EFFECTIVNESS OF INTRAVITREAL RANIBIZUMAB (LUCENTIS) IN ACUTE CENTRAL SEROUS CHORIORETINOPATHY TREATMENT

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ABSTRACT:

Background/Aims: *To study the effectiveness of intravitreal ranibizumab injection (IVR) in the treatment of acute central serous chorioretinopathy (CSCR).*

Methods: *A Prospective, randomized, single-center, parallel-arm, controlled trial study the involved patients had symptoms of CSCR with less than 3 months duration. Patients (n = 50/ divided into 2 groups) the anti-VEGF group with 30 patients injected with intravitreal Ranibizumab(IVR) (0.5 mg/0.05 ml) and an observation group where 20 patients were observed, each group were followed for 4 months. Best-corrected visual acuity (BCVA), and central macular thickness (CMT) were assessed by Ocular coherent tomography (OCT) for first baseline and then at regular follow-ups.*

Results: *All patients had improved and increased BCVA, with decreased CMT, and resolution of the subretinal fluid. The mean CMT in IVR and observation groups was 117.33±46.2µm and 196.70±36.9µm, respectively (*P *= 0.670) The mean BCVA and mean CMT improved significantly in both groups at 4 weeks , but the changes were not significantly different between both groups at 4months.*

Conclusions: *both IVR and observation for acute CSCR improved the resolution of subretinal fluid. BCVA and CMT did not differ at 4 months, between IVR and observation groups. So we advised a Further studies are required to determine the long-term benefits of IVR.*

Keywords*: Central Serous Chorioretinopathy (CSCR), Intravitreal Ranibizumab (IVR), best-corrected visual acuity (BCVA), central Macular thickness (CMT), Ocular coherent tomography (OCT).*

INTRODUCTION:

Central Serous Chorioretinopathy (CSCR) is manifested by a serous detachment of the neurosensory retina, with dysfunction of the retinal pigment epithelium (RPE) affecting macular area[(1)].

It affects males more than females, between the third and fifth decades of life. Certain factors related to its appearance such as emotional stress, type A personality, pregnancy, use of systemic corticosteroids, collagen vascular diseases (systemic lupus), and endocrine disorders such as Cushing's syndrome[(2)].

CSCR has two forms of presentation:

a) Acute, accumulation of subretinal fluid between the external segment of the photoreceptors and the RPE, which usually resolves spontaneously, and **b)** Chronic CSCR (lasting 3+ months): presence of focal and diffuse alterations in RPE with persistent sensorineural retinal detachment, which can evolve into foveal atrophy, and damage to the foveal photoreceptor layer, resulting in significant and irreversible vision loss [(3)].

Clinically, CSCR manifests itself most often as a unilateral lesion, blurred vision, micropsia, metamorphopsia, hyperopia (temporary), impaired color vision, and in some cases relative central or paracentral scotoma[(4)].

Medical treatment of CSCR have been used, the administration of low doses of acetylsalicylic (aspirin) improved visual

acuity and reduced recurrence of CSCR[5]. There is some controversy regarding certain more aggressive treatment alternatives such as argon laser or micro pulsed diode and photodynamic therapy (PDT), which are useful in chronic CSCR[3].

Recently, the intravitreal injection of antibodies against vascular endothelial growth factor (VEGF) has been proposed as a new therapeutic option based on the anti-permeability effect. Several reports have demonstrated acceptable results after intravitreal injection of the anti-VEGF agents[6-9].

AIM OF THE WORK:

As a result, this research was designed to compare the efficacy of intravitreal Ranibizumab when given immediately at time of diagnosis vs observation for the treatment of eyes with acute CSCR in Libyan population.

PATIENTS AND METHODS:

A Prospective, randomized, single-center, parallel-arm, controlled trial involved50 eyes of 50 patients presented to the outpatient department with acute CSCR. The patients divided randomly into two groups: the observation group (receiving no treatment) included 20 patients and the injected (anti-VEGF) group/ranibizumab group (IVR) which included 30 Patients. Both groups were followed for 4 months of period.

Inclusion criteria all patients older than 18 years, diagnosed as acute CSCR based on dilated fundus examination and an OCT picture showing subretinal fluid with duration less than 3 months. Patient with history more than 3 months and previous attack of acute CSCR, or with previous intraocular surgery, laser therapy or receiving previous treatment for CSCR, patients with history of thromboembolic conditions, including stroke, transient ischemic attacks, and myocardial infarction were excluded.

All patients followed post injection at 4-week, 2 months until 4 months. All findings from baseline and each visit were reported and compared.

Examination methods:

Detailed examination was performed pre & post injection including the best corrected visual acuity BCVA (which was converted into logarithm of the minimum angle resolution (Log MAR) for statistical analysis), slit-lamp examination of anterior segments and dilated fundus examination with stereoscopic +66D lens performed. Intraocular pressure pre and post injection was measured by Goldmann applanation tonometry. Ocular coherent tomography (OCT) by Topcon 3D OCT-2000 spectral-domain (ver. 8.01) (scan mode 3D [6.0 mm × 6.0 mm – 512 × 128]) was used to assess the subretinal fluid and to measure the Central macular thickness (CMT).

Dose of intravitreal Anti VEGF:

All patients in the injected group received a one injection of intravitreal Ranibizumab (IVR) in the operation room and under complete aseptic conditions. Under topical anesthesia, the dose of ranibizumab (0.5 mg in 0.05 ml) was injected pars plana.

Main outcome measures:

The primary outcome was the complete resolution for subretinal fluid during follow-up, and the secondary outcome was changes in BCVA and CMT.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS version 23.0; IBM Corporation, Armonk, New York, United States) used. Data presented as mean ± standard deviation and frequencies. A p-value $\leq$ 0.05 considered statistically significant

Ethical consideration:

This study received approval from ethics research committee of Benghazi teaching eye hospital and adhered to the principle of declaration of Helsinki [10/04/2023]. Before being included in this study written consent was obtained from all participants. Each patient has explained the nature of this study, its purpose, procedures, duration, potential risks and benefits involved , as well as any discomfort it might cause.

Each patient was informed that participation was voluntary, they could withdraw from this study at any time without giving explanations, and their decision to withdraw would not affect their medical treatment or their relationship with the treating physician.

RESULTS:

The 50 patients with 50 eyes , were 20 for the observation group and 30 were in the anti-VEGF group/ranibizumab (injected) group (IVR)

For the injected group, mean age was 45.43±1.2 years with 18 male eyes (60%), and in the observation group the mean age was 45.40±1.62 years with 13 male eyes (65%), the characteristics of the study groups before treatment are shown in Table.(1).

Table 1: Demographic and clinical characteristics of the study groups

	Injected (n = 30)	Observed (n = 20)	p- value
Age	45.43±1.24	45.40±1.62	0.487
Gender M/F	18/12	13/7	0.104
Intraocular pressure	19.28±.71	19.02±.49	0.600
Baseline (BCVA Log MAR)	.95±.30	.87± .20	0.323
Baseline mean central macular thickness (µm)	723.63±129.11	565.35±77.04	0.071

M/F=male/female; BCVA=best-corrected visual acuity; log MAR = logarithm of the minimal angle of resolution

For both study groups a complete or near complete resolution of subretinal fluid with demonstrated improvement in visual acuity during the follow-up period.

Best corrected visual acuity Log MAR improved significantly in the injected group (IVR) from .95±.30 before treatment to .08±.04 after treatment, and in the observation, group improved significantly by time from .87± .20 to .13± .07 ($p< 0.0001$, $p= 0.001$ respectively), see Table (2).

Although a statistically significant improvement in the BCVA Log MAR in both group after 4 months, but there is no statistically significant difference between the 2 groups ($p=.07$), Diagram (1).

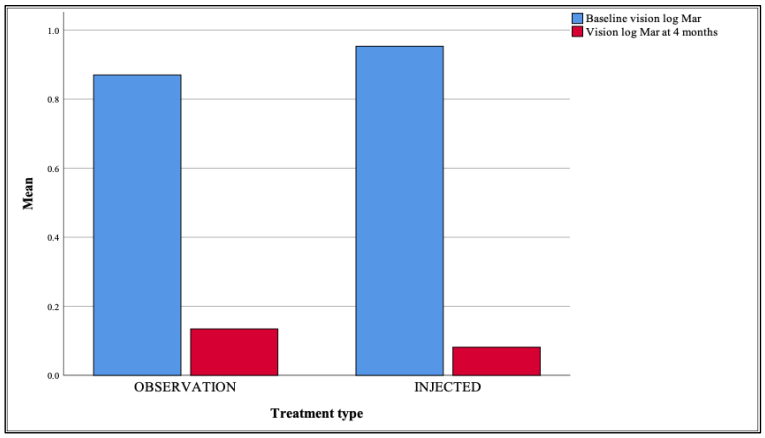

Diagram 1: changes in the Best corrected visual acuity log Mar of the study groups from baseline to the end of follow-up.

In the final visit at (4 months), the mean CMT in the injected group (IVR) and observation groups were 117.33±46.2µm and 196.70±36.9µm, respectively (*P* =0.670) Table (2).

Table 2: Changes in the vision and macular thickness of the study groups from baseline to the end of follow-up.

	Injected (IVR) (n = 30)	Observed (n = 20)
Best corrected visual acuity (BCVA log Mar)		
Baseline	.95±.30	.87± .20
After 4 months	.08± .04	.13± .07
Mean central macular thickness (µm)		
Baseline	723.63±129.11	565.35±77.04
4 weeks	323.00±97.01	418.75±79.84
8 weeks	212.12±90.24	294.40±83.38
4 months	117.33±46.21	196.70±36.98

IVR= Intravitreal Ranibizumab

In the first visit at (4 weeks), the mean CMT in the injected group (IVR) and observation groups were 723.63±129.11µm and 565.35±77.04µm reduced to 323.00±97.01 µm and 418.75±79.84 µm respectively with statistically significant P value (0.002).

A two-ways repeated measures ANOVA was performed for evaluation of the effective treatment over time on self-esteem score.

There is a statistically significant interaction between type of treatment and time on self-esteem score, F (3,46) =29.246, *p*<.001. Therefore, the effect of treatment variable was analyzed at each time point. *P*-value were adjusted using the Bonferroni multiple testing correction method. All pair wise differences on CMT were statistically significant (P's ≤ .019), Diagram (2).

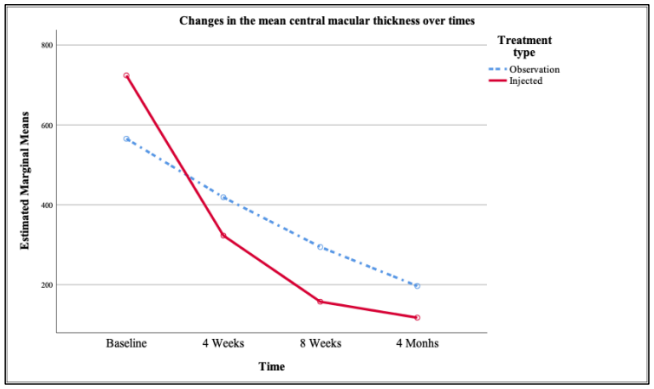

Diagram 2: changes in the mean central macular thickness of the study groups from baseline to the end of follow-up at 4 & 8 weeks.

No detected systemic or ocular complications related to IVR injection during the follow-up period.

DISCUSSION:

Despite the advancement of imaging technology, the pathological mechanism of central serous chorioretinopathy remains unclarified, however several hypotheses have been suggested. The most recently proposed concept is an increase in the permeability of choroidal capillaries[(1)].

Acute CSCR may show a spontaneous improvement in 1-4 months. However,

recurrences within one year are common in 30-50% of patients, and frequent recurrences may cause atrophy of retinal pigment epithelium with changes in the sensory neural retina, which can lead to permanent loss of visual function, so treatments such as photodynamic therapy and intravitreal anti-VEGF injection have been tried[1].

According to *Wang, et al.* early treatment for resolution of CSCR has the advantage of decreasing the rate of RPE degeneration[10].

The focal laser for CSCR is associated with persistent scotoma and the photo-dynamic treatment can lead to secondary RPE alterations with choroidal neovascularization[11-13].

In central serous chorioretinopathy, the anti-VEGF treatment has been used under the assumption that vascular endothelial growth factor (VEGF) is expressed when hypoperfusion and hypoxic conditions occur owing to changes in the function and structure of the choroid and retinal pigment epithelium[14].

It has been reported that inhibiting VEGF by intravitreal injection of anti-VEGF can reduce subretinal fluid by altering the hyperpermeability of choroidal blood vessels[15,16].

We observe a significant improvement in reduction of CMT in first visit in IVR injection group than observation group and this is in agreement with *kim, et al.* and *Tekin, et al.* Bevacizumab or ranibizumab has been proven to enhance anatomical improvement in acute central serous chorioretinopathy quicker than the observation group[17,18].

Bevacizumab, according to *Koh, et al.* was associated with a decreased recurrence rate of acute central serous chorioretinopathy[19].

Ranibizumab has theoretically potential advantages over bevacizumab because of its lower molecular size, higher binding affinity to VEGF, and deeper penetration to choroidal vascular hyperpermeability lesions[20].

In their study, *Jung, et al.* reported that in acute central serous chorioretinopathy, the aflibercept-treated group showed a significant improvement in choroidal thickness, and a faster improvement in visual vision than the control group[21].

Bevacizumab and aflibercept therapy exhibited morphological and functional improvements in prospective studies of chronic central serous chorioretinopathy [22,23].

In the present study, both the injected group (IVR) and the observation groups improved functionally and anatomically with significant gains in the best corrected visual acuity and reduction of the central macular thickness without complications.

In our study, when compared to the observation group, the injected group (IVR) does not appear to be superior in terms of recovery, and we did not discover significant differences on long term follow up by comparing each other, which is in consistent with *Kim, et al.* who showed no statistically significant difference between the ranibizumab and the observations groups at the sixth month[17].

Although *Ünlü, et al.* in their study on intravitreal Bevacizumab concluded that there was no statistical difference anatomically between the injected and the observation groups, they found that the vision in the observation group was markedly better than the injected group this difference from our study may be owed to two factors; the first factor is that *Ünlü, et al.* study was retrospective and did not differentiate between acute and chronic CSCR unlike our study which was on acute cases only, and the other factor is the longer mean duration of follow up in *Ünlü ,et al.*'s study which was 12.1 ± 12.8 (range: 3 to 43) months in the injected group and 8.8 ± 9.4 (range: 3 to 40) months in the observation group while in our

study all patients were followed up to 4 months[24].

Park, et al. showed no differences between the anti-VEGF group (bevacizumab or ranibizumab) and the observation group regarding BCVA and CMT at 12 months, but they showed a more rapid resolution of the subretinal fluid in the anti-VEGF group[25].

The present study was limited by the short follow-up period, only the acute CSCR was included, and only one type of anti-VEGF was used. We recommend future studies with longer duration of follow-up, comparing all forms of CSCR and using more than one type of anti-VEGF.

Conclusion:

It was confirmed that both the injected group (IVR) and the observation groups were effective in the functional and anatomical recovery of CSCR, but no group was superior to the other in comparing both for long term follow up.

Conflicting Interest :

The authors declare. no conflict of interest.

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حقن الرانيبيزوماب (لوسنتس) في اعتلال المشيمة و الشبكية المصلي المركزي الحاد

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الهدف من الدراسة: لتقييم فعالية حقن الرانيبيزوماب داخل الجسم الزجاجي (IVR) لعلاج اعتلال المشيمة والشبكية المصلي المركزي الحاد (CSCR).

الطرق المتبعة: دراسة الحالات والشواهد المرتقبة حيث شملت المرضى الذين يعانون من أعراض اعتلال المشيمة والشبكية المصلي المركزي الحاد CSCR لمدة تقل عن 3 أشهر. **المرضى** (العدد = 50/ مقسمون إلى مجموعتين) مجموعة مضادات عوامل تكوين الوعاء الدموي VEGF التي تضم 30 مريضًا تم حقنهم داخل الجسم الزجاجي بدواء الرانيبيزوماب Ranibizumab (IVR) (0.5 مجم/0.05 مل) ومجموعة المراقبة حيث تمت ملاحظة 20 مريضًا، وتمت متابعة كلا المجموعتين لمدة 4 أشهر. تم تقييم حدة البصر الأفضل تصحيحًا (BCVA) وسمك الماقولا المركزي (CMT) بواسطة التصوير المقطعي لمركز الابصار (الماقولا) للعين (OCT) عند خط الأساس وفي متابعات منتظمة.

النتائج: جميع المرضى لديهم زيادة في حدة البصر الأفضل تصحيحًا BCVA، وانخفاض سمك الماقولا المركزي CMT. وكان متوسط سمك الماقولا المركزي CMT في IVR ومجموعات المراقبة 117.33 ± 46.2 ميكرومتر و196.70 ± 36.9 ميكرومتر، على التوالي (P = 0.670) متوسط BCVA ومتوسط CMT تحسن بشكل ملحوظ في كلا المجموعتين، ولكن التغييرات لم تكن مختلفة بشكل كبير بين المجموعات في 4 أشهر.

الاستنتاجات: أدى كل من IVR والمراقبة لاعتلال المشيمة والشبكية المصلي المركزي الحاد CSCR إلى تحسين امتصاص السائل تحت الشبكي. في 4 أشهر، لم تختلف الاستجابة في كلا المجموعتين. و عليه ننصح بعمل المزيد من الدراسات لتحديد فوائد الحقن بالسائل الزجاجي (IVR) على المدى الطويل.