venous anastomosis in ischaemic central retinal vein occlusion: a non-randomised controlled clinical trial. *Br J Ophthalmol* 2005; **89**(1): 64–69.
- 9 Opremcak EM, Bruce RA, Lomeo MD, Ridenour CD, Letson AD, Rehmar AJ. Radial optic neurotomy for central retinal vein occlusion: a retrospective pilot study of 11 consecutive cases. *Retina* 2001; **21**(5): 408–415.
- 10 Greenberg PB, Martidis A, Rogers AH, Duker JS, Reichel E. Intravitreal triamcinolone acetonide for macular oedema

- due to central retinal vein occlusion. *Br J Ophthalmol* 2002; **86**(2): 247–248.
- 11 Park CH, Jaffe GJ, Fekrat S. Intravitreal triamcinolone acetonide in eyes with cystoid macular oedema associated with central retinal vein occlusion. *Am J Ophthalmol* 2003; **136**(3): 419–425.
 - 12 Ip MS, Gottlieb JL, Kahana A, Scott IU, Altaweel MM, Blodi BA *et al*. Intravitreal triamcinolone for the treatment of macular oedema associated with central retinal vein occlusion. *Arch Ophthalmol* 2004; **122**(8): 1131–1136.
 - 13 Cekic O, Chang S, Tseng JJ, Barile GR, Weissman H, Del Priore LV *et al*. Intravitreal triamcinolone treatment for macular oedema associated with central retinal vein occlusion and hemiretinal vein occlusion. *Retina* 2005; **25**(7): 846–850.
 - 14 Williamson TH, O'Donnell A. Intravitreal triamcinolone acetonide for cystoid macular oedema in nonischemic central retinal vein occlusion. *Am J Ophthalmol* 2005; **139**(5): 860–866.
 - 15 Gelston CD, Olson JL, Mandava N. Macular oedema in central retinal vein occlusion treated with intravitreal triamcinolone. *Acta Ophthalmol Scand* 2006; **84**(3): 314–318.
 - 16 Goff MJ, Jumper JM, Yang SS, Fu AD, Johnson RN, McDonald HR *et al*. Intravitreal triamcinolone acetonide treatment of macular oedema associated with central retinal vein occlusion. *Retina* 2006; **26**(8): 896–901.
 - 17 Gregori NZ, Rosenfeld PJ, Puliafito CA, Flynn Jr HW, Lee JE, Mavroufides EC *et al*. One-year safety and efficacy of intravitreal triamcinolone acetonide for the management of macular oedema secondary to central retinal vein occlusion. *Retina* 2006; **26**(8): 889–895.
 - 18 Iturralde D, Spaide RF, Meyerle CB, Klancnik JM, Yannuzzi LA, Fisher YL *et al*. Intravitreal bevacizumab (Avastin) treatment of macular oedema in central retinal vein occlusion: a short-term study. *Retina* 2006; **26**(3): 279–284.
 - 19 Campochiaro PA, Hafiz G, Shah SM, Nguyen QD, Ying H, Do DV *et al*. Ranibizumab for macular oedema due to retinal vein occlusions; implication of VEGF as a critical stimulator. *Mol Ther* 2008; **16**(4): 791–799.
 - 20 Viores SA, Youssri AI, Luna JD, Chen YS, Bhargava S, Viores MA *et al*. Upregulation of vascular endothelial growth factor in ischemic and non-ischemic human and experimental retinal disease. *Histol Histopathol* 1997; **12**(1): 99–109.
 - 21 Pe'er J, Folberg R, Itin A, Gnessin H, Hemo I, Keshet E. Vascular endothelial growth factor upregulation in human central retinal vein occlusion. *Ophthalmology* 1998; **105**(3): 412–416.
 - 22 Fischer S, Renz D, Schaper W, Karliczek GF. *In vitro* effects of dexamethasone on hypoxia-induced hyperpermeability and expression of vascular endothelial growth factor. *Eur J Pharmacol* 2001; **411**(3): 231–243.
 - 23 Rosenfeld PJ, Fung AE, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for macular oedema from central retinal vein occlusion. *Ophthalmic Surg Lasers Imaging* 2005; **36**(4): 336–339.
 - 24 Kreutzer TC, Alge CS, Wolf AH, Kook D, Burger J, Strauss R *et al*. Intravitreal bevacizumab for the treatment of macular oedema secondary to branch retinal vein occlusion. *Br J Ophthalmol* 2008; **92**(3): 351–355.
 - 25 Wu L, Arevalo JF, Roca JA, Maia M, Berrocal MH, Rodriguez FJ *et al*. Comparison of two doses of intravitreal bevacizumab (avastin) for treatment of macular oedema secondary to branch retinal vein occlusion: results from the Pan-American Collaborative Retina Study Group at 6 months of follow-up. *Retina* 2008; **28**(2): 212–219.
 - 26 Haritoglou C, Kook D, Neubauer A, Wolf A, Priglinger S, Strauss R *et al*. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular oedema. *Retina* 2006; **26**(9): 999–1005.
 - 27 Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, Sanchez JG, Wu L, Maia M *et al*. Primary intravitreal bevacizumab (Avastin) for diabetic macular oedema: results from the Pan-American Collaborative Retina Study Group at 6-month follow-up. *Ophthalmology* 2007; **114**(4): 743–750.
 - 28 Ferrara DC, Koizumi H, Spaide RF. Early bevacizumab treatment of central retinal vein occlusion. *Am J Ophthalmol* 2007; **144**(6): 864–871.
 - 29 McCuen II BW, Bessler M, Tano Y, Chandler D, Machermer R. The lack of toxicity of intravitreally administered triamcinolone acetonide. *Am J Ophthalmol* 1981; **91**(6): 785–788.
 - 30 Hida T, Chandler D, Arena JE, Machermer R. Experimental and clinical observations of the intraocular toxicity of commercial corticosteroid preparations. *Am J Ophthalmol* 1986; **101**(2): 190–195.
 - 31 Kivilcim M, Peyman GA, El-Dessouky ES, Kazi AA, Cheema R, Hegazy H. Retinal toxicity of triamcinolone acetonide in silicone-filled eyes. *Ophthalmic Surg Lasers* 2000; **31**(6): 474–478.
 - 32 Luthra S, Narayanan R, Marques LE, Chwa M, Kim DW, Dong J *et al*. Evaluation of *in vitro* effects of bevacizumab (Avastin) on retinal pigment epithelial, neurosensory retinal, and microvascular endothelial cells. *Retina* 2006; **26**(5): 512–518.
 - 33 Manzano RP, Peyman GA, Khan P, Kivilcim M. Testing intravitreal toxicity of bevacizumab (Avastin). *Retina* 2006; **26**(3): 257–261.
 - 34 Shahar J, Avery RL, Heilweil G, Barak A, Zemel E, Lewis GP *et al*. Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin). *Retina* 2006; **26**(3): 262–269.
 - 35 Maturi RK, Bleau LA, Wilson DL. Electrophysiologic findings after intravitreal bevacizumab (Avastin) treatment. *Retina* 2006; **26**(3): 270–274.
 - 36 Agrawal S, Agrawal J, Agrawal TP. Conjunctival ulceration following triamcinolone injection. *Am J Ophthalmol* 2003; **136**(3): 539–540.
 - 37 Jonas JB, Spandau UH, Schlichtenbrede F. Short-term complications of intravitreal injections of triamcinolone and bevacizumab. *Eye* 2008; **22**(4): 590–591.
 - 38 Nelson ML, Tennant MT, Sivalingam A, Regillo CD, Belmont JB, Martidis A. Infectious and presumed noninfectious endophthalmitis after intravitreal triamcinolone acetonide injection. *Retina* 2003; **23**(5): 686–691.
 - 39 Roth DB, Chieh J, Spirn MJ, Green SN, Yarian DL, Chaudhry NA. Noninfectious endophthalmitis associated with intravitreal triamcinolone injection. *Arch Ophthalmol* 2003; **121**(9): 1279–1282.
 - 40 Hsu J, Kaiser RS, Sivalingam A, Abraham P, Fineman MS, Samuel MA *et al*. Intravitreal bevacizumab (Avastin) in central retinal vein occlusion. *Retina* 2007; **27**(8): 1013–1019.
 - 41 Priglinger SG, Wolf AH, Kreutzer TC, Kook D, Hofer A, Strauss RW *et al*. Intravitreal bevacizumab injections for treatment of central retinal vein occlusion: six-month results of a prospective trial. *Retina* 2007; **27**(8): 1004–1012.