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Aflibercept for central retinal vein occlusions: long-term outcomes of a 'Treat-and-Extend' regimen

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ABSTRACT

Background/aims This study reports on the long-term functional and anatomical outcomes of patients with central retinal vein occlusion (CRVO) treated under the Bern treat-and-extend (T&E) protocol.

Methods Observational study. Treatment-naive patients with CRVO and consecutive macular oedema treated with aflibercept were included. The T&E protocol involved 2 monthly injections followed by an extension based on individual assessments. At each visit, best-corrected visual acuity (BCVA), optical coherence tomography imaging and a 2 mg aflibercept injection were administered. Changes in BCVA, proportion of patients gaining ≥15 letters, central subfield thickness (CST) and treatment intervals were analysed.

Results Out of 173 patients, 64 had a follow-up of at least 2 years. BCVA improved from 46.7±25.3 at baseline to 78.3±0.5 at year 9. The proportion of patients with ≥15 letters gained was 56%, 53%, 56%, 62%, 52%, 52%, 43%, 50% and 33% at years 1–9, respectively. CST decreased significantly from 660±242 µm at baseline to 359±63 µm at year 9. Treatment intervals extended from 4 weeks initially to an average of 13.0±4.1 weeks by year 8.

Conclusions The T&E regimen for CRVO shows sustained visual improvements and reduced CST over time. Patients maintained stable visual gains for many years, demonstrating the effectiveness of this treatment approach. However, no control group was available to compare our T&E regimen with other strategies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Anti-vascular endothelial growth factor (VEGF) treatments help improve vision and reduce macular oedema in patients with central vein occlusions. Regular injections are needed.

WHAT THIS STUDY ADDS

⇒ Our study provides long-term results. Anti-VEGF treatments in our patients with central vein occlusions reach up to 9 years of follow-up.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Patients might get a better impression of the therapy horizon and can be encouraged that visual acuity can be preserved in most cases.

INTRODUCTION

Retinal vein occlusion is a common cause of severe vision loss. With a prevalence of 1–2% in persons older than 40 years, it is the second most common vascular disease after diabetic retinopathy.[1 2] Untreated eyes with central retinal vein occlusion (CRVO) and consecutive macular oedema experience poor visual outcomes.[3] Large studies have demonstrated the benefits of regular treatments with vascular endothelial growth factor (VEGF) inhibitors.[4–7] The principle of this option is to ensure suppression of the neovascularisation, which through leakage causes vision-threatening macular oedema. Since the therapeutic target is the same as in age-related macular degeneration, established anti-VEGF agents like bevacizumab, ranibizumab and aflibercept have been used for CRVO too. Frequent and numerous injections are necessary to ensure oedema-free remission, which is why the strength of a drug lies in its duration of action.

Initially, fixed injection intervals for all patients have been suggested in order to provide maximal treatment. Later, 'as-needed' protocols did justice to the fact that patients respond individually to the treatment, and some of them needed the injections less frequently. Regular clinical visits including disease activity evaluation take place, but injections are only administered in cases of disease activity. As-needed protocols stand for a reactive approach, and more clinical visits than injections take place in order to provide adequate treatment. The treat-and-extend (T&E) regimen is the latest result of the individualised treatment attempt. Both disease activity evaluation and anti-VEGF injection take place at every visit. Depending on the disease activity state, the interval until the next visit is adjusted. This strategy ensures the best-individualised treatment with the lowest treatment burden and

has become the state of the art in anti-VEGF treatment in different diseases.[8–10]

To date, there is little information about long-term outcomes and real life-reports are scarce for patients treated with aflibercept in CRVO.[11–13]

With this study, we report long-term functional and anatomical outcomes for up to 9 years in patients treated with aflibercept, according to our Bern T&E regimen, modified without an exit strategy for use in CRVO.[14]

METHODS

In this single-centre, retrospective observational study, we included patients with macular oedema due to CRVO and a follow-up of at least 24 months. Eyes with significant visually significant comorbidities, that is, exudative macular degeneration or diabetic maculopathy, were excluded. We administered our Bern T&E protocol for the intravitreal treatment with aflibercept (EYLEA, Regeneron, Tarrytown, New York, USA). All patients were treated at the Department of Ophthalmology at the University Hospital in Bern, Switzerland. Therapy started between March 2014 and June 2021 and was carried out without an exit strategy. Because of the retrospective nature of the study, the need for informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki. Only patients without previous anti-VEGF treatment or other visual-impairing conditions were included. Only patients with a follow-up period of at least 2 years were included.

For the purpose of this study, retrospectively collected data included: patient age at diagnosis, name of the anti-VEGF drug, date of the first injection and all injection visits thereafter, date of the last follow-up appointment, lens status, baseline as well as 6 monthly values for early treatment diabetic retinopathy study (ETDRS) visual acuity, presence of subretinal and/or intraretinal fluid and central subfield thickness (CST).

Treat-and-extend regimen

Our specific Bern T&E protocol was applied. At every visit, visual acuity was evaluated according to the ETDRS. Spectral-domain optical coherence tomography (OCT, Heidelberg Engineering, Heidelberg, Germany) images were acquired, and the CST was noted as measured by the commercially available algorithm. At every visit, an intravitreal injection of 2 mg aflibercept was performed. The intervals between the visits were extended by 2 weeks after the second visit if at least one of the following stability criteria was reached: (1) Absence of intraretinal or sub-retinal pigment epithelium (RPE) fluid in the OCT. (2) Stability in subretinal or sub-RPE fluid and subfoveal fluid <50 µm and best-corrected visual acuity (BCVA) stability at the third consecutive control. Treatment intervals were extended until a recurrence of the macular oedema was detected. Intervals were then shortened by 1 week, until remission, and not extended for the following 6 months. We did not use an exit strategy; therefore, infinite extensions of the injection intervals were possible in stable patients.

Statistical analysis

We used the last-visit-carried-forward principle to correct for missing data. We applied the non-parametric Wilcoxon signed-rank test to check for significance in the BCVA and CST since visual acuity data did not pass the majority of the available normality tests. For further differentiation, a subgroup analysis of ischaemic versus non-ischaemic cases was performed. Data are presented as mean±SD, and $p<0.05$ values were considered statistically significant. Graphs are displayed with the mean and 95% CI of the mean. Ischaemic and non-ischaemic subgroups were tested for significance, using the Mann-Whitney test. Correction for multiple testing was performed with the Kruskal-Wallis and Dunn's test

RESULTS

Out of 173 patients with CRVO, 64 patients with a follow-up duration of at least 2 years could be included in the analysis. Of the 109 excluded eyes, 71 had a follow-up of less than 24 months, 28 had significant ocular comorbidities, 6 had large amounts of missing clinic data, 2 showed gross malcompliance with the treatment protocol and 2 more were treated with Ozurdex at some point during the follow-up. The maximum follow-up for the included eyes was 9 years. Of the 64 eyes in total, 64, 51, 41, 34, 22, 18, 9 and 5 patients were observed during a follow-up period of 2, 3, 4, 5, 6, 7, 8 and 9 years, respectively. The mean age at diagnosis was 68.1±13.8 years (range, 33–90). Seventeen (26.6%) patients were pseudophakic at the beginning of the treatment and a further 16 (25%) underwent phaco surgery during the follow-up. The treatment period amounted to 3.7±2.0 (mean±SD) years.

The proportion of patients who gained ≥15 letters was 56% at 1, 53% at 2, 56% at 3, 62% at 4, 52% at 5, 52% at 6, 43% at 7, 50% at 8 and 33% at 9 years. The mean BCVA increased from 46.7±25.3 SD (median: 50.0) letters at baseline to 65.7±18.5 letters ($p<0.001$, median: 71.0) at year 1, 63.4±21.6 letters ($p<0.001$, median: 68.5) at year 2, 63.9±25.2 ($p<0.001$, median: 75) at year 3, 66.8±21.9 ($p<0.001$, median: 75) at year 4, 71.1±19.6 ($p<0.001$, median: 77) at year 5, 66.9±22.6 ($p<0.005$, median: 75) at year 6, 70.3±20.3 ($p=0.005$, median: 77.5) at year 7, 70.9±20.2 (p=ns: 76.5) at year 8 and 78.3±0.5 (p=ns, median: 78) at year 9, as displayed in figure 1.

CST decreased significantly from 660±242 µm (mean±SD) at baseline to 289±74 (−151, $p<0.001$) at year 1, 306±109 (−177, $p<0.001$) at year 2, 299±91 (−180, $p<0.001$) at year 3, 292±64 (−173, $p<0.001$) at year 4, 332±151 (−173, $p<0.001$) at year 5, 336±136 (−173, $p<0.001$) at year 6, 304±56 (−173, $p<0.001$) at year 7, 314±83 (−173, $p=0.002$) at year 8 and 359±63 (−173, p=ns) at year 9, as shown in figure 2.

Treatment intervals (mean±SD, weeks) were extended from 4 weeks at baseline up to 9.0±2.7 at year 1, 11.6±4.6

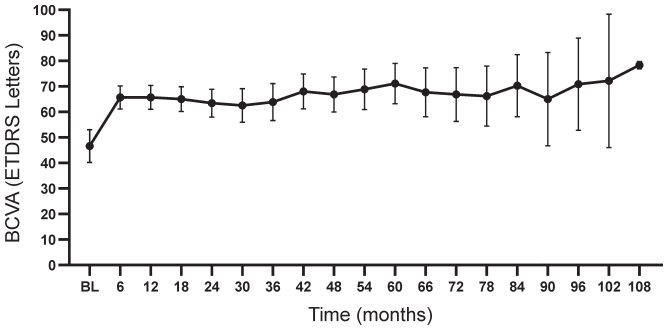

Figure 1 Visual acuity data of all patients from baseline until month 108. The values are displayed as mean±95% CI of the mean. BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study.

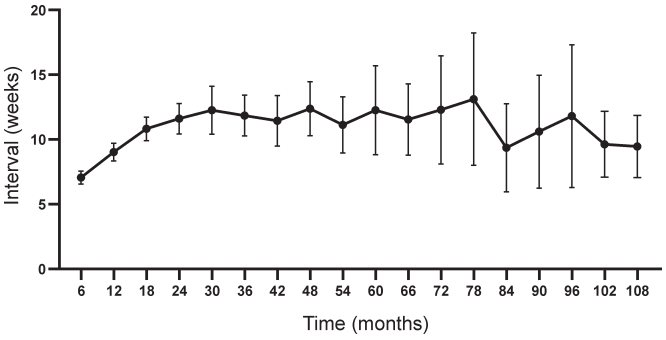

Figure 3 Injection intervals, from baseline until month 108, shown as mean±95% CI of the mean.

at year 2, 11.9±4.7 at year 3, 12.4±5.1 at year 4, 12.3±6.7 at year 5, 12.3±6.2 at year 6, 9.4±3.2 at year 7 and 13.0±4.1 at year 8 as displayed in figure 3. The average number of injections per year (mean±SD) was 7.8±1.5 at year 1, 5.3±2.5 at year 2, 5.2±2.4 at year 3, 5.0±2.1 at year 4, 5.2±2.2 at year 5, 5.3±3.1 at year 6, 6.4±3.3 at year 7, 4.9±1.7 at year 8 and 5.7±1.2 at year 9. There were six patients with significant relapses during their regular follow-up that required shortening of the interval back to 4 weeks. There were also six patients in total, who were on a four weekly follow-up interval at the final recorded visit.

The two groups of non-ischaemic (n=57) and ischaemic (n=7) were also analysed separately: CST and injection frequency did not show any significant difference between the two groups, while BCVA was significantly worse in the ischaemic group. There was no significant correlation between the visual acuity and the injection intervals nor was there any correlation between the number of injections at any time between baseline and year 9.

An analysis of OCT characteristics is displayed in figure 4. At baseline, 16.7% of the patients presented with subretinal fluid, 62.5% showed intraretinal fluid and 20.8% suffered from both intraretinal and subretinal fluid. After 4 years, 69% were dry and 30.8% still had intraretinal fluid detectable.

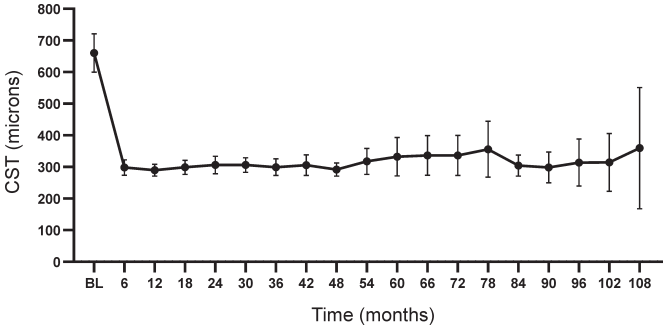

Figure 2 Central macular subfield thickness data of all patients from baseline until month 108. The values are displayed as mean±95% CI. CST, central subfield thickness

DISCUSSION

Our study results present stable visual acuity, even after up to 9 years of treatment. The main visual acuity gain occurred in the first 6 months of therapy, and visual acuity remained stable after 6 months throughout the study period. Our results are comparable to larger controlled studies, and we report a similar proportion of patients who gained ≥15 letters of visual acuity in 1 year: the GALILEO study reported a proportion of 60.2% and the COPERNICUS study had a proportion of 56.1% after 1 year, while this study reported 56%.[7] Our later year results carry on the results of the first year, with the proportion remaining constantly above 50% up to year 8, with increasing fluctuation and variability caused by the decreasing number of patients over time. Our visual acuity results are slightly above the ones of a long-term clinical trial of Iftikhar *et al*,[15] with a 2-year BCVA of 63 vs 61 and 4-year BCVA of 67 vs 60 letters, but are consistent with the real-life report of Eleftheriadou *et al*.[11] Compared with recent long-term outcomes of the SCORE2 study,(16) our results show comparable functional outcomes, with a slightly lower BCVA recovery at year 1 (65 vs 70 letters) but similar outcomes after years 2–5 (63 vs 64, 64 vs 65,

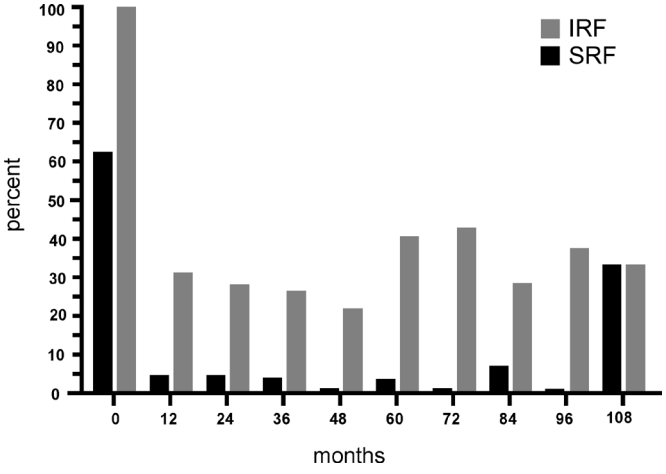

Figure 4 Patients in percentage and their OCT findings (dry, subretinal fluid (SRF), intraretinal fluid (IRF), subretinal and intraretinal fluid) at baseline up to year 9.

67 vs 67, 71 vs 63), respectively. Also, the proportion of patients gaining >15 letters was comparable.

OCT analysis showed a rapid decrease of CST, reaching below 300 µm after 2 months that remained stable during the follow-up. The decrease of CST in the first year is higher compared with the report of Spooner *et al*[12] (−371 vs −190 µm), however, we also had a higher baseline CST (660 vs 561 µm). Our CST findings seem consistent with our data on visual acuity. CST recovered fast after the initial treatment, reaching normal thickness values at 6 months. These results are also consistent with the SCORE2 results.[13] The proportion of fluid-free retina from year 1 onwards remained stable, with occasional relapses of subretinal fluid. This might on one hand be partially explained by the patients who discontinued treatment at their own will and presented again with a relapse of fluid, on the other hand by the nature of the T&E approach where it is expected to see fluid recurrence in an effort to maximise the treatment interval. Importantly though, this did not seem to affect the visual outcome. Also, some natural fluctuations in disease stability that are not directly influenced by the injection frequency might play a role.[16] Regarding the number of injections, our study results are comparable with the mentioned real life report from Eleftheriadou *et al*,[11] where the mean number of aflibercept injections was 8.0 in the first year (aflibercept), whereas our study reported 7.8 injections. In line with the interval extension we observed, the number of injections per year decreased until about year 2, after which we saw no further decrease. This again would argue for continued treatment in CRVO, even after years of prior treatment.[14]

For patients with stable and inactive disease, treatment continuation was administered with an infinite extension of the injection intervals in our setting. In certain cases, patients refused the continuation of the injections and demanded an exit approach. In other cases, the COVID-19 pandemic disrupted the regular follow-up scheduling.[17] Generally, the importance of regular clinical controls should be highlighted.[18] Since anti-VEGF protects against neovascularisation, fluorescein angiography should be considered after treatment discontinuation or in patients returning to the clinic after having been lost to follow-up.

This study has certain limitations, such as its retrospective nature and limited sample size, especially for longer follow-up times. Since we have no information about the patients lost to follow-up, a certain selection bias is unavoidable. Furthermore, subgroup analysis should be interpreted cautiously, due to the small sample size in the ischaemic group. Also, no control group was available to compare our T&E regimen with other strategies.

Since there is not much evidence about long-term outcomes in CRVO treated with anti-VEGF agents in a T&E setting, we hope that our results help encourage other clinicians to treat CRVO patients according to a T&E setting. Reducing unnecessary monthly dosed injections or unnecessary clinical visits in as-needed protocols might help to improve the patient's comfort and treatment burden.

CONCLUSION

This 'real-life' study using a T&E regimen for anti-VEGF therapy in patients with CRVA shows acceptable long-term outcomes, which are consistent with larger controlled trials and encourages using the T&E regimen in the clinical setting.

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Patient consent for publication Not applicable.

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