Guidelines for diagnosis and treatment of patients with retinal vein occlusion

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1. INTRODUCTION

Retinal vein occlusion (RVO) is defined as a retinal vascular disorder which is typically manifested by the overlapping, dilation and tortuosity of the retinal veins, predominantly by means of intraretinal haemorrhages and intraretinal edema, retinal ischemia including cotton wool spots, hard exudates and macular edema [1-8]. As soon as an area of the fovea is afflicted by macular edema, a deterioration of central visual acuity (VA) takes place, which leads to progressive and sometimes acute, painless loss of sight.

RVO is a relatively frequent cause of loss of sight in industrially developed countries. It represents the second most frequent cause of deterioration of vision in connection with retinal vascular disorder, immediately after diabetic retinopathy [9, 10], in which branch retinal vein occlusion (BRVO) occurs 2-3 times more frequently than central retinal vein occlusion (CRVO) [11, 12]. The incidence of vein occlusion recorded for the age group of 49 to 60 years is 0.7%, and 4.6% for persons aged over 80 years. At present it is estimated that approximately 520 new cases of RVO occur per million persons [13], of which 442 represent case of BRVO and 80 CRVO. RVO typically occurs in middle age and in older persons (over 50 years), and the occurrence is equal in both sexes.

To date, the etiology of RVO has not been fully clarified. A factor under consideration is external compression of the vein, in the case of central occlusion of the retinal vein (RV) on the level of the lamina cribrosa, in the case of branch occlusion of the RV on the level of arteriovenous crossing. A range of other factors may occur, including partial obstruction of the retinal vein system due to the occurrence of thrombosis [14, 15, 16].

According to localisation RVO is divided into: (1) CRVO, in the case that the entire retinal vein system is affected and the assumed point of increased resistance to the venous outflow is located in or behind the area of the lamina cribrosa, and also (2) BRVO, in the case that venous congestion affects only a branch of the retinal vein network. It may be limited to a small, peripheral arteriovenous crossing or affect the entire quadrant if it is located on the edge of the optic nerve (ON). If the upper or lower hemisphere of the retina is affected, the assumed location of the occlusion is one of two trunks of the intraneural central retinal vein, if this congenital abnormality exists. This entity (hemicentral RVO) is considered to represent a variant of central occlusion of the RV [9, 14, 15].

The clinical picture of CRVO includes edema of the disc of the ON, dilation and tortuosity of all retinal veins, deep and superficial retinal haemorrhages, cotton wool spots as a symptom of ischemia, edema of the retina and the area of capillary non-perfusion. According to the angiographic finding, we divide them into non-ischemic and ischemic occlusion of the trunk of the RV. Ischemic occlusion of the branch of the RV is defined on fluorescent angiography (FAG) by locating the zone of capillary non-perfusion within the scope of 10 and more surfaces of the disc of the optic nerve [17]. Occlusion of the trunk of the RV displays similar characteristics, which are however limited only to part of the retina [18].

The aim of this document is to provide an updated recommendation with regard to conducting treatment of RVO in the light of the latest advances in the field of diagnosis and treatment of BRVO and CRVO. It should serve both ophthalmological specialists and general practitioners. It also summarises the risk factors of RVO and recommendations relating to RVO.

2. METHODS

The group for processing the regulations for treatment of retinal vein occlusion in the Czech Republic comprises the two-member collective of authors (Jiří Řehák and Jan Studnička) and the 9-member group of opponents (Pavel Rozsíval, Šárka Pitrová, Jan Ernest, Pavel Němec, Petr Kolář, Štěpán Rusňák, Zora Dubská, Miroslav Veith, Martina Závorková).

For the purposes of this evaluation, research has been conducted on the literature in the MEDLINE / PubMed and Cochrane Library databases, and the British and European standards have been used as source materials (Management of Retinal Vein Occlusion – Consensus Document and Interim Guidelines for Management of Retinal Vein Occlusion).

3. PATHOPHYSIOLOGICAL AND RISK FACTORS

In general the prevailing opinion is that the etiopathogenesis of retinal vein occlusions is multi-factorial [19, 20]. Retinal vein occlusion is caused by a thrombosis inside the retinal veins (central, hemicentral or branch) [17, 19, 20], although it remains unclear as to whether this concerns a primary or secondary effect. Cardiovascular risk factors are most frequently health complaints in connection with central retinal vein occlusion. However, certain differences exist in the pathogenesis of occlusion of the branch and the main trunk of the RV, which render these conditions separate clinical units.

3.1 Central retinal vein occlusion

In the majority of cases a development of BRVO occurs in areas of retinal arteriovenous crossing, which share a common adventitia [9]. In almost all cases, the artery is located above the vein, which as a result becomes vulnerable to compression by the artery, resulting in a certain degree of stasis and turbulent flow, which may lead to a predisposition towards endothelial damage, and both factors are prone to the formation of a thrombosis [10, 11]. This process is exacerbated in the presence of atherosclerosis [9, 10, 12, 21]. Turbulent flow in areas of arteriovenous crossing has been demonstrated using FAG [5].

3.2 Central retinal vein occlusion

A number of hypotheses exist with regard to the pathogenesis of CRVO. A compression of the central retinal vein may occur due to the effect of the central retinal artery, since both are located in a common fibrous capsule [21]. A role

may also be played by a degenerative or inflammatory disorder of the wall of the central retinal vein, as well as haemodynamic factors such as hypotension and blood dyscrasia [16, 21-23]. The final result of all these mechanisms is a stagnation of the flow of the venous blood. On the basis of histopathological studies, it has been demonstrated that in all or most cases of CRVO a thrombosis forms in the location of the lamina cribrosa or close behind this formation [14]. It is assumed that the non-ischemic type of CRVO occurs more in a posterior position towards the lamina cribrosa, in which the increased accessibility of collaterals leads to a less complete occlusion [22].

4. RISK FACTORS

4.1 Systemic risk factors

The most frequently stated are cardiovascular risk factors in connection with occlusion of the central retinal vein or its branches [22, 24, 25]. Cardiovascular thrombogenic risk factors of venous damage, stasis and hypercoagulability have been determined by Virchow's triad [26]. In patients older than 50 years, one of the cardiovascular risk factors is usually present. In patients younger than 50 years there is a lack of a clear risk factor in 60% of cases [27, 28]. Over 90% of cases of RVO occur in the age group of over 50 years [26].

4.1.1 Hypertension and cardiovascular disorder

A frequent finding is recently diagnosed or poorly treated hypertension. This serious risk factor has a higher prevalence in patients with BRVO than in patients with CRVO. Over 64% of patients with RVO in the age group of over 50 years suffer from hypertension, which is also a predominant finding in the case of recurrent RVO (88%) [29, 30]. Similarly, in patients with existing RVO, vascular (cardiovascular, cerebral) events are observed more frequently [30].

4.1.2 Hyperlipidemia and hypercholesterolemia

This is a predominant risk factor of RVO in patients younger than 50 years. It also occurs in up to 50% of older patients [31]. It has been determined that 71.4% of all assessed patients with RVO suffer from hypercholesterolemia [32].

4.1.3 Diabetes mellitus

There is a significant connection between diabetes and CRVO [33]. However, this disorder has not been verified as an independent risk factor of BRVO [32, 34-40], perhaps due to the increased presence of misleading coexisting cardiovascular risk factors in these patients [29, 32, 42].

4.1.4 Other vascular risk factors

A connection has also been determined between RVO with a high body mass index and smoking, although these relationships demonstrate a lower consistency [31, 36, 43].

4.1.5 Thrombophilia

A causal connection between coagulation cascade disorders and RV occlusion has been under discussion for several decades. Amongst the most frequently mentioned disorders are deficit of Protein C and S, antithrombin, hyperprothrombinemia, and the greatest attention has been devoted to the role of Leiden mutation [20]. Due to the contradictory results of the available studies, it is not a simple matter to issue a general clinical recommendation as to whether it is necessary to perform routine screening for thrombophilic disorders in patients with RV occlusion. Essentially it is possible only to abide by the conclusions of the published meta-analyses, which have statistically evaluated all the available studies on the role of individual thrombophilic disorders [20, 26]. The results of the meta-analyses which demonstrated a causal connection between RVO and hyperhomocysteinemia, antiphospholipid syndrome and Leiden mutation can be considered to be valid [20]. However, the difference in the occurrence of these haematological disorders in comparison with the healthy population is not so high as to justify screening for haematological disorders in all patients with RVO.

With regard to the fact that thrombophilic disorders are mainly of genetic origin (with the exception of hyperhomocysteinemia, which in its essence is connected with diet), a certain insight can be provided by family anamnesis of thrombotic events (deep vein thrombosis, pulmonary embolism or multiple spontaneous miscarriages). A better chance for identification of risk patients is offered by screening according to positive personal or family anamnesis.

4.1.6 Less frequent connections

In younger patients (aged younger than 50 years), findings such as oral contraception and vasculidity of the disc of the optic nerve [27, 28] emerge to a greater extent. There is no consensus on the role played by these factors, whilst some authors state that these do not represent significant risk factors [54, 55].

4.1.7 Other observations

In 1% of patients in whom RVO is presented, myeloproliferative disorders are present (such as lymphoma and leukaemia) [33]. Further rare connections with RVO are inflammation disorders causing or in connection with retinal vasculidity. In these processes RVO frequently occurs in the location of retinal granulomatous infiltration or in peripheral distribution with affliction of several small blood vessels. Here also there is a tendency for younger persons to be affected. Amongst the disorders which must be taken into consideration are sarcoidosis, toxoplasmosis, tuberculosis, Behcet's disease, systemic lupus erythemoatosus, polyarteritis nodosa, Wegener's granulomatosis and Goodpasture's syndrome [26]. Recently a connection has been reported with sleep apnoea [56].

4.1.8 Summary

The demonstrated connection of RVO with systemic vascular disorders emphasises the need for screening of new patients with regard to vascular risk factors such as arterial hypertension, dyslipidemia and diabetes mellitus. The treatment of these basic causes is of fundamental significance from the perspective of preventing substantial morbidity. If no other evident etiology is present, it is appropriate to consider examination for thrombophilia [26].

4.2 Ocular risk factors: Glaucoma

The most frequent ocular factor causing a predisposition to RVO in patients is open-angle glaucoma. It is assumed that increased intraocular pressure impairs the flow through the retinal vein and causes stasis [29, 32, 44].

5. NATURAL COURSE AND PROGNOSIS OF RESULTING VISUAL ACUITY IN CENTRAL RETINAL VEIN OCCLUSION

In general it applies that the prognosis of central retinal vein occlusion is far more serious in comparison with branch retinal vein occlusion.

5.1 Central retinal vein occlusion

There are two main predictors of the result of visual acuity for CRVO: FAG and initial VA [57].

5.1.1 Fluorescent angiography

5.1.1.1 Ischemic CRVO

Quinlen states that 36% of CRVO was ischemic upon inception. All eyes in the ischemic group had initial VA of 6/30 or worse. 93% of eyes had final

VA of 6/60 or worse. Only 3% of eyes improved to VA 6/24 or better. These results demonstrate that ischemic CRVO is almost always connected with poor initial VA, and that correction of VA in the case of ischemic occlusion is highly improbable [57].

Non-ischemic CRVO

Quinlen states that 64% of CRVO were non-ischemic upon inception. Initial VA is highly variable: within the range of 6/9 – counting of fingers 50% of eyes had a final VA of 6/60 or worse, and a similar result is stated by Glacet-Bernard – 48% of eyes. If we examine the prevalence of final VA of 6/60 or worse with regard to initial VA, we find that eyes with poor initial VA have a substantially worse prognosis – where initial VA was 6/60 or worse, there was similarly poor final VA in 88% of cases, whereas in eyes with good initial VA this is far less – only 21% of eyes with final VA of 6/60 or worse. In general it applies that in the case of non-ischemic occlusion, the worse the initial VA, the worse the prognosis of the resulting level of vision [57].

5.1.2 Visual acuity

The most representative body of work on the natural development of CRVO (N = 728) was presented by the research group Central Vein Occlusion Study Group (CVO SG): 65% of eyes with initially good VA (6/12 or better) maintained similarly good VA at the end of the study. Patients with intermediate initial VA (6/15-6/60) recorded variable results: 19% improved to 6/12 or better, 44% remained in the intermediate group and 37% had a final VA of worse than 6/60. A patient who had poor VA upon the first visit of worse than 6/60 had an 80% chance of having VA of worse than 6/60 upon the final visit, regardless of whether this concerned ischemic or non-ischemic CRVO at the beginning. The authors state that initial VA is a strong predictor of VA in three-year observation in eyes with good and poor VA, however it is a poor predictor in eyes with intermediate VA at the beginning of the illness. It is stated that visual acuity is a more significant factor than FAG in determining the prognosis and designating the further treatment procedure. If VA deteriorates at any time during the observation of the development of the occlusion to a level worse than 6/60, it is highly probably that extensive capillary non-perfusions shall develop in this eye [8, 17].

On the basis of the study Standard Care vs. Corticosteroid for Retinal Vein Occlusion on (SCORE), it was reported that in at least 75% of eyes (with ischemic and non-ischemic CRVO) in the observed group, the value of VA after 12 months was 6/12 or worse [59]. On the basis of the study OZURDEX ® GENEVA it was determined that only 7.5% of patients (with ischemic and non-ischemic CRVO) in the observed group recorded improved sight by at least 15 letters 30 days after the beginning of observation, in which this percentage increased to 17.6% after 180 days [60]. In the meta-analysis of the authors McIntosh et al. [58], it is stated that in the case of ischemic CRVO the central deterioration of VA was 35 letters during the observation period of 12 months or more, in comparison with deterioration by an average of 3 letters during observation of at least 12 months in the case of non-ischemic CRVO.

5.1.3 Conversion of non-ischemic CRVO into ischemic form

Quinlen states a relatively low percentage – 9% - but at the same time notes that the actual prevalence of conversions may be higher, because many of her patients were first of all examined in decline, and it is not possible to exclude the possibility that several non-ischemic occlusions converted into ischemic form before they had been examined in the Wilmer Eye Institute. This is in accordance with the results of Chena et al., who published 15% of converted eyes [57, 61].

The largest amount of representative data is the CVO Study Group (N = 547 non-ischemic CRVO), which determined that during the first 4 months after the beginning of occlusion 15% of non-ischemic CRVO converted into ischemic form. However, during the following 32 months of observation, a further 19% of eyes converted into ischemic form. The total percentage of conversions over the course of 3 years is 34%. The development towards the loss of perfusion or towards ischemia was most rapid during the first four months, and decreased throughout the entire period of observation. The authors also state that as soon as an occlusion converts into ischemic form, these eyes then manifest the same characteristics as ischemic occlusion, including a similarly poor prognosis of sight and incidence of complications. It also applies that if a non-ischemic occlusion converts into ischemic form, it will never return back to non-ischemic form [17]. Whereas changes in the sense of capillary non-perfusion are irreversible, ischemia observed from the beginning may be only relative: delayed circulation, which is the result of vascular stasis and inflammation of a blood vessel are reversible upon the development of collaterals.

5.1.4 Neovascularisation

It has been determined that the incidence of secondary neovascularisation upon (incipient) non-ischemic CRVO fluctuates from 0 to 33% during the course of 12-15 months [58]. In one study [62] in which no CRVO sub-type was classified, an incidence as high as 50% was reported six months after the occurrence of central retinal vein occlusion. The strongest predictors of neovascularisation of the anterior segment (iris or chamber angle) were VA and the scope of non-perfused areas determined by FAG. According to CVO SG in the case of eyes which were classified from the beginning as ischemic or unclassifiable (due to extensive retinal haemorrhage), there was a development of neovascularisation of the iris or chamber angle in 35% of eyes, in comparison with 10% of eyes which were classified as non-ischemic from the beginning [17].

Ischemic CRVO is connected with a higher risk of neovascular glaucoma, the development of which has been stated in at least 23% of cases over the course of 15 months [58]. Neovascularisation in the early phase of development is detected with the help of gonioscopy as a fine vascular network adjacent to the trabecular meshwork. It may also be determined on the pupillary perimeter, where the fine vascular network causes ectropium of the iris. The result of the development of neovascularisations is a closure of the chamber angle and the development of neovascular glaucoma. After nine months an incidence of vitreous haemorrhage was documented in the case of CRVO at the rate of 10% [63].

5.1.5 Macular edema

Macular edema ranks amongst the main complications of ischemic and non-ischemic CRVO. In the majority of studies, the presence of macular edema is stated at the beginning of the illness. There are too few reported cases of the development of macular edema after RVO to enable a determination of its incidence. They include data on 0-73% resorption in the case of an ischemic type and approximately 30% in the case of a non-ischemic type over a period of 2-15 months [58].

Chronic macular edema is linked to a poor prognosis of development of VA, nevertheless it is necessary to treat this. Findings that the longer the period of duration of the edema, the greater the probability of structural damage to the fovea [58], argue in favour of timely intervention. On the

basis of the GENEVA study with the Ozurdex preparation, it was demonstrated that even if the improvement in the untreated control group was greater with a shorter duration of macular edema, the response to the treatment was not time-dependent [60].

5.1.6 Affliction of other eye

With regard to the presence of systemic risk factors, the risk of affliction of the other eye is similar. In approximately 5-10% of cases of CRVO, the development of RVO has been reported in the other eye within one year [58, 64-67].

5.2 Branch retinal vein occlusion

5.2.1 Natural course of branch retinal vein occlusion

Occlusion of a branch of the central retinal vein has a fairly good prognosis – in approximately 50-60% of patients the resulting VA is 6/12, and better even without laser treatment [2, 73, 101]. This favourable course depends in particular upon three anatomical factors: 1. localisation of the occlusion, 2. calibre of occluded vein and 3. degree of venous obstruction [102]. In the remaining 40% of eyes the resulting VA is 6/18 or worse. However, approximately one half of these eyes have a very poor resulting VA – 6/60 or worse, which represents approximately 20% of eyes from the total number of occlusions of a branch of the central retinal vein [101]. In the chronic phase, primarily chronic ME and neovascularisation share in the deterioration of sight. ME is present in 57% of occlusions of a branch of the central retinal vein [101]. (The prevalence of final VA of 6/60 or worse is stated at 23-30% in the untreated groups [70, 101, 103].

5.2.2 Prognosis of visual acuity

The natural course of occlusion of a branch of the central retinal vein and its prognosis is determined in particular by the location and degree of the occlusion, as well as the integrity of the arterial perfusion of the affected sector of the retina and the hemodynamic significance of the collateral circulation [73]. Chronic ME and vitreous haemorrhage from neovascularisation are the most frequent cause of poor resulting VA. Retinal neovascularisation and chronic, persisting ME are described in the literature in 25% and 60% respectively [2, 104]. Schilling observed a worse prognosis for sight in occlusions with ischemic ME as against non-ischemic ME [75]. However, Finkelstein states that in 91% of eyes out of a total number of 23 occlusions with ischemia of the macula, VA improved within 1 year to 6/12 or better [105]. These differing reports and the low number of subjects in these studies render it impossible to draw final conclusions with regard to the prognosis for sight in patients with occlusion of a branch of the central retinal vein [106]. Some authors however are convinced that the course of the occlusion cannot be predicted whatsoever [70, 103, 107].

In recent years there has been a significant shift in this problem. The most frequent cause of unsatisfactory final VA of all is chronic ME, which develops on the basis of complex intracellular and extracellular changes in the hypoxic retina [108]. In fact, even if the macula is not directly affected, other extracellular factors (such as VEGF, interleukins) share in the development of ME [109]. A whole range of prognostic factors are taken into consideration in patients with occlusion of a branch of the central retinal vein. A range of studies point to an indirect relationship between the thickness of the macular retina measured using OCT and VA in patients with diabetic ME [110, 111]. The SCORE study was recently published on patients with occlusion of a branch of the central retinal vein, and this showed a statistically significant correlation between the thickness of the central part of the macular retina (measured using OCT) and VA [112]. The regressive model shows a drop of 1.9 letters from the initial VA measured on ETDRS optotypes for each 100 μm of thickening of the central part of the macular retina. A possible correlation between VA and the integrity of the junctures between the internal and external layer of photoreceptors as the most significant indicator of the integrity of the external layer of photoreceptors detected using OCT has been studied by Ota [113]. The preserved integrity of the foveal layer of the photoreceptors before treatment was closely linked to good sight function after resorption of ME in patients with retinal vein occlusion. In 2011 a study was published, which demonstrated on the basis of a multivariate analysis on a large number of eyes that only initial VA and an age of over 70 years are entirely independent predictors of resulting VA. No sufficient significance was demonstrated in the case of other potential predicting factors – ischemic occlusion (defined as the presence of zones of capillary non-perfusion on FAG greater than an area of 5 papillary diameters, or if there is no possibility to evaluate FAG for extensive retinal haemorrhage the criterion for ischemic occlusion is the presence of cotton wool spots), sex, occlusion of the main branch/occlusion of the macular branch. "Prognostically unfavourable occlusion of a branch of the central retinal vein" is defined on the basis of these results, defined as an occlusion of the branch with initial VA of 6/24 or worse [68].

5.2.3 Neovascularisation

The incidence of neovascularisation is relatively low in the case of BRVO, with the exception of cases with extensive ischemia (affecting more than one third of the fundus). Nevertheless, there is not a sufficient number of significant studies on the theme of incidence of neovascularisation in patients with BRVO [69].

5.2.4 Macular edema

ME is present in 57% in occlusion of a branch of the central retinal vein [101]. According to the natural course, Gutman divides this into 3 groups:

1. Persistent or chronic ME (ME persisting for longer than 3 months) in 65%,
2. Transitional ME, which is spontaneously reabsorbed – present in 26%,
3. Macular edema, which appears in the later phase of the illness – present in 9%.

The last two groups – transitional ME and macular edema with late onset – have a good prognosis; resulting VA was 6/12 or better in all eyes. On the other hand, in the group of patients with chronic ME, only 14% maintained VA of 6/12 or better, whilst the remaining 86% of eyes showed a resulting VA of 6/18 or worse [101]. Therefore chronic macular edema has a poor prognosis with regard to resulting VA. Chronic ME – if it persists for too long – as a result culminates in irreversible structural damage to the retina such as: foveal cysts, degeneration of the RPE and preretinal membrane [20].

5.2.5 Affliction of other eye

Bilateral affliction at the time of recruitment to the studies was reported in 4.5-6.5% of patients [2, 72]. The report on the basis of BVO SG states 9% bilateral affliction, although it is not clear as to whether both eyes were affected or whether bilateral affliction developed over the course of time [70, 71]. Michels and Gass [73] state 10% development of BRVO in the other eye over time. On the basis of cross-sectional population data it is possible to estimate 5% of bilateral affliction [43, 64-67].

6. TREATMENT OF RETINAL VEIN OCCLUSION

Treatment of RVO concentrates on two main targets: (1) identification of risk factors and the therapeutic man-

agement thereof and (2) identification and management of complications which threaten sight.

6.1 Pharmaceutical treatment

6.1.1 Systemic risk factors

During treatment of RVO it is necessary to address a number of targets, which include identification and management of systemic risk factors (specifically arterial hypertension, cardiovascular disorder, diabetes mellitus, hyperlipidemia and thrombophilia). Treatment of basic health problems is necessary for the purpose of preventing events other than those affecting sight, for example myocardial infarction and cerebrovascular events [74, 75], as well as for the purpose of reducing the risk of vein occlusion in the other eye [76].

In the case of "pre-thrombosis" (incipient RVO), which is characterised by the presence of dilated retinal veins and a small number of scattered haemorrhages, without macular edema, in asymptomatic patients or in patients with transitory episodes of defocusing of vision, in whom a slight increase in the retinal circulation time may be perceptible on FAG, a medical examination of the basic systemic risk factors is recommended. Rapid management of systemic risk factors may avert the progression or lead to the correction of an existing occlusion [77]. The above-stated systemic disorders fall within the competence of a specialist in internal medicine or general practitioner.

With regard to the fact that the above-mentioned studies according to the population and multicentric prospective studies such as CVO SG have demonstrated a connection between RVO and glaucoma or arterial hypertension [7, 17, 29, 32, 40, 43], it is necessary to exclude these conditions, or if they are present, to treat them as appropriate.

6.1.2 Anticoagulants, fibrinolytic treatment and anti-clotting drugs

It may seem that these represent logical possibilities of treatment, nevertheless the results of the clinical trials with heparin, streptokinase and warfarin were disappointing, and provided only limited evidence of any effect with regard to undesirable side effects such as vitreous haemorrhage. Aspirin is not recommended as a primary prevention of cardiovascular events. With regard to the fact that it has not been successfully demonstrated that RVO may be a risk factor in mortality due to a cerebrovascular event or in vascular mortality, the role of aspirin in RVO remains unclear.

A report is available which refers to the significant effect of warfarin in ischemic CRVO, though on the precondition that treatment is of sufficient strength (INR 3-3.5) and length (1 year). The authors state conversion into ischemic form of CRVO in 5% of cases, which is the lower limit of the published data. In the case of ischemic CRVO, such treatment does not significantly influence final VA, but significantly reduces the incidence of neovascular glaucoma from 50% to 3% [78, 79]. The evidence of the report is however limited.

6.2.1 Conducting treatment of central retinal vein occlusion

6.2.1.1 Classification of subtypes of CRVO

The first step in the treatment of CRVO is a differential diagnosis between non-ischemic and ischemic CRVO, with assessment of non-perfused capillary areas of the posterior pole of the eye and the presence/scope of non-perfused zones of the periphery according to FAG. Indications for treatment of complications endangering sight using systematic and ocular treatment of CRVO are based on this differentiation.

In the case of non-ischemic CRVO, the main sight-threatening complications are macular edema and conversion to ischemia. In ischemic CRVO, the main such complication is the development of ocular neovascularisation, in particular in the anterior segment of the eye (iris and chamber angle, up to neovascular glaucoma). Macular edema may occur in all forms of CRVO. Although differentiation between ischemic and non-ischemic type may be difficult, at least from the beginning or in the early stages, a range of clinical and functional characteristics which are typical of ischemic CRVO [3, 8, 13, 17, 80] can help as a guide to determining diagnosis. Amongst these findings are: poor VA, relative afferent pupillary defect, presence of numerous dark, deep intraretinal haemorrhages, presence of cotton wool spots, presence of extensive retinal capillary non-perfusion (larger area than ten times the size of the disc without perfusion) determined using FAG, not only on the periphery, but also in the area of the macula [8].

The presence of macular ischemia (evaluated according to enlargement of the foveal avascular zone on FAG) is prognostically significant, since it indicates a lower probability of the renewal of VA. Even though FAG may be effective in determining the degree of vascular perfusion, a significant tool in conducting treatment in patients with retinal vein occlusion is spectral domain optic coherent tomography (SD-OCT), since this is objective and helps quantify the volume of cystoid macular edema, and also provides additional information, for example on whether the accumulated fluid is located predominantly inside the retinal layers or also in the sub-retinal space [81]. After resorption of this fluid, severe ischemia causes considerable contraction of the thickness of the macular area and its atrophy.

The final prognosis of the development of sight depends on the presence and integrity of external limiting membranes, as well as on internal and external segments of photoreceptors (interface between internal/external segment of photoreceptors). Hyperreflexive points on SD-OCT, mainly on the external layers, point to an inflammation reaction and may be a marker of the activity of the illness [82].

In the case of pre-occlusive disease (pre-thrombosis) with incipient intraretinal haemorrhages and tortuosity of retinal blood vessels, SD-OCT may show a normal appearance. In the case of threatening vein occlusion, spots of increased reflectivity with a shadow effect are present on the level of the internal plexiform layer. If an ischemic component is present, there is evident weakening of the layer of nerve fibres.

It has been well demonstrated that early treatment may be beneficial from a therapeutic perspective. This is important especially in opposition to the previously common conception that it is necessary to wait at least three months before the commencement of treatment of vein occlusion [60, 80].

6.2.1.2 Conducting treatment of non-ischemic CRVO

6.2.1.2.1 Non-ischemic CRVO and good VA

In patients with non-ischemic (well perfused) CRVO and good VA (6/9 or better), the prognosis is favourable and observation is possible. The primary aim is screening of risk factors. Treatment of the basic causes of retinal vein occlusion is significant in preventing complications. It is appropriate to consider examination for other risk factors only in the case that clinical anamnesis points to their presence, in the absence of any other clear etiology [26]. Local factors indicating a predisposition towards or connecting with CRVO such as open-angle glaucoma

must be excluded and treated appropriately in order to alleviate the risk of conversion to ischemic CRVO [43, 83]. The aim of monitoring during observation is to identify macular edema or conversion to ischemic CRVO. Amongst the main elements of clinical examination are assessment of VA, biomicroscopy and OCT. It is always suitable to conduct FAG in the case of doubt regarding progression or for the purpose of assessing the degree of ischemia.
It is suitable to monitor patients once per months during the first three months, and subsequently every two months during the first year. During this period of monitoring, it is necessary to instruct patients in the sense that they should report to the facility immediately in the case that they notice any deterioration of vision, which may indicate macular edema or conversion to ischemic CRVO.
A report is available which recommends anticoagulation treatment with warfarin (N = 50 non-ischemic CRVO, respectively N = 24 pre-thromboses). A 96% success rate is stated in the case of pre-thrombosis. Treatment can be set for 2 months after the clearance of retinal symptomatology. The authors point to the fact that at the moment with pre-thrombosis transforms into florid non-ischemic CRVO, the outlook for a good result is uncertain, and if the occlusion converts into an ischemic form the chance of a good result is minimal. However, the evidence for this report is limited [78, 79].

6.2.1.2.2 Non-ischemic CRVO and VA worse than 6/9

In the case of non-ischemic CRVO and VA of 6/12 or lower, it is appropriate to examine for macular edema. If this is present, it is necessary to commence treatment and not merely conduct observation.

6.2.1.2.3 Conducting treatment of macular edema in non-ischemic CRVO

6.2.1.2.3.1 Laser photocoagulation

According to CVO SG, grid laser photocoagulation leads to a reduction of macular edema, though it has not brought any statistically significant effect from the perspective of VA, with the exception of a group of young patients [88]. At present grid laser photocoagulation is not indicated.
The present possibilities for treatment cover approaches using corticosteroids and preparations against vascular endothelial growth factors (VEGF). In eyes afflicted by macular edema in CRVO it always is necessary to consider treatment if VA is lower than 6/9 [88].

6.2.1.2.3.2 Approach using corticosteroids

There are a number of corticosteroid preparations available, nevertheless not all steroids have the same potency and side effects. The reasons for use of steroids in treatment of macular edema are connected to their ability to reduce capillary permeability and inhibit VEGF gene expression and the VEGF metabolic pathway. Treatment with corticosteroids should be based on randomised clinical trials.

6.2.1.2.3.2.1 Dexamethasone

Dexamethasone has been used for a long time as a strong corticosteroid reducing inflammatory mediators which are envisaged in the case of macular edema. On the basis of the data available to date it is possible to reckon with fewer side effects than in the case of other corticosteroids.
Dexamethasone is highly soluble and after intravitreal injection has a short half-life of disintegration. For the purpose of ensuring the long-term level of dexamethasone, a slow-release biodegradable implant has been developed (Ozurdex; Allergan), which releases the drug towards the posterior pole of the eye for up to six months after implanting in the vitreous area. Its therapeutic effects on macular edema in connection with RVO have been examined within the framework of a six-month, randomised controlled clinical trial (GENEVA study with the Ozurdex preparation) [60]. The drug can be administered with the help of a single-use applicator, which contains 0.7 mg of dexamethasone in the form of an implant from polyglycolate acetate with slow release.
The GENEVA study with the Ozurdex preparation demonstrated that the biodegradable implant with a content of 0.7 mg of dexamethasone (Ozurdex) led to an improvement of VA, in which the peak of the effect was determined after two months, with a progressive decline to the initial values after six months. On average an improvement by 10 letters was attained in patients 60 days after implantation. An effective improvement in VA can be achieved during the course of a one-year observation after a second injection administered in the sixth month [60]. From an anatomical perspective, the improvement of macular edema was substantiated with the help of OCT.
The safety data showed a low occurrence of cataracts and a low degree of increase of intraocular pressure. A medium increase of intraocular pressure was determined in approximately 15% of cases, in which the peak of this occurrence was reached in the second month, though during observation it recorded a declining tendency, especially if treated using drops against glaucoma, which the majority of patients were able to cease using within six months after implantation. No undesirable events were connected with the injection.
Within the framework of the study it was also possible to demonstrate that timely treatment of macular edema is more beneficial from the perspective of renewing VA than delayed treatment. On the basis of a post-hoc analysis, the view was stated that in eyes treated within 90 days of the onset of cystoid macular edema there is a higher probability of improvement than in eyes in which treatment was not applied until after the elapse of this period. It is probable that a dexamethasone implant should be administered more frequently, according to the individual response of each patient during observation.

6.2.1.2.3.2.2 Triamcinolone acetonide

The preparation triamcinolone acetonide containing benzyl alcohol has been used for several years in the treatment of patients outside of the framework of the indications (Kenalog®, Squibb). With regard to the beneficial effects of this preparation in the treatment of macular edema in connection with non-ischemic CRVO, a range of small series of cases has been published [18]. However, Kenalog has a range of side effects, including cataracts and increased intraocular pressure. The presence of benzyl alcohol also leads to an increased risk of sterile endophthalmitis. Although the preparation is indicated for intra-articular use in joints, its use in the area of the eyes is within the regime of off-label treatment.

6.2.1.2.3.3 Anti-VEGF approach

Intravitreal administration of anti-VEGF substances such as ranibizumab, bevacizumab and pegaptanib has been examined.

6.2.1.2.3.3.1 Ranibizumab

Ranibizumab is a non-selective VEGF blocker (Lucentis®, Novartis), the effectiveness of which has been demonstrated

on the basis of the CRUISE clinical trial [84]. Ranibizumab was administered in the form of an injection once per month in two doses (0.3 and 0.5 mg) during the first six months, which led to a medium improvement of VA by 12.7 and 14.9 letters respectively in comparison with a placebo injection in the sixth month. After the first six months, all patients underwent an open extending phase with observation over the period of the next six months, with treatment for re nata (according to requirement).
The published results confirmed the effectiveness of treatment with ranibizumab after 1 year of treatment.

6.2.1.2.3.3.2 Bevacizumab
Bevacizumab is a non-selective VEGF blocker (Avastin®, Roche). Although no randomised clinical trial with bevacizumab in the case of RVO has been performed, nevertheless a range of unmonitored casuistic series show that its intravitreal administration may lead to an improvement of VA and to the correction of macular edema [85, 86]. Nevertheless, with regard to deviations in dosing and in the therapeutic regimes in these studies, the long-term outputs and safety data remain unclear.

6.2.1.2.3.3.3 Pegaptanib
Pegaptanib is a selective anti-VEGF165 blocker – Macugen®, Pfizer, for which no licence has yet been granted for use in indication for retinal vein occlusion (off label treatment). A clinical trial of phase II pointed to the possibility that an intravitreal dose of 0.3 mg of pegaptanib administered every six weeks over a six-month observation period led to an improvement of VA in the sixth month by approximately 7 letters [87].

6.2.1.2.3.4 Recommendations for further observation
Observation is monthly during the course of the first year, and 1x 3 months after stabilisation of the condition over the next year.

Indication criteria for repeated treatment
The indication criteria for repeated treatment correspond to the SPC of the individual means of treatment.
Treatment is applied on the basis of a decision of the doctor (see below).

6.2.1.2.3.6 Interruption of treatment
The criteria for interruption of treatment are:
1. Evidence that there is no benefit from the treatment, e.g. permanent deterioration/failure to achieve stabilisation of sight despite the relevant treatment. As a rule it applies that if there is no positive therapeutic response 3 months after the commencement of treatment, the prognosis is poor even despite continued treatment.
2. Increase of intraocular pressure in connection with pharmaceutical preparation.

6.2.1.3 Conducting treatment of ischemic CRVO
In patients with ischemic CRVO, the primary evaluation should be based on an assessment of the presence of macular perfusion and also the presence of neovascularisation.

6.2.1.3.1 Macular perfusion
In cases with macular edema and continuously perfused macula, it is appropriate to commence the same treatment as is outlined above for cases of non-ischemic CRVO.
In the case of non-perfused macula, it is necessary to commence treatment in cases where expectations of improvement of sight remain. However, VA of 6/60 or worse is connected with a high degree of macular ischema. If this condition persists for longer than 2 months, the expectation of correction of VA is very small, and as a result treatment is not indicated.

6.2.1.3.2 Peripheral non-perfusion
Peripheral retinal non-perfusion greater than ten times the diameter of the disc of the ON is generally characteristic of ischemic CRVO. The development of ocular neovascularisation is directly proportionate to the extent of non-perfusion. Cases with extensive retinal non-perfusion or limited compliance can be considered candidates for timely panretinal photocoagulation (PRP) in an endeavour to block the development of ocular neovascularisation. In less serious cases laser treatment (scatter photocoagulation) may be focused on the area without perfusion.
In addition to applicable treatment of macular edema, it is necessary to observe patients with ischemic CRVO without neovascularisation at least once per month and to perform examination of VA, biomicroscopy, OCT and FAG (if required).
In an endeavour to detect early signs of neovascularisation it is also appropriate to assess the corneal angle and the iris [95].

6.2.1.3.3 Conducting treatment of neovascularisation
6.2.1.3.3.1 Neovascularisation of anterior segment
Wherever neovascularisation of the

Table 1

<table>
<tr><td colspan="4">CRVO</td></tr>
<tr><td colspan="4">Determination of basic systemic disorder</td></tr>
<tr><td colspan="4">(arterial hypertension, cardiovascular disorder, diabetes mellitus, hyperlipidemia, thrombophilia)</td></tr>
<tr><td colspan="4">Determination of retinal ischemia</td></tr>
<tr><td colspan="4">Identification of complications threatening sight [neovascularisation (of retina, chamber angle, iris, disc of ON), glaucoma, macular edema]</td></tr>
<tr><td colspan="4">Monitor VA, examination of retina using biomicroscopy, OCT</td></tr>
<tr><td colspan="2">Non-ischemic</td><td colspan="2">Ischemic</td></tr>
<tr><td>VA≥6/9
Monitor
During first three months once per months, then once per two months for a period of 1 year. It is possible to consider application of anticoagulation treatment with warfarin as an alternative.</td><td>VA≤6/9
Monitor symptoms testifying to conversion to ischemic CRVO</td><td>Macula with perfusion
If ME is present:
- Lucentis or Ozurdex according to decision of clinician</td><td>Retinal ischemia
If ME is present:
- Lucentis or Ozurdex according to decision of clinician
- laser treatment of area of periphery of ischemia</td></tr>
</table>

In the case of intravitreal injections it is necessary to conduct observation of intraocular pressure, cataract etc.

anterior segment (neovascularisation of the chamber angle or iris) is determined, evidence-based medicine inclines towards the performance of PRP. Above all the extent of neovascularisation of the anterior segment (which explicitly requires PRP) has been defined as any neovascularisation of the angle or neovascularisation of the iris corresponding to two hours [8].
Although no randomised clinical trial of combined treatment has yet been conducted, it is nevertheless appropriate to administer an anti-VEGF intravitreal substance together with PRP, because this approach may lead to more rapid regression of neovascularisation of the anterior segment [96, 97]. With regard to treatment of neovascularisation of the anterior segment using anti-VEGF monotherapy, only limited experience is available to date [98].

6.2.1.3.3.2 Neovascularisation of posterior segment
Neovascularisation of the posterior segment (neovascularisation of the retina or disc of the optic nerve) may develop independently or in connection with neovascularisation of the anterior segment. Neovascularisation of the posterior segment can nevertheless be treated using PRP, in accordance with the above proposals.
As stated above, combination therapy using anti-VEGF and PRP may prove to be useful in effective control of the growth of neovascularisation. Monotherapy in the form of an intravitreal injection of anti-VEGF substances such as ranibizumab and bevacizumab may lead to a temporary regression of ocular neovascularisation [90, 91].
It is necessary to treat patients with advanced ocular neovascularisation using PRP as soon as possible. In particular with eyes with haemorrhage into the vitreous cavity, combination therapy with anti-VEGF substances may prove to be effective in halting the growth of neovascularisation, which should also enable immediate application of PRP within a pair of individual therapeutic applications (unless the vitreal haemorrhage is too severe, which would require vitrectomy and endolaser treatment).

6.2.1.3.3.3 Neovascular glaucoma
In the case of determination of neovascular glaucoma, it has been demonstrated that an intravitreally administered non-selective anti-VEGF preparation causes regression of new blood vessels in the iris and a decline in obstruction of the angle. From a comparative series of cases it ensues that new blood vessels in the iris may record more rapid regression after intravitreal administration of a non-selective anti-VEGF preparation together with PRP than upon treatment with PRP alone. These reports also state the possibility that a non-selective anti-VEGF preparation may reduce the requirement for a surgical procedure and may serve as an effective supplement to surgical filtration treatment. The alternative is cryosurgical combination therapy (cyclocryocoagulation and panretinal cryocoagulation of the retina) [93].

6.2.1.4 Juvenile CRVO
Juvenile CRVO, which occurs in persons aged under 50 years, according to everything represents a different entity as regards pathogenesis and clinical course, and it is necessary to differentiate this from CRVO which develops in patients over the age of 50. In certain cases, if the disorder is connected with a serious systemic disease, it is necessary to address the patient's condition on the basis of a complete systemic examination and the prognosis may be worsened.
Juvenile CRVO is often of a non-ischemic type, without any clearly identifiable risk factors, and is sometimes linked with inflammatory pathogenesis, as has been demonstrated on the basis of detection of cells of the vitreous area [27]. The prognosis of the development of sight is generally better in comparison with regular CRVO, even if potential complications include ocular neovascularisation and the development of macular edema.
There are certain materials demonstrating that systemic steroids may bring about a more rapid correction of the disorder. Although no randomised clinical trial is available, it is nevertheless acceptable to assume that intraocularly administered steroids, in particular a slow-release intravitreal implant of dexamethasone or ranibizumab may be effective in treating macular edema in the case of juvenile CRVO.

Algorithm of CRVO treatment (table 1)

6.2.2 Conducting treatment of branch retinal vein occlusion (BRVO)

6.2.2.1 Systemic risk factors and classification of subtypes of BRVO
Treatment of BRVO is in many respects similar to treatment of CRVO as regard the systemic risk factors, but at the same time manifests certain significant differences, since this type of RVO represents a smaller risk of progressive deterioration of VA and conversion to ischemia, and also a lower risk of neovascularisation.
Treatment of BRVO should thus focus on a number of aspects, including the following: identification and management of systemic risk factors (specifically arterial hypertension, cardiovascular disorders and diabetes mellitus); precise classification of the area of occlusion for determination as to whether this represents occlusion of the main branch or a secondary branch (in particular macular BRVO), in general it applies that the more distal the location of the occlusion is from the disc, the better the prognosis; assessment of the degree of peripheral perfusion and the degree of macular ischemia, and also application of treatment according to complications threatening sight (mainly persistent macular edema and neovascularisation).
As described above, diagnosis of BRVO is clinical. In borderline cases, in particular in the case of small occlusion, FAG may be conducted for confirmation of the diagnosis. FAG is especially useful in determining the extent of macular edema and ischemia. In studies of branch retinal vein occlusion, approximately 50% of untreated eyes with BRVO maintained vision of 6/12 or better, whereas in 25% of subjects the result was ≥ 6/60. Amongst the two main complications which may require treatment are macular edema and neovascularisation of the retina or disc. As has been demonstrated in two independent studies, neovascularisation of the retina occurs in 36% of eyes with > 5 papillary diameters (DD) and 62% with > 4DD of the area of non-perfusion [71, 74].

6.2.2.2 Treatment of neovascularisation
Neovascularisation of the disc or retina is an indication for photocoagulation of the ischemic retina (sector photocoagulation), although the available evidence testifies to the fact that waiting with laser procedure can be deferred until vitreal haemorrhage appears, which does not have an unfavourable impact on the prognosis for sight [71, 74]. New blood vessels appear only when there is at least a quadrant of the capillary end, and this usually happens six months after occlusion. In patients with one or more quadrants of retinal ischemia, check-ups are recommended at an interval of 3-4 months. Nevertheless, the general opinion predominates that upon the occurrence of neovascularisation of the retina

or optic disc it is suitable to perform sector laser photocoagulation. Fluorescent angiography is not always necessary before the laser procedure, because the ischemic zone is visible clinically (obliterated blood vessels). In the case of worse compliance or the impossibility of monitoring the patient, it is possible to recommend photocoagulation by laser in the zones of capillary non-perfusion.

6.2.2.3 Treatment of macular edema

6.2.2.3.1 BRVO with perfused periphery and normal VA

In the case of BRVO with perfused periphery and normal VA, the prognosis is favourable and it is possible merely to monitor the situation. In this case it is not necessary to recommend any treatment. Upon examination during observation it is necessary to search for potential macular edema, using examination of VA, biomicroscopy and OCT. In the case of doubts it is suitable to perform FAG.
During the first three months it is necessary to observe patients once per month, and subsequently once every two months during the first year. During this period of monitoring it is necessary to instruct patients in order to report to the facility quickly in the case of deterioration of VA.
In clinical practice we encounter cases in which good VA is preserved over the long term even despite the presence of ME. However, every edema is by its nature linked with a certain degree of ischemia or hypoxia. The macula is able to tolerate an oxygen deficiency for a certain amount of time, and then as a rule suddenly decompensates, which is accompanied by a further deterioration of VA, frequently then of a permanent character. The length of time for which the macula will be able to resist hypoxia is highly individual – this depends on several factors: the larger the ME, the higher the connected degree of hypoxia as a rule, and the macula shall be able to resist such a condition for a shorter period of time, especially if there is no tendency towards resorption of ME or ME in fact deepens. There effective auto-regulating mechanisms are present, the macula may resist hypoxia for a very long time. With advancing age the effectiveness of auto-regulation deteriorates as a manifestation of the natural ageing process. Decompensation of the macula is anatomically accompanied by the transition of microcystic changes into macrocystic. These changes can be detected by careful biomicroscopy, today they can be detected highly effectively using OCT examination. This concerns a perceptible onset of structural, irreversible changes in the macula. Sometimes it is possible to perform effective biomicroscopic observation of the blood level on the bed of the macrocyst. This represents an urgent condition – if we do not succeed in achieving resorption of cystoid ME within a short time, the deterioration of VA will deepen and in particular the deterioration of VA will be permanent [20].
In summary: in branch retinal vein occlusion with VA of 6/12 or better, it is possible to wait with regard to therapy, but it is however necessary to monitor the condition on the retina carefully.

6.2.2.3.2 BRVO and symptomatic deterioration of VA

In cases of BRVO and symptomatic deterioration of VA it is necessary to perform an examination focusing on the possible presence of macular edema. If OCT points to the presence of macular edema, it is necessary to consider treatment according to the following brief description.
In 2011 a study was published demonstrating that initial VA is an entirely independent predictor of resulting VA [68]. The worse the VA, the worse the prognosis of branch occlusion. This is linked to the fact that the level of central VA is a very sensitive indicator of the oxygen ratios in the central retinal landscape [20]. The degree of hypoxia of the macula then correlates with the urgency of any effective treatment. On the basis of this knowledge there are 2 fundamental indicators of treatment of BRVO: (1) Timely treatment in the case of prognostically unfavourable occlusion, i.e. upon initial VA of 6/24 or worse. The sooner we commence treatment, the better – the macula is afflicted by a high degree of hypoxia, in which the development of structural changes in the central retinal landscape in connection with permanent impairment of VA frequently occurs fairly rapidly. It is possible to permit immediate treatment in the case of occlusion with initial VA of 6/18. (2) Microcystic changes in the macular convert to macrocystic. This represents a perceptible onset of structural, irreversible changes in the macula. This indication applies also for VA of 6/6 [20].

6.2.2.3.3 Therapeutic approaches in treatment of macular edema in the case of BRVO

6.2.2.3.3.1 Laser photocoagulation techniques

At present 2 laser photocoagulation techniques are used – generally widespread grid photocoagulation, which is the universally recognised standard, and all other new therapeutic approaches should be compared with this standard, with a clear conclusion that the new approach brings better results or not. The second laser photocoagulation technique is arteriolar constriction.

6.2.2.3.3.1.1 Grid laser photocoagulation.

Grid laser photocoagulation has been the standard of care for several years, and is recommended for patients with macular edema in connection with branch retinal vein occlusion, who meet the criteria for qualification of BVO SG (VA of 6/12 or lower, persistent macular edema with duration of four months or longer and also resorption of macular haemorrhage). This concerned a multicentric, randomised, controlled clinical trial, which was designed in such a manner as to enable issues regarding the treatment of complications upon occlusion of a branch of the central vein to be addressed [70, 71]. Grid photocoagulation can be repeated 1x every 4 months. Patients with serious loss of visual acuity (less than 6/60) and patients in whom the symptoms have appeared for over one year will probably not benefit from photocoagulation [75].
However, grid photocoagulation is not an appropriate technique for haemodynamically severe haemorrhagic occlusions, which are almost always linked to a low level of VA, and thus a high degree of macular ischemia. Photocoagulation of the haemorrhagic retina is generally regarded as a contraindication for the formation of hypercoagulation lesions and a high risk of formation of an epiretinal membrane and subsequent traction into the macula [20].

6.2.2.3.3.1.2 Arteriolar constriction ("crimping technique")

This technique was first described in 1975 by L'Esperance ("crimping technique"). The author assumes that the functioning of this technique is based on a decline in arterial pressure in the occluded region and a subsequent improvement in the drainage of ME as a consequence of a reduction of the inflow into the location of occlusion [114]. In 1984 Jalkh used his own modification of arteriolar constriction (ACo) in the treatment of chronic ME in 41 eyes. His modification resides in the application of merging coagulation lesions along the arteriola, which supplies the area of the retina with ME [115].

In 1993 Řehák described a modification of ACo, which resided in an application of merging coagulation points directly across the inflow arteriola [116]. The extent of the procedure on the arteriola depends on the severity of the occlusion, and on the other hand is limited by the possibilities of finding a section of the arteriola which is not covered by a haemorrhage or is not in close proximity to a haemorrhage. Constriction can be performed also outside of the area of occlusion, but this must concern an arteriola which supplies the occluded area. Other reports on the use of this technique in the foreign literature are isolated: In the year 2000 Erdol and Akyol attained better results in a group when the combined photocoagulation and ACo in comparison with simple grid photocoagulation, but the difference was not statistically significant [117].
ACo is an appropriate technique for treatment of haemodynamically severe occlusions with extensive retinal haemorrhages and high macular ischemia (poor initial VA). However, to date no study is available with sufficient evidence of the effectiveness of this approach.

6.2.2.3.3.2 Intravitreally applied pharmaceuticals

6.2.2.3.3.2.1 Intravitreal steroids

6.2.2.3.3.2.1.1 Triamcinolone acetonide (TRIVARIS)
The SCORE clinical trial documented that in patients with BRVO, a laser procedure has a more favourable benefit to risk ratio than triamcinolone acetonide (TRIVARIS).

6.2.2.3.3.2.1.2 Biodegradable implants with dexamethasone
In the GENEVA study with a long-term dexamethasone (Ozurdex) releasing biodegradable implant, two identical randomised, prospective, multicentric, masked phase III clinical trials with a placebo control and parallel groups demonstrated a statistically significant effect and fast action, in which the maximum effect was attained at 60 days and its decline commenced at 90 days, though it persisted for 180 days. The second injection was in fact slightly more effective than the first. No undesirable events were linked with the administration of the injection, the occurrence of cataracts was very low and there was similarly a very low occurrence of persistent increase of intraocular pressure.
The proportion of patients who attained an improvement in VA by at least 15 letters or 10 letters from the beginning was significantly larger in the group with dexamethasone 700 mg than in the group with the placebo treatment, from day 30 to day 90. The greatest response was observed on day 60.
On the basis of a later analysis of the results of the GENEVA study [60] it was determined that treatment of macular edema in BRVO with a short duration had a better effect than deferral of treatment. The percentage of reduced hope for improvement by 15 letters upon treatment on day 180 was 54% if the edema persisted for 6 months, 32% if it persisted for 3 months and only 12% if it persisted for 1 month. Ozurdex is considered to represent an effective treatment of BRVO.

6.2.2.3.3.2.2 Anti-VEGF preparations

Ranibizumab
This is a non-selective VEGF blocker (Lucentis), the effectiveness of which has been demonstrated on the basis of the BRAVO clinical trial.
In the BRAVO trial [94] there was an improvement of sight by 15 letters or more in the 6th month in 55% of patients who received Lucentis in a dose of 0.3 mg, and in 61% of patients who received Lucentis in a dose of 0.5 mg, in comparison with 29% of patients who received a placebo injection and on whom laser treatment by grid coagulation was performed.
In the 6th month, with an average of 5.7 injections during the first six months, the median improvement of sight was 16.6 and 18.3 letters (0.3 and 0.5 mg), in comparison with 7.3 letters in the group with the placebo treatment. From the 3rd to the 5th month a one-off application of laser photocoagulation as a salvage treatment was permitted in all the branches of the study. From the 6th to the 12th month, patients were treated by an open method for re nata. The beneficial effect on sight was preserved in a median number of 2.7 further injections during the second six months. A benefit was determined also in patients in the group with a placebo treatment, even if the degree of improvement of sight did not reach the same values as with the patients who received treatment from the beginning. More than half of the patients in the BRAVO clinical trial had macular edema of a short duration (51.5-53.8%).
Ranibizumab is considered an effective treatment for BRVO.

6.2.2.3.3.2.2.2 Bevacizumab
At present an increasing amount of data from short-term studies supports the fact that repeated intravitreal injections of bevacizumab reduce macular edema, which occurs as a manifestation of retinal vein occlusion, and this applies also in the case of patients in whom prior laser treatment has failed [95-99]. The most common regime of dosage is two to three injections during the course of the first 5-6 months. However, further randomised controlled studies are required for an evaluation of the long-term effectiveness and safety of intravitreally administered bevacizumab. At present no recommendation with regard to intravitreal administration of bevacizumab can be issued.

Pegaptanib
The first multicentric randomised study dealing with the effect of an anti-VEGF agent in the treatment of RVO was designed in order to enable an assessment of the effectiveness of the sodium salt pegaptanib.
In the group treated with pegaptanib sodium salt within a dose of 1 mg, a higher occurrence of improvement by 5 letters or more was determined, as well as a lower occurrence of deterioration by 15 letters or more than in the control group ($p<0.05$ or $p<0.01$) [100].
Pegaptanib is a selective blocker anti-VEGF165 – Macugen®, Pfizer, for which no licence has been granted for use in indication of retinal vein occlusion (off label treatment).

6.2.2.3.3.3 Criteria for repeated treatment
1. Indication criteria for repeated treatment corresponding to SPC of individual means of treatment. Treatment is applied on the basis of the decision of the doctor (see below)
2. Repeated treatment modified by laser photocoagulation in intervals of once every 4 months should be considered

6.2.2.3.3.4 Interruption of treatment
1. Treatment may be interrupted in the case of permanent damage to sight or morphology of the macula.
2. The criteria for interruption of treatment are:
a. Evidence that there is no benefit from the treatment, e.g. permanent deterioration/failure to achieve stabilisation of vision even despite two consecutive visits.

b. Increase of intraocular pressure, which does not respond sufficiently to treatment with an effective pharmaceutical for reduction of intraocular pressure.

Algorithm of BRVO treatment (table 2)

6.2.3 Algorithm upon hemispheric vein occlusion

1. Treatment of hemispheric vein occlusion is similar to treatment of retinal vein occlusion. In particular macular edema as a consequence of hemispheric vein occlusion is treated in a similar manner as with BRVO.
2. The risk of rubeosis in ischemic occlusion of the hemicentral vein is greater than in the case of BRVO, but smaller than in CRVO. Examination for neovascularisation of the anterior segment, including gonioscopy, is therefore indicated. Treatment of neovascularisation of the iris or chamber angle is the same as in CRVO.

7. CONCLUSION

The guidelines for diagnosis and treatment of patients with retinal vein occlusion contain the procedures for care of patients with closure of retinal veins, which are recommended by the Czech Vitreoretinal Society and approved by the Czech Ophthalmological Society.

Table 2

<table>
<tr><td colspan="4">BRVO</td></tr>
<tr><td colspan="4">Determination of basic systemic disorder</td></tr>
<tr><td colspan="4">(arterial hypertension, cardiovascular disorder, diabetes mellitus, hyperlipidemia, thrombophilia)</td></tr>
<tr><td colspan="4">Identification of location of occlusion</td></tr>
<tr><td colspan="4">Assessment of extent of peripheral and macular ischemia (according to fluorescent angiography)</td></tr>
<tr><td colspan="4">Identification of complications threatening sight such as macular edema, neovascularisation (ON disc, retina, iris, chamber angle)</td></tr>
<tr><td colspan="4">Observation of VA, biomicroscopy of fundus, OCT</td></tr>
<tr><td colspan="2">Perfused periphery</td><td colspan="2">Non-perfused periphery</td></tr>
<tr><td>Normal VA or deterioration of VA to 6/12 inclusive
Monitor
during first three months once per month, then once per two months for a period of 1 year.
If macrocystic ME is shown on OCT, treatment is indicated as with sympathetic deterioration of VA.</td><td>Symptomatic deterioration of VA to worse than 6/12
If ME is present:
- Lucentis or Ozurdex according to decision of clinician
- Laser treatment may be recommended in case of insufficient effect of treatment with steroids or anti-VEGF, or as an alternative to other treatment options</td><td>Macula with perfusion
If ME is present:
- Lucentis or Ozurdex according to decision of clinician
- Laser treatment may be recommended in case of insufficient effect of treatment with steroids or anti-VEGF, or as an alternative to other treatment options
- Laser treatment of area of peripheral ischemia</td><td>Retinal ischemia
If ME is present:
- Lucentis or Ozurdex according to decision of clinician
- Laser treatment may be recommended in case of insufficient effect of treatment with steroids or anti-VEGF, or as an alternative to other treatment options
- laser treatment of area of periphery of ischemia, in case of neovascularisation perform sector PRP</td></tr>
</table>

In the case of intravitreal injections it is necessary to conduct observation of intraocular pressure, cataract etc.

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